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"Skip the stoma, opt for delayed colo-anal anastomosis- the smooth move in low anterior resection surgery!"

Syariz Ezuan S[1], Syafiqa Al-Azua AJ[2], Mohd. Fahmi I[2], Muhammad Ash-Shafhawi A[2]

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SUMMARY

Delayed CAA without a diversion ileostomy is an alternative to immediate CAA for management of low rectal cancer. Traditionally, temporary diversion ileostomy is used to mitigate complications such as anastomotic leaks. However, Turnbull-Cutait introduced a two-stage approach in 1961 that eliminates the need for an ileostomy. Two cases of low rectal adenocarcinoma are described. Both patients underwent neoadjuvant chemotherapy, laparoscopic ultralow anterior resection and trans-anal colonic pull-through, followed by delayed CAA within 3-5 days. Both recovered uneventfully with preserved sphincter function. Histopathology revealed early-stage disease (T1N0 and T2N0). Recent literature suggests that delayed CAA offers outcomes comparable to immediate CAA in terms of pelvic morbidity, anastomotic leakage and function while reducing the need for diversion ileostomy. Advantages include improved quality of life, elimination of stoma-related complications, cost savings and shorter recovery times.

INTRODUCTION

Colorectal cancer ranks as the third most prevalent cancer in men and the second most common cancer in women globally. The incidence of colorectal cancer exhibits considerable geographical diversity, with a notable surge in its occurrence observed in various Asian countries, including Malaysia. The overall incidence rate in Malaysia stands at 21.32 cases per 100,000 individuals, emphasizing the significance of understanding and addressing the escalating trend of colorectal cancer in this region.[1,2]

The prevailing standard of care for the surgical management of low rectal cancer involves low anterior resection, TME and CAA.[3] Given that the incidence of anastomotic leak is relatively low among the majority of patients, it is imperative to recognize that the implementation of loop diversion ileostomy does not preclude the occurrence of additional complications. Furthermore, it is noteworthy that up to 25% of initially intended temporary ileostomies may undergo a transition to a permanent stoma.[4]

The concept of delayed colo-anal anastomosis subsequent to rectal surgery was originally introduced by Turnbull and Cutait in the context of Hirschsprung's disease, Chagas disease affecting the upper rectum and sigmoid. This technique involves a two-stage operative approach. In the initial stage, following rectal resection, a segment of the colon measuring 5-10cm is transanally exteriorized and maintained externally. Subsequently, in the second stage, conducted at mean of 7 days later (range 5-10 days), the externalized colon is sectioned, and hand sewn CAA anastomosis with interrupted absorbable suture.[5] The primary aim of employing this technique is to escape morbidity of diversion ileostomy.[6]

CASE PRESENTATION

Case 1

The case involves an elderly woman with chronic per-rectal bleeding. A colonoscopy revealed a low rectal tumour with histological study proven to be well-differentiated adenocarcinoma. Pre-operative Wexner score was 0. Baseline CEA was normal, and radiological staging conclude T3N0M0 tumour. In a view of locally advanced rectal cancer, neoadjuvant chemoradiotherapy Xelox regime for 6 cycles was given. A laparoscopic ultralow anterior resection with trans-anal colonic pull through was performed without an ileostomy as depicted in Figure 1. After 3 days, a delayed hand sewn trans-anal CAA was completed without complications as illustrated in Figure 2. The patient was discharged well with preserved sphincter function. HPE indicated T1N0 disease with no need for adjuvant therapy. Subsequent surveillance follow-up was uneventful with functional Wexner score 1. Patient was pleased as she avoided having stoma and did not require any additional surgeries.

Case 2

A senior gentleman with a medical history notable for stage 1 low rectal adenocarcinoma, having undergone Transanal Minimally Invasive Surgery (TAMIS) three years prior, presented with per rectal bleeding. Colonoscopy revealed a recurrent adenocarcinoma in the low rectum, confirmed by HPE. Pre-operative Wexner score was 0. Imaging studies indicated locally advanced low rectal cancer T3N0M0, lead to the decision for neoadjuvant chemoradiotherapy. Subsequently, the patient underwent laparoscopic ultra-low anterior resection with trans-anal colonic pull-through. Hand sewn delayed CAA was performed five days later, contributing to the patient's uneventful recovery with preserved sphincter function. HPE revealed T2N0 disease, and follow-up assessment during surveillance showed no concerns. Patient expressed satisfaction with Wexner score of 2, relieved by the absence of stoma and need for further surgical procedures.

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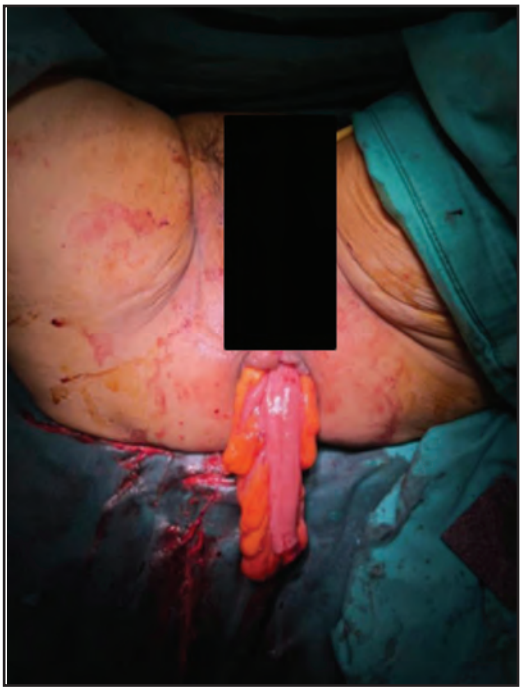

Fig. 1: Colonic segment of trans-anal pull through

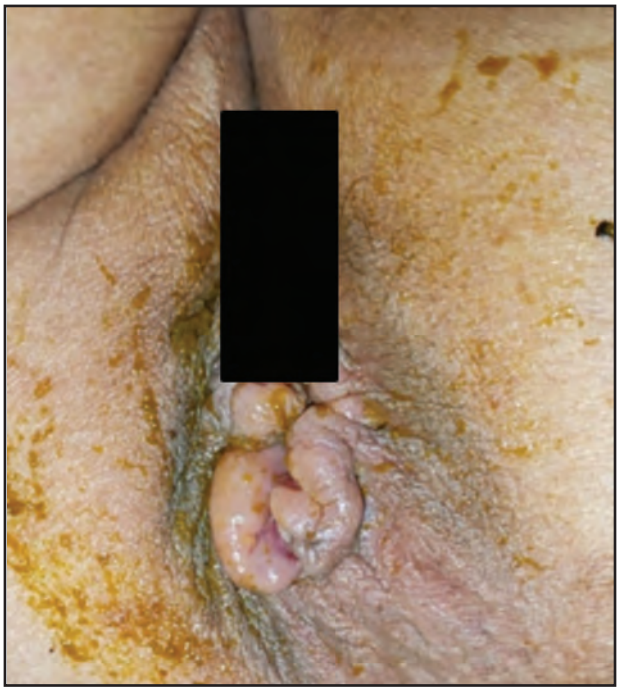

Fig. 2: Post hand sewn colo-anal anastomosis

DISCUSSION

The selection criteria for this surgical approach include histologically confirmed adenocarcinoma of low rectum, with tumour located within 5 cm from the anal verge and a maximum primary tumour length of 5 cm. Candidates must demonstrate good anal function, as assessed by Wexner incontinence score < 5. Patients with recurrent rectal cancer or a history of prior colorectal surgery are excluded. Comprehensive preoperative evaluations, including colonoscopy and tumour staging, are essential. Additionally, prehabilitation to optimize patient's physiological status is undertaken to enhance the surgical outcomes.

Contemporary literature suggests that the delayed implementation of CAA subsequent to low anterior resection produces outcomes on par with immediate CAA. A randomized control trial conducted by Sebatiano et al. in 2020 revealed through a comprehensive study that pelvic morbidity, anastomotic leakage, and functional results were comparable within a 30-day composite post-operative complications period.[7] In particular to this technique, possible anastomotic leak, pelvic abscess, necrosis of the colonic pull-through segment, resulting in reoperation or stoma creation was reported.[8] In the two cases presented, no surgical complications of failure were noted. Both patients recovered uneventfully with acceptable postoperative Wexner score without need for any additional interventions.

The anastomosis is typically performed 5-7 days after the colonic pull through, though in some minority studies they even perform it as early as 3 days. This interval allows the colon to stabilize and form adhesions, reducing the risk of leaks while maintaining viability.[7,8] Currently, there is insufficient evidence or research to establish the optimal timing for delated CAA. In this present case series, one patient underwent anastomosis on postoperative day 3 and another on postoperative day 5, both with favourable outcomes.

The incorporation of a diversion ileostomy during low anterior resection has proven effective in reducing both the incidence and morbidity associated with anastomotic leakage; however, this intervention introduces its own set of complications related to the stoma. It is imperative to conduct a thorough examination of the morbidity and mortality associated with diversion ileostomy, considering factors such as dehydration due to heightened stoma output, infectious complications, herniation, obstruction, haemorrhage, and skin excoriation.[4] The closure of an ileostomy also presents inherent potential complications with overall rate of 16.4%, including ileus, intestinal obstruction, wound infection, and cardiopulmonary complications. It is noteworthy that the implementation of delayed CAA has been associated with a diminished likelihood of necessitating a diversion ileostomy. This not only positively impacts the patient's quality of life but also serves to avert complications associated with ileostomy without compromising oncological and functional outcomes.

The utilization of delayed CAA procedure, by circumventing the need for temporary stomas, may offer potential advantages in diminishing the incidence of permanent stomas when compared to the conventional approach of standard CAA coupled with diverting ileostomy. Given the decreased postoperative morbidity associated with omitting stoma closure following radical surgery, there is a potential for a reduction in the direct cost of hospital admission. However, it is essential to acknowledge that formal research and comprehensive studies addressing the cost-benefit analysis especially hospital length of stay of this procedure

remain limited, necessitating further in-depth exploration and detailed investigation.

Presently, there is a scarcity of comparative studies evaluating delayed CAA against the conventional approach of immediate CAA accompanied by diversion ileostomy in low anterior resection. Additionally, on-going research interest persists in evaluating functional outcomes, incorporating metrics such as the Wexner incontinence score and the Low Anterior Resection Syndrome (LARS) score.

CONCLUSION

Based on current data, delayed CAA generally does not elevate the risk of post-operative morbidities when compared to the standard approach of immediate CAA accompanied by diversion ileostomy. This suggests that delayed CAA could be deemed a viable alternative strategy, allowing for the avoidance of a temporary ileostomy following low anterior resection for low rectal cancer. The advantages of circumventing diversion ileostomy and its associated complications, coupled with the absence of an increased post-operative morbidity rate, position this technique as a prospective candidate for standard practice in the foreseeable future.

ACKNOWLEDGEMENT

All the authors have no conflict of interest to declare.

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CASE REPORT

Bjornstad syndrome: a case report of progressive hearing loss and motoric deterioration

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SUMMARY

Bjornstad syndrome is a rare autosomal recessive disorder caused by a mutation in the BCS1L gene, crucial for mitochondrial function and complex III assembly in the electron transport chain. It is characterized by twisted hair shafts, bilateral sensorineural hearing loss, alopecia, and mental retardation. The presented case involves a 7-month-old with delayed speech development, feeding difficulties, and distinct hair abnormalities. Audiological testing revealed initial mild to moderate hearing impairment, which progressed to profound sensorineural hearing loss, confirming the diagnosis. Over three years, the patient's condition deteriorated, necessitating cochlear implant surgery due to worsening hearing loss. This case underscores the progressive nature of hearing loss in Björnstad syndrome and highlights the critical need for early diagnosis and ongoing monitoring. Comprehensive auditory evaluations and timely interventions are essential, and a multidisciplinary approach involving otolaryngologists, audiologists, geneticists, and speech therapists is crucial for effective management and improved patient outcomes.

INTRODUCTION

Bjornstad syndrome is an extremely rare inherited autosomal recessive disorder. Its exact prevalence is unknown, but it is considered extremely rare, with fewer than 50 cases reported in medical literature.[1] This condition is associated with the mutation of BCSL1 gene located on chromosome 2q35.[2] The gene encodes a member of the ATPases 'Associated with diverse cellular a Activities' (AAA) family of ATPases, which is essential to assemble complex III in the mitochondria.[2] Mutation in this gene have been previously associated with two other conditions, complex III deficiency and GRACILE (Growth retardation, Aminoaciduria, Cholestasis, Iron overload, Lactic acidosis, and Early death) syndrome.[3]

Bjornstad syndrome is primarily characterized by abnormality twisted hair shaft (pili torti) before the age of two and bilateral sensorineural hearing loss resulting from inner ear abnormalities. The hearing loss is caused by changes in the inner. It typically becomes evident in early childhood and affects both ears.[2,4] The author reports a case report aiming to describe the clinical presentation and progressive hearing deterioration in a patient with Björnstad syndrome, highlighting the importance of early diagnosis, regular follow-up, and comprehensive care to address the multisystemic nature of the syndrome, with particular emphasis on its auditory manifestation.

CASE PRESENTATION

A 7-months-old baby was referred to the ENT department for hearing screening due to delayed speech development. He hasn't begun babbling at 6 months of age and does not respond toward loud sound sources. His parents also reported feeding difficulties characterized by frequent vomiting during mealtimes, which led to low weight. The mother noted that his twisted, dry hair and sparse eyebrows resembled those of his deceased sister, although other family members did not exhibit these features. The prenatal course was uneventful, with no history of infections or complications. The pregnancy concluded with a term delivery of a healthy baby weighing 2850 grams and an APGAR score of 9/10. No complications, such as hyperbilirubinemia, occurred during pregnancy or at birth. There was no history of exposure to chemicals, mechanical trauma, or heat that could damage the hair shaft. Additionally, there was no prior medical history of seizures, altered consciousness, or medication use. The child was born to non-consanguineous parents.

Physical examination revealed underweighted child with stable vital signs, showing disinterest in his surroundings and lacking eye contact. He presented with microcephaly and hair and eyebrows that were twisted, short, thin, brittle, and sparse, with no visible scarring. His skin and nails appeared normal (Figure 1) (Figure 2A). Central hypotonia was noted, and although he could sit without maternal assistance, he achieved this milestone with a delay. Both testicles were normal in size and position. Examination of the outer ears was normal, with intact tympanic membranes.

Microscopic examination of extracted scalp hairs showed a twisting of the hair shaft along its axis, creating alternating light and dark segments known as pili torti (Figure 2B). Audiological testing revealed outer hair cell dysfunction in both cochlea on otoacoustic emissions (OAE). Tympanometry indicated stiffness and limited movement of the tympanic membrane. Auditory Brainstem Response (ABR) testing showed wave V at 30 dB for click stimuli and at 50 dB for tone bursts 1000 Hz in both ears. During the audiology testing, the patient was on a nasogastric tube for feeding support due to ongoing feeding difficulties (Figure 3A). These findings

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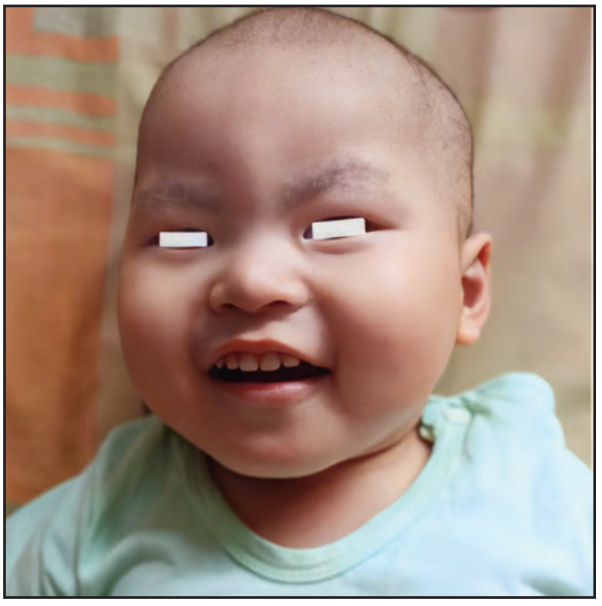

Fig. 1: Patient with pilli torti (hair and eyebrow)

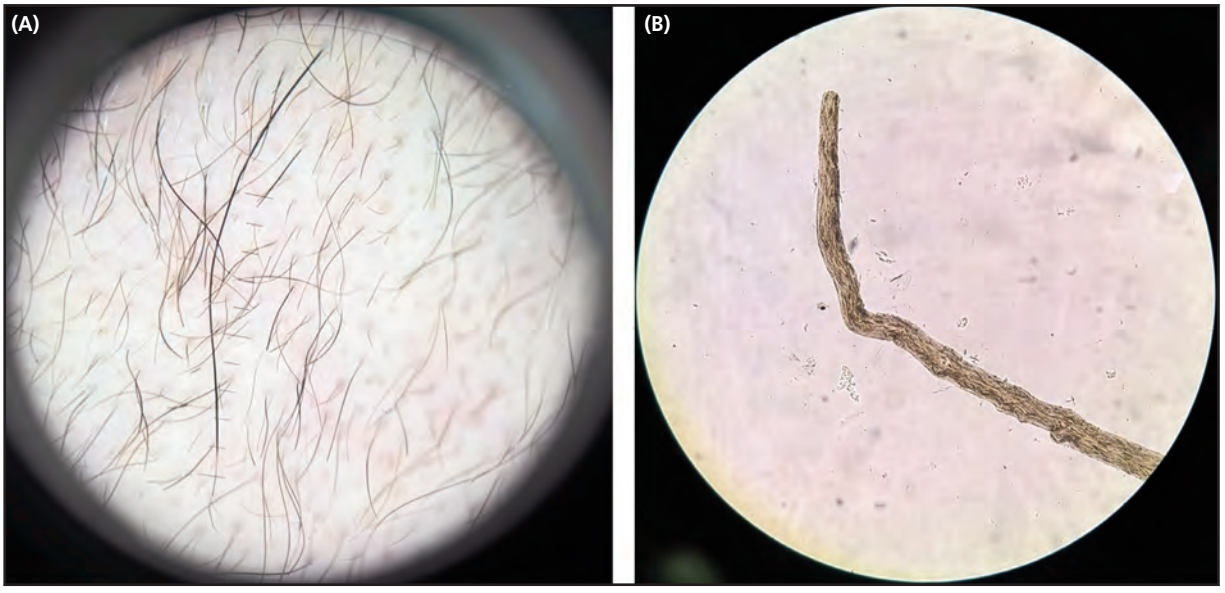

Fig. 2: (A) Hair sample under magnification; (B) Hair sample under 40x microscope

suggest that the patient exhibits mild to moderate hearing impairment at 1000 Hz, associated with conductive hearing loss. Genomic testing using CentoXome® Solo, including NGS-based CNV analysis, identified a positive variant in the BCSL1 gene, consistent with autosomal recessive mitochondrial complex III deficiency nuclear type 1. A diagnosis of Björnstad syndrome was confirmed. The patient's parents were advised to undergo regular hearing monitoring and to use hearing aids, but the parents defaulted from the treatment plans.

Two years later, the patient returned for follow-up hearing monitoring after the initial assessment, with no significant improvement in their condition. Additionally, there was no prior history of seizures, altered consciousness, or medication use. Anthropometric measurements indicated a weight of 11.35 kg and a height of 86 cm. Re-evaluation audiological assessment using ABR click revealed wave V responses at 70 dB in both ears, indicating moderate sensorineural hearing loss (Figure 3B).

At the three-year-follow-up after the initial assessment, the patient returned after being referred by the pediatric team for hearing assessment. He still could not speak, and his condition had deteriorated. Previously able to sit independently, he was now unable to sit and spent most of his time lying down. There was no history of seizures, altered consciousness, or drug intake. On physical examination, he was underweight (12.94 kg, 93 cm) with stable vital signs, showing no interest in his surroundings and lacking eye

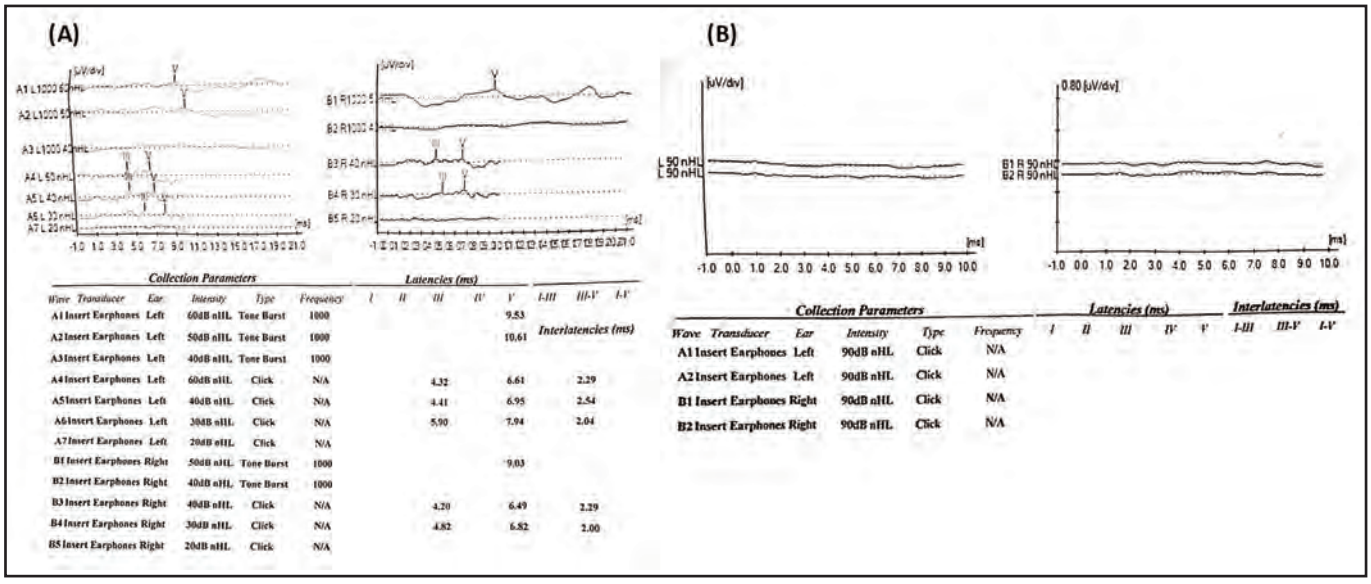

Fig. 3: (A) ABR test result at the age of 7 months, wave V detected at 30 Db (ABR click) and 50 Db (ABR tone burst) in both ears; (B) Recent ABR test, wave V detected at 90 dB in both ears

contact. The physical findings remained consistent with microcephaly, hair and eyebrow was twisted, thin, and sparse. Skin and nails were normal, but central hypotonia was noted. Examination of the outer ears revealed no abnormalities, with intact tympanic membranes. However, ABR hearing examination indicated a worsening to profound sensorineural hearing loss, with wave V was not detected at 90 dB in both ears (Figure 3C). Due to the severity of hearing loss, cochlear implant surgery was recommended for the patient. However, the parents opted for hearing aids instead, citing socio-economic challenges that made the recommended treatment infeasible.

DISCUSSION

In our case, the patient exhibited significant hearing impairment. He had not begun babbling by six months and had not spoken any word by the age of four. Ancillary examinations revealed a shift in hearing loss from conductive to sensorineural, with a further decline in auditory function. ABR testing confirmed this deterioration; wave V previously detected at 30 dB (click) 50 dB (tone burst) in both ears, to 70 dB in both ears ear (click) and was now not detected at 90 dB (tone burst) in both ears.

Hearing impairment is one of the two major primary clinical manifestations of Bjornstad syndrome, resulting from changes in the inner ear that lead to varying degrees of sensorineural hearing loss. This loss typically bilateral, ranging from mild, where individuals may not be able to hear sound at certain frequencies to severe, where complete deafness occurs.[4] Although the progressivity nature of hearing loss is not frequently highlighted in the literature, it usually becomes evident in early childhood and progress differently overtime, indicating that the condition may progressive overtime.[5,6] The progression usually stabilizes around puberty, likely due to cellular adaptation and developmental milestones when further degeneration of the auditory system becomes less pronounced.[7] In addition to hearing impairment and pili torti, additional symptoms that may raise suspicion to Bjornstad syndrome include abnormal skin and hair findings (alopecia, anhidrosis, brittle hair), mental retardation and developmental delays, and hypogonadism.[6] In most cases, Björnstad syndrome is suspected due to similar clinical presentations in relatives and families.[6]

The patient's progressive sensorineural hearing loss, attributed to a mutation in the BCS1L gene, which is crucial for mitochondrial function, particularly in forming complex III in the electron transport chain. This mutation disrupts oxidative phosphorylation, reducing ATP production and leading to the accumulation of unreacted electrons that combine with oxygen to produce reactive oxygen species (ROS). These ROS degrade cellular components such as DNA, lipids, and proteins, ultimately resulting in cellular damage and progressive degeneration of the inner ear structure responsible for hearing.[2]

In this case, the patient's worsening condition over three years, including the inability to sit and deteriorated hearing, highlights the importance of early diagnosis and regular monitoring of disease progression, including hearing loss and other clinical manifestation. Infants suspected Björnstad syndrome should undergo a comprehensive series of auditory tests to assess potential hearing issues, establish a baseline for comparison, and facilitate early intervention. This evaluation includes behavioral audiometry, OAE, and ABR testing.[8,9]

The patient's deteriorated hearing, with wave V was not detected at 90 dB, underscores the necessity of timely intervention. A study by Gulsen et al. reported two cases of Björnstad syndrome with profound hearing loss, where cochlear implantation resulted in significant improvement, reducing hearing loss to a mild-to-moderate level. In this

context, the recommendation for cochlear implant surgery is consistent with the need for advanced hearing restoration methods given the patient's severe hearing impairment.[10] Additionally, other interventions option such as hearing aids and speech therapy are essential for optimizing sound perception and addressing communication delays, reinforcing the need for a tailored approach to manage and improve outcomes in similar case. These suggest that, while Björnstad syndrome may cause debilitating hearing loss, its impact on the patient's daily functioning and quality of life can be mitigated with early diagnosis and timely intervention.[10] Furthermore, to this date, no literature has reported a lethal variant of Björnstad syndrome, indicating its low mortality rate yet potentially significant morbidity.[1]

A multidisciplinary approach is crucial in managing Bjornstad syndrome due to its complex, multisystemic nature. Otolaryngologists play a key role in diagnosing and treating hearing loss, while audiologists monitor hearing function and provide interventions such as hearing aids or cochlear implants. Geneticists contribute by identifying the BCS1L gene mutation, offering genetic counseling to families. Speech therapists address communication delays caused by hearing impairment, helping patients achieve better language outcomes. Pediatricians coordinate care, ensuring that all specialists work together effectively, while neurologists assess any potential neurological issues related to mitochondrial dysfunction. Psychologists provide emotional support to patients and families, and physical or occupational therapists help manage motor function challenges. This coordinated, team-based approach ensures that all aspects of the patient's health are addressed, improving both medical outcomes and quality of life.

This case reports present with some limitations. follow-up evaluations after cochlear implantation could not be conducted, as the patient declined the procedure due to socio-economic challenges. This restricts the ability to assess the potential outcomes and benefits of cochlear implantation, focusing instead on the progression of hearing loss and the effectiveness of alternative interventions like hearing aids.[10] Further reports are required to confirm whether this anomaly is an incidental finding or a feature associated with Björnstad syndrome.

CONCLUSION

The patient's case highlights the progressive nature of hearing impairment in Bjornstad syndrome, with a shift from conductive to sensorineural hearing loss and a decline in auditory function confirmed by ABR testing. The hearing loss, attributed to a BCS1L gene mutation affecting mitochondrial function, leads to progressive degeneration, which may stabilize around puberty due to a combination of genetic, cellular, and developmental factors. As the body adapts and compensates for underlying cellular damage, the progression of sensorineural hearing loss slows. This underscores the importance of early diagnosis and regular monitoring to manage disease progression effectively. A multidisciplinary approach, involving otolaryngologists, audiologists, geneticists, speech therapists, and other specialists, is crucial in addressing the complex, multisystemic nature of the condition and improving the patient's overall quality of life.

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None

DECLARATIONS

The patient's parents had given consent for this case publication. No external funding was received for this study.

ABBREVIATIONS

dB: Decibel (sound intensity)
Hz: Hertz (frequency)
cm: Centimeter (length)
kg: Kilogram (weight)

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CASE REPORT

A rare spectrum of branchi-oto-renal syndrome

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SUMMARY

This case describes an eight-year-old boy who presented with bilateral progressive hearing loss and speech impediments. Physical examination revealed small cutaneous opening on both sides of the neck and an asymmetrical ear formation, specifically a 'bat-ear' deformity on the right side. Auditory testing confirmed the loss of hearing bilaterally, and extensive radiological evaluations uncovered complete bilateral branchial fistulas and anomalies in the external, middle, and inner ear structures, with no kidney abnormalities detected, leading to the diagnosis of Branchiootic Syndrome. These findings highlight the importance of considering this rare syndrome when encountering patients with similar auditory and physical signs, guiding clinicians toward accurate diagnostic and therapeutic strategies.

INTRODUCTION

Branchi-oto-renal spectrum disorder (BORSD) is a genetic disorder inherited in an autosomal dominant manner characterized by structural ear malformations alongside branchial and renal anomalies.[1,2] This spectrum encompasses both branchi-oto-renal (BOR) syndrome, which includes renal anomalies, and branchiootic (BO) syndrome, which spares the kidneys.[1] While BOR has an estimated incidence of 1 in 40,000, BO is even rarer, and both syndromes exhibit high phenotypic variability.[1,3] Diagnosing BORSD typically requires meeting major and minor criteria based on Chang et al. in 2004 which may include branchial anomalies, hearing loss, auricular deformities, and preauricular pits.[2] Early recognition of BO can improve outcomes, especially in cases where auditory rehabilitation is critical for speech development.[3] Here, we present a case of BO syndrome in a young boy, highlighting the clinical presentation, diagnostic process, and management, underscoring the importance of a detailed workup in similar cases.

CASE PRESENTATION

An eight-year-old boy was seen in the outpatient clinic with a two-year history of progressive bilateral hearing loss and associated speech challenges. His teacher initially observed the problem, noting that the boy often seemed confused when given verbal instructions. His articulation was impaired, and he had started using gestures to aid in communication. Apart from worsening hearing, he had no symptoms of ear discharge, dizziness, facial weakness, or tinnitus.

On physical examination, bilateral cutaneous fistula (Figure 1 and Figure 2) openings were noted anterior to the sternocleidomastoid muscles, which occasionally discharged a clear, colorless, and odorless fluid. The right pinna was positioned lower than the left and was cup-shaped, resembling a "bat-ear" (Figure 3). Bilateral preauricular sinuses were also present but were not actively discharging. Audiometry performed in June 2023 showed moderate-to-severe mixed hearing loss with a reverse sloping configuration. Tympanometry was type A bilaterally. Follow-up audiometry a year later indicated moderate-to-profound mixed hearing loss on the right and mild-to-severe loss on the left, with no change in tympanometry results. At the time of initial assessment, the patient's speech was limited, and he increasingly relied on sign language due to his declining auditory responses.

The family history was significant, as the patient's mother reported bilateral hearing loss and branchial sinus anomalies, although she had never been formally evaluated. The patient's younger brother also displayed similar physical findings, and further assessment was planned.

Given the clinical presentation, the patient underwent contrast-enhanced computed tomography (CECT) of the neck, a CT fistulogram, high-resolution computed tomography (HRCT) of the temporal bones, and a renal ultrasound. The CECT demonstrated complete bilateral branchial fistulas, originating from cutaneous openings on the neck and extending internally to the inferior poles of the palatine tonsils. HRCT of the temporal bones revealed structural abnormalities bilaterally. On the right side, a dilated eustachian tube was noted, along with malformed ossicles fixed to the attic and a hypoplastic cochlea with 1.5 spiral turns and medial deviation of the apex seen. A funnel-shaped internal auditory canal and a 0.4 cm dehiscence in the superior semicircular canal were also observed. The left side had similar findings, with the addition of a dilated vestibular aqueduct instead of semicircular canal dehiscence. The patient denied any urinary-related symptoms, such as dysuria, frequency changes, or hematuria. However, we proceeded with renal profile tests and a renal ultrasound to confirm the absence of abnormalities. The renal ultrasound revealed normal kidney structure and function, ruling out renal involvement. Typically, BOR is associated with renal agenesis, pelviectasis, calyceal cysts, and hydronephrosis, none of which were present here, supporting the diagnosis of BO.[1]

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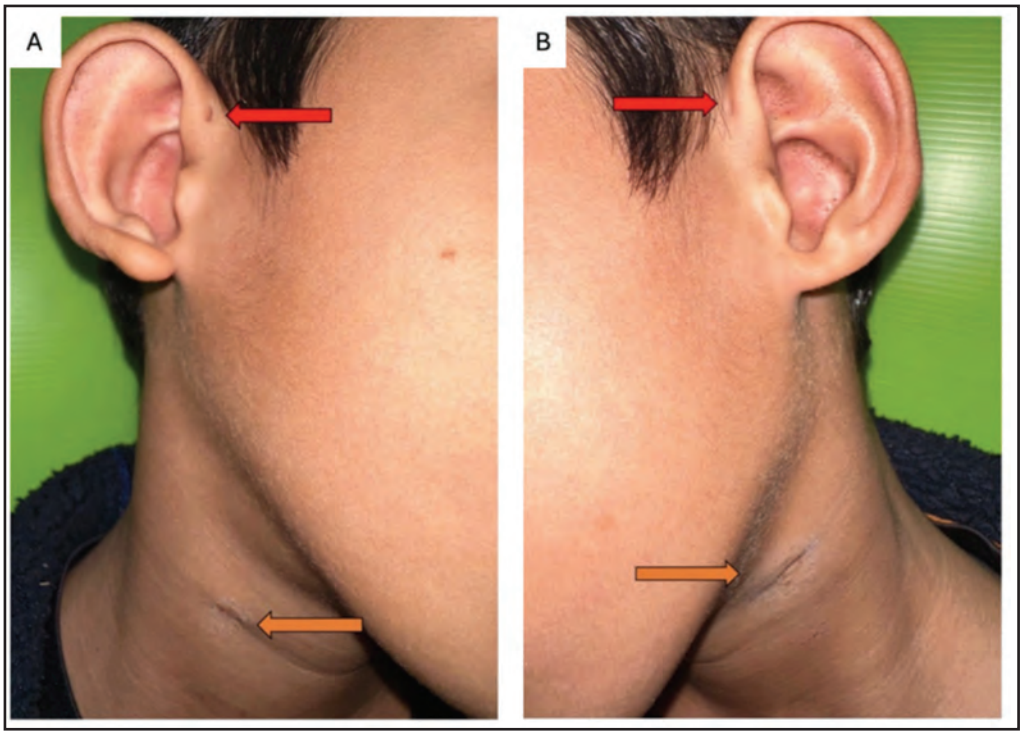

Fig. 1: Figure A shows right preauricular sinus (red arrow) with right cervical fistula (orange arrow) while figure B shows left preauricular sinus (red arrow) with left cervical fistula (orange arrow)

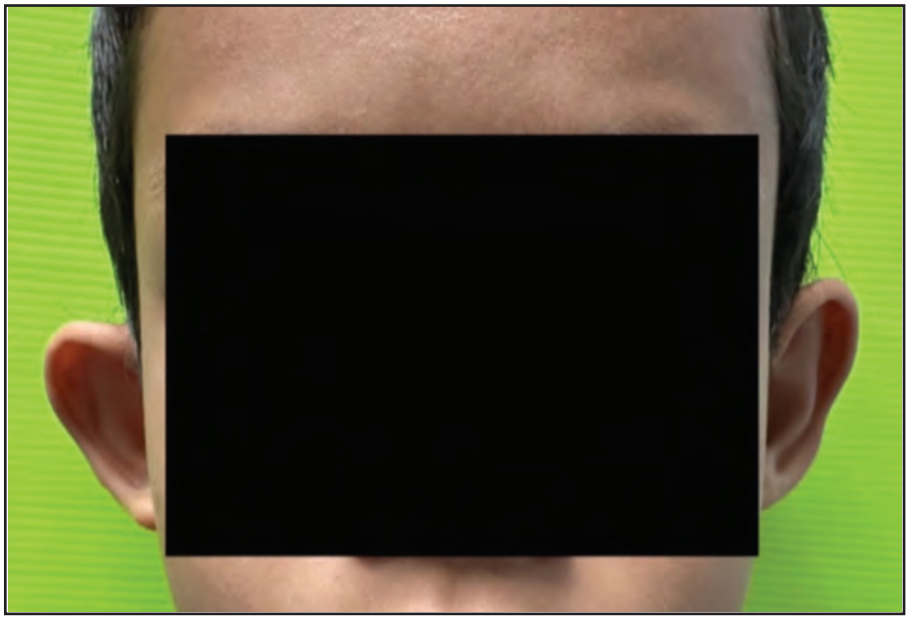

Fig. 2: The right ear displays a 'bat-ear' deformity, positioned more laterally and inferiorly compared to the left ear

Treatment included surgical planning for excision of the branchial fistulas, as well as fitting hearing aids to address his auditory deficits. Post-hearing aid trial, the patient showed improved auditory perception and was more engaged in communication. Speech therapy was recommended to enhance articulation and overall language development.

DISCUSSION

This case report describes a young boy with BO, presenting with classic features of branchial and ear anomalies without renal involvement. Differentiating BO from BOR relies on the absence of renal abnormalities.[1]

In BORSD, a family history can aid the diagnosis. However, when such a history is lacking, a diagnosis can be made based on the presence of either three major criteria or two

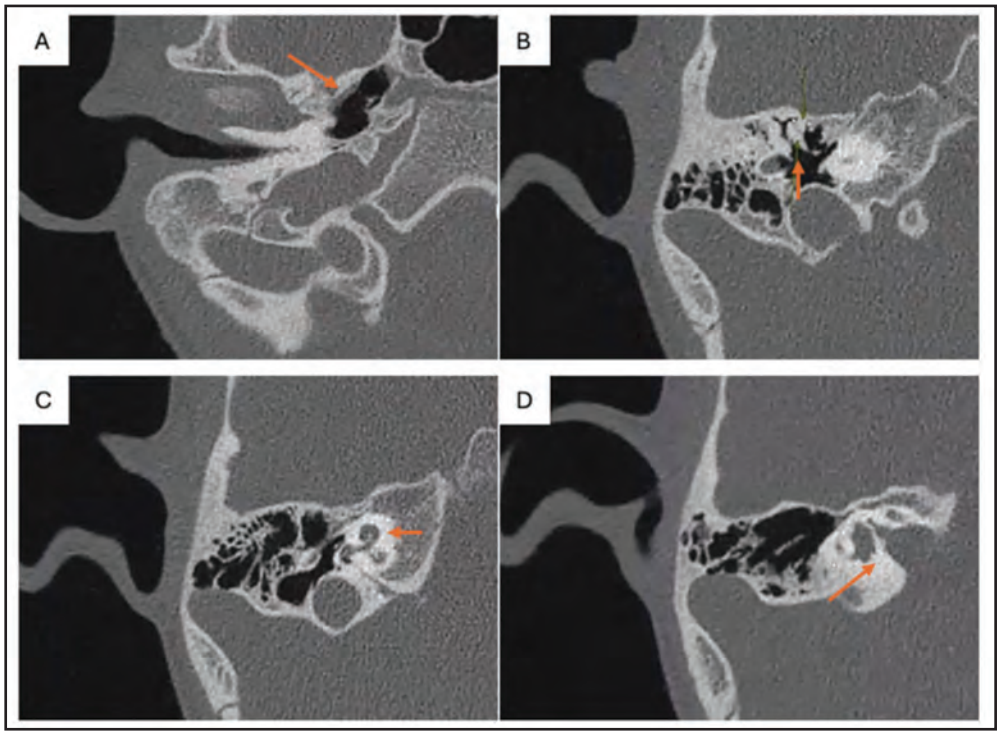

Fig. 3: HRCT temporal bone images (bone window) in axial view, showing the abnormalities (Orange coloured arrows). A; right patulous eustachian tube, B; malformed incus and malleus and fixed in the attic, C; hypoplastic apical turns of cochlear (1.5 spiral turns), D; funnel-shaped internal auditory meatus

major and two minor criteria. Major criteria include second branchial anomalies, hearing loss, preauricular pits, auricular malformations, and renal anomalies. Minor criteria encompass abnormalities of the external auditory canal, middle ear, inner ear, preauricular tags, facial anomalies, and palate abnormalities.[1] The phenotypic variability within BORSD is well documented, with incomplete penetrance and variable expressivity contributing to a wide range of clinical manifestations, even among relatives within the same family.[2]

High-resolution computed tomography (HRCT) of the temporal bone in BORSD often reveals distinctive abnormalities, including an aberrant facial nerve course, funnel-shaped internal auditory canals, and a patulous eustachian tube. Additional findings may include malformed semicircular canals, a reduced tympanic cavity, and an abnormal ossicular chain, which can contribute to conductive hearing loss. Atresia of the external auditory canal is also commonly observed, further impacting ear function.[4] Another specific feature of BORSD is cochlear hypoplasia type 4, also known as the "unwound cochlea," which should prompt a renal evaluation in undiagnosed patients due to its link to renal abnormalities.[5] HRCT of the temporal bones is critical for identifying the specific anatomical anomalies in BO, as it provides detailed images of the middle and inner ear structures, helping guide aural rehabilitation strategies.[4]

Associated renal anomalies in BORSD include renal agenesis, ureteropelvic junction obstruction, calyceal cysts or diverticula, caliectasis, pelviectasis, hydronephrosis, and vesicoureteral reflux. Since renal insufficiency often progresses slowly and with subtle symptoms, a diagnosis may be delayed until significant renal impairment is present.[6]

One of major criteria for BORSD is second branchial arch anomalies. In our case, the patient presented with bilateral complete branchial fistulas, which are notably rare as most cases fistulas present in incomplete form.[7] In a retrospective study of 106 patients with branchial cleft and pouch anomalies conducted by Ford et al., only two cases of complete fistulas were identified.[8]

Management modalities of patients with BO vary depending on the extent and severity of manifestations. Regular audiological assessments are crucial due to the potential impact on hearing, with semi-annual examination is required to check for hearing impairment and annual audiometry is important to assess for the progression of hearing loss.[1] Following the Malaysia Neonatal Hearing Screening Guideline, newborns from families with known cases of BORSD should undergo hearing screening at birth, with subsequent referrals to audiologists for further evaluation, even if they pass the initial screening, given the risk of delayed onset hearing loss.[9] Early aural rehabilitation is imperative for speech development and psychosocial well-being. For patients with hearing loss, aural rehabilitation options such as hearing aids or implants should be considered based on the type and degree of hearing impairment.[1] Surgical excision may be indicated for discharging branchial cleft/fistula, although conservative management is viable for asymptomatic cases.

Given the autosomal dominant inheritance pattern of BORSD, genetic counselling is crucial for affected families. Molecular testing for mutations in the EYA1, SIX1, and SIX5 genes can confirm the diagnosis, particularly in cases without a clear family history[1]. Since each child born to a parent with BORSD has a 50% chance of inheriting the disorder, genetic counselling and prenatal testing can provide valuable guidance for family planning.

CONCLUSION

This case illustrates the need for a thorough evaluation of children with branchial and ear anomalies to accurately distinguish between BOR and BO syndromes. Early recognition of BO can lead to timely interventions that enhance the patient's quality of life, as well as facilitate genetic counselling and support for families.

ACKNOWLEDGMENT

We extend our gratitude to the patient's family for their cooperation and consent in sharing this case.

DECLARATION

The authors declare no conflict of interest.

CONSENT

Consent to publish this case report together with the images was obtained from the patient's parents.

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CASE REPORT

Poorly differentiated ovarian teratoma: case report with a 17-year survival after undergoing cytoreductive surgery

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SUMMARY

Immature ovarian teratomas are rare malignant tumors originating in ovarian germ cells, representing about 1% of ovarian cancer cases. Main treatment is surgery and chemotherapy. The degree of differentiation is an important prognostic factor. A well-differentiated teratoma (G1/G2) is usually associated with a higher survival rate than poorly differentiated tumors (G3). The current report shows a case of poorly differentiated immature ovarian teratoma diagnosed in a 42-year-old patient with a disease-free survival above the mean rate described in the literature (17 years), highlighting the importance of cytoreductive surgery in advanced cases conducted by specialized surgical oncologists.

INTRODUCTION

Immature teratomas are malignant tumors that derive from cells that have the potential to develop into different types of tissues in the body, including the skin, internal organs and muscles. Immature ovarian teratoma is a rare cancer that represents about 1% of ovarian cancers. Main treatment is surgery and chemotherapy.[1] The degree of differentiation of teratomas plays a primordial role in determining patient prognosis. Patients with more differentiated tumors (G1/G2) have a five-year survival of 91.4%, in comparison to those with poorly differentiated (G3) tumors, where the survival rate is 56%.[2] Therefore, early identification and accurate pathological classification are essential for appropriate treatment.

The aim of this study is to report a case of immature ovarian teratoma that underwent surgical and chemotherapy interventions and has had a long-term survival (17 years), compared to the mean survival rates reported in the literature. The importance of complete cytoreduction by surgeons specialized in gynecologic oncology is highlighted.

CASE PRESENTATION

A 42-year-old woman, with important history of past illness (arterial hypertension, diabetes mellitus, smoking and alcohol consumption), was referred to our service in February/2008 with a history of ovarian cancer previously treated with surgery and chemotherapy in another healthcare service. She reported vague abdominal symptoms and had been diagnosed with left ovarian tumor, measuring 17 cm, with bowel loop involvement. In both previous surgeries in April 2007, a bilateral salpingoophorectomy, omental biopsy and peritoneal fluid collection were performed. Peritoneal carcinomatosis was considered unresectable. Chemotherapy was indicated in the hope that surgical rescue could be attempted later. Alpha fetoprotein (AFP) and β-HCG levels were normal.

Histopathology study revealed a poorly differentiated (G3) immature ovarian teratoma, measuring 16 cm in the right ovary, and with disease in the left ovary. The fallopian tubes showed no disease. There was disease in the epiploon, and oncotic cytology was negative.

The patient underwent chemotherapy with four cycles of BEP (bleomycin, etoposide and cisplatin). In August/2007, a new surgery was attempted and again the disease was considered unresectable. Only peritoneal biopsies were done, confirming the diagnosis of poorly differentiated teratoma, and the patient was referred to palliative chemotherapy. She was also referred to another surgical team where she underwent total hysterectomy, total pelvic peritonectomy (Figure 1), epiploectomy and resection of a tumor of the epiploon measuring 15 cm, along with removal of the spleen and tail of the pancreas (Figure 2).

Furthermore, resection of multiple peritoneal implants was performed with residual tumor implants of less than 3 mm, considered a suboptimal cytoreduction. There were no suspicious pelvic and retroperitoneal lymph nodes, and resection of retroperitoneal lymph nodes was not performed. After surgery, the patient received three cycles of chemotherapy with BEP, demonstrating a favorable clinical response and improvement of the symptoms reported. Total abdominal tomography and laboratory tests performed after treatment did not reveal any evidence of peritoneal cancer.

Regular follow-up of the patient was performed with imaging tests and physical examination. However, local and distant

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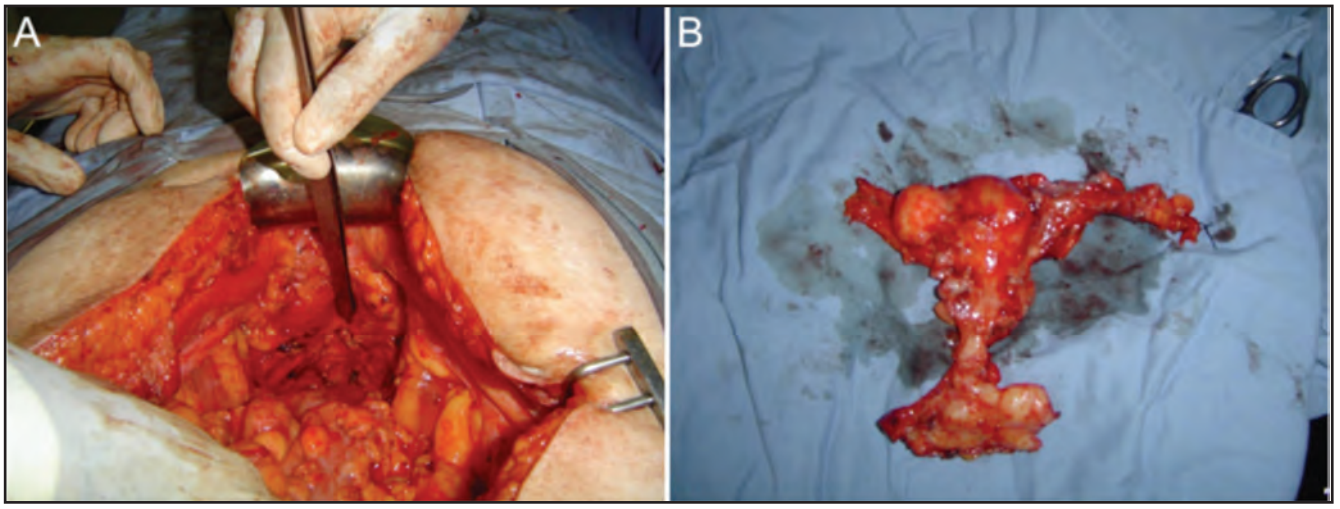

Fig. 1: A: Total pelvic peritonectomy. B: Surgical specimen of total hysterectomy with pelvic peritoneum

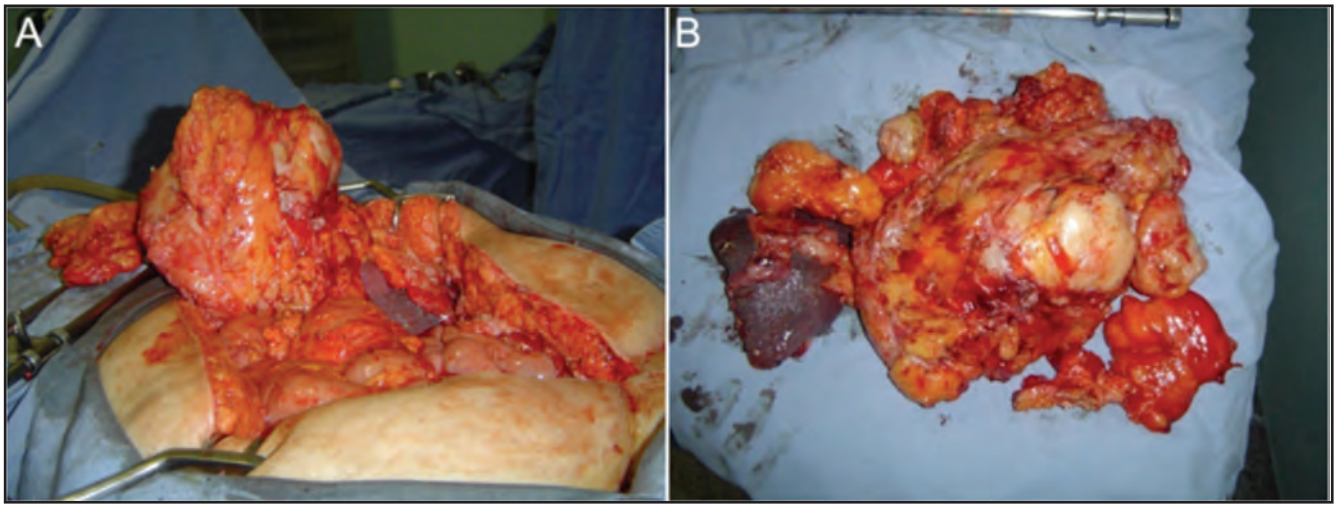

Fig. 2: A: Tumor in the epiploon and visualization of spleen adhesion to tumoral mass. B: Surgical specimen of resection of the epiploon, spleen and tail of the pancreas

disease recurrences were not observed during follow-up care. In June/2013, on the abdominal tomography for control, a solid lesion suspicious of tumor recurrence, measuring around 5 cm in its largest diameter was identified in the vaginal vault. Imaging tests showed no other abdominal or thoracic lesion, and the asymptomatic patient was in good general health. During the clinical exam of the vagina, the vaginal vault lesion was not palpated. Complete resection of the vaginal vault lesion was done by the abdominal and vaginal route. No other lesions were identified in the abdominal cavity during surgery. The patient had a good postoperative recovery without any complications.

Histopathological and immunohistochemical tests of the vaginal vault lesion demonstrated a benign myxoid fusocellular tumor. Immunohistochemical panel test showed AE1/AE3 negative, AML positive, Q-BEND10 focal positive, desmin negative, EMA negative, S100 negative and estrogen and progestrone receptor negative. Subsequently, benign bilateral breast masses were detected, in addition to simple kidney cysts and multiple thyroid nodules that were benign on cytology analysis by fine-needle aspiration (FNA). Nowadays, 17 years after the diagnosis of immature teratoma, the patient is in good overall health. She performs her normal work activities, has a good quality of life and has no evidence of active disease. She is taking transdermal and vaginal estradiol.

This study is part of a cancer patient project approved by the Research Ethics Committee of the State University of Piauí, with Technical Report No 4.311.835. The patient signed the Free Informed Consent Term (FICT).

DISCUSSION

Immature ovarian teratoma occurs predominantly in children and women in reproductive age. Around 80% of these cases are unilateral tumors. Histological analysis shows three immature germ layers containing embryonic elements that may include the neuroepithelium.[3]

Immature teratoma may manifest itself as a calcified pelvic mass, abnormal uterine bleeding or pelvic discomfort. The most common sites of dissemination are the peritoneum and retroperitoneal lymph nodes. Hematogenous spread to the lungs, liver or brain is rare. In approximately half of these cases, there is an increase in tumor markers, such as alpha fetoprotein (AFP) and β-HCG levels.[4] However, in the patient mentioned here, the results of these markers were within the normal range, which may also be related to the better prognosis presented.

Among the tumor markers, AFP is highlighted. It is the major fetal serum protein whose main function is plasma transport and regulation of oncotic pressure. Furthermore, AFP serum level provides an estimate of tumor growth period. In addition, β-HCG (human chorionic gonadotropin), an essential marker for diagnosis and monitoring of patients with germ cell tumors, was ordered to conduct a more specific evaluation of the clinical situation of the patient.[4]

In the case reported, the patient was a female in her forties. She is alive and without disease 17 years after diagnosis, although her case was considered inoperable in the first two surgeries. The presence of poorly differentiated immature cells is a poor prognostic factor, increasing the risk of recurrence. Nevertheless, when cytoreduction (even suboptimal) is achieved, it may contribute to determine a long survival period, as shown in the current case.[2]

Surgical intervention is the first treatment option for women with immature teratomas. This approach not only allows adequate tumor staging, but also enables the performance of optimal cytoreduction, which is the surgical goal to be pursued, improving the results of adjuvant treatment. In early-stage cases, fertility-sparing surgery should be offered to patients who wish to conceive in the future.[5] The patient in the case presented already had offspring and there was no longer any reproductive desire.

Qualification in gynecologic oncology surgery is fundamental in the prognosis of ovarian cancer patients. Staging and prognosis of these early-stage and advanced tumors improve when these patients undergo treatment with surgical teams specialized in complex surgeries, including multivisceral resection, as performed in the patient described in this report.[6]

Ultrasound diagnosis of immature ovarian teratomas is difficult, since these tumors often present with heterogeneous characteristics, including solid areas and diffuse calcifications.[5] Abdominal pelvic ultrasonography is essential, since it enables the confirmation of tumor origin and evaluation of tumor characteristics, e.g. size, extension, contents and the presence of septum, among other findings. Furthermore, based on these parameters it is possible to infer whether the tumor is benign or malignant. CAT scans and MRIs have specific indications in dubious cases and for the evaluation of the presence of recurrence and metastases.[7]

The introduction of chemotherapy, usually reserved for G3 or even G2 tumors, has improved the survival rates in women with malignant germ cell ovarian tumors. The most widely used protocol is the BEP.[5] In the follow-up period, the patient had a suspicious lesion in the vaginal vault. However, resection of the lesion demonstrated a rare benign lesion---myxoid fusocellular tumor.

The mean survival of patients with immature ovarian teratoma is five years. Nevertheless, patients whose tumors were completely removed have a 5-year survival rate of about 94%, while the expected survival rate in those with partial resection (as the patient described here) is lower than 50%.[2]

CONCLUSION

Experience with the case report that described a survival rate above the mean survival time reported in the literature (17 years) after cytoreductive surgery, shows the benefit in patients with advanced-stage ovarian tumors, mainly in those where cytoreductive surgery is a determining factor for survival, under specialized care of gynecologic oncology surgical teams. In this case, the importance of other possible less measurable factors in the presented outcome is also highlighted, such as biological characteristics of the tumor (e.g. normal levels of AFP and β-HCG) and tumor response to chemotherapy carried out after suboptimal cytoreduction.

CONFLICTS OF INTEREST

None.

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Non-immune hydrops fetalis due to αlpha(α)-thalassemia: Ethical dilemmas and grief following perinatal loss

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SUMMARY

Hydrops fetalis is a serious condition with a poor prognosis for the affected fetus. While the incidence of immune hydrops fetalis has significantly decreased, cases of nonimmune hydrops fetalis are becoming more common. Nonimmune hydrops can result from hemoglobinopathies, such as α-thalassemia. This case report discusses the diagnosis and management of nonimmune hydrops fetalis due to α-thalassemia. Given the high prevalence of thalassemia in Sabah, Malaysia, it is recommended that all cases of hydrops fetalis in this region be investigated for thalassemia. The case underscores the importance of early screening and highlights the ethical and psychological challenges associated with decisions regarding pregnancy termination. Counselling was provided to support the patient through the decision-making process, addressing both ethical dilemmas and emotional challenges. Postpartum, the patient experienced grief over the loss but was able to achieve emotional resolution with the support of her family and healthcare providers.

INTRODUCTION

Hydrops fetalis is a serious fetal condition characterized by the accumulation of excess fluid in two or more body compartments. It can be classified into immune hydrops fetalis, caused by maternal hemolytic antibodies, and nonimmune hydrops fetalis, which results from various other causes. Before the introduction of prophylactic anti-D immunoglobulin, immune hydrops was the most common type. However, immunologic causes now account for less than 20% of cases. In Southeast Asia, nonimmune hydrops fetalis is more prevalent, with an incidence ranging from 1 in 500 to 1 in 1500 cases.[1] α-thalassemia is a significant genetic blood disorder in this region, with a prevalence of 17.3% in Malaysia and a notably higher prevalence of 33.6% among the Kadazandusun ethnic group in Sabah.[2] Severe forms of α-thalassemia, such as Hb Bart's hydrops fetalis, cause fetal anemia due to impaired α-globin production, leading to high-output cardiac failure and fluid accumulation in multiple fetal compartments. Today, early diagnosis of hydrops fetalis and other congenital anomalies is possible through ultrasound, karyotyping, and molecular genetic testing. Due to the poor prognosis associated with hydrops fetalis, pregnancy termination is often considered. This report presents a case of nonimmune hydrops fetalis due to homozygous α-thalassemia, diagnosed late in pregnancy, and discusses the challenges faced by the medical team and the family in managing this condition.

CASE PRESENTATION

A 32-year-old Dusun woman, primigravida, was referred from a private clinic at 23 weeks of gestation due to suspected hydrops fetalis. She reported no symptoms of anaemia, fever, or bleeding. She had no history of blood transfusions or menorrhagia and had not been previously diagnosed with thalassemia. She was unsure of any family history of thalassemia. Concerned for her first child's health, she sought further evaluation.

On physical examination, the patient's height was 150 cm, weight 55 kg, and BMI 24.4 (normal). Vital signs were within normal limits. Although her conjunctivae appeared pale, she displayed no physical features typical of thalassemia. The uterus was appropriately sized for gestational age, with a symphysis-fundal height of 23 cm. There was no hepatosplenomegaly, and other systemic examinations were unremarkable.

Blood tests revealed the following key findings:

The DNA analysis revealed that both the patient and her husband were α-thalassemia carriers (Table I). Peripheral blood film (PBF), iron studies, and stool examination results were normal. Ultrasound findings showed fetal ascites in multiple compartments, including the abdomen, lungs, and heart. Doppler studies, including middle cerebral artery peak systolic velocity (MCA-PSV), were not performed in this case.

Table I: Patient's and husband's blood test panel

Test	Patient	Husband	Normal range
Hemoglobin (Hb)	9.9 g/dL	14.1 g/dL	12.0–16.0 g/dL (female) 14.0-18.0 g/dL (male)
Mean Corpuscular Volume (MCV)	69.2 fL	70.0 fL	80–100 fL
Mean Corpuscular Hemoglobin (MCH)	22.1 pg	21.4 pg	27–32 pg
DNA Analysis	Carrier of α-thalassemia	Carrier of α-thalassemia	Not Applicable

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Breaking the news of the fetal abnormalities was emotionally challenging for both the couple and the clinician. The diagnosis, its causes, and the poor prognosis of hydrops fetalis were communicated to the couple in a clear and empathetic manner. Termination of pregnancy was presented as an option, and the steps and potential outcomes were explained in simple terms. The couple was given time to consider their decision and encouraged to ask questions. Clear communication and empathy were crucial in supporting the patient. After careful consideration, the patient chose to continue the pregnancy, and her decision was respected. Acknowledging the complexity of the case, the primary care team referred the patient to a maternal-fetal medicine (MFM) specialist for co-management and guidance on fetal monitoring and potential interventions.

At 24 weeks, the MFM specialist counselled the patient regarding the option of pregnancy termination. The couple participated in the discussion and received information on the fetus's condition and prognosis. Although termination was offered, the patient decided to continue the pregnancy. Her autonomy was respected, and the ongoing support from her husband helped her cope with her worries. She occasionally felt guilt, but she was reassured that the fetal anomaly was beyond her control. She did not exhibit symptoms of depression or anxiety during the visit.

By the 30-week follow-up at the MFM clinic, the patient had developed severe preeclampsia and became edematous. She presented with headache, blurred vision, elevated blood pressure at 163/109 mm Hg, and proteinuria (2+). She was admitted to stabilize her blood pressure and underwent an emergency caesarean section due to severe preeclampsia. Unfortunately, the fetus was born prematurely and, despite supportive care, died shortly after birth due to non-viability.

During her postpartum visit, her blood pressure remained stable with antihypertensive medication (Tablet Labetalol 200 mg TDS). She expressed grief over the pregnancy loss, often blaming herself for not recognizing the pregnancy earlier, though no depressive or anxiety symptoms were present. Her emotions were acknowledged, and she was reassured that the outcome was beyond her control. She received strong support from her husband, which was crucial in preventing complicated grief or depression. A referral to a psychologist was offered, and she was scheduled for a follow-up in two weeks, with instructions to return sooner if depressive symptoms emerged.

At subsequent follow-ups, her grief had resolved. She opted for long-acting reversible contraception and was advised to pursue early booking and referral to an MFM specialist clinic for prenatal testing if she becomes pregnant in the future.

DISCUSSION

α-thalassemia can lead to severe fetal conditions, such as hydrops fetalis, which often results in poor outcomes. In this case, the patient was informed of the fetus's prognosis and the option of pregnancy termination. Despite the severity, the patient chose to continue the pregnancy, influenced by personal and cultural factors. In Southeast Asian cultures, particularly in the Kadazandusun community, beliefs surrounding the sacredness of life and family values significantly impact such decisions. The patient's decision was supported by her husband, and cultural norms that emphasize continuing pregnancy regardless of fetal health likely played a role. The healthcare team respected the patient's autonomy while offering emotional support and counselling.

This case highlights the importance of cultural sensitivity in decision-making and the need for healthcare providers to balance ethical principles such as respect for autonomy, beneficence, and non-maleficence while considering the patient's values and preferences. Additionally, the parents were unaware of their α-thalassemia carrier status until the 23rd week of gestation, underscoring the need for early screening and genetic counselling before conception or during the first trimester. Early detection can reduce psychological distress and support timely decision-making regarding prenatal diagnosis and reproductive options.

While Malaysia has a national screening program targeting adolescents, there are gaps in the system, especially in high-risk regions like Sabah, where higher thalassemia carrier rates exist. Comprehensive screening strategies in these areas would allow for earlier identification of at-risk couples. Currently, most screening occurs during adolescence and early pregnancy, but many couples in high-risk areas may not receive adequate prenatal counselling or testing until later in pregnancy. This delay limits options for timely interventions and decisions regarding pregnancy outcomes. To address these gaps, earlier prenatal testing for couples with known risk factors is crucial.

Screening should be considered for couples with red cell abnormalities like microcytosis and hypochromia in the absence of iron deficiency.[3] In Sabah, where α-thalassemia is prevalent, investigating nonimmune hydrops fetalis for potential α-thalassemia is particularly important. Early identification of carrier status through expanded prenatal screening by the end of the first trimester could facilitate better decision-making and reduce emotional distress. Integrating genetic counselling into routine antenatal care for high-risk populations would help ensure families are fully informed, allowing for informed decisions when complications arise.

Improving accessibility to screening programs and raising awareness in high-risk communities through educational campaigns could encourage early diagnosis, reducing the incidence of late-stage diagnoses and improving clinical outcomes and patient well-being. The emotional and psychological impact of pregnancy loss, particularly after the diagnosis of severe fetal anomalies like hydrops fetalis, is significant. Grief counselling and support are vital in helping parents cope and preventing complicated grief. Research has shown that early intervention in grief counselling can significantly reduce the risk of complicated grief.[4]

Timely emotional support, active listening, and reassurance that the loss was beyond their control are essential. Referring parents to mental health professionals, such as psychologists,

can aid in managing deep emotional distress. Support groups for parents who have experienced similar losses provide validation and a network for shared experiences. Follow-up care is essential to monitor the development of complicated grief, and research shows that early grief counselling can significantly reduce the risk of prolonged mourning, anxiety, or depression. Offering emotional support, facilitating open discussions, and respecting cultural beliefs surrounding grief can aid in the recovery process. Structured grief counselling can prevent escalation into clinical conditions like depression and anxiety, promoting better long-term psychological outcomes.[5] Additionally, acknowledging the role of partners in the grieving process and encouraging shared support within the family unit is crucial.

CONCLUSION

Early screening for α-thalassemia is vital to identify at-risk couples early, allowing for timely counselling and decision-making, particularly in high-prevalence regions like Sabah. Empathetic and ethical communication is essential in managing complex cases, ensuring that patients are fully informed, supported, and respected in their decisions, ultimately improving both clinical and emotional outcomes.

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CONFLICT OF INTEREST

There is no conflict of interest to declare.

CONSENT FOR PUBLICATION

Written informed consent was obtained from the patient for publication of this case report.

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CASE REPORT

A case report on an acute schizophreniform disorder in an octogenarian with hearing and visual impairment: is combined medical-mental health unit a solution for the ageing population in Malaysia?

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SUMMARY

Psychosis in older adults is often attributed to advancing dementia, cognitive impairment, and sensory deprivation. The emergence of very late-onset schizophrenia-like psychosis (VLOSLP) is expected to rise with the global ageing population. This condition, which can be diagnosed as Acute Schizophreniform Disorder if the duration of psychosis is less than six months, poses a significant challenge for both psychiatrists and geriatricians. This case report underscores the unique difficulties in diagnosing this condition in older adults with multiple sensory impairments. The management of such cases, which requires skilled nursing and a tranquil environment, can be particularly challenging in a general medical ward, leading to delayed informal admission to the psychiatry ward. In a centre without a geriatric psychiatrist, a recommended admission pathway from the emergency department to respective wards was developed between the medical and psychiatry departments. The case also highlights the need for ongoing research and development in the medical management of older adults with acute psychosis in Malaysia.

INTRODUCTION

Schizophrenia is a serious psychiatric condition with severe symptoms that affect how a person thinks, acts or feels. Schizophrenia is most commonly present early in life, but 20% of patients have onset after the age of 40 years and another peak at the age of 60 years.[1] According to the International Late-Onset Schizophrenia Group, late-onset schizophrenia is defined by the onset of illness after 40 years of age, and very late-onset schizophrenia-like psychosis (VLOSLP) is the onset after 60 years of age.[2] Schizophreniform disorder is a mental health condition that is similar to schizophrenia and has a limited duration. The key feature of schizophreniform disorder is that the symptoms last at least one month and for less than six months, while people diagnosed with schizophrenia experience symptoms for more than six months. Diagnosis of schizophreniform disorder is evaluated with DSM-5.[3] The patient should have two or more of the following: 1) delusions, 2) hallucinations, 3) disorganised speech and thoughts, 4) disorganised behaviour, 5) catatonic behaviour, and/or 6) negative symptoms such as difficulty with self-care, withdrawal and blunted emotional response. There is a dearth of research in this area, and a review of schizophrenia research in Malaysia did not address this condition among older adults.[4]

Early diagnosis and treatment are crucial as they can help to limit damage to the person's life, family, and other relationships. Another aspect of this disorder is the specialist care that they should receive. Ideally, this condition is best managed by geriatric psychiatrists. Acute admission for psychosis is best managed in a properly designated ward, where the environment is supportive, and staff are well-trained. However, in a centre where there is no dedicated psycho-geriatric ward for older patients with acute psychosis, a proper protocol must be developed to safeguard the patients and staff because a patient with psychosis can have severely disruptive behaviour that may cause injury to people or damage to properties. This case report illustrated a challenging diagnosis and management of an 88-year-old man with psychosis admitted to a centre with no geriatric psychiatrist, no gazetted ward for involuntary psychiatry admission, and developed severe disruptive behaviours in the general internal medicine ward.

CASE PRESENTATION

An 88-year-old gentleman presented with a 3-month history of auditory and visual hallucinations and persecutory delusion of people trying to harm him. He has an underlying visual and hearing impairment, as well as hypertension, dyslipidemia, and coronary artery disease. He was well until the COVID-19 pandemic, when the country went into multiple phases of movement control orders, and he missed his cataract surgery and became socially deprived. Two weeks before the admission, the family noticed disorganised behaviour and progressively worsening auditory hallucinations that disturbed him from performing prayers. The auditory hallucinations presented as a group of other people talking about him and criticising his prayers, making him angry and refusing to continue praying. The visual hallucination presented as confusion on a family member's

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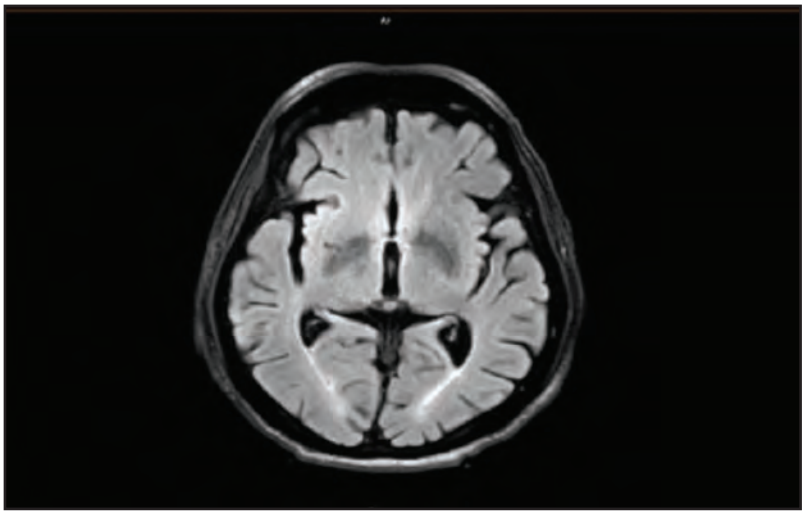

Fig. 1: MRI of the brain showing small vessel disease and age-related cerebral atrophy

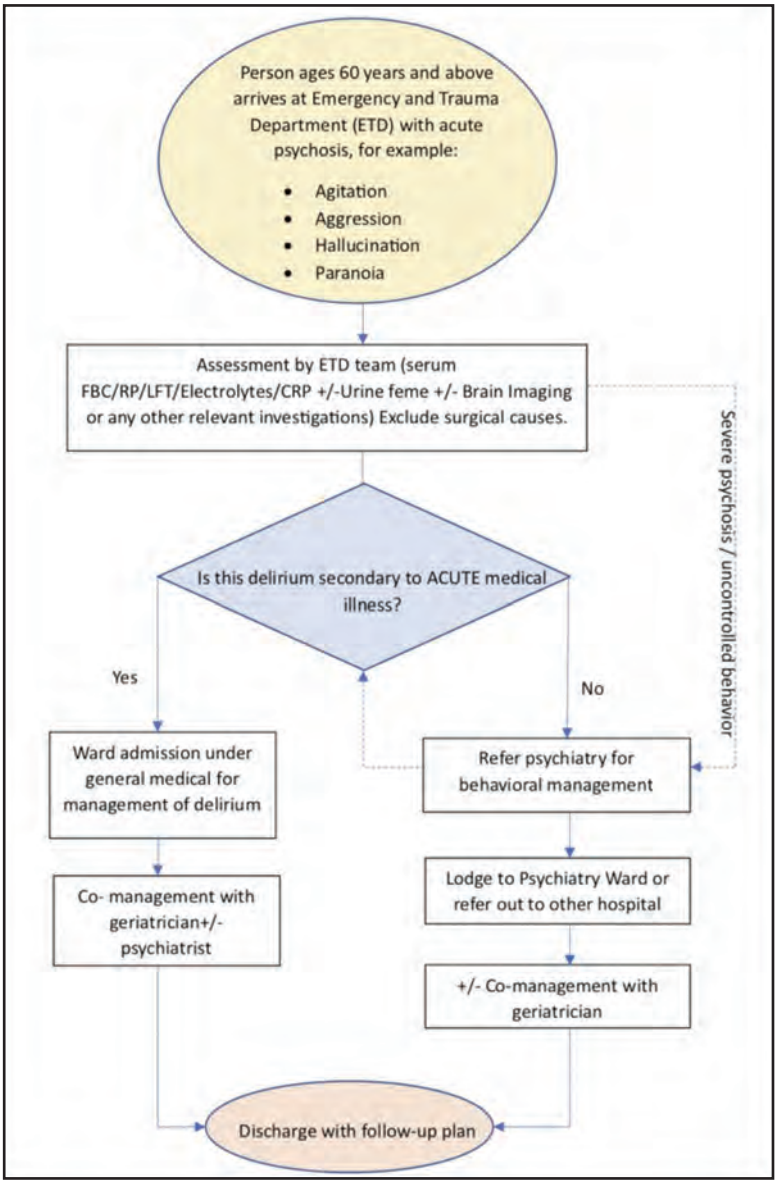

Fig. 2: Flowchart for older patients with acute psychosis in ETD. (Dashed line means that an early referral to the psychiatry team can be made while waiting for the investigation results)

face (mistaking his daughter for someone else) and seeing a family member come when he/she did not come at all. He also wanted to see a friend who had passed away long ago. He became aggressive and combative on the day of the presentation to the hospital, which caused a head haematoma to the son as the son prevented him from going to his late friend's house. He adamantly believed that the friend was still alive as he saw him. Functionally, he was living alone, still able to take care of himself, including cooking and doing house chores.

A general examination noted that he has good hygiene and motor function. There was no fever or any localising signs suggesting infection or neurological deficit. His gait was normal, and there were no signs of parkinsonism. A Mini-Mental State Examination (MMSE) was done and showed he had good attention (score 5/5) and short-term recall (score 3/3), but was unable to be completed due to visual impairment, hearing impairment, and he became uncooperative towards the end of the test. Apart from showing paranoia to the attending healthcare practitioners, he had good eye contact and communicated coherently. He refused to eat and said people tried to poison him. We were unable to complete the Geriatric Depression Scale as he became suspicious midway and refused to answer.

He was admitted to the general medical ward, where co-management was done between a geriatrician and general psychiatrists. He was given a diagnosis of acute schizophreniform disorder as the duration was less than 6 months to fulfil the DSM-V criteria for schizophrenia. Differential diagnoses included delirium secondary to sensory deprivation and dementia with Lewy bodies. Given that good baseline memory from history and MMSE were inconclusive in showing significant cognitive impairment (due to the hearing and visual impairments) compared to the degree of behavioural disorder, we proceeded with a particular neuropsychological test for individuals with hearing impairment. We found that the test again was inconclusive as this patient also has visual impairment. To the best of our knowledge, no specific neuropsychological tests assessed cognition in persons with double sensory impairment (visual and hearing).

Blood investigation showed normal complete blood count, electrolytes, thyroid function tests, Vitamin B12 level and liver function tests. Septic markers were negative. Magnetic Resonance Imaging (MRI) of the brain revealed small vessel disease (FAZEKAS 1) and generalised age-related cerebral atrophy (Figure 1).

He required multiple types and doses of anti-psychotics while in the medical ward because of his paranoia and aggressive behaviours. The noise and busy environment in the acute general medical ward were detrimental to the control of his behaviour, requiring him to be transferred to the psychiatry ward, which was more conducive and quieter. On admission, he was started on intramuscular (IM) Haloperidol 2.5mg stat and tablet (T) Quetiapine 50mg twice a day (BD). This did not control the aggression and Syrup Risperidone 1mg BD was started. As we were titrating the dose, he remained uncooperative. Three days later, the medication was changed to orodispersible T.Olanzapine 5mg BD as he refused to take regular medications and kept saying people were poisoning him. T.Olanzapine was titrated within three days to 15mg BD. After 3 days on this dose, he was still uncooperative and showed aggressive behavior towards staf and other patients, needing IM Haloperidol 2.5mg BD. He seemed to respond to this dose and T. Haloperidol 2.5mg BD was started after two days of stabilization and later titrated to 5mg BD. He developed symptoms of tardive dyskinesia while on Risperidone and Olanzapine, and his behaviour was difficult to control on Quetiapine. He was finally stabilised on T.Haloperidol 5 mg BD. He was discharged to his family's home. Unfortunately, he passed away at home three months after being discharged from the ward.

DISCUSSION

This case illustrated the complex presentation of late-life psychosis in an older adult and the challenge of reaching a diagnosis, as there was no objective cognitive test that was suitable for an older adult with dual sensory impairment. The most important approach was determining whether this was a delirium with reversible causes. The diagnosis of VLOSLP requires clinical evidence and supportive features lasting more than six months, such as a two-stage progression of psychotic episodes, partition delusions, multimodal hallucinations and lack of formal thought disorder or negative symptoms. These features are not pathognomonic but rather highly suggestive of VLOSLP. Previous literature showed that underlying cerebrovascular risk factors (such as long-standing hypertension and dyslipidaemia) and age-specific neurobiological processes contributed to the pathophysiology of VLOSLP.[5] His brain imaging showed a small vessel disease change, which was not significant (FAZEKAS 1) to cause cognitive impairment and also age-related cerebral atrophy.

The management of acute psychosis with underlying acute medical illness (e.g. infection, stroke, fracture) in Malaysia is typically co-managed by two departments – namely medicine and psychiatry. According to the latest data in 2022 from the Malaysian Society of Geriatric Medicine, there were only 63 geriatricians in the country, with 20 public-funded geriatric services to cater for 2.5 million older adults aged 65 and above. On the other hand, there were only 19 geriatric psychiatrists in the country. In centres with geriatricians in the medical department, the case will be managed by geriatricians, with or without psychiatrists. In our scenario, the problem arises if the older patient has acute psychosis but no acute medical illness to suggest a potentially reversible cause of delirium. Traditionally, the best personnel to manage is a geriatric psychiatrist. However, in our setting, there is no geriatric psychiatrist, and there is no gazetted psychiatric ward for involuntary admission of patients with acute psychosis. Admission to a medical ward for patients with no acute medical illness will expose them to nosocomial infections, especially if they need a longer time to stabilise the psychotic episodes.

There may be a legal implication as the admission to a psychiatry ward will be an involuntary admission, with the next of kin must sign a consent form for admission. Previous literature has shown that older adults were at the greatest risk for 'informal admission' to the mental health unit due to the

lack of capacity to provide informed consent for treatment and admission itself.[6] A systematic review of the prevalence of incapacity towards admission and treatment decisions in medical and psychiatry settings showed an average weighted proportion of 45% and 34%, respectively.[7] The same review also mentioned that incapacity in the psychiatry setting was greater in those with dementia, psychosis and mania, while in the medical setting, those with delirium, learning disability and neurological disorders.

In Malaysia, the legal criteria for detaining a patient state that they must be experiencing a "mental disorder of a nature or degree" that justifies admission to a psychiatric hospital for assessment or treatment. This is necessary either for the patient's own health and safety or to protect other individuals.[8] Under the Malaysian Mental Health Act 2001, a person can be admitted involuntarily if they are suspected of having a mental disorder. An application for detention can be made by a relative of the individual to the medical director of the psychiatric hospital. Alternatively, it can be made based on the recommendation of a medical officer or registered medical practitioner who has conducted a personal examination of the individual no more than five days prior to admission. The Act specifies that "no consent is required for other forms of conventional treatment," which includes psychiatric medication. Unlike in some jurisdictions, such as the United Kingdom (UK), where an approved mental health professional can also submit an application, the authority to apply for detention rests solely with the medical profession.

On the other hand, inappropriate admission of patients with acute psychosis to general medical wards might lead to property damage from aggressiveness and injury to the staff and other patients. The open ward, the high load of patients and the noisy environment (from the syringe-pump machines and visitors) of the general medical ward are deemed not conducive for patients with psychosis, who often require a quiet environment and, perhaps, one-to-one care.

Following this case, a geriatrician and two psychiatrists drafted a protocol for admission, as the pathway is complex when the resources are limited. Our centre is a relatively new hospital (started operating in 2020) with only a few trained healthcare professionals in psychosis management, no acute delirium ward, no gazetted psychiatry ward for involuntary admission for acute psychosis, and no geriatric psychiatrist. This protocol was then validated through a series of consensus development conferences with another two senior consultants from internal medicine and psychiatry,respectively (Figure 2).

As our centre is not gazetted for involuntary admission for psychosis, 'lodging' in Figure 2 means the patient is a medical patient but admitted to the psychiatry ward while investigations are ongoing to rule out delirium. Under the hospital system, the medical team was the primary team. Hence, this case illustrates whether, in the future, we need to have a medical mental health unit (MMHU) rather than just a liaison old age psychiatry (LOAP) or a stand-alone psychiatry ward. This unit is a gap in our clinical service provision in Malaysia.

A randomised controlled trial done in the UK on the MMHU in managing older people with delirium and dementia has shown improved carer satisfaction, better patient experience, and was cost-effective compared to standard care (management in either general medical or geriatric unit). This and other models have been summarized by the Malaysian Ministry of Health Medical Development Division.[9] Alternatively, LOAP has been implemented to offer psychiatry services in medical and surgical wards, as well as training the general medical staff.[10] Service delivery for the mental health of older adults also requires more dedicated research as it involves resource and financial implications for the nation in the long run.

Many times, in the event of acute psychosis, the carer was stressed and exhausted. Therefore, care and empathy must be exercised to allow respite and counselling. Some of the carers will need mental health support from psychologists and psychiatrists to manage behaviours at home. Crisis-plan interventions and education must be given to the carers so that they can be prepared if such an event occurs again, and steps must be taken to possibly prevent it.

CONCLUSION

In a resource-limited setting, safeguarding older adults with acute psychosis is of utmost importance. Admission to an appropriate ward is crucial to avoid health-related implications, to allow stabilisation of the psychosis and to provide respite to the carer. An MMHU or other joint behavioral units, co-managed by geriatricians and psychiatrists, has been shown to be beneficial and cost-effective. However, if the unit is deemed to involve substantial financial and resource implications, then the LOAP service can be implemented. Finally, it is recommended that each healthcare facility have a structured pathway of admission for older adults with acute psychosis.

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CONSENT

Written consent was obtained from the next-of-kin as the patient had been deceased at time of writing.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

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Fungal keratitis complicated with corneal perforation by dematiaceous fungi humicola fuscoatra

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SUMMARY

A 42-year-old immunocompetent man presented with a painful red eye with blurred vision in his right eye post-exposure to dust from wall scraping during a house renovation. His visual acuity was 6/24. He had a corneal ulcer with endothelial plaque, posterior synechiae, and hypopyon. He was empirically treated as fungal keratitis and corneal scraping yielded dematiaceous fungi, later identified as Humicola fuscoatra. He received topical, intrastromal, and intracameral amphotericin B but later developed corneal perforation. This was treated with corneal glue and bandage contact lens without needing penetrating keratoplasty. His vision improved to 6/12, though residual corneal scarring and anterior synechiae remained. Larger and deeper infiltration with hypopyon increases the risk of corneal perforation, and targeted therapies (intrastromal and intracameral injections) can help reduce infiltration size. In this case, topical, oral, and targeted therapy of fluconazole and amphotericin B effectively treated fungal keratitis caused by Humicola fuscoatra.

INTRODUCTION

Fungal keratitis has taken a significant role in causing ocular morbidity and preventable blindness, with higher incidence in subtropical and tropical countries.[1] Dematiaceous fungi are melanised fungi that produce pigments, with Curvularia spp reported most.[1] We would like to present a rare case of fungal keratitis complicated with a perforated ulcer caused by Humicola fuscoatra.

CASE PRESENTATION

A 42-year-old gentleman presented to our eye clinic with persistent right eye pain for eight days, with a foreign body sensation, redness, and tearing, since exposure to dust from wall scraping during a house renovation. He noticed an enlarging white spot in his right eye for one week, with increasing blurred vision. He had no significant previous medical or ocular history.

His right visual acuity was 6/24. The slit lamp examination noted a 3.4 x 3mm paracentral corneal ulcer with endothelial plaque touching the iris at the temporal region. There was posterior synechiae with 1mm hypopyon. The patient also had injected conjunctiva with grade II nasal pterygium (Figure 1). Intraocular pressure (IOP) was 12 mmHg, the lens was clear, and the fundus was normal. The left eye examination was unremarkable.

Corneal scraping was performed, yielding a fungal-like organism on Sabouraud dextrose agar (SBA). The sample was sent to the Institute for Medical Research in Kuala Lumpur for identification. The polymerase chain reaction (PCR) testing confirmed the presence of Humicola fuscoatra, but a susceptibility test was not done.

Based on the history and clinical examination he was treated as right eye fungal ulcer empirically and started on topical amphotericin B 0.15% and topical fluconazole 0.2% hourly, topical gentamicin 0.9% hourly, topical ceftazidime 0.9% hourly, topical atropine 1% three times daily, oral fluconazole 100 mg twice daily and tablet vitamin C 1 gram daily.

After four days of treatment, the ulcer's size was similar, but the infiltrate was deeper, and the endothelial plaque worsened. The right eye's IOP was 8 mmHg. A B-scan of the right eye showed no evidence of endophthalmitis. Subsequently, he received a combination of intrastromal and intracameral injections of 5 mcg/0.1 ml and 10 mcg/0.1 ml amphotericin B, respectively, once.

Post-procedure, there was an increase in flare and inflammation, with raised IOP to 25 mmHg, which was controlled with topical timolol 0.5% twice daily. The hypopyon was reduced, but the ulcer remained the same, with persistent endothelial plaque. After 5 days, the anterior chamber became shallow, with a positive Seidel's test, and he was treated as a perforated fungal ulcer. A bandage contact lens with cyanoacrylate glue was applied for one month, with the addition of topical moxifloxacin 0.5% 4 times daily (Figure 2a).

Three months later, the infiltrate and endothelial plaque improved with residual corneal scarring at the previous ulcer site. Anterior synechia was still present, and no cells were found in the anterior chamber. His vision improved to 6/12, and all medications were discontinued. (Figure 2b)

DISCUSSION

Humicola fuscoatra is a dematiaceous fungus from the Chaetomiaceae family, commonly isolated from soil, room

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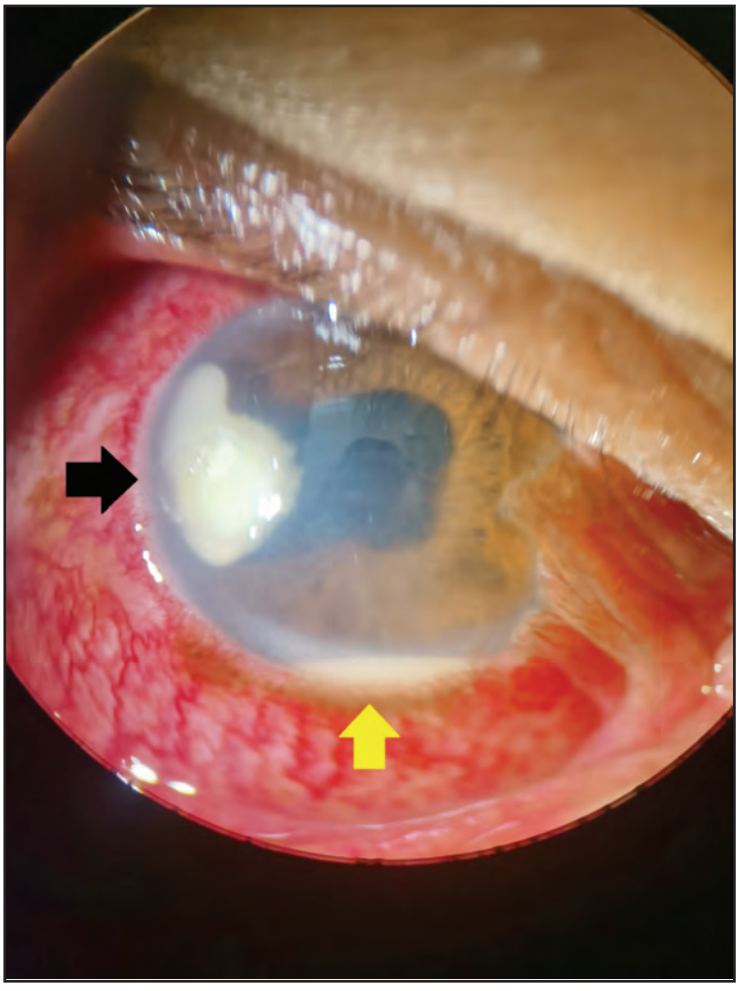

Fig. 1: paracentral corneal ulcer with endothelial plaque (black arrow) and hypopyon (yellow arrow) in right eye

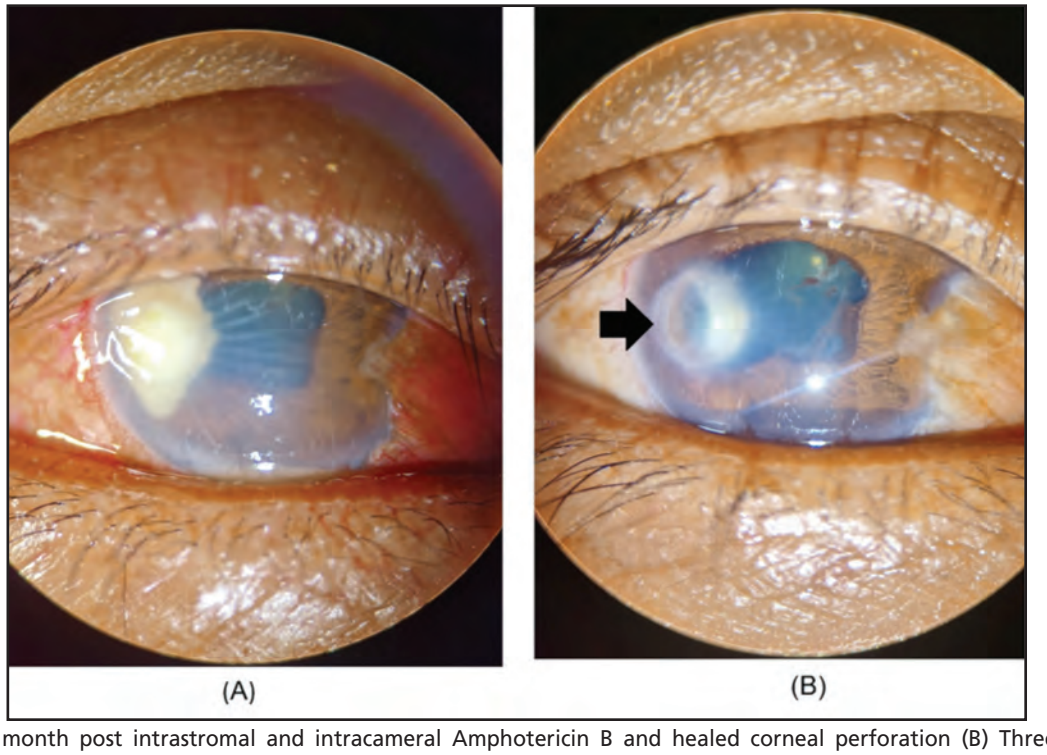

Fig. 2: (A) one month post intrastromal and intracameral Amphotericin B and healed corneal perforation (B) Three months post treatment discontinuation. Note the presence of corneal scarring (black arrow)

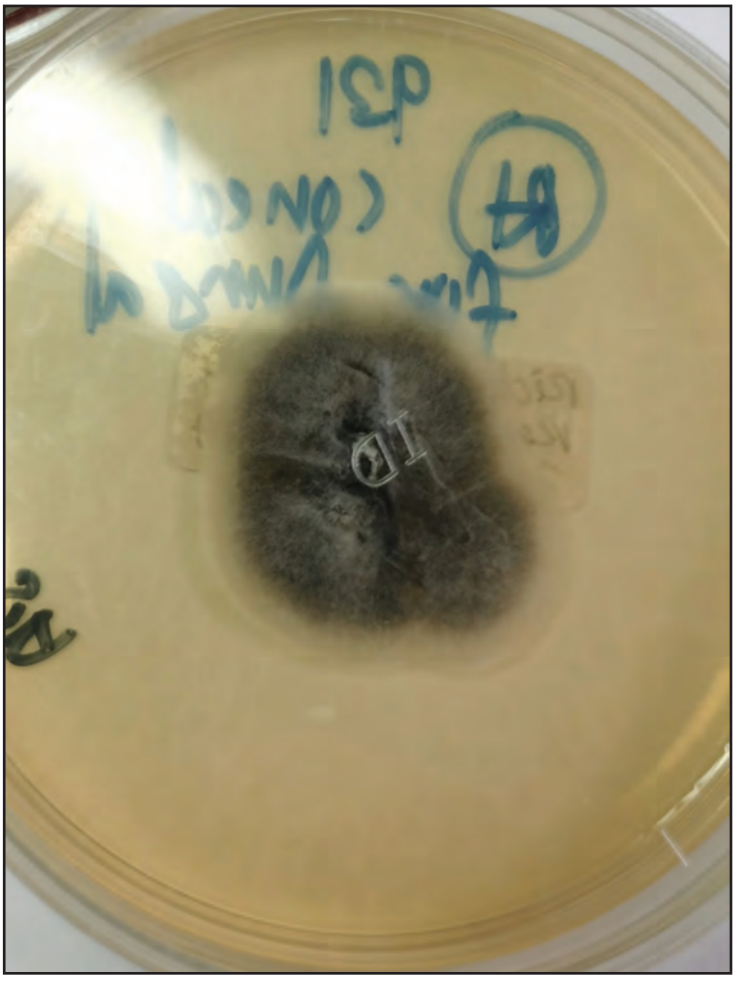

Fig. 3: Humicola fuscoatra on SBA. Dematiaceous fungi have black filaments and appear dark on the culture plate

environment, plant debris, or cat furs.[2] This hyphomycete genus fungus also produces thick-walled and single-celled spores, which are formed laterally or terminally on hyphae or conidiophores.[3] On SBA, it yields central white filamentous colonies with edge entire, black pigmentation at the edges when old (Figure 3).

Humicola sp also had the potential as a microbial biocontrol agent for plant disease, albeit commonly infecting tomato roots but not pathogenic.[3,4] It is also a rare cause of systemic human infection, with a reported case of Humicola-associated hypersensitivity pneumonitis as well as two cases of peritoneal dialysis-associated peritonitis, in which all patients were treated with antifungals or reduced exposure to the fungus.[2,5,6] To our knowledge, this was the third case of Humicola sp associated keratitis apart from the two cases of fungal keratitis reported by Garg et al.[7]

Natamycin is the first-line treatment for fungal keratitis, while voriconazole offers better coverage for filamentous fungi.[8] Our patient achieved satisfactory visual recovery despite being treated with Amphotericin B and fluconazole. We attribute this success to the patient's adherence to hourly topical treatments and the use of intrastromal and intracameral injections, which improve drug delivery and bioavailability for deep mycoses. However, optimal dosage and injection intervals remain to be determined, and further research is needed to assess the treatment's efficacy for filamentous dematiaceous fungi, especially in centres lacking access to penetrating keratoplasty.[9]

Severe fungal keratitis might lead to corneal perforations and severe vision loss. As the ulcerations and inflammation advance, it leads to corneal thinning through stromal lysis and the formation of descemetocele before perforation occurs. Early application of cyanoacrylate glue with soft contact lenses can help in impending perforations.[10]

CONCLUSION

In this case, we presented a classical presentation of fungal keratitis by the rare organism Humicola fuscoatra and the challenges of managing this case in a resource-limited district hospital. We found that the typical clinical features allowed early empirical treatment without formal corneal scraping results, which aids in hastening visual recovery. Moreover, even with the complications of corneal perforation and lack of cornea subspecialty service in the district hospitals, careful counselling and patient adherence to therapy can help to improve the visual prognosis. Intrastromal and intracameral antifungals can be considered in managing persistent endothelial plaque.

ACKNOWLEDGEMENTS
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DECLARATIONS
Patient consent was obtained, and no funding was provided.

CONFLICT OF INTEREST
There are no conflicts of interest to be declared by the authors.

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Streptococcus suis spinal infection: a case report highlighting an emerging pathogen

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SUMMARY

Being a multiracial country, Malaysia has been well positioned as a food paradise, serving a wide range of foods, including pork. While Streptococcus suis (S. suis), a facultative anaerobic gram-positive coccus, commonly colonizes the upper respiratory tract, gastrointestinal tract, and genital organs of various animals, especially pigs. Recently, S. suis infections have emerged as a concern in several states, particularly Sabah. This report details the case of a patient who developed a cervical spine infection, outlining the clinical presentation, suspected mode of acquisition, and outcome. Given the ongoing public health threat posed by zoonotic infections like S. suis, priorities should include accurate epidemiological surveillance, regulation of pig farming and slaughtering practices, and continued promotion of safe pork handling and consumption.

INTRODUCTION

Although often overlooked, *Streptococcus suis (S. suis)* is a zoonotic pathogen of significant concern. It has been responsible for large outbreaks of sepsis in China and is a leading cause of bacterial meningitis in adults in Vietnam and Hong Kong, ranking as the most common and third most common cause, respectively.[1] Humans typically acquire *S. suis* infections through contact with pigs, either during slaughter or by handling and consuming undercooked pork products.[2]

Two cases of *S. suis* meningitis with concurrent sepsis have been reported in Sabah, Malaysia. Both patients received a 2-week course of intravenous antibiotic therapy and experienced clinical recovery.[3] However, one patient developed otological complications, including reduced hearing and vertigo. Herein, we report a case of *S. suis* cervical pyogenic spondylodiscitis, including a discussion of the suspected transmission route, clinical manifestations, and outcome.

CASE PRESENTATION

A 71-year-old woman complained of persistent posterior neck pain that persisted even at rest and throughout the night. The pain was accompanied by intermittent fever. She denied experiencing headaches or radicular pain. It is noteworthy that she frequently handles and prepares raw pork for her husband and had recently sustained a minor, improperly managed cut on her thumb while doing so.

Although her initial cervical radiograph (Figure 1) demonstrated disseminated idiopathic skeletal hyperostosis (DISH), no obvious features suggestive of spondylodisciitis changes. Her blood investigations showed elevated septic parameters, including increased white blood cell count (WCC), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP). Subsequent magnetic resonance imaging (MRI) of the cervical spine revealed spondylodisciitis changes affecting the C4, C5, and C6 vertebrae (Figure 2). Blood culture was positive for *Streptococcus suis* and Echocardiography demonstrated mitral valve endocarditis. The patient was treated aggressively with six weeks of intravenous ceftriaxone, resulting in significant clinical improvement. Follow-up cervical radiographs revealed fusion of C5/C6, and repeat echocardiography showed resolution of the endocarditis.

DISCUSSION

Significant geographical differences are observed in the epidemiology of *S. suis* infection. In Western regions like Europe and North America, cases are primarily concentrated among individuals with occupational exposure to pigs, such as abattoir workers, butchers, and pig breeders. Conversely, Asian regions often report higher infection rates, linked to cultural practices involving the consumption of raw or undercooked pork products, including blood, organs, and meat.[1] In this case, we hypothesize that the patient likely acquired the *S. suis* infection through the improperly managed cut on her thumb, which occurred while she was handling raw pork. A similar case of Streptococcus suis infection was recently reported in Sabah, Malaysia, involving a butcher who had an injured thumb prior to becoming infected.[2] This underscores the importance of proper wound care, regardless of size, before handling raw food. Taking this precaution can help prevent potentially serious zoonotic infections.

Human *S. suis* infections commonly manifest as meningitis or septicemia. Other reported manifestations include endocarditis, arthritis, cellulitis, spondylodiscitis, rhabdomyolysis, pneumonia, peritonitis, uveitis, and endophthalmitis.[1] In this case, the patient presented with both cervical spondylodiscitis and mitral valve endocarditis,

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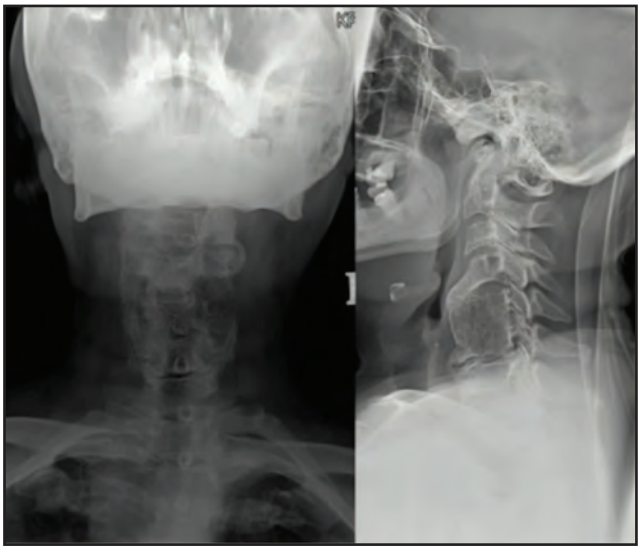

Fig. 1: Cervical radiograph demonstrating bridging osteophytes involving C4, C5, C6 and C7, suggesting disseminated idiopathic skeletal hyperostosis (DISH)

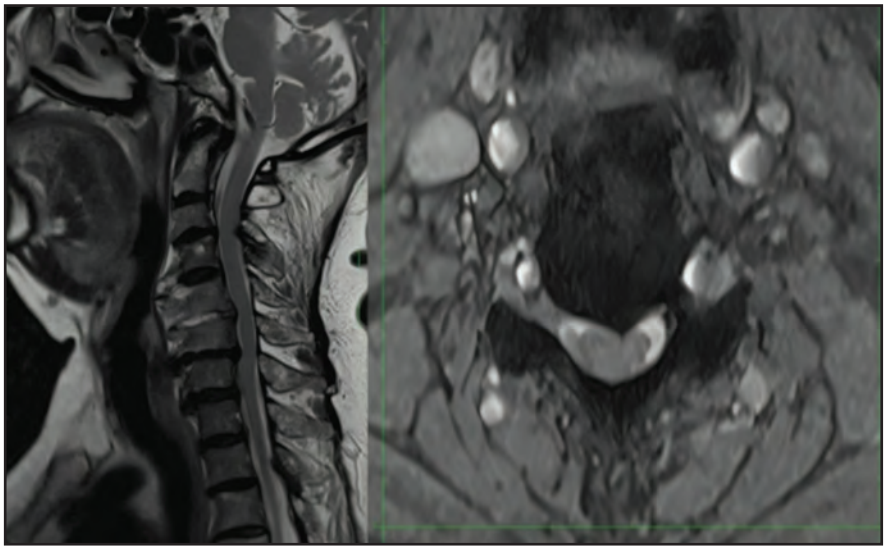

Fig. 2: MRI depicting sagittal and axial (C5/C6 level) views of the cervical spine, revealing C5/C6 discitis, vertebral body edema (anterior), and a small paravertebral collection without epidural abscess formation

the first case reported in Malaysia. This contrasts with two previously reported cases from Sabah, which both presented with meningitis.[2]

Malaysia's National Antimicrobial Guideline, issued by the Ministry of Health, recommends intravenous cloxacillin administered every four hours as the preferred empirical therapy for spinal infections.[3] This primarily targets potential *Staphylococcus aureus* infection. IV cefazolin is considered a second-line empirical therapy option. However, it's important to note that empirical therapy should generally be withheld unless the patient presents with sepsis or neurological compromise. In such cases, a CT-guided biopsy or aspiration is recommended.[3]

In this case, empirical antimicrobial therapy was initiated due to the patient's septic state and subsequently tailored based on blood culture results. While CT-guided biopsy can be a valuable diagnostic tool, it was not pursued initially due to several factors. Studies have shown a relatively low positive yield (approximately 33%) from image-guided biopsies in such cases.[4] Additionally, there are inherent risks associated with the procedure, including potential injury to surrounding structures and exposure to ionizing radiation.[4] However, we acknowledge that CT-guided biopsy may be warranted in specific scenarios. These include immunocompromised patients where atypical organisms, such as Candida species, are a concern; cases with clinical or MRI findings suggestive of tuberculous spondylodiscitis; instances where the diagnosis of spondylodiscitis remains uncertain based on clinical and imaging data; and situations where there is no clinical improvement after six weeks of targeted antibiotic therapy.

Following the Malaysian national antimicrobial guidelines, intravenous antibiotic therapy can be transitioned to oral administration after a minimum of two weeks in cases with good clinical response and oral antibiotic bioavailability.[3] The total duration of antibiotic treatment, whether IV or oral, should be a minimum of six to twelve weeks. Factors influencing treatment duration include the presence of an undrained paravertebral abscess, infection with drug-resistant organisms, and the extent of bone destruction.[3] Our patient received a six-week course of intravenous ceftriaxone for the concurrent diagnoses of uncomplicated cervical spondylodiscitis and native valve endocarditis.

While MRI is imaging modality of choice for diagnosing spondylodiscitis, its utility in post-treatment monitoring remains unclear. Research indicates that MRI often reveals ongoing or worsening bone and disc abnormalities, such as changes in bone enhancement/edema volume, disc height, and signal intensity, even in patients showing clinical improvement.[5] This persistence of bone signal changes on MRI, despite positive clinical responses, could be attributed to the rich vascularization of bone tissue or the proliferation of granulation tissue.[5] Therefore, routine follow-up imaging is not typically advised for patients exhibiting favorable clinical and laboratory results. However, MRI may be selectively employed in cases where unfavorable clinical and laboratory response. When assessing treatment response in such cases, changes observed in soft tissues, such as the size and signal characteristics of psoas, paravertebral, or epidural abscesses, may provide a more dependable indication compared to bone and disc findings.[5]

CONCLUSION

To our knowledge, this case study presents the first documented instance of Streptococcus suis cervical spondylodiscitis in Malaysia. This finding underscores the critical importance of personal protective measures, such as wearing gloves and masks when handling raw pork, to mitigate the risk of zoonotic transmission. Furthermore, it highlights the potential necessity of image-guided cervical tissue biopsy in cases lacking positive blood culture results. Notably, this case also demonstrates the effectiveness of antibiotic treatment alone in managing *S. suis* cervical spondylodiscitis in patients without neurological complications or spinal instability.

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CONSENT

Informed consent was secured from the patient.

CONFLICT OF INTEREST

All the authors declare that they have no conflicts of interest to disclose.

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CASE REPORT

Community-acquired MRSA complicated pneumonia in 2 Infants

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SUMMARY

Community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) infection prevalence is increasing worldwide. The true prevalence of CA-MRSA is unknown in Malaysia. We present two cases of CA-MRSA complicated pneumonia in two healthy infants. They had prolonged hospitalization and required surgical intervention eventually. The outcomes were favourable in both cases, with complete clinical resolution at discharge. This article emphasizes the risk factors and the main presenting symptoms of CA-MRSA complicated pneumonia to aid in the treatment of such cases in the future.

INTRODUCTION

Community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) is defined as a positive culture of MRSA within 48 hours of hospitalization, provided the patient does not have previous history of hospitalization, surgery, residence in a long-term care facility, dialysis within the last 12 months, presence of percutaneous device or indwelling catheter or previous MRSA infection or colonization; as per CDC guideline.[1] Based on the history of the emergence of CA-MRSA associated infections, it was first reported in the 1980s in the United States.[1] Since the 2000s, there have been multiple reports of CA-MRSA from different countries across the globe, with large outbreaks reported in the United States, Taiwan, Canada and Australia.[1] CA-MRSA prevalence is increasing and has become more common than hospital-acquired MRSA (HA-MRSA).[2] It is now recognized as a significant disease burden in the paediatric community worldwide.[2,3] CA-MRSA has emerged as the predominant cause of *Staphylococcus aureus* pneumonia in children in the United States.[4]

There are a few reports on CA-MRSA infections in Malaysia. The first case series of CA-MRSA was published in 2008 by a group of microbiologists in University Malaya.[5] Several clinicians from Sabah reported 37 isolates of CA-MRSA among children up to 10-year-old in a period of 18 months from 2015 until 2017.[6] To date, the true prevalence of CA-MRSA in Malaysia is still largely unknown, highlighting the need for further research and awareness among health care workers.

There are several differentiating features between CA-MRSA and HA-MRSA. At the molecular level, CA-MRSA comprises of Staphylococcal cassette chromosome *mec (SCCmec)* type IV and V, while HA-MRSA contains SCCmec Type I, II or III.[3,5] CA-MRSA commonly causes skin and soft tissue infection. However, it can also cause invasive and severe infections such as severe sepsis, osteomyelitis and complicated pneumonia.[3,5] Epidemiologically, CA-MRSA affects young and healthy individuals compared to HA-MRSA infections which affect the elderly, prolonged hospitalized patients and individuals with chronic disease.[1,5]

We describe two paediatric cases of CA-MRSA complicated pneumonia, which affects two healthy infants with no known medical illness.

CASE PRESENTATION

Case 1

AH, a four-month-old girl with no known medical illness, presented to a district hospital with a three days history of lethargy and reduced oral intake. The general practitioner prescribed one dose of oral antibiotic on the second day of illness. She was born full-term via vaginal delivery with no significant birth or post-natal issues. On arrival to the hospital, she was in severe respiratory failure with a respiratory rate of 66 breaths per minute, heart rate of 190 beats per minute, oxygen saturation of 94% under face mask oxygen 5L/min, moderate subcostal recessions and reduced breath sound over the right lung. The rest of the clinical examinations were unremarkable. Her chest X-ray showed loculated effusion over right lung with right lower lobe consolidation (Figure 1a). Ultrasound thorax demonstrated right pleural effusion, with the maximum thickness of 3cm and multiple locules seen, supporting the diagnosis of complicated pneumonia with stage II empyema thoracis. Laboratory values included a raised total white count of 24,000 with predominant neutrophils (59%) and a C-reactive protein of 188mg/L.

The patient was empirically started on intravenous cloxacillin and ceftriaxone and was put on bilevel positive airway pressure (BPAP) support in paediatric intensive care unit (PICU). A right pigtail catheter was inserted and 12ml of seropurulent fluid was drained. Trial of intrapleural urokinase further drained 60-80ml (12-16ml/kg) of fluid per day. On day three of admission, the patient developed right pyopneumothorax with right lower lobe collapse (Figure 1b). Bedside aspiration through the pigtail catheter was done and the pneumothorax resolved. She completed five days of intrapleural urokinase and was weaned off respiratory support upon completion of urokinase.

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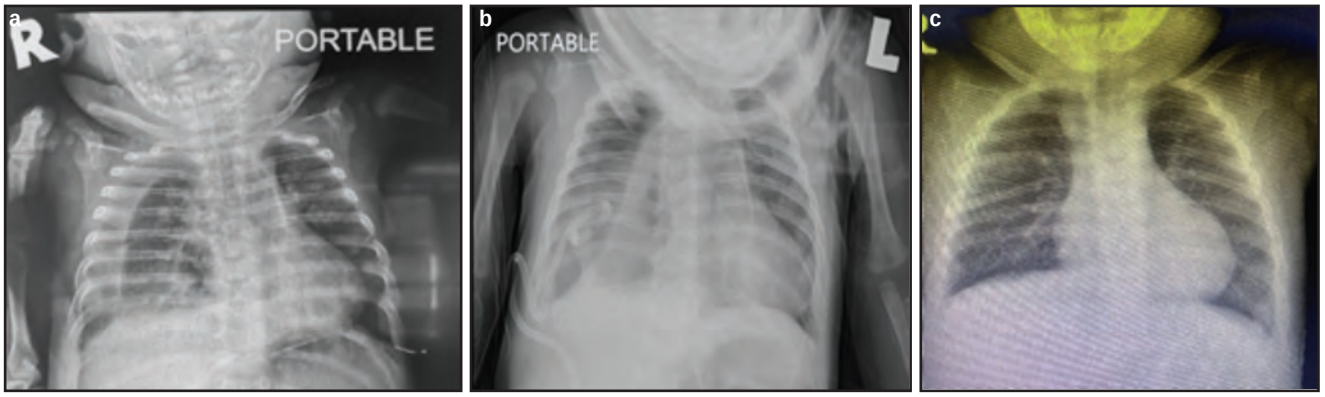

Fig. 1: Chest radiographs of the patient. (a) Frontal supine radiograph shows loculated effusion (arrow) at the right upper and middle zone with right lower lobe collapse evidenced by tenting of the right hemidiaphragm and lower zone opacity). Bilateral air space opacities (including retrocardiac region) suggesting active lung infection. (b) Follow-up chest radiograph showed persistent right loculated effusion with right lower lobe collapse, complicated with pneumothorax. Drainage catheter tip at the area of effusion. (c) Radiograph during review three weeks later in the clinic which showed complete resolution of effusion and lower lobe collapse with no new active lesion seen

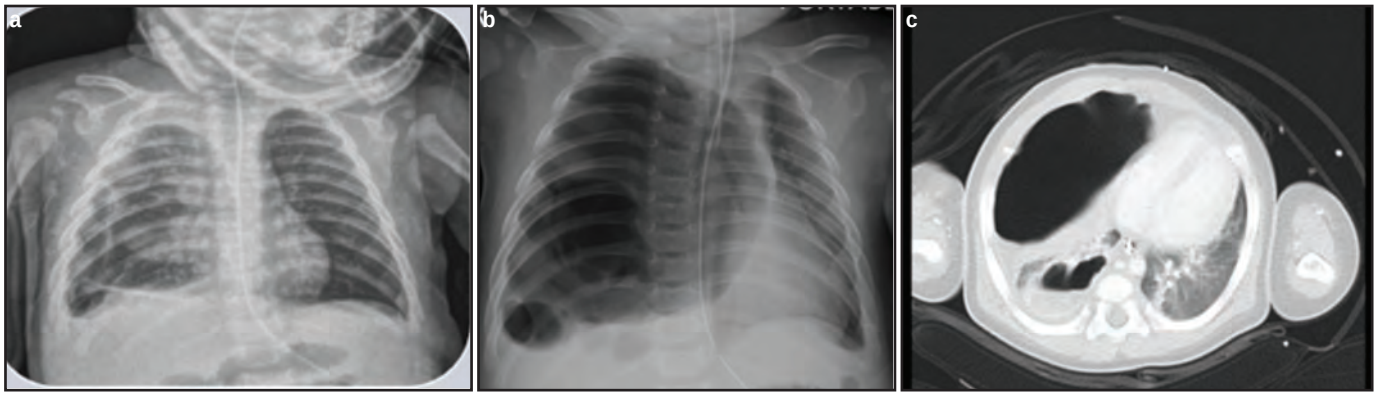

Fig. 2: Imaging of an infant with pleural effusion and CA-MRSA complicated pneumonia. (a) Frontal chest radiograph showed right pleural effusion with right lower lobe collapse. Patchy air space opacities overlying right upper and middle zone represented lung infection. (b) Follow up radiograph showed worsening right pleural effusion with air locule (cavity) extending into right mid-zone. Right lung hyperinflation with mediastinal shift to the left. (c) CECT thorax shows gross right hydropneumothorax with mediastinal shift. The right pleural lining appears thickened and enhancing. There is a cystic lesion with air-fluid level (arrow) in the right lower lobe and adjacent segmental lung collapse

The analysis of the pleural fluid fulfilled Light's criteria for exudative pleural effusion. The pleural culture showed MRSA SCCmec Type IV (CA-MRSA), which was sensitive to co-trimoxazole, gentamicin, rifampicin, and vancomycin but resistant to penicillin, cloxacillin, and clindamycin. The antibiotic was changed to intravenous vancomycin. The blood culture showed no growth.

The right pigtail catheter was not draining nor bubbling for three consecutive days; hence, it was removed. However, one day later, she had worsening respiratory distress due to new onset pneumothorax, which required re-insertion of a right chest drain. Four days later, the chest tube partially dislodged and caused re-accumulation of the right pneumothorax. The persistent air leak gave rise to a clinical suspicion of a right bronchopleural fistula. Following the cardiothoracic surgeon's referral, a mini-thoracotomy with right lung repair was done. A bronchopleural fistula was found in the right lower lobe, and a small 3x4 cm cavity was observed. AH improved tremendously and was discharged home one-week post-surgery (a total of 28 days of hospitalization). She completed ten days of intravenous vancomycin and four weeks of oral sulfamethoxazole and trimethoprim in combination with rifampicin. She recovered completely clinically and radiologically (Figure 1c) upon review three weeks later in our clinic.

Case 2

HT, a 3-month-old girl who was previously healthy, was acutely ill on presentation after six days history of fever and cough. She was born full term via vaginal delivery with no significant birth or post-natal issues. She was in a severe respiratory failure state, with a respiratory rate of 56 breaths per minute, a heart rate of 200 beats per minute and pulse oximetry reading of 96% under room air. On auscultations, there were reduced breath sounds over the right lung. She required BPAP and fluid resuscitation at the emergency department. Her chest X-ray revealed homogenous opacity over the entire right hemithorax, and ultrasound thorax showed right pleural effusion with septation, which was

consistent with stage II empyema thoracis. Laboratory values included a raised white count of 38,700 and CRP of 198mg/L. Her diagnosis was complicated pneumonia with stage II empyema thoracis.

Intravenous cloxacillin and ceftriaxone were initiated. A right chest drain was inserted and drained 95ml (18ml/kg) of seropurulent fluid. On the second day of admission, she was transferred to the PICU in a tertiary hospital. Unfortunately, the chest drain dislodged; however, repeated ultrasound thorax revealed no more effusion. She was continued with respiratory support and intravenous antibiotics.

Pleural fluid culture grew MRSA SCC*mec* type IV (CA-MRSA), and the drug sensitivity results indicated that it was sensitive to vancomycin, cotrimoxazole, rifampicin, sulfamethoxazole, and trimethoprim. Intravenous antibiotic was changed to intravenous vancomycin.

Serial chest X-ray from day three of admission showed an air-filled cavity of increasing size over the right hemithorax (Figure 2a and b). Contrast-enhanced Computerized Tomography (CECT) thorax demonstrated gross right pyopneumothorax with mediastinal shift and a cystic lesion with an air-fluid level in the right lower lobe with communication with the adjacent pyopneumothorax (Figure 2c). GH then underwent right mini-thoracotomy and lung decortication with intra-operative findings of ruptured lung abscess and extensive necrotic tissue within the pleura. Pleural tissue culture was consistent with MRSA. Her primary caretakers were screened positive for MRSA nasal carriers; hence, decolonization with mupirocin ointment and chlorhexidine was done.

She recovered well and was discharged home ten days after surgery (a total of 19 days of admission). She completed two weeks of intravenous vancomycin and four weeks of sulfamethoxazole and trimethoprim. Upon review in the clinic, she was asymptomatic with full radiological resolution within three months.

DISCUSSION

Both cases involved healthy infants under the age of 6 months with severe CA-MRSA complicated pneumonia. They had prolonged recovery and required surgical intervention eventually. The outcomes were favourable in both cases, with a complete clinical resolution upon discharge.

Complicated pneumonia is defined as severe pneumonia with local complications such as parapneumonic effusion, empyema thoracis, lung abscess, bronchopleural fistula, necrotizing pneumonia or systemic complications such sepsis, multiorgan failure and acute respiratory failure. Complicated pneumonia predominantly affects healthy children with no known medical illness. Complicated pneumonia is treated with a prolonged course of antibiotics. The initial choice of antibiotics depends on local guidelines and antibiotic resistance profile. Symptomatic effusion should be drained, followed by intrapleural fibrinolytic if indicated. Surgical interventions such as video-assisted thoracoscopy and thoracotomy, may be needed in advanced empyema thoracis and for those who do not respond to non-surgical interventions.[7]

Community-acquired methicillin-resistant Staphylococcus aureus (CA-MRSA) frequently occurs in otherwise young and healthy individuals.[1,4] In a large case series done in Texas Children's Hospital involving 117 patients, the mean age of CA-MRSA was 0.8 years.[4] This finding was similar to another study in Hawaii, United States.[8] However, a study done in Likas Hospital, Sabah, showed the most prevalent age for CA-MRSA infection is 1 to 5 years old.[6] Besides young age, other risk factors for CA-MRSA infection include MRSA colonization, prior infection among close contacts, overcrowding and low socioeconomic status.[3,6]

CA-MRSA is highly associated with respiratory infections and severe pneumonia compared to methicillin sensitive *Staphylococcus aureus* (MSSA).[2] MRSA pneumonia often involves unilateral consolidation, pneumatocele formation and pneumothorax.[8] They are more prone to develop complicated pneumonia such as necrotizing pneumonia, lung abscess or empyema thoracis as compared to *Streptococcus pneumoniae*.[3] The increased prevalence of Panton-Valentine leucocidin (PVL) toxin in the CA-MRSA strain could explain this clinical condition as PVL promotes white blood cell lysis and causes tissue necrosis.[3] Furthermore, numerous studies found that systemic complications such as sepsis and septic shock, ventilatory support, intensive care unit admission, pleural drainage or surgical intervention are more frequent among CA-MRSA infected patients.[3,8] These undoubtedly cause higher morbidity and increase the length of hospitalization stay.

As a general rule, CA-MRSA is primarily resistant to beta-lactam antibiotics (penicillin, cephalosporin, carbapenem), aminoglycosides and macrolides.[3] Hence, the antibiotic choices remaining are vancomycin, clindamycin, linezolid, trimethoprim-sulfamethoxazole, rifampicin and doxycycline. The Infectious Disease Society of America (IDSA) recommended empirical anti-MRSA therapy for hospitalized children with severe community-acquired pneumonia.[9] Intravenous vancomycin is recommended.[9] Most case series in the developed country used intravenous vancomycin as an empirical antibiotic.[4] However, this is not commonly practised in Malaysia. Both of our patients were given intravenous vancomycin after reviewing the pleural fluid culture result, and they responded well.

Clindamycin is frequently used as the next alternative drug of choice in mild to moderate CA-MRSA infection or oral alternative to intravenous vancomycin.[4,9] However, CA-MRSA may develop inducible resistance to clindamycin, and there is an increasing trend in the resistant profile for clindamycin in Malaysia.[1,5] Clindamycin can be considered after reviewing the drug susceptibility profile.

Linezolid is FDA approved for treating MRSA pneumonia in children;[9] however, its use has been restricted due to high cost. Due to its excellent susceptibility profile, trimethoprim-sulfamethoxazole is the alternative oral drug for treating CA-MRSA pneumonia.[2,5] Rifampicin has bactericidal activity against *Staphylococcus aureus* and achieves high intracellular

levels.[9] It is commonly used in combination with other agents due to the rapid development of resistance if used as monotherapy.[1,9] Further research is needed to look into the role of rifampicin as adjunctive therapy in CA-MRSA infections.[9]

Prevention of CA-MRSA infection relies on good personal and environmental hygienic practices. Close contacts should be screened for CA-MRSA infection if household transmission is suspected.[9] Appropriate decolonization in the patient and family members may be done in recurrent skin and soft tissue infections; however, its efficacy in preventing recurrent CA-MRSA infection is still debated.[9]

CONCLUSION

Treating physicians should be aware of the increasing prevalence of CA-MRSA in the paediatric cohort. Early recognition of clinical and radiological findings of CA-MRSA pneumonia is critical in the appropriate and timely management of this infection. This case series also highlight the need to review the local epidemiology of CA-MRSA among the paediatric population and the subsequent clinical implications in the choice of appropriate empiric and targeted antibiotics for such infections.

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CASE REPORT

Cavernous sinus syndrome: a rare presentation of nasopharyngeal carcinoma

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SUMMARY

Cavernous sinus syndrome (CSS) encompasses a range of potential pathologies that can pose significant diagnostic challenges and often necessitate extensive evaluation. Given its potential to threaten both sight and life, timely and accurate diagnosis is critical. Here in, we present a rare case of CSS secondary to nasopharyngeal carcinoma. A 72-year-old man presented with a right eye ptosis, and diplopia lasting for two weeks, preceded by recurrent episodes of epistaxis and nasal obstruction. Clinical examination revealed right-sided cranial nerve palsy affecting the oculomotor, trochlear, and abducent nerves. Neuroimaging revealed a mass in the right cavernous sinus and another mass in the left torus tubarius. Endoscopic examination revealed a mass in the posterior left nasopharynx, which was histopathologically confirmed as a non-keratinizing nasopharyngeal carcinoma. The patient was scheduled for radiotherapy and chemotherapy but ultimately declined further treatment and succumbed to his illness eight months later. Cranial nerve involvement is a common manifestation of nasopharyngeal carcinoma, often signifying advanced disease.

INTRODUCTION

Cavernous sinus syndrome is a clinical condition arising from any pathology affecting the cavernous sinus. This condition can manifest with ophthalmoplegia, double vision, proptosis, ptosis, Horner syndrome, and decreased corneal sensation due to the involvement of cranial nerves in this region. The aetiologies of CSS include tumours, infections, inflammation, vascular disorders, and trauma. While primary tumours of the cavernous sinus are rare, more commonly, tumours involve the cavernous sinus either through direct extension from adjacent head and neck tumours or via hematogenous spread from distant sites. Nasopharyngeal carcinoma (NPC) is a type of squamous cell carcinoma that arises in the head and neck region. It is particularly prevalent in certain populations, such as those in Southeast Asia, southern China, the Middle East, and North Africa. Males are at a higher risk of developing NPC than females. Risk factors for NPC include Epstein-Barr Virus (EBV) infection, tobacco smoking, consumption of salt-preserved fish and other preserved foods, as well as a family history of NPC. Radiation therapy and chemotherapy are the standard non-invasive treatments for locally advanced NPC.[1] In this report, we present a rare case of CSS secondary to nasopharyngeal carcinoma.

CASE PRESENTATION

A 72-year-old Chinese gentleman presented to the Emergency Department with a two-week history of drooping of the right upper eyelid. He also experienced binocular horizontal diplopia, particularly noticeable in primary and left gaze positions. He reported no history of trauma, headaches, vomiting, body weakness, unsteady gait, or fever. Additionally, there were no complaints of loss of appetite or significant weight loss. His medical history included chronic smoking, hypertension, diabetes mellitus, and chronic obstructive pulmonary disease, for which he was using a Salbutamol inhaler. He was poorly compliant with his oral hyperglycaemic and antihypertensive medications.

His visual acuity was 20/40 in both eyes, with unremarkable findings in both the anterior and posterior segments. Examination revealed moderate ptosis and restricted extraocular muscle movement (EOM) indicative of right oculomotor nerve involvement. The right pupil was normal in size and reactive. Other cranial nerve examinations were unremarkable. His blood pressure was 196/90 mmHg, and blood glucose was 5.2 mmol/L. He was initially diagnosed with right oculomotor nerve palsy secondary to mononeuritis multiplex and was observed for further progression. At a follow-up visit one week later, the ptosis in his right eye had worsened, and he now experienced significant diplopia in all gazes. He also developed sharp stabbing pain in the right eye, along with episodes of mild epistaxis and nasal blockage. However, there was no history of reduced smell or hearing loss. His visual acuity remained 20/40 in both eyes, and there was no relative afferent pupillary defect. The ptosis in the right eye had become severe. EOM examination revealed

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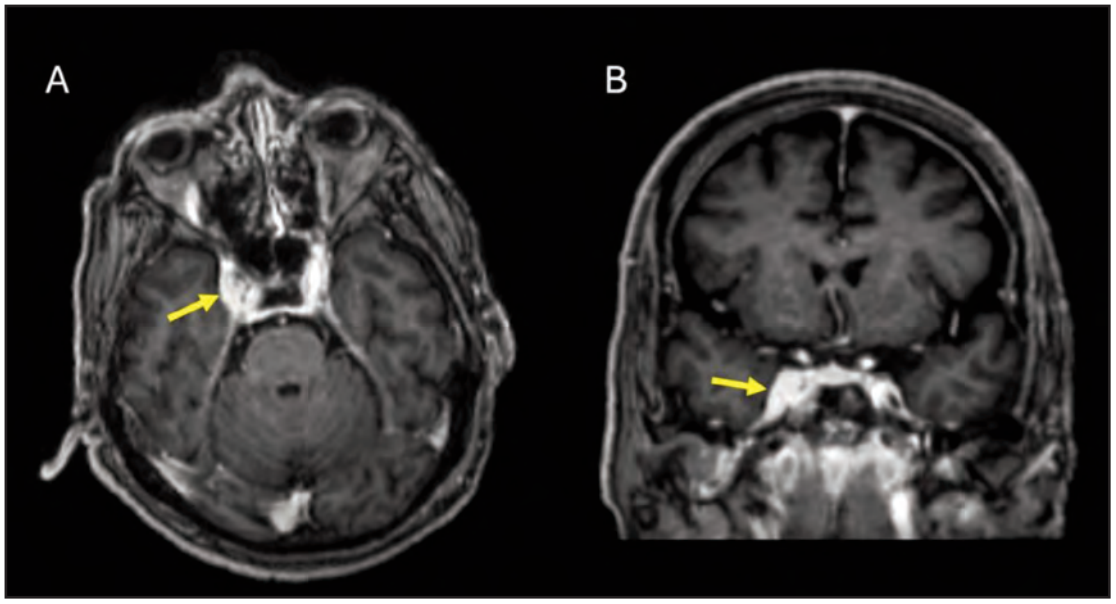

Fig. 1: MRI of the brain in T1-weighted post gadolinium in axial (a) and coronal (b) views showed a right cavernous sinus mass with enhancement post-contrast (yellow arrow)

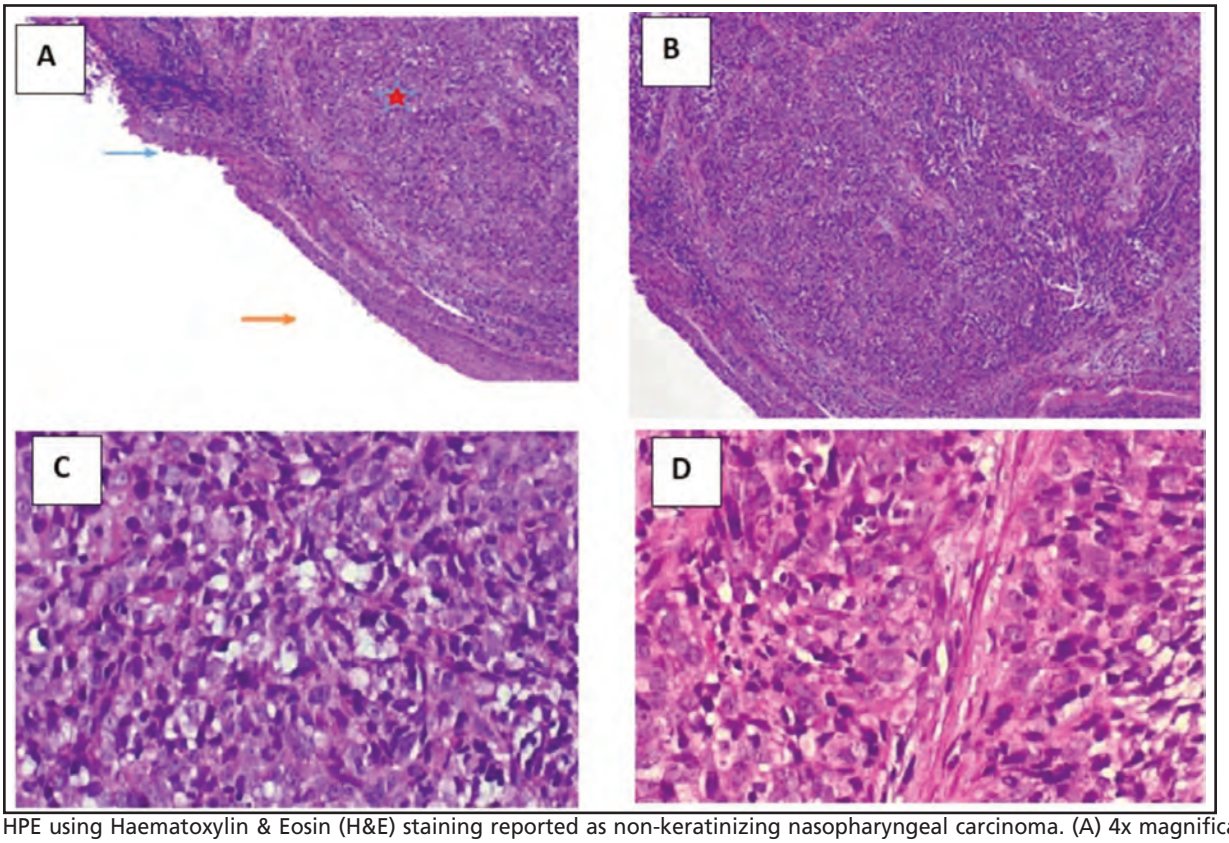

Fig. 2: HPE using Haematoxylin & Eosin (H&E) staining reported as non-keratinizing nasopharyngeal carcinoma. (A) 4x magnification, section from the fossa of Rosenmüller (FOR) partly covered by non-keratinized stratified squamous epithelium (orange arrow) and respiratory type epithelium (blue arrow), (B) exhibiting sheets of malignant tumour infiltrating the subepithelial stroma. (C) 60x magnification, the tumour cells exhibit moderate to marked nuclear pleomorphism, with irregular nuclear membranes, round to oval hyperchromatic vesiculated nuclei, prominent nucleoli, and vacuolated cytoplasm. However, keratin pearls or individual keratinization are absent. (D) 60x magnification, mitosis is seen

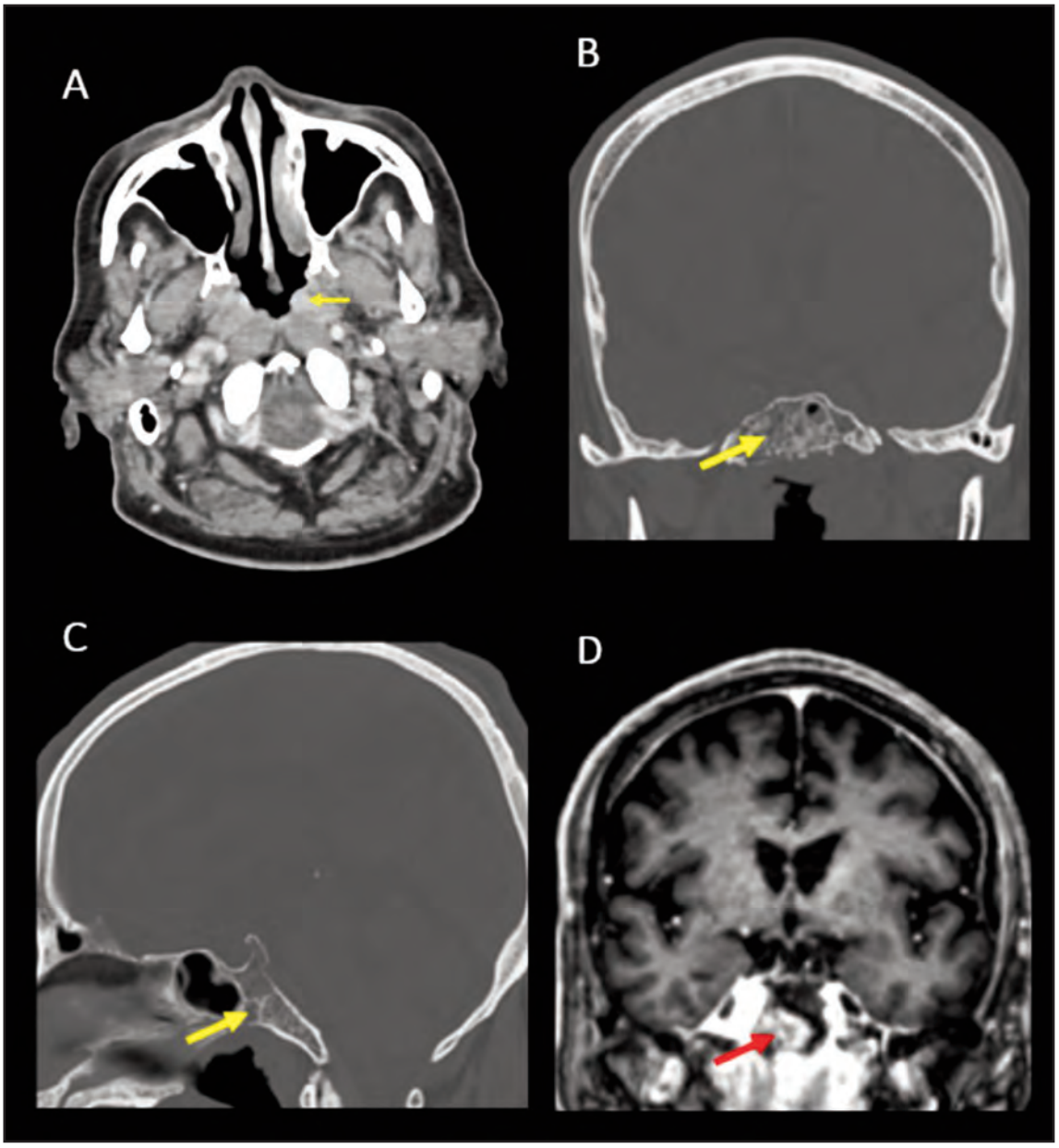

Fig. 3: Contrast-enhanced CT neck and MRI Brain. (A) A sub-centimeter enhancing mass at the left torus tubarius (yellow arrow), consistent with the primary tumour of NPC. CT Brain in bone window in coronal view (B), sagittal view (C), reveal bony erosion of the sphenoid bone (yellow arrow), sparing the clivus. (D) Contrast enhanced MRI of the brain in coronal view showed an enhancing mass (red arrow) within the bony erosion, extending towards the right cavernous sinus while sparing the left cavernous sinus

involvement of the third, fourth, and sixth cranial nerves. The right conjunctiva was white, with no dilated episcleral vessels. Intraocular pressure in the right eye was slightly elevated at 22 mmHg, while the left eye remained within normal limits at 18 mmHg. The corneal reflex in the right eye was reduced, with hypoesthesia involving the right ophthalmic and maxillary branches of the trigeminal nerve. The central nervous and cerebellar systems were normal. Submental and auricular lymph nodes were palpable, with tenderness in the right auricular lymph node. At this point, the patient was diagnosed with right CSS.

Blood investigations, including full blood count, renal profile, liver profile, erythrocyte sedimentation rate, fasting blood glucose, and C-reactive protein, were within normal limits. Contrast-enhanced computed tomography (CECT) of the brain and orbit revealed bulging of the right cavernous sinus, suggestive of a mass, which was later confirmed by magnetic resonance imaging (MRI) of the brain and orbit (Figure 1). Subsequently, the otorhinolaryngology (ORL) team performed a nasal endoscopy and biopsy. Endoscopy revealed a mass in the posterior left nasopharynx, and histopathological examination (HPE) confirmed non-keratinising nasopharyngeal carcinoma (Figure 2).

Computer tomography (CT) of the neck, thorax, and abdomen identified a primary tumour at the left torus tubarius, obliterating the fossa of Rosenmüller (Figure 3a), with bilateral cervical lymphadenopathy and no distant metastasis. During the retrospective review of the previous imaging, bony erosion with cortical break of the sphenoid bone on the right, just anterior to the clivus was revealed. There was an enhancing soft tissue component within, extending towards the right cavernous sinus, indicating the local extension of the tumour from the left nasopharynx to the right cavernous sinus, while sparing the left cavernous sinus (Figure 3b, 3c, 3d). The patient was scheduled for a series of radiotherapy and chemotherapy but ultimately refused treatment and defaulted on follow-up. He succumbed to his illness eight months after the diagnosis.

DISCUSSION

The cavernous sinus is an interconnected series of venous channels located in the middle cranial fossa on each side of the sphenoid bone. It is formed by the splitting of the dura mater at the body of the sphenoid bone. The oculomotor, trochlear, and trigeminal nerves (ophthalmic and maxillary branches) lie along the lateral walls of the cavernous sinus, while the internal carotid artery and abducent nerve run centrally within it. As a result, any pathology in this area can lead to cranial nerve palsy.

CSS is most commonly caused by tumours. In a study by Keane et al., which summarized 151 cases of CSS, 30% were due to tumours, 24% to trauma, 23% to inflammation, with the remaining cases attributed to infections, aneurysms, and other factors.[2] This finding aligns with Fernandez et al., who reported that tumours were the primary cause in 80 out of 126 cases of CSS.[3] NPC, a malignancy common in Southeast Asia, Southern China, the Middle East, and North Africa, is more prevalent in men, with a male-to-female ratio of 2 to 3:1.[1] In Malaysia, NPC is the most common head and neck cancer among men, following lung cancer.[4] Risk factors for NPC include EBV infection, consumption of salt-preserved fish and other preserved foods, tobacco smoking, and alcohol consumption, many of which were present in our patient.

NPC arises from the epithelium of the nasopharynx and spreads via local or perineural spread, hematogenous and lymphatic routes. For local spread, the tumour can invade surrounding structures and tissues. Since the nasopharynx is near the cavernous sinus, the tumour may invade posteriorly or laterally through the pharyngeal wall, leading to encroachment on the cavernous sinus. Additionally, NPC can cause perineural spread by infiltrating the maxillary (V2) and mandibular (V3) nerve branches, which have an anatomical relationship with the nasopharynx. The cancer cells may then track along the course of the maxillary nerve towards the cavernous sinus, potentially affecting other cranial nerves within the cavernous sinus. According to Chong et al., NPC can infiltrate the pterygopalatine fossa and trigeminal nerve, leading to subsequent spread to the cavernous sinus. In their study, this route was observed in 4 out of 17 patients with pterygopalatine fossa infiltration, where contrast enhancement of the maxillary nerve resulted in infraorbital neuropathy.[5] Haematogenous spread occurs through invasion of the skull base marrow and the venous plexus of the parapharyngeal region, while lymphatic spread is facilitated by the rich lymphatic tissue in the posterior nasopharynx. NPC can infiltrate the intracranial space through the skull base, particularly via the foramen ovale and lacerum, entering the cavernous sinus and presenting as CSS.

Distant metastasis commonly involves the liver, bone, and lungs. Patients with intracranial involvement, such as orbit and cranial nerve infiltration, typically have a poorer prognosis, as observed in our patient, who had a survival rate of only eight months post-diagnosis. Aziz et al. found that the common presentations of NPC include a neck mass (70.9%), unilateral nasal obstruction (33.3%), and epistaxis (29.2%). Less common symptoms (20.9%) include headaches, diplopia, and facial paraesthesia.[6] Ophthalmic manifestations as the initial presentation of NPC are rare, occurring in about 5.4% of cases, with a 1.8% risk of blindness.[7] The presence of cranial nerve involvement in NPC indicates advanced disease. The trigeminal (12.5%) and abducent (10.5%) nerves are most commonly affected.[8,9] Our patient's initial presentation with 3rd cranial nerve palsy, initially diagnosed as right oculomotor nerve palsy secondary to mononeuritis multiplex, was unusual and evolved into multiple cranial nerve palsies within a week.

Radiological imaging is crucial in identifying potential causes of CSS, including mass lesions, infections, or inflammation. However, imaging findings alone are often inconclusive, necessitating clinical correlation to establish an accurate diagnosis. In cases of cavernous sinus metastasis, CECT may reveal an enhancing mass within the cavernous sinus and sometimes associated with bony erosion. Conversely, cavernous sinus thrombosis, a life-threatening condition that must be excluded, is characterized by a filling defect in the cavernous sinus, manifesting as heterogeneous enhancement and dilation of the superior ophthalmic vein on CECT. However, MRI is superior for diagnosing NPC compared with CECT because it provides excellent contrast resolution for soft tissues allowing better differentiation between normal anatomical structure and pathological lesion.

NPC is typically diagnosed via biopsy obtained through nasopharyngeal endoscopy. MRI is the preferred imaging modality for diagnosing and staging NPC, particularly in detecting subclinical masses that may be missed by endoscopic biopsy. However, CT and PET scans remain valuable for radiotherapy planning, staging, and detecting distant metastasis. In our case, the diagnosis of NPC was confirmed by nasopharyngeal biopsy, with contrast-enhanced CT (CECT) of the neck, thorax, abdomen, and pelvis performed for staging.

Management of CSS depends on the underlying aetiology. NPC is highly sensitive to radiotherapy, making it the cornerstone of treatment. Chemotherapy is indicated for locally advanced regional disease and distant metastases. Surgery is typically reserved as a salvage option, particularly in cases of local recurrence, radiation-resistant cancer, or for lymph node removal following chemoradiation. Our patient was offered radiotherapy and chemotherapy but ultimately refused treatment.

The overall 5-year survival rate for NPC patients who seek treatment ranges from 32% to 62%.[9] Among these, the survival rate for those treated with radiotherapy alone is 22.5%, while those treated with chemoradiotherapy combined with adjuvant chemotherapy have a survival rate of 61.4%. A study by Siti-Azrin et al. identified poor prognostic factors such as advance age, stage 4 disease, and the presence of metastases. NPC with cranial nerve involvement is associated with a poorer prognosis, with a 1.74-fold higher risk of death.[10]

CONCLUSION

Clinical symptoms of CSS can be misleading, masking an underlying lethal malignancy such as advanced NPC. Given NPC's aggressive nature and rapid progression, prompt diagnosis is vital for initiating timely treatment and improving outcomes. Intracranial involvement often carries a poor prognosis, underscoring the need for vigilant assessment and swift intervention.

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Tasteless thalamus: an isolated case of dysgeusia post thalamic stroke

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SUMMARY

Dysgeusia, an altered or unpleasant taste sensation, is a rare but distressing neurological symptom often overlooked in clinical practice. We present a 33-year-old healthy gentleman, who presented with left sided limb heaviness, slurred speech and facial asymmetry upon awakening. Initial assessment revealed right sided third-cranial nerve palsy, contralateral mild motor and sensory impairment with appendicular ataxia. Imaging showed a right thalamic infarct without large vessel occlusion. Notably, dysgeusia was not reported on presentation but was retrospectively identified three months later during follow-up, when the patient recalled altered taste sensation since the index event. His blood investigations including young stroke workup were normal. Taste perception involves complex neural pathways which includes the thalamus and cortices. Dysgeusia is an underrecognized sequalae of thalamic strokes due to its subtle presentation which is often overshadowed by more troubling symptoms. Our case supports the association between thalamic infarct and gustatory dysfunction with MRI finding correlating with the deficits. Our case highlights the need for greater awareness among clinicians regarding rare stroke manifestations and emphasizes the value of comprehensive history taking and neurological examination.

INTRODUCTION

Dysgeusia refers to a disorder characterized by a persistent, unpleasant, abnormal, or altered taste sensation.[1] Due to its rarity, it is often overlooked by healthcare professionals which can be distressing for the patient. Up to 30% of patients in an observational study were found to experience dysgeusia post stroke. However, it was not reported as a singular symptom post stroke but rather grouped with other neurological deficits. Multiple areas of the central nervous system can be implicated in impaired taste perception, including cerebral cortical, subcortical, thalamic, or brainstem regions.[2] The most frequent infarct location resulting in dysgeusia is localised in the frontal lobe (52%), followed by the thalamus (6%). Lesions at these areas can result in a range of taste disturbances including ageusia, hypoageusia or dysgeusia.[3] Here, we present an intriguing case of a patient who developed dysgeusia following an ischemic stroke, a symptom that was initially overlooked during the acute phase of the event.

CASE PRESENTATION

A 33-year-old male, an active smoker with no known comorbidities, presented with left-sided upper and lower limb heaviness upon waking, associated with facial asymmetry and slurred speech. He reported no other neurological deficit at this time. He presented to the Emergency Department 12-hours later, where he was noted to have right-sided-third cranial nerve palsy, contralateral mild motor weakness, sensory impairment and appendicular ataxia. Cranial nerves that influence taste sensation including facial nerves, glossopharyngeal nerves, vagus nerves and olfactory nerves were intact on examination.

His National Institutes of Health Stroke Scale (NIHSS) score was 3 points, reflecting ataxia involving the left side of the body and moderate loss of sensation. A non-contrast CT brain revealed an established infarct in the right thalamus and the CT angiography did not demonstrate large vessels occlusion. At this point, he did not report dysgeusia, however, this aspect of his medical history was not specifically explored by the treating medical team. He was admitted to the ward, where symptoms significantly improved with intensive rehabilitation. He was discharged ambulating with minimal residual diplopia and was able to return to work one month later.

During his clinic review 3 months after index event, the patient reported an altered sense of taste affecting both sides of his tongue. Upon further exploration of his presenting history, he recalled that the dysgeusia had been present from the onset of the stroke. Objective testing with sweet, sour and bitter food revealed that patient was unable to distinguish them, though he could still differentiate hot and cold sensations. No new or residual neurological deficits were noted on assessment. He had not been prescribed medications commonly known to alter taste, such as angiotensin-converting enzyme inhibitors, antibiotics or antihistamines.

His blood investigations were within normal limits, including haemoglobin, calcium, thyroid function tests, homocysteine, connective tissue screening, antiphospholipid syndrome screening, tumour markers, and lactate dehydrogenase. The patient reported some ongoing improvement in his sense of taste during the 6-month review and will continue to be followed up. An MRI was performed 8 months after index event (Figure 1 & 2).

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Table I: Causes of Dysguesia

Division	Causes
Local Cause Damage to the nerves of taste sensation	 Direct Trauma (burns, laceration, surgery) Infection such as Ramsey Hunt or Varicella Zoster Infection or labyrinthitis Mononeuritis multiplex due to DM, Infection such as HIV, Lyme disease, Autoimmune condition such as Polyarteritis nodosa, Eosinophilic granulomatosis polyangiitis Neoplasm causing nerve impingement Radiation therapy
Dietary Deficiencies	Zinc deficiency
Systemic Conditions	Pernicious anemia Crohn disease Hypothyroidism Amyloidosis
Neoplasm	Sarcoidosis Cerebellopontine angle tumour (meningioma or neurinoma) Base of skull neoplasm (chondromas, chondrosarcomas) Head and neck cancers (nasopharyngeal cancer, lymphoma)
Medication Antibiotics Neurology medication Cardiovascular medication Antipsychotics	 Ampicillin, macrolides, quinolones Antiparkinsonism, CNS stimulants, migraine medication Antihypertensive medication, diuretics, antiarrhythmics Tricyclic antidepressants
Aging	

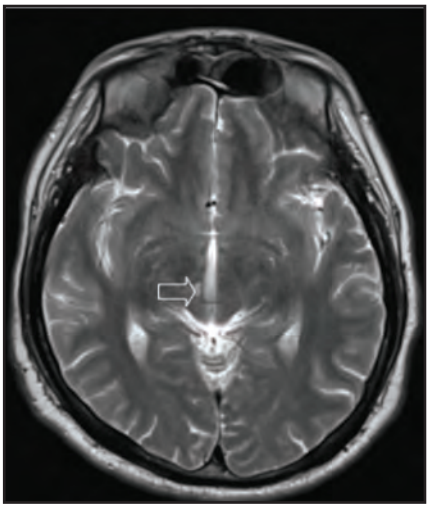

Fig. 1: T2-weighted MRI of the brain demonstrating hyperintensity of the right thalamus (white arrow) suggestive of a chronic infarct

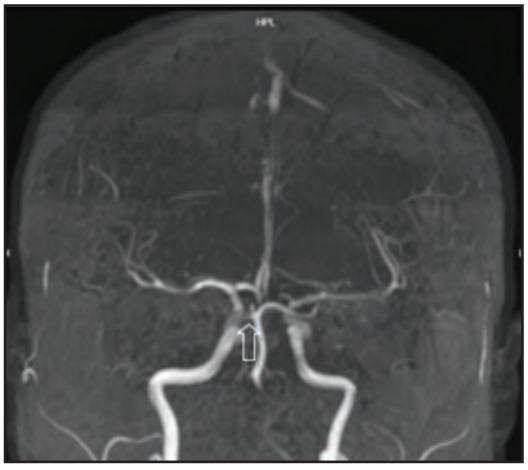

Fig. 2: MRA time-of-flight (TOF) demonstrating flow void (white arrow) over right proximal (P1 segment) Posterior Cerebral Artery suggestive of a focal occlusion

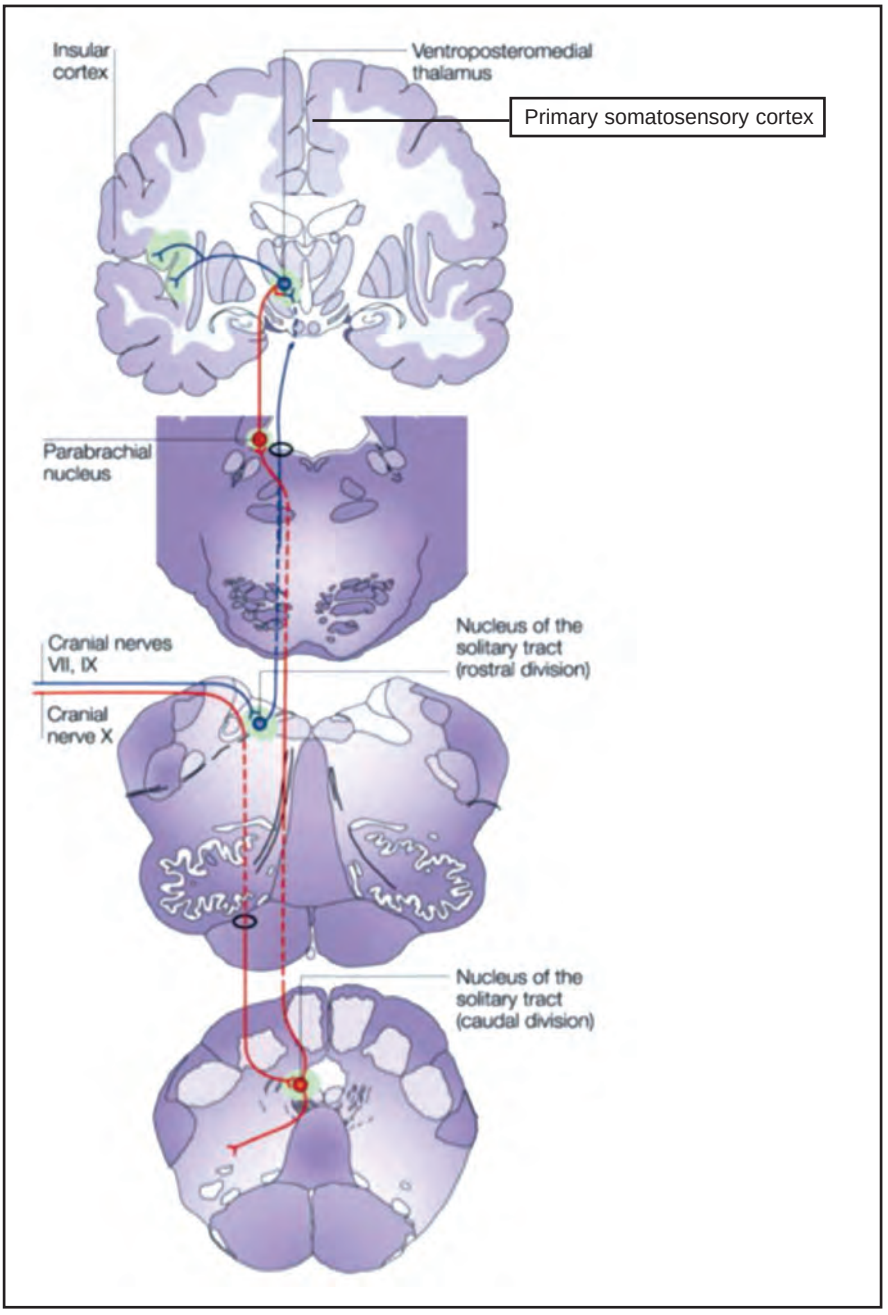

Fig. 3: Anatomical overview of the central taste pathways
(Adapted from (Oliveira-Maia AJ, Roberts CD, Simon SA, and Nicolelis MA. Gustatory and reward brain circuits in the control of food intake. Advances and technical standards in neurosurgery 2011; 36:31-59) with permission from the publisher Springer Nature)

DISCUSSION

We present a young gentleman with symptoms of thalamic and brainstem stroke, characterized by persistent dysgeusia despite resolution of other symptoms. Taste perception is a complex process involving various types of sensory input and multisensory integration, where the brain processes and integrates the sensory inputs from different modalities to form a unified perception and appropriate response.[4]

The perception of taste is influenced by multiple senses, including visual, smell, and touch. The involvement of both ipsilateral and decussated pathways, in activating bilateral cerebral cortex is well documented.[5] Several case reports have documented dysgeusia secondary to infarcts in specific locations, namely pons, cortex and thalamic nuclei, with a particular focus on thalamic infarcts as a cause of bilateral hypogeusia.[6] A Korean case report details an acute left unilateral thalamic infarction leading to bilateral loss of taste. However, the PET scan revealed only a unilateral left insular hypometabolism instead of a bilateral cortical involvement, even though the dysgeusia was noticed on both sides of the tongue. It was postulated that the smaller area of infarct and the possibility of left hemisphere being dominant in taste perception could explain these findings.[7]

In our case, the patient had an infarct involving the right thalamus and right midbrain which likely resulted in taste alteration. Tastant signals from cranial nerves VII, IX, and X reach the rostral nucleus tractus solitarius (rNTS) in the medulla, and are then relayed via the central tegmental tract to the ventroposterior medial nucleus of the thalamus (VPMpc), which then projects to the primary gustatory cortex. This cortex connects to somatosensory regions corresponding to the face and oral cavity and sends signals to the amygdala, hypothalamus and midbrain. Additionally, it projects to the orbitofrontal cortex (secondary taste cortex), where gustatory and olfactory inputs influence flavour perception and satiety. Cortical taste areas also provide feedback to the rNTS and PBN for top-down modulation of taste processing (Figure 3).[8]

Spontaneous recovery of symptoms following the index event for all causes of dysgeusia is documented to be progressive, with the earliest improvement typically seen after 6 months.[6] This is similar to our case as the patient notices improvement in the taste sensation 6 months post index event. Table I shows the list the common causes associated with dysgeusia. However, our patient belonged to a young age group, had no associated comorbidities and was not on any medication leading us to consider the possibility of the aetiology being due to the primary infarct determining the recovery period. Notably, our patient only reported symptoms three months after the primary event which is not surprising as dysgeusia is often overlooked. During follow-up, other potential causes of dysgeusia were thoroughly investigated but not identified.

Currently, there are no targeted treatments for this disabling symptom although the gustatory reward pathway has been well documented.[9] Among the mixed evidence exist on treatments, the use of carbamazepine in a study for stroke-related dysgeusia reports improvement in half of the patients with dysgeusia, however further trials are needed to substantiate its effectiveness.[10]

Our case highlights the rare manifestation of significant dysgeusia resulting from a thalamic infarction is a young, healthy individual. It emphasizes the importance of a thorough history during the initial presentation and the need for a focused, goal-directed rehabilitation program tailored for dysgeusia, as well as further research into targeted pharmacotherapy for this debilitating yet overlooked symptom.

CONSENT

The consent for publication and the usage of MRI images has been obtained from the patient.

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Cholesteatoma co-existing with schwannoma

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SUMMARY

Schwannoma is a benign, encapsulated tumor of Schwann cell origin. Approximately 25-45% of all Schwannomas occur in the head and neck. Still, schwannomas of the external auditory canal are a rare finding, and less than 10 cases are reported in literature worldwide. This report presents a rare case of a 55-year-old female with concurrent cholesteatoma and schwannoma in the external auditory canal, a combination seldom reported. Initially diagnosed as cholesteatoma based on clinical findings and imaging, the patient underwent modified radical mastoidectomy. Histopathology revealed the unexpected coexistence of schwannoma and cholesteatoma. Complete surgical excision ensured symptom resolution, with no recurrence over two years of follow-up. This case highlights the importance of histopathological evaluation in ear pathologies to uncover rare coexisting conditions, emphasizing accurate diagnosis and tailored management to optimize patient outcomes in clinical otology. This case report further emphasizes the distinction between cholesteatoma and schwannoma, as demonstrated through imaging characteristics and histopathological findings.

INTRODUCTION

A solitary schwannoma also referred to as a neurinoma or neurilemmoma, is characterized as a benign tumor encapsulated well, exhibiting slow growth, and often associated with pain.[1] These tumors originate from Schwann cells of nerves, explaining their diverse occurrence across the body, as Schwann cells are ubiquitous in peripheral nerves.[1,5] Notably, certain nerves, such as the optic and olfactory nerves, lack the Schwann cell coating, making them exempt from schwannoma development.[1,2] Head and neck regions harbor approximately 25-45% of all schwannomas,[1,4,7] with the cranial nerve VIII representing the most frequent intracranial site and the lateral aspects of the neck being the most common extracranial location.[1,5] According to Morais et al, the cranial nerve VIII in the head is the most afflicted, followed by the sensory nerves in order of frequency, as the motor nerves are only very seldom impacted.[1] This paper presents the incidental finding of schwannoma of the external auditory canal, evidenced by histopathological examination post-surgery for a patient who was clinically being treated as cholesteatoma and outcome based on our therapeutic management. It also emphasizes the distinction between cholesteatoma and schwannoma, as demonstrated through imaging characteristics and histopathological findings.

CASE PRESENTATION

A 55-year-old female, with 3 weeks history of chronic right otorrhea, reduced hearing, and otalgia, been treated by a General Practitioner multiple times with antibiotic ear drops however the pain persists and hence was referred to our centre for further management. Clinically patient appears well, not septic looking, and hemodynamically stable with intact facial nerve function. Further, otoendoscopy revealed a friable polyp totally occluding the right external auditory canal (EAC) (Figure 1). On palpation, the base of the polyp seems to arise from the floor of the EAC. A punch biopsy was done which revealed inflamed polypoid granulation tissue with acute on chronic inflammation. Computed tomography (CT) mastoid performed, showed large soft tissue density filling the right EAC and middle ear with erosion of scutum (Figure 2) erosion of the posterior EAC wall with extension into the mastoid air cells (Figure 3). The absence of abnormalities in the facial nerve bony canal reduces the likelihood of a facial nerve schwannoma. Pure tone audiometry done revealed moderate to severe hearing loss over right ear whereas left ear mild to moderate hearing loss.

Pre-operative diagnosis of cholesteatoma made based on clinical findings and Imaging done. The patient was counselled for surgery and underwent a right-modified radical mastoidectomy. Intra-operatively, the polyp was pedunculated at the anterior EAC wall and was excised fully with its base and sent for Histopathological examination. Further exploration revealed a large cholesteatoma sac medial to the excised polyp. The sac extended through an erosion of the posterior EAC wall extending into the mastoid and causing bony dehiscence over the sigmoid sinus. The cholesteatoma also extended medially onto the middle ear with erosion of the malleus. The stapes supra structure was preserved and the temporalis fascia was laid over this. Post-operative recovery was uneventful, with no cranial nerve palsy and hearing been improved.

The patient is currently about 2 years post-surgery, and there has been no recurrence of the schwannoma nor cholesteatoma based on clinical and otoendoscopy findings. From a histological perspective, the tumor is comprised of long, spindle-shaped cells, commonly arranged in a palisade pattern around their elongated nuclei. Antoni type A (Verocay Body) refers to areas with dense cell concentrations, while Antoni type B refers to areas with loose, asymmetrically placed cells. A positive S-100 protein indicates the origin of Schwann cells.[6,7]

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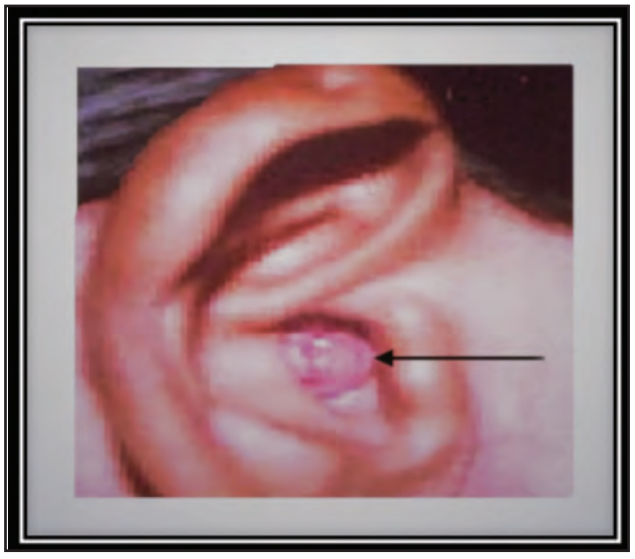

Fig. 1: Direct visualization of aural polyp over the EAC

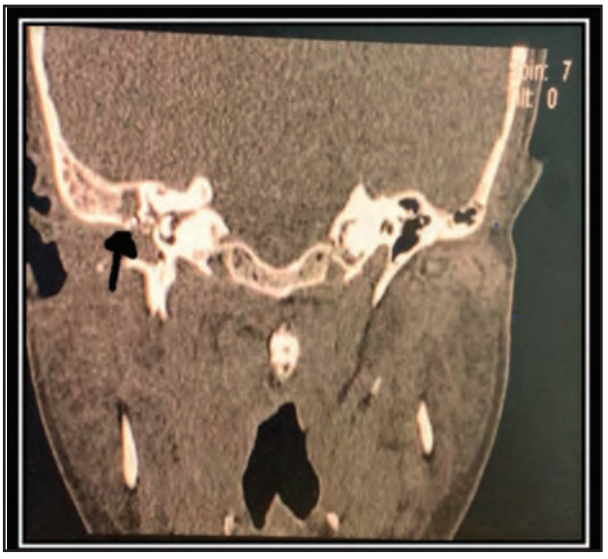

Fig. 2: CT scan without contrast Mastoid Coronal view showing scutum erosion (black arrow)

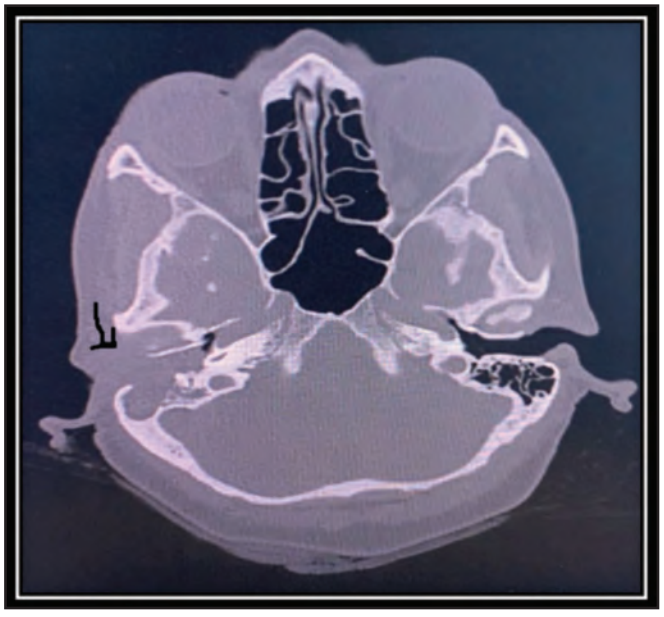

Fig. 3: CT scan without contrast Mastoid Axial view showing middle ear opacity over the right side with erosion of posterior EAC wall with extension into mastoid air cells (black arrow)

The recommended treatment for schwannoma is complete surgical excision. Although the diagnosis for the patient was confirmed post-operatively, she did not require further surgery because the lesion was prudently completely excised.

DISCUSSION

Solitary schwannomas are benign tumors that were first described in 1908 by Verocay, who named them neurinomas. In 1974, Batsakis introduced the name schwannoma. These tumors have been referred to by various terms, including neurinoma, neurilemmoma, mioschwannoma, and schwannoglioma.[1] The occurrence of schwannoma and cholesteatoma presenting concurrently is exceedingly rare. Schwannoma may arise alone or in conjunction with type 2 neurofibromatosis (NF2). It is also possible to see many schwannomas, particularly when NF2 or schwannomatosis is present.[3] Most extracranial schwannomas in the head and neck originate from branches that innervate the muscles or skin of the brachial or cervical plexus.[3,4,6]

The auriculotemporal nerve (V), the nervus intermedius of Wrisberg (VII b), and the auricular branch of the vagus nerve (X) make up the complex sensory innervation of the external auditory canal.[3,5,6,8,9] As a result of this, it can be tricky to determine the nerve that gives rise to an external auditory canal schwannoma, as in this case.[3,8]

The primary symptom of schwannoma is typically a slow-growing, painless mass. It is uncommon for schwannomas to cause neurogenic symptoms like pain or paresthesia, or motor issues, particularly when the tumor affects a motor nerve.[3] Managing this combination of pathologies necessitates careful consideration of the risks and benefits associated with various treatment options. It is uncertain whether the reduced hearing and otalgia experienced by our patient were linked to the schwannoma or chronic inflammation in the middle ear, as both conditions can manifest with these same symptoms. Presently, the preferred treatment for chronic middle ear inflammation with cholesteatoma involves a canal wall-down procedure with the complete removal of middle ear pathologies. It is crucial to ensure thorough removal of the cholesteatoma matrix.[1]

The concurrent presentation of cholesteatoma and schwannoma posed a diagnostic and therapeutic challenge. Our patient was initially diagnosed with cholesteatoma along with hearing impairment. The symptoms of the schwannoma were obscured by the diffuse symptoms of the cholesteatoma. The hearing impairment was initially attributed to the prolonged symptoms of the cholesteatoma. A routine preoperative CT scan confirmed a large soft tissue

Table I: Difference of external ear schwannoma and cholesteatoma

Differentiation Between Schwannoma of the External Ear and Cholesteatoma

Characteristic	Schwannoma (External Ear)	Cholesteatoma
Definition	A benign tumor arising from Schwann cells of the nerve sheath.	A collection of keratinizing squamous epithelium in the middle ear or external ear.
Etiology	Arises from nerves (e.g., auriculotemporal or great auricular nerve).	Chronic ear infections or eustachian tube dysfunction leading to retraction pockets.
Location	Typically occurs in the external auditory canal or adjacent areas.	Commonly found in the middle ear or mastoid; rarely extends to the external auditory canal.
Growth Pattern	Slow-growing, well-encapsulated mass.	Expansive and erosive growth that destroys adjacent bone.
Symptoms	- Painless mass in the external auditory canal.	- Otorrhea (foul-smelling discharge), hearing loss, ear pain.
	- Hearing loss or tinnitus (rare).	- Recurrent infections or fullness in the ear.
Appearance on Examination	Smooth, firm, and well-circumscribed lesion in the canal.	Whitish, irregular debris with granulation or bony erosion.
Imaging Findings	- Well-defined mass; no bony erosion unless large.	- Bony destruction on CT; hyperintense lesion on T2-weighted MRI with peripheral enhancement.
	- No keratin or soft tissue opacity.	- Soft tissue opacity and signs of infection or granulation tissue.
Histopathology	- Antoni A (cellular) and Antoni B (myxoid) regions.	- Keratinizing squamous epithelium with cholesterol crystals and inflammation.
	- Positive for S-100 protein.	- No S-100 positivity.
Management	Surgical excision with preservation of nerve function.	Surgical removal (e.g., tympanomastoidectomy) to prevent recurrence and complications.
Prognosis	Excellent; recurrence is rare.	Variable; recurrence or complications (e.g., intracranial spread) possible if not treated.

Table II: MRI findings to differentiate external ear schwannoma and cholesteatoma

Characteristic	Cholesteatoma	Schwannoma (External Ear)
Signal Intensity on T1	- Typically hypointense (low signal) due to keratin and debris.	- Isointense or slightly hypointense relative to muscle.
Signal Intensity on T2	- Hyperintense (bright) due to fluid content in keratin debris.	- Hyperintense (bright), especially in Antoni B regions, due to the myxoid stroma.
Contrast Enhancement	- Minimal to no enhancement after gadolinium contrast, as cholesteatoma lacks vascularity.	- Strong, uniform, or heterogeneous enhancement post-gadolinium due to vascularized Schwann cells.
Diffusion-Weighted Imaging (DWI)	- Hyperintense on non-echo-planar DWI due to restricted diffusion of keratin debris.	- Typically no restricted diffusion or only mild hyperintensity due to cellularity in Antoni A regions.
Location and Pattern	- Irregular, non-encapsulated lesion, often associated with bone erosion in middle ear or canal.	- Well-circumscribed, encapsulated lesion without bone destruction unless very large.
Bone Involvement	- Frequently involves bone erosion or destruction visible on adjacent CT imaging.	- Rarely causes bone erosion unless it reaches a significant size.

density lesion in the right external and middle ear, along with suspicious erosion of the scutum due to extensive cholesteatoma. MRI examination is not typically part of the routine evaluation for cholesteatoma cases. The definitive diagnosis was established postoperatively based on histopathological findings revealing a benign spindle cell neoplasm suggestive of schwannoma.[1]

Schwannomas are firm, smooth-surfaced tumors covered by normal skin. Originating from nerve sheaths, they are encased in a perineurium capsule and grow by expanding, pushing nerve fibers toward the periphery. Due to their similarities with other soft tissue tumors, the differential diagnosis includes conditions such as sebaceous adenoma, eosinophilic granuloma, fibroma, chondroma, and leiomyoma.[3] From a histological perspective, the tumor is comprised of long, spindle-shaped cells, commonly arranged in a palisade pattern around their elongated nuclei. Antoni type A (Verocay Body) refers to areas with dense cell concentrations, while Antoni type B refers to areas with loose, asymmetrically placed cells. A positive S-100 protein indicates the origin of Schwann cells.[6,7] The summarized tables detailing the presentations and MRI findings of external ear schwannomas and cholesteatomas as below (Table I and Table II).[10]

After thoroughly analyzing the treatment options in the case presented, we discussed the available choices with the patient and their family members upon receiving the histopathological specimen suggestive of schwannoma post-surgery. The choices of treatment that were explained to the patient and family members after receiving the histopathology were conservative treatment (serial monitoring by otoscopic and symptoms as intraoperatively the lesion has been completely excised), or performing MRI to assess further and keep in view for surgical excision if indicated, however patient and family members keen for conservative management by serial monitoring. From a socioeconomic perspective, since the family provided financial support for the patient's treatment, and clinical outcomes showed improved hearing, the family preferred the conservative treatment approach.

CONCLUSION

This case underscores the rare coexistence of schwannoma and cholesteatoma in the external auditory canal, initially misdiagnosed as isolated cholesteatoma. Histopathological examination was crucial for accurate diagnosis, preventing misidentification as granulation tissue. Given its rarity, our findings provide valuable insight, emphasizing the importance of thorough surgical assessment and routine histopathological evaluation and distinguish characteristics of cholesteatoma and schwannoma accordingly.

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Characterizing Dementia Types through F-18 FDG PET-CT: a Case Series from a Tertiary Institution

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SUMMARY

Dementia, a major neurodegenerative disorder, presents a diagnostic challenge due to its gradual onset and overlapping symptoms among various types. This case series highlights the role of F-18 FDG PET imaging in distinguishing between different dementia types by illustrating their specific metabolic patterns. We evaluated four patients with suspected dementia using F-18 FDG PET-CT at our center. Each patient underwent F-18 FDG PET-CT imaging following a standardized preparation protocol, and images were analyzed qualitatively and quantitatively using Cortex ID software for Z-score and 3D-SSP assessments. F-18 FDG PET imaging revealed specific hypometabolic patterns in different types of dementia, namely Alzheimer's disease, frontotemporal dementia, corticobasal syndrome and vascular dementia, aiding in accurate diagnosis and differentiation. The integration of metabolic imaging with anatomical correlation and statistical mapping enhances diagnostic precision and supports tailored therapeutic strategies. F-18 FDG PET is a valuable diagnostic tool for identifying dementia types through detailed metabolic analysis. It facilitates early and precise diagnosis, guiding effective treatment planning and improving disease management.

INTRODUCTION

Dementia is a primary neurodegenerative disorder caused by the progressive deterioration of neuronal structure and interconnectivity, manifesting as a gradual decline in higher cognitive functions and memory loss, which leads to occupational and societal dysfunction.[1] The most common type of dementia is Alzheimer's disease (AD), followed by vascular dementia, dementia with Lewy bodies (DLB), and frontotemporal dementia (FTD).[1] The assessment of a patient presenting with cognitive impairment entails a comprehensive medical history, detailed physical and neurological examinations, standardized cognitive testing, and targeted laboratory investigations to identify potential underlying etiologies, such as hypothyroidism, major depressive disorder, or the use of pharmacological agents, including anticholinergics or benzodiazepines, which may contribute to cognitive dysfunction. Anatomical imaging with computed tomography (CT) and magnetic resonance imaging (MRI) has also become standard practice in identifying structural, inflammatory, demyelinating, or vascular etiologies.[2] However, neuropathological confirmation remains the definitive standard for diagnosing dementia.[3]

Dementia presents a diagnostic challenge due to its gradual onset and significant symptom overlap among various types. While there is some commonality among dementia syndromes, each differs in clinical progression, complications, and management. Accurate early diagnosis guides timely interventions and therapeutic strategies, including non-pharmacologic treatments. For instance, cholinesterase inhibitors and memantine are effective for AD but not for FTD.[4] Early diagnosis also aids families in understanding the likely course of the disease and may help reduce overall healthcare costs. The most commonly used positron emission tomography (PET) tracer for dementia is Fluorine-18 fluorodeoxyglucose (F-18 FDG) PET, in which the uptake reflects not only local neuronal and synaptic activity but also remote effects, such as deactivation of projection neurons without direct local neuronal damage. A well-known example of this phenomenon is crossed cerebellar diaschisis. This case series demonstrates the utility of F-18 FDG PET in distinguishing between four different types of dementia commonly evaluated at our center.

CASE PRESENTATION

Patient preparation and study procedures followed the European Association of Nuclear Medicine (EANM) procedure guidelines for brain PET imaging using F-18 FDG.[5] Patients were required to fast for 4 to 6 hours and to avoid caffeine, alcohol, or drugs that may affect cerebral glucose metabolism. Blood glucose levels had to be below 10 mmol/L before patients were injected with 0.1 mCi/kg or 3.7 MBq/kg of F-18 FDG, as elevated glucose levels may interfere with brain FDG uptake. Post-injection, the patients were placed in a quiet, dimly lit room, advised not to vocalize, and instructed to keep their eyes open. Image acquisition was performed using a dedicated PET-CT scanner, the General Electric (GE) Discovery MI Digital Ready. Imaging began 30 minutes post-injection, starting with a CT scan of the head (120kV, 10mAs), followed by a PET scan of the same bed position. The CT data was used for morphological correlation and attenuation correction. The reconstructed multiplanar images in axial, coronal, and sagittal views (CT, PET, and fused PET-CT) were then reviewed on a dedicated GE Advantage Workstation (ADW 4.7).

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Image interpretation was conducted both qualitatively and semiquantitatively using Cortex ID software, which includes the creation of Z-score and 3D-SSP images to assess areas of reduced tracer uptake or hypometabolism. The Z-score represents the standard deviation from a normal age-matched database of patients. In normal subjects, FDG uptake is prominent in the caudate nucleus, putamen, thalamus, and cortical gray matter (Figure 1). The diagnosis of dementias and their types are based on specific spatial patterns, severity, and extent of reduced FDG uptake, which can be reproducibly visualized using statistical mapping technology. The different patterns of FDG uptake in the brain were analyzed alongside MRI findings and categorized based on cortical hypometabolic involvement.

Case 1: Alzheimer's Disease
A 40-year-old woman presented with a 2-year history of forgetfulness and a strong family history of young-onset dementia. She had no history of diabetes, hypertension, or any other comorbidities, nor any past surgical history or prior medication. There was no history of headache, fever, trauma, loss of consciousness, dizziness, or weight loss. The patient experienced low mood and declined in activities of daily living. General examination was unremarkable. Her Mini-Mental State Examination (MMSE) score was 16/30. All baseline laboratory investigations were insignificant, and CSF examination was normal. MRI showed progressive generalized cerebral volume loss with focal predilection for the bilateral parietotemporal and precuneus regions. Blood sugar level at the time of F-18 FDG injection was 4.3mmo/L. F-18 FDG PET scan demonstrated a large area of hypometabolism in the bilateral frontotemporoparietal cortices, bilateral precuneus, and posterior cingulate cortices. These findings were consistent with Alzheimer's dementia (Figure 2A).

Case 2: Frontotemporal dementia
A 58-year-old woman presented with progressive dysphasia, bulbar palsy, and right-sided body weakness, which later progressed to the left side over one year, accompanied by progressive cognitive decline. No history of behavioural changes or vulgarity of speech.

The patient was neither a smoker nor an alcoholic, and there was no history of trauma or fever. Her MMSE score was 21/30. MRI of the brain showed non-specific T2/FLAIR hyperintense foci in the juxtacortical left parieto-occipital region, indicative of small vessel disease. Blood sugar level at the time of F-18 FDG injection was 4.9mmo/L. F-18 FDG PET scan demonstrated diffuse FDG hypometabolism in the bilateral frontotemporal and parietal cortices. These findings were consistent with frontotemporal dementia (FTD) or FTD-Motor neuron disease (Figure 2B).

Case 3: Corticobasal syndrome-Corticobasal degeneration
A 54-year-old gentleman presented with a one-year history of memory decline, visual hallucinations, Parkinsonian features of bradykinesia, childish behaviour, and disinhibition. He also reported to have slow volume speech. His MMSE score was 18/30. T2/FLAIR-weighted MRI of the brain showed an old lacunar infarct in the genu of the left internal capsule, with the status of ventricles and subarachnoid spaces consistent with age. Blood sugar level at the time of F-18 FDG injection was 6.0mmo/L. F-18 FDG PET demonstrated asymmetrical FDG hypometabolism predominantly on the left side, affecting the bilateral frontal, parietal, temporal, and posterior cingulate cortices, as well as the thalamus and midbrain. There was also the presence of right cerebellar diaschisis. These findings were consistent with corticobasal syndrome-corticobasal degeneration type (Figure 3A).

Case 4: Vascular dementia
A 54-year-old gentleman presented with short-term memory loss and a sudden onset of left-sided visual hallucinations over the past 6 months. There has been a progressive 'step-wise' deterioration in memory with MMSE score, dropping from 26 to 22 within 6 months. An MRI of the brain using T2/FLAIR weighting revealed multifocal old infarcts with a hemorrhagic component and severe small vessel disease, indicative of vascular dementia. Blood sugar level at the time of F-18 FDG injection was 6.6mmo/L. Additionally, F-18 FDG PET scan showed hypometabolism in the bilateral frontal cortices and the right anterior striatum (including the caudate head and ventral striatum), which, in conjunction with the MRI findings, further supports the diagnosis of vascular dementia (Figure 3B).

DISCUSSION

The brain relies on glucose for energy, and neuronal activity correlates with glucose metabolism. F-18 FDG, a glucose analog with fluorine-18 replacing a hydroxyl group, is used in PET-CT imaging to map brain metabolism. Glucose is transported into the brain by GLUT1 and GLUT3, phosphorylated by hexokinase to glucose-6-phosphate, and metabolized to ATP.[5] However, F-18 FDG accumulates in the brain as it cannot proceed beyond glucose-6-phosphate due to the lack of glucose-6-phosphatase.[5] Dementia causes neuron loss, gliosis, and reduced synaptic connections, leading to hypometabolism visible on F-18 FDG PET-CT. The specific patterns of hypometabolism help to differentiate types of neurodegenerative dementia.[4] In addition, based on patterns and severity of FDG uptake changes together with the statistical mapping analysis, it provides diagnostic clues and supports clinical evaluation, potentially reducing overall healthcare costs for the patient. F-18 FDG PET scan provides a comprehensive assessment by minimizing the need for repeated anatomical or laboratory testing, reduces the time spent on prolonged clinical investigations, and lowers indirect costs such as patient travel, lost workdays, and additional consultations.

PET-CT combines metabolic imaging with anatomical correlation from non-contrast CT. Image interpretation requires recognizing spatial distribution and magnitude of FDG uptake changes, which can be subtle and diffuse. Therefore, visual analysis is complemented by quantitative methods. PET images are standardized using stereotactic coordinates and compared to age-matched databases to create Z-score maps.[5] This approach improves diagnostic performance of readers.[5] PET scan can reveal changes in F-18 FDG uptake in regions affected either directly or indirectly. To accurately differentiate dementing disorders, careful

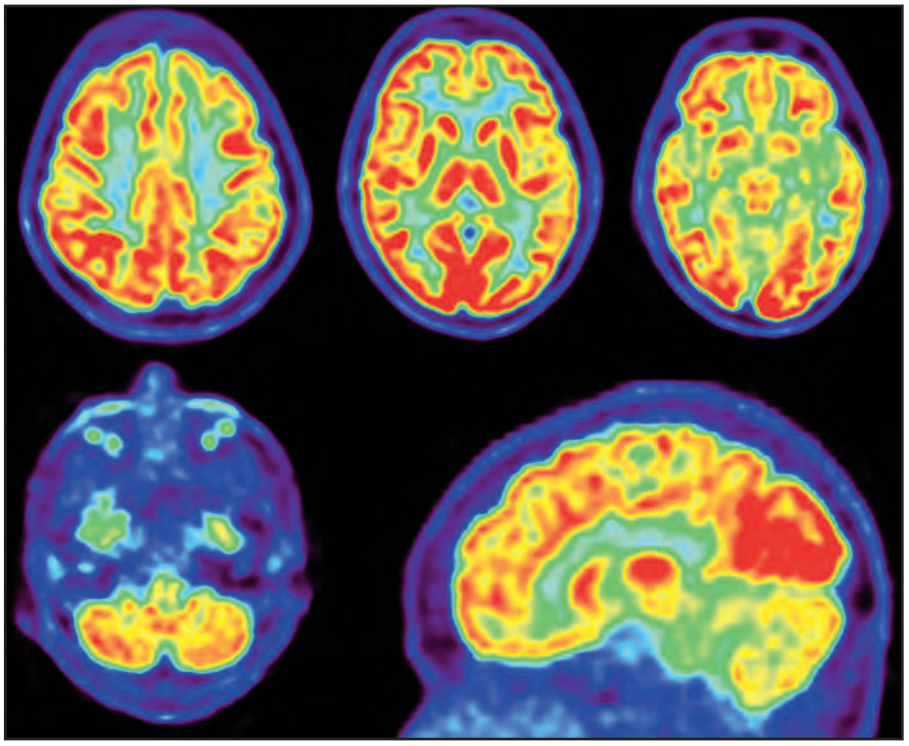

Fig. 1: Selected transaxial and sagittal F-18 FDG PET images showed a normal FDG metabolism distribution in the brain. Red regions indicate the highest FDG uptake, primarily in the subcortical putamen, caudate nucleus, and thalamus, with high uptake also in the cortical grey matter (frontal, parietal, and occipital areas) compared to the temporal cortex, especially the medial temporal region and hippocampus. Green regions represent intermediate uptake, while blue regions show the lowest FDG uptake

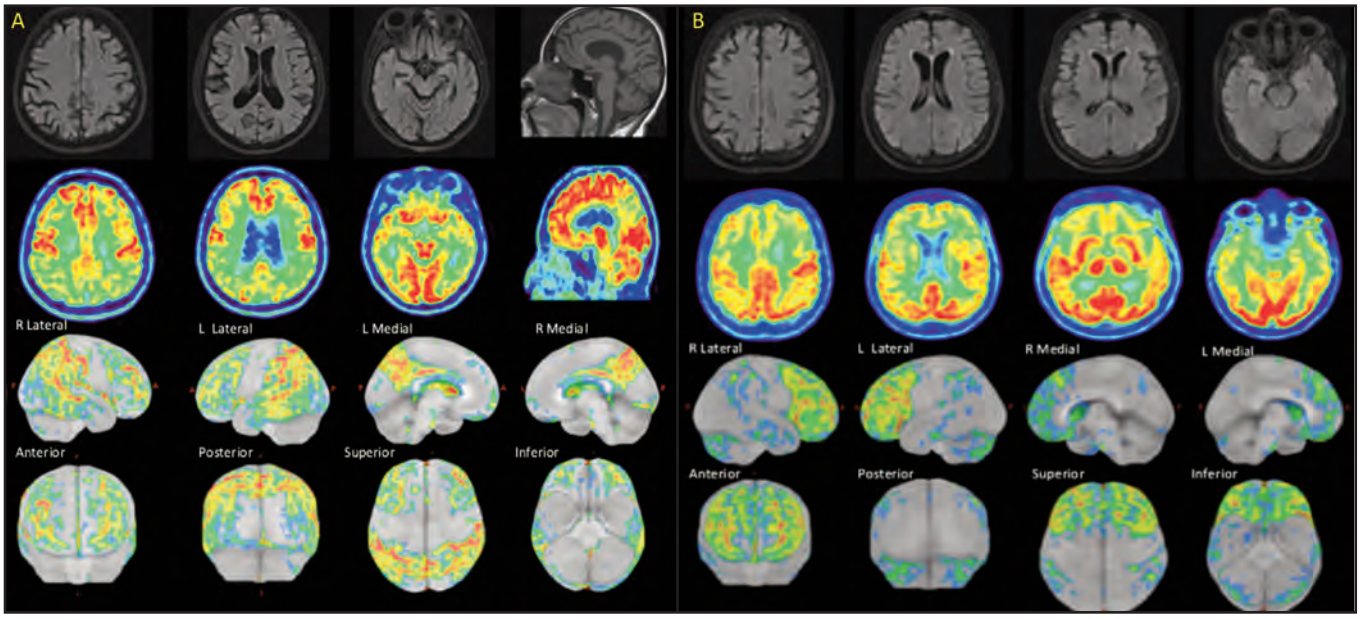

Fig. 2: A&B (Alzheimer's Disease & Frontotemporal Dementia). (2A) Transaxial and sagittal T2/FLAIR images (top row) revealed progressive generalized cerebral volume loss, particularly in the bilateral parietotemporal regions and precuneus. Transaxial F-18 FDG PET images (second row) and Z score maps referencing the pons (third and fourth rows) showed significant hypometabolism in the bilateral frontotemporoparietal cortices, precuneus, and posterior cingulate cortices. (2B) T2/FLAIR weighted images (top row) revealed non-specific hyperintense foci in the left parieto-occipital region, suggesting small vessel disease. F-18 FDG PET images (second row) and Z score maps (third and fourth rows) showed diffuse FDG hypometabolism in the bilateral frontotemporal and parietal cortices

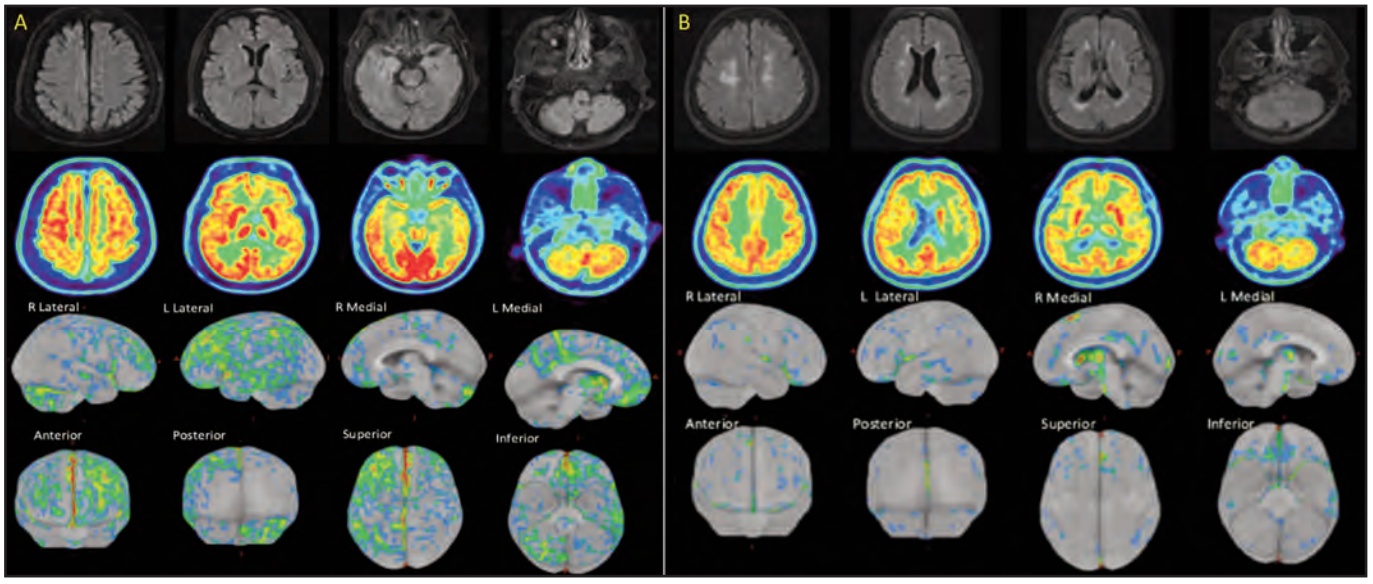

Fig. 3: A&B (Corticobasal Degeneration & Vascular Dementia). (3A) T2/FLAIR images (top row) showed an old lacunar infarct in the left internal capsule's genu. Ventricles and subarachnoid spaces were age-appropriate. F-18 FDG PET images (second row) and Z score maps (third and fourth rows) revealed asymmetrical FDG hypometabolism predominantly on the left, affecting the bilateral frontal, parietal, temporal, and posterior cingulate cortices, as well as the thalamus and midbrain. Right cerebellar diaschisis was also noted. (3B) T2/FLAIR images (top row) showed multifocal old infarcts with hemorrhagic components and severe small vessel disease, suggesting vascular dementia. F-18 FDG PET images (second row) and Z score maps (third and fourth rows) revealed FDG hypometabolism in the bilateral frontal cortices and right anterior striatum (caudate head and ventral striatum).

Table I: Typical brain FDG PET patterns of hypometabolism in neurodegenerative disorders

BRAIN REGION	DISORDERS			
	Alzheimer Disease	Frontotemporal dementia	Corticobasal syndrome	Vascular dementia
Frontal lobe	Early disease: Normal Advanced disease: Decreased	Decreased	Decreased asymmetrically	Normal or decreased, depending on the extent and location of ischemic damage
Anterior temporal lobe	Normal	Decreased	Normal	Normal or minimally affected
Parietal/Posterior temporal lobes	Decreased	Early disease: Normal Advanced disease: Decreased	Normal or asymmetrically decreased	Normal or patchy hypometabolism; often asymmetrical
Anterior cingulate gyrus	Normal	Decreased	Decreased	Normal or decreased, depending on the extent and location of ischemic damage
Posterior cingulate gyrus	Decreased	Early disease: Normal Advanced disease: Decreased	Decreased asymmetrically	Normal
Precuneus	Decreased	Early disease: Normal Advanced disease: Decreased	Normal or asymmetrically decreased	Normal
Basal ganglia	Normal	Normal (typical) or decreased	Decreased asymmetrically; thalamus may also be decreased	Decreased in some cases, reflecting subcortical vascular injury
Primary sensory motor cortex	Normal	Normal (typical) or decreased	Decreased asymmetrically	Normal or decreased, depending on the extent and location of ischemic damage.
Occipital lobe	Normal Lateral occipital decreased asymmetrically (in Posterior cortical Atrophy variant of AD)	Normal	Normal	Normal Unless directly affected by ischemia

assessment of both the spatial distribution and the extent of the regional uptake alteration should be made. Table I summarizes the typical brain FDG PET patterns of hypometabolism in various neurodegenerative disorders.

In specific dementia types as shown in this case series, the classic hypometabolic pattern of Alzheimer's disease on FDG PET is initially observed in the posterior cingulate gyrus during the early stages of AD.[3] This hypometabolic pattern may extend to the precuneus, and parietotemporal association cortex. Frontal association cortex involvement is seen in advanced cases.[6] FDG PET has the ability to detect AD even before noticeable symptoms appear and the degree of hypometabolism correlates with the severity of dementia.[6] However, in a clinical subtype of AD with behavioural variant (bvAD), frontal lobe involvement may be evident at an early stage.[4] This early involvement can make it challenging to distinguish bvAD from behavioural variant of frontotemporal dementia.[4] Findings in AD can be relatively symmetric or asymmetric. The metabolic activity in the primary sensory motor and primary visual cortices, as well as in the anterior cingulate gyrus, basal ganglia, thalamus, pons and cerebellum, remains intact in bvAD.[3,4] However, in the case of posterior cortical atrophy (PCA) variant of AD, occipital lobe hypometabolism is a common finding with asymmetrical lateral occipital involvement.[3]

Characteristically, the behavioral variant of frontotemporal dementia (bvFTD), or classic Pick's disease, demonstrates hypometabolism in the frontal association cortex, anterior temporal lobe, anterior cingulate gyri, and insula, with sparing of the motor cortex, similar to the findings in our patient (Figure 2B).[3] Additionally, the hypometabolic region may extend to involve the caudate nucleus and thalamus. In the early stages of the disease, hypometabolic changes are seen in the frontal cortex, and over time, these changes may extend into the temporal and parietal lobes.[3] Hemispheric metabolic asymmetry is common in FTD cases.[4] The degree of hypometabolism worsens with time, correlating with disease progression.[7] Crossed cerebellar diaschisis may be observed in FTD, although this finding may also be seen in AD and CBS.[4] As temporoparietal involvement may also be seen in AD, the strongest distinguishing features for FTD are the involvement of the anterior temporal cortex and anterior cingulate gyrus, with diagnostic specificities reported as 79.3% and 93.1%, respectively.[3]

Corticobasal syndrome (CBS) is a rare neurodegenerative disorder marked by asymmetric akinetic-rigid syndrome, uncontrollable limb movements (often termed "alien limb syndrome"), higher-order sensory deficits, and cognitive impairment.[8] This condition includes several neuropathologic subtypes, such as corticobasal degeneration (CBS-CBD), Alzheimer's disease (CBS-AD), and progressive supranuclear palsy (CBS-PSP), with CBD being the most frequently diagnosed, followed by AD and PSP.[8] In CBS, asymmetrical FDG hypometabolism is typically observed in the frontal, temporal, and parietal cortices, as well as the precentral gyrus.[8] The distinct underlying pathologies within CBS significantly influence the pattern of FDG-PET metabolism, making it a crucial diagnostic biomarker. For example, typical posterior temporoparietal or medial-frontal patterns are seen in CBS-AD or CBS-PSP respectively, and frontoparietal cortex, thalamus and caudate nucleus in CBS-CBD cases. Specifically, the pathologic diagnosis of CBS-CBD was associated with asymmetric hypometabolism of perisylvian frontotemporal cortex, frontoparietal association cortex, caudate nucleus and thalamus contralateral to the more affected limbs as well as the caudate nucleus and the motor cortex in the less affected hemisphere.[8]

Progressive cerebrovascular disorders can lead to diminished cerebral blood flow, which may result in significant cognitive decline and the development of vascular dementia.[9] This condition encompasses a range of clinicopathologic processes, including large-vessel strokes, multiple smaller infarcts, microangiopathy, subcortical arteriosclerotic encephalopathy, amyloid angiopathy, and cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL).[3] Typically, vascular dementia is associated with stroke-related damage, characterized by periods of cognitive stability interspersed with abrupt declines in function.[9] Additionally, subcortical white matter disease due to small vessel pathology often causes a gradual cognitive decline over many years.[9] Neuroimaging findings in subcortical vascular dementia commonly reveal leukoaraiosis, including extensive periventricular rims and patchy deep white matter hyperintensities.[10] While some degree of leukoaraiosis is common in individuals over 75, its extent can be indicative of vascular dementia. F-18 FDG PET imaging in those with leukoaraiosis may show global or frontal hypometabolism.[10] The distribution of hypometabolism reflects underlying ischemia, infarction, and encephalomalacia.

In addition to F-18 FDG, several other PET radiotracers are used in dementia evaluation. Amyloid imaging agents like F-18 Florbetaben and F-18 Flutemetamol detect beta-amyloid plaques, while tau tracers such as F-18 Flortaucipir target tau protein tangles. In addition to that, dopaminergic tracers like F-18 Fluorodopa assess dopamine function in conditions like Parkinson's disease dementia. However, a detailed description of these radiotracers is beyond the scope of this article.

CONCLUSION

F-18 FDG PET is a key diagnostic tool for cognitive impairment, revealing early and distinct patterns of synaptic and neuronal dysfunction. It aids in early diagnosis, assesses disease severity, and predicts cognitive decline. Statistical mapping enhances FDG PET's ability to differentiate types of dementia, which is crucial for prognosis and treatment planning. Early and accurate diagnosis supports effective therapeutic strategies and better disease management.

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A Case Report - Discovering Cardiac Myxoma through Microscopic Hematuria

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SUMMARY

Cardiac myxoma is the most common primary benign cardiac tumours, often located in the left atrium. It usually presents with obstructive cardiac, embolisation or constitutional symptoms, which prompt echocardiography or further imaging studies to confirm the diagnosis. Surgical resection is the treatment of choice for these patients. We present a case with an unusual presentation of microscopic haematuria which resolved completely six months after surgical resection. Interleukin-6 (IL-6) is a proinflammatory cytokine, and the excessive IL-6 production commonly seen in patients with cardiac myxoma has been linked to constitutional symptoms. Overproduction of IL-6 can mimic inflammatory, antibody-mediated autoimmune diseases, vasculitis, and glomerular diseases, leading to glomerular injury, proteinuria, and microscopic haematuria.

INTRODUCTION

Cardiac myxoma is the most common benign cardiac tumours, typically found in the left atrium. It is more frequently observed in women between the ages of 30 and 60. Cardiac myxoma can be either sporadic or familial, with sporadic cases being more prevalent.[1] The presentation of cardiac myxoma usually depends on the location, size, and mobility of the myxoma, with a classical triad of obstructive cardiac, constitutional symptoms or systemic embolization.[1] A transthoracic echocardiogram (ECHO) is usually performed to visualise and diagnose cardiac myxoma, because it is widely available in all hospitals and often yields adequate information necessary for surgical intervention. There have been reports of cardiac myxoma cases presenting with abnormal urinalysis findings, such as proteinuria combined with microscopic haematuria,[2] or proteinuria along with right heart failure.[3] However, no cases have been reported where microscopic haematuria was the sole presenting symptom. Here, we report a case of a patient who presented with microscopic haematuria, without other accompanying renal findings.

CASE PRESENTATION

A 68-year-old woman with underlying hypertension and dyslipidaemia was found to have persistent microscopic haematuria on a urine dipstick examination during routine surveillance for hypertension. She denied having any urinary tract symptoms. Her blood tests showed normocytic normochromic anaemia. A computed tomography (CT) renal 4 phase scan was performed, which did not reveal any renal pathology. Instead, splenic cyst (0.7 x 0.6 cm), cholelithiasis, and a left atrial myxoma (2.5 x 5.0 x 3.5cm) arising from the intra-atrial septum were seen.

She was referred to the cardiothoracic surgery department for further management. She did not have any obstructive cardiac, embolic, or constitutional symptoms. Her transthoracic ECHO showed an ejection fraction of 55-60%, a dilated left atrium, mild mitral regurgitation, and a LA myxoma measuring 12cm^2. CT angiogram of the coronary arteries showed mild coronary arterial disease with a calcium score of 196 and a left atrial mass arising from the interatrial septum with peripheral calcification.

She was scheduled for a left atrial myxoma excision. A transoesophageal ECHO was performed after the patient was under general anaesthesia, showing a 5 x 4 cm left atrial myxoma (Figure 1). A median sternotomy approach was used, and the patient was placed on cardiopulmonary bypass and cooled down to 32ºC. An aortic cross-clamp was applied, and antegrade cardioplegia was administered to achieve diastolic cardiac arrest. A transseptal atrial approach was taken to access the left atrial myxoma. The myxoma measured 5 x 4 cm, with its stalk attached to the fossa ovalis. The myxoma was removed intact, the interatrial septum was closed with a bovine pericardial patch, followed by closure of the right atriotomy. After the patient was rewarmed and the aortic cross clamp was removed, cardiopulmonary bypass was weaned off and terminated uneventfully. The sternum was closed, and the patient was transferred to the cardiothoracic intensive care unit for postoperative care. Transoesophageal ECHO showed satisfactory valve function with no interatrial defects.

Postoperatively, she recovered well and was discharged five days after surgery. Histopathology confirmed a cardiac myxoma with cords and stellate myxoma cells in the background of an abundant myxoid matrix. There were areas of haemorrhage, haemosiderin-laden macrophages, and fibrin deposition. There was no mitosis or nuclear atypia. Follow-up transthoracic ECHO at our clinic showed no residual myxoma, and her urine examination six months later showed resolution of microscopic haematuria.

DISCUSSION

Cardiac tumours can be categorised as primary and secondary tumours, with primary tumours further divided into benign and malignant. Cardiac myxoma is the most

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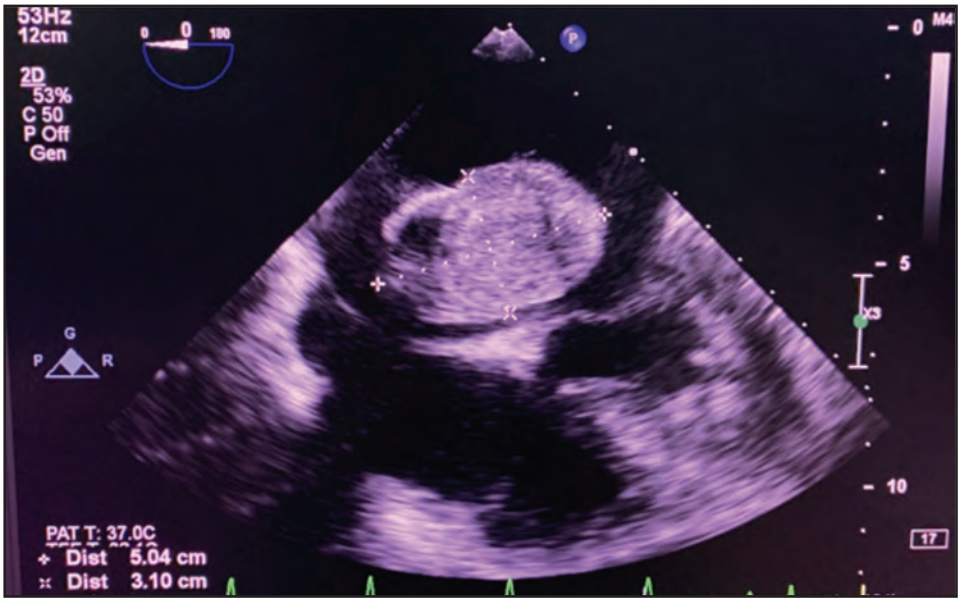

Fig. 1: Left atrial myxoma on transesophageal ECHO intraoperatively

common primary benign cardiac tumours (75%).[1] It has a female predominance and is commonly seen in patients in their third to sixth decade of life. Cardiac myxomas are most commonly found in the left atrium (75%), followed by the right atrium (15-20%), left ventricle (3-4%), and right ventricle (3-4%).[1] Patients with cardiac myxoma usually present with symptoms that form part of the triad of obstructive cardiac, constitutional symptoms, and systemic embolization.[1] However, the patient in this case report presented with persistent microscopic haematuria rather than the typical triad of symptoms, which is an uncommon presentation for a cardiac myxoma in the absence of additional clinical symptoms or signs.

Several studies, including those by Mendoza et al[4] and Jougasaki et al[5], have reported elevated interleukin-6 (IL-6) levels in patients with cardiac myxoma. IL-6 is a proinflammatory cytokine produced by various cell types, such as monocytes, B cells, T cells, fibroblasts, keratinocyte, mesangial cells,[6,7] endothelial cells, vascular smooth muscle cells, and cardiac myocytes.[4,5] IL-6 plays a role in various biological processes, including immune regulation, inflammation, haematopoiesis, oncogenesis, metabolism, and tissue regeneration.[5,7] Excess IL-6 production is associated with constitutional symptoms such as fever, malaise, and weight loss,[2] with higher IL-6 levels correlating with more severe and diverse systemic manifestations.[4] Additionally, IL-6 levels have been positively correlated with tumour size index.[4,5] In our case report, the absence of constitutional symptoms in the patient could be attributed to a tumour size below the threshold required to produce significant IL-6 levels. However, there are no reports establishing the threshold level necessary for constitutional symptoms.

Jougasaki et al[5] demonstrated that circulating IL-6 in patients with cardiac myxoma originates from neoplastic myxoma cells, which further amplify IL-6 production through autocrine and paracrine mechanisms. The classic signaling pathway activates intracellular transduction systems such as Janus kinase (JAK)-signal transducer and phophatidylinositol-3-kinase (PI3K) / Akt. In contrast, the trans-signaling pathway primarily activates the signal transducer and activator of transcription (STAT) 3 and PI3K/Akt pathways.

Renal cells, including podocytes, endothelial cells, mesangial cells, and tubular epithelial cells, are also capable of secreting IL-6. As a result, IL-6 overproduction by cardiac myxoma, in conjunction with activation of the JAK, PI3K/Akt, and STAT3 pathways, may contribute to renal autoimmune, glomerular, and inflammatory disease.[6] These pathways trigger mesangial cell proliferation, glomerular hypertrophy, interstitial fibrosis, tubular atrophy, and extracellular matrix deposition, ultimately resulting in glomerular injury, haematuria, and proteinuria. IL-6 has also been shown to initiate endothelial injury by reducing endothelial nitric oxide synthase and adiponectin expression, which contributes to renal dysfunction.

In addition, renal cells respond to IL-6 by influencing renal cell injury and repair processes, as well as contributing to immune, metabolic, ischaemic and toxin-mediated renal diseases. This has been demonstrated in animal models of systemic lupus erythematosus, where the absence of IL-6 makes mice resistant to immune and inflammatory-mediated tissue injury, resulting in delayed onset of haematuria and proteinuria.[6]

Excessive IL-6 production can also cause cardiac myxoma to mimic inflammatory diseases, antibody-mediated autoimmune diseases,[7] or vasculitis such as Takayasu arteritis,[8] giant cell arteritis,[8] microscopic polyangiitis,[9] and granulomatosis with polyangiitis.[10] The latter two are systemic small-vessel vasculitis associated with elevated anti-neutrophil cytoplasmic autoantibodies (ANCA) levels.

These ANCA-associated vasculitis leads to granuloma formation and inflammation of small arteries, arterioles, venules and capillaries. Affected patients may present with constitutional symptoms or specific end-organ involvement, with the kidneys being most commonly affected (65%) and rapidly progressive glomerulonephritis being a major cause of morbidity and mortality.[9] Excessive IL-6 production by cells in the glomeruli, interstitium, and perivascular sites plays a role in recruiting neutrophils and monocytes, driving further inflammation and potential renal dysfunction. This is supported by renal biopsy findings showing scattered endothelial cells and infiltrating inflammatory cells,[9] as well as focal and necrotizing crescentic glomerulonephritis with immunoglobulin deposition in vessel walls.[10] Hence, patients with ANCA-associated vasculitis typically present with microscopic haematuria, proteinuria, and sometimes elevated serum creatinine levels.[10]

Other case reports[2,3] describe patients with cardiac myxoma presenting with abnormal renal findings. This differs from our patient, who presented only with microscopic hematuria without proteinuria, suggesting a milder degree of renal involvement. Renal biopsy findings in patients with clinical remission from small vessel vasculitis, as reported by Geetha et al,[10] suggest that persistent haematuria represents chronic glomerular injury from prior episodes of vasculitis. Therefore, the resolution of haematuria 6 months post-surgery in our patient supports the role of IL-6 and tumour burden in glomerular dysfunction, and milder renal injury compared to the other 2 case reports. The absence of proteinuria and the presence of anaemia highlight unique aspects of her presentation, reinforcing the variable renal manifestations of cardiac myxoma.

CONCLUSION

Cardiac myxoma is a rare disease, often presenting with symptoms that include the triad of obstructive cardiac manifestations, embolisation, and constitutional symptoms. IL-6 is a proinflammatory cytokine that is excessively produced in cardiac myxoma, where its production is amplified through autocrine and paracrine mechanisms. IL-6 overproduction contributes to renal autoimmune, glomerular, and inflammatory disease, causing changes as such glomerular hypertrophy, interstitial fibrosis, and endothelial injury, ultimately leading to renal dysfunction. Excessive IL-6 in cardiac myxoma can also imitate inflammatory diseases, antibody-mediated autoimmune diseases, or various forms of vasculitis. ANCA-associated vasculitis affects the kidney in 65% of cases and can lead to abnormal urinary findings. Renal biopsy findings in patients with elevated ANCA-associated vasculitis have shown inflammatory cells and glomerulonephritis with immunoglobulin deposition in vessel walls. Hence, cardiac myxoma should be considered in the evaluation of patients with abnormal urinary findings associated with renal diseases such as vasculitis, and systemic lupus erythematosus. The overproduction of IL-6 by cardiac myxoma and its impact on renal cells may be the only indication of the presence of cardiac myxoma.

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DECLARATION

Verbal consent for publication and accompanying images were obtained from the patient. All authors have no conflict of interest to declare. This manuscript did not receive any funding.

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CASE REPORT

A Malaysian case series on anifrolumab treatment for haematological manifestations in systemic lupus erythematosus

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SUMMARY

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease often presenting with a wide range of manifestations, including haematological abnormalities. Anifrolumab, a first-in-class type I interferon receptor antagonist, was recently approved in Malaysia as an add-on treatment for moderate-to-severe active autoantibody-positive SLE in adult patients. Though the phase III TULIP trials demonstrated the efficacy of anifrolumab in improving disease activity and haematological parameters in SLE patients, real-world data on its haematological impact have been limited. This case series presents five Malaysian patients with moderate-to-severe SLE, all of whom had significant haematological manifestations and sub-optimal responses to conventional treatments. Each patient demonstrated marked clinical and laboratory improvements after initiating anifrolumab, including reductions in corticosteroid dosage. Two patients completely discontinued corticosteroids, while others significantly tapered their doses. Haematological parameters, such as haemoglobin level, white blood cell (WBC) count, and platelet count, improved consistently across the cases. This series highlights the potential of anifrolumab as an effective therapeutic option for managing haematological manifestations of SLE, particularly in patients struggling with the adverse effects of prolonged corticosteroid use. These findings contribute valuable real-world evidence supporting the use of anifrolumab in the broader management of SLE, addressing a critical gap in the current literature.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a multisystemic disease which includes the presence of haematological manifestations. The haematological changes in SLE can be an initial manifestation and a predominant sign during the initial years. However, because haematological abnormalities can be found in a variety of medical conditions, the diagnosis of SLE may elude physicians, who often label them as idiopathic or primary conditions.[1] In Malaysia, 51.6% of SLE patients were reported to have haematological manifestations and was the third most common presentation following malar rash (61.3%) and arthritis (52.3%).[2]

Anifrolumab, a first-in-class type 1 interferon receptor antagonist, was approved in 2023 in Malaysia as an add-on therapy for adult patients with moderate to severe, active autoantibody-positive SLE despite standard therapy.[3] Currently, there is limited real-world evidence to demonstrate the effectiveness of anifrolumab in improving SLE haematological manifestations.[4] This case series presents five SLE patients with haematological manifestations treated with anifrolumab due to failure of disease control with standard treatment. A summary of the cases is presented in Table I.

CASE PRESENTATION

Patient 1

In 2017, VA, a 22-year-old woman, presented with autoimmune haemolytic anaemia (AIHA), fever, arthritis, malar rash, and oral ulcers. Her laboratory findings revealed low complements, elevated antinuclear antibody (ANA), elevated anti-double-stranded DNA (dsDNA) titres and a positive anti-Smith antigen (anti-Sm) and anti-Sjögren's-syndrome-related antigen A (SSA) antibody. Initial treatments included hydroxychloroquine, prednisolone >15 mg/day, with ciclosporin 75 mg twice daily. Ciclosporin was then discontinued due to hirsutism, and disease control needed to be maintained with high GC (glucocorticoid) doses.

While pursuing her PhD in July 2023, she presented with a stress-related SLE flare with arthralgia, oral ulcers, fatigue, alopecia, anaemia, and thrombocytopenia with a Safety of Estrogen in Lupus Erythematosus National Assessment (SELENA)-Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score of 15. At that time, her medications were hydroxychloroquine 200mg/day, prednisolone 20mg/day, and azathioprine 125 mg/day.

Due to longstanding steroid exposure, she had developed steroid-induced osteopenia and voiced concerns about inadequate disease control.

Laboratory analyses during the July 2023 flare revealed significant worsening of haematological parameters (Table II). The lactate dehydrogenase (LDH) level was 535 U/L (more than double the upper limit of normal [ULN]), indicating ongoing haemolysis. Given the ongoing active disease, poor quality of life, and inability to reduce GC despite optimum doses of azathioprine, a new treatment strategy was advocated.

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Table I: Summary of cases

Case study	Age	Features	Haematological parameters	Pre-anifrolumab steroid dose (duration)	Reasons for starting anifrolumab	Duration of anifrolumab	Post-anifrolumab steroid dose
Cases shared by the first author							
1	22	AIHA Fever Arthritis Malar rash Oral ulcers	Cytopenia Anaemia Thrombocytopenia WBC - normal	20 mg daily (6 years)	SLE flare with SLEDAI 15. Long-standing steroid-induced osteopenia. Rituximab not started as it is generally reserved as rescue and salvage treatment in the author's practice, while anifrolumab was chosen as it had a clear indication/approval for moderate-to-severe SLE and haematological manifestations of SLE.	6 months 9 months	7.5 mg daily 3 mg daily
2	31	Arthritis Malar rash Fatigue Alopecia Anaemia Leukopenia	Leukopenia Lymphocytopenia Anaemia Platelet - normal	12.5 mg daily (11 years)	Intolerance and failure to respond to SOC. Long-standing steroid-induced osteoporosis, weight gain, cataracts, fatty liver, lipidaemia, genital warts. Rituximab not started as it is generally reserved as rescue and salvage treatment in the author's practice, while anifrolumab was chosen as it had a clear indication/approval for moderate-to-severe SLE and haematological manifestations of SLE.	6 months	4 mg daily
Cases shared by the second author							
3	36	Arthritis Malar rash Fatigue Alopecia Anaemia Leukopenia	Anaemia Leukopenia Neutropenia	10-15 mg daily (1 year 7 months)	Active disease after tapering initial steroid dose to <7.5 mg daily. Chronic steroid dependence. Rituximab was not considered as it was during the peak of the COVID-19 pandemic.	4 months 6 months	5 mg daily 2.5 mg daily
4	39	Arthritis Malar rash Fatigue Alopecia Anaemia Leukopenia	Leukopenia	15-20 mg daily (1 year 5 months)	Inadequate response to Azathioprine. Failed response to 2 doses of rituximab with worsening biochemical parameters when prednisolone dosage was reduced to 10 mg daily. Significant dyspepsia and nausea with mycophenolate mofetil.	5 months	7.5 mg daily
5	36	MCTD with active SLE Skin rash Oral ulcers Alopecia Recurrent joint pain and swelling Raynaud's symptoms Fatigue	Anaemia (mild) Lymphopenia	15-20 mg daily (1 year 5 months)	Allergies to hydroxychloroquine and dapsone. Inadequate response to methotrexate. Though there was partial response to rituximab with some improvement in biochemical parameters such as complements and leucopoenia, skin rashes and alopecia began to worsen by four months post-rituximab. Persistent high-dose steroid requirement.	1 month 8 weeks	5 mg daily Discontinued

AIHA, autoimmune haemolytic anaemia; MCTD, mixed connective tissue disease; SLE, systemic lupus erythematosus; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; SOC, standard of care; WBC, white blood cell.

Table II: Laboratory parameters, pre- and post-anifrolumab treatment

	Hb (g/dl)	WBC (x 10^9/L)	Lymphocyte (x 10^3/µl)	Platelet (x 10^3/µl)	ESR (mm/hour)	C3 (g/L)	C4 (g/L)	dsDNA (IU/ml)
Patient 1: VA								
Mar 2023	9.0	-	-	96	51	0.56	0.08	945
Jul 2023	8.8	-	-	90	60	0.53	0.05	2600
Aug 2023	9.0	-	-	110	45	-	-	-
Oct 2023	10.8	-	-	112	36	0.68	0.10	627
Jan 2024	12.1	-	-	147	18	0.87	0.14	496
May 2024	12.4	-	-	156	19	0.86	0.16	244
Patient 2: LPK								
Mar 2023	9.4	3.2	-	-	36	0.46	0.08	229
May 2023	9.5	3.3	-	-	46	0.44	0.06	302
Jun 2023	9.8	3.8	-	-	40	-	-	-
Aug 2023	10.4	4.1	-	-	28	0.78	0.12	160
Dec 2023	11.3	4.2	-	-	17	0.89	0.10	112
Mar 2024	10.8	3.9	-	-	32	0.80	0.08	216
June 2024	11.6	4.8	-	-	20	0.91	0.10	220
Patient 3: LKJ								
Jul 2023	11.7	6.2	0.93	268	6	0.67	0.09	189
Aug 2023	12.1	5.5	2.42	342	7	0.78	0.10	-
Oct 2023	11.9	11.9	1.50	295	2	0.71	0.09	-
Nov 2023	12.6	6.2	1.18	330	14	1.00	0.17	-
Jan 2024	11.9	4.9	1.76	324	2	0.71	0.10	-
Mar 2024	12.1	5.2	1.54	310	2	0.71	0.09	-
Patient 4: WMY								
Aug 2023	13.8	2.8	-	238	3	0.49	0.15	-
Nov 2023	15.1	10.2	-	269	4	0.59	0.20	-
Dec 2023	14.3	8.4	-	241	5	0.69	0.19	-
Feb 2024	14.5	5.9	-	274	4	0.67	0.16	-
Apr 2024	13.8	5.0	-	273	2	0.69	0.17	-
Patient 5: TSY								
Feb 2024 (baseline in 2020)	12.3	2.8	0.62	242	9	0.63	0.14	71.7
Mar 2024	12.1	5.4	0.97	365	12	0.70	0.13	-
Apr 2024	12.6	5.4	0.97	327	5	0.68	0.14	0.00

Anifrolumab initiation for Case 1 (VA): July 2023, Case 2 (LPK): May 2023, Case 3 (LKJ): July 2023 (dsDNA was only taken at baseline), Case 4 (WMY): November 2023, and Case 5 (TSY): February 2023. All patients had progressive improvements in their blood parameters post-treatment initiation.
C, complement; dsDNA, double-strand DNA; ESR, erythrocyte sedimentation rate; Hb, haemoglobin; IU, international unit; WBC, white blood cells.

In 2023, VA was started on intravenous (IV) anifrolumab 300 mg every four weeks. After 6 months of anifrolumab, prednisolone was tapered to 7.5 mg/day, and azathioprine reduced to 100 mg/day. Her laboratory parameters improved significantly; haemoglobin, platelet count, erythrocyte sedimentation rate (ESR), and C3 and C4 levels almost normalised, while dsDNA levels decreased by nearly 80%. She reported reductions in pain, fatigue, and hair loss. Her clinical and laboratory parameters significantly improved (Table II) with a SELENA-SLEDAI score of 4 and with prednisolone reduced to 3 mg/day by May 2024.

Patient 2

LPK, a 31-year-old lady diagnosed with moderate SLE in September 2012, initially presented with arthritis, malar rash, fatigue, alopecia, anaemia and leukopenia. Treatment history between 2012 and 2023 included hydroxychloroquine, prednisolone >10 mg/day, azathioprine (stopped due to elevated liver enzymes), methotrexate (stopped due to gastrointestinal [GI] symptoms), and leflunomide. After 11 years on moderate-to-high doses of corticosteroids, LPK had developed long-term corticosteroid complications such as osteoporosis, weight gain, cataracts, fatty liver, lipidaemia, and genital warts. Due to her chronic joint inflammation, she also developed Jaccoud's arthropathy. At this time, her treatment encompassed hydroxychloroquine 200 mg/day, prednisolone 12.5 mg/day, leflunomide 20 mg/day, and denosumab 60 mg every six months.

Her laboratory results in May 2023 indicated persistently active disease (Table II), with high ANA titres (1:640), elevated anti-dsDNA, lymphocytopenia (0.73/ml), and anaemia (9.4 g/dl). Due to her suboptimal disease control, poor quality of life, complications from disease and treatment, and intolerance and failure to respond to standard of care (SOC), IV anifrolumab 300 mg every four weeks was initiated.

In December 2023, six months after anifrolumab, there were significant improvements in the resolution of rash and joint synovitis; prednisolone was reduced to 4 mg/day while leflunomide was discontinued. Her Hb, WBC, ESR, C3/C4, and dsDNA levels also improved (Table II).

However, the patient defaulted two subsequent anifrolumab infusions, resulting in a minor SLE flare affecting her skin and musculoskeletal system, and deterioration in blood parameters (Table II). Considering the resurgence in disease severity, anifrolumab was recommenced in April 2024, with a good clinical response seen after the first dose.

Patient 3

LKJ, a 36-year-old female with moderate SLE (based on SLEDAI-2000), presented in December 2021 with fever, joint pain, rash and oral ulcers. Investigations revealed low C3/C4 levels, anaemia and leukopenia. ANA, anti-dsDNA, and extractable nuclear antigen antibodies (ENA) were positive. She was initially treated with prednisolone 1 mg/kg/day with gradual tapering to <7.5 mg/day, hydroxychloroquine and azathioprine. In July 2023, she continued to exhibit active disease, with leukopenia, anaemia, skin rash, alopecia, oral ulcers, joint pain and vasculitis. This was complicated by fever, frequent infections secondary to oral immunosuppressants and chronic steroid dependence (GC < 10 mg/day). Her last findings revealed significantly high ANA and anti-dsDNA, positive ENA for SmD1, Ro-60, La and nucleosomes, low C3/C4 levels, leukopenia (2.4 x 10^9/L), neutropenia (1.01 x 10^9/L), anaemia (Hb 9.6 g/dL) and elevated LDH (567 U/L).

Considering LKJ's overall clinical picture, IV anifrolumab 300 mg every four weeks was added in July 2023. At nine months of anifrolumab, dose reductions were possible in her prednisolone, hydroxychloroquine 400 mg/day alternating with 200 mg/day to 200 mg/day, azathioprine 125 mg/day to 75 mg/day and prednisolone 10-15 mg/day to 2.5 mg/day. The prednisolone was successfully tapered to 5 mg/day by the fourth month and to 2.5 mg/day by the sixth month. Progressive improvements were seen in haematological parameters (resolved lymphopenia), except for the C3/C4 levels, which remained roughly the same (Table II). Clinically, LKJ experienced less fatigue and no frequent infections.

Patient 4

WMY, a 39-year-old woman, presented with SLE in June 2022. She had moderate disease based on SLEDAI-2000 with joint pain, skin rashes, and oral ulcers that had begun two months postpartum. Biochemical abnormalities included low complement levels and leukopenia. Intolerant to azathioprine (headaches and neutropenia,) she was started on IV rituximab, 1 g for two doses at two-week intervals, which led to a partial response (improved C3/C4 levels and leukopenia). However, tapering the prednisolone to <15 mg/day four weeks after rituximab therapy, she experienced joint pain and declining blood parameters. Mycophenolate mofetil up to 1 g twice daily was started, but she experienced constant dyspepsia and nausea. Other immunosuppressives were not prescribed as the patient had concerns about experiencing similar adverse events (AE). Optimising the prednisolone dose was challenging; she experienced constant fatigue when the dose was tapered but suffered from insomnia when it exceeded 10 mg/day.

Given her AEs to conventional immunosuppressive agents, persistent prednisolone dependency, constant disease activity, and poor well-being, IV anifrolumab 300 mg every four weeks was started in November 2023. At that time, her treatment regimen included hydroxychloroquine, 200 mg/day alternating with 400 mg/day, prednisolone 15-20 mg/day, and mycophenolate mofetil 1500 mg/day. After five months, her treatment regimen improved significantly: hydroxychloroquine was reduced to 200 mg/day, the prednisolone to 7.5 mg/day, and discontinued mycophenolate mofetil. Her blood parameters also showed improvement (Table II), as did her fatigue and insomnia.

Patient 5

In 2020, TSY, a 36-year-old woman, was diagnosed with mixed connective tissue disease (MCTD) with a predominant active lupus component. She initially presented with skin rashes, oral ulcers, increased hair fall, recurrent joint pain, swelling, Raynaud's (digital) symptoms, and fatigue. Her investigations revealed mild anaemia (Hb 11.7 g/dL), lymphopenia (0.9 x 10^9/L), low C3/C4, elevated ESR, and were positive for ANA (1:1280) and ENA (positive for U1-SmRNP, SmD1, PCNA, P0). Skin biopsy showed subacute cutaneous lupus erythematosus (SCLE) and was diagnosed with moderate SLE using the SLEDAI-2K score.

She was initially treated with hydroxychloroquine and methotrexate. However, she developed allergic reactions to hydroxychloroquine and had an inadequate response to methotrexate, which worsened her skin rash and caused cytopenia. Rituximab, administered at 1 g for two doses two weeks apart every six months, also proved inadequate after three doses, as she had persistently low C3/C4 levels, leukopenia (<4.0 x 10^9/L), and dependence on high-dose prednisolone (>10 mg/day). During multiple disease flare-ups on rituximab, she required intermittent pulses of IV methylprednisolone at 500 mg. Unfortunately, during the rituximab regimen, she experienced spontaneous pregnancy that resulted in intrauterine demise at eight weeks of amenorrhea.

Due to persistently active disease, intolerance, inadequate responses, worsening leukopenia, and low C3/C4 levels despite rituximab treatment, as well as persistent corticosteroid dependence, IV anifrolumab 300 mg every four weeks with prednisolone 10 mg/day was initiated in February 2024. In a month, prednisolone was tapered to 5 mg/day and discontinued within eight weeks. Her haematological parameters improved, except for C3/C4 levels, which remained stable (Table II). Clinically, she showed marked improvement after three months of anifrolumab therapy, with complete resolution of her cutaneous rash, alopecia, and oral ulcers.

DISCUSSION

The cases presented highlight the effectiveness of anifrolumab in treating SLE patients with sub-optimal responses, intolerable AEs with SOC, and who were on high GC doses. Fifty percent to 70% of SLE patients may present with anaemia, while leukopenia (65%) and lymphopenia (50%) are frequently observed. Although SLE-related thrombocytopenia is less common (10-25%), severe thrombocytopenia can result in morbidity and mortality.[5]

Current SOC includes corticosteroids, anti-malarial and immunosuppressants. GCs have potent anti-inflammatory effects, but long-term use of >5 mg/day prednisone equivalent may cause irreversible organ damage, prompting recommendations to taper and ultimately withdraw GC.[4,6]

With the availability of biologics like belimumab and anifrolumab, the 2023 European Alliance of Associations for Rheumatology (EULAR) SLE treatment guidelines recommended prompt biologic initiation, rather than after multiple SOC treatment failures, due to more robust clinical trial evidence to control disease and facilitate GC sparing. The guidelines also recommended anifrolumab as a second-line option for mild SLE patients and as first-line for moderate-to-severe SLE patients when the response to hydroxychloroquine is suboptimal or inability to taper GC doses to ≤5 mg/day prednisolone equivalent to control disease activity.[4]

Clinical trials show significantly more anifrolumab patients achieved a GC of ≤7.5 mg/day from weeks 40-52 compared to placebo (52% vs. 30%, p=0.01).[7] At year four, 36.4% of anifrolumab patients were free of GC (0 mg/day), while 74.4% received doses between 0 - <5 mg/day with an acceptable safety profile.

In all cases presented, the patients were on high GC doses that could not be reduced due to disease recurrence or flare-ups, and none was trialled with belimumab. However, with anifrolumab treatment, two patients reduced their GC doses to < 5 mg/day, two reduced their doses by more than 50%, and one discontinued GC within eight weeks. In real-world clinical practice, anifrolumab enabled GC-dependent patients to align with the EULAR 2023 SLE recommendations to lower the daily GC dose to ≤5 mg/day.[4]

In a post-hoc analysis of the TULIP long-term extension (LTE) trial, improvement in the SLEDAI-2K haematological domain was more frequent in the anifrolumab 300 mg group compared to placebo at Week 208. Patients receiving anifrolumab also showed improved haemoglobin, platelet, and lymphocyte counts compared to placebo over the 4-year TULIP LTE study period.[9]

All the patients in this case series exhibited improvements in their SLE symptoms including the haematological parameters. It should be noted that other causes of the haematological abnormalities were ruled out and generally mild-to-moderate but were considered significant as adding conventional immunosuppressants during treatment would potentially further deviate the value of the counts. Interestingly, patient 5 showed significant cytopenia improvement, with a marked increase in WBC counts within three cycles of anifrolumab. This patient, who presented with AIHA, demonstrated a substantial increase in haemoglobin levels, rising by 36% from 8.8 g/dl to 12.0 g/dl within six months. Additionally, the patient's platelet count increased from 96 to 146 x 10^3/L, and the erythrocyte sedimentation rate (ESR) decreased from 51 to 18 mm/hour. Patient 2 highlights the potential rebound effect of abruptly discontinuing anifrolumab and underscores the importance of treatment compliance. Reassuringly, disease activity improved upon recommencing treatment.

CONCLUSION

The presented cases reinforced the role of anifrolumab as a viable treatment option in improving haematological parameters and reducing corticosteroid dependence in patients with moderate-to-severe SLE. These findings align with clinical trial data, while further real-world studies will be beneficial in strengthening the evidence and ultimately guide optimal patient management.

DECLARATION

It is hereby confirmed that consent for publication has been obtained from the patient or their caregiver.

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A rare case of ESBL *Escherichia coli* empyema with concurrent liver abscess

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SUMMARY

***Escherichia coli (E. coli)* is a common bacterium in the intestinal flora that often causes urinary tract infections, cholecystitis, and traveller's diarrhoea. Isolation of *E. coli* from pleural fluid is rare. We describe a 58-year-old gentleman with poorly controlled diabetes who presented with lung empyema. Pleural fluid revealed extended-spectrum beta-lactamase (ESBL) *E. coli*. Since *E. coli* is a rare entity found in the pulmonary system, an abdominal ultrasound was performed to look for possible sources of infection, which showed a multiloculated liver collection at segment VII. Contrast-enhanced computed tomography of the thorax and abdomen revealed a ruptured liver abscess complicated with right-sided empyema and a well-marked hypoechoic collection in segments VII and VIII of the liver that were percutaneously drained. We highlight a case of ESBL *E. coli* empyema, a rare presentation of extraintestinal *E. coli* infection. This case emphasises the importance of investigating unusual pathogens, such as ESBL *E. coli*, in patients with uncontrolled diabetes since they have an impaired immune response, which renders them at a higher risk of disseminated infections and atypical presentations without classical signs. Thus, it necessitates an extensive workup to ensure the early recognition of liver abscesses, and prompt treatment is vital for a better clinical outcome.**

INTRODUCTION

Empyema is defined as a collection of pus in the pleural cavity, gram stain of the fluid is positive for bacteria or culture-positive from the pleural fluid.[1] Infection from a hepatic abscess spreads most commonly by transdiaphragmatic, haematogenous, inhalation of *Entamoeba histolytica*, and direct trauma, and 15% of these mechanisms are unknown. Diabetes mellitus is a reported risk factor in 15% of liver abscess cases.[2] Concurrent thoracic empyema with liver abscess is rare but carries significant morbidity if diagnosis is delayed. We describe a case of an ESBL *E. coli* empyema concurrent with a liver abscess and highlight a few clinical recommendations for clinicians.

CASE PRESENTATION

A 58-year-old man with poorly controlled diabetes mellitus, hypertension, heart failure, and dyslipidemia presented with breathlessness for one day, associated with right-sided chest pain and cough for one week. His diabetes had been managed with metformin and insulin. Otherwise, he denied fever, abdominal symptoms, recent travel, or sick contacts. On examination, he was afebrile, tachycardic, and tachypneic, requiring face mask oxygen at 5 L/min. Lung examination revealed reduced breath sounds in the right lower zone. Other systemic examinations were unremarkable.

His initial blood investigations revealed leukocytosis with white blood cells of 13.60 x 10^3/uL and high C-reactive protein of 99.5 mg/L (Table I). His chest radiograph demonstrated a right massive pleural effusion with homogeneous opacity in the right hemithorax (Figure 1A). A thoracic ultrasound showed multiloculated right pleural effusion (Figure 2). Given the ultrasound thorax showed multiloculated pleural effusion, we decided on a right intercostal drainage (ICD) using pigtail Bioteq size 08Fr x 30 cm insertion, and straw-coloured fluid was drained. The patient underwent diagnostic and therapeutic thoracentesis with drainage of straw-coloured fluid and revealed exudate with LDH of 3019 U/L and pleural pH of 6.85. The patient's pleural pH of below 7.2, strongly indicating empyema. Pleural fluid analysis fulfilled the criteria for empyema given the pus cells seen on gram stain, and fluid culture grew ESBL *E. coli*. His peripheral blood and urine culture and sensitivity showed no growth.

The antibiotic was escalated to intravenous meropenem. Given E. coli is a rare entity to be present in the pulmonary system, hence, we proceeded with an ultrasound abdomen to look for a possible source of infection. Ultrasound abdomen showed multiloculated liver collection at segment VII. Contrast-enhanced computed tomography (CECT) thorax and abdomen were arranged subsequently and revealed multiloculated abscess collection seen at segment VII of the liver measuring 6 x 5.3 x 3.9 cm (Figure 3); however, there was no obvious sonographic evidence of communication between the liver abscess and right empyema. He then underwent percutaneous drainage of the liver abscess.

Despite flushing of the right ICD, the pleural fluid was not draining effectively. His chest radiograph showed minimal improvement, and repeated bedside ultrasound confirmed the persistent multiloculated right pleural effusion. Hence, we decided to administer intrapleural fibrinolytic therapy (IPFT) using streptokinase (STK) 500,000 IU for three doses. Post-IPFT, the pleural fluid drained well, and we were able to wean

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Table I: Blood investigation report of the patient

	Upon admission	Upon discharge	2 months clinic review
Total White Cell Count	13.60 x10^3/uL	4.88 x10^3/uL	7.90 x10^3/uL
Haemoglobin	10.1 g/dL	8.7 g/dL	9.3 g/dL
Platelet	313 x10^3/uL	261 x10^3/uL	189 x10^3/uL
ALT (normal range: < 55 U/L)	10 U/L	14 U/L	11 U/L
ALP (normal range: 43-115 U/L)	150 U/L	105 U/L	118 U/L
Total Bilirubin (normal range: 5- 21 umol/L)	7.6 umol/L	6.1 umol/L	5.2 umol/L
CRP (normal range: 0-5 mg/L)	99 mg/L	<1.0 mg/L	<1.0 mg/L

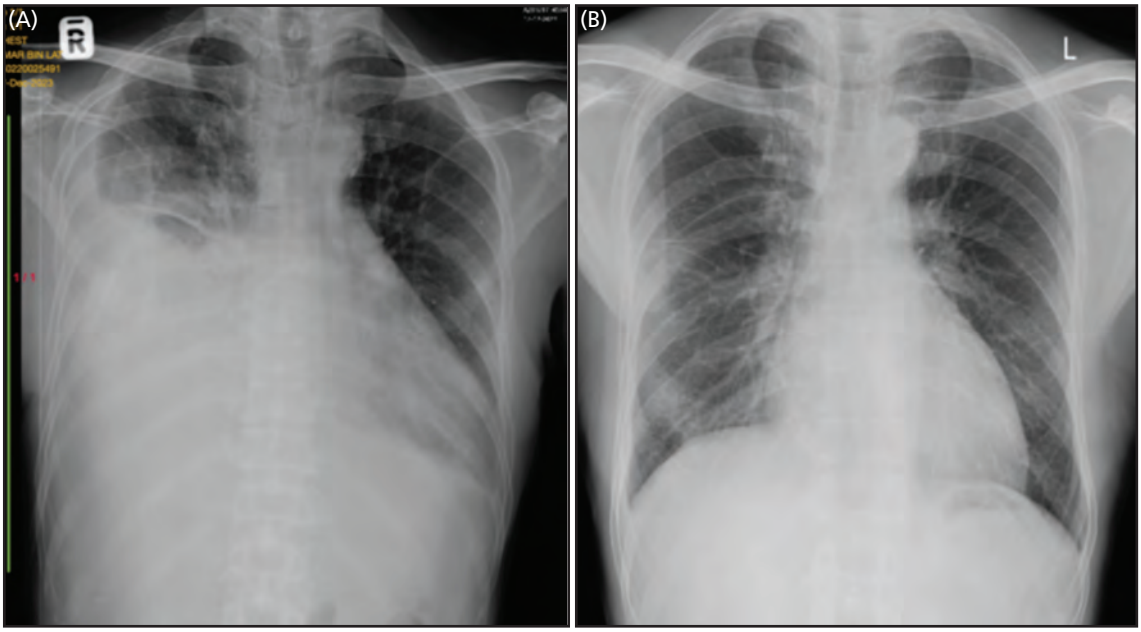

Fig. 1: (A) Chest radiograph on admission showing a massive right-sided pleural effusion. (B) Follow-up chest radiograph during clinic review demonstrating complete resolution of the right pleural effusion

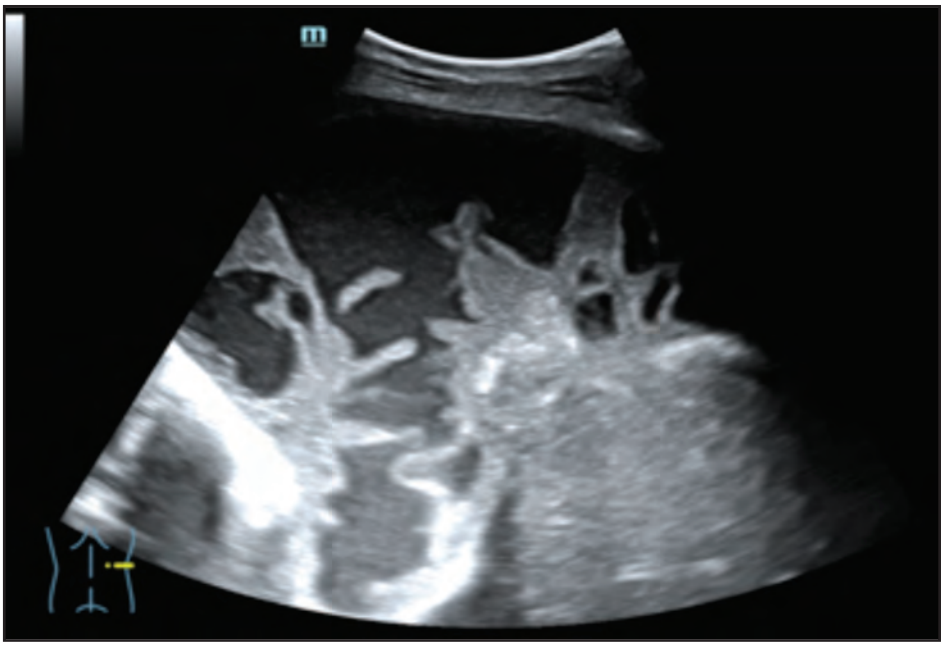

Fig. 2: Thoracic ultrasound showing multiloculated right pleural effusion

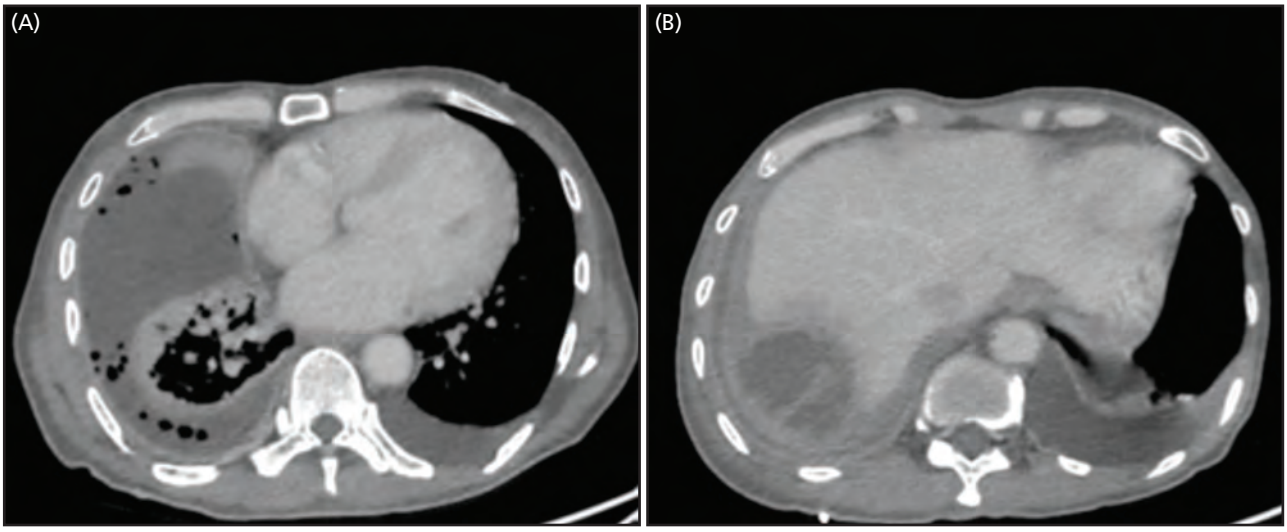

Fig. 3: CECT thorax and abdomen (A) Large right sided pleural effusion with air pockets within and enhancing pleural lining in keeping with empyema thoracis. (B) multiloculated abscess collection seen at segment VII of liver measuring 6 x 5.3 x 3.9 cm

him off oxygen therapy. He then completed intravenous meropenem for 42 days and symptomatically improved. During clinic review at two months after completing antibiotics, he remained well with no fever. Chest radiograph showed no pleural effusion (Figure 1B), and a surveillance ultrasound of the abdomen revealed a resolved liver abscess. His initial glycated haemoglobin (HbA1c) was 9.7%, necessitating basal-bolus insulin therapy. The patient was referred to the Diabetes Resource Centre at our hospital for further education and support. Upon follow-up, his HbA1c improved to 7.9%, indicating better glycaemic control. His blood glucose levels are now significantly better managed.

DISCUSSION

Empyema is commonly linked to pneumonia; however, it can also arise from thoracic trauma or surgery. Empyema is associated with risk factors such as diabetes, gastro-oesophageal reflux disease (GERD), alcohol addiction, prolonged corticosteroid usage, illicit drug use, thoracic or esophageal surgery, aspiration, or trauma.[3] Gram-positive bacteria are more prevalent in community-acquired empyema. Gram-negative bacteria are associated with patients with conditions such as diabetes, GERD, and alcohol abuse.[3]

As the case illustrated, we found ESBL *E. coli* isolated in pleural fluid culture. It typically originates in the large intestine and is seldom seen in the pleural cavity. The liver was likely the initial site of infection, given its role in filtering intestinal blood through the portal vein. This is supported by the patient's one-week history of right-sided chest pain, which may have been referred pain from the liver abscess or a result of diaphragmatic irritation. This case highlights hematogenous spread from a liver abscess, likely seeded via portal bacteremia, as there was no radiological evidence of transdiaphragmatic communication. The incidence of *E. coli* pneumonia is reported to be around 3-12% of pneumonia infections, which is a rare phenomenon.[4] ESBL is an enzyme that degrades most beta-lactamase drugs, including penicillin, cephalosporin, and monobactam. Infection-causing ESBL-producing bacteria have contributed to poor patient outcome. Even though ESBL-producing bacteria were previously thought to be primarily responsible for nosocomial infections, community-acquired infections have recently been documented, raising concerns that the frequency of such cases would grow in the future.[5]

In our patient, who presented with community-acquired lung empyema without gastrointestinal symptoms and a negative urine culture, presents a diagnostic challenge. The presence of poorly controlled diabetes should alert clinicians of a wider array of possible organisms, in this case ESBL *E.coli*. Further investigations are needed to reveal occult infections from gastrointestinal sources that are consistently linked to *E. coli* infections.

Concurrent empyema and hepatic abscesses are rarely documented in the literature.[6] In Asia, *Klebsiella pneumonia* is the most common pathogenic bacteria causing liver abscesses, followed by *Streptococcus sp.* and *E. coli*.[7] Certain risk factors promote the development of liver abscesses, such as diabetes, cirrhosis, male gender, elderly age, immunocompromised patients, and people with proton pump inhibitor usage. The initial test of choice is an abdominal ultrasound, followed by computed tomography with contrast.[8] Drainage of the abscess and antibiotic treatment are the cornerstones of treatment. If the liver abscess is larger than 5 cm or if there are complications such as peritonitis and abscess rupture, surgery or drainage is required. The duration of antibiotic therapy should be decided based on the number of abscesses and clinical response. Patients with liver abscesses with empyema should have antibiotics for four to six weeks.[9] The management of empyema usually involves the drainage of the fluid with tube thoracostomy and the administration of adjunctive antimicrobial medications.

In our patient, he has a complicated right pleural effusion. The right ICD was inserted. However, the pleural fluid was

not draining well. Repeated bedside ultrasound thorax demonstrated persistent multiloculated right pleural effusion. Intrapleural fibrinolytic therapy has been proven to improve fluid drainage in complex pleural effusions. Video-assisted thoracic surgery (VATS) or IPFT are the options for managing loculated pleural effusions with unsuccessful tube drainage. IPFT is an effective, safe, and cost-efficient treatment option for loculated pleural effusion with failed tube drainage when VATS is unavailable.[10]

CONCLUSION

Our case demonstrated an uncommon but important recognition of empyema concurrent with a liver abscess especially when a risk factor such as a poorly controlled diabetes is present. We highlighted the importance of an extensive workup in ESBL *E. coli* empyema to ensure the early diagnosis of liver abscesses. Early recognition by the treating physician and prompt initiation of therapy are vital for achieving better clinical outcomes.

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DECLARATION

The authors have no conflict of interest to disclose.

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Successful assisted conception in a case of recalcitrant chronic urticaria treated with omalizumab: a case report

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SUMMARY

Chronic urticaria (CU) is a debilitating disease characterized by recurrent wheals, angioedema, or both, lasting for at least six weeks. Although self-limiting, it remains a challenging condition to manage, particularly in patients with specific comorbidities. We report the case of a 39-year-old woman with recalcitrant CU and polycystic ovarian syndrome (PCOS), along with a history of adverse obstetric events. Her CU was successfully treated with subcutaneous omalizumab, providing excellent symptom control and enhancing her quality of life. Subsequently, she underwent an uneventful assisted reproduction technology (ART) procedure with a meticulously timed, resulting in the birth of healthy twins. This case highlights the role of omalizumab in treating recalcitrant CU during the preconception period and its continuation throughout pregnancy. It also underscores the importance of a comprehensive multidisciplinary approach in achieving a successful outcome.

INTRODUCTION

Chronic urticaria presents as recurrent episodes of wheals, angioedema, or both, persisting for at least six weeks. CU can be classified into either spontaneous or inducible forms. This condition is driven by mast cells, whose activation triggers the release of histamines and cytokines, leading to sensory nerve activation, vasodilation, and plasma extravasation. Globally, the point prevalence of CU is estimated to range from 0.1% to just under 1%.[1] As CU significantly affects a patient's quality of life, the Urticaria Activity Score 7 (UAS7) serves as a valuable tool for evaluating disease severity based on daily symptoms over the past seven days. A UAS7 score below 7 indicates well-controlled urticaria.[2]

CASE PRESENTATION

A 39-year-old woman with a history of three miscarriages and no living child was under follow-up at an Infertility Clinic since her last spontaneous miscarriage in 2013. She was diagnosed with polycystic ovarian syndrome (PCOS) based on her irregular anovulatory cycles and polycystic ovaries observed on transvaginal ultrasound. She had chronic spontaneous urticaria (CSU) and chronic inducible urticaria (CIndU) for the past 14 years, with wheals occurring spontaneously, over areas with sustained pressure (delayed pressure urticaria), and after exercising (cholinergic urticaria). Notably, she was labeled allergic to ibuprofen, mefenamic acid, metronidazole, ciprofloxacin, azithromycin, metoprolol, prazosin, perindopril, amlodipine, tranexamic acid, and micronized progesterone due to coincidental wheals appearing when those medications were initiated. She was treated with second-generation H1 antihistamines (SgAH) under dermatology follow-up for the past year. Her chronic urticaria was initially managed with SgAH at a twofold standard dose, which was then increased to a fourfold dose.

Over two years, she underwent two cycles of intrauterine insemination (IUI). The first IUI cycle was performed with clomiphene citrate but was unsuccessful despite a good follicular response. During her second IUI attempt using clomiphene citrate and low-dose gonadotropin, she developed multiple follicles, leading to the procedure being converted to in-vitro fertilization (IVF). She developed breathlessness and chest pain five days after ovum retrieval. Her cardiac enzymes, electrocardiogram, and echocardiogram were normal. A computed tomography pulmonary angiography (CTPA) showed no evidence of pulmonary embolism, but it revealed mild cardiomegaly and mild pleural effusion (Figure 1). She was diagnosed with moderate to severe ovarian hyperstimulation syndrome (OHSS). She also experienced worsening urticaria, along with vomiting and abdominal pain, occurring within several hours to days after each assisted reproductive treatment. A dermatology consult was sought for treatment optimization before proceeding with further fertility treatment.

In 2018, her Urticaria Activity Score 7 (UAS7) ranged from 16 to 18 (Figure 2) despite the addition of montelukast; therefore, oral cyclosporin was initiated. Her UAS7 remained unchanged while on cyclosporin at 2.5 mg/kg/day. After two months, cyclosporin was discontinued as she developed peripheral numbness. She was started on subcutaneous omalizumab 300 mg in March 2019. After three weeks of treatment, her UAS7 score dropped to 7 (Figure 2). She experienced a headache after the injection; thus, the dose was reduced to 150 mg every four weeks.

Three months after starting omalizumab, she underwent frozen embryo transfer (FET). An artificial cycle using

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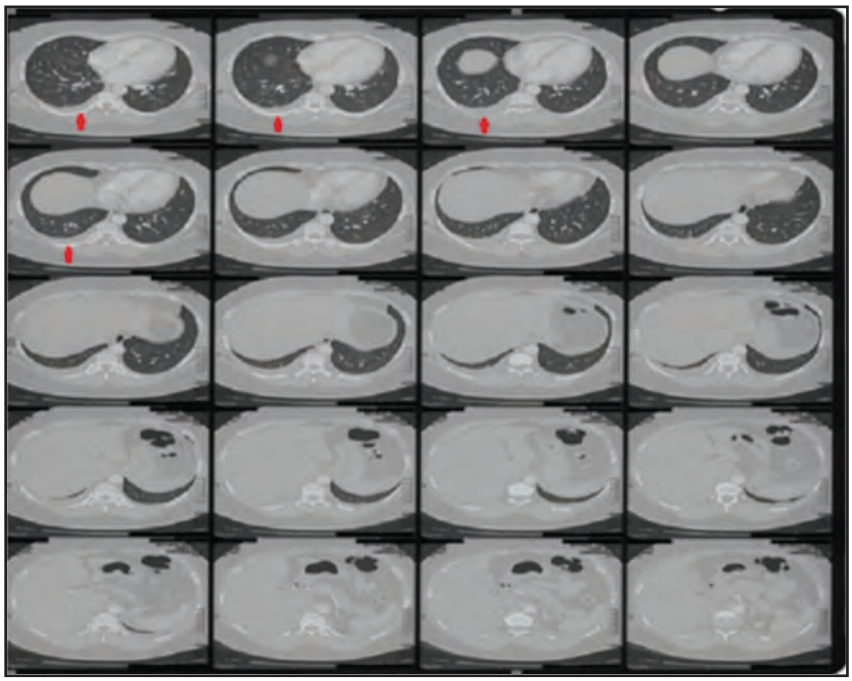

Fig. 1: Mild pleural effusions detected in the right lung base (indicated by red arrow)

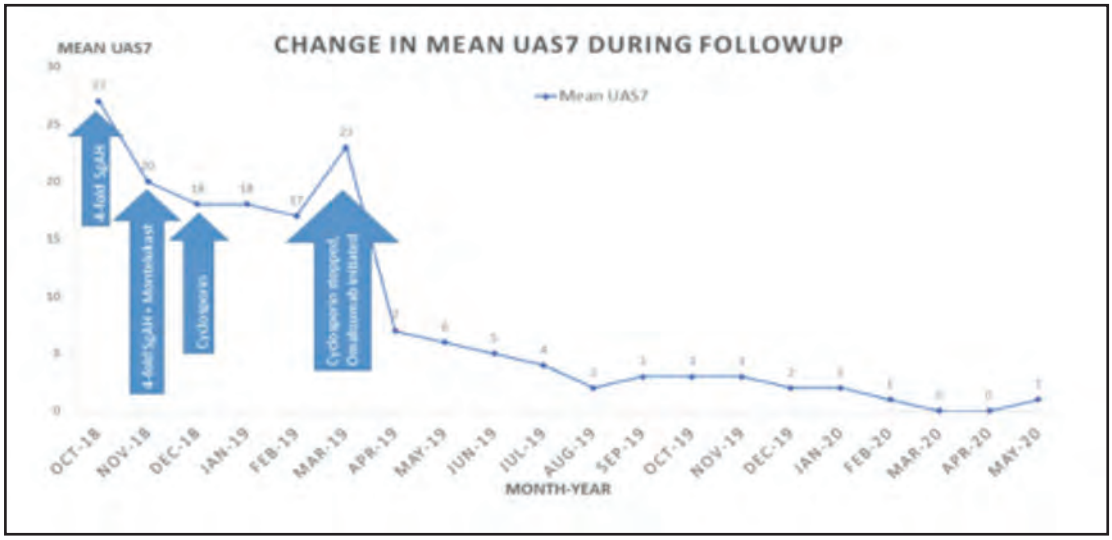

Fig. 2: showed reduction in the patient's UAS7 score chart after omalizumab initiated

estradiol valerate 4 mg twice daily was initiated. By day 10 of the cycle, her endometrial lining measured 8 mm and displayed a trilaminar pattern. On the day of transfer, two of her embryos had proliferated to more than 10 cells, and one had developed early compaction features. She experienced nausea and urticaria after the procedure. Her serum tryptase levels were normal. Two weeks after the embryo transfer, her serum βhCG level was 925 IU/L, and the subsequent ultrasound confirmed the presence of two gestational sacs (Figure 3).

She was closely monitored by the maternal-fetal medicine team throughout the antenatal period. Monthly subcutaneous omalizumab at 150 mg was continued with good efficacy. Both twins were growing appropriately for gestational age. At 34 weeks of gestation, she went into preterm labour and underwent an emergency Lower Segment Caesarean Section (LSCS). She breastfed both her babies, who remained well until one month of age with no evidence of neonatal thrombocytopenia.

DISCUSSION

OHSS is a complication of controlled ovarian hyperstimulation. The pathogenesis of OHSS involves the shift of fluid from the intravascular compartment into the third space. Various theories explain the development of OHSS. The first is the role of vascular endothelial growth

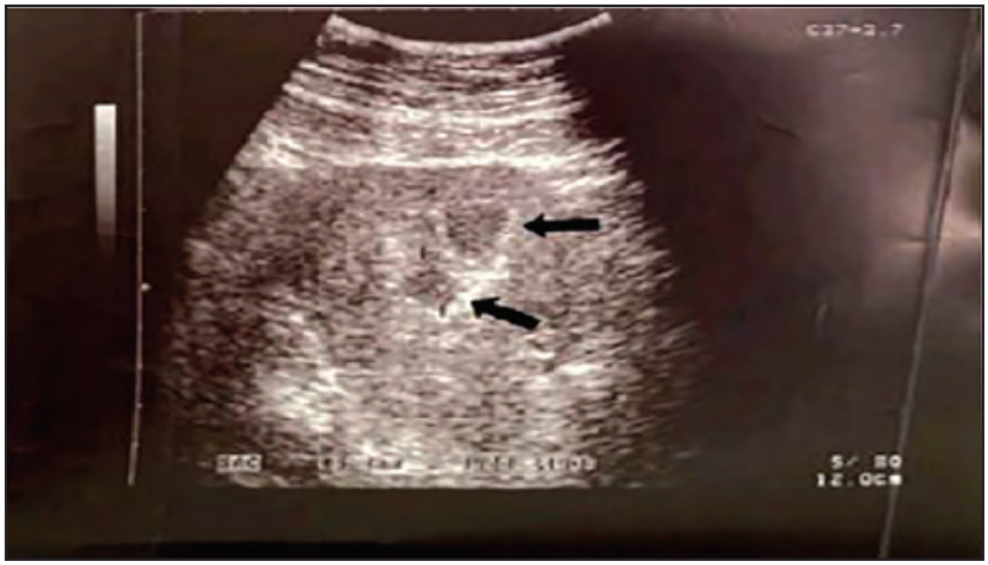

Fig. 3: Ultrasound showed presence of two gestational sacs indicating twin pregnancy

factors (VEGF), which mediate capillary permeability and increase the risk of ascites. Another theory involves interleukin 6 (IL-6), which has been found to be elevated in cases of OHSS.[3]

Our patient had CSU with concomitant inducible urticaria since the age of 25, with varying disease severity. It has been reported that delayed pressure urticaria occurs in 10% to 50% of patients with CSU, often presenting with greater severity and a longer duration of illness.[4,5] She was classified as allergic to multiple medications, likely due to the appearance of wheals that coincided with medication use. She had poorly controlled CSU and physical urticaria.

As our patient was refractory to SgAH at four times the standard dose, montelukast, and cyclosporin, she was initiated on omalizumab for CSU management. Omalizumab is a recombinant monoclonal anti-IgE antibody approved for the treatment of chronic urticaria unresponsive to SgAH.[1] Omalizumab binds to the Fc portion of immunoglobulin E (IgE), preventing IgE from binding to its receptor, FcεRI. This leads to a significant reduction in serum-free IgE. Additionally, there is a downregulation of FcεRI.[6]

Omalizumab has not been approved for CSU treatment during pregnancy, despite being assigned a Pregnancy Category B rating by the FDA.[7] An editorial reported that omalizumab, an IgG antibody, is transferred to the baby via the placenta, with the greatest exposure occurring in the third trimester.[8] Moreover, IgG complexes are transferred through neonatal Fc receptor-mediated transcytosis.

The largest published study on the safety of omalizumab in pregnancy is the expect study, in which 250 pregnant women with asthma received at least one dose of omalizumab within 8 weeks before conception or at any time during pregnancy. There was no increased prevalence of major congenital anomalies, prematurity, or small-for-gestational-age infants compared to pregnant women with asthma who were not exposed to omalizumab. Furthermore, no increased risk of neonatal thrombocytopenia was found in the cohort, a concern previously reported in non-human primates.[7]

To date, several case reports have documented the use of omalizumab in pregnancy for CSU with favourable outcomes. However, data on omalizumab use for CIndU remain limited, as these patients were excluded from randomised controlled trials of omalizumab. Nonetheless, there is growing evidence that both CSU and CIndU can be successfully treated with omalizumab.[5]

Furthermore, Vieira dos Santos et al. reported a case of a pregnant woman with CSU and CIndU (pressure urticaria and dermographism) who was effectively treated with omalizumab, highlighting its similar mechanism of action across urticaria subtypes.[9] Liao et al. reported two cases in which patients became spontaneously pregnant while receiving omalizumab for CSU. One patient was exposed to omalizumab at 300 mg every four weeks for two months and was later found to be 10 weeks pregnant at a follow-up visit. The other patient conceived three months after being treated with omalizumab, and both were reported to be well without complications.[10]

Although most cases support the use of omalizumab in pregnancy and its safety, further research is needed.

To our knowledge, this is likely the first case to describe the use of omalizumab for CU in conjunction with FET as part of ART in a patient with infertility, PCOS, and recurrent miscarriage.

CONCLUSION

Omalizumab has a good safety profile and is effective for refractory CU. Therefore, it should be considered a treatment option for pregnant women with this condition. Further studies are needed, particularly to evaluate its long-term safety, efficacy, and effects when used during the periconceptional period.

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