CASE REPORT

The Madura stump: A case report of an atypical presentation

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SUMMARY

Madura foot or mycetoma is a rare disease in Malaysia. It is a chronic, slowly progressive, and deforming infection involving the subcutaneous tissue and bone. Characterized by a triad of painless subcutaneous mass, multiple discharging sinus, and visible coloured grains, it is caused by bacteria (actinomycetoma) or fungal (eumycetoma) or both. Here, we describe a case of a 36-year-old man infected with human immunodeficiency virus on anti-retroviral therapy, presented with a 3-year history of right below knee amputation (BKA) stump's ulcerated nodules associated with pus discharge. He had right BKA for non-healing ulcerated nodules of right foot for 4 years. Extensive investigations showed that he had mycetoma of the right BKA stump. He was treated with a prolonged course of multidrug therapy with complete resolution after 14 months of treatment.

INTRODUCTION

Mycetoma is a rare, chronic destructive infection of the skin, subcutaneous tissue and connective tissue, muscle and bone caused by fungi (eumycetoma) or filamentous aerobic and anaerobic bacteria (actinomycetoma).[1] Here, we described a case of eumycetoma occurring on a right below knee amputation (BKA) stump with the aim to highlight the great challenges to reach the final diagnosis for this patient as well as the prolonged treatment duration that was needed to treat the infection.

CASE REPORT

A 36-year-old transgender woman was referred to us in 2020 with multiple painful ulcerated nodules on his right BKA stump. He was a hair dresser, with underlying human immunodeficiency virus (HIV) disease, taking tenofovir, emtricitabine, and efavirenz since 2009. He had tuberculosis lymphadenopathy diagnosed and treated in 2008. He grew up in a long house. He had been working in Kuala Lumpur for many years. He did not engage with any activity or hobby that led to direct skin contact with soil in the city. He, however, visited his home town yearly, which was situated in the interior remote area of Sarawak.

He first developed multiple painful nodules with haemo-purulent discharges on his right foot since 2012 (Figure 1a and b) which failed to improve with multiple courses of antimicrobials and wound debridement. He underwent right BKA in 2016. His wounds did not heal completely. Eight months post-BKA, multiple painful nodules gradually developed over his right BKA stump. Treatment with multiple short courses of antibiotics was again ineffective. Several skin biopsies were done between 2017 and 2019, which only showed chronic inflammatory responses with predominant neutrophilic infiltrates. There was no granuloma and no malignant cells were seen in the biopsied tissue. Computerised tomography (CT) scan of right BKA stump in 2019 showed subcutaneous fat stranding at the right BKA stump region with no focal enhancing collection, bony lytic, or sclerotic lesions. The findings were suggestive of infection. Ultrasonography of right BKA stump in 2019 showed multiple subcutaneous and intramuscular collections of the right knee extending to proximal tibia and fibula.

When the patient presented to us early 2020, there were multiple tender ulcerated nodules and plaques of various sizes at the right BKA stump and the medial aspect of right knee (Figure 1c and d). At this junction, a few differential diagnoses were considered including mycetoma, non-tuberculous mycobacterial infection, cutaneous tuberculosis (tuberculosis gumma), and subcutaneous fungal infections like sporotrichosis.

Laboratory investigations revealed normochromic normocytic anemia and thrombocytosis with hemoglobin of 8.3 g/dl, total white cell of 10×10^9/L, and platelet count of 703×10^9/L. His erythrocyte sedimentation rate (ESR) was 97mm/hour, C-reactive protein was 52.3 mg/dL. His CD4 count was 383 cells/mm^3 with a HIV viral load<20 copies/ml. His renal and liver profiles were normal. His chest radiograph revealed no focal lung lesions with a normal cardiac size. Radiographic examination of right tibial stump showed periosteal reaction suggesting early osteomyelitis. Sonographic examination demonstrated multiple subcutaneous and intramuscular collection at the stump extended to the extra-articular of knee joint with subperiosteal extension and sinus tract to the overlying skin. His skin biopsy tissue for bacterial, fungal, and mycobacterium cultures revealed no growth. Skin tissue for mycobacterium and fungal PCR were negative. Histological examination of a nodule revealed dense inflammation with neutrophils predominantly in dermis and subcutaneous tissue, together with lymphocytes and foamy macrophages (Figure 1e). At higher magnification, there were eosinophilic

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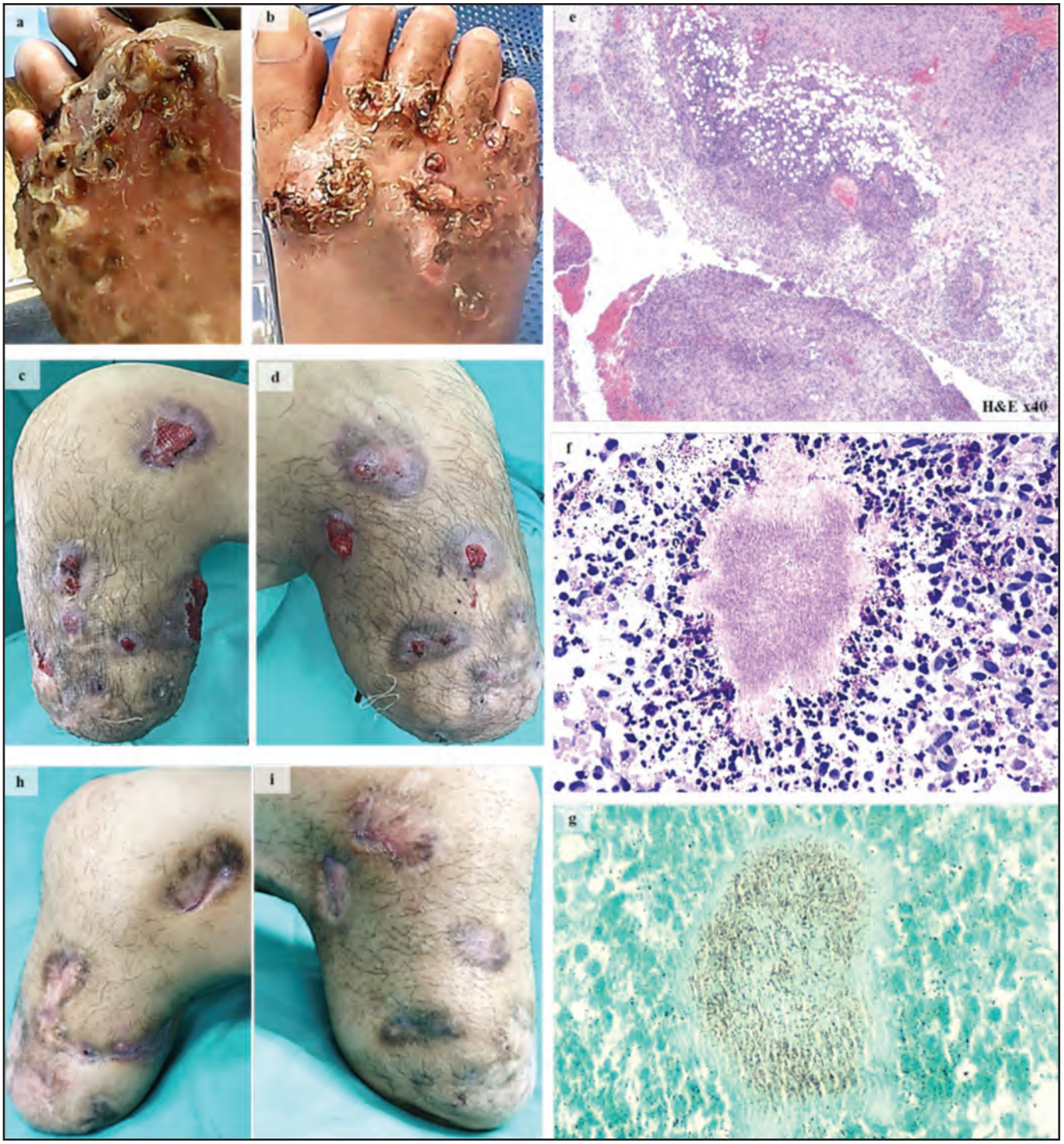

Fig. 1: Images of the patient's limb and histopathological specimen. (a&b, patient's own photographs) Multiple crusted nodules with haemo-purulent discharges on the dorsum and the sole right foot before below knee amputation (BKA); (c&d) multiple ulcerated nodules and plaques at the right stump 8 months after BKA; (e) Dense inflammation with neutrophils predominantly in dermis and subcutaneous tissue together with lymphocytes and foamy macrophages (hematoxylin and eosin H&E stain, x40); the grain with filamentous materials stained positive for (f) periodic acid-Schiff stain (x200) and (g) Grocott-Gomori's methenamine silver stain (x200); (h&i) right BKA stump healed completely with dyspigmented atrophic scars 14 months after combination of antimicrobials.

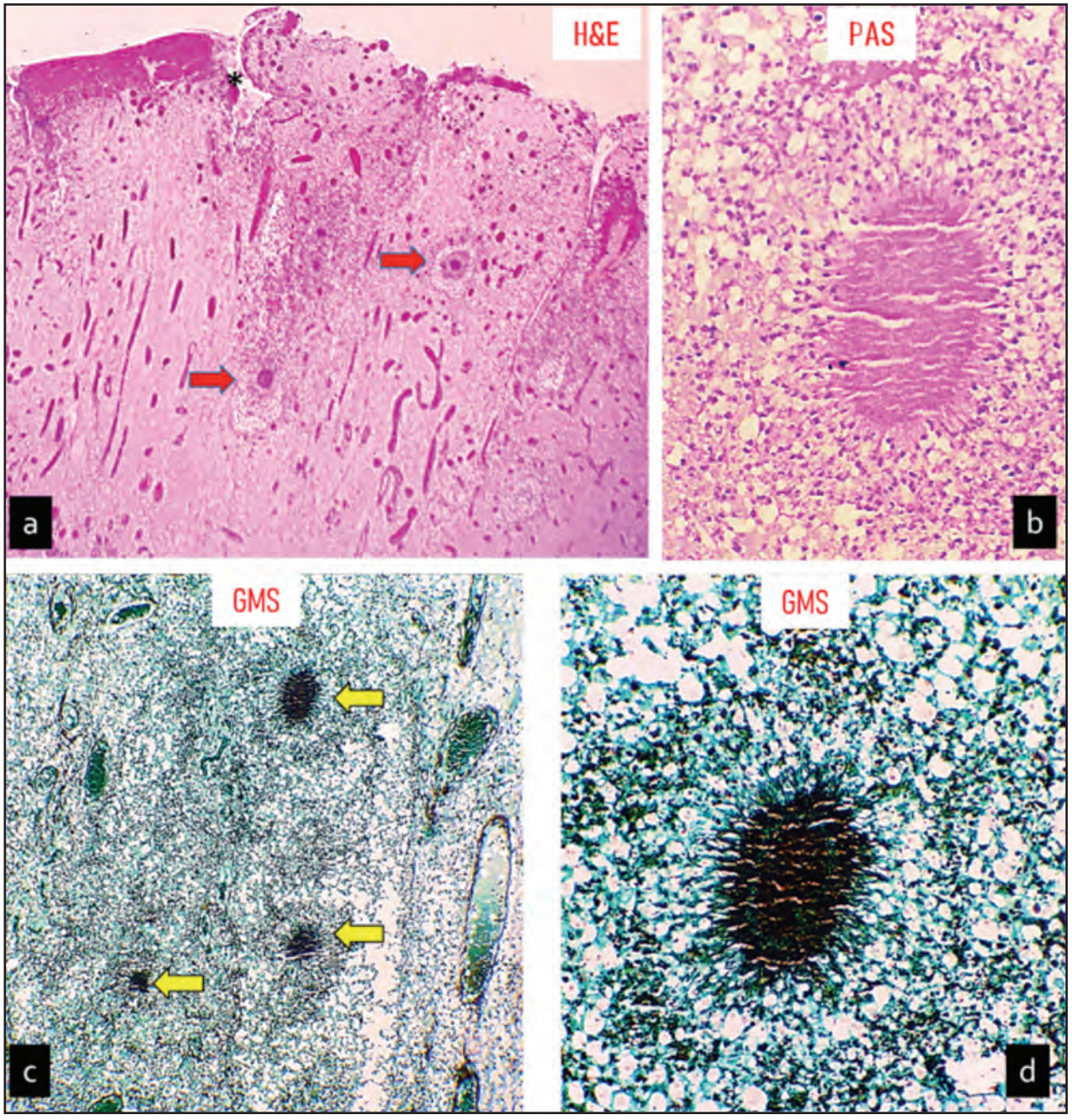

Fig. 2: The histology of the amputated right foot in 2016. (a, H&E x2.5) there were sinus formation with narrow opening (asterisk) to the ulcerated surfaces; the sinus contained organism (red arrows); (b, PAS) the organisms were stained positive under Periodic acid Schiff (PAS) and (c & d) Grocott methenamine silver (GMS). There were filamentous tangles (yellow arrows) surrounded by neutrophils forming the Splendore-Hoeppli phenomenon seen on the high powered field (b, PAS x40; c, GMS x10; d, GMS x40).

structures in a starburst pattern forming the Splendore-Hoeppli phenomenon. Filamentous materials stained positive for both Periodic acid–Schiff (Figure 1f) and Grocott-Gomori's methenamine silver stain (Figure 1g) were seen.

In addition, the tissue block from amputated right foot performed in 2016 was retrieved, recut, and stained. With hematoxylin and eosin (H&E) stain, it showed inflammatory cells which predominantly neutrophils with lymphocytes and foamy macrophages. Sinus formation with narrow opening to ulcerated surface was seen (highlighted with black asterisk), and there were organisms present in the sinus track (highlighted with red arrow, Figure 2a). There were filamentous tangles of organism surrounded by neutrophils forming the Splendore-Hoeppli phenomenon. These organisms were stained positive with Grocott's Methenamine Silver and periodic acid-Schiff (Figure 2b–d).

A diagnosis of eumycetoma of the right BKA stump (and right foot) was finally made eight years after his first

symptoms in 2012. He was initially given empirical combination of antibiotics [intravenous (IV) amikacin (2 weeks), oral clarithromycin (6 months), oral doxycycline for (5 months)], and antifungals [IV amphotericin B (cumulative dose of 513 mg), combination of oral terbinafine and itraconazole]. The antibiotics were stopped after the definitive diagnosis of eumycetoma was finally established. He received a total 14 months of oral itraconazole and terbinafine. His anti-retroviral therapy and haematinics were continued without interruption. In addition, simple occlusive dressing was performed to all the ulcerated nodules daily until all wounds healed. His anaemia resolved; renal and liver profiles remained normal throughout the treatment course. All the wounds of his right BKA stump healed completely with dyspigmented atrophic scars at the end of medical therapy (Figure 1h and i).

DISCUSSION

Mycetoma was first reported in the medical literature in 1694 and is commonly known as "Madura foot" after the description of a case reported in the mid-19th century in the Indian town of Madurae. It is a neglected disease listed in the Drug for Neglected Disease Initiative, DNDi, since 2016.[1] The true incidence and prevalence of mycetoma are not well known. Most cases of mycetoma are reported from the "mycetoma belt" and occur in tropical and subtropical environments characterized by short rainy seasons and prolonged dry seasons that favour the growth of thorny bushes.[2] These include Brazil, Mexico, and Venezuela in southern America, Senegal, Somalia, and Sudan in Africa, Saudi Arabia and Yemen in the Middle East, and India in Asia. About 75% of cases come from Mexico, Sudan, and India.[1]

Mycetoma is obtained after exposure to contaminated soil and inoculation of the organism into the skin. The trauma event may be subtle. Up to 80% of the patients may not recall any event of direct trauma before the infection. Young adults, particularly men aged between 20 and 40 years, are most affected. Students, farmers, and workers are the most common occupation groups being associated with mycetoma.[1]

Mycetoma is classified into actinomycetoma and eumycetoma. Actinomycetoma is caused by filamentous aerobic and anaerobic bacteria such as *Actinomadura madurae, Norcadia spp*. Eumycetoma is caused by true fungi like *Madurella mycetomatis, Trematosphaeria grisea (Madurella grisea)* etc. In South East Asia, *Madurella mycetomatis* is the predominant agent of eumycetoma while *Nocardia* asteroids is the predominant agent of actinomycetoma.[3]

Madura foot has a clinical triad of painless subcutaneous masses, multiple sinuses, and discharge and visible coloured grains.[4] Only about 30% of patients complain of pain. Discharge happens in 80% of the patients. More than three quarter develop lesions over the foot. However, any part of the body may be affected including the perineum. About 2% had lesions involving multiple anatomical sites.[5] Very often, the colour of the grains may provide some clues as specific organism produce grains of specific colour. Black grains can be seen in eumycetoma (fungus). Actinomycetoma may discharge grains with colour of yellow, brown, and red to pink in certain species.

With the history and clinical appearance of the lesion, a provisional diagnosis of mycetoma could be made. Clinical examination alone neither identifies the causative organism nor detects the spread of disease along the different tissue planes and bone. Imaging like X-ray, ultrasound, MRI, CT scan is needed to assist the diagnosis. To identify the organism, fine needle aspiration cytology (FNAC), skin biopsy, grains culture, molecular techniques, and serology test are essential.[6]

The rarity of mycetoma results in knowledge gaps[4] in the recognition of it, as depicted in our case. A combination of radiographic and laboratory techniques is required to reach a diagnosis.[4,6] Furthermore, it is difficult to treat disease as there is lack of standard guideline on the best treatment strategy.[4,7] Numerous antibiotics and antifungals, either alone or in combination have been used.[4,7] Various agents have been described in treating actinomycetoma including bactrim, dapsone, amikacin, clofazimine, doxycycline, tetracycline, rifampin, minocycline etc. Antifungal like itaconazole, voriconazole, parenteral miconazole, amphotericin B, flucytosine, and terbinafine have been used in eumycetoma.[7] The length of the treatment duration to achieve the disease cure described in the literature varies from months to years. Generally, treatment is continued until the complete resolution of lesions.[7] Surgical intervention alone including debridement, excision, and amputation, without appropriate duration of antimicrobials is not adequate.[4]

The susceptibility of eumycetoma and treatment responses in patients with cell-mediated immune deficiency is unknown. Some had reported immune deficiency in actinomycetoma[8] while others had shown that no immune defects were detected.[9] Our patient, although being infected with HIV, had a good CD4 counts with low viral load. He responded to a prolonged course of combined antimicrobial and antifungal chemotherapy without needing further surgical intervention.

CONCLUSION

We described a challenging case of eumycetoma occurring on a right BKA stump. Raising awareness of this debilitating neglected tropical disease among clinicians is necessitous. Prompt and appropriate treatment is crucial to reduce morbidity.

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CONFLICT OF INTEREST

None to declare.

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