CASE REPORT

Thymoma-associated paraneoplastic syndromes: A case series unveiling diagnostic challenges and therapeutic outcomes

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SUMMARY

This study aims to explore the association between thymoma and various paraneoplastic syndromes (PNS), focusing on diagnostic challenges and treatment responses. We retrospectively analysed four cases diagnosed with thymoma and associated PNS, managed via uniportal video assisted thymomectomy and subsequent clinical follow-up. The cases presented with nephrotic syndrome, Good's syndrome, and two instances of pure red cell aplasia (PRCA). Surgical intervention resulted in varying outcomes among the paraneoplastic conditions. The Good's syndrome case showed improvement post-thymectomy with the patient remaining infection-free at the last follow-up. One of the PRCA cases achieved complete remission post-thymectomy without further adjuvant therapy. Nephrotic syndrome presented alongside thymoma contributed to a more challenging course, with the patient's renal function deteriorating postoperatively. This case series underlines the importance of a personalized approach in managing PNS associated with thymomas due to the unpredictable therapeutic outcomes. It also highlights the necessity for multi-disciplinary involvement in care and the urgent need for further research to establish a standardized treatment protocol. This study contributes valuable insights into the natural history and management of these complex syndromes in the context of thymoma.

INTRODUCTION

The landscape of thymomas and their associated paraneoplastic syndromes (PNS) represents a confluence of oncological and immunological intricacies. The pioneering observation by Weigert et al. in 1901, identifying a thymoma in conjunction with myasthenia gravis (MG), marked the inception of our investigation into this complex interplay.[1] The International Thymic Malignancy Interest Group (ITMIG) has refined our understanding of the epidemiological and clinical dimensions of these associations.[2]

Transitioning from historical theories of "bad humours" to contemporary autoimmune paradigms has been pivotal. Thymoma cells can secrete cytokines and peptides, instigating aberrant immune responses.[3] These molecules can trigger the activation of autoreactive T cells or the production of autoantibodies targeting distant organ systems, leading to a spectrum of PNS.[4] The disruption of thymic architecture inherent in thymomas derails the T-cell maturation process, compromising central immune tolerance and paving the way for autoimmunity.[5]

In this series, we delve into four case studies, each presenting a unique facet of thymoma-associated PNS, including nephrotic syndrome, Good's syndrome, and 2 cases of pure red cell aplasia (PRCA). These cases highlight the heterogeneity in clinical presentations and therapeutic responses, underscoring the imperative for individualized management strategies.

CASE PRESENTATION

Case 1

A 61-year-old lady was referred for an incidental finding of a mediastinal mass during a routine chest X-ray. She had chronic kidney impairment (stage 4), diabetes mellitus type 2, and hypertension. Over the past year, she developed bilateral lower limb swelling and significant proteinuria (5611 mg/litre). A CT scan revealed a well-defined mass in the mediastinum. An image-guided biopsy suggested a Thymoma Type AB. She underwent a right uniportal video assisted thoracoscopic thymomectomy in September 2023. Postoperatively, upon follow up, there was no recurrence detected in surveillance CT of the Thorax. Her urine protein readings however remained static, and she refused a renal biopsy despite multiple counselling efforts. Her renal function deteriorated, and she was ultimately counselled for long-term renal replacement therapy.

Case 2

A patient presented with breathlessness and reduced effort tolerance for three weeks in February 2019. Diagnosed with PRCA in January 2019, she had been managed with immunosuppressants and zinc supplements. A chest radiograph revealed a right-sided pleural effusion, and a CT scan showed a large mediastinal mass suggestive of thymoma. Bronchoscopy ruled out bronchial involvement. An image-guided biopsy confirmed Thymoma Type AB. She underwent a right anterolateral thoracotomy and thymomectomy in June 2019. Postoperative recovery was uneventful, and she achieved total remission of PRCA without further treatment. She has been medication-free for four years, with no evidence of recurrence on follow-up CT scans.

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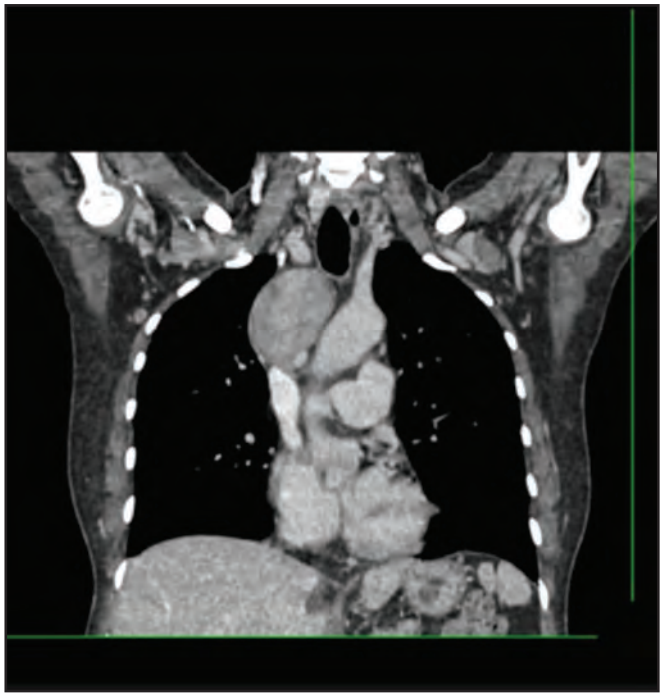

Fig. 1: Pre-operative CT Thorax for Case 4

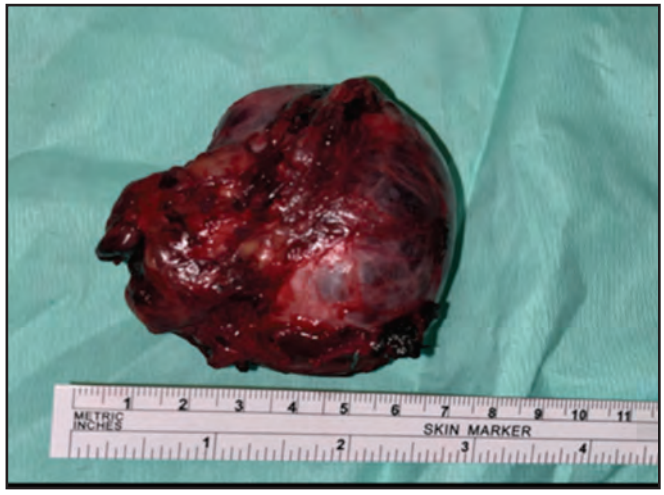

Fig. 2: Thymoma specimen

Case 3

A 58-year-old gentleman with hypertension and oral lichen planus presented with reduced effort tolerance and palpitations in November 2022. He was found to be severely anaemic (Hb 4.9 g/dl) and required immediate transfusion of four units of packed cells. A chest X-ray revealed a right hilar opacity, and a subsequent CT scan showed a large anterior mediastinal mass. An image-guided biopsy confirmed a Thymoma Type AB. He underwent a uniportal right video assisted thoracoscopic thymomectomy in January 2023. Postoperative recovery was uneventful. Follow-up histopathological examination confirmed the thymoma. Surveillance CT thorax in August 2023 showed no recurrence, but the patient remains on ciclosporin therapy for PRCA control.

Case 4

A 58-year-old ex-smoker with recurrent lung infections from March to June 2023 had a thymoma with hypogammaglobulinemia. She was repeatedly admitted for respiratory infections caused by pathogens like Extended Spectrum Beta Lactamase Klebsiella and Pseudomonas Aeruginosa. A chest radiograph showed a widened mediastinum, and a CT scan revealed a mediastinal mass as shown in Figure 1. An image-guided biopsy confirmed a Thymoma B2 subtype. She underwent a uniportal right video assisted thoracoscopic thymomectomy in August 2023. Postoperatively, she remained free from infections with regular IVIg therapy. Follow-up CT scans showed no recurruence, but her serum immunoglobulin levels remained low, with her IgA, IgG and IgM results being <0.10g/L, 5.07 g/L and <0.20 g/L respectively, necessitating continued IVIg therapy.

DISCUSSION

Thymomas are unique tumours that have a significant impact on the immune system, often leading to paraneoplastic syndromes (PNS). These syndromes, such as nephrotic syndrome, pure red cell aplasia (PRCA), and Good's syndrome, present distinct clinical challenges and require tailored management approaches.

Nephrotic Syndrome

Nephrotic syndrome associated with thymoma is rare and poses a significant treatment challenge. The disruption of T-cell maturation and the release of cytokines by thymoma cells contribute to renal impairment. Our patient's refusal of a renal biopsy limited our ability to confirm the exact type of nephropathy, complicating the treatment strategy. Studies suggest that while some patients respond well to thymectomy, others may experience persistent or worsening renal dysfunction. This variability underscores the need for comprehensive preoperative evaluation and long-term renal monitoring post-thymectomy. Further research is needed to understand the mechanisms driving nephrotic syndrome in thymoma patients and to develop targeted therapies.[6]

Several studies have suggested a link between thymoma and various renal pathologies, such as minimal change disease, membranous nephropathy, and focal segmental glomerulosclerosis (FSGS). These conditions often manifest after the initial treatment of the thymoma. The largest case series by Karras et al. reported that 47% of thymoma-associated nephropathy cases occurred post-thymoma treatment, with a significant proportion progressing to end-stage renal failure.[7] This highlights the importance of vigilant monitoring and potential adjunctive therapies to manage renal complications effectively.

Summary of Case Discussions

Case	Symptoms	PNS association	Co-morbidities	Treatment	Follow up	Outcome
Thymoma AB	Bilateral Lower Limb swelling. Frothy Urine.	Nephrotic Syndrome.	Hypertension. Diabetes Mellitus Type II.	Right Video Assisted Thoracoscopic Thymomectomy.	Refusal of renal biopsy, unable to confirm subtype. Further deterioration of renal function.	Long term consideration of Renal Replacement Therapy.
Thymoma AB	Breathlessness. Reduced effort tolerance.	Pure Red Cell Aplasia.	None.	Right Anterolateral Thoracotomy and Thymomectomy.	Resolution of anemia.	Remission of PRCA and medication free.
Thymoma AB	Reduced effort tolerance. Palpitations.	Pure Red Cell Aplasia.	Hypertension.	Right Video Assisted Thoracoscopic Excision of Mediastinal Mass.	Persistence of anemia	PRCA control with ciclosporins.
Thymoma AB	Recurrent respiratory tract infections.	Good's Syndrome	None	Right Video Assisted Thoracoscopic Thymomectomy.	Cessation of recurrent respiratory tract infections.	3 weekly administrations of Intravenous Immunoglobulins.

The variability in outcomes for nephrotic syndrome patients post-thymectomy highlights the complexity of these cases. It suggests that while thymectomy can help manage the underlying tumour, additional treatments may be necessary to address renal complications. The involvement of nephrologists in the care team can help optimize treatment plans and monitor renal function closely, ensuring timely interventions when necessary.

Pure Red Cell Aplasia (PRCA)

PRCA is characterized by severe anaemia and a low reticulocyte count. The pathogenesis of PRCA in thymoma patients involves the secretion of inhibitory cytokines by thymoma cells, which suppress erythroid precursors.[8] Our two cases of PRCA demonstrated different outcomes post-thymectomy. One patient achieved complete remission without additional treatment, while the other required ongoing immunosuppressive therapy. This variability is reflected in the literature, where some patients achieve remission post-thymectomy, while others require additional interventions such as immunosuppressants, steroids, or splenectomy. The Mayo Clinic's 50-year study highlighted the need for adjuvant therapies in most cases.[9] These findings indicate that thymectomy alone may not be sufficient for PRCA management, and a personalized treatment plan should be developed for each patient.

The literature on PRCA suggests that while thymectomy can lead to remission in some cases, the response is highly variable. Schmid et al. reported that some patients did not achieve remission even with additional steroid therapy post-thymectomy, necessitating further interventions such as blood transfusions.[9] This underscores the need for a comprehensive treatment plan that includes both surgical and medical management to address the underlying autoimmune dysfunction.

The management of PRCA requires a multidisciplinary approach, involving haematologists to guide immunosuppressive therapy and monitor for potential side effects. Regular follow-up and blood tests are crucial to ensure that the patient's anaemia remains under control and to adjust treatment plans as needed. Additionally, patient education on the importance of adherence to therapy and regular monitoring can improve outcomes.

Good's Syndrome

Good's syndrome, a rare combination of thymoma and immunodeficiency, presents significant clinical challenges. The syndrome is characterized by hypogammaglobulinemia and recurrent infections, as seen in our patient. The management of Good's syndrome requires a multidisciplinary approach involving oncologists, immunologists, and infectious disease specialists. Thymectomy can reduce the tumour burden, but its impact on immunodeficiency is variable. Our patient showed improvement in infection rates post-thymectomy with regular IVIg therapy, but long-term immune function monitoring is necessary. The literature emphasizes early diagnosis and treatment of immunodeficiency to prevent severe infections. Further research is needed to understand the long-term outcomes of thymectomy and the best management strategies for the immunodeficiency component of Good's syndrome.[10]

Good's syndrome is particularly challenging due to its impact on both humoral and cellular immunity. Patients often present with recurrent infections caused by opportunistic pathogens, highlighting the need for ongoing immunoglobulin replacement therapy. The literature suggests that while thymectomy can help reduce tumour burden, it may not fully restore immune function. Long-term follow-up and management of immunodeficiency are critical to improving patient outcomes,[10] Additionally, patients with Good's syndrome are at an increased risk for developing other autoimmune conditions, necessitating regular monitoring and comprehensive care.[10]

The management of Good's syndrome should involve regular follow-ups with immunologists to monitor immunoglobulin levels and adjust IVIg therapy as needed. Patients should be educated on infection prevention measures, and prompt treatment of infections is crucial to avoid complications. A comprehensive care plan that addresses both the thymoma

and the immunodeficiency can help improve the patient's quality of life.

Key Insights and Future Directions

The cases presented in this series highlight the heterogeneous nature of PNS associated with thymoma and the importance of a personalized approach in their management. Thymectomy remains a cornerstone treatment for thymoma, but its efficacy in resolving associated PNS varies significantly. The unpredictable nature of these syndromes necessitates a multidisciplinary approach involving various specialists to manage both the tumour and its systemic effects.

Additionally, there is a critical need for more extensive studies to elucidate the underlying mechanisms of PNS in thymoma patients. Understanding the specific cytokines, autoantibodies, and genetic factors involved can pave the way for the development of targeted therapies. Collaborative efforts combining clinical expertise with basic and translational research are essential to improve diagnostic and therapeutic strategies.

The variability in patient responses to treatment also underscores the importance of patient education and counselling. Patients should be informed about the potential outcomes and the necessity for long-term follow-up and adjunct therapies. Establishing standardized treatment protocols based on robust clinical evidence will enhance patient care and improve prognoses.

CONCLUSION

This case series provides critical insights into the varied presentations and treatment outcomes of paraneoplastic syndromes (PNS) associated with thymoma, revealing a spectrum of clinical challenges and the importance of individualized therapeutic strategies. Our findings affirm that while thymectomy remains a pivotal treatment for myasthenia gravis and offers potential remission for conditions like PRCA, the management of PNS such as nephrotic syndrome, particularly when occurring alongside thymoma, demands a nuanced approach due to the inherent complexity and individual variability of these diseases.

The study also highlights the need for a multidisciplinary approach that extends beyond surgical intervention, emphasizing the role of ongoing monitoring and adjunct therapies in addressing the autoimmune dysregulation characteristic of these conditions. Notably, for disorders like Good's syndrome, thymectomy may serve as an initial step in management, but the overarching goal is to restore immune homeostasis, necessitating long-term immunological support and surveillance.

The outcomes detailed in this series underscore the critical need for a more substantial evidence base to guide clinical decision-making. As such, there is an urgent call for further research to deepen our understanding of the pathophysiological mechanisms underlying PNS associated with thymoma and to develop standardized treatment protocols that can enhance patient prognosis and quality of life.

Ultimately, the complexity of thymoma-associated PNS challenges us to look beyond one-size-fits-all solutions, advocating for personalized medicine backed by rigorous research and collaborative care strategies. Our continued commitment to investigating these syndromes will pave the way for innovative treatments and improved outcomes for patients grappling with the dual burden of thymoma and its paraneoplastic manifestations.

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DECLARATION

The authors declare no conflicts of interest.

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