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Coincident thymoma and SLE in an adult female patient: Hickam's dictum in practice

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ABSTRACT

Background: Thymoma is a rare tumour originated in the epithelial cells of the thymus and is often accompanied by Paraneoplastic Syndromes (PNS). While myasthenia gravis is the most common PNS associated with thymoma, thymoma-associated PNS harbor a wide spectrum of autoimmune diseases.

Case Presentation: We represent a 42-years-old female patient who presented to the emergency department complaining of dyspnea. Clinical manifestations, along with imaging, histopathology, and serologic testing enabled diagnoses of thymoma and Systemic Lupus Erythematosus (SLE) in our patient.

Conclusion: Thymoma may rarely be complicated by SLE. To bear in mind Hickam's dictum aids the clinician to accommodate a comprehensive clinical judgement.

Keywords: thymoma, paraneoplastic syndrome, systemic lupus erythematosus

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INTRODUCTION

The thymus, a bilobed mediastinal organ comprised of various cell types, including epithelial, dendritic, mesenchymal, and endothelial cells, is the central organ responsible for the differentiation and maturation of T cells [1]. Epithelial cells of the thymus may give rise to Thymic Epithelial Tumours (TET), which entertain a host of histopathological heterogeneity, including thymoma and thymic carcinoma [2]. Although TETs account for a minute proportion of all human neoplasms, they are one of the most common types of mediastinal tumours [3]. TETs are of particular interest in that they are often accompanied by Paraneoplastic Syndromes (PNS). While TET patients may develop a PNS in their disease course, many patients suffering from autoimmune disorders are found to have a TET. A wide variety of TET-associated PNS are described in the literature, however, the causal relations and their pertinent pathophysiology are elusive [4-6].

Systemic Lupus Erythematosus (SLE) is a chronic multi-organ autoimmune disorder, most frequent in women of reproductive age. Involved organs in the SLE patient, not only dictate the semiology but also weigh in prognostication [7, 8]. Similarly, the prognosis of SLE is adversely affected in cases complicated with a neoplastic disease. The association of SLE and neoplasia is complex, however, it is meticulously established that SLE patients are at increased risk for at least a multitude of neoplastic diseases [9-12].

The most common TET-associated PNS is by far Myasthenia Gravis (MG); to a surprisingly high degree that such terms as myasthenic thymoma or thymoma-associated MG are customary vocabulary in the pertinent literature [13-15]. Likewise, SLE is largely associated with hematologic neoplasms [9-12]. Nevertheless, there is a growing body of evidence referring to SLE and thymoma occurring in the same patient [3, 16, 17]. Hereby, we represent a female patient diagnosed with both SLE and thymoma.

CASE PRESENTATION

A 42-years-old woman presented to our clinic complaining of pruritic lesions and facial swelling, which developed after diagnostic dilation and curettage due to uterine polyps. Laboratory investigation showed elevated erythrocyte sedimentation rate and decreased CH50 and C4 levels. The remainder of the laboratory tests, including ANA, anti-dsDNA, anti-CCP, anti-

Scl, CRP, liver transaminases, urinalysis, and serum Creatinine (Cr) returned within normal limits. The patient was started on prednisolone (5 mg twice daily) and fexofenadine (180 mg once daily). Symptomatic resolution was achieved and the medications were tapered. The patient's history included hypothyroidism for which she was receiving levothyroxine (50 mcg once daily).

Three months later, the patient presented to the Emergency Department (ED) complaining of new-onset abrupt dyspnea, palpitation, and chest pain in the supine position. The patient was, at the time, receiving estradiol and enoxaparin for 5 days earlier for a planned in vitro fertilization. Her vital signs in the ED included a systolic and diastolic blood pressure of 140 and 90 mmHg, respectively, a pulse rate of 140, a peripheral oxygen saturation of 99%, and a temperature of 37.1°C. The physical examination was significant for decreased respiratory sounds bilaterally, and bilateral pitting edema of lower limbs with a depth of 4 mm-6 mm. An electrocardiogram was obtained and yielded no pathological patterns. A microcytic hypochromic anemia was revealed by the complete blood count. D-dimer was within normal limits, and other laboratory tests were insubstantial (Table 1).

Tab. 1. Laboratory workup and echocardiography report

WBC (*10^3/mcL)	12.7
RBC (*10^6/mcL)	3.67
Hemoglobin (g/dL)	9.6
MCV (fL)	83
Platelet (*10^3/mcL)	388
Random Blood Glucose (mg/dL)	110
Urea (mg/dL)	20
Creatinine (mg/dL)	1
AST (IU/L)	17
ALT (IU/L)	11
ALP (IU/L)	33
Total bilirubin (mg/dL)	2.4
Direct Bilirubin (mg/dL)	1
Serum Iron (mcg/dL)	15
TIBC (mcg/dL)	210
ESR (mm/h)	102
C4 (mg/dL)	21.2
C3 (mg/dL)	163
CH50 (IU/mL)	94
Lupus Anticoagulant (GPL)	68
Urinalysis	
Urine pH	5
Blood	1+
RBC (/hpf)	18-20
WBC (/hpf)	06-8
Protein	1+
Bacteria	Rare
Echocardiography	
LVEF = 55%, mild pericardial effusion without respiratory variation or RA and RV collapse, RVOT=1.4 cm, fibrin strands observed.	

NOTE: WBC: White Blood Cell, RBC: Red Blood Cell, MCV: Mean Corpuscular Volume, AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase, ALP: Alkaline Phosphatase, IU: International Units, TIBC: Total Iron-Binding Capacity, ESR: Erythrocyte Sedimentation Rate, HPF: High-Power Field, LVEF; Left Ventricular Ejection Fraction, RA: Right Atrium, RV: Right Ventricle, RVOT: Right Ventricular Outflow Tract

Echocardiographic examination exhibited pericardial effusion without respiratory variation and right atrium or ventricle collapse (Table 1). A comprehensive bedside ultrasound and Doppler examination failed to detect any evidence of lower limb thrombosis, while moderate left-sided pleural effusion was evident. A sample was obtained through thoracocentesis and proved exudative with a high count of lymphocytes.

The patient was admitted to the Cardiac Care Unit (CCU) and was treated with one dose of Intravenous (IV) furosemide (20 mg) and colchicine (0.5 mg twice daily), adjunct with supportive care. The patient was stabilized and a thoracic computed tomography scan was obtained, which revealed a pan-mediastinal mass, highly

suggestive of lymphoma (Figure 1). A percutaneously attained needle biopsy specimen laid the ground for a histopathological and immunohistochemical diagnosis of type A thymoma (Figures 2 and 3).

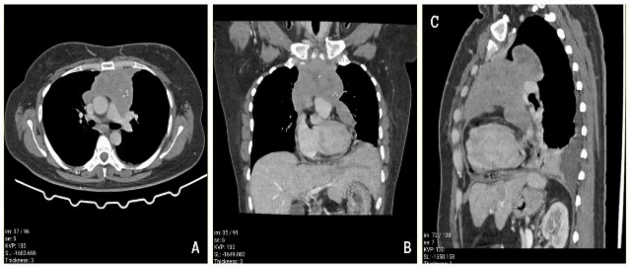

Fig. 1. Computed tomography of the chest, A transverse view, B coronal view, C sagittal view, heterodense mass (100 mm × 67 mm) is seen in the superior, anterior, and middle mediastinum with invasion to pericardial and mediastinal pleura and foci of calcification

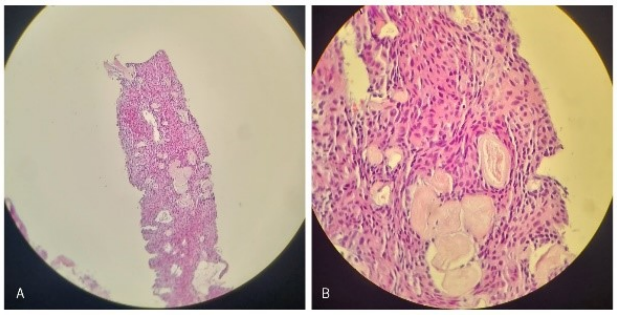

Fig. 2. Thymoma histopathologic sample, haematoxylin and eosin stain. A 10x objective magnification, B 40x objective magnification. Thymic epithelial tumoral cells seen as cell sheets with perivascular rosette formation. Tumoral cells show ovaloid, round, and spindle-shaped cell nuclei. A number of Hassall's corpuscles are seen within the fibro collagenous stroma

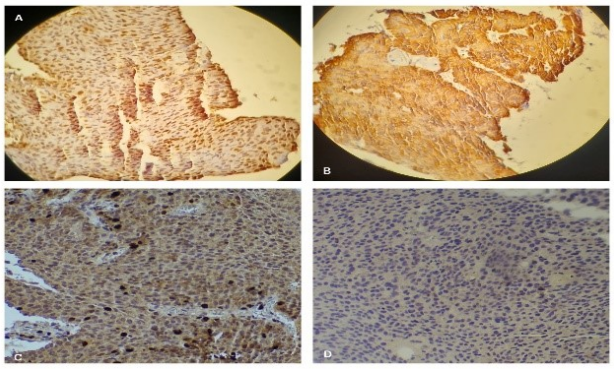

Fig. 3. Immunohistochemical staining of thymoma sample. A positive nuclear reaction to P63, B positive membranous reaction to pan-cytokeratin, C positive reaction to Ki67 in 10% of tumoral cells, D negative reaction to TTF1

Further laboratory workup, despite normal Anti-CCP, C4, and serum Cr levels, showed an ANA titer of 1/80 and a lupus anti-coagulant of 68 GPL. The patient developed proteinuria (1+ protein) as suspected by urinalysis and subsequently confirmed in a 24-hours urine sample (volume=4300 mL, protein=1247 mg, Cr=2.2 mg/dL). Renal ultrasound examination showed increased cortical thickness, which was further investigated through percutaneous needle biopsy. The immunohistochemical analysis of the specimen was positive (1+) for the glomerular reaction of immunoglobulin G, and otherwise insignificant. A diagnosis of SLE was made, and the patient received hydroxychloroquine (200 mg once daily), furosemide (40 mg once daily), eplerenone (25 mg once daily), and IV dexamethasone (4 mg every 8 hours).

With symptomatic alleviation, the patient was transferred to the rheumatology ward after five days. The stabilized condition of the patient allowed for discharge with an outpatient regimen of hydroxychloroquine (200 mg once daily), prednisolone (5 mg once daily), and aspirin (80 mg once daily). She was referred to the oncology clinic for further treatment.

DISCUSSION

The thymus is comprised of 2 identical lobes each structurally divided into cortex and medulla. Various classification systems are proposed to classify primary TETs, all of which principally take into account the cortical and medullary content that predominantly characterizes the tumour [1, 18]. The widely utilized World Health Organization (WHO) classification of primary TETs sorts thymomas into two markedly distinct spectrum of tumours, including primarily medullary (types A and AB) and cortical (types B1-3), both of which are genomically distinguished from thymic carcinomas [19]. Thymoma-associated MG, while well-described in association with thymomas type B1-3, hardly accompanies type A (as in our patient) thymomas [20-22]. Additionally, type A thymoma is the least common thymoma histopathological subtype, which renders investigations into its paraneoplastic relations difficult to interpret [23].

Previous studies estimate that 2% of thymomas are complicated by SLE, although a more recent systematic review in surgically

treated patients approximates SLE in up to 4.1% of thymoma cases [6, 24]. Such studies differ in their diagnosis of SLE from formal SLE investigations, since the application of formal SLE diagnostic criteria (e.g. EULAR/ACR criteria might not be practical due to the scarcity of reported cases [25]. Moreover, the diagnosis of SLE in patients with thymoma is further complicated by serologic interpretation; many patients with thymoma are observed to have SLE-associated autoantibodies without convincing evidence of SLE [17, 26, 27]. Comparatively, the literature provides that thymoma-associated autoimmune disorders not only may be diagnosed simultaneously with the diagnosis of thymoma, but also before or after it [17].

Treatment options for thymoma include surgical resection, chemotherapy, or radiotherapy. Successful treatment of thymoma and remission of its associated PNS is described in various studies [6, 14]. In contrast, Zhao et al. in their systematic review of surgically treated thymoma patients, estimate up to 20% of such patients may develop a new PNS only after their thymoma is surgically resected [6]. Noël et al argue that thymoma-associated SLE may represent a latent disease course manifested after the diagnosis of thymoma [17]. Accordingly, one might argue autoimmune PNS presented after surgical resection of thymoma are in fact a detached entity and not a paraneoplastic manifestation. Comprehensively, neither it is feasible to conclude among thymoma and its associated PNS which condition preceded the other, nor it is of consequential clinical value; the treatment options for thymoma and its associated PNS are, to date, best followed as previously addressed.

In this article, we described a 42-years-old female patient complaining of dyspnoea. While pericardial effusion was identified as the mechanistic culprit of her dyspnoea, an etiological diagnosis was yet to be made. While a mediastinal mass, later histopathologically diagnosed as type A thymoma, was found through imaging, should the clinicians have been satisfied with their presumed final diagnosis, the diagnosis of SLE would have been missed and the patient undertreated. Likewise, if the diagnosis of SLE was made and the pericardial effusion interpreted as its complication, the thymoma would be missed and have progressed into a higher stage. Interestingly, one-third to half of thymoma patients are symptomatic; the remainder of patients owe their symptoms to paraneoplastic manifestations of thymoma, which highlights the level of caution needed not to miss the comprehensive clinical picture. Subsequently, based on our observation, it is a noteworthy reminder, as Hickam's dictum advises, to account for all the reasonable scenarios in the process of clinical decision-making [8, 28]. One might argue, and safely so, that SLE in our patient was in fact a thymoma-associated PNS and not in and of itself an isolated diagnosis. Nevertheless, the fact remains that attending clinicians ought to be wary of the possibility of such rare co-occurrences.

CONCLUSION

Thymoma, although one of the most common mediastinal tumours, is a rare neoplastic disease, and when symptomatic, it is most often found through the diagnostic workup of its paraneoplastic manifestations. Clinicians should bear in mind Hickam's dictum when assessing and drawing conclusions from pertinent clinical scenarios.

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