Multifocal Thymic Tumors with Systemic Hypercoagulability: A Rare Autopsy Case Report

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ABSTRACT

Thymic tumors (TM) are rare epithelial neoplasms that are typically associated with autoimmune disorders, but their potential role in systemic hypercoagulability remains largely unexplored. We report an unusual autopsy case of a deceased male in his 60s, in which seven distinct TM were identified throughout his mediastinum. Histologic analysis confirmed WHO subtype B2 thymomas, characterized by lobulated architecture, abundant lymphocytes, and focal necrosis. Strikingly, multiple ante-mortem thrombi were found in the coronary, pulmonary, mesenteric, and carotid arteries, raising concern for a paraneoplastic hypercoagulable state akin to Trousseau's syndrome. While thrombotic complications are well-recognized in other malignancies, they are exceedingly rare in thymomas, particularly in cases with multifocal involvement and widespread arterial thrombosis. This case highlights the need for increased clinical awareness of potential coagulation abnormalities in thymic neoplasms and supports further investigation into their pathophysiological mechanisms.

Keywords: Thymic tumors; Multifocal thymomas; Hypercoagulability; Paraneoplastic thrombosis; Arterial thromboembolism; Systemic coagulopathy; Mediastinal neoplasms

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INTRODUCTION

Thymic tumors (TM), including thymomas and thymic carcinomas, are rare neoplasms that arise from the anterior mediastinum and thymic epithelium. Best known for their association with autoimmune disorders such as myasthenia gravis, pure red cell aplasia and Good's syndrome, the relationship between thymomas and systemic hypercoagulability remains inadequately understood [1]. In a broader sense, thrombosis is recognized as a hallmark of malignancy, particularly in association with Trousseau's syndrome, a paraneoplastic condition characterized by recurrent and migratory thrombi [2]. This report explores an autopsy finding of multifocal thymomas and systemic thrombosis, raising suspicion for an underrecognized mechanism in TM.

CASE PRESENTATION

During routine anatomical dissection of the thoracic cavity in a deceased male in his 60s with unknown

past medical history and medication use, multiple masses were identified in the mediastinum. A total of seven TM were observed, five within the middle mediastinum and two in the posterior mediastinum. The two largest masses measured approximately 9 x 5 cm and 6 x 3.5 cm (Figure 1), while the remaining tumors were all less than 1 cm in diameter. All lesions were well-circumscribed, well-encapsulated, cystic in nature, and displayed a white-tan-yellow hue on gross examination.

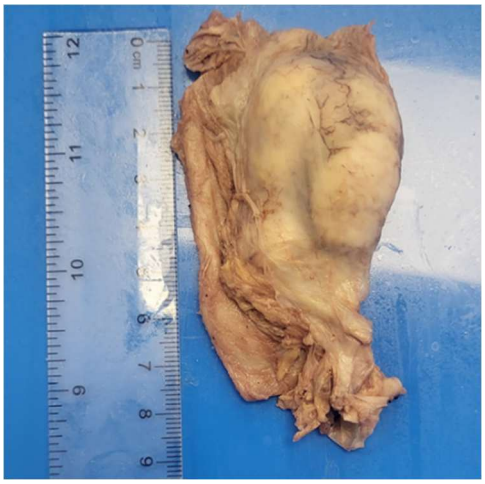

Figure 1: Gross pathology of a resected thymoma from the mediastinum. The mass is well-circumscribed and encapsulated, displaying a tan-white lobulated cut surface with focal cystic changes.

Multiple thrombi were noted in key vascular structures, such as the coronary arteries, pulmonary arteries, superior mesenteric artery, and carotid arteries. These ante-mortem thrombi were adhered to the vessel wall indicating formation during life and consistent with an in-vivo hypercoagulable state. Post-mortem clots were also identified in multiple regions and demonstrated a dual-layer appearance: a red or deep purple dependent layer, and a lighter yellow-tan upper layer. These clots were not only separated but they were also very loosely attached to the vessel wall. Histological analysis of the larger TM revealed a lobulated architecture separated by fibrous septa under low magnification. High magnification demonstrated abundant small lymphocytes, polygonal epithelial cells, and patchy necrosis, consistent with a diagnosis of thymoma. The thymoma WHO classification is B2 thymoma due to the abundant lymphocytes, distinct polygonal epithelial cells, and lobulated architecture with fibrous septa. The lack of cytologic atypia, sheet-like epithelial growth, or squamous cell differentiation rules out Type B3 or carcinoma [3].

DISCUSSION

The link between cancer and thrombosis has been established for many decades. Venous thromboembolism (VTE) contributes to both direct mainly deep venous thrombosis and pulmonary embolism and indirect mortality in cancer patients [4]. In addition, 1 in 5 VTE patients has cancer, and VTE is associated with a significantly increased risk of death for all stages and cancer types except certain renal cancers [4]. Both chemotherapy and interventional cancer drugs have also been associated with increased thrombosis, both atrial thromboembolism (ATE) and VTE, in patients [4]. Although a majority of patients die from cancer progression, the second leading cause of death was shown to be thromboembolism, and the rate of VTE is increasing [4].

The mechanisms of cancer-associated thrombosis (CAT) differ from that of thrombosis in patients without cancer, primarily due to the role of tissue factors (TFs) produced by cancer cells [5]. Cancers release cytokines, increasing inflammation and damage of vascular endothelium. TFs amplify the coagulation cascade targeting this damaged endothelium and therefore promote platelet activation and multiple thrombi [5]. Cancer cells also release plasminogen activator inhibitor 1, decreasing lysis of fibrin and leading to the buildup of fibrin. All these factors contribute to a state of disseminated intravascular coagulation. Overall, all three aspects of Virchow's triad, used to categorize risk factors for thromboembolism, are exacerbated by tumor effects, increased coagulation activity, and cancer interventions [5].

TM, specifically thymomas, have a higher association with autoimmune disorders (AIDs) and paraneoplastic syndromes (PNS) among other malignancies [1]. The thymus functions to create competent immune cells, but the presence of tumors can significantly disrupt the selection and maturation of T cells, leading to auto reactive behavior. Specific factors include decreased or diminished expression levels of AIRE (autoimmune regulator) genes and MHC Class II during the negative selection stage of T cell maturation, reduced levels of regulatory T cells, quick and uncontrolled proliferation of thymoma clones, and overall disorderly alterations to the thymus structure and environment [1]. The escape of these abnormal T cells into systemic circulation can potentially lead to severe infections and

secondary malignancies in immunocompromised individuals [1].

Associated autoimmune disorders and paraneoplastic syndromes appear in various organ systems, especially in the central nervous and peripheral neuromuscular system [1]. Up to 40% of patients with thymomas develop thymoma-associated myasthenia gravis (TAMG) and up to 20% of patients with MG have a thymoma, presenting with weakness in various muscle groups and most commonly anti-AChR-antibodies [1,6]. In thymoma-associated encephalitis, patients typically have VGKC-complex antibodies that is most common to the Caspr2 protein, but other autoantibodies against neuronal antigens have been seen (Lancaster). This same antibody complex against Caspr2 has also been seen in Morvan's syndrome, with thymomas present in many of those patients [6]. Finally, an association may exist between thymomas and late-age-onset systemic lupus erythematosus (SLE), with a poor prognosis for these comorbidities [6].

Trousseau syndrome, or cancer-related thrombosis, is a paraneoplastic, hypercoagulable state associated with recurrent and migratory thromboembolic events. Though most commonly linked to mucin-secreting adenocarcinomas, such as pancreatic and lung malignancies, recent literature suggests that it may also develop in association with less common malignancies [2,7]. The presence of ante-mortem thrombi in several vascular beds in this patient, including the coronary, pulmonary, mesenteric, and carotid arteries, suggests the systemic, multisite thrombotic process that is seen in Trousseau syndrome [7]. Despite these specific arteries being rarely reported, the observations raise concern that thymic neoplasms can potentially play a role in systemic hypercoagulability by tumor-mediated mechanisms, such as release of tissue factor or pro-inflammatory cytokines.

Thrombosis in malignancy commonly results through the interaction of tumor cells with the vascular endothelium, platelet activation, and procoagulant factor release [7]. Thrombotic events may also present prior to a diagnosis of cancer as both an initial clinical clue and a marker of poor prognosis [8], Although Trousseau syndrome has been reported with pulmonary and gastrointestinal cancer, it is underdiagnosed in thymic malignancies. The case is posed to highlight the importance of putting unusual tumors, such as thymomas, into the differential for migratory or unexplained thromboses, particularly when thrombi are disseminated or atypical in nature.

We searched scientific databases for similar cases demonstrating an association between thymic neoplasms and hypercoagulable states. Our investigation of the literature found that such cases are incredibly rare, with only five cases demonstrating such a correlation [9-13]. One case report demonstrated a patient presenting to the ER with symptoms consistent with Disseminated Intravascular Coagulation (DIC), whose subsequent imaging and biopsy with immunohistochemistry revealed an anterior mediastinal mass consistent with thymic carcinoma [9]. Another report from 1973 demonstrated a case of thymoma-mediated Cushing syndrome and DIC, where the patient passed away from sequelae of staphylococcal bacteremia [10]. A similar report from 1983 showed a patient with thymic carcinoma-mediated Cushing syndrome with DIC, passing away from sequelae of an unknown infectious etiology and negative blood cultures [11]. A report from 1994 showed a case of thymoma presenting with a triad of DIC, Superior Vena Cava (SVC) syndrome, and cardiac tamponade. This patient was treated but died due to complications from the DIC [12]. Another report demonstrated a case of a thymoma that paradoxically regressed due to a thrombus compromising its own blood supply, causing coagulative necrosis within the tumor [13]. These all show that further research needs to be performed in an attempt to establish a cause-effect relationship between TM and hypercoagulable states.

Thromboembolic complications associated with TM (thymomas or thymic carcinomas) are exceedingly rare. Most reported cases involve venous thromboses related to local tumor effects, such as SVC syndrome or deep vein thrombosis (DVT) in the upper body from vascular compression by an invasive anterior mediastinal mass [14]. True paraneoplastic hypercoagulability (Trousseau's syndrome) due to thymic neoplasms is only sparsely documented. In fact, a recent autopsy report of an invasive thymoma found no prior published cases of Trousseau's syndrome associated with thymomas [15]. Thymic carcinomas, which are more aggressive, have been described in rare instances to present with distant thrombotic events. For example, one case of thymic carcinoma initially manifested as extensive inferior vena cava and renal vein thromboses without local invasion [16] and another metastatic thymic carcinoma case exhibited a large right atrial thrombus

(successfully treated with anticoagulation) [17]. Arterial thromboembolism appears even less common – for instance, there is an isolated report of a thymoma associated with antiphospholipid antibodies causing recurrent cerebral infarctions [18] and no prior case in the literature details the kind of multisystem arterial thromboses (coronary, pulmonary, mesenteric, and carotid arteries) observed in our patient. Moreover, the multifocal nature of our patient's TM is unique. Synchronous multifocal thymomas are extremely uncommon in general (fewer than 30 reported cases) [19], and none of the published thromboembolic cases involved multiple separate tumors. Finally, our patient's tumors were WHO subtype B2 thymomas. While one previous B2 thymoma case was reported in conjunction with unusual thromboses (bilateral upper-extremity DVTs due to SVC compression) [14], we found no reports specifically linking thymoma histologic subtype to heightened thrombotic risk. Overall, the combination of multifocal B2 thymomas and such widespread arterial thromboembolism in our case appears to be without precedent in the literature.

CLINICAL IMPLICATIONS

Although thymomas have never classically presented with an elevation of thrombotic burden, recent case series show that the thymic neoplasms can precipitate a state of hypercoagulability through the secretion of pro-inflammatory cytokines such as IL-6 and deposition of tissue factor by the neoplasm, mimicking Trousseau's syndrome seen with other malignancies [20,21]. There have been arterial and venous thrombosis described in several case reports. These include pulmonary embolism, carotid thrombosis, and myocardial infarction in thymoma patients, often prior to diagnosis or without traditional thrombotic risk factors [22]. These findings suggest the potential for thymomas to cause systemic coagulation disorders and the suggestion that screening for thrombosis would be beneficial to identify asymptomatic but clinically significant events prior to the development of devastating events.

Against an increasing awareness of malignancy-related coagulopathy, and since thymomas may have multifocal thrombi as exemplified here, it is reasonable to consider baseline and periodical thrombosis screening for patients diagnosed with thymoma. Prophylactic anticoagulation also in some situations may be considered [23]. Especially in the case of the large, invasive, or multicentric tumors, after weighing between bleeding hazards. While practice today does not yet support routine anticoagulation in thymoma, the evidence does support an aggressive approach of thrombotic risk stratification and prevention in this population [24]. These steps may be needed, but future studies will need to put them into practice.

CONCLUSION

This case of multifocal TM with systemic thrombosis suggests a possible paraneoplastic hypercoagulable state, a phenomenon rarely documented in the literature. The simultaneous presence of arterial thromboemboli in multiple vascular beds, in conjunction with synchronous B2 thymomas, raises concern for an underrecognized manifestation of thymic neoplasms. While current guidelines do not support routine thrombosis screening or prophylactic anticoagulation in thymoma patients, our findings support the need for heightened clinical suspicion, especially in patients presenting with unexplained thrombotic events. Future research should aim to clarify the pathophysiological mechanisms linking TM to systemic coagulopathy, and to develop evidence-based strategies for screening and thromboprophylaxis in this unique population.

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