Dissolution of metastatic thymic carcinoma–associated right atrial thrombus with rivaroxaban

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Abstract
Thymic carcinoma typically exhibits more clinically aggressive behavior and portends a worse prognosis as compared to thymoma. Venous thromboembolism is a significant cause of morbidity and mortality in oncologic patients. Traditionally, the standard-of-care management of cancer-associated venous thromboembolism has been therapeutic anticoagulation with low molecular weight heparins; however, with the advent of direct oral anticoagulants, there is an ongoing paradigm shift to transition to these novel agents in an attempt to attenuate cancer-associated venous thromboembolism events. We describe an exceedingly rare case of metastatic thymic carcinoma–associated right atrial thrombus with high-risk embolic features, which subsequently underwent near-complete dissolution with rivaroxaban after 3 months.

Keywords
Thymic carcinoma, thymoma, thrombus, rivaroxaban, direct oral anticoagulation

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Introduction
Thymic carcinoma, derived from thymic epithelial cells, was initially identified by Shimosato et al.¹ in 1977. The interplay between thymoma and thymic carcinoma is still controversial with thymic carcinoma, typically exhibiting more clinically aggressive behavior and portending a worse prognosis.² Currently, there is a striking paucity of literature describing thymic carcinoma, which is considered to be relatively rare.³ The incidence of thymic carcinoma has minimally increased from 0.03% to 0.07% from 2001 to 2015, respectively.⁴,⁵ The International Thymic Malignancies Interest Group (ITMIG) was established to increase collaborative efforts in the treatment of these tumors.⁶,⁷

Venous thromboembolism (VTE), including deep vein thrombosis and pulmonary embolism, is a significant cause of morbidity and mortality in patients with cancer.⁸ The cumulative relative risk ranges from 7-fold to as high as 28-fold in advanced neoplasia.⁹ Traditionally, the standard-of-care management of cancer-associated VTE has been therapeutic anticoagulation with low molecular weight heparins (LMWHs); however, with the advent of direct oral anticoagulants (DOACs), there is an ongoing paradigm shift to these novel agents in an attempt to attenuate cancer-associated VTE events.¹⁰,¹¹

We describe an exceedingly rare case of metastatic thymic carcinoma–associated right atrial thrombus with high-risk embolic features, which subsequently underwent near-complete dissolution with rivaroxaban after 3 months.

Case report
A 33-year-old Caribbean Black woman with no prior medical history presented to the emergency department with a 1-week history of fever, dyspnea, and generalized weakness. There was no reported history of night sweats. The patient

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experienced a 5-month duration of unintentional weight loss of approximately 20 pounds. The patient is a medical doctor; however, there was no exposure to patients with tuberculosis. The family history was significant for first-degree relatives with Hodgkin’s lymphoma and cholangiocarcinoma.

The patient was tachycardic at 130 beats per minute, tachypneic at 24 breaths per minute, saturating 92% on high flow nasal cannula. There was decreased air entry at the lower base of the left lung. A chest radiograph revealed complete opacification of the left lung zone (“white-out”) and a mediastinal mass. A 12-lead electrocardiogram demonstrated marked sinus tachycardia with secondary ST-T changes suggestive of “demand-ischemia.” An arterial blood gas sample was consistent with mixed respiratory and metabolic acidosis. The initial tentative diagnosis was suspected type 1 respiratory failure, likely multifactorial from the large pleural effusion in addition to suspected pulmonary embolism. A subsequent computed tomography “pulmonary embolism protocol” scan confirmed an anterior mediastinal mass (6.9 cm × 3.2 cm × 2.6 cm) with an associated large-sized left pleural effusion with perihilary lymphadenopathy and metastatic nodules. It also revealed a large right atrial thrombus (3.8 cm × 2.5 cm × 3.2 cm) without overt pulmonary emboli (see Figures 1 and 2).

She was subsequently transferred to the intensive care unit, where she was stabilized and initiated upon therapeutic enoxaparin, low-dose aspirin, statin, ibrutinib, and beta-blockade based on her high-risk Khorana score of 3.12 Her routine blood investigations were reflective of dehydration (see Table 1). She also had 350 mL of serosanguinous fluid aspirated from her left lung via thoracentesis. Blood, urine, and pleural fluid cultures returned without bacterial growth. During her ensuing 2-week hospitalization, histopathology revealed features suggestive of thymic carcinoma. Neoadjuvant therapy comprising cisplatin, doxorubicin, vincristine, and cyclophosphamide (ADOC) was commenced. Surgical resection of the mass was performed where it was discovered that the tumor had metastasized to the left lung. Subsequent biopsies confirmed this diagnosis, and the neoplasia was staged as pT4 Nx M1. A transesophageal echocardiogram and cardiac MRI confirmed the presence of the right atrial thrombus (see Figures 1 and 2) with a preserved ejection fraction and no McConnell’s13 sign.

She was discharged on most of her inpatient regimen and also transitioned from enoxaparin to oral rivaroxaban at 15 mg twice daily for 3 weeks, thereafter at 20 mg daily for 3 months based on her intermediate-risk HAS-BLED score of 2. During this period, she underwent six cycles of gemcitabine and capecitabine chemotherapy, and a subsequent computed tomography scan 3 months later revealed near-complete right atrial thrombus dissolution (1.1 cm × 2.1 cm × 0.9 cm) (see Figure 3). She has a scheduled serial scan in 3 months with interim outpatient cardiology follow-up appointments.

**Discussion**

The pathophysiology of cancer-associated thrombosis (CAT) is complex and not fully elucidated. Several complex and interrelated mechanistic effects, including tumor cells, host...
cells, and the coagulation cascade results in a thrombophilic milieu. Platelets and plasmatic factors also play a crucial role, culminating in the hypercoagulable state via proaggregatory and procoagulant pathways. Some of these involve the release of inflammatory and angiogenic cytokines, and direct interaction with host vasculature and erythrocytes through adhesion molecules. Specific chemotherapeutic regimens and radiotherapy can also accentuate activation of the coagulation cascade.

There are three echocardiographic classifications for right heart thrombi (RiHTs), namely type A, which is the most common, serpiginous and has the highest risk of embolization; type B which is firmly attached to the chamber wall, ovoid shape; and finally, type C, which is rare and mimics cardiac myxomas. Based on the cardiac magnetic resonance and transesophageal imaging sequences, our patient’s thrombus was most consistent with type B.

The Masaoka staging system is the most widely accepted system for staging and prognostication for thymic carcinoma. However, most patients are at an advanced stage at index presentation, and its clinical utility is dubious at best. According to the current literature, the 5-year survival rate for thymic carcinoma is bordering 30%, and an optimal management algorithm has yet to be devised and hence, the rationale for ITMIG in an attempt to harmonize management strategies.

Table 1. Routine blood and urine investigations.

| Tests performed                  | Result          | Reference range          |
|----------------------------------|-----------------|--------------------------|
| Hemoglobin (Hb)                  | 9.7 g/dL        | 14.0–17.5 g/dL           |
| White cell count (WCC)           | $11.2 \times 10^9$/L | 4.5–11.0 $\times 10^9$/L |
| Platelet count                   | $402 \times 10^9$/µL | 156–373 $\times 10^9$/µL |
| Serum sodium                     | 132 mmol/L      | 135–145 mmol/L           |
| Serum potassium                  | 3.2 mmol/L      | 3.5–5.1 mmol/L           |
| Serum creatinine (Cr)            | 1.2 mg/dL       | 0.5–1.2 mg/dL            |
| Serum osmolality                 | 275 mOsm/kg     | 275–295 mOsm/kg          |
| Blood urea nitrogen (BUN)        | 20 mg/dL        | 3–20 mg/dL               |
| Fasting blood sugar              | 83 mg/dL        | 60–120 mg/dL             |
| Alanine aminotransferase (ALT)   | 22 IU/L         | 20–60 IU/L               |
| Aspartate aminotransferase (AST) | 32 IU/L         | 5–40 IU/L                |
| Total bilirubin                  | 1.1 mg/dL       | 0.2–1.2 mg/dL            |
| Alkaline phosphatase (ALP)       | 94 IU/L         | 40–129 IU/L              |
| Albumin                          | 3.5 g/dL        | 3.5–5.5 g/dL             |
| Albumin-corrected calcium        | 10.8 mg/dL      | 9.6–11.2 mg/dL           |
| Serum cortisol level             | 18.3 µg/dL      | 10–20 µg/dL              |
| Thyroid-stimulating hormone      | 0.62 mU/L       | 0.5–5.0 mU/L             |
| Urine osmolality                 | 686 mOsm/kg     | 300–900 mOsm/kg          |
| Urine sodium                     | $<20$ mEq/L     | 40–220 mEq/L             |
| Erythrocyte sedimentation rate (ESR) | 33 mm/h    | 0–22 mm/h                |
| C-reactive protein (CRP)         | 6.3 mg/dL       | 0.0–1.0 mg/dL            |
| D-dimer                          | 823 ng/mL       | $<500$ ng/mL             |
| Blood cultures                   | Negative        | Positive or negative     |
| Urine culture                    | Negative        | Positive or negative     |

Figure 3. Computed tomography imaging (CT) series: (a) Transverse view demonstrating the encircled residual thrombus burden, which has been considerably attenuated by direct oral anticoagulation with rivaroxaban for 3 months and (b) sagittal view again demonstrating the residual thrombus burden.
VTE complicates the clinical course of almost one-third of all oncologic patients. Anticoagulation in these patients is often a challenging dilemma as it poses an intricate juxtaposition between thromboembolic events and bleeding risk. LMWHs have long been the conventional mainstay pharmacotherapy; however, they require subcutaneous administration, whereas, conversely, the DOACs possess preferable pharmacokinetic and pharmacodynamic profiles, such as oral administration, immediate onset of action, and short half-lives as demonstrated in the cardiovascular arena. Data are now emerging for the use of DOACs in the oncologic subpopulation from dedicated clinical trials. Two recent systematic reviews, including the SELECT-D trial and Hokusai VTE trials, demonstrated that DOACs are non-inferior to LMWH for the prevention of recurrent VTE, albeit with an increased bleeding signal. Low-dose aspirin and statin can also be considered as they confer a marginally protective benefit in high-risk cancers presenting with VTE.

The patient was initiated upon rivaroxaban for a myriad of reasons, including local accessibility, track-record in the SELECT-D trial, and prior cardiovascular experience in left ventricular mural thrombus dissolution. The recommended dosage was instituted in addition to low aspirin and statin therapy as the multidisciplinary team considered the patient to be an advanced oncologic patient, given the metastatic thymic carcinoma and Khorana score of 3 coupled with an intermediate-risk HAS-BLED score. When cancer is included as an independent risk factor to bleeding risk merits consideration, possibly as part of the B criterion (“bleeding tendency or predisposition”) of the HAS-BLED score. The HAS-BLED score has good predictive validity for bleeding risks in patients with VTE, where a HAS-BLED score of ≥4 indicated a clear delineation for those at high risk for major bleeding when comparing risk for major bleeding among cancer and non-cancer patients. In addition, the inclusion of cancer as an independent risk factor to bleeding risk merits consideration, possibly as part of the B criterion (“bleeding tendency or predisposition”) of the HAS-BLED score.

The thrombus burden was substantial; in addition to displaying some embolic features, we opted for a robust, individualized regimen with a 3-month interval imaging, which displayed a markedly attenuated residual thrombus. In light of her intermediate-risk HAS-BLED score, we also added adjunctive high-intensity statin therapy in addition to aspirin in an attempt to mitigate recurrent VTEs, fully acknowledging that this may increase her bleeding risk.

Conclusion

Direct oral anticoagulation with rivaroxaban instead of conventional therapy with LMWH represents an evolving pharmacotherapeutic alternative for right atrial thrombus dissolution in advanced oncologic patients. Presently, there is a paradigm shift, where individualized antithrombotic regimens with this novel class are being adopted due to their key advantageous characteristics. Furthermore, there are several emerging and ongoing studies that are assessing the clinical safety and efficacy of these agents in CAT.

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Data sharing statement
All available data can be obtained by contacting the corresponding author.

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