CASE REPORT
Rarity among the rare-large and invasive thymoma, a case report and review
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ABSTRACT
Thymomas are rare tumors of the thymic epithelium with an incidence of 1.5 cases in a million, with a wide spectrum of morphological, pathologic characteristics, and clinical presentations. Despite its benign histological appearance, it can invade nearby structures or metastasize hence clinicians need to have a high index of suspicion for early diagnosis. The natural history of the disease is seldom predictable and ranges anywhere from indolent to aggressive malignant course. In this review, we report a case of invasive thymoma in a patient whose presenting complaint was intermittent chest pain x 2 years that had gone undiagnosed. Complete surgical resection is the cornerstone of treatment in early presentation, but with the case of our patient who presented with a locally advanced thymoma treatment, her treatment options were challenging and had to be a multimodal approach with a combination of surgery, chemotherapy and radiation therapy to reduce the chances of recurrence and improve survival. Given the rarity of this presentation, the clinicopathological characteristics that influence the survival of patients with these tumors are still under debate, and guidelines for management for advanced disease are yet to be defined hence warranting our review on this discussion.

1. Introduction
Tumors arising from the thymus are among the rarest [1–5] neoplasms with an incidence of 0.15 cases per 100,000 [6]. Thymoma accounts for 20% of mediastinal tumors and is the most common tumor of the anterior mediastinum, accounting for approximately 50% of all mediastinal tumors in adults, the remainder occurring in the neck or other mediastinal areas.

The two subtypes include thymomas which are neoplasms that show no atypia of epithelial components, versus thymic carcinoma which is clinically quite different and shows clear atypia [7]. Prognosis of thymomas is variable, ranging from an indolent non-invasive course to an aggressive nature with infiltration of surrounding mediastinal tissues and metastasis. When present at an early stage, the tumor is usually well encapsulated; the advanced disease is a less common presentation and is a well-recognized strong risk factor for both local recurrence and generalized metastasis.

2. Case presentation
A 53 y/o Caucasian female, immigrant from Brazil (moved to the USA when she was young) with no significant PMHX presented to our emergency department with non-specific symptoms of worsening exertional shortness of breath x 1 week, and intermittent exertional chest pain x 2 years with associated joint pain, 10lb unintentional weight loss (over 6 months), poor appetite, night sweats, fatigue, and hoarseness of voice. She denied fevers, chills, chest tightness, wheezing, leg swelling, or dysphagia. Social history was negative for smoking, alcohol, or any illicit drug use, but did report significant passive smoke exposure. Family history positive for breast cancer in grandmother and leukemia in grandfather on the paternal side.

Vital signs were notable for a blood pressure 96/41, but the rest were within normal limits. Her cardiopulmonary examination was significant for poor air movement with difficult to appreciate air entry in lung fields bilaterally. Heart sounds were normal. The rest of her physical examination was unremarkable.

2.1. Lab values on admission
The rest of her blood work, including TSH, urinalysis, troponin x 3 were all normal.

A thoracentesis showed an exudative effusion with the absence of malignant cells in the sample. Prior to discharge, the patient underwent a CT-guided biopsy, pathology for which showed groups of epithelial cells and background of small lymphocytes with a dense, fibrous capsule, consistent with thymoma. This visual assessment was confirmed with immunohistochemical stains for MCK, CD20, and CD3 are supportive of the diagnosis. The pathologist commented that the biopsy samples were too limited to fully classify the thymoma.

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Further bloodwork done revealed positive AchR antibodies (7.75 nmol/L (NML < 0.30 nmol/L)), for myasthenia gravis, but EMG studies were normal. Subsequently, she started chemotherapy on 23 May 2019 with a regimen consisting of cyclophosphamide, doxorubicin, and cisplatin and had 3 cycles of this with the hopes that this would shrink the thymoma so that it could be amenable to surgery, but this was unsuccessful.

There was then a discussion on whether she should be started on proton beam therapy but given the proximity to the heart and pulmonary vasculature, this was thought to be dangerous. She eventually had radio sensitizing carbo-Taxol added to her regimen and underwent the 4th cycle of chemotherapy. This was her last cycle of chemotherapy, as her course was complicated by worsening leukocytosis with limited tumor response; hence, she was switched to weekly radio sensitizing Carbo-Taxol and began proton therapy.

After 6 weeks of Carbo-Taxol, repeat CT chest showed an anterior mediastinal mass now reduced in size from $8.2 \times 5.7$ cm to $6.4 \times 4.5$ cm with a mild decrease in enhancement. On 12/18, she underwent a sternotomy for a thymectomy, bilateral lung wedge resection, and left phrenic nerve and innominate vein sampling. Marginal invasion of the mass was appreciated in all sections of the thymus and the resected thymus measured $8.9 \times 4.3 \times 3.3$ cm with biopsy results on immunostaining positive for p40 and negative for synaptophysin, c-kit, CD5, and CD20, supporting classification as thymoma.

Post-operative hospital course was complicated by hypercapnic respiratory failure requiring intubation attributed to limited diaphragmatic movement from respiratory weakness and loss of the left phrenic nerve rather than classic neuromuscular from a myasthenic crisis. After a prolonged 2-month long recovery, patient was able to have her tracheostomy and PEG tube successfully removed. Repeat AchR antibodies measured at 1.35 nmol/L. She was discharged to sub-acute rehab with a final diagnosis of invasive thymoma Masaoka-Koga III, without regional lymph node involvement with a current treatment plan of close observation and monitoring.

2.2. Discussion

Thymic neoplasms are rare tumors accounting for less than 1% of all adult malignancies. Peak incidence occurs in the fourth and sixth decades of life, with no sexual predilection [8]. Most thymomas are solid neoplasms that are encapsulated and localized to the thymus, but approximately a third of these invade the tumor capsule and the surrounding structures. There can be associations with systemic and autoimmune disorders such as myasthenia gravis where approximately 10% to 15% of patients with myasthenia are found to have a thymoma, and 20% to 25% of patients with thymoma have myasthenia gravis [9,10].

Given the slow-growing nature of thymomas, one-third to half of all persons are asymptomatic, and the mass is often identified as an incidental finding on imaging performed for an unrelated problem [11]. The tumor does tend to recur locally but is unlikely to metastasize hematogenously or to regional lymphatics. Other ways it can manifest may be through symptoms of compression of surrounding organs from the expansile mass in the form of superior vena cava syndrome, dysphagia, or chest pain [11].

Imaging is an essential part of the workup of thymomas to aid in diagnosis and properly staging of thymoma. It is important to be able to distinguish thymic hyperplasia (thymus symmetrically enlarged

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**Table 1.**

| Lab                        | Result     | Normal Range       |
|----------------------------|------------|--------------------|
| WBC                        | 13,260/µL  | 4,000–11,000/µL    |
| Hemoglobin                 | 11.7 g/dL  | 12.5–15 g/dL       |
| Hematocrit                 | 35.8%      | 38.0%–47.0%        |
| Platelets                  | 570,000/µL | 150,000–450,000/µL |
| Erythrocyte Sedimentation Rate | 110 mm/hr | =/< 30 mm/hr       |
| C-Reactive Protein         | 22.23      | =/< 0.5 mg/dL      |
| Beta-type Natriuretic Peptide | 665.7 pg/mL | =/< 125.0 pg/mL     |

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**Figure 1.** (a) Chest radiograph showing diffuse bilateral hilar adenopathy with questionable calcified granuloma at the hila (black arrows) noted in Figure 1 (a) and (b). This adenopathy obscures the hilum and the cardiac silhouette. There are bilateral pleural effusions, left greater than right, also appreciated. (b) The lateral view shows a large mass obscuring cardiac silhouette (black arrows) in the anterior compartment of the mediastinum.

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with smooth borders and preservation of normal thymus shape) from a thymoma (well-defined round or oval mass located anterior to the great vessels and heart) [11] as this will direct the mode of treatment.

Various staging systems of thymomas have been defined based on the degree of invasiveness, but the most common one is the Masaoka-Koga system (Table A1) [11] which has been widely used because it is a prognostic indicator for thymic malignancy and a predictor of tumor recurrence [12,13] (Table A2). Seventy to eighty percent of tumors are classified as stage I (completely encapsulated), while stages II through IV demonstrate the invasive form of the disease. These are further subdivided into Type I tumors which are malignant and have features of an encapsulated thymoma but exhibit local invasion or distant metastases, versus type II known as thymic carcinomas which already demonstrate cytological attributes characteristic of malignancy which are very aggressive neoplasms in which local invasion and distant metastases are present at initial diagnosis in 50–65% [2,13].

Owing to a lack of prospective studies in a rare disease, data from retrospective studies still advocate for surgical resection of the entire thymus gland and surrounding mediastinal fat via partial or total median sternotomy approach as the mainstay of management for most thymoma stages I & II [11]. This has been recently challenged with the introduction of minimally invasive surgical techniques like VATS (video-assisted thoracic surgery) or RATS (robotic-assisted thoracic surgery) [14], although studies have shown no superiority to the other. Medico-economics studies are needed to evaluate the cost–benefit ratio of these two options [14].

However, 40% of thymic tumors are invasive and management of these advanced thymomas with Masaoka stages III–IV is still challenging. The approach is multimodal, with targeted chemoradiation prior to surgery to increase resectability and improve survival which achieves complete or partial response (77% of cases) [2,4]. Unresectable disease can be defined as an extensive tumor involving middle mediastinal organs (trachea, great arteries, and/or heart). In this case, maximal debulking should be undertaken (removal of 90% or more of tumor burden) followed by chemoradiation. Anthracyclines and cisplatin are the basis of most protocols. To date, the best results in phase II trials have been the combinations of cisplatin, doxorubicin, vincristine and cyclophosphamide (ADOC) regimen and cisplatin, doxorubicin and cyclophosphamide (PAC) regimen with ADOC regimen being superior [15].

If complete resection is not achievable after 2–4 cycles, or if the patient is not deemed a good surgical candidate, definitive radiotherapy is then recommended as part of a sequential chemotherapy strategy. A total dose of 60–66 Gy in 30–33 fractions may be considered with cisplatin, etoposide chemotherapy. However, for advanced, non-resectable, non-irradiable, or metastatic (stage IVB) tumors, chemotherapy should be offered as

Figure 2. CT chest angiogram in figures 2 (a) and (b) showing mildly lobulated, mildly heterogeneously enhancing anterior mediastinal mass measuring approximately 9.5 × 6.7 × 10.0 cm. The mass label ‘M’ in figures 2 (a) and (b) appears to be compressing a portion of the left pulmonary artery and concerning for massive, compressive thymoma. In figure 2 (c) The thickened pericardium is seen (double-headed arrow) as well as moderate-sized pericardial effusion (single-headed arrows). A mild pleural effusion (*) is seen on the right and a moderate pleural effusion (**) is seen on the left.
Thymomas and thymic carcinomas are rare anterior mediastinal tumors. They may be often go undiagnosed given their indolent nature. Although rare, clinicians should have a high index of suspicion, especially in a patient presenting with symptoms suggestive of anterior mediastinal mass, paraneoplastic disorders like myasthenia gravis, or incidentally found to have an enlarged mediastinum [2]. The prognosis and treatment depend on the stage and histologic type of the tumor. Surgery is the initial treatment of choice for all patients with a thymoma. Given the rarity of this presentation, challenges in identifying a good treatment plan for patients with advanced thymomas we felt an urgent need to increase awareness and prompt discussion amongst physicians for further investigation on this.

2.3. Conclusion

Thymomas and thymic carcinomas are rare anterior mediastinal tumors. They may be often go undiagnosed given their indolent nature. Although rare, clinicians should have a high index of suspicion, especially in a patient presenting with symptoms suggestive of anterior mediastinal mass, paraneoplastic disorders like myasthenia gravis, or incidentally found to have an enlarged mediastinum [2].

The prognosis and treatment depend on the stage and histologic type of the tumor. Surgery is the initial treatment of choice for all patients with a thymoma. Given the rarity of this presentation, challenges in identifying a good treatment plan for patients with a large tumor not amenable to surgical intervention, and the lack of effective guidelines to guide the care of patients with advanced thymomas we felt an urgent need to increase awareness and prompt discussion amongst physicians for further investigation on this.

Disclosure statement

No potential conflict of interest was reported by the authors.

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References

[1] Kheiralla OAM. Case report of unusual presentation of invasive thymoma in a 49 years old male. Int J Med Res Health Sci. 2016;5(1):101.
[2] Donoiu I, Radu R, Giucă A, et al. CASE REPORT Invasive thymoma. Rom J Morphol Embryol. 2010;51(3):573–575. Available from: http://www.rjme.ro/RJME/resources/files/510310573575.pdf
[3] Rajan A, Giaccone G. Treatment of advanced thymoma and thymic carcinoma. Curr Treat Options Oncol. 2008;9(4–6):277–287.
[4] Froudarakis ME, Tiffet O, Fournel P, et al. Invasive thymoma: a clinical study of 23 cases. Respiration. 2001;68(4):376–381.
[5] Bergonzi M, Orlandoni G, Corbella F, et al. Prolonged survival in advanced thymoma: effectiveness of sequential multiple lines of chemotherapy in an inoperable case. Oncol Lett. 2011;2(3):499–502.
[6] Riedel RF. Thymoma: benign appearance, malignant potential. Oncologist. 2006;11(8):887–894.
[7] Thymoma and Thymic Carcinoma Treatment (Adult) (PDQ®)—Health Professional Version. National Cancer Institute; 2019, October 1. Available from website: https://www.cancer.gov/types/thymoma/hp/thymoma-treatment-pdq
[8] Safieddine N, Liu G, Cuningham K, et al. Prognostic factors for cure, recurrence and long-term survival after surgical resection of thymoma. J Thorac Oncol. 2014;9:1018.
[9] Beydoun SR, Gong H, Ashikian N, et al. Myasthenia gravis associated with invasive malignant thymoma: two case reports and a review of the literature. J Med Case Rep. 2014;8:1.
[10] Rao S. Rare case presentation of thymoma. Int J Healthcare Biomed Res. Voulme:04, Issue: 04, 2016 July 4.
[11] Benveniste MFK, Rosado-de-Christenson ML, Sabloff BS, et al. Role of imaging in the diagnosis, staging, and treatment of thymoma. Radiographics. 2011;31(7):1847–1861.
[12] Deterbeck FC, Stratton K, Giroux D, et al. The IASLC/ITMIG thymic epithelial tumors staging project: proposal for an evidence-based stage classification system for the forthcoming (8th) edition of the TNM classification of malignant tumors. J Thorac Oncol. 2014;9(9):S65–S72.
[13] Juanpere S, Cañete N, Ortuño P, et al. A diagnostic approach to mediastinal masses. Insights Imaging. 2012;4(1):29–52.
[14] Drevet G, Stéphane C, Tronc F, et al. Optimal management of thymic malignancies: current perspectives. Cancer Manag Res. 2019;11:6803–6814.
[15] Venuta F, Anile M, Diso D, et al. Thymoma and thymic carcinoma. Eur J Cardiothorac Surg. 2010;37(1):13–25.
[16] Girard N, Ruffini E, Marx A, et al. Thymic epithelial tumours: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015;26:v40–v55.
Appendix

TABLE A1. The Masaoka-Koga staging system [10,13].

| Stage | Definition                                                                 |
|-------|---------------------------------------------------------------------------|
| I     | Macroscopically and microscopically completely encapsulated               |
| IIA   | Microscopic trans capsular invasion                                       |
| IIB   | Macroscopic invasion into surrounding fatty tissue or grossly adherent to but not through mediastinal pleura or pericardium |
| III   | Macroscopic invasion into neighboring organs (pericardium, great vessels, lung) |
| IVA   | Pleural or pericardial dissemination                                      |
| IVB   | Lymphogenous or hematogenous metastasis                                   |

Table A2. Thymoma prognosis by Masaoka-Koga staging system [6,10].

| Stage | Prognosis                                                                 |
|-------|---------------------------------------------------------------------------|
| I     | Has a 84% 10-year survival rate                                           |
| II    | Has a 83% 10-year survival rate                                           |
| III   | Has a 70% 10-year survival rate and 29% recurrence rate for thymoma and 59% recurrence rate for thymic carcinoma |
| IVa   | Has a 42% 10-year survival rate and a 71% recurrence rate for thymoma and 76% for thymic carcinoma |
| IVb   | Has a 53% 10-year survival and 57% recurrence for thymoma and 54% recurrence rate for thymic carcinoma |

Table A3. Thymoma treatment options according to Masaoka-Koga staging system [11].

| Stage | Treatment                                                                 |
|-------|---------------------------------------------------------------------------|
| I     | Complete surgical resection                                               |
| II    | Complete surgical resection; if resection is incomplete, post-operative radiation therapy |
| III   | Neoadjuvant chemotherapy followed by complete surgical resection; if resection is incomplete, postoperative radiation therapy |
| IVa   | Neoadjuvant chemotherapy followed by complete surgical resection; if resection is incomplete, postoperative radiation therapy |
| IVb   | Palliative chemotherapy                                                  |