CASE REPORT

Massive Thymic Hyperplasia Masquerading as Cancer: A Case Report and Review of the Literature

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ABSTRACT

A 34-year-old woman presenting with abdominal pain, chest pressure, weight loss, and tachycardia was found to have an 11.4-cm anterior mediastinal mass associated with intrathoracic lymphadenopathy on chest computed tomography (Fig. 1*A*). Core needle biopsy was concerning for a type B1 thymoma. During this patient's initial workup, she was found to have both clinical and laboratory evidence of Graves' thyroiditis, raising diagnostic suspicion for thymic hyperplasia rather than thymoma. The case discussed here highlights the unique challenges that arise in the evaluation and management of thymic masses and serves as a prudent reminder that both benign and malignant disorders may present with mass-like changes.

Keywords: Thymic mass; Thymic hyperplasia; Thymoma; Thymectomy; Graves' thyroiditis; Case report

Introduction

Thymomas are a heterogeneous group of tumors that vary in clinical behavior, and prognosis is dependent on pathologic stage, histologic classification, and surgical resectability. Notably, neither the histologic subtype nor pathologic stage can be confirmed on core needle biopsy (CNB) due to the limited architecture visible on small tissue samples; thus, large biopsy specimens or complete surgical resection are often required for definitive diagnosis and classification.

Thymic hyperplasia (TH) is a reactive phenomenon that develops in the setting of physiological stress or systemic disease (e.g., autoimmunity, human immunodeficiency virus) and will generally regress on treatment of the underlying process. This concept is perhaps best illustrated by the relationship between TH and Graves' autoimmune thyroiditis.

Ongoing evaluation of the patient's thymic mass was pursued. A second CNB revealed features of both type B1

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thymoma and TH. A repeat chest magnetic resonance imaging (MRI) obtained 1 month after antithyroid initiation revealed no interval change in the size of the thymic mass. Despite extensive multidisciplinary efforts, diagnostic uncertainty persisted. The patient ultimately underwent a total thymectomy, confirming a diagnosis of massive benign TH.

The diagnostic uncertainties manifested in this case serve as an important reminder that thymectomy for a benign process is not a rare occurrence. Although the relationship between Graves' thyroiditis and TH is well described in the endocrine literature, we believe that this is an area of unmet need for the thoracic oncology community. Furthermore, there have only been a small number of reports describing massive thymic enlargement as found in this case. As oncology experts, it is critical that our multidisciplinary teams recognize benign and malignant thymic disorders alike and that we are agile in the strengths and shortcomings of standard diagnostic tools (i.e., cross-sectional imaging and limited biopsy samples) in the diagnostic evaluation of such entities—particularly so as to avoid unnecessary and invasive diagnostic and therapeutic interventions in such cases. Thus, clinical evaluation of thymic disease necessitates a comprehensive assessment for both benign and malignant causes of thymic enlargement—particularly thyroid function. Multidisciplinary specialists evaluating such patients should be reminded of the nuanced differences between benign TH and thymic neoplasms. We provide a review of the published literature, with emphasis on the radiographic and pathologic findings associated with thymoma versus benign TH, so as to provide guidance on optimal diagnostic evaluation in such cases.

Thymic disorders include both benign (e.g., hyperplastic) and malignant conditions, with primary thymic epithelial tumors (thymoma, thymic carcinoma) accounting for 20% of thymic masses.

Here, we report a case of a large thymic mass presenting in a patient with previously undiagnosed Graves' disease and concern for thymic neoplasm. Despite clinical suspicion for TH, the clinicopathologic and radiographic findings yielded persistent diagnostic uncertainty such that thymectomy was ultimately pursued—and revealed massive benign TH.

This patient's case highlights the clinical, radiographic, and pathologic complexities involved in the diagnosis and management of thymic disorders. It also reinforces the need for comprehensive expert multidisciplinary evaluation with emphasis on identifying nonmalignant causes of thymic enlargement, as this may obviate the need for unnecessary diagnostic procedures and therapeutic interventions. The authors herein provide an illustrative case report and review of the literature.

Case Presentation

A 34-year-old previously healthy woman presented with abdominal pain. CT scan result incidentally revealed an 11.4-cm thymic mass with diffuse intrathoracic lymphadenopathy. A CNB was pursued, with initial pathology concerning for a type B1 thymoma. She was referred to our medical center for expert oncologic consultation.

On presentation to our institution, the patient noted symptoms of mass effect. Clinical and biochemical hyperthyroidism were also newly noted. Serologies confirmed a previously unknown diagnosis of Graves' thyroiditis, and the patient was started on propranolol and methimazole under the guidance of endocrinology.

Multidisciplinary review was undertaken in conjunction with Pathology, Radiology, Thoracic Surgery, Medical Oncology, Radiation Oncology, and Endocrinology.

Results of MRI of the chest revealed a homogenously enhancing mass with moderately restricted diffusion, suggestive of thymoma. There was no local invasion, though the mass abutted critical intrathoracic structures (Fig. 1). Positron emission tomography (PET)-CT revealed fluorodeoxyglucose (FDG) avidity in the thymic mass (maximum standardized uptake value = 5.3) with no other sites of disease. Mediastinal CNB was re-reviewed, noting morphologic and immunophenotypic features suggestive of a B1 thymoma; TH was also considered given the diagnosis of untreated Graves' disease. A second CNB was performed. Again, normal thymic architectural and cytologic features were noted, precluding exclusion of a B1 thymoma. Repeat MRI chest 1 month after initiation of antithyroid medications was unchanged.

Given persistent diagnostic uncertainty and bulky disease burden with limited therapeutic window for curative resection, the patient underwent complete thymectomy. The diagnosis of massive TH in the setting of Graves' disease was affirmed 10 weeks after initial presentation (Fig. 2).

Discussion

Space-occupying lesions of the thymus identified on imaging studies—whether benign or malignant—can represent a diagnostic challenge from both a radiographic and a pathologic perspective.

TH and thymoma can both present as an anterior mediastinal mass, either incidentally or with symptoms of mass effect. Because of overlapping radiographic features, the ability to distinguish between these two

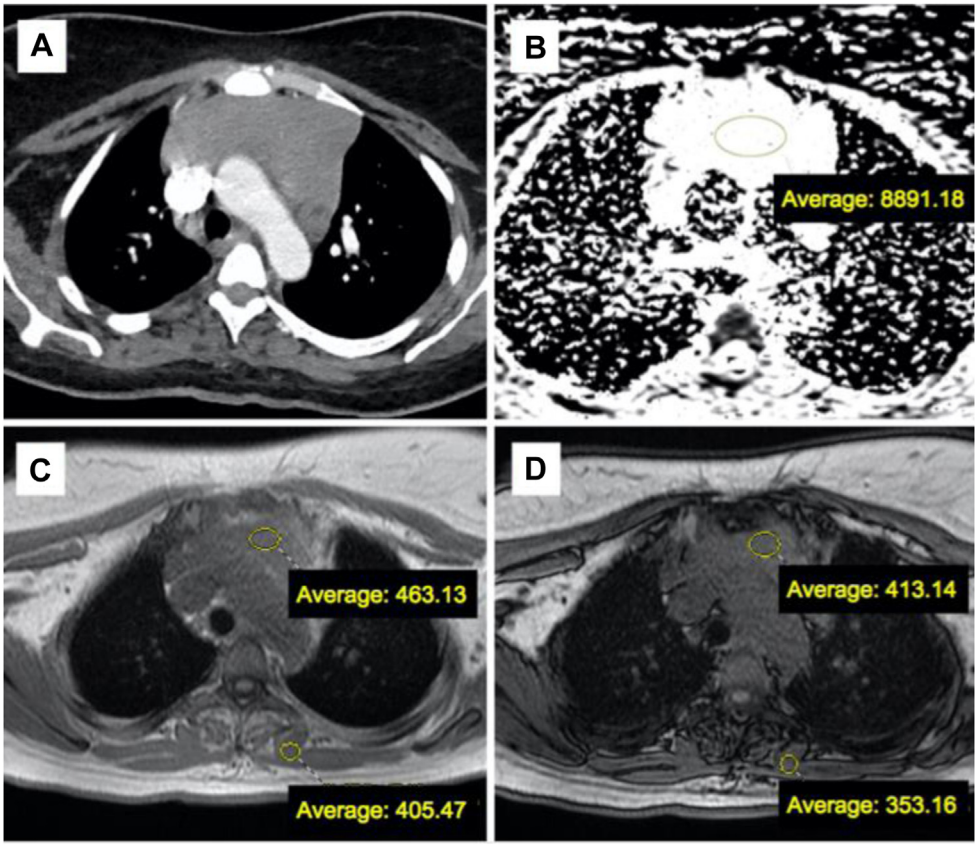

Figure 1. (*A*) Axial contrast-enhanced CT images reveal a diffusely enlarged and homogeneously enhancing soft tissue mass in the anterior mediastinum. (*B*) Axial diffusion-weighted MR images of the anterior mediastinal mass reveal an ADC value of 8.9 cm^3. (*C*) Axial in-phase and (*D*) out-of-phase MR images of the upper mediastinum reveal a mild loss of signal in the anterior mediastinal mass on out-of-phase images relative to in-phase images (*C*), with a calculated CSR of 0.97 and an SII of 10.7%. ADC, apparent diffusion coefficient; CSR, chemical shift ratio; CT, computed tomography; MR, magnetic resonance; SII, signal intensity index.

using cross-sectional imaging alone remains challenging. FDG-positron emission tomography is generally not useful in this setting, because both benign and malignant thymic disorders can have FDG avidity. Chemical shift MRI may help differentiate between TH and thymoma by revealing normal fat infiltration in a normal or hyperplastic thymus (Table 1).[1]

From a histopathologic perspective, distinguishing between TH and thymic neoplasm presents additional challenges. Graves' hyperthyroidism results in the following: (1) true TH and (2) thymic lymphoid hyperplasia. True TH is made up of histologically normal, lobulated thymic tissue; thymic lymphoid hyperplasia consisted of normal thymic tissue and prominent lymphoid follicles with germinal centers. In contrast, thymomas encompass a group of thymic epithelial tumors categorized histologically by the ratio of neoplastic epithelial cells to thymic lymphocytes, including the retention of organotypical features of the normal thymus. As such, thymic epithelial tumors require microscopic examination of the lesion en bloc to accurately determine the histologic type, presence of capsular invasion, and involvement of adjacent organs.[2] The diagnosis and classification of thymic epithelial neoplasms can be challenging by fine-needle aspirate (FNA) or CNB. In particular, type B1 thymomas resemble the normal thymus, and the few neoplastic epithelial cells present can be overshadowed by the numerous small lymphocytes that comprise most of the tumor (Table 2).

TH is found in up to 40% of patients with thyrotoxicosis, though massive enlargement is described in only a small number of case reports. Up to half of patients with massive TH undergo unnecessary surgical resection, primarily due to concern for thymoma.[3] Notably, the incidence of thymoma and Graves' disease is exceedingly rare. Reduction in thymic size after initiation of antithyroid therapies for Graves' disease can take between 5 and 24 months.[2] Furthermore, TH is associated with dynamic changes in thymic dimensions; thus, continued thymic enlargement does not necessarily invoke a malignant diagnosis.

In the case presented here, symptomatic disease burden coupled with diagnostic uncertainty relating to the distinction between B1 thymoma and massive TH

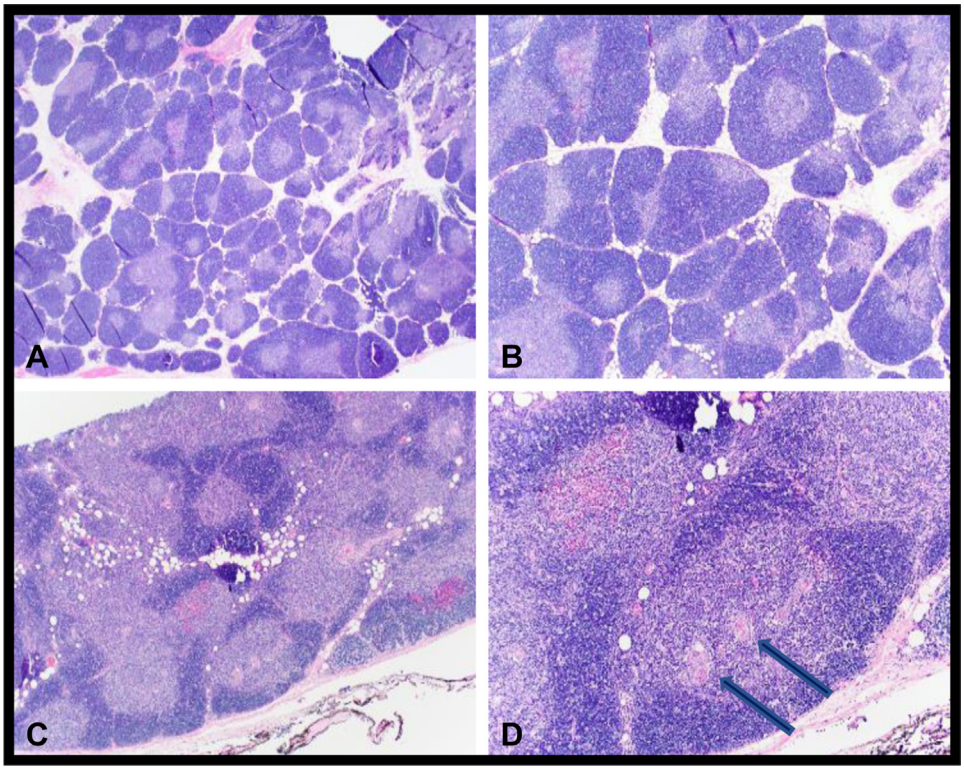

Figure 2. (*A*, *B*) Thymectomy revealing thymic hyperplasia. Lobulated thymic hyperplasia consisting predominantly of normal appearing thymic tissue with intervening adipose tissue-rich septa and prominent medullary islands (magnification *A*—2× and *B*—4×). (*C*) Areas of the thymectomy specimen with more confluent thymic lobules with preserved prominent medullary islands, less to markedly decreased intervening fat and thin fibrous capsule (magnification 4×). (*D*) Scattered Hassall's corpuscles composed of concentrically organized bland epithelial cells found within the medulla (arrows, magnification 10×). FNA or CNB represented in panels *C* and *D* may be challenging to differentiate from thymoma type B1. The residual presence of fat between lobules, preserved prominent medullary islands with scattered Hassall's corpuscles, and absence of thick fibrous septa should prompt the pathologist to a likely case of thymic hyperplasia. CNB, core-needle biopsy; FNA, fine-needle aspirate.

yielded urgency in arriving at a definitive histopathologic diagnosis. Antithyroid therapies for TH do lead to cytoreduction—though this takes time. Thymomas are progressive in nature, and surgical resection provides the best chance of cure. Thus, the option of delaying surgical resection while awaiting cytoreductive effects of antithyroid treatment may raise concern re: inferior oncologic outcomes.

The diagnostic uncertainties manifested in this case serve as an important reminder that thymectomy for a benign process is not a rare occurrence. According to the 2015 manuscript by Ackman et al., the nontherapeutic thymectomy rate between 2006 and 2012 at their institution was 26% (32 of 122). Resection was performed largely due to concern for thymoma, with final operative pathology yielding diagnoses of thymic bed cysts (17 of 32), TH (12 of 32), and reactive or atrophic tissue (3 of 32). Among these, there were significant differences in morphology, circumscription, homogeneity of attenuation, fatty intercalation, coexistent lymphadenopathy, overt pericardial invasion, and mass effect.[4]

On the basis of the authors' review of the available literature, it may be reasonable to proceed with antithyroid therapy and active surveillance alone in a patient with confirmed Graves' thyroiditis and thymic enlargement that is homogenous, does not invade surrounding structures, lacks calcification, and is noncystic.[2] If there is less than a 50% reduction in thymic volume after 6 months of a euthyroid state, then an MRI, biopsy, or thymic resection should be considered.[5] If tissue biopsy is ultimately pursued, CNB is preferred over fine-needle aspirate—though thymic architecture remains difficult to evaluate on all small biopsy specimens. The diagnosis of thymoma type B1 is favored more than TH if there is evidence on biopsy of the following: (1) large lobules separated by fibrous bands, (2) dilated perivascular spaces, (3) few scattered malignant epithelial cells surrounded by numerous small lymphocytes, (4) few medullary-like foci, and (5) rare Hassall corpuscles.

The case presented here highlights the unique challenges that arise in the evaluation and management of thymic masses and serves as a prudent reminder that both benign and malignant disorders may present with mass-like changes. Thus, clinical evaluation of thymic

Table 1. Radiographic Characteristics of Thymic Hyperplasia Versus Type B1 Thymoma

Radiographic Features	Normal	Thymic Hyperplasia	Type B1 Thymoma	Case Patient
General findings				
Pattern of enlargement	N/A	Normal (45%) Symmetric/diffuse (35%) Asymmetric/focal mass (20%)	Asymmetric/focal mass: Round/oval (48%) Lobulated (45%) Amorphous (2%)	Diffuse
Location	N/A	Midline (if focal mass)	Eccentric	N/A
Calcification	−	−	±	−
Lymphadenopathy	−	−	−	+
Changes in size over time	Decreases	Can increase or decrease	Increases	Decreases
CT				
Density	<20 y: soft tissue density 20–50 y: heterogeneous (from progressive fatty infiltration) >50 y: fat density	Homogeneous vs. heterogeneous (if macroscopic fat is present)	Homogeneous vs. heterogeneous (if necrosis, hemorrhage, cystic change, calcification is present)	Homogeneous
Enhancement	Homogeneous	Homogeneous	Heterogeneous	Homogeneous
MRI				
CSR	0.5–0.6	0.5–0.6	0.8–1.0	0.97
SII, %	>8.92	>8.92	<8.92	10.8
Diffusion-weighted imaging (ADC values)	$>2.01 \times 10^{-3}$	$>1.625 \times 10^{-3}$	$<1.625 \times 10^{-3}$	8.9×10^{-3}
Nuclear medicine				
FDG uptake (SUV)	1.0–1.8	2.0–2.8	>4.0	5.3
Indium-111-DTPA-octreotide uptake	−	−	+	Not performed

ADC, apparent diffusion coefficient; CSR, chemical shift ratio; CT, computed tomography; FDG, fluorodeoxyglucose; MRI, magnetic resonance imaging; N/A, not applicable; SII, signal intensity index; SUV, standardized uptake value.

Table 2. Pathologic Characteristics of Thymic Hyperplasia Versus Type B1 Thymoma

Pathologic Features	Thymic Hyperplasia	Type B1 Thymoma
Epithelial cells (neoplastic component)	Scant Normal, round cells, abundant cytoplasm	Scant Large, round cells, mild atypia, high N:C, prominent nucleoli
Lymphocytes (non-neoplastic component)	Numerous small lymphocytes, single or in aggregates	Numerous small lymphocytes, single or in aggregates, rarely in sheets
Ki67% (epithelial cells)	Low	Low, <2%
Encapsulation	Absent	Present
Hassall's corpuscles	Multiple	Rare
Medullary islands	Prominent	Focal, may contain a Hassall Corpuscle
Dilated perivascular spaces	Not described	Present
Fibrous capsule	Thin	Thin, but thicker than normal
Fibrous septae	Thin	Thin, but thicker than normal, separating large lobules

disease necessitates a comprehensive assessment for both benign and malignant causes of thymic enlargement—particularly thyroid function—so as to avoid unnecessary or invasive diagnostics. Multidisciplinary specialists evaluating such patients should be reminded of the nuanced differences between benign TH and thymic neoplasms.

CRediT Authorship Contribution Statement

Emily Stern Gatof: Conceptualization, Formal analysis, Investigation, Writing—original draft, Writing—review and editing, Visualization.

Sarmad H. Jassim: Formal analysis, Investigation, Writing—review and editing, Visualization.

Leah Ahn: Formal analysis, Investigation, Writing—review and editing, Visualization.

Zsu-Zsu Chen: Writing—review and editing.

Paul A. VanderLaan: Investigation, Writing—review and editing, Supervision.

Deepa Rangachari: Conceptualization, Formal analysis, Writing—original draft, Writing—review and editing, Supervision.

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