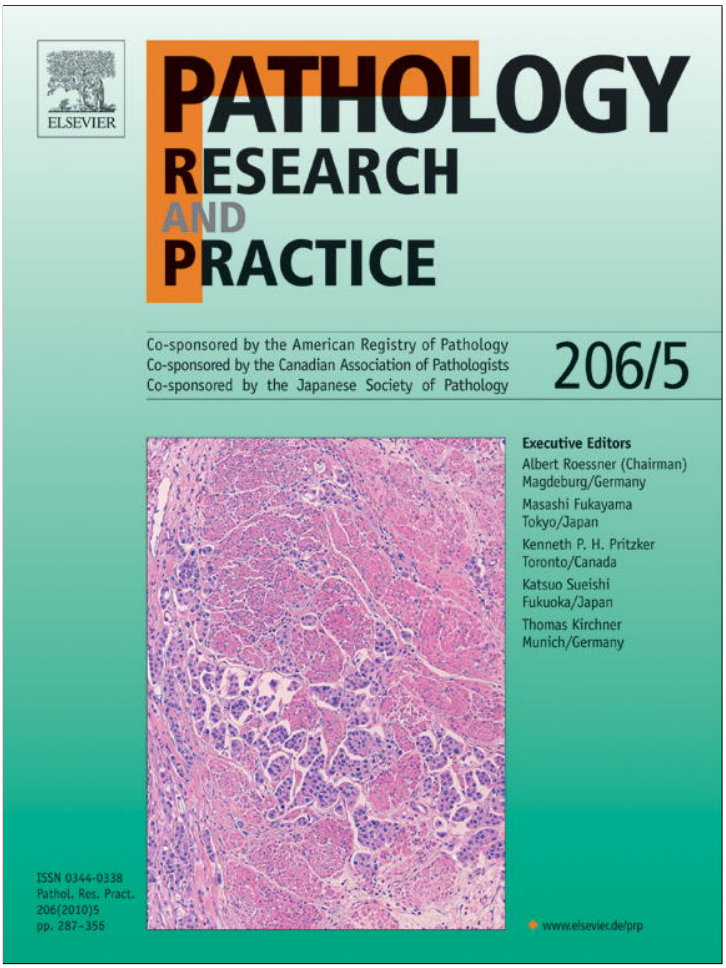

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Teaching Case

True thymic hyperplasia associated with thymic hemorrhage in an adult patient

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ABSTRACT

A case of true thymic hyperplasia (TTH) associated with thymic hemorrhage (TH) was observed in a 22-year-old male patient who presented with persistent cough and thoracic pain due to an anterior mediastinal mass. The diagnosis of TTH was supported by the observation that the mediastinal mass was essentially composed of histologically normal thymic lobules with preserved cortico-medullary differentiation. The TTH tissue presented multiple areas of hemorrhage associated with the presence of large, tortuous, abnormal vessels in the thymic stroma. Foci of spindle cell proliferations resembling an epitheliod hemangioma were also seen. This finding raises the possibility that vascular malformations, perhaps due to an abnormal growth of the thymus, may be responsible for some cases of TH associated with TTH.

Introduction

True thymic hyperplasia (TTH) is a rare entity of unknown etiopathogenesis characterized by enlargement of the thymus beyond the upper limits normal for that age [1,2]. The hyperplastic thymus is histologically similar to the normal thymus, is organized in small lobules with cortico-medullary differentiation, and is active in substaining T-cell differentiation/maturation [3]. Rare cases of TTH have also been described in adults, but, generally, they appeared after successful chemotherapy of malignant diseases [4].

Thymic hemorrhage is an exceedingly rare event in newborns and infants [5]. Most of the cases are caused by the bleeding of a thymic cyst, which may occasionally cause severe complications such as shock and respiratory distress [6,7]. Acquired multilocular thymic cysts are a common reactive process following chemotherapy or in association with a tumor (mostly nodular sclerosis, Hodgkin's lymphoma, or seminoma). A case of TTH associated with thymic cyst bleeding was recently described in a 5-week-old infant [8]. In the present study, we describe a case of TTH associated with thymic hemorrhage in a 22-year-old male patient.

Case presentation

A 22-year-old male presented with acute retrosternal pain that occurred immediately after a physical exercise. The patient had been free of respiratory problems before. No previous thoracic radiograms were available. He had no history of previous neoplasms or chemotherapy treatment. A chest radiogram revealed the presence of a mediastinal mass. The CT scan showed an anterior mediastinal mass ($8 \times 6\,cm^2$) pushing the left venous trunk and the superior vena cava. Enlarged vessels could be recognized within the mass (Fig. 1). Pleural effusions or pleural thickenings were not present.

The blood cell counts revealed mild anemia (hemoglobin 11.8 g/L; 3,900,000 erythrocytes $\times 10^9$/L), modest leukocytosis with neutrophilia and eosinophilia (white blood cell count $11{,}089 \times 10^9$/L; neutrophils 78.8%, lymphocytes 7.7%, monocytes 6.8%, eosinophils 6.4%, basophils 0.3%), and normal platelet counts ($268{,}000 \times 10^9$/L). The patient underwent diagnostic mediastinoscopy with biopsy. The histological diagnosis on the mediastinal biopsy was: "Histological picture consistent with TTH, assuming that the sample is representative of the lesion". The patient underwent anterior mediastinotomy and thymectomy. The patient had no signs of Myasthenia gravis, had no previous diagnosis of malignancy, nor had he received chemotherapy for other reasons. Eight months after the intervention, he is alive and well.

Pathology

True thymic hyperplasia

The thymus was massively and uniformly enlarged, the two lobes measured 7×5.5 cm and 8.5×4.5 cm, respectively, and the parenchyma was whitish-yellow with hemorrhagic areas. The

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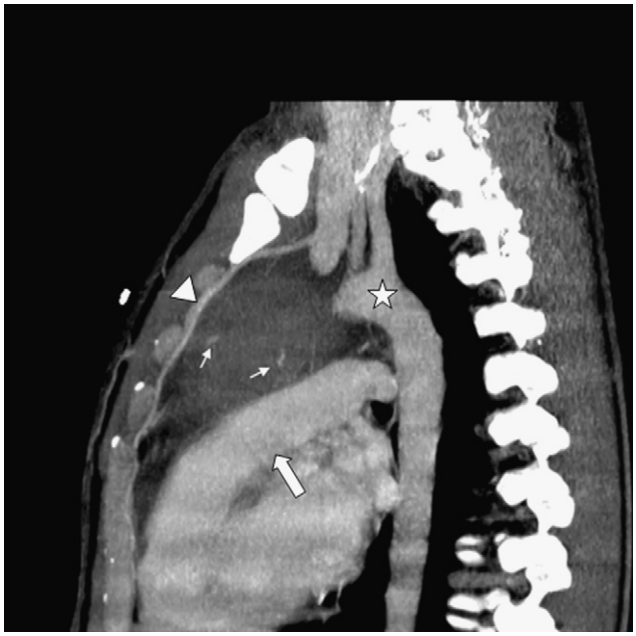

Fig. 1. Computed tomography with injection of contrast material, sagittal reconstruction. A large mass is evident in the anterior mediastinum with enlarged thymic vessels (small arrows). The arrowhead indicates the mammary artery; the large arrow the pulmonary trunk, and the asterisk shows the arch of aorta. (sagittal MPR view).

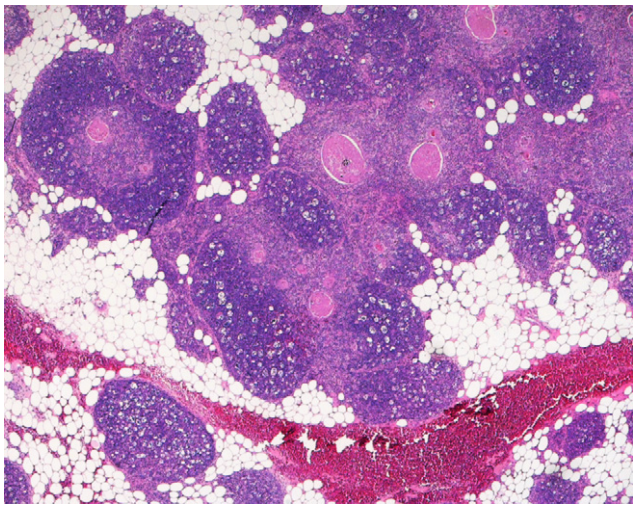

Fig. 2. True thymic hyperplasia in an adult patient. Small thymic lobules are organized in cortical and medullary areas; the latter are more prominent and often centered by large Hassall's bodies. Adipose involution is present at lobule periphery. Fibrous septa of the thymus are diffusely hemorrhagic (H&E, 25 ×).

diagnosis of TTH was supported by the observation that the enlarged thymus essentially consisted of histologically normal lobules with preserved cortico-medullary differentiation (Fig. 2). Compared to TTH of infancy, the medullary areas were more expanded, Hassall's bodies were more numerous and larger, and there was adipose substitution at the lobule periphery. B-cell follicles could not be recognized by morphology or CD20 immunostaining. In some thymic lobules, there were numerous starry-sky macrophages with phagocytosed nuclear debris, suggestive of acute cortical involution (Fig. 3). All these findings are consistent with the age of the patient (22 years old) and suggest that the TTH tissue may have undergone involutive changes.

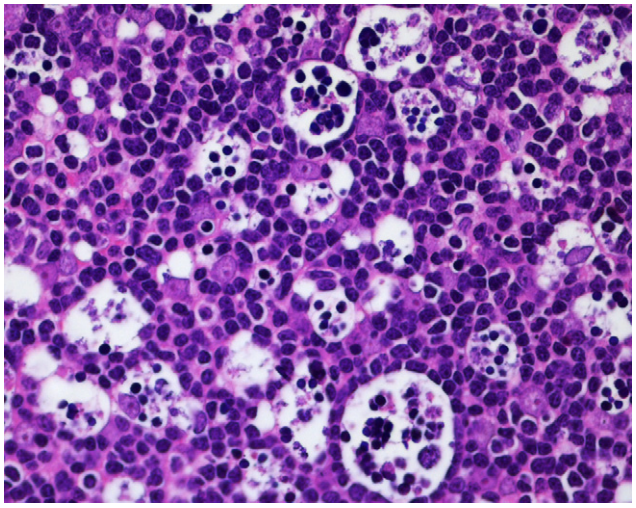

Fig. 3. High magnification of the cortex with evidence of acute cortical involution characterized by the presence of numerous macrophages containing apoptotic thymocytes (H&E, 400 ×).

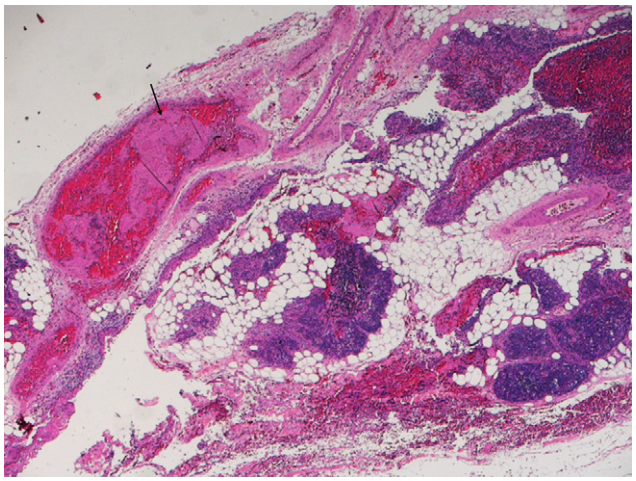

Fig. 4. True thymic hyperplasia with hemorrhage. Large, tortuous, muscular veins are present in the stroma (arrow) (H&E, 25 ×).

Thymic hemorrhage

The TTH tissue was characterized by the presence of micro-cysts filled with blood and of diffuse hemorrhage in the fibrous septa (Fig. 2). Large, tortuous, muscular veins were occasionally seen in the thymic stroma (Fig. 4). Adjacent to the cysts were foci of spindle cell proliferation with a Kaposi-like appearance (Fig. 5). Immunohistochemistry revealed that most spindle cells were of fibroblast origin since they were CD31−/CD34−/HHV-8−; only a few CD34+ endothelial cells were organized in tubules and were admixed with numerous CD68+ macrophages and eosinophils. Up to 7 mitoses/10 HPF were counted in the areas of spindle cell proliferation.

Discussion

This is the second report describing an association between TTH and TH, and the first description in an adult patient. Eifinger et al. [8] were the first to describe this association in a 5-week-old infant. The supposed pre-operative diagnosis based on CT scan was that of malignant lymphoma or thymoma, although the latter

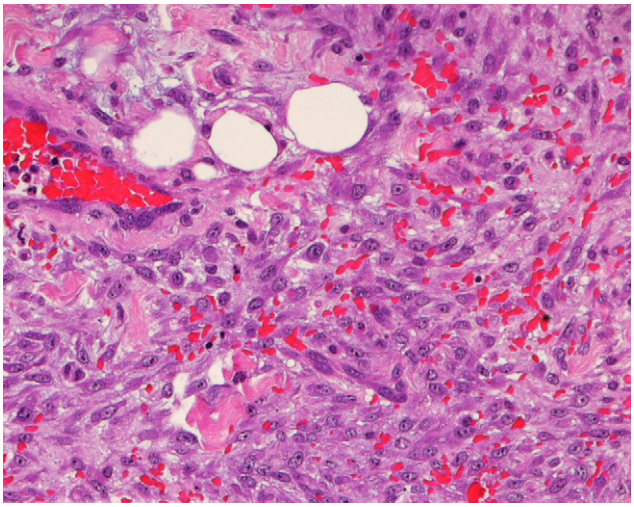

Fig. 5. Foci of spindle cell proliferation were seen adjacent to the hemorrhagic areas. These cells were intermingled with erythrocytes assuming a Kaposi-like appearance, but were negative for CD34 and HHV8 (H&E, 200 ×).

seemed to be more unlikely because of the young age of the patient. The lack of necrosis, calcification, and infiltration of vascular structure did not support the diagnosis of terathoma. Thymolipoma was excluded because areas with adipose tissue density were absent.

The patient underwent diagnostic mediastinoscopy with biopsy. During intervention, a frozen section diagnosis was required, and its interpretation was rather problematic. In detail, the bioptic samples could be interpreted as remnants of the normal thymus, externally pushed by the underlying mediastinal mass or, alternatively, they might represent the lesion which, in that case, should be interpreted as TTH. A definitive diagnosis of TTH was made only on the basis of the surgical specimen when it became apparent that the entire mediastinal mass exhibited the lobular structure of a normal thymus. The distinction of TTH from a B1 organoid thymoma was obvious and was based on the small size of the lobules and on the prominent medullary differentiation [1–3]. In fact, organoid thymomas are generally made of larger lobules with a predominant cortical differentiation [9]. The distinction of TTH from thymic follicular hyperplasia was based on the absence of B-cell follicles. The cause of TTH in our patient remains unknown; nevertheless, it can be ruled out that it was secondary to chemotherapy for malignant diseases.

TH was apparent both at the gross and microscopic levels. Hemorrhagic cysts and areas of diffuse hemorrhage in the fibrous stroma were observed in different areas of the TTH mass. It seems reasonable to postulate that TH derives from vascular malformations, perhaps, due to defective organogenesis of the hyperplastic thymus. A defect in coagulation can be excluded since coagulation factors were normal in our patient. In our case, TH was asymptomatic, but in other cases, rupture of the hemorrhagic cysts into the pleural cavity represented the onset of the disease. We have observed that some hemorrhagic cysts were associated with foci of spindle cell proliferation, which might recall an epithelioid hemangioma. In the literature, there are a few reports describing vascular tumors originating from the thymus. They consisted of two hemangiomas [10,11] and two spindle cell hemangioendotheliomas [12,13], one of the two with Kaposiform appearance [11]. It cannot be excluded that vascular malformations may occasionally occur within the thymus, which can give rise to TH and/or to vascular tumors resembling hemangiomas or hemangioendotheliomas. Even more rarely, vascular malformations may be associated with an abnormal growth of the organ, probably of dysontogenetic origin, resulting in TTH with TH.

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