

A Case Report of Large Thymic Hyperplasia Associated with Hyperthyroidism

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A 32-year-old female case of large thymic hyperplasia with hyperthyroidism is reported. A computed tomography (CT) examination disclosed a large mediastinal mass (16 × 11 cm) with a heterogeneous internal structure containing both soft tissue density areas and fat density areas. The mass was histologically diagnosed as thymic lymphoid hyperplasia. The thymic mass enlarged during hyperthyroidism and then regressed markedly after treatment with antithyroid drugs. After the thymic mass decreased by about one third of its maximum volume, the mass stopped regressing and has remained the same size for more than 6 years. A CT scan showed a decrease in the soft tissue density area and predominance of the fat density area. The potential response to antithyroid therapy must be considered before recommending resection of thymic tumors diagnosed as hyperthyroidism-related thymic hyperplasia. (Ann Thorac Cardiovasc Surg 2009; 15: 404–407)

Key words: thymic hyperplasia, hyperthyroidism, thymolipoma

Introduction

Although benign thymic hyperplasia (BTH) is a known feature of hyperthyroidism,¹ this is infrequently appreciated by clinicians. Surgical resection is a common approach to an anterior mediastinal mass, whereas recognition of the benign nature of BTH would prevent a major surgical procedure.² Although several reports have described regression of the anterior mediastinal mass following treatment of hyperthyroidism, according to our literature survey, this is the first paper to report that a thymic hyperplasia increased during hyperthyroidism and regressed as

thyroid function normalized. Among the cases of thymic hyperplasia with hyperthyroidism reported to date, the present case is the largest that has regressed as a result of treatment for Graves' disease.

Case Report

A 32-year-old female noticed edema of her bilateral lower limbs and consulted our hospital. A chest X-ray revealed a large anterior mediastinal mass without chest symptoms (Fig. 1A). She was found to have symmetrical diffuse enlargement of the thyroid gland, tachycardia, and heavy perspiration. A thyroid function test demonstrated free thyroxine (free T4) to be 6.4 ng/dl (normal: 0.8–2.1 ng/dl), free triiodothyronine (free T3) to be 14.2 ng/dl (normal: 3.2–5.7 ng/dl), thyroid stimulating hormone (TSH) < 0.01 uU/ml (normal: 0.3–5.0 uU/ml), TSH receptor antibody (TR-Ab) at 48% (normal: 0%–9%), thyroglobulin passive agglutination (TGPA) test < 100 (normal: 0.5–100.5), and microsome passive agglutination (MCPA) test at 400 (normal: 0.5–100.5). These findings were consistent with Graves' disease.

A chest computed tomography (CT) scan showed a

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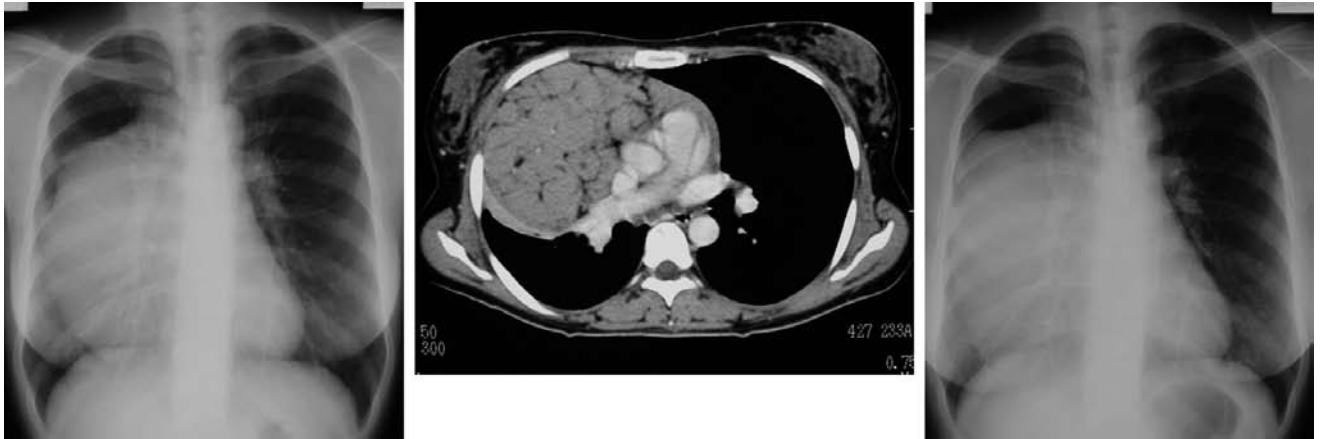


Fig. 1.

- A: A posteroanterior chest radiograph taken on admission showing a large mass in the right anterior mediastinum.
 B: A chest CT scan (mediastinal window) showing 16 × 11 cm lobulated soft tissue attenuation in the lesion separated with fat attenuation in the mass.
 C: During the uncontrolled hyperthyroid period, the anterior mediastinal mass enlarged to 17 × 12 cm in size.

A | B | C

16 × 11 cm mass composed of a complex mixture of soft tissue density areas and fat density areas on the right side of the anterior mediastinum. The soft tissue area was predominant and was separated with a meshlike structure of fat density areas. The lesion of soft tissue density was slightly enhanced with contrast medium (Fig. 1B). The middle lobe of the right lung was compressed by the huge mass, resulting in atelectasis. It was clinically diagnosed that this huge mediastinal mass was a thymic hyperplasia associated with hyperthyroidism.

Treatment with thiamazol was started. However, thiamazol caused severe nettle rash, so the antithyroid drug was switched to propylthiouracil. For the first month of treatment, the hyperthyroidism was not well controlled. During this period, the mediastinal mass increased in size (Fig. 1C). An anterior mediastinotomy biopsy was performed to confirm a definitive diagnosis. Pathological examination with hematoxylin-eosin, Mic2, and CD79a showed an increased number of lymphoid follicles with germinal center formation, largely composed of B lymphocytes (Fig. 2), and also an increased number of Hassall's corpuscles with keratin stain. The large mediastinal mass was histologically diagnosed as thymic lymphoid hyperplasia.

As the hyperthyroidism was normalized with propylthiouracil, the thymic hyperplasia began to decrease in size. After 19 months of treatment with antithyroid drugs, the volume of the thymic mass decreased to 34% of its maximum. A chest CT scan showed a decrease in the soft tissue attenuation component and a relative increase in

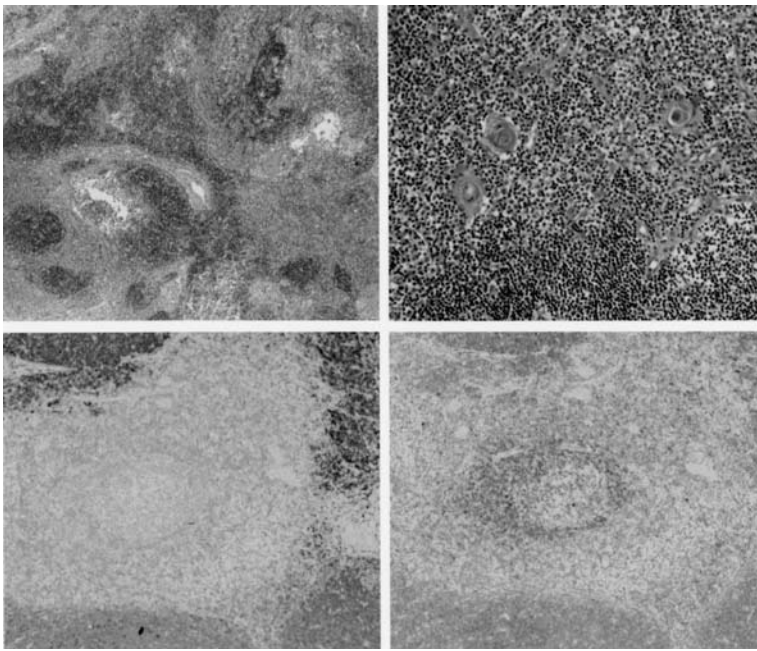
the fatty tissue attenuation component (Fig. 3). Although thyroid function remained normalized, the mass did not regress further in the subsequent 6 years.

In July 2003, the patient experienced normal pregnancy and delivery. Thyroid function was well controlled within the normal range, and no size or structural change of the mass was observed during the perinatal period.

Discussion

Histological examination of Graves' thymic glands has disclosed lymphoid follicle proliferation (thymic hyperplasia) in approximately one third of patients.¹⁾ Moreover, the enlarged thymus was shown to regress as a result of hyperthyroidism treatment with an antithyroid agent.³⁻⁵⁾ Also in animals, thyroidectomy was followed by thymic involution.⁶⁾ The possible existence of a thymic thyrotropin receptor that acts as an autoimmune antigen in patients with Graves' disease has been demonstrated.⁷⁾ TR-Ab and expression of the thyrotropin receptor in the thymus may play a principal role in the development of thymic hyperplasia in Graves' disease.

Although anecdotal case reports indicate that thymic enlargement or thymic hyperplasia is associated with Graves' disease, about half of them were reported after surgical resection of the thymic mass.²⁾ Although BTH has been shown to regress following treatment of hyperthyroidism, median sternotomy and surgical resection is a common approach for anterior mediastinal masses because thymic



A	B
C	D

Fig. 2. Microscopic findings of the mass.

A: An increased number of lymphoid follicles with germinal center formation is present. (HE: $\times 16$)

B: An increased number of Hassall's corpuscles is present. (HE: $\times 50$)

C,D: Pathological examination with Mic2 (C) and CD79a (D) showing lymphoid follicles with germinal center formation, which are largely composed of B lymphocytes. ($\times 25$)

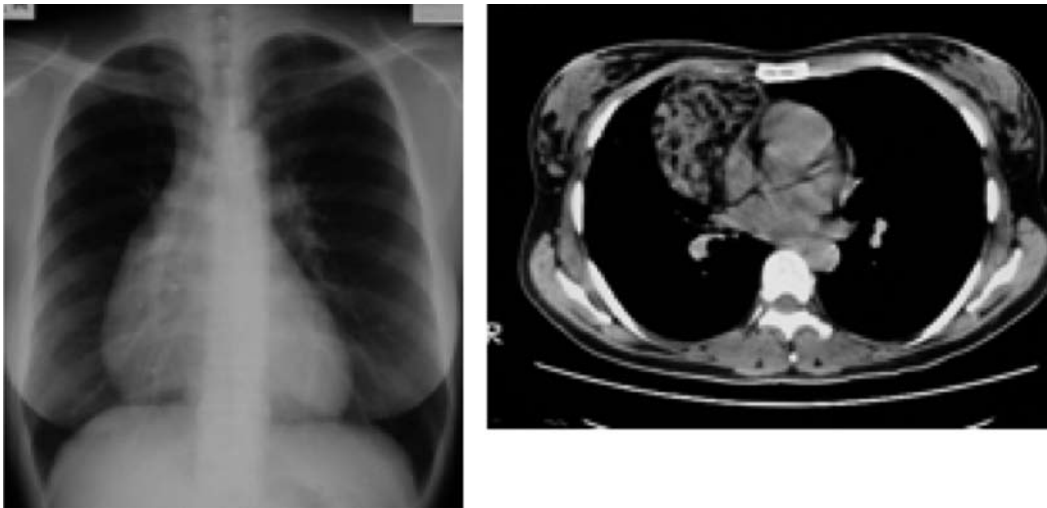


Fig. 3. A chest radiograph (A) and CT scan (B) showing a significant decrease in the size of the mass. Involution of the soft tissue attenuation area is marked. As a result, the fatty tissue attenuation component is predominant.

A	B
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neoplasms or other malignancies cannot be completely excluded. Recognition of the association of thymic hyperplasia with hyperthyroidism and its benign course following treatment for hyperthyroidism would contraindicate a major surgical procedure. Therefore in cases with a nonspecific anterior mediastinal mass, screening of the thyroidal function is essential. If hyperthyroidism is proved

without malignant signs, the clinician should consider observation of the anterior mediastinal mass with the administration of antithyroid drugs. Differential diagnosis of an anterior mediastinal mass should be carefully done because it may include malignant entities, such as thymic cancer, germ cell tumors, and malignant lymphoma. Thymic hyperplasia in Graves' disease has a benign nature

as a consequence of hyperthyroidism. Treatment with appropriate antithyroid therapy results in regression of the thymus. Invasive diagnostic procedures, such as anterior mediastinotomy biopsy, can be used when regression does not occur or when the possibility of a malignant tumor in the mediastinum cannot be ruled out.

CT scans and MR imaging are powerful tools for diagnosis, but few reports have showed images of such a large thymic hyperplasia. A chest CT scan of the present case showed a unique appearance: an anterior mediastinal mass consisting of soft tissue density with meshlike fatty-rich tissue. The lesion of soft tissue attenuation was predominant over the fat lesions before the treatment of hyperthyroidism. It was slightly enhanced with contrast medium (Fig. 1B). The regression of the thymic mass and the decrease of soft tissue attenuation may represent reduction in hyperplastic thymic tissue.

In the present case, after 19 months of treatment with antithyroid drugs, the volume of the thymic mass significantly regressed to 34% of its maximum volume (Fig. 3). The mass stopped regressing and remained in the right side of the anterior mediastinum for the following 6 years. What is the nature of this decreased residual mass? Graves' disease has occasionally been associated with thymolipoma.^{8,9)} Benton et al. proposed a possibility that involution of thymic hyperplasia is one of the causes of thymolipoma.¹⁰⁾ The changes observed in the CT image in the present case may represent the involution of hyperplastic thymic tissue and fatty replacement. According to Benton's hypothesis,¹⁰⁾ this may be the first case in which the development of thymolipoma has been observed. Malignant transformation of thymolipoma or recurrence after surgical excision has not been reported. However, most cases of thymolipoma cannot be observed during the development process because surgical resection is required for diagnosis. Although the mediastinal mass has not been resected, the present case with long-term observation for more than seven

years suggests that the process of regression from thymic hyperplasia is not a malignancy, and surgical resection of the residual mass would have little significance or benefit.

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References

1. Gunn A, Michie W, Irvine WJ. The thymus in thyroid disease. *Lancet* 1964; **2**: 776–8.
2. Yamanaka K, Nakayama H, Watanabe K, Kameda Y. Anterior mediastinal mass in a patient with Graves' disease. *Ann Thorac Surg* 2006; **81**: 1904–6.
3. Kondo K, Kobayashi T, Urakami T, Kasugai T, Iwata M, et al. Three cases of thymic hyperplasia associated with hyperthyroidism. *Jpn J of Thorac Dis (Nihon Kyobu Shikkan Gakkai Zasshi)* 1997; **35**: 900–4.
4. Bergman TA, Mariash CN, Oppenheimer JH. Anterior mediastinal mass in a patient with Graves' disease. *J Clin Endocrinol Metab* 1982; **55**: 587–8.
5. Rose JS, Lam C. Thymic enlargement in association with hyperthyroidism. *Pediatr Radiol* 1982; **12**: 37–8.
6. Fabris N. Immunodepression in thyroid-deprived animals. *Clin Exp Immunol* 1973; **15**: 601–11.
7. Murakami M, Hosoi Y, Negishi T, Kamiya Y, Miyashita K, et al. Thymic hyperplasia in patients with Graves' disease. Identification of thyrotropin receptors in human thymus. *J Clin Invest* 1996; **98**: 2228–34.
8. Tokitsu K, Tachibana S, Kawakami M, Orino T, Nakao K, et al. A case of thymolipoma with Graves' disease. *Jpn J Chest Surg* 1997; **11**: 636–41.
9. Takahashi H, Harada M, Kimura M, Kato H. Thymolipoma combined with hyperthyroidism discovered by neurological symptoms. *Ann Thorac Cardiovasc Surg* 2007; **13**: 114–7.
10. Benton C, Gerard P. Thymolipoma in a patient with Graves' disease. Case report and review of the literature. *J Thorac Cardiovasc Surg* 1966; **51**: 428–33.