Thymic enlargement in childhood

Turgay Öcal[1], Aydın Türken[2], Arbay Özden Çiftçi[2], Mehmen Emin Şenocak[2]
F. Cahit Tanyel[2], Nebil Büyükpamukçu[2]

Departments of [1]Anesthesiology and [2]Pediatric Surgery, Hacettepe University Faculty of Medicine, Ankara, Turkey.

SUMMARY: Öcal T, Türken A, Çitçi AÖ, Şenocak ME, Tanyel FC, Büyükpamukçu N. Thymic enlargement in childhood. Turk J Pediatr 2000; 42: 298-303.

Thymic masses constitute one of the least common mediastinal masses in childhood. While producing symptoms of airway compromise, they also raise the suspicion of malignancy when detected. Radiological, operative and pathological findings of patients that have been operated for thymic masses in our instituion is presented in this paper. Nine patients were operated in our institution during a 12-year-period between 1985-1997 for thymic masses. Ages of the patients ranged from four months to 13 years. With the exception of one, who was diagnosed with a routine chest x-ray, all the patients had respiratory complaints. All the patients had been evaluated with computed tomography preoperatively. In total, seven sternotomies and four thoracotomies were performed to reach the anterior mediastinum. The distribution of masses was as follows two malignant thymomas, three thymic hyperplasia, one lymphocyte-rich thymoma, one epithelial thymoma, one cystic thymoma and one lymphoblastic lymphoma. Although rare, thymic enlargement may be a cause of intractable respiratory complaints in childhood. Because of the high incidence of primary malignancy of the mediastinal neoplasms in childhood, thymic enlargement requires accurate pathological diagnosis and treatment. Median sternotomy with intensive anesthetical care allows proper tumoral exposure.

Key words: thymus, anterior-superior mediastinal mass, respiratory distress.

The thymus normally occupies the anterior and superior mediastinum. Great vessels, a network of lymphatic structures as well as connective and adipose tissue are the other structures found in the anterosuperior mediastinum[1]. Embryologically, the thymus develops as sacculations from the ventral aspect of the third pharyngeal pouch during the sixth week of intrauterine life. Migrational defects during embryogenesis may cause ectopic thymic localization[2].

The thymus is composed of lymphatic tissue, with the characteristic Hassall's corpuscles of epithelial origin. The mean weight of the thymus at birth is 22 ± 13 g. It reaches the maximal weight of 30-40 g at puberty, but when the percentage ratio of thymus to body weight is taken into account, it is greatest at birth with a percentage of 0.76 which declines to 0.19 at one to six years of age[3,4].

It has long been known that thymocytes play an important role in the immune mechanism. The thymus is also related with myasthenia gravis; a thymectomy has been shown to relieve the symptoms of the myasthenic patients. Thymic neoplasms are also associated with some conditions which are called thymic syndromes, like pure red cell aplasia, pemphigus, lupus erythematosis, and Sjögren's syndrome[3]. Unlike the situation in adults, myasthenia gravis and other thymus-related disorders are very uncommon in childhood[5].

Twenty-six percent of the primary childhood mediastinal neoplasms are anteriorly[6] located. Thymic lesions constitute 2.5 percent of overall mediastinal neoplasms[1]. Because of the high incidence of malignancy in mediastinal lesions in the pediatric age group, thymic enlargement requires prompt assessment of pathological diagnosis. The low incidence and the relative inexperience with thymus-related masses in childhood may create a diagnostic dilemma. For these reasons patients with anterior mediastinal

masses require general anesthesia for diagnostic and therapeutic procedures in which fatal or life-threatening complications can occur both during and after its application. Compression of the major airway, pulmonary artery and/or the superior vena cava can occur unexpectedly at any time during anesthesia and surgery including induction, intubation, positioning or extubation[7,8]. Therefore, we evaluated the medical records of patients operated for thymic masses in our institution to find preoperative, peroperative and postoperative surgical and anesthetical clues for thymic enlargement in childhood.

Material and Methods

During a 12-year period between 1985 and 1997, nine patients were operated for thymic masses in our institution. All the patients had complete blood count, peripheral smear, blood biochemistry, urinalysis, bone marrow aspiration, posteroanterior and lateral x-ray projections of the chest, and computed tomography of the thorax routinely before the operation.

Venous access was secured with a 20 or 22 gauge cannula in a peripheral arm vein. No premedication was commenced. All patients received an anticholinergic and standard monitoring consisting of electrocardiogram, blood pressure cuff and pulse oximeter. After confirming preparation and presentation of the pediatric rigid bronchoscope, anesthesia was induced with an intravenous opioid (1 mg/kg fentanyl citrate) and sodium thiopental (4-5 mg/kg). After ventilation of the lungs, tracheal intubation was facilitated with succinylcholine (1-2 mg/kg). Anesthesia was maintained with halothane or isoflurane and increments of fentanyl and vecuronium as required.

As the first surgical intervention, seven complete midline sternotomies and two antero-lateral thoracotomies were performed under general anesthesia to expose the mediastinum. Additionally, two second-look thoracotomies and one emergent sternotomy because of massive bleeding were later required. The clinical data of the patients are summarized in Table I.

Table I. Summary of Clinical Data

Case No.	Sex	Age at operation	Incision and procedure	Complication	Diagnosis	Result
1	M	13 yr	Sternotomy biopsy	–	Malignant thymoma	Alive
2	M	5 yr	Sternotomy thymectomy	–	Lymphocyte-rich thymoma	Alive
3	M	5 yr	Thoracotomy thymectomy	–	Thymic hyperplasia	Alive
4	M	13 yr	Thoracotomy biopsy	–	Malignant thymoma	Alive
5	F	14 mo	Sternotomy thymectomy	Pneumothorax	Thymic hyperplasia	Alive
6	M	5 yr	Sternotomy thymectomy	–	Epithelial thymoma	Alive
7	M	4 mo	Sternotomy thymectomy	Bleeding	Thymic hyperplasia	Alive
8	M	6 yr	Sternotomy thymectomy	–	Lymphoblastic lymphoma	Alive
9	M	12 yr	Sternotomy thymectomy	Pneumothorax	Cystic thymoma	Alive

Results

The sex distribution of the patients were eight males and a female. The ages ranged from four months to 13 years. Except for the 9th case who was on follow-up with a diagnosis of systemic lupus erythematosus (SLE), all the other patients had symptoms associated with the respiratory system. Common symptoms were coughing and dyspnea. Duration of symptoms ranged from 20 days to 1.5 years. Most of the patients received some courses of antibiotic therapies. Case 2 received asthma therapy for one year in another institution.

After obtaining chest x-rays (Fig. 1), all patients were evaluated by computed thoracic tomograms. In all patients, computed tomography revealed masses filling the anterior mediastinum with heterogeneous density enhancement (Fig. 2). In Cases 6 and 8, which were an epithelial thymoma and a lymphoblastic type lymphoma, the trachea was found deviated in tomograms. In Case 7, who was a four-month-old boy with severe respiratory symptoms, the upper lobe of the right lung revealed marked atelectasis. Other laboratory work-up peripheral blood smear, blood biochemistry, urinalysis and bone marrow aspiration provided no additional information for the diagnosis.

While seven patients underwent complete midline sternotomy, antero-lateral thoracotomy was chosen as the surgical approach in two patients. No adverse hemodynamic and

respiratory events occurred in either patient as a result of their peroperative anesthetic experience. All patients were extubated successfully. Total excision of the tumoral mass was possible in six of the seven patients who underwent midline sternotomy. In Case 1, the biopsy obtained by sternotomy from the irregular, large solid gray mass adherent to the right pleura revealed malignant thymoma. The case was considered as stage III and received 4400 rad irradiation to the mediastinum with 3000 rad to the pericardium. After one year of radiotherapy with a chemotherapy course of vincristine, adriamycin and prednisone, total excision of the mass was managed by right antero-lateral thoracotmy.

Fig. 1. Postero-anterior chest x-ray showing a mediastinal mass projecting from superior to left hemithorax.

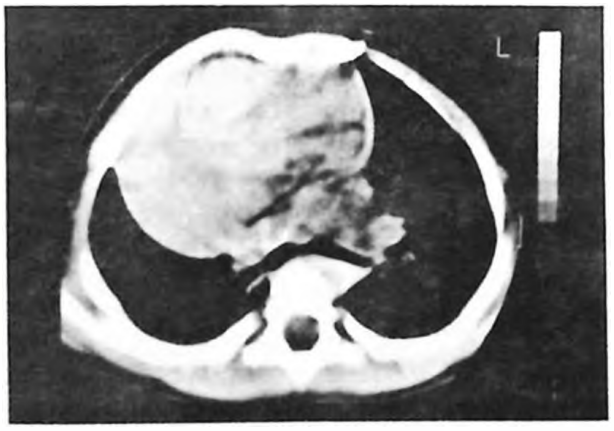

Fig. 2. CT scan showing anterior mediastinal mass with heterogeneous density enhancement.

In Cases 3 and 4, right and left antero-lateral thoracotomies were preferred because the mediastinal masses were mainly occupying the right and left hemithorax, respectively. Total excision was possible in Case 3, a thymic hyperplasia weighing 371 grams, in which a reversible atelectasis of the right upper lobe was observed. In Case 4, the tumor was densely adherent to the pericardium and pleura, in which small nodular, metastatic-like lesions were observed, making total excision impossible. The pathological diagnosis of the specimen that could be obtained was malignant thymoma. The case was considered as stage III. After receiving a total irradiation of 4400 rad to the mediastinum, 2000 rad to the left lung, and 3000 rad to the pericardium, re-exploration through the same incision revealed a necrotic mass which was totally excised after seven months of radiotherapy and chemotherapy course. No complication was observed after thoracotomies.

Pleural tears occurred in Case 5, a mass of thymic hyperplasia weighing 360 grams and in Case 9 who was a cystic thymoma. They healed in a few days by underwater chest tube drainage.

Massive bleeding, which required re-exploration the same night of the surgery, was observed in Case 7, in whom a very large mass, beginning from the anterior mediastinum and extending to the posterior, compressing the right upper lung, and weighing 278 grams, was excised (Figs. 3-4). Oozing from the tumoral bed was controlled in the emergency sternotomy.

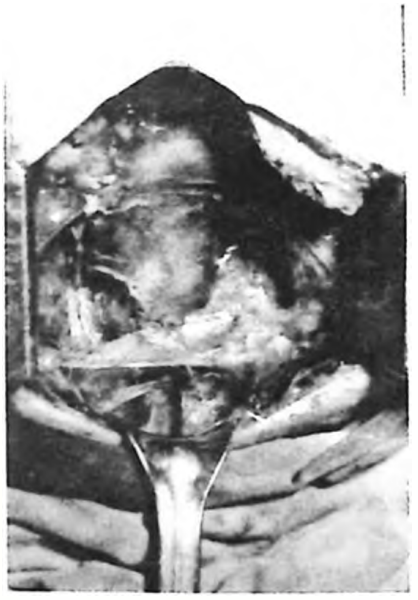

Fig. 3. Peroperative view of the thymic mass (hyperplasia) compressing the adjacent lobe.

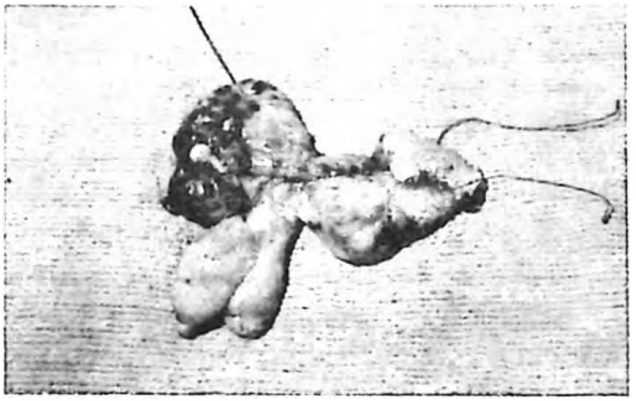

Fig. 4. Operating room gross photograph of the true thymic hyperplasia involving both lobes of the thymus.

Case 7, considering his age and severity of respiratory symptoms, and Cases 6 and 8 due to tracheal deviation, received 2 mg/kg of prednisolone preoperatively for one week. No improvement of respiratory distress was obtained in any of the cases.

Although myasthenia gravis was not encountered in any patient, Case 9 was in follow-up for systemic lupus erythematosus, which is considered as one of the thymic syndromes. This case, a cystic thymoma, also had a history of idiopathic thrombocytopenic purpura which healed after corticosteroid therapy.

Discussion

Although the thymus is recognizable on chest radiograms up to two to three years of age, tumors and tumor-like enlargement of the thymus are among the least frequent lesions in childhood[5]. After four years of age, enlarged thymic shadow is rarely encountered in radiograms.

Thymic lesions constitute 2.5 percent of all childhood mediastinal lesions[1]. Because of the rarity of thymic lesions in childhood, most of the reports about the thymus are single cases[4,9-11]. Welch et al.[3] reported their experience on 17 patients with thymic cysts and neoplasms, excluding thymic hyperplasia and lymphomas, located in the anterior mediastinum. However, considering the similarity of the preoperative radiographic findings and need for the same surgical approach as required for thymic lesions, we included lymphoma of the thymus in our series.

Thymic hyperplasia can be considered as one of the rare conditions of abnormal thymic growth. Recent studies have shown that histological and immunohistochemical staining patterns of thymic hyperplasia are similar to those of normal thymic tissue occurring in immunologically normal children, exhibiting rapid growth of both thymocyte and epithelial elements with normal thymic architecture. Thymic hyperplasia grows no differently in long term culture and responds no differently to cytokine than does normal thymic tissue[9]. These data suggest that thymic hyperplasia can be considered as a benign hypertrophy of the thymus. On the other hand, quantitative and comparative cytoenzymatic studies suggest that massive thymic hyperplasia represents an intrathymic accumulation of immature T cells, a condition which may be related with a failure of cell differentiation connected with some thymic hormonal activity[12]. Massive hyperplasia of the thymus should be differentiated from "lymphoid", "follicular", or "germinal center" hyperplasia of the thymus, which are encountered in adulthood and most often are associated with myasthenia gravis. Such an association is a very unique condition in childhood[13].

Although Rice et al.[9] proposed that thymic hyperplasia is usually an asymptomatic lesion, Ricci et al.[14] emphasized the presence of respiratory distress in a clinicopathological study of four patients[14]. Quite similar to that report, all three patients with thymic hyperplasia in our series expressed the most severe respiratory distress, particularly four-and 14-month-old infants. While steroid administration failed to relieve respiratory distress, total excision of the lesions provided a prompt relief in symptoms. The surgical approach has both diagnostic and therapeutic roles for thymic hyperplasia in childhood. Grossly, true thymic hyperplasia involves the whole thymus, whereas thymoma may involve either one or both thymic lobes, always presenting with some unaffected thymus tissue[15].

Thymoma has been defined as a neoplasm of thymic epithelial cells that differentiate towards either the slender, long branching epithelial cells that characterize the normal thymic cortex or the more rounded epithelial cells of the thymic medulla[16]. While thymomas represent approximately 20 percent of all mediastinal tumors in all age groups, it has been estimated that only one percent of them occur in childhood. Like thymic hyperplasia, no association has been demonstrated between myasthenia gravis and childhood thymomas[17].

The distinction between benign and malignant thymoma for a pediatric surgeon can be made by the finding of an encapsulated versus truly invasive lesion during surgery. Encapsulated thymoma can be treated by surgery alone. While not being uniformly practiced, a multimodal treatment has been recommended for thymomas. The obvious treatment of choice accepted by all authors is complete resection of the tumor. Debulking procedures have been implied to have no value on prognosis. Aggressive surgical intervention has been advised for all tumors of the thymus[3,18-20]. To achieve this goal, pleura-pneumonectomy, lobectomy, resection of the pericardium, diaphragm, both innominate veins or superiof vena cava may be required. It has been speculated that thymomas should be considered adherent rather than truly invasive, and complete resection has been advised even with the anterior pericardium[3]. As the tumoral masses were found densely adherent to pleura and pericardium, only a limited surgical intervention was performed in Cases 1 and 4, both malignant thymomas. In such a circumstance, a large patch of anterior pericardial resection has been recommended to establish a plane of dissection. Limited experience about the nature of thymic neoplasms probably led to the less invasive surgery, in those cases.

Operative complications during resection of the thymus include resection of the phrenic nerve, vocal cord paralysis, Horner's syndrome, and bleeding from the tumoral bed, as in our Case 7, and severe pneumothorax, as in our Cases 5 and 9. Superior vena cava and the aortic arch can be found adherent to the lesion, which could handicap establishing a clean removal plane. Similarly, segmental resection and reanastomosis or bridging by an intercostal nerve graft of the phrenic nerve may be needed if it is found enveloped by the thymic mass[3,19]. Airway obstruction may occur due to relaxation of the tracheal musculature, causing collapse and complete obstruction with fatal consequences. Cardiovascular involvement may be related to the direct compression of the heart or of the great vessels. If the child has arrhythmias, pulsus paradoxus, hypotension or superior vena cava syndrome, the risk of general anesthesia increases dramatically. So the site and the degree of airway obstruction must be assessed preoperatively[21].

Although the association of thymoma and myasthenia gravis is extremely rare in childhood, a tension test has been suggested before any surgical intervention for all patients presenting with an anterior mediastinal mass and a history compatible with muscle weakness to prevent postoperative respiratory failure[22].

Lymphomas of the thymus should be mentioned while speculating on thymic lesions. The most common lesion is the lymphoblastic lymphoma of the thymus, which is most often encountered in males, usually in the second decade[18]. Although rare it can be seen in children, as in our Case 8, who was a six-year-old boy with respiratory complaints for 1.5 months. His preoperative diagnostic studies revealed nothing other than an anterior mediastinal mass which could not be distinguished from a thymic mass.

Another group of lymphoma, histiocytic type, may present as an anterior mediastinal mass, which is usually encountered in the third to fourth decades. Hodgkin's disease may also arise primarily from the thymus and is regarded as a variety of thymoma by some authors (granulomatous lymphoma). However, lymphomas of the thymus seldom create problems in the differential diagnosis of thymic lesions for pathologists[16].

Thymolipoma is another rare cause of thymic enlargement that should be listed in the differential diagnosis of thymic lesions. Histologically there is a prevalence of mature fatty tissue with a moderate lipomatous involution, but the main component is the normal hyperplastic thymic tissue[16,23].

In conclusion, thymic enlargement can be a rare cause of respiratory distress and intractable respiratory tract symptoms in childhood. The symptoms may be due to the direct compression of the airway or to the atelectasis of the compressed lung segments, and the patient can still be receiving doses of antibiotics or even asthma therapy. Lack of thymic markers, similarity of the radiological findings, high malignancy risk of mediastinal lesions, and presence of airway compression symptoms require a dynamic surgical approach to the thymic lesions. The anesthesiologist must stay alert for the development of severe airway obstruction and cardiovascular complications during the anesthesia of symptomatic or

asymptomatic patients with anterior mediastinal masses. A rigid bronchoscope must be available in the operating room in case of a possible complication. If airway obstruction occurs, the position of the patient must be changed rapidly to lateral and/or prone.

The pathological evaluation of the lesion does not create as much confusion as the preoperative work-up. Thus, a radical surgical intervention with total excision of the thymic lesion and intensive anesthetical care are the most important means of managing thymic lesions of childhood.

REFERENCES

1. Phillippart AI, Farmer DL. Benign mediastinal cysts and tumors. In: O'Neill JA, Rowe MI, Grosfeld JL, et al. (eds). Pediatric Surgery. St. Louis: Mosby-Year Book; 1998: 839-851.
2. al-Salem AH. Ectopic thymic tissue simulating a posterior mediastinal mass. Eur J Pediatr Surg 1992; 2: 106-107.
3. Welch KJ, Tapper D, Vawter G. Surgical treatment of thymic cysts and neoplasms in children. J Pediatr Surg 1979; 14: 691-698.
4. Lee Y, Moallem S, Clauss RH. Massive hyperplastic thymus in a 22-month-old infant. Ann Thorac Surg 1979; 27: 356-358.
5. Dehner LP, Martin SA, Summer HW. Thymus related tumors and tumor-like lesions in childhood with rapid progression and death. Hum Pathol 1977; 8: 53-66.
6. Grosfeld JL, Weinberger M, Kilman JW, Clatworthy HW Jr. Primary mediastinal neoplasms in infants and children. Ann Thorac Surg 1971; 12: 179-190.
7. Ferrari LR, Bedford RF. General anesthesia prior to treatment of anterior mediastinal masses in pediatric cancer patients. Anesthesiology 1990; 72: 991-995.
8. Akhtar TM, Ridley S, Best CJ. Unusual presentation of acute upper airway obstruction caused by an anterior mediastinal mass. Br J Anesth 1991; 67: 632-634.
9. Rice HE, Flake AW, Hori T, Galy A, Verhoogen RH. Massive thymic hyperplasia: characterization of a rare mediastinal mass. J Pediatr Surg 1994; 29: 1561-1564.
10. Halpern SR, Schoelzel E, Johnson RB. Thymoma in a young child producing symptoms of asthma. Am J Dis Child 1966; 11: 99-104.
11. Arliss J, Scholes J, Dickson P, Messina JJ. Massive thymic hyperplasia in an adolescent. Ann Thorac Surg 1988; 45: 220-222.
12. Nezelof C, Normand C. Tumor-like massive thymic hyperplasia in childhood: a possible defect of T-cell maturation, histological and cytoenzymatic studies of three cases. Thymus 1986; 8: 177-186.
13. Ichiki S, Komatsu C, Ogata H, Mitsudome A. A case of myasthenia gravis complicated with hyperthyroidism and thymic hyperplasia in childhood. Brain Dev 1992; 14: 164-166.
14. Ricci C, Pescarmona E, Rendina EA, Venuta F, Ruco LP, Baroni CD. True thymic hyperplasia: a clinicopathological study. Ann Thorac Surg 1989; 47: 741-745.
15. Pescarmona E, Giardini E, Brisigotti M, Callea F, Pisacane A, Baroni CD. Thymoma in childhood: a clinicopathological study of five cases. Histopathology 1992; 21: 65-68.
16. Levine GD, Rosai J. Thymic hyperplasia and neoplasia: a review of current concepts. Hum Pathol 1978; 9: 495-515.
17. Youssef S. Thymectomy for myasthenia gravis in children. J Pediatr Surg 1983; 18: 537-541.
18. Kaplinsky C, Mor C, Cohen IJ, et al. Childhood malignant thymoma: clinical, therapeutic, and immunohistochemical considerations. Pediatr Hematol Oncol 1992; 9: 261-268.
19. Cohen DJ, Ronnigen LD, Graeber GM, et al. Management of patients with malignant thymoma. J Thorac Cardiovasc Surg 1984; 87: 301-307.
20. Offner F, Vallaeys J, Roels H, Vander Straeten M. Thymoma: a clinicopathological comparative study of 25 cases. Eur Respir J 1991; 4: 1060-1065.
21. John RE, Narang VP. A boy with an anterior mediastinal mass. Anaesthesia 1998; 43: 864-866.
22. Furman WL, Buckley PJ, Green AA, Stokes DC, Chien LT. Thymoma and myasthenia gravis in a 4-year-old child. Case report and review of the literature. Cancer 56; 1985: 2703-2706.
23. Lack EE. Thymic hyperplasia with massive enlargement: report of two cases with review of diagnostic criteria. J Thorac Cardiovasc 1981; 81: 741-746.