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Thoracic Intrathymic Thyroid

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Objective
The authors introduce thoracic intrathymic thyroid as a clinical entity.

Summary Background Data
Although accessory aberrant thyroid has not been found in other tissues in the mediastinum, a thoracic intrathymic location has not been described previously. It is believed that mediastinal thyroid tissue represents accessory ectopic tissue from the median thyroid anlage. Moreover, the close association of the thymus and thyroid supports the theory that mediastinal ectopic thyroid tissue develops from abnormal descent of these structures during embryogenesis.

Methods
Benign thoracic intrathymic thyroid lesions are described in patients with mediastinal masses.

Conclusion
Thoracic intrathymic thyroid is a distinct entity. Its occurrence is supported both clinically and embryologically.

A common theory for ectopic mediastinal thyroid is that during embryogenesis, there is a mutual descent of the thymus and thyroid glands. This report describes patients with thoracic intrathymic masses and presents the embryologic reasons for this anomalous development.

CLINICAL DATA

A 61 year-old black male nonsmoker presented in 1985 for a routine examination after exposure to asbestos. A previous chest film 11 years earlier was normal. Apart from a 3-year history of mild hypertension, the patient was in excellent health. On physical examination, he appeared well, with stable vital signs. The neck was supple without thyromegaly. The heart and lungs were normal, and there was no adenopathy. Routine laboratory studies included a hematocrit of 43, white blood cell count of 7000, platelets of 252,000, and normal electrolytes. The chest film revealed an anterior mediastinal mass (Figs. 1A and 1B). Computed tomography (CT) scan (Fig. 2) showed a $7 \times 5 \times 7$ cm mass with delineated tissue planes overlying the pulmonary artery and aorta.

A 41 year-old white male presented at another hospital in 1991 complaining of an episode of substernal chest pain radiating to the left shoulder. There was no history of cardiac disease other than some vasovagal syncopal episodes. He had a 10 pack year smoking history, but was otherwise quite healthy. The physical examination was normal; routine laboratory values and electrocardiogram were normal. The chest film demonstrated an anterosuperior mediastinal mass, and the diagnostic assessment included CT and nuclear scans (Fig. 3). Mediasti-

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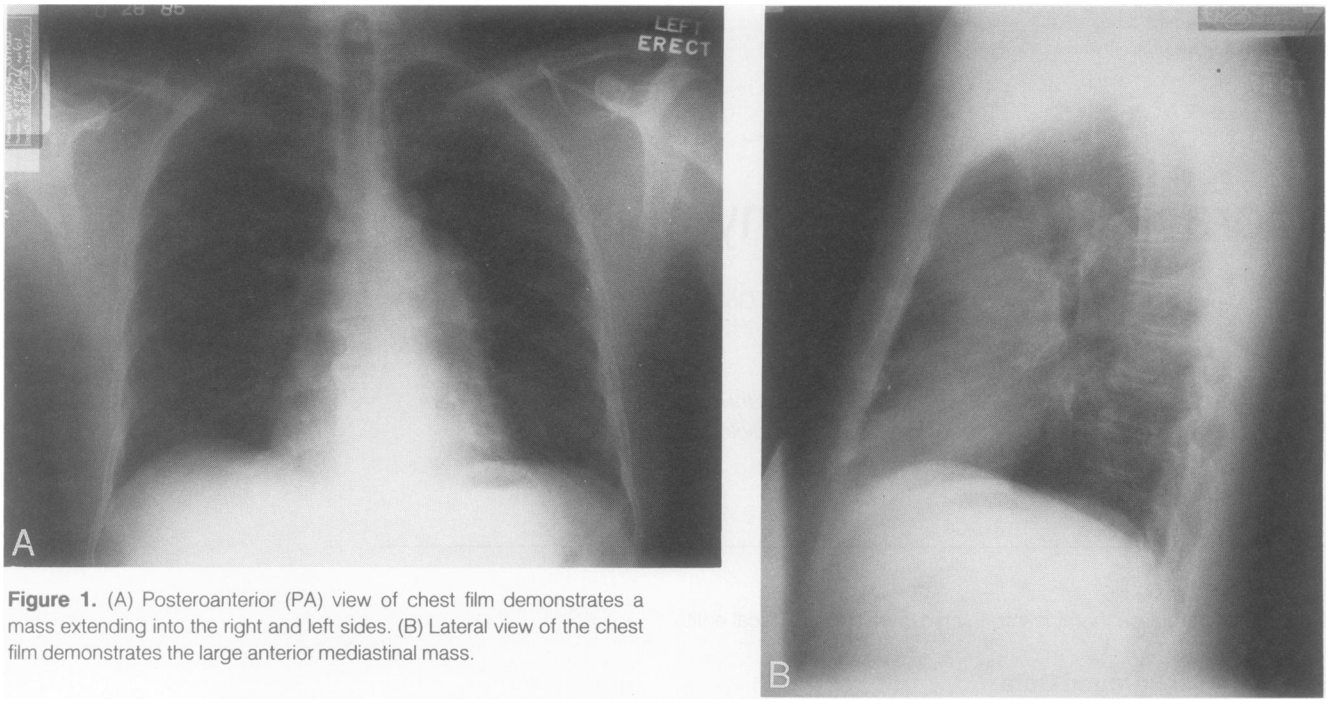


Figure 1. (A) Posteroanterior (PA) view of chest film demonstrates a mass extending into the right and left sides. (B) Lateral view of the chest film demonstrates the large anterior mediastinal mass.

noscopy with needle biopsy was attempted but aborted when pericardial tamponade developed. The patient was resuscitated, and the pericardial hematoma was evacuated by an anterior thoracotomy and pericardiotomy. Postoperatively, the patient remained hemodynamically stable and was neurovascularly intact. After recovery, the patient was transferred to the Duke University Medical Center. Electrophysiologic monitoring, echocardiogram, and endocrine studies were normal.

OPERATIVE COURSE

At operation, the chest was opened through a median sternotomy in both patients. On entering the thoracic cavity, a large mass was seen in the anterosuperior aspect of the mediastinum, located within the body of the thymus gland, without evidence of invasion into the pericardium or sur-

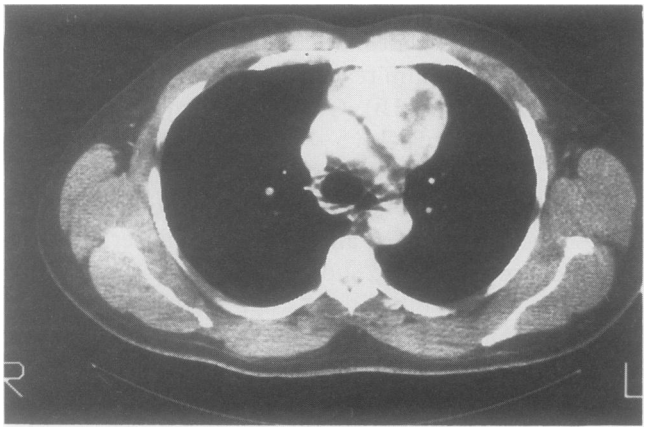


Figure 2. Computed tomography scan demonstrates a tissue plane existing between the mass and its associated structures, suggesting its benign nature.

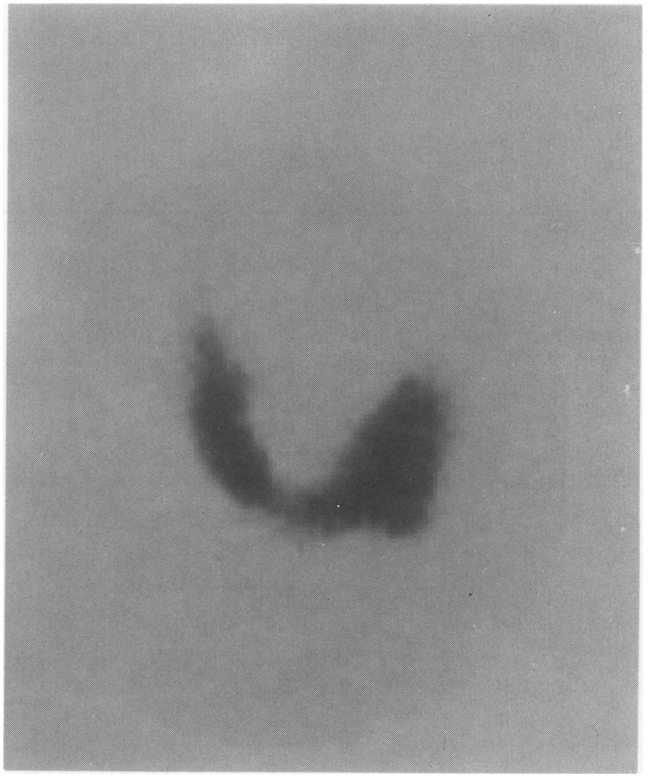


Figure 3. Preoperative thyroid scan shows normal uptake in the usual pretracheal location.

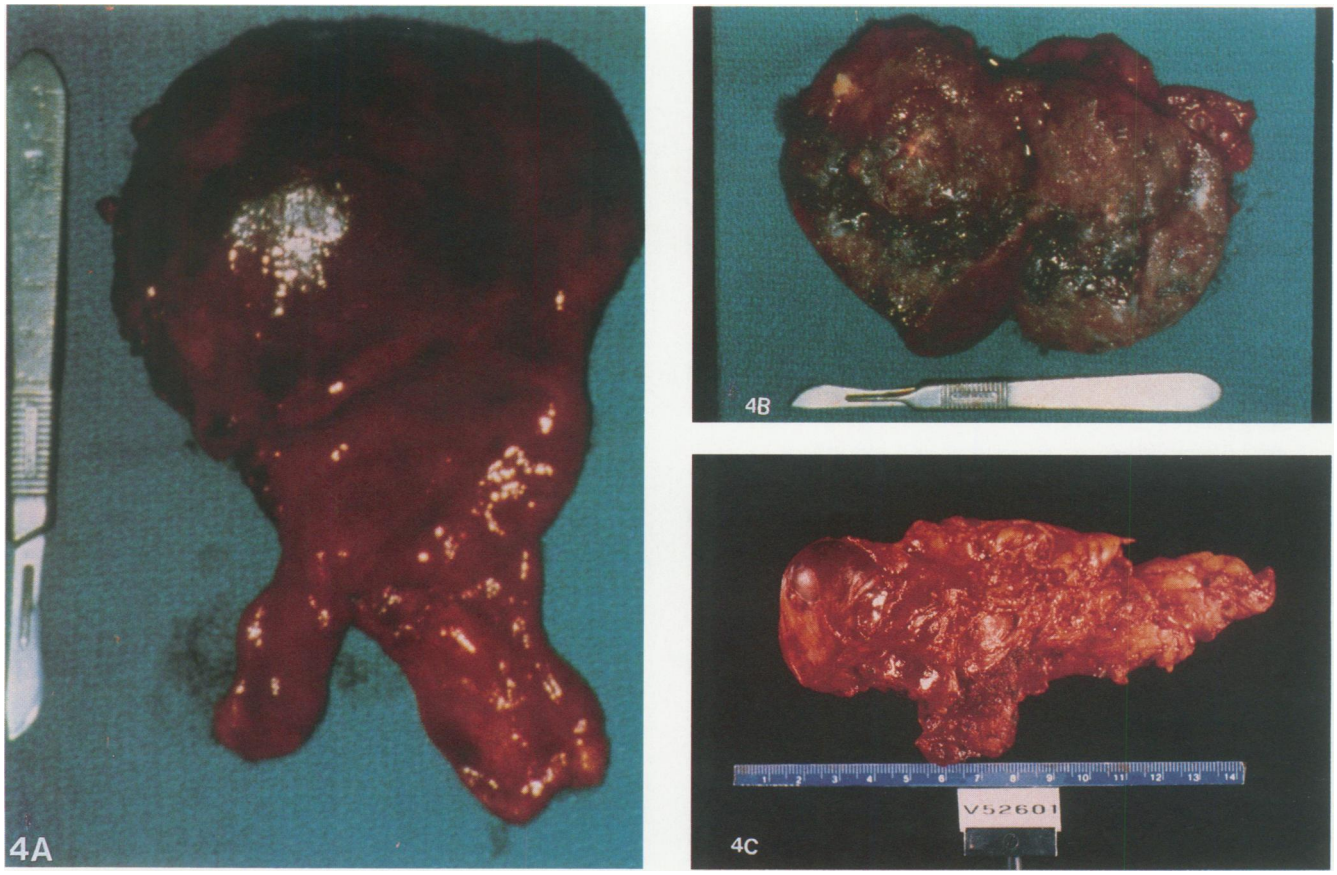


Figure 4. (A) 10.5 × 9 × 4 cm, 259 g intrathymic thyroid mass removed in Case #1. (B) This mass is bivalved and the capsular surface shows characteristics of fat and thymus. The central tissue is tan-yellow, characteristic of thyroid tissue with focal areas of degenerative hemorrhage. (C) 9 × 6 × 2.5 cm, 49 g intrathymic thyroid mass excised in Case #2.

rounding great vessels. The inferior poles of the thymus were dissected free from the surrounding mediastinal fat, and the intrathoracic vessels entering it were ligated. The mass was elevated and the dissection was continued superiorly into the neck. Both poles of the thymus with the mass were delivered into the operative field (Figs. 4A–4C). There was no pedicle connecting the mass to the cervical region. Frozen section indicated intrathymic thyroid tissue, with no evidence of thyroid or thymic malignancy.

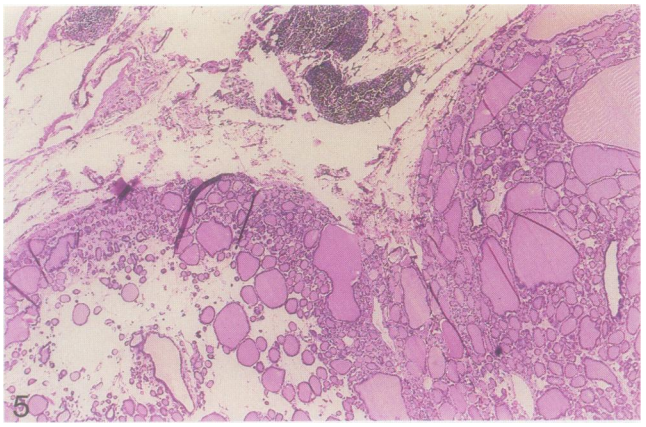
The postoperative course of both patients was uncomplicated. Thyroid function tests performed 5 days and 6 weeks postoperatively were normal. Nuclear scans in both patients showed normal uptake in bilobed thyroid glands in the neck. Follow-up examination at 8 and 2 years revealed both patients to be in excellent health.

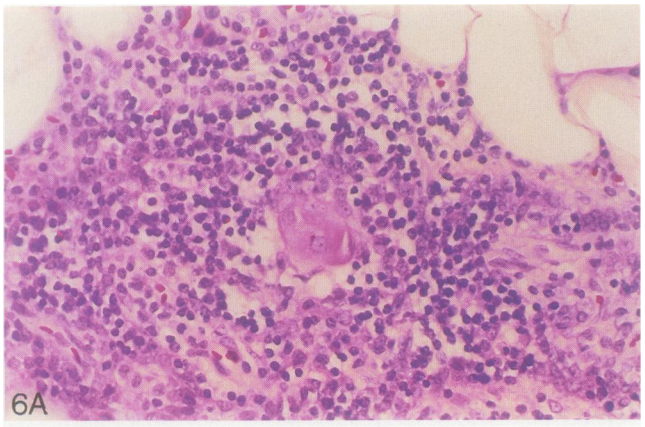
PATHOLOGY

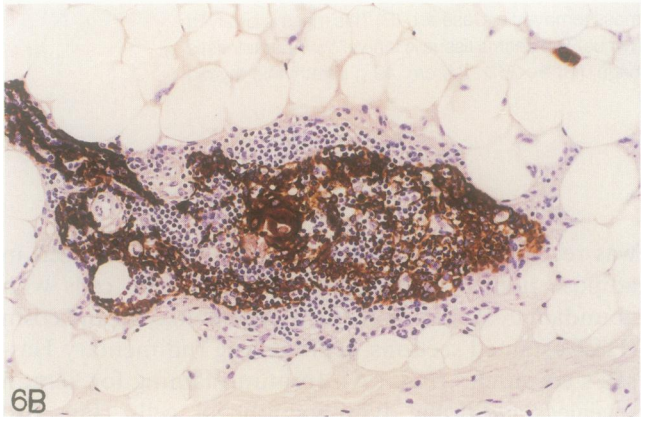
The specimens consisted of thyroid tissue closely associated with atrophic thymic tissue (Fig. 5). Thymic tissue was recognized as lymphoid aggregates interspersed in adipose tissue. A few clusters of epithelial cells with abundant cytoplasm were seen in hematoxylin and eosin (H&E)-stained sections, representing rudimentary Hassall's corpuscles (Fig. 6A). Immunostaining for keratin revealed additional lymphoepithelial cells (Fig. 6B) (Antikeratine AE1/AE3, Boehringer Mannheim Corp., Indianapolis, IN, and antikeratin Cam 5.2, Becton Dickinson, San Jose, CA).

DISCUSSION

The embryology of human development, especially of the head and neck, is a complicated process during which many organs and systems develop synchronously. Anomalies can easily develop from imprecise timing. A knowledge of embryology facilitates a deeper understanding of specific clinical anomalies.







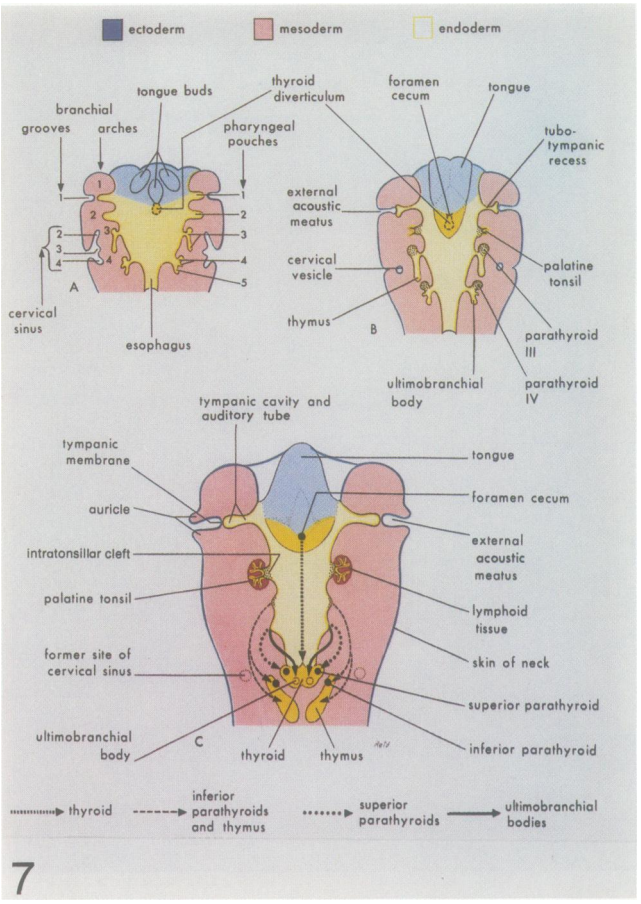


Figure 5. Atrophic thymic tissue is seen in close association with mediastinal thyroid tissue (H&E, original magnification 12×).

Figure 6. (A) Occasional rudimentary Hassall's corpuscles were identified in the thymic tissue, and (B) immunostaining for keratin revealed additional lymphoepithelial aggregates (A—H&E, original magnification 400×. B—Keratin immunostaining, original magnification 250×).

Figure 7. Schematic horizontal sections illustrating the adult derivatives of the pharyngeal pouches. (A) 5 weeks; (B) 6 weeks; (C) 7 weeks. Note that the second branchial or pharyngeal arch grows over the third and fourth arches, thereby burying the second to fourth branchial or pharyngeal grooves in the cervical sinus. Note the migration of the developing thymus, parathyroid, and thyroid glands into the neck (Published with permission from Moore KL, Persaud TVN. The Developing Human: Clinically Oriented Embryology. 5th ed. Philadelphia: WB Saunders, 1993, p. 194).

The thyroid, parathyroid, and thymus share a common origin from the primordial pharynx and its pouches (Fig. 7). Between the sixth and eighth weeks of embryonic life, these tissues are positioned in their final anatomic location. The thyroid, which originates from anlage of pharyngeal epithelium located at the future site of the foramen caecum in the base or pharyngeal portion of the tongue, descends into the neck anterior to the trachea. It forms from the fusion of the median anlage and the ultimobranchial body, the source of parafollicular or C (calcitonin) cells. The thymus and the inferior parathyroid glands, which are derived from the third pair of branchial pouches, descend to their normal positions in the mediastinum and neck, respectively; the superior parathyroid glands and the ultimobranchial bodies develop from the fourth pair of pharyngeal pouches. In unusual cases, the fourth branchial cleft may contribute to the development of the thymus.[1] Developmental anomalies in these structures may cause agenesis or hemigenesis, failure to descend, accentuated descent, differenti-

ation in abnormal positions, and cyst and fistula formation.[1-4]

Ectopic thyroid is a frequent anomaly and usually is identified along the normal route of its descent from the base of the tongue to the thyroglossal duct.[4-6] However, ectopic thyroid tissue also can be found throughout the mediastinum. During embryogenesis, as the heart descends, the thyroid is drawn caudally, and such ectopic mediastinal thyroid tissue is thought to be caused by abnormal mechanical relationships to the heart. Because of cardiac influences, a wide spectrum of clinical presentations occur, ranging from lingual thyroid to intracardiac deposits. A lack of contact causes lingual thyroid, whereas prolonged contact results in an endothelial cardiac location. The origin of lateral aberrant thyroid tissue is more controversial. Some believe it arises from the failure of the ultimobranchial bodies to fuse with the median anlage, while others believe it is not of ultimobranchial body origin. Developmental lateral aberrant thyroid tissue is rare, and the majority of cases are caused by metastatic disease.[2,3]

Lingual thyroid tissue is the most common of the ectopic thyroid tissues; microscopic intralingual thyroid deposits are found in as many as 10% of autopsies, although they become clinically relevant in only 1 in 4000 patients with thyroid disease.[7] Approximately 30% of patients with a lingual thyroid have a normal pretracheal thyroid.[8] Accessory ectopic thyroid is more unusual and has been reported in intrapharyngeal,[9] intralaryngeal,[10] intratracheal,[11-13] intraesophageal,[14] retroesophageal,[15] intrapericardial,[16] intracardiac,[17-20] and aortic[21] locations. (Fifty per cent of dogs have thyroid tissue in the mediastinum and heart.[22]) Single cases include the gall bladder,[23] groin,[24] vagina,[25] and sella turcica[26] as locations of ectopic thyroid tissue, although developmental explanations are difficult to substantiate. Struma ovarii[27] is thought to represent an anomaly of functioning thyroid tissue as part of a teratoma, rather than a developmental anomaly. In addition, thyroid inclusions[3,28] have been described, leading to rare instances of intrathyroidal thymus, parathyroid, and salivary glands.

Mediastinal thyroids[29-34] constitute approximately 15% of all goiters, and of these, as many as 50% have co-existent cervical goiters. There is a small but definite association of disease in the ectopic thyroid and pretracheal thyroid tissue. More than half of mediastinal goiters are symptomatic, and thoracic goiters are more common in women—especially older than 45 years—and occur in 1 in 5000 patients.[32]

Mediastinal thyroid may be differentiated into primary and secondary forms.[34] True primary mediastinal goiters, such as the two patients presented here are quite rare, occurring in less than 1% of all goiters. Their blood supply is from thoracic vessels, and thus, a substernal surgical approach is necessary. Primary thoracic masses represent portions of the gland that remained attached to the pericardium or great vessels during the period of cervical elongation, when the thyroid was drawn from the heart. In contrast, the more common, secondary thoracic masses represent large cervical goiters, which extend substernally into the superior mediastinum from mechanical and gravitational forces. These masses derive their blood supply from thyroid vessels in the neck, are connected with the main thyroid gland, and usually are approached through cervical incisions. Collectively, thoracic goiters usually occur in the anterior mediastinum. Thyroid tissue originating from the lower pole or the isthmus of the thyroid enters the anterior mediastinum, whereas the more posteriorly located thyroid tissue may enter the posterior mediastinum.[35] Usually, such ectopic mediastinal tissue is irrelevant. However, on rare occasions, it may be the only functioning thyroid in the body. Likewise, aberrant ectopic thyroid may hypertrophy after thyroidectomy and become symptomatic.[13] Moreover, primary ectopic carcinoma may be discovered in ectopic thyroid[36] or teratomatous tissue.[37]

Intrathymic pathological changes can be explained by the close embryologic relationship with other organs (Fig. 7). Although intrathymic thyroid tissue has not been identified previously, intrathymic parathyroid is well established.[38] Weller refers to the parathyroid glands as "parathymic" glands.[39] In an autopsy study, as many as 20% of inferior parathyroid glands invaded the thymic capsule in the neck or mediastinum.[40] In addition to being embedded within the thyroid gland, aberrant thymic nodules can occur independently, along the path of their descent, in as many as 20% of humans, or can be associated with the parathyroid glands. It appears likely that the closely associated descent of the thyroid and thymus in the patients in this report gave rise to the intimate association of the two tissues in the mediastinum. It appears that thyroid tissue adhered to the halves of the thymus as they passed by the thyroid gland and fused in the median plane. Other possibilities considered for ectopic thyroid in the literature include metastatic spread of an unidentified thyroid primary malignancy and teratomatous derivation.

Serum thyroid tests and thyroid nuclear scans may be useful in the preoperative and postoperative stages in the diagnosis of a mass and in clinical management. The results of these studies were normal in the patients reported here, and this reflects nonfunctioning or minimally functioning ectopic thyroid tissue. Isotope scans[41-43] are important because, potentially, ectopic thyroid may be the only functioning tissue. A positive uptake confirms a thoracic goiter, but a negative scan does not exclude its diagnosis.

These patients, with thoracic intrathymic thyroid tis-

sue, represent a new clinical entity and broaden the differential diagnosis of masses in the anterior mediastinum.

References

1. Gilmour JR. The embryology of the parathyroid glands, the thymus and certain associated rudiments. J Path Bact 1937; 45:507–522.
2. Gray SW, Skandalakis JE. Embryology for Surgeons. 3rd ed. Baltimore: William & Wilkins, 1993.
3. Livolsi VA. Surgical Pathology of the Thyroid. Philadelphia: WB Saunders, 1990.
4. Moore KL, Persaud TVN. The Developing Human: Clinically Oriented Embryology. 5th ed. Philadelphia: WB Saunders, 1993.
5. Baughman RA. Lingual thyroid and lingual thyroglossal tract remnants. Oral Surg 1972; 34:781–799.
6. Larochelle D, Arcand P, Belzile M, Gagnon NB. Ectopic thyroid tissue — a review of the literature. J Otolaryngol 1979; 8:523–530.
7. Sauk JJ Jr. Ectopic lingual thyroid. J Pathol 1970; 102:239–243.
8. Montgomery ML. Lingual thyroid: a comprehensive review. Western J Surg 1935; 43:661–669.
9. Epstein HC, Loeb WS. Thymic tumor of the pharynx. J Pediat 1955; 47:105–108.
10. Richardson GM, Assor D. Thyroid tissue within the larynx. Laryngoscope 1971; 81:120–125.
11. Myers EN, Pantangco IP. Intratracheal thyroid. Laryngoscope 1975; 85:1833–1840.
12. Donegan JO, Wood MD. Intratracheal thyroid — a familial occurrence. Laryngoscope 1985; 95:6–8.
13. Randolph J, Grunt JA, Vawter GF. The medical and surgical aspects of intratracheal goiter. N Engl J Med 1963; 268:457–461.
14. Postlethwait RN, Detmer DE. Ectopic thyroid nodule in the esophagus. Ann Thoracic Surg 1975; 19:98–100.
15. Arriaga MA, Myers EN. Ectopic thyroid in the retroesophageal superior mediastinum. Otolaryngol Head Neck Surg 1988; 99:338–340.
16. Willis RA. Pathology of Tumors. London: Butterworth, 1953.
17. Rogers WM, Kesten HD. Embryologic bases for thyroid tissues in the heart. Anat Rec 1962; 142:323.
18. Pollice L, Caneso G. Struma cordis: ectopic thyroid goiter in the right ventricle. Arch Pathol Lab Med 1986; 110:452–453.
19. Kantelip B, Lusson JR, DeRiberolles C, Lamaison D, Bailly P. Intracardiac ectopic thyroid. Hum Pathol 1986; 17:1293–1296.
20. Shemin RJ, Marsh JD, Schoen FJ. Benign intracardiac thyroid mass causing right ventricular outflow tract obstruction. Am J Cardiol 1985; 56:828–829.
21. Kampmeier OF. Origin and development of the mediastinal and aortic thyroids and the periaortic fat bodies. Univ Illinois Bull (Illinois Med Dent Monogr [Vol. 2]) 1937:35(12):1–82.
22. Stephens LB, Saunders WJ, Jaenke RS. Ectopic thyroid carcinoma with metastases in a beagle dog. Vet Pathol 1982; 19:669–675.
23. Curtis LE, Sheahan DG. Heterotopic tissues in the gallbladder. Arch Pathol Lab Med 1969; 88:677–683.
24. Rahn J. An unusual heterotopia of the thyroid gland tissue. Zentralbl Allgemeine Pathologie Pathologisne Anatomie 1959; 99: 80–86.
25. Kurman RJ, Prabha AC. Thyroid and parathyroid glands in the vaginal wall. Am J Clin Pathol 1973; 59:503–507.
26. Ruchti C, Balli-Antunes M, Gerber HA. Follicular tumor in the sellar region without primary cancer of the thyroid. Am J Clin Pathol 1987; 87:776–780.
27. Kempers RD, Dockerty MB, Hoffman DL, Bartholomew LG. Struma ovarii-ascitic, hyperthyroid and asymptomatic syndromes. Ann Intern Med 1970; 72:883–893.
28. Carpenter GR, Emery JL. Inclusions in the human thyroid. J Anat 1976; 122:77–89.
29. DeAndrade MA. A review of 128 cases of post-mediastinal goiter. World J Surg 1977; 1:789–797.
30. DeSauza FM, Smith PE. Retrosternal goiter. J Otolaryngol 1983; 12:393–396.
31. Fallor WH, Kelly TR, Jackson JB. Intrathoracic goiter. Surg Gynecol Obstet 1963; 117:604–610.
32. Reeve TS, Rundle FF, Hales IB, et al. The investigation and management of intrathoracic goiter. Surg Gynecol Obstet 1962; 115: 223–229.
33. Lahey FH, Swinton NW. Intrathoracic goiter. Surg Gynecol Obstet 1934; 59:627–637.
34. Willis RA. The Borderland of Embryology and Pathology. 2nd ed. London: Butterworth, 1962.
35. Sweet RH. Intrathoracic goiter located in the posterior mediastinum. Surg Gynecol Obstet 1944; 89:57–66.
36. Fish J, Moore RM. Ectopic thyroid tissue and ectopic thyroid carcinoma. Ann Surg 1963; 157:212–222.
37. Gould SF, Lopez RL, Speers WC. Malignant struma ovarii. J Reprod Med 1983; 28:415–419.
38. Gilmour JR. Some developmental abnormalities of the thymus and parathyroids. J Path Bact 1941; 52:213–218.
39. Weller GL. Development of the thyroid, parathyroid and thymus glands in man. Contrib Embryol Carneg Inst 1933; 141:93–140.
40. Nathaniels EK, Nathaniels AN, Wang CA. Mediastinal parathyroid tumors: a clinical and pathological study of 84 cases. Ann Surg 1990; 171:165–170.
41. Salvatore M, Gallo A. Accessory thyroid in the anterior mediastinum. J Nucl Med 1975; 16:1135–1136.
42. Asp A, Hasbargen J, Blue P, Kidd GS. Ectopic thyroid tissue on thallium technetium parathyroid scan. Arch Intern Med 1987; 147:595–596.
43. Thakore K, Vansant J. Hyperthyroidism due to toxic, intrathoracic thyroid tissue with absent cervical thyroid gland. Clin Nucl Med 1993; 18:535–536.