A 16-year-old girl was diagnosed with FMF at the age of 10 years and was given colchicine. The patient was diagnosed as having secondary amyloidosis based on a renal biopsy performed to find out the cause of her clinical symptoms. On her last physical examination she had a bilateral, firm and diffusely enlarged thyroid gland. Her serum T3, T4, and TSH levels were all normal. A subtotal thyroidectomy was performed, with no complications. Grossly, the cut surface of the subtotal thyroidectomy material had a solid, white to pale-tan appearance and measured 8×6×3.5 cm. Microscopic examination by hematoxylin-eosin stained sections taken from both lobes of the thyroid revealed extensive infiltration of the parenchyma by an eosinophilic amorphous material consistent with amyloid substance (Figure 1). There was extensive fat cell metaplasia in the thyroid interstitium. The lining cells of the thyroid follicles were flattened and atrophic. There was no evidence of malignancy. Methyl violet stain was metachromatically positive in the involved tissue. This material stained intensely with Congo red and was apple green in color when examined microscopically under polar-
ized light (Figure 2). Immunohistochemical staining patterns were consistent with amyloid AA (Clone mc1, Novocastra).

**CASE 2**

A 33-year-old male with secondary amyloidosis and chronic renal failure was admitted with rapidly growing goiter associated with hoarseness. Serum levels of the thyroid hormones and TSH were all normal. The patient underwent a subtotal thyroidectomy. The resected portion of the right lobe was enlarged and measured 10.5 cm in its greatest dimension. The resected portion of the left lobe was enlarged and measured 11 cm in greatest dimension. On gross examination of the thyroid gland, cut surfaces of both lobes of the thyroid had a largely solid, yellow-tan and irregular appearance. Both of the thyroid lobes were largely replaced by ill-defined solid, yellow-tan, fatty lesions. Microscopically, eosinophilic amorphous deposits were identified in interfollicular and perifollicular locations displacing and compressing the follicles. Areas of mature adipose tissue were seen intermixed with residual thyroid parenchyma and the eosinophilic amorphous deposits. Methyl violet stain was metachromatically positive in the involved tissue. These deposits stained intensely with Congo red and were apple green in color when examined microscopically under polarized light. Immunohistochemical evaluation demonstrated the presence of amyloid AA immunoreactivity (Clone mc1, Novocastra) (Figure 3).

**DISCUSSION**

Amyloidosis results from the deposition of insoluble, fibrous amyloid proteins, nearly always in the extracellular spaces of organs and tissues. Named by Virchow in 1854 on the basis of the color after staining with iodine and sulfuric acid, all amyloid proteins share a unique fibrillar ultrastructure. Depending upon the biochemical nature of the amyloid precursor protein, amyloid fibrils can be deposited locally or systemically, involving virtually every organ system of the body. Amyloid fibril deposition may have no apparent clinical consequences or may lead to severe pathophysiologic changes. Regardless of etiology, the clinical diagnosis amyloidosis is usually not made until the disease is far advanced.7

Amyloidosis can involve the thyroid as part of a systemic disease or as a localized primary amyloid tumor. Amyloid goiter is extremely rare and presents more frequently as an autopsy finding than in surgical material. The thyroid gland may be asymptptomatically involved by amyloid substance in nearly 30% to 80% of patients with primary or secondary amyloidosis.1,4 Amyloid substance might also be encountered in the thyroids of 50%
Amyloid goiter may be associated with either primary or secondary amyloidosis. In Turkey, FMF is the most common cause of secondary amyloidosis. The most common clinical manifestation of FMF-related amyloid is the development of the nephrotic syndrome and eventually uremia. However, the initial presence of a goiter caused by amyloid deposition is uncommon. Twelve cases of amyloid goiter complicating FMF were reported in the literature. One of our patients amyloid goiter was also associated with FMF. Most commonly amyloid goiter presents as a rapidly growing neck mass causing compression symptoms including dyspnea, dysphagia and/or hoarseness. The enlargement of the gland is relatively rapid, occurring in weeks to several months. It usually presents as diffuse thyroid involvement, affecting both lobes, with a certain nodularity and associated firmness. In our patients, one had a rapidly enlarged thyroid associated with hoarseness. The other patient was diagnosed with FMF with secondary amyloidosis and on her last physical examination she had a bilateral, firm and diffusely enlarged thyroid gland. Altparmak et al have reported three patients with amyloid goiter in FMF, although none of their patients had rapidly growing thyroids.

The diagnosis of amyloid goiter should be considered in any patient with systemic amyloidosis presenting with an enlarging diffuse goiter and euthyroid state. In patients with amyloid goiter, thyroid function tests are often nonspecifically altered, and most patients are clinically euthyroid despite the diffuse involvement by the disease. However, there are rare reports of patients with hypothyroidism or hyperthyroidism. As previously stated, our patients had normal levels of T4, T3 and TSH.

The definitive diagnosis must be made by histologic evaluation of the resected thyroid gland, and although a fine needle aspirate may result in a definitive diagnosis, examination of resected tissue is usually necessary. Amyloid is usually present extracellularly as an amorphous, eosinophilic, proteinaceous substance in the light microscope. In cases of amyloid goiter, amyloid material is commonly seen infiltrating the parenchyma, distorting the normal tissue architecture. Other histologic features occurring in amyloid goiter include large foci of fatty metaplasia and rarely, squamous metaplasia as demonstrated by one of our patients as well. Histochemical stains aid in the confirmation of amyloid. These stains include Congo red, thioflavin T, and crystal violet stains. Congo red, the most frequently used technique, imparts a unique apple green birefringence when viewed under polarized light and is considered a pathognomonic feature of amyloid. Immunohistochemical techniques may help differentiating amyloid A from other types of amyloid.

The presence of amyloid in the thyroid gland must raise the differential diagnosis of medullary carcinoma of the thyroid. In some cases amyloid may appear to almost completely obscure the underlying carcinoma. However, the lack of calcitonin reactive neoplastic cells and the presence of a background of C-cell hyperplasia can help to make this distinction. Amyloid deposition can also be seen in other conditions such as multiple myeloma, solitary plasmacytoma, infections, FMF, rheumatoid arthritis and a hyalinizing trabecular adenoma. However, these lesions each have a unique and different histologic appearance which renders discrimination easy.

The preoperative diagnosis of amyloid goiter should be suspected in patients with longstanding predisposing diseases such as FMF, hemodialysis, or with known amyloidosis who present with a rapidly growing diffuse goiter associated with euthyroid state. Histopathologic confirmation of the diagnosis is essential. We have described two patients with extensive involvement of the thyroid gland by amyloid substance, characteristic of amyloid goiter.
AMYLOID GOITER

REFERENCES

1. Arean VM, Klein RE. Amyloid goiter: review of the literature and report of a case. Am J Clin Pathol. 1961;36:341-55.
2. Villami CF, Massimi G, D’Avella J, Cole SR. Amyloid goiter with parathyroid involvement: a case report and review of the literature. Arch Pathol Lab Med. 2000;124:281-283.
3. Livolsi VA. Medullary carcinoma. In: Bennington JL, editor. Surgical pathology of the thyroid. Philadelphia: WB Saunders; 1990. 213-252p.
4. Amado JA, Ordiviela R, Palacios S, Casanova D, Marzanos J, Freijanes J. Fast growing goiter as the first clinical manifestation of systemic amyloidosis. Postgrad Med. 1982;58:171-172.
5. Perez Fontan FJ, Mosquera Oses J, Pombo Felipe F, Rodriguez Sanchez I, Arnaiz Pena S. Amyloid goiter in a child US, CT and MR evaluation. Pediatr Radiol. 1992;22:393-394.
6. Altiparmak MR, Pamuk ON, Pamuk GE, Apaydin S, Ataman R, Serderecti K. Amyloid goiter in familial Mediterranean fever: report on three patients and review of the literature. Clin Rheumatol. 2002;21:927-930.
7. Sipe JD, Cohen AS. Amyloidosis. In: Fauci AS, editor. Harrison’s principles of internal medicine (14th edition). Singapore: McGraw-Hill; 1998. 1856-1860p.
8. Briggs MSW. Amyloidosis. Ann Intern Med. 1961;35:943-957.
9. Rosai J. Thyroid gland. In: Rosai J, editor. Rosai and Ackerman’s surgical pathology. London: Mosby; 2004. 515-534p.
10. Sai A, Wechsler B, Leenhardt L, Beauflis H, Hoang C, Meneaux F, Piette JC. Case history amyloid goiter as the initial manifestation of systemic amyloidosis due to familial Mediterranean fever with omozzygous MEFV mutation. Thyroid. 2001;11:297-400.
11. Hamed G, Heffess CS, Shmookler BM, Wening BM. Amyloid goiter. A clinicopathologic study of 14 cases and review of the literature. Am J Clin Pathol. 1985;104:306–302.
12. Kimura H, Yamashita S, Ashizawa K, Yokoyama N, Nagataki S. Thyroid dysfunction in patients with amyloid goiter. Clin Endocrinol. 1997;46:769-774.
13. Kostina ZJ. Amyloid goiter in amyloidosis secondary to pulmonary tuberculosis. Probl Tuberk. 1970;48:40-44.
14. Kanoh T, Shimada H, Uchino H, Maunuma K. Amyloid goiter with hypothyroidism. Arch Pathol Lab Med. 1989;113:542-544.
15. Van Rijswijk MR, Van Heusden CW. The potassium permanganate method for differentiating amyloid AA from other forms of amyloid in routine laboratory practice. Am J Pathol. 1979;97:43-58.