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Review

Amyloid goiter

F. Villa, G. Dionigi*, M.L. Tanda, F. Rovera, L. Boni

Endocrine Surgery Research Center, Department of Surgical Sciences, University of Insubria, Viale Borri 57, 21100 Varese, Italy

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ABSTRACT

Background and aim: Amyloidosis refers to a variety of conditions in which amyloid proteins are abnormally deposited in organs and/or tissues. Amyloidosis is a rare occurrence in thyroid gland.

Methods: A systematic review of the published data on amyloid goiter was carried out by searching Medline and other online databases (such as Scopus and Endnote) for the period from 1951 to March 2008. A total of 127 publications (case series, single case reports and reviews) was found, of which 31 were case series published from February 1995 to March 2008. Six articles have been considered for our review because they regard amyloid goiter as a manifestation of both primary and secondary amyloidosis (a total of 30 cases have been analyzed). Exclusion criterion was the presence of primary thyroid cancer.

Results: The preoperative diagnosis of amyloid goiter should be considered in patients with known systemic amyloidosis or with a long-standing predisposing disease who present a rapidly growing thyroid volume in association with a euthyroid state. Fine-needle aspiration biopsy can be performed to exclude primary malignant lesions of thyroid gland and immunohistochemical studies can identify and characterize the amyloid deposits.

Conclusion: Amyloid goiter has to be suspected in all patients with a progressive, rapidly growing, bilateral thyroid enlargement and a concomitant history of chronic inflammatory processes. Moreover, this should be suspected in patients who are known to have disease predisposing to amyloid deposition.

1. Introduction

Amyloid goiter (AG), defined by the presence of amyloid within the thyroid in such quantities as to produce a clinically apparent enlargement of the gland, is a rare pathologic entity associated with both primary amyloidosis, a syndrome in which there is deposition of insoluble proteinaceous, amorphous and eosinophilic material in the exracellular matrix of some organs, and secondary amyloidosis, which occurs as a result of the accumulation of amyloid A (AA), which is a portion of the acute-phase serum amyloid A (SAA) protein produced by the liver at times of inflammation. In autopsy-based studies intra-thyroidal amyloid is present in approximately 80% of patients with secondary amyloidosis and in 50% of those with primary amyloidosis.[1]

Amyloidosis can be classified based on the biochemical nature of amyloid protein deposits. In primary amyloidosis the major fibrillar protein is amyloid L (AL), based on the light chain components of immunoglobulins. In secondary amyloidosis, the fibril subunit is amyloid A (AA).[1]

The presence of amyloid in association with thyroid gland enlargement is also frequently seen in medullary carcinoma of the thyroid, being identified in 50–70% of the cases, and in association with long-standing inflammatory disorders such as rheumatoid arthritis, ankylosing spondylitis, Crohn's disease and familial Mediterranean fever (FMF).

Amyloid goiter is a well-established entity that was presented for the first time in 1855 by Rockitansky, who described the first case of amyloid infiltration of thyroid gland in patients with systemic amyloidosis.[1] It was in 1858 that Beckmann described the "condition" characterized by clinically detectable thyroid mass with enlargement of the gland because of amyloid deposition; this "condition" was later named "amyloid goiter" by Eiselberg in 1904.[1]

Before being coined as a specific diagnosis, some cases of AG were reported in the literature, under other names such as "hamartomatous adiposity with superimposed amyloidosis of thyroid gland" (Fuller RH, *Am J Clin Pathol* 1950) or "fatty infiltration in amyloid goiter" (Sirsat MV, *J Pathol Bacterial* 1961). [2]

Different authors have written in the literature about systemic amyloidosis and have reported necropsy cases (e.g. Walker, 1942; Arean and Klein, 1961; Shapiro, Koluit and Potter, 1971).

2. Methods and results

This review included a total of 30 patients. In detail, ten patients had disease predisposing to secondary amyloidosis such as chronic

* Corresponding author. Tel.: +39 033 227 8450; fax: +39 033 226 0260.
E-mail address: gianlorenzo.dionigi@uninsubria.it (G. Dionigi).

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suppurative infections (osteomyelitis, chronic obstructive pneumonia, pulmonary tuberculosis, bronchiectasis, rheumatoid arthritis and chronic psoriasiform arthritis). Thirteen patients were affected by FMF, a hereditary disease with autosomal recessive inheritance characterized by acute episodes of fever and serositis of the peritoneal cavity, pleura and joints, more frequently seen in Mediterranean countries such as Turkey and Israel. FMF is associated with widespread deposition of amyloid in tissue, and is indistinguishable from reactive systemic amyloidosis; the most site involvement seen in amyloidosis was the kidney. All patients with FMF considered in our study had a nephrotic syndrome and three of them were renal transplantation patients with non-functional graft. Moreover, seven patients had a primary amyloidosis involving the thyroid gland: this is a rare occurrence and reports in the literature are limited to case reports.

The mean age of patients considered for our review was 43.7 years with ages ranging from 23 to 75 years; 20 were male and 10 were female.

Amyloid goiter was manifested, in 21 cases, as non-tender rapidly (over a period of 6 weeks to 1–2 years) enlarging neck mass; of these six patients had upper airway obstructive symptoms such as dyspnea, stridor hoarseness and dysphagia.

In the setting of a rapidly enlarging thyroid mass, a malignant neoplasm of the gland must be excluded. Of particular concern would be on anaplastic carcinoma or a non-Hodgkin's malignant lymphoma, both associated with a rapidly enlarging thyroid mass and local pressure symptoms. However, in contrast to malignant thyroid tumors that are often a unilateral disease, AG affects the thyroid most commonly in a bilateral and diffuse manner.

The remaining nine cases were identified at autopsy. In the autopsy cases, in addition to the thyroid the organs invariably involved by amyloid deposition included the kidney, adrenal, liver and spleen. Other less common sites of involvement included heart, pancreas, gastrointestinal tract, lung bone marrow, lymph nodes, parathyroid gland, salivary glands and testis.

Using physical findings we categorized each patient's goiter based on World Health Organization guidelines[4] as follows: stage 0, patients with no goiter; stage IA, patients with goiter palpable but not visible; stage IB, goiter palpable but visible only when neck fully extended; stage II, goiter easily visible with neck in normal position; stage III, very large goiter.

We classified the patients of our study as follows: 9 patients in stage 0 (one diagnosed at autopsy); 6 patients in stage IA; 9 patients in stage II and the remaining 6 patients in stage III.

Laboratory studies showed euthyroidism in 24 cases; in 4 cases (all of them affected by FMF) a euthyroid syndrome was documented (normal TSH level in spite of low value of T3) and 2 cases, also affected by FMF, showed hyperthyroidism which manifested with tremors, palpitations and diarrhea.

Ultrasound examination was performed in 14 patients and in all of them diffuse enlargement of the thyroid gland was revealed. Focal amyloid deposition was detected as complex or hypoechoic masses; some of the patients had hypoechoic masses but in others the thyroid gland contained hyperintense areas or had a nodular appearance.

Tc-99m scintigraphic and computed tomographic (CT) studies werenot performed systematically in all patients. Frequently thoracic had been performed in those patients with secondary amyloidosis with chronic obstructing pneumonia and bronchiectasis.

The diagnosis of AG may be facilitated by the use of ultrasound fine-needle aspiration (FNA) cytology which was performed in 19 patients. Cytological examination of air-dried hematoxylin–eosin stained smears revealed abundant irregular fragments of pink-stained amorphous material in 12 cases. The material was more solid and hyaline-like than colloid in nature. The smears stained with Congo-red were examined under polarized light, and positively stained amyloid strands exhibited the characteristic apple-green birefringence; in the remaining cases the FNA cytology revealed atypical follicular cells. Although helpful in establishing the presence of amyloid, histochemistry (Congo-red and violet stains) is less sensitive and specific than immunohistochemical evaluation; all types of amyloid stain positively with Congo and have a similar appearance under polarized light. Potassium permanganate treatment of Congo red-stained sections may be helpful in differentiating amyloid A from other types of amyloid.

The definitive diagnosis of AG rested with histological evaluation of resected surgical specimens; surgical treatment was performed in all patients but one, who was treated with Dexamethasone. Total thyroidectomy was performed in 11 patients, subtotal thyroidectomy in 6 patients and in the others the type of surgery was not specific. The patient treated with medical therapy manifested the goiter as the first sign of a primary systemic amyloidosis and did not need surgical treatment because of the decrease in size of the goiter (from 32.8 to 23.3 ml) after the therapy.

At definitive histology, the thyroid gland appeared enlarged in all cases and bilateral involvement was seen in all but one patient. Thyroid parenchyma was characterized by multiple inhomogeneous nodules, varying in diameter from a few millimeters to several centimeters, and from firm to soft gelatinous nodules in consistency, with the presence in some cases of simple cysts and in others of hemorrhagic ones; the cut surface varied in color from gray-white to light brown or pale yellow.

In all cases histologic sections stained with hematoxylin–eosin showed pronounced deposition of an eosinophilic, waxy substance in the perifollicular site. This substance determined the more or less complete replacement of the thyroid parenchyma. Vascular involvement with amyloid was not described in any cases; however, perivascular deposition was frequently seen.

Also described was the presence in the thyroid parenchyma of lymphocytic infiltrate, foreign-body type giant cells and adipose tissue, the latter varying in appearance from lobules or clusters of mature adipocytes replacing the thyroid tissue to focal scattered adipocytes within the stroma.

3. Discussion

Diffuse enlargement of the thyroid gland secondary to infiltration by amyloid is infrequent, even if involvement of the gland by amyloid is a relatively common phenomenon. Amyloid goiter can be defined as the presence of amyloid within the thyroid gland in such quantities as to produce a clinically apparent enlargement of the gland. Focal microscopic deposits of amyloid substance may often be found within the thyroid gland in association with systemic amyloidosis, medullary carcinoma, and less frequently, primary amyloidosis of the thyroid.[5,6]

The diagnosis of amyloid goiter should be considered in any patient with systemic amyloidosis and FMF presenting with a bilateral, diffuse goiter associated with a euthyroid state. Usually laboratory studies show normal results for thyroid function tests, even if in a minority of cases a hypothyroid or hyperthyroid state is detected.

Rarely, amyloid goiter may occur as the first sign of systemic amyloidosis.[3,7]

Occasionally in AG, the amyloid can also involve the parathyroid glands, as reported in one of the cases considered for the review.[7,8]

Many affected patients present symptoms of compression such as dysphagia, hoarseness or dyspnea. The diagnosis AG must be distinguished from the more common types of goiter. FNA biopsy has been used to aid in the diagnosis of amyloid goiter and to exclude other differential diagnoses. FNA of the thyroid is a valuable and sensitive method, and is a safe and easily performed procedure, even if the definitive diagnosis of AG is most often made after thyroidectomy.

In conclusion, amyloid goiter should be suspected in all patients with a progressive, rapidly growing, bilateral thyroid

enlargement and a concomitant history of chronic inflammatory processes; a state of euthyroidism can help in the diagnosis. In many cases fine-needle aspiration biopsy can be performed to exclude malignant lesions. In order to diagnose amyloid goiter definitively thyroidectomy is often necessary. Surgical intervention is indicated either for aesthetic purposes or to relieve the pressure symptoms.

Conflict of interest
None declared.

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