

Diffuse amorphous, eosinophilic deposition in thyroid gland of three cases with familial mediterranean fever: amyloid goitre

Ailesel akdeniz ateşi olan 3 olguda tiroid bezinde diffüz amorföz eozinofilik birikim: Amiloid guatr

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Abstract

Amyloidosis is a disease of unknown etiology characterized with the accumulation of an amorphous, proteinaceous material in various organs and tissues of the body. Amyloid goitre is a rare entity defined by the presence of amyloid within the thyroid gland and reveals itself as markedly enlarged thyroid gland clinically. Amyloid goitre occurs in association with both primary and secondary systemic amyloidosis, more commonly in the latter. In addition, amyloid accumulation in thyroid gland may also be seen in cases of medullary thyroid carcinoma. In this report we described, diffuse and dense accumulation of amyloid within the thyroid gland in three cases with the previous history of Familial Mediterranean Fever. Determination of diffuse enlargement at the thyroid gland during routine physical examination lead the patients to thyroid ultrasonography and multiple nodules were established. The first patient had subtotal thyroidectomy. Dense extracellular amorphous eosinophilic material infiltration and loss of normal follicular pattern within thyroid parenchyma, thinning of follicular epithelium and atrophy were determined in H/E sections. The other two cases had subtotal thyroidectomy too. The cut surface of thyroid gland was yellow in colour and showed pink, amorphous collection within interfollicular and perifollicular spaces which compress the follicles, diffuse fat cell metaplasia mixed with ordinary parenchyma within the interstitium, microscopically. The amorphous material accumulated in all three cases stained pink-orange

Özet

Amiloidoz çeşitli doku ve organlarda amorföz, proteinöz bir materyalin birikimiyle karakterize, etyolojisi bilinmeyen bir hastalıktır. Amiloid guatr tiroid bezi içinde amiloid varlığı ve klinik olarak belirgin büyümüş tiroid bezi ile kendini gösteren nadir bir antitedir. Amiloid guatr daha sık sekonder sistemik amiloidoz olmak üzere primer ve sekonder sistemik amiloidoz ile ilişkili olarak ortaya çıkabilmektedir. Ek olarak medüller tiroid karsinomu olgularında da tiroid bezinde amiloid birikimi görülebilmektedir.

Biz burada Ailesel Akdeniz Ateşi tanısı ile takip edilen, tiroid bezinde diffüz ve yoğun amiloid birikimi olan 3 olguyu sunduk. Olguların rutin takiplerinde, fizik muayenede tiroid bezlerinde diffüz büyüme saptanması üzerine yapılan ultrasonografide multipl nodüller görüldü. İlk olguya sağ total, sol subtotal tiroidektomi uygulandı. Mikroskopik incelemede tiroid parankiminde yoğun ekstrasellüler amorföz eozinofilik materyal infiltrasyonu ve normal folliküler paternde kayıp ile folliküler epitelde incelleme ve atrofi saptandı. Diğer 2 olguya subtotal tiroidektomi uygulandı. Tiroid bezinin kesit yüzü sarı renkteydi, mikroskopik olarak interfolliküler ve perifolliküler alanlarda, follikülleri komprese eden pembe amorföz birikim ve olağan parankimle karışık diffüz yağ hücre metaplazisi görüldü. Histokimyasal yöntemle amorföz materyal 3 olguda da Kongo-red ile diffüz olarak pembe-turuncu renkte boyandı ve polarize ışık mikroskopunda elma yeşili birefrejans gösterdi. İmmunohistokimyasal

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with Congo-red diffusely and showed apple green birefringence under polarized microscope histochemically. This material stained positively with amyloid AA (Clone mc1, Dako) immunohistochemically. All three cases were diagnosed as “amyloid goitre”

Key word: Thyroid, amyloid, familial mediterranean fever

olarak bu materyal amyloid AA (clone mc1, Dako) ile pozitif boyandı.

Her 3 olguya “Amiloid Guatr” tanısı konuldu.

Anahtar kelimeler: Tiroid, amiloid, ailesel akdeniz ateşi

Introduction

Amyloidosis is a group of diseases, all characterized by deposition of protein fibrils. These amyloid deposits composed of protein fibrils are derived from different protein precursors, and thus variations in the clinical picture of amyloidosis are related to the type of involved precursor protein^{1,2}. According to the etiologic factors, amyloidosis is classified as primary or secondary. In secondary amyloidosis, clinical features depend on the nature of the underlying disorders such as Crohn's disease, rheumatoid systemic arthritis, osteomyelitis and tuberculosis³. Infiltration of amyloid within the thyroid gland in patients with amyloidosis was first reported by Rokitansky in 1855, and later confirmed by Virchow^{3,4}. The term “amyloid goiter” as diffuse expansion of the thyroid gland due to amyloid deposition was introduced into the literature by von Eisenberg in 1904. Recently, it is defined as the presence of amyloid within the thyroid gland that causes enlarged thyroid gland which is clinically obvious⁵. Although thyroid gland is among the many organs that could be infiltrated in systemic amyloidosis, diffuse amyloid deposition in the thyroid gland secondary to systemic amyloidosis associated with Familial Mediterranean Fever (FMF) is rare and as true amyloid goiter secondary to amyloidosis associated with FMF, only a very few cases have been reported to date^{6,7}.

In this report, we describe extensive involvement of the thyroid gland by amyloid substance in three cases with known FMF.

Case 1

A 51-year-old woman had been diagnosed with FMF 14 years ago and was given colchicine. As she was on colchicine treatment, she developed chronic renal failure and started routine hemodialysis program. After hospitalization of the patient for renal transplantation, examination of thyroid gland and thyroid function tests of the patient were in normal range for ten years. But, on her last physical examination bilateral, firm and diffusely enlarged thyroid gland was determined. Serum T₃, T₄, and TSH levels were unremarkable. Also, the antibodies for antithyroid peroxidase, antithyroglobulin

and TSH were unremarkable. Ultrasonographic examination confirmed the presence of multiple nodules. Right total and left subtotal thyroidectomy was performed, with no complications. Grossly both lobes were enlarged and completely encapsulated. Cut surface of both lobes revealed diffuse involvement of the gland with multiple lobulated nodules which contains hemorrhagic and congested areas. Routine microscopic examination of hematoxylin-eosin stained sections taken from both lobes of the thyroid revealed extensive extracellular infiltration of the thyroid parenchyma and disruption of the normal follicular pattern in some areas by an eosinophilic amorphous material (**Figure 1a and b**). This material stained intensely pink with Congo red and showed apple green birefringence under polarized microscopy (**Figure 1c**). The lining cells of the thyroid follicles were flattened and atrophic. Histologic findings seen in other samples, were consistent with focal lymphocytic thyroiditis. There was no evidence of malignancy. Immunohistochemical staining patterns were consistent with amyloid AA (Clone mc1, Dako) (**Figure 1d**). There was no evidence of C-cell hyperplasia or medullary carcinoma.

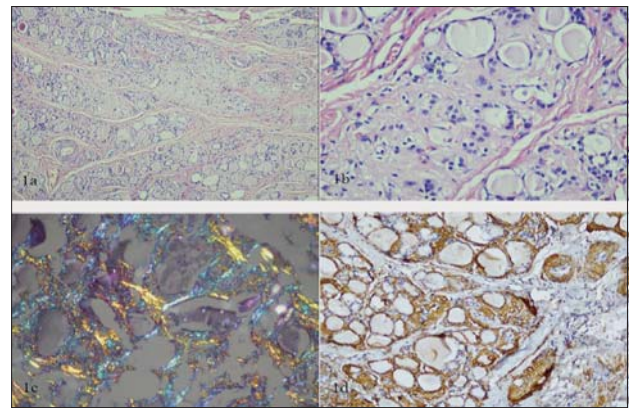


Figure 1: The thyroid tissue shows follicular patterns of different sizes. Eosinophilic and hyalen amorphous substance accumulation is seen in the arterial wall and interstitium (**a and b**), homogeneous pink substance was confirmed apple green under polarized microscope (**c**), immunohistochemically, eosinophilic material is positive with Amyloid AA (Avidin biotin, DAB Chromogen, original magnification) (**d**).



Figure 2: Macroscopic appearance of the thyroid gland after surgery, cross-sectional view.

Case 2

A 33-year-old male with a previous medical history of secondary amyloidosis and renal transplantation due to chronic renal failure was admitted with rapidly growing thyroid gland and hoarseness. On current physical examination of the patient, bilateral, firm and diffusely enlarged thyroid gland was found. Serum T_3 , T_4 , and TSH levels were in normal range. Also, the antibodies for antithyroid peroxidase, antithyroglobulin and TSH were unremarkable. Due to the presence of multiple nodules in ultrasonographic examination of thyroid gland, the patient underwent a subtotal thyroidectomy. The resected portion of the right lobe was enlarged and measured 8 cm in its greatest dimension. The resected portion of the left lobe was also enlarged and measured 6 cm in greatest dimension. Cut surfaces of both lobes of the thyroid had a largely solid, yellow-tan and irregular appearance on gross examination (**Figure 2**). Both of the thyroid lobes were largely replaced by ill-defined, solid, yellow-tan, fatty lesions. Microscopically, there was extensive fat cell metaplasia in the thyroid interstitium. Eosinophilic amorphous deposits were identified in interfollicular and perifollicular locations displacing and compressing the follicles (**Figure 3a**). Areas of mature adipose tissue were seen intermixed with residual thyroid parenchyma and the eosinophilic amorphous deposits (**Figure 3b**). These deposits stained intensely with Congo red and showed apple green birefringence under polarized microscope (**Figure 3c**). Immunohistochemical evaluation demonstrated the presence of amyloid AA positivity (Clone mcl, Dako) (**Figure 3d**).

Case 3

A 37-year-old female with secondary amyloidosis and renal transplant due to chronic renal failure presented with rapidly growing thyroid gland. On current physical examination of the patient, diffusely enlarged thyroid gland was determined. Serum T_3 , T_4 , and TSH levels were in normal range. Repeated ultrasound showed multiple nodules in thyroid gland and the patient underwent a subtotal thyroidectomy. Gross and microscopic examination of the thyroid gland is similar to the second case. Microscopically, there was fat cell metaplasia in the thyroid interstitium, eosinophilic amorphous deposits in interfollicular and perifollicular spaces. Areas of mature adipose tissue were seen intermixed with residual thyroid parenchyma and the eosinophilic amorphous deposits. These deposits stained intensely with Congo red and showed apple green birefringence under polarized light. Immunohistochemical evaluation demonstrated the presence of amyloid AA positivity (Clone mcl, Dako).

Discussion

Asymptomatic focal amyloid deposits in thyroid gland may be seen in nearly 30–80% of patients with amyloidosis⁸. Amyloid substance within thyroid gland might also be encountered in %50-%80 of patients with medullary thyroid carcinoma⁹. But, diffuse amyloid deposition associated with amyloidosis is seen very focally, thus amyloid deposits are incidentally diagnosed in autopsies or surgical specimens. As a result, amyloid goiter as diffusely enlarged thyroid gland due to amyloid deposition is seen very rarely¹⁰.

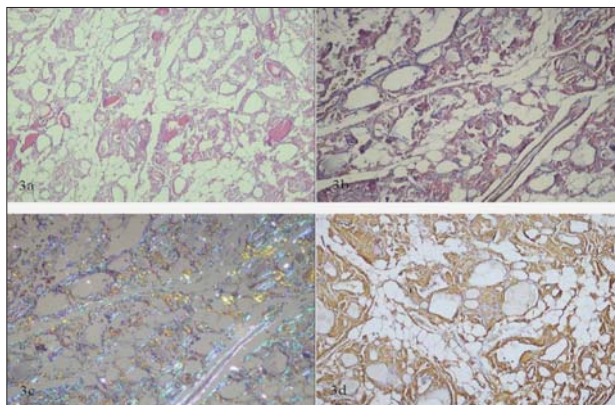


Figure 3: : Areas of mature adipose tissue are seen intermixed with residual thyroid parenchyma and the eosinophilic amorphous deposits (**a**), there is extensive fat cell metaplasia in the thyroid interstitium (**b**), homogeneous eosinophilic substance is confirmed apple green under polarized microscope (**c**), immunohistochemically, eosinophilic material is positive with Amyloid AA (**d**).

Amyloid goiter basically is a symptomatic mass or clinically detectable condition and may be associated with either primary or secondary amyloidosis. Secondary amyloidosis is seen in chronic inflammatory conditions such as rheumatoid arthritis, tuberculosis Crohn's disease, osteomyelitis and renal failure; and serum amyloid protein deposition (SAA) is responsible for secondary amyloidosis^{11,12}. The most common cause of secondary amyloidosis is FMF in Turkey. FMF is a recurrent inflammatory disease characterized by episodic fever and inflammation of serosal surfaces¹³. It is complicated by amyloid deposition in several organs, especially kidney, gastrointestinal tract, liver, spleen, heart and very rarely thyroid gland. The most common clinical manifestation of FMF-related amyloidosis is the development of the nephrotic syndrome and eventually uremia¹⁴. However, the presence of goiter that is seen as a result of amyloid deposition in these cases, is very uncommon. Only several cases of amyloid goiter complicating FMF were reported in the English literature⁷. Also, in our patients amyloid goiter was associated with FMF. In amyloid goiter, amyloid accumulates extracellularly in the thyroid parenchyme and, thus disrupts the normal follicular patterns. The amyloid deposits are often accompanied by extensive mature adipose tissue. In two of the presented three cases in literature, extensive fat cell metaplasia in the thyroid interstitium was noted.

Thyroid function tests are in normal range in most of the cases presented with amyloid goiter in the literature; likewise, our patients's medical records revealed normal thyroid function tests before iodine exposure. In symptomatic cases with amyloid goiter reported, the enlargement of the thyroid gland generally occurs rapidly in weeks to several months, sometimes causing obstructive symptoms. In our patients, the enlargement of the thyroid gland was slower in terms of years. In first case, she had mostly position-dependent obstructive symptoms and though colchicine treatment may have slowed the progression, it was ultimately not able to prevent the definitive outcome for the thyroid gland.

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 non-specifically altered, and most patients are clinically euthyroid despite the diffuse involvement by the disease. Our patients had normal also levels of T₄, T₃ and TSH.

Although a fine needle aspirate may result in a definitive diagnosis, focal depositions may be difficult to demonstrate with a FNAB, and thus, the diagnosis may be missed. So, the definitive diagnosis must be made by histologic evaluation of the resected thyroid gland. 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 as demonstrated by two of our patients as well and rarely, squamous metaplasia. 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 under polarized light and is considered as a pathognomonic feature of amyloid. Immunohistochemical techniques may help differentiating amyloid A from other types of amyloid.

In conclusion, amyloid accumulation in the thyroid gland does not usually cause thyroid dysfunction and most patients are euthyroid. As a result of these circumstances; 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, diagnosis of amyloid goiter should be suspected preoperatively. Histopathological examination of the resected material is essential for confirmation of the diagnosis and we also suggest that examination of thyroid gland should be performed in all patients with FMF even if their laboratory/clinical findings are euthyroid.

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