A RARE OF COMPLICATION OF RHEUMATOID ARTHRITIS: AMYLOIDOSIS OF THYROID AND INTRATHYROID LOCATED PARATHYROID GLAND

İsmail Hakkı Ersoy,[1] Banu Kale Köroğlu,[1] Oğuzhan Aksu,[1] İbrahim Metin Çiriş,[2] Fatih Ermiş,[3] Yunus Ugan,[4] Atila Altuntaş,[5] Mehmet Numan Tamer[1]

[1] Süleyman Demirel University Med. School, Dept. of Internal Medicine, Division of Endocrinology and Metabolism, Isparta, Turkey
[2] Süleyman Demirel University Medical School, Department of Pathology, Isparta, Turkey
[3] Isparta State Hospital, Department of Gastroenterology, Isparta, Turkey
[4] Süleyman Demirel University Medical School, Department of Internal Medicine, Division of Rheumatology, Isparta, Turkey
[5] Süleyman Demirel University Medical School, Department of Internal Medicine, Division of Nephrology, Isparta, Turkey

ABSTRACT

Amyloidosis is characterized by accumulation of amorphous, proteinaceous material in various organs and tissues of the body. Amyloid goiter is an extremely rare pathologic condition due to massive amyloid infiltration of the thyroid tissue. Clinically significant thyroid involvement is found in only a small percentage of cases, although a finding of amyloid deposit in autopsies is not infrequent. We present a case of amyloid goiter. The patient was diagnosed with rheumatoid arthritis 10 years previously and hospitalized for nephrotic levels of proteinuria. She was referred to our department for a rapid, painful growth in the thyroid gland. The patient finally underwent thyroidectomy due to progressive growth of the thyroid gland with compressive symptoms. In her thyroid pathology specimens there were amyloid deposits in the the entire thyroid tissue and in the arteriolar wall of parathyroid gland which was located intrathyroid.

Key Words: *Amyloidosis, goiter, rheumatoid arthritis, thyroid, parathyroid gland.* ***Nobel Med 2014; 10(1): 88-91***

ROMATOİD ARTRİT'İN NADİR BİR KOMPLİKASYONU: TİROİD AMİLOİDOZU VE TİROİD İÇİ YERLEŞİM GÖSTEREN PARATİROİD BEZİ

ÖZET

Amiloidoz vücudun çeşitli doku ve organlarında amorf protein içerikli materyalin birikmesi ile karakterize bir durumdur. Amiloid guatr tiroid dokusunda masif amiloid infiltrasyonu nedeniyle görülen çok nadir patolojik bir durumdur. Otopsilerde tiroid dokusunda amiloid depolanması nadir olmamasına rağmen klinik olarak önemli tiroid tutulumu vakaların küçük bir kısmında görülür. Biz burada amiloid guatr vakası sunucağız. Vakamız 10 yıl öncesinde romatoid artrit teşhisi konan ve nefrotik düzeyde proteinüri nedeniyle hastaneye yatırılmış idi. Tiroid bezinde ağrılı ve hızlı bir büyüme olması üzerine hasta departmanımıza yönlendirildi. Sonuç olarak tiroid dokusunda progresif büyüme ve bazı semptomları nedeniyle hasta tiroidektomiye yollandı. Tiroid dokusunun patoloji numunesinde tüm tiroid dokusunda amiloid depolanması vardı ve tiroid içi lokalizasyonlu paratiroid bezi tespit edildi.

Anahtar Kelimeler: Amiloidoz, guatr, romatoid artrit, paratiroid gland **Nobel Med 2014; 10(1): 88-91**

INTRODUCTION

Amyloidosis is characterized by accumulation of insoluble, proteinaceous, amorphous and eosinophilic material which was called amyloid in the extracellular matrix of several tissues.[1] Major fibrillar protein amyloid L which is derived from immunoglobulin light chain accumulates in primary amyloidosis whereas amyloid A accumulates in secondary amyloidosis which is derived from serum amyloid A (SAA) protein. SAA protein is an acute phase protein produced by the inflammatory process in the liver.[2] →

Amyloidosis deposition in the thyroid gland is often asymptomatic and sometimes it can cause thyroid gland enlargemant which could lead to symptomatic disease. Amyloid accumulation is observed in both primary and secondary amyloidosis in surgical and autopsy material series at microscopic levels about 50% and 80%, respectively. Amyloid accumulation is also observed in the thyroid gland in medullary thyroid cancer.[3] Amyloid goiter is defined as the accumulation of amyloid in thyroid that leads to thyroid gland enlargement. Except a few cases, most of these patients are adults.[4] Amyloid goiter can be seen in both primary and secondary amyloidosis in ratios of 43% ve 57%, respectively.[5] Systemic amyloidosis only with thyroid gland involvement rarely emerges without involvement of other organs.[6] Here we present a thyroid amyloidosis case who had intrathyroidal parathyroid glands involvement. Our case was secondary amyloidosis due to rheumatoid arthritis.

CASE REPORT

A 56-year-old woman diagnosed with rheumatoid arthritis for nearly 10 years was admitted to our endocrine outpatient clinic complaintments with sore throat, rapidly growing mass in the neck region and weight loss during the last month. On physical examination a hard nodule in size of 4-5 cm in the thyroid isthmus was palpated. Breath sounds were also diminished in the right lower lobe. Bilateral wrist movements were restricted and ulnar deviation was determined on both hands (Figure 1). Laboratory results were as follows: WBC: 15100/mm^3, Hb:128 g/L, erythrocyte sedimentation rate:76 mm/h, C-reactive protein:25 mg/L, rheumatoid factor:71 IU/mL, glucose:90 mg/dl, urea:47 mg/dl, creatinine:0.99 mg/dl, AST:22 IU/L, ALT:13 IU/L, Na:139 mmol/L, K:4.09 mmol/L, Ca:9.1 mg/dl, P:4.1 mg/dl, total cholesterol:294 mg/dl, triglyceride:412 mg/dl, HDL-cholesterol: 45 mg/dl, serum albumin 2.39 g/dl, proteinuria:3.6 g/day. Cardiothoracic ratio was increased in chest x-ray and echocardiography revealed pericardiac effusion. Subcutaneous biopsy was performed considering the etiology of amyloidosis for protenuria but the biopsy was negative for amyloidosis. Duodenum and rectal biopsies were also performed but amyloid material was detected only in the rectal mucosa. Thyroid function tests were as follows: FT3:2.27 pg/ml (2.5-3.9), FT4:1.13 ng/dl (0.61-1.12), TSH:0.11 mIU/L (0.34-5.6), Anti-TPO: 937 IU/mL (0-35), AntiTG: 1880 IU/mL (0-40), PTH:139 pg/ml (12-65), 25-OH vitamin D:30 ng/mL. In her medical history she had reduced kidney stones 30 years ago. In dual energy x-ray absorptiometry (DEXA) scanning she had more prominent osteoporosis in femur.

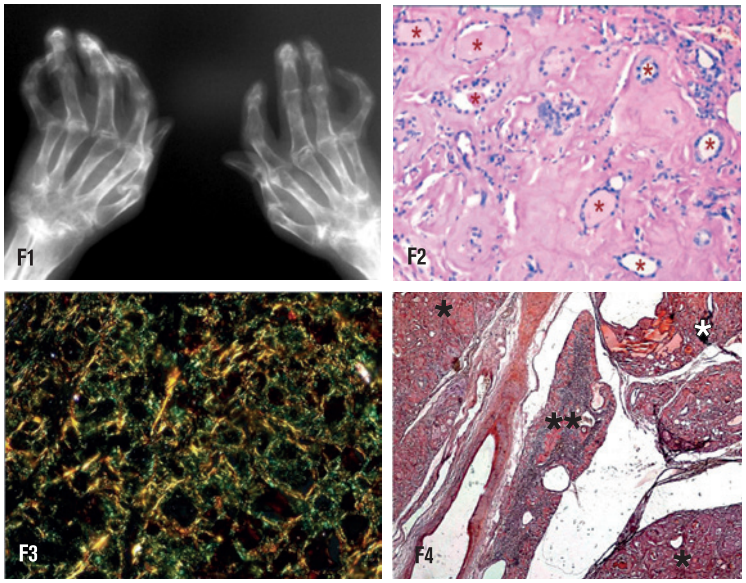

Figure 1. Image of the affected joints, bilateral ulnar deviation observed
Figure 2. Widespread deposition of amorphous eosinophilic material are observed between constricted thyroid follicles (*: follicles marked) (H&E, 200x)
Figure 3. Amyloid accumulation in thyroid tissue, gren bire fringence with Kongo Red stain under polarized light view (Kongo Red, 200x)
Figure 4. Amyloidosis involvement in parathyroid (**) gland within the thyroid (*) gland tissue (Kongo Red, 100x)

On thyroid ultrasonography both thyroid lobes were heterogenous and there was a heterogenous, degenerative, mixed nodule of 45x18 mm in size in the isthmus. There were also a cystic nodule of 13x8 mm in size in inferior right lobe, a mixed nodule of 12x11 mm in size in lateral left lobe and a heterogenous, mixed nodule of 18x10 mm in size in isthmus junction. Thyroid scintigraphy showed low uptake in the thyroid gland, but the background activity was observed to be increased. Aspiration biopsy of the largest nodule in isthmus showed benign features. Beta-blocker treatment was commenced keeping in mind the diagnoses of subacute thyroiditis, silent thyroiditis or Hashimoto's thyroiditis. Propylthiouracil therapy was also used for 3 months to achieve the euthyroid phase. Since the patient had multiple and large number of nodules, thyroidectomy was performed after euthyroid phase had been obtained. According to macroscopic pathological examination thyroid gland was encapsulated with brown color and weighed 167 grams. Right lobe was in 3.5x5.5x4.2 cm in size where as left thyroid lobe was 7.5x4x3.5 cm in size. Histological examination revealed amyloid deposits throughout the entire thyroid tissue and intrathyroidal localized parathyroid gland's arteriol wall. There was accumulation of amorphous eosinophilic material between the follicular structures. Amyloid material was stained as PAS (+) and congo red (+) with histochemical method. Amyloid A (+) was also observed in immunohistochemical analysis (Figures 2-4). She is on the postoperative 15th month follow up and takes levothyroxine (100 mcg/day) →

and leflunomide 20 mg/day and methotrexate 15 mg/week for rheumatoid arthritis.

DISCUSSION

Amyloidosis is the accumulation of amorphous material which is called amyloid in tissues according to inflammatory, immune, hereditary or neoplastic reasons.[1] Amyloid goiter is defined in 1904, firstly and very rarely seen among other thyroid lesions.[7] Amyloid goiter is seen in both types of amyloidosis but it is seen more common in secondary amyloidosis due to inflammatory diseases such as tuberculosis, bronchiectasis, cystic fibrosis, Crohn's disease, rheumatoid arthritis, ankylosing spondylitis and familial mediterranean fever (FMF).[3] In a review of investigated thirty cases of amyloid goiter 13 were FMF, 10 were secondary amyloidosis due to other inflammatory diseases and 7 were primary amyloidosis. There were amyloid accumulation in renal, adrenal, liver and spleen tissues except thyroid tissue in the autopsy of 9 patients.[5] Amyloid goiter could rarely present as the first symptom of systemic amyloidosis.[6,8] Our case was secondary amyloidosis due to rheumatoid arthritis with kidney and thyroid involvement. Amyloid goiter usually appears as a diffuse growth of thyroid gland within weeks and months. Hoarseness, dyspnea, dysphagia, and regional lymphadenopathy may be accompanied with goiter. According to Villa et al.'s review of 21 amyloid goiter patients, all described rapid growing, painless neck mass. 6 had upper airway obstruction.[5] Anaplastic thyroid cancer and non-Hodgkin's lymphoma of the thyroid also should be considered when encountered with rapid growing goiter. In both cases thyroid gland growth is usually unilateral while amyloid goiter often grows bilateral. Our case was similar to cases reported in the literature, she was admitted to endocrinology outpatient clinic with a complaint of a rapidly growing painful mass in the neck, but had no obstructive symptoms.

Thyroid function tests are usually determined in euthyroid state in amyloid goiter.[9] Patients with hyperthyroidism and hypothyroidism have also been reported.[10,11] In our case due to abnormal thyroid function tests with a painful goiter, subacute thyroiditis was considered primarily but histological examination did not confirm that diagnosis. In addition, pathological examination of the material was not compatible with chronic thyroiditis. Ikenoue et al. were the first who reported 2 cases of thyroid amyloidosis clinically characterized by recurrent subacute thyroiditis in 1988.[12] Histological examination of the cases was not in favor of subacute thyroiditis but serological and histological evidence of Hashimoto's patients had been shown in one patient. Subacute thyroiditis-like symptoms have been reported in 2 cases of thyroid amyloidosis, too.[13,14] Amyloid goiter and Hashimoto's thyroiditis in one and amyloid goiter and silent thyroiditis combination had been reported in the other case.[11,15] Coincidence of rheumatoid arthritis and Hashimoto's thyroiditis is mentioned in the literature, coincidence of other autoimmune diseases is often emphasized in this relation.[16]

Fine needle aspiration biopsy is a quite safe, sensitive and easily applicable method in the diagnosis of thyroid pathology. In Villa et al.'s study fine needle aspiration biopsy showed irregular pink-staining amorphous material and were green under congo red by polarized light examination in 12 out of 19 amyloid goiter patients. Seven patients had negative results for amyloidosis in biopsy.[5] Thyroid fine needle aspiration biopsy was also insufficient in our case to demonstrate amyloidosis.

Histological evaluation of the thyroid gland is necessary for accurate diagnosis of amyloid goiter. There are multiple, non-homogeneous nodules in the thyroid parenchyma changing in a few milimeteres to centimeters in size. These nodules are hard or soft gelatin consistency and sections of these nodules are gray-white or light-brown or pale yellow in color. Amyloid deposits are observed in perifolliculer region as in forms of waxy eosinophilic structures. Mature adipose tissue regions are found among residue thyroid parenchyma and amyloid deposits.[5,17] Congo red, thioflavin T, crystal violet stainings are used for diagnosis of amyloidosis. Congo red is the most used one. Green birefringence image with congo-red staining under polarized light microscope image is a pathognomonic feature of amyloidosis. Amyloid A can be distinguished from other types of amyloidosis with immunohistochemical methods.[18]

In our case histological examination revealed amyloid deposits throughout the entire thyroid tissue and intrathyroidal localized parathyroid gland's arteriol wall. Parathyroid gland was observed adjacent to thyroid. Although specific parathyroid gland staining was not performed, parathyroid tissue was distinguished by histologic appearance and negativity of synaptophysin, chromogranin and thyroglobulin. Green birefringence image was observed with congo-red staining under polarized light microscope. Amyloid A (+) was observed in immunohistochemical analysis. In our case intrathyroidal parathyroid tissue also included amyloid material (Figure 3). Although local amyloid storage has been seen 10% to 16% in primary hyperparathyroidism this coincidence was very rarely seen.[19,20] Ellis et al. observed some changes in →

arteries, arterioles and capillaries of parathyroid glands of all 8 patients who died due to chronic renal failure. Stromal amyloidosis was seen only in 3 patients.[21,22] The presence of amyloid within the parathyroid gland in this case raises the possibility of a more diffuse form of the disease. We found previously published two case reports in the literature.[23,24] Intrathyroidal located parathyroid gland involvement in this location could be considered as medullary thyroid carcinoma accidentally because both of them show similar histopathological characteristics. In this contact synaptophysin and chromogranin negativity but thyroglobulin positivity with immunohistochemical analysis helped us to distinguish amyloid goiter from medullary thyroid carcinoma.

As a result, patients with suspicion of primary or secondary amyloidosis especially in those with rapid growing goiter and obstructive symptoms amyloid goiter should be kept in mind. Differential diagnosis of thyroid malignancies should be done absolutely. Fine needle aspiration biopsy is helpful but the definitive diagnosis is made by postoperative complete tissue histopathologic evaluation.

CORRESPONDING AUTHOR: İsmail Hakkı Ersoy Süleyman Demirel University Medical School, Department of Internal Medicine 32260 Çünür, Isparta hakkiersoy@gmail.com

DELIVERING DATE: 01 / 02 / 2013 • **ACCEPTED DATE:** 27 / 03 / 2013

REFERENCES

1. Cohen AS. Proteins of the systemic amyloidoses. Curr Opin Rheumatol 1994; 6: 55-67.
2. Falk RH, Comenzo RL, Skinner M. Systemic amyloidosis. N Engl J Med 1997; 337: 898-909.
3. Hamed G, Heffess CS, Shmookler BM, Wenig BM. Amyloid goiter. A clinicopathologic study of 14 cases and review of the literature. Am J Clin Pathol 1995; 104: 306-312.
4. Perez Fontan FJ, Mosquera Oses J, Pombo Felipe F, et al. Amyloid goiter in a child-US, CT and MR evaluation. Pediatr Radiol 1992; 22: 393-394.
5. Villa F, Dionigi G, Tanda ML, Rovera F, Boni L. Amyloid goiter. Int J Surg 2008; 6: 16-18.
6. Siddique MA, Gertz M, Dean D. Amyloid goiter as a manifestation of primary systemic amyloidosis. Thyroid 2007; 17: 77-80.
7. Eiselberg F. Uber einen Fall von Amyloid. Kropt Arch Win Chir 1904; 73: 649-655.
8. Amado JA, Ondiviela R, Palacios S, et al. Fast growing goiter as the first clinical manifestation of systemic amyloidosis. Postgrad Med 1982; 58: 171-172.
9. Kimura H, Yamashita S, Ashizawa K, Yokoyama N, Nagataki S. Thyroid dysfunction in patients with amyloid goiter. Clin Endocrinol 1997; 46: 769-774.
10. Tokyol C, Demir S, Yilmaz S, et al. Amyloid goiter with hyperthyroidism. Endocr Pathol 2004; 15: 89-90.
11. Bando Y, Ushiogi Y, Toya D, Tanaka N, Fujisawa M. Painless thyroiditis associated with severe inflammatory reactions in amyloid goiter: a case report. Endocr J 2001; 48: 323-329.
12. Ikenoue H, Okamura K, Kuroda T, et al. Thyroid amyloidosis with recurrent subacute thyroiditis-like syndrome. J Clin Endocrinol Metab 1988; 67: 41-45.
13. Nagai Y, Ohta M, Yokoyama H, Takamura T, Kobayashi KI. Amyloid goiter presented as a subacute thyroiditis-like symptom in a patient with hypersensitivity vasculitis. Endocr J 1998; 45: 421-425.
14. Lee YS, Moon SS, Kim S, Lee JI. A Case of thyroid amyloidosis misrecognized as subacute thyroiditis. Endocrinol Metab 2010; 25: 360-364.
15. Chaiban JT, Kalache SM, Abu Alfa AK, Shabb NS, Salti IS. The association of Hashimoto disease and congo red negative amyloidosis. Am J Med Sci 2008; 336: 293-296.
16. Nakao E, Mitsunaga A, Hamano T, et al. Case report of rheumatoid arthritis associated with type A gastritis and Hashimoto thyroiditis. Nippon Shokakibyo Gakkai Zasshi 2010; 107: 1927-1932.
17. Sbai A, Wechster B, leenhardt L, et al. Amyloid goiter as the initial manifestation of systemic amyloidosis due to familial mediterranean fever with homozygous MEFV Mutation. Thyroid 2001; 11: 397-400.
18. Van Rijswijk MH, van Heudsen 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.
19. Anderson TJ, Ewen SW. Amyloid in normal and pathological parathyroid glands. J Clin Pathol 1974; 27: 656-663.
20. Leedham PW, Pollock DJ. Intrafollicular amyloid in primary hyperparathyroidism. J Clin Pathol 1970; 23: 811-817.
21. Ozdemir D, Dagdelen S, Erbas T. Endocrine involvement in systemic amyloidosis. Endocr Pract 2010; 16: 1056-1063.
22. Ellis HA, Mawhinney WH. Parathyroid amyloidosis. Arch Pathol Lab Med 1984; 108: 689-690.
23. Villamil 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.
24. Abdou AG, Kandil MA. A case of amyloid goiter associated with intrathyroid parathyroid and lymphoepithelial cyst. Endocr Pathol 2009; 20: 243-248.