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Chronic Diseases® and Translational Medicine

CORRESPONDENCE

Amyloid goiter secondary to familial Mediterranean fever with E148Q mutation: A unique case

Dear Editor,

Goiter is defined as the enlargement of the thyroid gland. It is currently divided into diffuse and nodular and subdivided into toxic (associated with hyperthyroidism) or nontoxic (associated with normal thyroid stimulating hormone [TSH] levels).[1] The most common cause of goiter is iodine deficiency,[2] and other causes are increased levels of TSH, natural goitrogens, iron and vitamin A deficiency, genetic factors (*DICER1* syndrome and *PTEN* hamartoma tumor syndrome), and hereditary (Plummer syndrome) factors.[3]

A rare entity known as familial Mediterranean fever (FMF) can present with amyloid goiter. This is an autoimmune disorder that affects the Mediterranean littoral.[4] These patients present with fevers and abdominal and chest pain. This condition can produce fibrillar depositions of amyloid protein, usually affecting the kidney[5] but rarely involving the thyroid. We present a case of a 21-year-old woman with no medical history who presented to our hospital with a nontoxic diffuse goiter with initial presentation and pathologically confirmed as amyloid deposition secondary to FMF.

The patient is a 21-year-old Asian American woman with no significant medical history. She presented to our institution with dyspnea and dysphagia. An ultrasound from an outside hospital revealed diffuse thyroid enlargement. Our in-house laboratory results showed normal TSH, T4, T3, and elevated TPO antibody and erythrocyte sedimentation rate. A CT scan was performed on the patient showing heterogenous thyromegaly wrapping around the trachea and esophagus (Figure 1). A fine needle aspirate was performed, which showed a fibroinflammatory lesion. The patient started on steroids with no improvement, and a total thyroidectomy was performed. Macroscopic examination revealed a poorly defined, firm mass with pale tan areas of discoloration (Figure 2). Microscopic examination revealed an atrophic thyroid parenchyma with diffuse adipose cell metaplasia and diffuse interfollicular deposition of acellular amorphous material consistent with amyloid (Figure 3). Multifocal areas of chronic inflammation were also seen. Congo red stain was positive for amyloid (Figure 4A) with apple-green birefringence under polarized light (Figure 4B). Liquid chromatography tandem mass spectrometry was performed on peptides extracted from the Congo red-positive/microdissected areas of the paraffin-embedded thyroid specimen. The detected peptide profile was consistent with AA (SAA)-type amyloid deposition. The patient consequently had genetic testing showing a homozygous E148Q mutation. This confirms the clinical syndrome of FMF. After continuous follow-up, 10 years later, she developed end-stage renal failure with a renal biopsy confirming Renal AA amyloidosis. Since then, she has been on hemodialysis and is now on the waiting list for a renal transplant.

Amyloid goiter is only seen in 0.04% of patients with systemic amyloidosis.[6] Amyloid depositions may be localized or systemic, as in our patient who developed both but initially presented as localized goiter. The International Society of Amyloidosis guidelines defines amyloid as an extracellular deposition of a fibrillary protein that is recognizable by its affinity for Congo red and its apple-green birefringence under polarized light.[7] We confirm the amyloid depositions in our case with the latter ancillary studies.

To date, there are 36 proteins identified as amyloidogenic in humans. AL, which is amyloidosis derived from immunoglobulin light chain, is the most common presentation of systemic amyloidosis in the developed world.[8] In our case, we identified a cause of AA-type amyloid deposition, amyloid fibrils derived from serum amyloid A protein, which is the leading cause of systemic amyloidosis in developing countries.[9] The AA protein is associated with hereditary autoimmune diseases, such as, in our case, FMF.

FMF has autosomal recessive inheritance with gene polymorphism and can result in amyloidosis. This entity results from the gain of function mutations of the Mediterranean fever gene (*MEFV*) located on chromosome 16 (16p13.3).[10] MEFV gene has 10 exons, and there are more than 370 variants identified to date. The most pathogenic mutations in FMF are M694V, M694I, M680I, and V726A in exon 10,[11] which

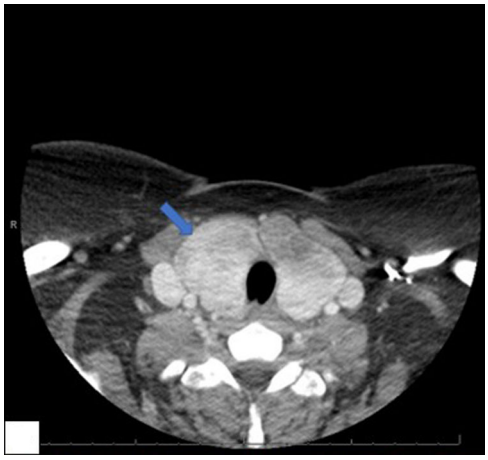

FIGURE 1 Neck CT scan: Heterogenous thyromegaly wrapping around the trachea and esophagus (arrow).

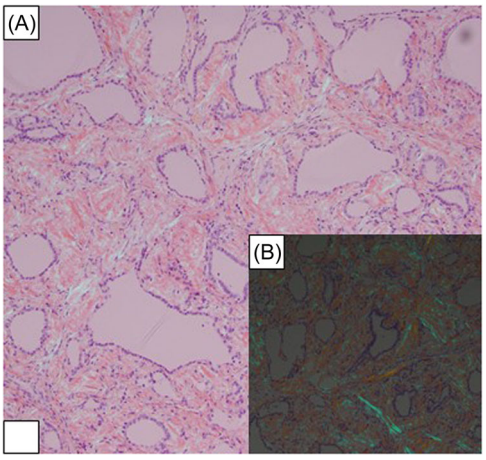

FIGURE 4 (A) Congo red stain: 10× Positive for amyloid. (B) Apple-green birefringence under polarized light.

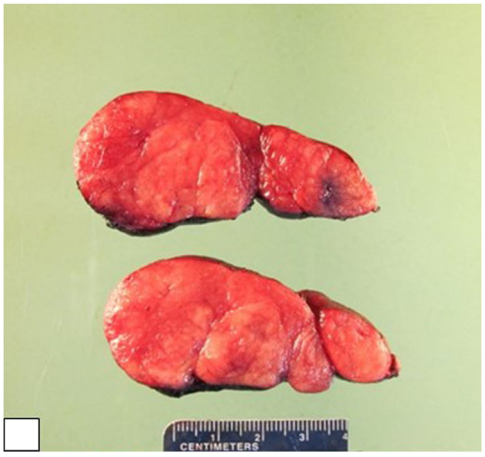

FIGURE 2 Gross image: Poorly defined, firm mass, with pale tan areas of discoloration.

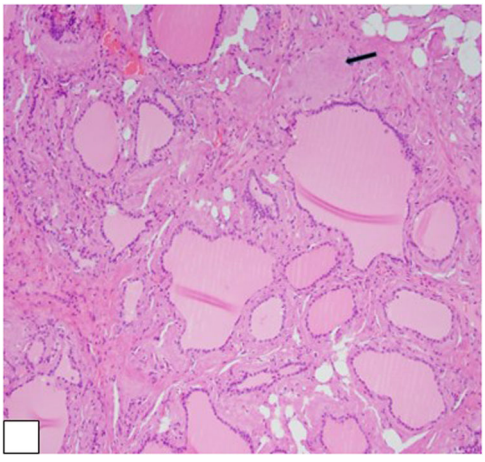

FIGURE 3 Hematoxylin and Eosin stain: 10× Atrophic thyroid parenchyma with diffuse adipose cell metaplasia and diffuse interfollicular deposition of acellular amorphous material consistent with amyloid (arrow).

were not found in our case. The E148Q variant in exon 2 is one of the most common substitutions in the *MEFV* gene[11] in most FMF cases. It occurs as the only identified variant or in parallel with other variants, including exon 10 mutations. Limited evidence supports that homozygous E148Q is a disease-causing mutation. In our patient, this was the variant detected. The E148Q variant in exon 2 is found frequently in Japanese patients with FMF,[12] which possibly correlates with our patient's Asian American heritage. According to the literature, patients with homozygous E148Q variant may present with late-onset and mild disease,[13,14] although none of these cases presented with amyloid goiter. The exact prevalence of amyloid goiter in this entity is yet to be established. Approximately 15.00% was found by Vergneault et al.,[15] 45.00% in the Ozdemir study,[16] and 0.27% in Altiparmak et al.[17] findings. None of the previous reports had genetic testing on the patients. Most of these cases had other systemic symptoms, renal failure being the most common. Our patient developed renal failure in a prospective fashion.

This case of isolated amyloid goiter is a unique presentation of FMF. Despite the literature having reports of amyloid goiter, most of the patients had other systemic diseases at the time of presentation of the disease. The homozygous E148Q variant in this case is interesting, due to its mild disease presentation and lack of association with amyloid goiter in the literature. It is important to recognize that diffuse goiter can be the early clinical presentation of FMF.

AUTHOR CONTRIBUTIONS

Juan C. A. Moreno worked on the case report conception and contributed to the data collection. Juan C. A. Moreno, Suimin Qiu, and Eduardo Eyzaguirre contributed to the pathological slides review and data analysis. Juan C. A. Moreno was responsible for getting the CT

images from the medical records of the hospital. Eduardo Eyzaguirre and Suimin Qiu provided explanations about the case reported. Juan C. A. Moreno worked on the histology figures, figure illustrations, and case study timeline presentation. Suimin Qiu was responsible for the study supervision. All authors critically revised and edited the manuscript before approving the final draft of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest. Professor Suimin Qiu is a member of Chronic Diseases and Translational Medicine editorial board and is not involved in the peer review process of this article.

DATA AVAILABILITY STATEMENT

None.

ETHICS STATEMENT

The work has been carried out in accordance with the code of ethics of the world medical association (*Declaration of Helsinki*).

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