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Systemic light-chain amyloidosis incidentally diagnosed after subtotal parathyroidectomy and thyroid lobectomy

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SUMMARY

A 74-year-old woman with a history of primary hyperparathyroidism, thyroid nodules, atrial fibrillation and pacemaker placement for sick sinus syndrome presented with fatigue, constipation and persistent lower extremity oedema. She underwent subtotal parathyroidectomy and left thyroid lobectomy. Histopathology revealed amyloidosis affecting the thyroidand parathyroids confirmed by Congo Red Staining with Mayo Clinic subtyping of light chain kappa-type amyloidosis. She was found to have combined systolic and diastolic cardiac dysfunction, carpal tunnel neuropathy and pre-diabetes suggestive of systemic amyloidosis with involvement of the heart, nerves and pancreas. Congo red stain was positive for amyloidosis on bone marrow biopsy suggestive of a diagnosis of systemic amyloidosis. She was treated with daratumumab with good clinical response. This case illustrates the necessity of considering systemic amyloidosis in patients with incidentally discovered diffuse amyloid deposits on biopsy of an endocrine organ, as endocrine effects are a rare but likely underdiagnosed consequence of systemic amyloidosis.

BACKGROUND

Systemic amyloidosis is a rare disorder in which misfolded proteins deposit extracellularly throughout the body that can result in organ failure and death. The incidence of the most common variety of systemic amyloidosis, immunoglobulin light-chain (AL) amyloidosis, is 3–5 per million persons per year.[1] The classic presentation of systemic amyloidosis includes nonspecific symptoms of fatigue, peripheral oedema and weight loss. Deposition of amyloid may occur in any tissue throughout the body, but commonly results in cardiac, renal, nervous, hepatic or bowel dysfunction. Due to the non-specific clinical presentation, systemic amyloidosis is often underdiagnosed.[1]

Rarely, systemic amyloidosis may manifest through amyloid deposition in endocrine organs such as the thyroid or parathyroid glands. These cases are generally clinically silent and discovered only at autopsy.[2] Amyloid found in the thyroid is commonly associated with medullary thyroid carcinoma, although it can also be associated with papillary thyroid carcinoma or amyloid goitre secondary to systemic amyloidosis.[3]

Given the rarity of disease and wide spectrum of clinical manifestations of systemic amyloidosis, timely diagnosis for intervention can prove challenging. We present a case wherein systemic amyloidosis was diagnosed incidentally, illustrating the need for further workup in patients with incidentally found amyloid on thyroid and parathyroid histopathology specimens.

CASE PRESENTATION

A 74-year-old woman with a history of stage 1 estrogen receptor (ER) positive, progesterone receptor (PR) positive, human epidermal growth factor receptor 2 (HER2) negative bilateral breast cancer in remission after bilateral mastectomy (never on hormonal therapy, chemotherapy or radiation treatment), atrial fibrillation, and sick sinus syndrome with pacemaker placement presented to endocrine clinic for workup of hypercalcaemia. Her symptoms included fatigue, constipation and lower extremity oedema. She denied any family history of hypercalcaemia or current tobacco, alcohol or drug use. On examination, her vital signs were normal but her physical exam was notable for bilateral 1+ pitting lower extremity oedema. Her serum total calcium was 10.7 mg/dL (reference 8.6–10.4 mg/dL), 25-OH vitamin D 59 ng/mL (reference 20–50 ng/mL), intact parathyroid hormone (iPTH) 95 pg/mL (reference 11–51 pg/mL), creatinine 1.2 (reference 0.6–1.3 mg/dL) and albumin 4.2 g/dL (reference 4.1–5.3 g/dL). She was euthyroid. A 24-hour urine calcium was 206 mg/24 hours (reference 0–300 mg/24 hours) and a 24-hour urine creatinine was 1210 mg/24 hours (reference 1000–1800 mg/24 hours), with a calculated calcium/creatinine clearance ratio of 0.016. Her medications included cholecalciferol 2000 IU daily and chlorthalidone 25 mg daily. She was not taking any calcium-containing supplements.

A Tc-99M sestamibi scan showed increased activity at the left inferior pole of the thyroid suggestive of a parathyroid adenoma. Thyroid and parathyroid ultrasound showed three thyroid nodules with the largest measuring 1.3 cm with coarse calcifications suggestive of malignancy in the left thyroid lobe, and a left inferior parathyroid adenoma. Fine-needle aspiration (FNA) of the left thyroid nodule was nondiagnostic. The patient underwent parathyroidectomy with left thyroid lobectomy due to the moderately suspicious sonographic appearance of the thyroid nodule. While awaiting surgery, the patient noticed worsening lower extremity oedema, dyspnoea and orthopnoea

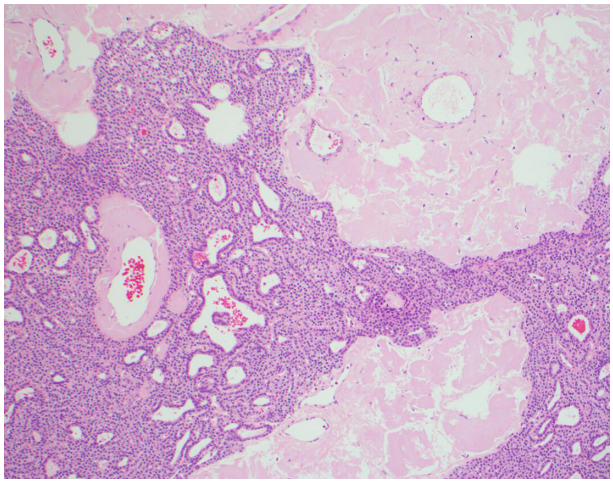

Figure 1 A Hematoxylin and Eosin (H&E) stain demonstrates hypercellular parathyroid tissue with extensive amyloid deposition present as nodules and in vessel walls.

requiring increased diuretic use. Intraoperatively, she was found to have parathyroid hyperplasia. She underwent successful subtotal parathyroidectomy and left thyroid lobectomy with a subsequent decrease iPTH to 9 pg/mL (reference 11–51 pg/mL) and total calcium to 8.9 mg/dL (reference 8.6–10.4 mg/dL).

Surgical pathology showed a hypercellular left superior (weight: 0.17 g), left inferior (weight: 0.37 g) and a right superior (weight: 0.63 g) parathyroid gland. Diffuse parathyroid gland hyperplasia on pathology report was attributed to amyloid deposition. Biopsy of the right inferior parathyroid gland also showed hypercellular parathyroid tissue. The left thyroid lobectomy showed a fully encapsulated 3 mm incidental papillary thyroid microcarcinoma follicular variant with no lymphovascular invasion, no extrathyroidal extension, negative surgical margins and nodular hyperplasia with degeneration. Gross pathology showed a well-circumscribed nodule measuring 1.5×1.2×1.0 cm and corresponding histology showed an adenomatous nodule with oncocytic changes. In all specimens, including the thyroid gland, there was diffuse amyloid deposition in the vasculature confirmed by positive Congo red and Trichrome/Elastin van Gieson (EVG) stains (figures 1 and 2). There is a region (at least 1.5×0.5 cm) which consists of large vessels and extensive amyloid deposition,

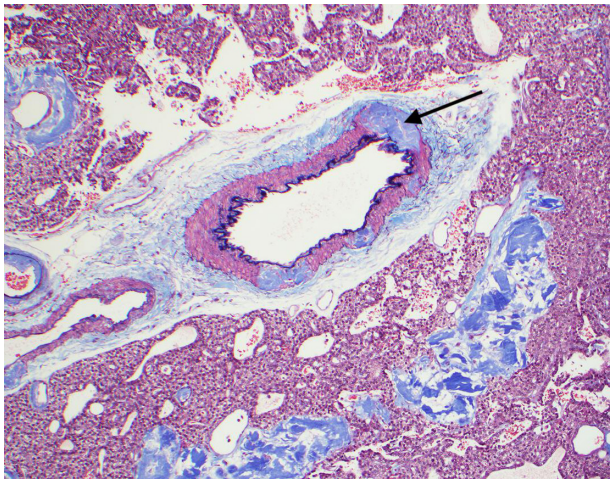

Figure 2 A trichrome/elastin stain highlights amyloid deposits seen in blue as nodules and unevenly distributed within vessels walls (arrow).

expanding their usual space. The patient was diagnosed with parathyroid hyperplasia, and Mayo Clinic subsubtyping showed AL kappa-type amyloidosis. She developed postoperative hypothyroidism and was treated with levothyroxine. In addition, due to worsening congestive heart failure symptoms, she was referred to cardiology where she had an echocardiogram that showed combined systolic and diastolic dysfunction, suggestive of cardiac amyloidosis. She was also found to have pre-diabetes with haemoglobin A1c of 6.0% (normal <5.7%) and bilateral carpal tunnel syndrome treated with bilateral carpal tunnel release, suggestive of amyloidosis involvement in the pancreas and peripheral nerves, respectively.

Further evaluation by haematology showed an elevated serum kappa to lambda ratio of 18.59 and urine monoclonal kappa light chains. Bone marrow biopsy was positive for amyloidosis with a positive Congo Red Stain. A 24-hour urine study was negative for renal amyloidosis.

TREATMENT

Patients with systemic amyloidosis generally receive treatment to reduce supply of precursor proteins and reduce systemic amyloid deposition. The patient was enrolled in a phase III clinical trial, using a humanised IgG monoclonal antibody called NEOD001 which targets misfolded light chain aggregates and amyloid deposits. While on this clinical trial, she was started on bortezomib and dexamethasone for 7 months but was switched daratumumab after showing progression on free-light chain assays. Nine months later, she was discontinued from the clinical trial due to lack of response from the antibody drug. Four years after her initial amyloidosis diagnosis, she is doing well on single agent daratumumab with good haematological and clinical response.

OUTCOME AND FOLLOW-UP

At the 4 year follow-up, the patient reports overall feeling well with minimal symptoms of congestive heart failure. She has some fatigue but is able to walk three miles and climb fifteen flights of stairs with rest in between. Her most recent labs showed progression to chronic kidney disease (CKD) stage 3b, normal calcium of 9.5 mg/dL, mildly elevated 25-OH vitamin D of 60 ng/mL and mild elevation of iPTH at 70 pg/mL likely attributed to secondary hyperparathyroidism from underlying CKD. She had improvement in her haemoglobin A1c to 5.5% with lifestyle modifications. Her neuropathy in her bilateral hands and feet, although minimal, had slightly worsened since chemotherapy initiation and controlled with low dose gabapentin (100 mg nightly). She continues to have good haematological response of her amyloidosis with chemotherapy, but mild fatigue after the daratumumab infusions.

DISCUSSION

There have been very few published cases of clinically evident thyroid or parathyroid involvement in patients with systemic amyloidosis. Endocrine dysfunction secondary to the effects of systemic amyloidosis is largely limited to the compressive effects of collections of amyloid, such as in the case of amyloid goitre, defined by massive infiltration of the thyroid gland by amyloid to produce a clinically detectable mass.[2–5]

However, more extensive amyloid deposition in multiple endocrine organs may be more prevalent in systemic amyloidosis than clinical symptomatology would suggest. A review of endocrine involvement in systemic amyloidosis by Ozdemir *et al*[2] noted that asymptomatic amyloid deposition could be found in the thyroid glands of 30%–80% of patients. A study by Ehman

et al[6] investigating detection of asymptomatic AL amyloid via positron emission tomography/computed tomography (PET/CT) showed deposition of amyloid in the thyroid of patients who had no clinical or biochemical evidence of endocrine dysfunction. Incidental amyloid deposition in the parathyroids found at autopsy in patients with systemic amyloidosis and no evidence of parathyroid dysfunction has also been reported in the literature.[2]

Given the clinically silent nature of amyloid deposition in the thyroid and parathyroid glands, diagnosis of amyloid involvement in these structures usually occurs following thyroid or parathyroid biopsy or surgery for other indications, as was seen in our case. Incidental findings of amyloid in the thyroid and parathyroid should raise the suspicion for systemic amyloidosis. Amyloid deposition in the thyroid is a finding traditionally associated with medullary, and less frequently, papillary thyroid carcinoma.[3 5] However, in the absence of any evidence of thyroid malignancy, performing a workup for systemic amyloidosis, including electrocardiogram (ECG), echocardiogram and 24-hour urine protein—particularly in the context of symptoms such as extreme fatigue or oedema—may be appropriate. Although special staining was not used for our FNA biopsy, one case report suggests that it can also be used to make the diagnosis of thyroid amyloidosis which can lead to timely haematological workup and diagnosis.[7]

Gallagher *et al*[8] reported a similar case in 2018 where incidentally discovered amyloidosis in a patient with primary hyperparathyroidism revealed underlying systemic amyloidosis. This case of primary hyperparathyroidism co-occurring with systemic amyloidosis raises the question of whether amyloid deposition in the thyroid and parathyroid glands may be as clinically silent as previously believed. While the parathyroid adenoma found in the case reported by Gallagher *et al*[8] could constitute the explanation for the presence of primary hyperparathyroidism, the pathology of our patient showed only hypercellularity. The co-occurrence of amyloid deposition with hyperparathyroidism merits further investigation into a relationship between amyloid deposition and development of parathyroid and thyroid pathologies.

Interestingly, the patient reported in this case developed prediabetes with a haemoglobin A1C of 6.0%, suggesting further endocrine involvement and dysfunction due to amyloid deposition. The review of endocrine involvement in systemic amyloidosis done by Ozdemir *et al*[2] describes several case reports of patients in which the pancreas was found to have amyloid infiltration at autopsy, though only one was reported to have diabetes.

Amyloid deposition in endocrine organs, while rare, may not be clinically silent. Incidentally found amyloid on endocrine biopsy in patients with clinical features consistent with systemic amyloidosis should receive a full workup for systemic amyloidosis. Though systemic amyloidosis is rare, it is also underdiagnosed and incidental findings of amyloid in endocrine biopsy provide an avenue to initiate therapy before irreversible sequelae develop.

Patient's perspective

I noticed that in retrospect my signs and symptoms of congestive heart failure, particularly swelling in my ankles and shortness of breath, as well as carpal tunnel symptoms of numbness, tingling and pain in my hands, were unusual at the time, given that I was otherwise an active golfer and in relatively good health. I believe that I may have had indolent amyloidosis that would not have been detected had it not been for my incidental finding from my parathyroidectomy.

Learning points

Clinical pearls

- Clinically silent amyloid deposition in the thyroid or parathyroid glands may be seen in patients with systemic amyloidosis.
- Amyloid subtyping, as well as full workup for systemic amyloidosis, should be performed in cases of incidentally found diffuse amyloid on biopsy of an endocrine gland.
- Endocrine involvement in systemic amyloidosis is more common than classic symptomatology would suggest.

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REFERENCES

1 Wechalekar AD, Gillmore JD, Hawkins PN. Systemic amyloidosis. *Lancet* 2016;387:2641–54.
2 Ozdemir D, Dagdelen S, Erbas T. Endocrine involvement in systemic amyloidosis. *Endocr Pract* 2010;16:1056–63.
3 Pinto A, Nosé V. Localized amyloid in thyroid: are we missing it? *Adv Anat Pathol* 2013;20:61–7.
4 Siddiqui MA, Gertz M, Dean D. Amyloid goiter as a manifestation of primary systemic amyloidosis. *Thyroid* 2007;17:77–80.
5 Cannizzaro MA, Lo Bianco S, Saliba W, *et al*. A rare case of primary thyroid amyloidosis. *Int J Surg Case Rep* 2018;53:179–81.
6 Ehman EC, El-Sady MS, Kijewski MF, *et al*. Early Detection of Multiorgan Light-Chain Amyloidosis by Whole-Body ^{18}F-Florbetapir PET/CT. *J Nucl Med* 2019;60:1234–9.
7 Di Crescenzo V, Garzi A, Petruzziello F, *et al*. Nodular goiter with amyloid deposition in an elderly patient: fine-needle cytology diagnosis and review of the literature. *BMC Surg* 2013;13 Suppl 2:S43.
8 Gallagher KC, Geromes AB, Stokes J, *et al*. Rare undiagnosed primary amyloidosis unmasked during surgical treatment of primary hyperparathyroidism: a case report. *J Endocr Soc* 2018;2:112–6.