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Rare Undiagnosed Primary Amyloidosis Unmasked During Surgical Treatment of Primary Hyperparathyroidism: A Case Report

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Primary amyloidosis (PA) is a protein deposition disorder that presents with localized or multisystemic disease. The incidence is low in the general public, ranging from three to eight cases per million, and with nonspecific presenting symptoms typically occurring later in life. Due to late presentation, substantial and irreversible damage has usually already occurred by the time of the diagnosis. However, if inadvertent diagnosis occurs before irreversible damage has taken place, as it did in the following case, some patients may benefit from the disease-arresting treatment. A 70-year-old female with a history of obstructive sleep apnea, hypertension, and arthritis presented with worsening dysphagia and biochemically confirmed primary hyperparathyroidism (PHPT). Further workup demonstrated multinodular goiter with compressive symptoms and substernal extension, osteopenia, and discrepant parathyroid localization on imaging. Intraoperatively, markedly difficult dissection and obliteration of tissue planes were encountered. Extensive, diffuse amyloid deposition in both the normal and pathologic parathyroid glands and thyroid tissue on surgical pathology leads to subsequent fibril typing by mass spectrometry and leads to the diagnostic of primary amyloid light-chain (AL) amyloidosis (PA; λ light chains). Subsequent workup for the underlying cause of the amyloid deposition revealed an immunoglobulin A monoclonal gammopathy of unknown significance. The surgical treatment of PHPT and compressive thyroid nodule unmasked an undiagnosed PA, allowing for early workup and monitoring of the progression of amyloidosis. The temporal comorbidity of PHPT and PA raises an interesting and, as yet, unanswered question regarding the pathophysiologic association between the two conditions.

Freeform/Key Words: amyloid, lambda light chains, multinodular goiter, primary amyloidosis, primary hyperparathyroidism

1. Patient Presentation

A 70-year-old female with a long-standing history of dysphagia, obstructive sleep apnea requiring continuous positive airway pressure overnight, hypertension, and arthritis presented to the Endocrine Surgery Clinic with biochemically confirmed primary hyperparathyroidism (PHPT) preceded by 2 years of hypercalcemia. The patient had no past history of head and neck radiation, previous neck surgery, malignancies, or family history of

Abbreviations: AL, amyloid light-chain; IgA MGUS, immunoglobulin A monoclonal gammopathy of undetermined significance; PA, primary amyloidosis; PHPT, primary hyperparathyroidism; PTH, parathyroid hormone; VAMP, Vanderbilt Amyloidosis Multidisciplinary Program.

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endocrinopathies. Presenting symptoms included dysphagia to solids requiring several esophageal dilations, depression, polydipsia, polyuria, constipation, reflux, fatigue, and short-term memory difficulties. The patient denied any history of bone pain, fragility fractures, or nephrolithiasis. No additional studies were completed prior to her presentation to the clinic.

2. Diagnosis and Treatment

Biochemical workup was completed to confirm the diagnosis of PHPT. Laboratory results revealed hypercalcemia (serum calcium = 11.3 mg/dL) and elevated parathyroid hormone (PTH) level (81 mg/mL), with normal creatinine (1.0 mg/dL), normal 24-hour urine calcium (156 mg/dL), and normal 25-hydroxy vitamin D (D25-OHT; 35 ng/dL) levels. These values supported the biochemical diagnosis of PHPT. A bone densitometry scan revealed osteopenia (T score, –1.3) in the femoral neck.

Imaging modalities were used to evaluate the thyroid and parathyroid glands. Ultrasonography of the neck identified a multinodular goiter with dominant bilateral nodules and heterogeneous echogenicity of the thyroid gland with possible lymphocytic thyroiditis in the background. Sestamibi scan demonstrated sustained uptake in the left inferior parathyroid corresponding to the dominant left thyroid nodule. A four-dimensional computed tomography scan of the neck was performed for parathyroid localization and demonstrated a 1.0-cm right superior parathyroid adenoma, a 1.8-cm left thyroid nodule, and an enlarged left thyroid lobe extending substernally into the superior mediastinum without significant tracheal compression or deviation.

Fine needle aspiration of the left thyroid nodule was read as "benign" per Bethesda criteria, indicating likely nodular hyperplasia. Surgical options were discussed, and the patient elected to proceed with left thyroid lobectomy and resection of the substernal component via cervical approach for the compressive symptoms from the left thyroid goiter and parathyroidectomy with intraoperative PTH monitoring based on the American Association of Endocrine Surgeons' Criteria for the Definitive Management of Primary Hyperparathyroidism [1].

Intraoperatively, all four parathyroid glands were assessed, and enlarged right and left superior glands were resected. Intraoperative PTH level fell from a preoperative baseline of 69 to 16 pg/mL within 15 minutes, indicating a biochemical cure of PHPT. Dissection of a firm, "rock-hard" thyroid gland off the trachea was challenging due to a lack of clear dissection planes secondary to dense fibrotic tissues obliterating all surgical planes, including parathyroid and thyroid glands, the strap muscles and surrounding soft tissues, and dense circumferential encasement of the trachea.

Pathologic analysis of all submitted normal and abnormal parathyroid and thyroid tissue revealed hypocellular, globular, eosinophilic material with ring-like deposition in blood vessel walls. The enlarged parathyroid glands demonstrated hypercellular architecture associated with hyperfunctioning glands and, in this case, double adenomas; and the thyroid tissue revealed nodular hyperplasia without evidence of malignant cells, suggestive of papillary, follicular, or medullary cancer. Congo red special staining showed strong orange staining of the amorphous material with apple-green birefringence under polarized light, features diagnostic of amyloidosis (Fig. 1). In absence of thyroid malignant cells, we then proceeded with fibril typing by mass spectrometry at a reference laboratory (Mayo Clinic, Rochester, MN), which demonstrated presence of λ light chains. Together, these findings were diagnostic of a rare case of primary amyloid light-chain amyloidosis in thyroid and parathyroid glands.

The patient was referred to the Vanderbilt Amyloidosis Multidisciplinary Program (VAMP) for further evaluation of incidentally diagnosed amyloidosis. The patient's bone marrow biopsy results revealed presence of 5% to 10% plasma cells with $\kappa{:}\lambda = 0.28$, placing her in the immunoglobulin A monoclonal gammopathy of undetermined significance (IgA MGUS) category. These findings, together with bone scan and serum studies, did not meet the CRAB criteria (CRAB: C, elevated calcium; R, renal failure; A, anemia; B, bone lesions) used to diagnose multiple myeloma, nor did she have any myeloma-defining events [2]. Therefore, active multiple myeloma was ruled out as the underlying cause of her PA. Serum

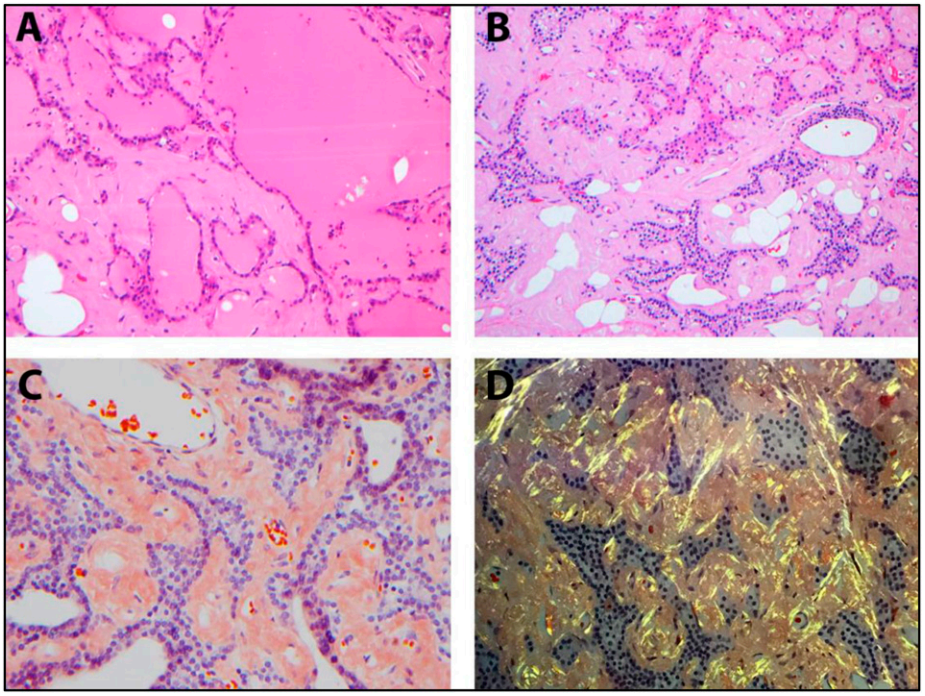

Figure 1. (A) The thyroid gland shows colloid-containing follicles surrounded by amorphous, eosinophilic material (×20). (B) The parathyroid gland shows similar material surrounding chief and oxyphil cells and adipose tissue (×20). (C) A Congo red special stain performed on sections of the parathyroid gland shows strong staining in the amorphous material (×40). (D) An apple-green birefringence under polarized light confirmed the presence of amyloid (×10).

immunofixation electrophoresis revealed an IgA λ monoclonal band and an M spike of 0.5 g/dL. Urine immunofixation electrophoresis revealed no monoclonal bands, indicating that the PA had not yet progressed to renal involvement at the time of her initial assessment. Thus, the patient was diagnosed with IgA MGUS.

Cardiac evaluation was completed to rule out any cardiac involvement associated with progression of amyloidosis. Electrocardiogram showed sinus rhythm with low QRS voltages. Low QRS voltages have been linked to an increased risk of arrhythmias and sudden cardiac death in patients with a diagnosis of PA [3]. Echocardiogram demonstrated mild mitral regurgitation, but was otherwise deemed normal. Cardiac magnetic resonance imaging revealed a left ventricle ejection fraction of 53% with normal ventricle sizes and a mildly enlarged left atrium.

Nearly a year postparathyroidectomy, following the diagnosis of PA with subsequent referral to VAMP for evaluation, the patient progressed and developed rapidly worsening proteinuria. A kidney biopsy revealed amyloid deposition in the renal glomeruli, arteries, and interstitium. New-onset renal involvement was considered an indication for treatment of her amyloidosis by the VAMP team, and a 28-day cyclophosphamide, bortezomib, and dexamethasone treatment was initiated.

In summary, a 70-year-old woman presented with a compressive multinodular goiter and PHPT and was found to have parathyroid double adenomas, multinodular goiter with left substernal extension, and thyroid nodular hyperplasia intraoperatively, and on histopathology, she was diagnosed with PA involving both the parathyroid and thyroid glands. The incidental diagnosis of IgA MGUS carried no indication for immediate treatment in early postoperative period for this patient; however, it helped establish a reliable, specialized, multidisciplinary, long-term follow-up necessary for close monitoring of the amyloidosis progression and timely initiation of early treatment with chemotherapy for the new-onset renal involvement.

3. Discussion

In the setting of thyroid and parathyroid amyloid deposition, the amyloid fibril type is of major clinical significance. Amyloid deposition in parathyroid tissue can be due to PA (λ light chain deposition) or secondary amyloidosis, resulting in calcitonin amyloid deposition from adjacent medullary thyroid carcinoma, and, less commonly, misfolded PTH protein [3, 4]. In the case of our patient, the absence of medullary thyroid cancer diagnosis prompted us to further our analysis with the definitive amyloid fibril typing. Based on the constellation of clinical data and histopathologic findings and additional analysis, no further workup was carried to suspect or rule out a multiple endocrine neoplasia type 2 A.

A review of the literature from January 1974 to present has identified several case series of parathyroid amyloid deposition in patients with PHPT, so the co-occurrence of the two conditions is rare but not unprecedented. Leedham and Pollock [5] described a series of 88 PHPT cases in which nine patients (10%) were found to have intrafollicular amyloid deposition in the parathyroid glands. The amyloid type in these cases was neither AL nor amyloid A, and seven of the nine patients had been diagnosed with "pluriglandular syndrome," likely describing multiple endocrine neoplasia type 1 syndrome and its constellation of parathyroid, pancreatic, and parathyroid tumors. Therefore, the investigators initially postulated that the amyloid pattern was the result of a hormone-synthetic process, similar to the deposition of misfolded calcitonin proteins seen in medullary thyroid carcinoma. However, the differences in deposition pattern and the lack of a medullary thyroid carcinoma diagnosis in these patients led the authors to hypothesize that amyloid deposition in their parathyroid specimens may have simply been the result of an overactive, adenomatous gland producing too much peptide product (misfolded PTH), as had already been defined in pancreatic islet cell tumors and medullary thyroid carcinoma. Later, Anderson and Ewen [6] described a series wherein 9 of 56 (16%) parathyroid glands surgically removed to treat PHPT contained amyloid deposits. They also identified two cases of systemic amyloidosis, postmortem, that demonstrated parathyroid involvement. Anderson and Ewen noted differences in distribution between the intrafollicular amyloid, found within the follicle, and the amyloid deposited in systemic amyloidosis, found in the periarterial and interstitial spaces.

The cases described previously are all examples of localized, nonprimary amyloidosis involving the parathyroid glands. Our case, however, is a very rare example of systemic PA causing deposition of AL amyloid in the thyroid and parathyroid glands. Villamil *et al.* [7] reported the first case of primary, systemic amyloidosis involving the parathyroid glands in the setting of amyloid goiter. Although several papers discuss the relationship between PHPT and monoclonal gammopathies, Anderson and Ewen [6] and Villamil *et al.* [7] are the only other groups to report AL amyloid deposition within the parathyroid tissue.

The concurrent presentation of PHPT and PA is very rare and further highlights our lack of knowledge about the exact relationship between these two conditions. The presence of the IgA MGUS is considered to be the primary cause of systemic amyloid deposition in this patient; however, we cannot comment upon the temporal or physiologic relationship between amyloid deposition and parathyroid dysfunction with absolute certainty in the case of our patient. Given the diffuse extensive amyloid infiltration of both the hypercellular resected parathyroid glands and normocellular parathyroid gland biopsy specimens, we postulate that the two processes are independent. Future studies focusing on histopathologic and physiologic evaluations may further elucidate the interplay between the endocrine system, plasma cell dyscrasias, and PA.

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