CASE REPORT

Multiple Myeloma Presenting as Massive Amyloid Deposition in a Parathyroid Gland Associated with Amyloid Goiter: A Medullary Thyroid Carcinoma Mimic on Intra-operative Frozen Section

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Abstract Clinical examples of amyloid deposition in parathyroid glands are exceedingly rare and usually present as an incidental finding in a patient with amyloid goiter. Here, we present the first histologically documented case of parathyroid amyloid deposition that presented as a mass. The patient did not have hyperparathyroidism. The parathyroid gland was submitted for intra-operative frozen section and concern for medullary thyroid carcinoma was raised. An important histologic clue arguing against medullary thyroid carcinoma was the evenly dispersed nature of the amyloid. Histologic perinuclear clearing and parathyroid hormone immunohistochemistry confirmed parathyroid origin on permanent sections. The patient was also found to have associated amyloid goiter. Mass spectrometry of the amyloid showed it to be composed of kappa light chains. On further work-up, the patient was diagnosed with multiple myeloma. Awareness of parathyroid amyloid deposition is important as it is a histologic mimic of medullary thyroid carcinoma, especially on frozen section. Amyloid typing with evaluation for multiple myeloma in any patient with kappa or lambda light chain restriction is also important.

Keywords Amyloid · Amyloid goiter · Parathyroid · Medullary thyroid carcinoma · Frozen section

Introduction

Medullary thyroid carcinoma is the most common source of amyloid deposition in the thyroid gland encountered in surgical pathology. Amyloid is present in approximately 80% or more of medullary thyroid carcinomas and is composed of calcitonin that is secreted by the tumor cells [1, 2]. However, amyloid deposition may also be seen in patients with localized or systemic (primary or secondary) amyloidosis. Autopsy studies of patients with known systemic amyloidosis show some degree of thyroid amyloid deposition in 30–80% of patients [3]. This is typically an incidental finding and only rarely leads to a clinically apparent enlargement of the thyroid gland, termed amyloid goiter.

More than 100 cases of amyloid goiter have been reported in the English literature [4]. The typical histologic findings include extensive infiltration of the thyroid parenchyma by amyloid, distortion of residual follicles, and fatty metaplasia [4]. Amyloid is typically seen in an interstitial, perifollicular and perivascular distribution, in contrast to the intratumoral distribution of amyloid deposition that is seen in medullary thyroid carcinoma. Amyloid goiter has been reported to occur in various types of systemic amyloidosis but appears more common in secondary amyloidosis, especially amyloid A (AA), compared to primary or amyloid light chain (AL) amyloidosis [3–9].

Although small amounts of amyloid deposition have been identified with the aid of special stains in a subset of both normal parathyroid glands and from patients with primary hyperparathyroidism, significant and histologically identifiable amyloid deposition is usually associated with systemic amyloidosis and only very rarely comes to clinical attention [10, 11]. It is almost always an incidental histologic finding, often at autopsy examination or in a parathyroid removed inadvertently during thyroid surgery [12–16].

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Clinical enlargement of a parathyroid gland caused by amyloid deposition, is exceedingly rare, with only one example in the literature that lacked histologic documentation [17].

Here, we present a case of massive amyloid deposition in a parathyroid gland occurring in a patient who also had amyloid goiter. The patient did not have hyperparathyroidism. The enlarged parathyroid gland presented intraoperatively as a retropharyngeal mass that was submitted for intraoperative frozen section. On frozen section, the amyloid deposition raised concern for medullary thyroid carcinoma. Subsequent evaluation revealed that the patient had AL amyloidosis secondary to multiple myeloma.

Case Report

The patient was a 60-year-old woman whose past medical history was notable for multinodular goiter with dysphagia, status-post total thyroidectomy in 2011 at another institution, as well as pulmonary sarcoidosis, chronic obstructive pulmonary disease, asthma and hypertension. One year following total thyroidectomy the patient noted an enlarging right neck mass. She also reported recurrence of dysphagia. Ultrasound showed a nodular lesion in the right thyroid operative bed, with a sonographic appearance suggestive of recurrent goiter. Ultrasound-guided fine needle aspiration biopsy of the dominant nodule showed a benign follicular thyroid lesion. Thyroid functions tests showed a normal thyroid-stimulating hormone level of 1.65 mIU/ml and a normal free thyroxine (FT4) of 1.22 ng/dl. Serum calcium was also normal (9.3 mg/dl).

Two years after her initial total thyroidectomy, the patient was taken back to surgery for resection of the recurrent right-sided goiter. At that time, two separate masses were found in the neck. A right paratracheal mass measured 6.5 cm in greatest dimension and was clinically consistent with thyroid tissue. A second well-circumscribed right retropharyngeal mass measured 3.0 cm (Fig. 1). Both were submitted for intra-operative frozen section. Neither the pathology slides or the report from the patient's prior thyroidectomy were available at the time of surgery. The larger right paratracheal mass was confirmed to be thyroid tissue on frozen section. It was noted to contain focal pale-pink amorphous material suspicious for amyloid. The right retropharyngeal mass showed a nested, monotonous population of cells with hyperchromatic, round nuclei embedded in evenly dispersed, pale-pink amorphous material consistent with amyloid (Fig. 2). The monotonous and nested appearance of the cells resembled a neuroendocrine tumor. The neuroendocrine appearance, combined with the presence of amyloid and uncertain pathologic findings in the patient's prior total thyroidectomy, was initially concerning for medullary thyroid carcinoma. However, there were

Fig. 1 Intra-operative gross photograph of the retropharyngeal specimen showing a red-tan, homogeneous and well-circumscribed mass

Fig. 2 Intra-operative frozen section of the right retropharyngeal mass showed eosinophilic material consistent with amyloid which surrounding nests of monotonous cells with hyperchromatic, round nuclei. Perinuclear clearing was not appreciated on the frozen section slides. These features were concerning for medullary thyroid carcinoma (hematoxylin and eosin staining $\times 200$)

several features atypical for medullary thyroid carcinoma. The amyloid was much more evenly dispersed than is typically seen in medullary thyroid carcinoma and similar extracellular eosinophilic material was also present in the thyroid tissue but was not associated with a neoplasm. The frozen section diagnosis was, therefore, deferred, pending review of permanent sections. A central neck dissection was not performed as would have been indicated for medullary thyroid carcinoma in this situation.

Permanent sections of the larger 6.5 cm right paratracheal mass showed characteristic features of amyloid goiter (Fig. 3). Benign thyroid follicles were separated and surrounded by extensive amyloid deposition. Amyloid was also present in a perivascular distribution. A Congo red stain showed characteristic 'apple green' birefringence under

Fig. 3 Permanent sections of the right paratracheal mass showed diffuse deposition of amorphous eosinophilic material between benign thyroid follicles with interspersed adipocytes, consistent with amyloid

goiter (**a**). Amyloid deposition was also noted in a perivascular distribution (**b**) (hematoxylin and eosin staining $\times 100$ for **a**, $\times 200$ for **b**)

polarized light. Fatty metaplasia, a typical feature of amyloid goiter, was noted throughout the thyroid parenchyma. The original pathology report from the patient's prior total thyroidectomy was obtained. This documented a diagnosis of nodular hyperplasia, and contained a comment that amyloid was present in the thyroid gland. There was no further description of the amyloid. The pathology slides could not be located for review.

Permanent sections of the 3.0 cm right retropharyngeal mass again showed a monotonous and nested population of bland cells with round, dark nuclei separated by abundant, evenly distributed amyloid, highlighted by a Congo red stain (Fig. 4). Cytoplasmic perinuclear clearing typical of parathyroid tissue, which had not been appreciable on the frozen section slides, was noted on the permanent sections. A parathyroid hormone immunostain was also diffusely positive (Fig. 4), while a calcitonin immunostain was negative,

supporting the diagnosis of massive amyloid deposition in an enlarged parathyroid gland rather than medullary thyroid carcinoma. Postoperative serum calcitonin was also less than 5.0 pg/ml, while parathyroid hormone was normal (40 pg/ml). The formalin-fixed paraffin-embedded tissue block was sent for amyloid typing by mass spectrometry, which showed the amyloid subtype to be AL (kappa subtype). Further work-up was diagnostic of multiple myeloma.

Discussion

Amyloid deposition in parathyroid glands occurs mainly in patients who have systemic amyloidosis but usually goes clinically undetected. Autopsy studies suggest that amyloid deposition in parathyroid glands from patients with systemic amyloidosis may not be uncommon. An autopsy series of

Fig. 4 Permanent section of the right retropharyngeal mass showed evenly distributed amyloid deposition surrounding nests of monotonous cells with round, hyperchromatic nuclei and perinuclear clearing (**a**). Amyloid deposition was confirmed by Congo red staining show-

ing 'apple-green' birefringence under polarized light (**b**). A positive parathyroid hormone immunostain confirmed parathyroid origin (**c**) (hematoxylin and eosin staining $\times 400$ for **a**, Congo red $\times 400$ for **b**, and immunohistochemical staining $\times 400$ for **c**)

30 parathyroid glands obtained from eight patients with systemic amyloidosis found amyloid deposition in parathyroid glands from all of the patients [16]. The amyloid was primarily distributed in the vasculature, with arteries, arterioles, and capillaries affected to varying degrees in all patients [16]. Stromal amyloid deposition was seen in three of the patients [16].

However, there are only exceedingly rare clinical (non-autopsy) examples of amyloid deposition in parathyroid glands. Review of the literature yielded four cases (Table 1) [13–15, 17]. In two of these cases amyloid deposition was noted in parathyroid glands that were removed incidentally in patients who were undergoing thyroidectomy for compression symptoms related to amyloid goiter [13, 14]. In one of these cases, the parathyroid was intrathyroidal [14]. Ordonez et al. also reported amyloid deposition in an intrathyroidal parathyroid in a patient with hyperparathyroidism for whom an abnormal parathyroid was not localized preoperatively [15]. The thyroid lobe was submitted for intra-operative frozen section and a diagnosis of medullary thyroid carcinoma was made, for which the surgeon performed completion thyroidectomy [15]. On permanent sections, it was determined to be parathyroid tissue with amyloid deposition, which was confirmed with immunohistochemistry, and was the source of the patient's hyperparathyroidism [15]. This example and our case highlight the need for caution on intra-operative frozen section. In our case, the main histologic clue that lead us away from a diagnosis of medullary thyroid carcinoma on frozen section was the very even distribution of amyloid. Amyloid distribution in medullary thyroid carcinoma is patchy and forms variably sized deposits rather than being evenly distributed throughout the tumor [18]. Lastly, there is one additional example in the literature of

an enlarged, 2 cm parathyroid gland with amyloid deposition that was associated with an amyloid goiter secondary to familial Mediterranean fever [17]. However, there was no histologic documentation of parathyroid amyloid deposition in the report. To our knowledge, our case represents the only documented example of a clinically enlarged (3.0 cm) parathyroid gland secondary to amyloid deposition.

Another unique feature of our case is that amyloid goiter was the initial presentation of the patient's multiple myeloma. The majority of amyloid goiters described in the literature are due to deposition of AA-type amyloid secondary to chronic inflammatory conditions with AL (or primary) amyloidosis being a less common etiology [3–9]. Of the four examples in the literature of amyloid deposition in parathyroid glands, two were thought to be secondary amyloidosis and in one case an etiology could not be determined consistent with localized amyloidosis [13, 14, 17]. One report did not mention whether the patient was evaluated for systemic amyloidosis [15]. Our case is the first clinical example of AL amyloidosis involving a parathyroid gland and highlights the importance of amyloid typing in such cases. If clonal kappa or lambda light chains are identified, the patient should be evaluated for multiple myeloma.

In summary, here we present the first documented example of a massively enlarged 3.0 cm parathyroid gland secondary to amyloid deposition. The patient did not have hyperparathyroidism but was found to have AL amyloidosis with amyloid goiter secondary to multiple myeloma. This case highlights the need to be cautious, especially on intra-operative frozen section, because amyloid deposition in a parathyroid gland is a histologic mimic of medullary thyroid carcinoma. Even distribution of the amyloid is an important histologic clue that argues against medullary thyroid

Table 1 Cases of amyloid deposition in parathyroid glands [13–15, 17]

Article	Age/sex	Type of amyloidosis	Parathyroid location/size	Presentation	Parathyroid function	Amyloid goiter?
Ordonez et al. [15]	71/F	Unknown	Intrathyroidal/unknown size	Incidental finding on frozen section of thyroid	Hyperparathyroid	Unknown
Villamil et al. [13]	40/M	Secondary (Crohn's disease)	Right inferior/unknown size	Incidental	Normal	Yes
Abdou and Kandil [14]	39/M	Localized (no etiology identified)	Intrathyroidal/unknown size	Incidental	Unknown	Yes
Ori et al. [17]	40/M	Secondary (familial Mediterranean fever)	Right superior/2 cm	Noted to be enlarged intra-operatively	Normal	Yes
Present case	60/F	Primary/AL (multiple myeloma)	Retropharyngeal/3.0 cm	Mass noted intra-operatively and submitted for frozen section	Normal	Yes

F female, M male

carcinoma. Further, patients found to have AL amyloidosis should be evaluated for multiple myeloma.

Compliance with Ethical Standards

Conflict of interest The authors have no sources of funding or conflicts of interest to disclose.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

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