CASE REPORT

A Herald of Plasma Cell Myeloma: A Report of Malignant Plasma Cells Identified in Parathyroid Adenoma and a Review of Non-parathyroid Malignancies in Parathyroid Glands

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Abstract Involvement of the parathyroid glands by non-parathyroid neoplasia is an infrequent event. Rare cases of metastases to the parathyroid gland have been reported in parathyroidectomies and autopsies of patients with known solid or hematopoietic malignancies. Here, we present a case of atypical clonal plasma cells incidentally identified within a parathyroid adenoma resected for hyperparathyroidism and hypercalcemia, which served as the sentinel event for a subsequent diagnosis of plasma cell myeloma. To our knowledge, this is the only reported case of a hematopoietic malignancy involving a parathyroid adenoma and the only reported case of malignant hematopoietic cells initially detected in parathyroidectomy.

Keywords Parathyroid adenoma · Myeloma · Hypercalcemia · Incidental

Background

Enlarged parathyroid glands resected for primary or secondary hyperparathyroidism are common surgical pathology specimens. At The University of Chicago, approximately 150 parathyroidectomies are performed annually, many of

which include multiple parathyroid glands. The incidental recovery of a parathyroid gland during thyroidectomy is also often encountered. A recent review demonstrated incidental parathyroidectomy occurring during 16.2% of thyroidectomies at our institution [1]. The most frequent histopathologic diagnosis rendered on a parathyroid gland is enlargement by weight and concurrent hypercellularity related to adenoma or hyperplasia.

Rare cases of solid tumors metastatic to parathyroid adenomas (“tumor-to-tumor” metastases) have been reported [2–12] (Table 1). This finding is often attributed to the increased vascularity of the adenoma fostering a conducive environment for metastatic deposits. With the exception of a single reported case of metastatic bronchogenic carcinoma diagnosed in a parathyroid adenoma [10], all metastatic solid tumors to parathyroid adenomas have been in patients with known malignancies. Thymic neuroendocrine tumor has been reported in a case of a patient with MEN 1 syndrome and an enlarged parathyroid gland [11]. Metastatic disease involving non-adenomatous parathyroid tissue is also uncommon. Autopsy studies have suggested that the prevalence of incidental involvement of the parathyroid glands by metastatic tumor to be between 5.3 and 11.9% in deceased patients with a known malignancy at the time of death [13]. In these studies, metastatic breast carcinoma involving benign parathyroid glands was the most common tumor type present, though hematopoietic malignancies, including a single case of multiple myeloma, were the second most common tumor type to involve the otherwise normal parathyroid gland at autopsy [13]. The parathyroid glands are occasionally involved by direct extension of tumor from an adjacent carcinoma, though these cases have been excluded from this discussion.

A recent large review by Bauer et al. identified a similar spectrum of disease where 66.9% of metastases to

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Table 1 Summary of reported metastatic solid tumor malignancies in parathyroid adenomas/hyperplasias

Author, year	Patient age and sex	Malignant tumor type	Previously known primary malignancy?
Fulciniti et al., 2011 [2]	56 F	Breast carcinoma	Yes
Inoshita and Laurain, 1985 [3]	81 M	Malignant melanoma	Yes
Lee et al., 2013 [4]	65 F	Breast carcinoma	Yes
Lee et al., 2011 [5]	53 M	Hepatocellular carcinoma	Yes
Boixeda et al., 1991 [6]	82 F	Hepatocellular carcinoma	Yes
Woolner et al., 1958 [7]	54 F	Breast carcinoma	Yes
Schwartz et al., 1982 [8]	79 F	Renal cell carcinoma	Yes
Margolis and Goldenberg, 1969 [9]	55 F	Breast carcinoma	Yes
Shifrin et al., 2015 [11]	60 M	Neuroendocrine thymic carcinoma	Yes
Venkatraman et al., 2007 [10]	75 F	Bronchogenic carcinoma	No
Benisovich et al., 1991 [12]	75 F	Lung adenocarcinoma	Yes

parathyroid glands come from breast carcinoma, followed by melanoma (11.8%) and lung carcinoma (5.5%). Of the cases reviewed, 5.5% were “tumor-to-tumor” metastases to parathyroid adenomas, and few other cases represented metastases to hyperplastic parathyroid glands [14]. To our knowledge, there are no reported cases of malignant hematopoietic cells involving parathyroid adenomas.

Case Presentation

The patient was a 68 year old female with a medical history significant for osteoporosis, gastroesophageal reflux disease, glaucoma, and nephrolithiasis who presented to her primary care provider with a 1 month history of nausea. Serum calcium levels were elevated to 16.6 mg/dL with an ionized calcium of 7.5 mg/dL. Serum creatinine was elevated to 2.2 mg/dL. Serum parathyroid hormone levels were increased at 83 pg/mL and subsequent ultrasound studies revealed a 2.1 cm nodular lesion adjacent to the left inferior pole of the thyroid gland suggestive of a parathyroid adenoma. Sestamibi scan reportedly localized a single abnormal gland in the left neck.

The enlarged left lower parathyroid gland was surgically resected. Intraoperatively, parathyroid hormone levels trended downward from 103 pg/mL preoperatively to 30 pg/mL 10 min postoperatively. The gland had a weight of 860 mg and a size of 2.2 cm in greatest dimension. The parenchymal cut surface was homogenous, tan-white, and smooth. The specimen was entirely submitted for histologic evaluation. Microscopically, the parathyroid gland was composed of nests and sheets of monomorphic small cells with round, dark, nuclei and moderate pale eosinophilic to clear cytoplasm. Adipose tissue was absent. The border was well-defined and there were no increased mitoses, necrosis, or local tissue invasion. Located within this enlarged,

hypercellular parathyroid gland were numerous perivascular foci of atypical dyscohesive cells with scant cytoplasm and variably-sized, wrinkled, irregular nuclei. Some cells had eccentrically-located nuclei with eosinophilic cytoplasm. Occasional mitoses were identified. The differential diagnosis included a hematopoietic neoplasm, a neuroendocrine neoplasm, and parathyroiditis. The presence of nuclear atypia and mitoses and absence of parathyroid atrophy, fibrosis, parenchymal injury argued against parathyroiditis. The abnormal perivascular cells were strongly positive for CD138, focally positive for CD79a, and negative for CD20, CD3, CD45, CAM5.2, PTH, GATA-3, synaptophysin, and calcitonin. Conversely, the parathyroid cells were positive for CAM5.2 and GATA-3, and negative for the remaining markers. By in situ hybridization, the perivascular cells strongly expressed kappa light chain with only rare cells expressing lambda light chain (Fig. 1). Based on these findings, the diagnosis of a malignant neoplasm with plasma cell differentiation was rendered and bone marrow biopsy was recommended.

Follow-up studies showed reduced levels of serum IgG (627 mg/dL), IgA (26 mg/dL), IgM (6 mg/dL) but elevated free kappa light chain (1020 mg/dL) and a kappa:lambda ratio of > 1000. Peripheral blood smear showed red cell rouleaux formation with circulating plasma cells that accounted for 7–8% of cells in the peripheral blood. Bone marrow biopsy was hypercellular for the patient's age with an overall cellularity of 60%, primarily due to proliferation of plasma cells that accounted for 80% of the bone marrow cellularity. The plasma cells were phenotypically abnormal (CD19–, CD56+) and kappa monotypic, consistent with bone marrow involvement by plasma cell myeloma. Plasma cell target FISH analyses showed loss of IGH, gain of 1q21, trisomy 12 and loss of chromosome 13.

Post-parathyroidectomy, her serum calcium levels remained mildly elevated with normalized parathyroid

Fig. 1 Low power hematoxylin and eosin-stained image of the parathyroid gland demonstrates a uniform population of cells with round, dark, nuclei and eosinophilic to clear cytoplasm, consistent with parathyroid adenoma. A distinct basophilic cell population is present in a perivascular distribution (a). On higher magnification, this second population has irregular, wrinkled, eccentrically placed nuclei

with coarse chromatin, minimal cytoplasm, and occasional mitoses (arrow) (b). Strong and diffuse immunohistochemical expression of CD138 in the perivascular cells confirms plasmacytoid differentiation (c). In situ hybridization for kappa light chain is also diffusely positive and lambda highlights only rare cells (not pictured), confirming a monoclonal malignant population (d)

hormone levels, suggesting a significant contribution by myeloma to her initial hypercalcemia. A radiographic skeletal survey revealed innumerable calvarial radiolucencies secondary to myeloma. Her serum calcium and creatinine levels normalized in the weeks following initiation of chemotherapy with cyclophosphamide, bortezomib, and dexamethasone.

Discussion

Primary hyperparathyroidism affects up to 4 per 1000 adults in the United States [15]. Parathyroidectomy is fundamental to the treatment of parathyroid adenoma, with an increasing frequency of parathyroidectomies performed annually. Current estimates project that more than 173,000 parathyroidectomies will be performed in the United States in 2020 [16]. Parathyroid specimens are routinely encountered by both subspecialty and general surgical pathologists, and do not usually prove a significant diagnostic challenge. Some histologic variability is often encountered in the microscopic

evaluation of adenomatous parathyroid glands. Chief cells can have clear cell or oncocytic changes, and multinucleation is common. Architectural patterns can vary from cords, sheets, and nests to occasional trabeculae, follicles, and glands. Follicles may contain colloid-like material recapitulating thyroid gland histology. Random “endocrine-type” nuclear atypia (enlargement and hyperchromasia) is often identified and is not of diagnostic or prognostic significance [17]. Cystic change has been described in adenomatous parathyroid nodules, as well as spindle cell changes and papillary architectural formation [18].

Metastatic tumors rarely involve the parathyroid glands, with autopsy studies demonstrating parathyroid metastases in up to approximately 12% of deceased patients with known malignancies [13]. So-called “tumor-to-tumor” metastasis, or malignancy involving a parathyroid adenoma, have been reported in the literature, the most frequent being breast carcinoma [13, 14]. Although hematopoietic malignancies including myeloma have been documented in otherwise normal parathyroid glands at autopsy, there are no reported cases of malignant hematopoietic cells in parathyroid

adenomas. We believe ours to be the first reported case of a hematopoietic malignancy directly involving a parathyroid adenoma, as well as the first reported case in which an otherwise unknown hematopoietic malignancy was diagnosed via identification of tumor cells during microscopic evaluation of parathyroid tissue. A recently reported case of multiple myeloma diagnosed following histologic evaluation of a parathyroid gland involved by massive amyloid deposition without myeloma cells further illustrates the wide variation in disease processes which may manifest in the parathyroid glands [18].

Extramedullary involvement by plasma cell myeloma is relatively uncommon and, when present, is typically restricted to the soft tissues adjacent to the axillary skeleton. A 1000 patient Mayo Clinic review identified extramedullary disease prior to a diagnosis of myeloma in 0.4% of patients [19], while a separate review of more than 1000 multiple myeloma patients showed extramedullary disease in 7% of patients at the time of diagnosis, with another 6% of patients developing extramedullary disease during long-term follow-up [20]. In this second cohort, the presence of extramedullary disease at the time of diagnosis or during follow-up was associated with significantly shorter overall survival. Involvement of solid organs by myeloma accounted for a minority of patients (between 15 and 28%) with extramedullary disease. The majority of patients with extramedullary disease have involvement of only the soft tissues adjacent to the skeleton. The most common solid organs involved by myeloma included lymph nodes, skin, central nervous system, liver, breast, airway, testis, and gastrointestinal tract. The parathyroid gland was not a documented site of involvement in this study. Interestingly, the incidence of extramedullary disease in plasma cell myeloma appears to be increasing, though this is likely attributable to enhanced methods of detection and diagnosis [20].

Clinically confounding in this case is that both primary hyperparathyroidism and plasma cell myeloma cause hypercalcemia. In this patient, elevated preoperative serum parathyroid hormone was consistent with hypercalcemia secondary to parathyroid adenoma, however, postoperative serum calcium levels remained above the normal range following normalization of parathyroid hormone levels. Hypercalcemia in patients with concurrent myeloma and parathyroid adenoma has been well-reported [21–23]. Additionally, recurrent or persistently elevated calcium following parathyroidectomy has occasionally lead to a new diagnosis of myeloma [24, 25]. However, none of these reported cases have shown parenchymal involvement of the parathyroid by myeloma cells on histologic examination. In our case, identification of the atypical plasma cells in the parathyroidectomy directly lead to hematologic workup, helped confirm the etiology of her continued postoperative hypercalcemia, and expedited the diagnosis of plasma cell myeloma.

Conclusion

In summary, involvement of the parathyroid glands by non-parathyroid neoplasia is infrequent. We report a case of atypical clonal plasma cells incidentally identified within a parathyroid adenoma, which prompted diagnosis of plasma cell myeloma on bone marrow biopsy. To our knowledge, this is the only reported case of a hematopoietic malignancy directly involving a parathyroid adenoma and the only reported case of a hematopoietic malignancy heralded by histologic identification of malignant cells within parathyroid tissue.

Compliance with Ethical Standards

Conflict of interest Dr. Cracolici, Dr. Grogan, Dr. Sukhanova, Dr. Cheng, Dr. Gurbuxani, and Dr. Cipriani declares that they have no conflict of interest.

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

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