Case Report

NEUROENDOCRINE THYMIC CARCINOMA METASTATIC TO THE PARATHYROID GLAND THAT WAS REIMPLANTED INTO THE FOREARM IN PATIENT WITH MULTIPLE ENDOCRINE NEOPLASIA TYPE 1 SYNDROME: A CHALLENGING MANAGEMENT DILEMMA

Alexander L. Shifrin, MD[1]; Virginia A. LiVolsi, MD[2]; Min Zheng, MD, PhD[3]; Danielle E. Lann, MD[4]; Svetlana Fomin, MD[5]; Evan C. Naylor, MD[6]; Peter J. Mencel, MD[7]; Angela M. Fay, MS, CGC[8]; Brian S. Erler, MD[3]; Theodore J. Matulewicz, MD[3]

ABSTRACT

Objective: To describe a unique case of a metastatic thymic carcinoma to the hyperplastic parathyroid gland and to present a challenging management dilemma.

Methods: Our patient is 60-year-old, intellectually disabled man with history of the multiple endocrine neoplasia type 1 (MEN1) syndrome, a surgery in 1985 for hypercalcemia with removal of one parathyroid gland, surgery in 2007 with findings of extensively necrotic well differentiated neuroendocrine carcinoma (carcinoid tumor) of the thymus. In 2012, he presented with persistent hypercalcemia (calcium level 11.7 mg/dL [range, 8.6-10.2]), and a parathyroid hormone (PTH) level of 225 pg/mL (range, 15-65 pg/mL). He underwent a repeat neck exploration with removal of 2 small inferior and a large left superior 4.5 × 2.5 × 1.5cm parathyroid glands, all of which showed hyperplasia on intraoperative frozen section. A small portion of the superior gland was reimplanted into the patient's forearm. Final pathology showed the presence of a focus of neuroendocrine tumor within the left superior parathyroid gland with immunostain identical to the thymic carcinoma. His postoperative PTH level was 14 pg/mL and calcium 8.5 mg/dL. A positron emission tomography – computed tomography (PET-CT) and octreotide scans revealed an extensive metastatic disease within the lung, mediastinum, and bones.

Results: We decided to leave a portion of the reimplanted parathyroid gland with possible metastatic thymic carcinoid in his forearm because of the presence a widespread metastatic disease and his intellectual disability that would result in noncompliance with calcium replacement in case of permanent hypocalcemia.

Conclusion: Metastatic thymic carcinoma to the parathyroid gland has never been reported in the literature. We have described the first case and presented a challenging management dilemma. **(Endocr Pract. 2013;19:e00-e00)**

Abbreviations:
IGF-1 = insulin-like growth factor-1; **MEN1** = multiple endocrine neoplasia type 1 syndrome; **PP** = pancreatic polypeptide; **PTH** = parathyroid hormone; **SUV** = standardized uptake values; **VIP** = vasoactive intestinal polypeptide

CASE REPORT

Our patient is a 60-year-old, intellectually disabled man living at a nursing home. His history included cerebral palsy, nephrolithiasis, and surgery in 1985 for hypercalcemia. An operative report described excision of the right superior parathyroid gland with findings of normal size right and left inferior glands but inability to find the left superior gland. The patient has remained hypercalcemic

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From the [1]Department of Surgery, Jersey Shore University Medical Center, Neptune, New Jersey, [2]Department of Pathology, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania, [3]Department of Pathology, Jersey Shore University Medical Center, Neptune, New Jersey, [4]Department of Endocrinology, Jersey Shore University Medical Center, Neptune, New Jersey , [5]Shore Endocrinology Associates, Pt. Pleasant, New Jersey, [6]Southern Ocean Medical Center, Manahawkin, New Jersey, [7]Atlantic Hematology Oncology, Manasquan, New Jersey, and [8]Hereditary Cancer Risk Program, Meridian Health System, Neptune, New Jersey.
Address correspondence to Dr. Alexander L. Shifrin, Jersey Shore University Medical Center, Department of Surgery, 1945 State Route 33, Neptune, NJ, 07754. E-mail: ashifrin@meridianhealth.com
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despite surgery. In 2007 he was found to have a thymic tumor and had surgery with findings of extensively necrotic thymic neuroendocrine carcinoma. This was followed by a course of radio therapy. The patient is the second generation member of a family with known multiple endocrine neoplasia type 1 syndrome (MEN1) syndrome (Figure 1).

In 2012, he presented to our group with persistent hypercalcemia. His calcium level was 11.7 mg/dL (range, 8.7-10.2 mg/dL) and parathyroid hormone (PTH) level was 225 pg/mL (range, 15-65 pg/mL). A prolactin level was 21 ng/mL (<15.2 ng/mL), but no evidence of pituitary adenoma was noted on a head magnetic resonance imaging (MRI). A chromogranin A level was 23 nmol/L (<5 nmol/L). A 24-hour urine calcium, serum insulin-like growth factor-1 (IGF-1), vasoactive intestinal polypeptide (VIP), gastrin, somatostatin, and pancreatic polypeptide (PP) levels were all within normal limits. Genetic testing showed a mutation in the tumor suppressor gene MEN1, exon 2, consisting of a single base deletion in codon 103 (CTG to TG) (c417delC), consistent with a diagnosis of MEN1. This mutation of MEN1 gene was initially described and documented by Agarwal et al. and has been shown to cause alteration of encoded a 610-amino acid protein menin, resulting in MEN1 syndrome (7,8). A sestamibi scan revealed the presence of the persistent uptake in the left superior mediastinum (Figure 2*A*). An octreotide scan showed two small foci of an increased activity in the superior mediastinum corresponding to the area on sestamibi scan (Figure 2*B*). A neck ultrasound showed bilateral thyroid nodules each less than 1 cm in size.

He underwent a repeat neck exploration. Findings included two small inferior left and right parathyroid glands that were completely encased within scar tissue at inferior thyroid poles. His largest gland was the left superior parathyroid measuring a 4.5 cm × 2.5 cm × 1.5 cm, which was retroesophageal and dropped down into the mediastinum. The location of this gland corresponded to the findings on a sestamibi scan. All glands showed hyperplasia on intraoperative frozen sections. Because of a small size and significant scarring around two inferior glands, a small portion of the left superior parathyroid gland was reimplanted into the patient's forearm. At this point his intraoperative PTH

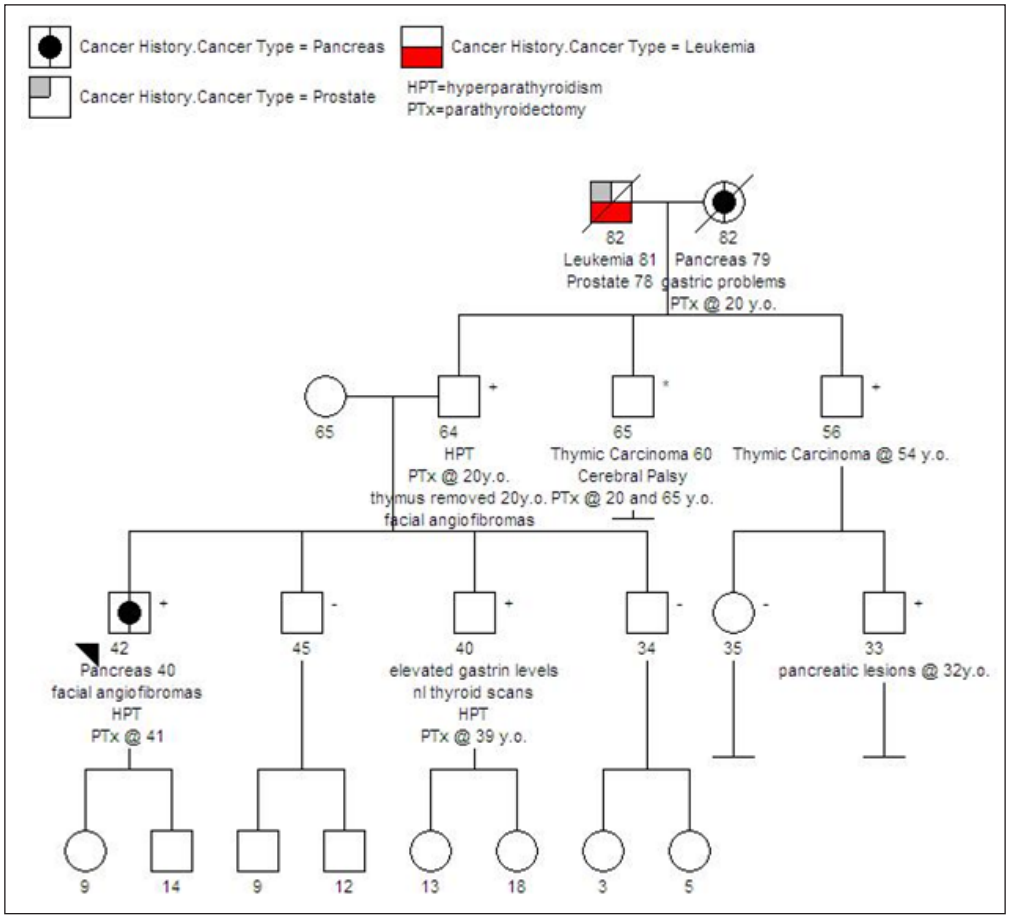

Fig. 1. The patient's pedigree.

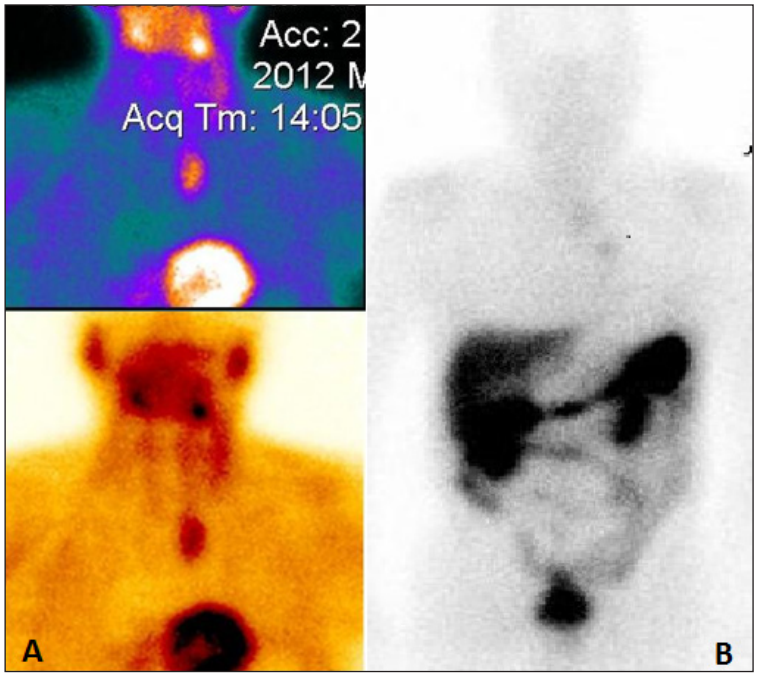

Fig. 2. Preopertaive sestamibi (A) and octreotide (B) scans.

level dropped to 51 pg/mL (range, 15-65 pg/mL). Final pathology showed marked hyperplasia of all parathyroid glands with a focus of neuroendocrine tumor within the left superior parathyroid gland (Figure 3). The immunostain results in the intraparathyroid lesion were identical to the thymic neuroendocrine carcinoma (removed in 2007) and different from the background hyperplastic parathyroid (see immunohistology table in Figure 3).

Three weeks postoperative a PTH level was 14 pg/mL and calcium 8.5 mg/dL. Because the final pathology has revealed a metastatic focus of thymic neuroendocrine carcinoma within the same gland that was reimplanted into the patient's forearm, we had a dilemma to either leave it or remove it. A sestamibi scan showed no activity in the patient's neck and forearm, but one month postoperative PTH level was 29 pg/mL with calcium 9.3 mg/dL, indicative of a functioning parathyroid implant. A serum chromogranin A level was 26 (range, <5 nmol/L). VIP, 5-hydroxyindoleacetic acid (5-HIAA), gastrin, and insulin levels were within normal limits. CT scan showed diffuse osseous metastases and a 1.6 cm × 2.2 cm mass in the mediastinum (Figure 4*A*). A positron emission tomography – computed tomography (PET-CT) revealed a 1.9 × 2.4 cm mass in the anterior mediastinum with standardized uptake values (SUV) of 2.5; a 0.9 × 1.1 cm metastasis at the left pleural space with SUV 7.2, a 0.5 cm metastasis in the upper lobe of the left lung with SUV 3.3, and diffuse osseous metastatic disease in the bilateral ileal bones with SUV 2.6 (Figure 4*B*).

We have decided to leave the reimplanted parathyroid gland with possible metastatic thymic neuroendocrine carcinoma in patient's forearm because of his extensive metastatic disease in lungs mediastinum and bones and because his intellectual disability would make him noncompliant with permanent calcium replacement therapy for permanent hypocalcaemia

Two months after the surgery, an octreotide scan showed the presence of persistent two foci in the left chest and an additional two foci in the epigastric area. Six months after the surgery the patient developed bone pain. A CT scan showed a 1.8 × 2.4 cm anterior mediastinal mass, stable in size lung and paramediastinal nodules but development of a new left humerus and multiple thoracic vertebra sclerotic lesions consistent with bony metastases. We initiated octreotide acetate and denosumab therapy every 4 weeks. The patient has shown a partial response at 6 months with decreased bone pain.

DISCUSSION

Metastasis to the parathyroid gland, especially hyperplastic parathyroid gland or parathyroid adenoma, is very rare and only single cases have been reported in the literature. With only about a 100 cases of so-called "tumor-to-tumor" metastases have been reported only a few of them were into a parathyroid adenoma. With a "tumor-to-tumor" metastasis a "donor" tumor is usually more aggressive than a "recipient" tumor. Lee et al. reported a synchronous metastasis of hepatocellular carcinoma into the parathyroid adenoma in 53-year-old male, who was diagnosed with primary hyperparathyroidism during his admission for a liver segmentectomy (1). He was found

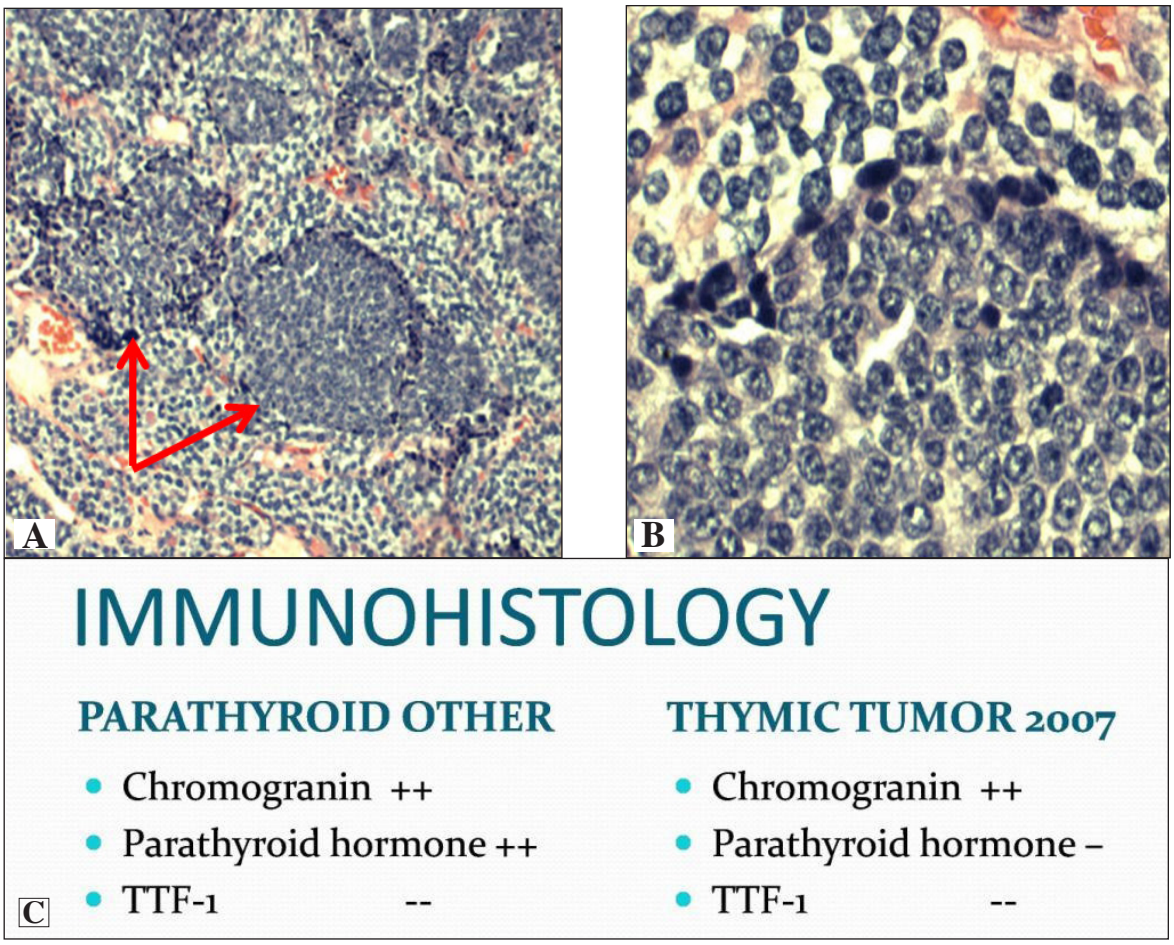

Fig. 3. Pathology of the parathyroid gland showing distinct cellular nests of metastatic thymic neuroendocrine carcinoma cells with high nuclear. Cytoplasmic ratio (arrows) on a background of diffuse parathyroid hyperplasia (*A*, 40x; *B*, 400x). Immunohistology table.

to have a 0.2 cm focus of metastatic hepatocellular carcinoma in the removed parathyroid adenoma (1). Fulciniti et al. described a 56-year-old woman with a history of left breast carcinoma who was found to have a palpable neck mass next to the thyroid lobe (2). A fine-needle aspiration with cytopathological evaluation revealed malignant cells consistent with breast origin. A pathological diagnosis after the excision of this mass was consistent of parathyroid adenoma with multiple small foci of metastatic high-grade breast ductal carcinoma (2). Tang et al. described 20 cases of parathyroid involvement in 911 patients with papillary thyroid carcinomas (3). Some of them had a direct invasion, but others had metastatic disease as well (3).

The one autopsy study by Horitz et al. examined the parathyroids in 160 autopsies in patients with cancer (4). In 19 cases (11.9%) the parathyroid glands showed metastatic disease. Additional retrospective review of 750 necropsies in patients with known cancers showed 40 of 750 patients (5.3%) had parathyroid involvement by their malignancies. The most common primary sites of cancer were: breast, melanoma, lung, soft tissue sarcoma, and leukemia/lymphomas (4). Thirteen patients of those two study groups (160 prospective and 750 retrospective cases) had hypercalcemia, but no histological confirmation of parathyroid hyperplasia; one had metastases into two parathyroid glands.

Gattuso et al. in a letter to the editor mentioned two cases of metastatic bronchogenic adenocarcinoma into parathyroid glands but further details were not given (5). Venkatraman et al reported a case 75-year-old woman with a primary hyperparathyroidism (6). Her postoperative pathological evaluation was consistent with findings of metastatic bronchogenic adenocarcinoma in one of two hyperplastic parathyroid glands and in one suspicious submandibular lymph node that was also removed. She subsequently died of widespread metastatic disease from a presumed primary lung carcinoma (5).

Metastatic thymic carcinoma to the parathyroid gland has never been reported in the literature. This case is especially unique because it was a metachronous metastatic

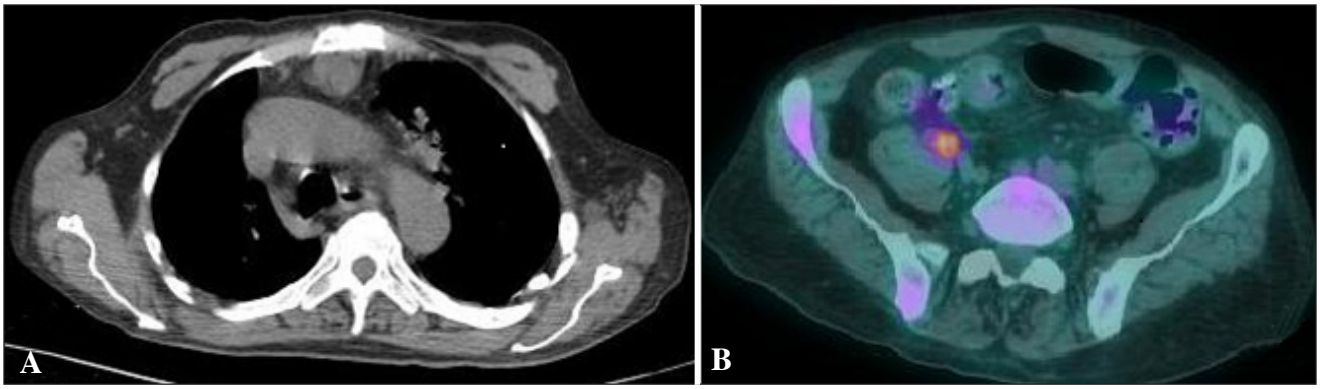

Fig. 4. Postoperative computed tomography (CT) of the chest (A) and positron emission tomography – computed tomography (PET-CT) PET CT (B) scans of the chest, abdomen and pelvis

disease into the hyperplastic parathyroid gland in patient with MEN 1 syndrome. The patient had an initial parathyroid exploration 37 years prior that was only resulted in removal of one parathyroid gland and has remained hypercalcemic. Subsequently, the patient developed thymic carcinoid and had excision of the tumor 5 years prior to this evaluation. Parathyroid reexploration reveled hyperplasia of remaining glands. They were removed and a portion of one gland was reimplanted into the patient's forearm. The final pathology disclosed that the gland had a focus of metastatic thyroid carcinoid. This is a unique case with a challenging management dilemma. Because of finding of this metastasis, further postoperative metastatic work-up was performed and has revealed a widely metastatic thymic carcinoid to lungs and bones as well as mediastinal recurrence.

We have decided to leave the reimplanted parathyroid gland with possible metastatic thymic neuroendocrine tumor in his forearm. The rationale for that was the presence of extensive metastatic disease; the removal of this implanted gland would not have a palliative effect on his disease. In addition, because of his intellectually disability, he might not be compliant with permanent calcium replacement therapy for permanent hypocalcaemia. At this time he is normocalcemic from the functioning parathyroid implanted in his forearm.

CONCLUSION

In conclusion, this is the first description of thymic neuroendocrine carcinoma metastatic into the hyperplastic parathyroid gland in a patient with the MEN1 syndrome. Challenging management of this patient, multidisciplinary approach and postoperative work-up has revealed widely metastatic thymic neuroendocrine carcinoma in his mediastinum, lungs, and bones. We have faced the treatment dilemma by leaving a portion of this parathyroid gland reimplanted into his forearm since this has resulted in a normocalcemic state.

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DISCLOSURE

The authors have no multiplicity of interest to disclose.

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