Several case reports have noted an association between parathyroid adenomas and mediastinal thymomas.1,2 The concurrent presentation of both tumors is extremely rare and has been attributed to their similar embryologic origins from the third branchial pouch.1 We present a case of a parathyroid hormone (PTH)-secreting thymoma in the setting of a parathyroid adenoma. In our literature search, we were able to identify 1 prior case of a PTH-secreting thymoma and 3 cases involving other types of PTH-secreting tumors.

Report of a Case

A woman underwent evaluation at Wexner Medical Center for persistent hypercalcemia and hyperparathyroidism with a suspected ectopic mediastinal parathyroid adenoma. She reported slight fullness in her neck, diarrhea, and abdominal pain. She denied dysphagia or shortness of breath. She had no history of kidney stones, gallbladder stones, or pathologic fractures.

Results of the laboratory workup were notable for a serum calcium level of 11.1 mg/dL (to convert to millimoles per liter, multiply by 0.25) and urine calcium level of 402 mg/dL (to convert to millimoles per liter, multiply by 0.323). The findings were consistent with primary hyperparathyroidism. The thyrotropin level and additional basic laboratory findings were within the reference ranges.

The patient was referred to us after delayed imaging with a technetium Tc 99m sestamibi scan and computed tomography (CT) demonstrated a mass in the anterior mediastinum (Figure 1) that was consistent with an ectopic parathyroid adenoma. Mild asymmetric uptake in the right inferior thyroid gland was attributed to the heterogeneous uptake of a multinodular goiter on immediate imaging and a decreased signal on delayed imaging (Figure 2).

Given the location of the mass in the mediastinum, the patient was referred to our thoracic surgery colleagues for surgical intervention. The patient consented to and underwent upper sternotomy for complete resection of the mass. An intraoperative PTH assay was used to confirm removal. The laboratory values were obtained after a 10-minute inter-
val from removal of the tumor and demonstrated an acceptable drop in PTH levels of greater than 50% (from 202 to 96 pg/mL). Intraoperative pathological findings were suggestive of a possible malignant neoplasm, so the procedure was concluded. The patient recuperated well in the postoperative period.

The histopathological evaluation showed an invasive type AB thymoma, according to World Health Organization (WHO) classification, with microscopic invasion into the mediastinal adipose tissue, Masaoka stage pTIIa3 (Figure 3). At this point, the patient again underwent evaluation with CT of the chest, which demonstrated no remaining soft-tissue masses or lymphadenopathy. She underwent a full sternotomy, completion thymectomy, and lymphadenectomy with pericardial resection and reconstruction with bovine pericardium. The final pathological evaluation demonstrated negative margins and normal lymph nodes. No parathyroid adenoma was found on serial sections of either surgical specimen.

When PTH and calcium levels were measured postoperatively, the PTH level initially decreased to 86.5 pg/mL after the thymoma resection. Subsequent PTH levels measured 1 month after surgery once again increased to 136 pg/mL. Subsequent immunohistochemical analysis of the thymoma revealed diffuse PTH present within the tumor itself despite no parathyroid adenoma (Figure 4). A second technetium Tc 99m sestamibi scan demonstrated a definite mass inferior to the right thyroid gland and posterior to the proximal right clavicle that was compatible with parathyroid adenoma. Preoperative ultrasonography revealed the suspected adenoma posterior to the right inferior thyroid lobe.

The patient consented to a resection of a parathyroid adenoma. The intraoperative PTH assay results showed a reduction of the PTH level from 165 to 22 pg/mL at 10 minutes after resection of the mass. The patient recovered well in the postoperative period, with return of calcium levels to 9.7 mg/dL (within the reference range). She was discharged home in improved condition. Results of her laboratory tests remained within reference ranges at the 3-month follow up.

Discussion

The original technetium Tc 99m sestamibi scan results were false-positive for a mediastinal parathyroid adenoma and
false-negative for an adenoma in the neck. The intraoperative drop in PTH levels and temporary resolution of abnormal laboratory values with resection of a mediastinal thymoma confounded the picture. This result drove us to perform immunohistochemical staining for PTH on the thymoma specimen, with strongly positive results. Finally, we repeated the technetium Tc 99m sestamibi scan after the first resection. The results demonstrated significant uptake in the true adenoma, findings that were equivocal before the thymoma resection.

**Imaging**

The sensitivity and positive predictive values of the technetium Tc 99m sestamibi scan are 82.1% and 93%, respectively. The protocol involves intravenous administration of the technetium Tc 99m sestamibi complex followed by single-photon emission CT or radiography. For the purposes of detecting a parathyroid adenoma, a 1- to 2-hour washout period allows the signal to fade from the thyroid gland as the complex “washes out” of the gland.

False uptake of the technetium Tc 99m sestamibi complex has been documented in benign and malignant tissues with high mitochondrial content. Most false-positive findings on technetium Tc 99m sestamibi scans are of thyroid disease (a 9% false-positive rate is reported by Piñero et al). However, other tissues, such as lung, brain, bone, carcinoid tumors, lymphoma, and thymomas, can also produce false-positive results.

Several case reports have described uptake in thymomas and other mediastinal tumors. Fiorella et al compared the histologic classification of thymomas with their uptake on technetium Tc 99m sestamibi-labeled single-photon emission CT. They used the data to generate a score comparing the tumor with normal tissue (T/N score). They found a statistically significant difference in T/N score when comparing low-risk thymoma and other benign tumors with high-risk thymoma, thymic carcinoma, and other malignant tumors. They concluded that the uptake correlates with the WHO classification and Masaoka stage. Following their protocol, we retrospectively calculated a T/N score for our patient. However, our findings did not correlate well with those of Fiorella et al. For a WHO classification type AB thymoma, their T/N mean (SD) score approximated 1.4 (0.07). The T/N score for our patient was 3.57, which would have correlated with a WHO classification of type C thymic carcinoma. Possible explanations for this finding include differences in imaging equipment and software.

In addition to the false-positive mediastinal parathyroid adenoma, the uptake on the technetium Tc 99m sestamibi scan resulted in a false-negative result for a cervical parathyroid adenoma. A retrospective review of the first technetium Tc 99m sestamibi scan showed very faint uptake that was not noted on initial interpretation. Previous studies report false-negative findings on technetium Tc 99m sestamibi scans attributed to ectopic glands, anatomic variability, low preoperative PTH levels, and low parathyroid weight. However, none of these attributions explain the false-negative finding in our case, leaving the suppressed uptake on the patient’s first technetium Tc 99m sestamibi scan unexplained.
This discussion reinforces caution in reading these scans when the clinical context is atypical. In our case, obtaining an ultrasonogram of the neck before the first surgical procedure would likely have identified the parathyroid adenoma and prompted a neck exploration. However, if we had obtained the ultrasonogram without a technetium Tc 99m sestamibi scan, the thymoma would have been missed. This possibility questions whether both scans should be standard in the workup of parathyroid adenomas. Given the rare entity discussed in this report, we find that altering the diagnostic algorithm for primary hyperparathyroidism to include both scans would be unnecessary. Instead, we advocate using a technetium Tc 99m sestamibi scan and an ultrasonogram in unclear cases.

Histological Findings and PTH Level
Early in our attempt to explain the abnormal drop in PTH level with resection of the thymoma, we explored the possibility of cross-reactivity between the PTH and PTH-related protein (PTHrP) assays. Parathyroid hormone and PTHrP are known to be secreted from adenomas, and PTHrP is secreted in low levels in many other tissues. In addition, PTH and PTHrP act at the PTH receptor at the amino-terminal domain. However, very little cross-reactivity occurs between the assays, making it unlikely that PTHrP would have played a role in this scenario.

Suppression of PTH-secreting parathyroid adenoma by an ectopic source of PTH or PTHrP has been reported. This result could explain the intraoperative drop in PTH level with the thymoma resection and the subsequent rise of PTH level during the next month. Although thymomas are associated with paraneoplastic syndromes in approximately one-third of cases and have a history of secreting PTHrP, only one case of a PTH-secreting thymoma has been reported. Rizzoli et al published a case in 1994 reporting the presence of a PTH-secreting thymoma. They documented the presence of the PTHrP in the thymoma through an immunoradiometric assay and the PTH messenger RNA (mRNA) transcript in the thymoma tissue via Northern blot analysis. In that report, they discussed four prior cases of PTH mRNA found in other tumors, including a primitive neuroectodermal malignant neoplasm, ovarian cancer, and small cell lung cancer. Triggiani et al in 2006 published a report of a PTH- and PTHrP-secreting lymphoepithaloid thymoma that presented in a patient with myasthenia gravis.

Given this information, we reviewed our pathology records for similar findings. No evidence of parathyroid adenoma on serial sections of the thymoma specimen was detectable. On staining for PTHrP, we found a significant presence of thymoma tissue via Northern blot analysis. In that report, they discussed four prior cases of PTH mRNA found in other tumors, including a primitive neuroectodermal malignant neoplasm, ovarian cancer, and small cell lung cancer. Triggiani et al in 2006 published a report of a PTH- and PTHrP-secreting lymphoepithaloid thymoma that presented in a patient with myasthenia gravis.

Conclusions
Mediastinal uptake on a technetium Tc 99m sestamibi scan should raise awareness of the rare occurrence of a thymoma and potentially a PTH-secreting thymoma. In these circumstances, we suggest ultrasonography of the thyroid and central neck be considered owing to the possibility of uptake suppression and a concurrent parathyroid adenoma. Given the rare occurrence of tumors like this one, alterations in the evaluation and treatment protocols for routine primary hyperparathyroidism are not recommended.

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