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A GASTROINTESTINAL STROMAL TUMOR IN A PATIENT WITH MULTIPLE ENDOCRINE NEOPLASIA TYPE 2A AND METASTATIC MEDULLARY THYROID CANCER TO THE OVARIES

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Abstract

Objective—To describe the first reported case of a patient with multiple endocrine neoplasia type 2A and a gastrointestinal stromal tumor, as well as the second reported case of metastatic medullary thyroid cancer to the ovary.

Methods—We present the clinical, imaging, surgical, and pathologic findings of the study patient and review the relevant literature.

Results—A 57-year-old woman with a clinical diagnosis of multiple endocrine neoplasia type 2A presented with a new mass in the right lower quadrant. Surgical exploration identified a 5-cm pedunculated small-bowel mass approximately 25 cm from the ileocecal junction, as well as bilaterally firm ovaries. Bilateral oophorectomy revealed medullary thyroid cancer in both ovaries and fallopian tubes. Pathology of the resected mass revealed a gastrointestinal stromal tumor of uncertain malignant potential, mitotic rate of 1/50 per high-power field, with positive staining for c-kit and smooth muscle actin and negative staining for CD34 and S-100.

Conclusions—This case is the first description of a gastrointestinal stromal tumor in a patient with multiple endocrine neoplasia type 2A, potentially representing a new paraganglioma/gastrointestinal stromal tumor syndrome. This case also highlights the possibility of the ovary as a metastatic site for medullary thyroid cancer.

INTRODUCTION

Mutations in protooncogenes have been identified in numerous tumor syndromes. Mutations in the *RET* protooncogene on chromosome 10, encoding a transmembrane receptor tyrosine kinase, has been linked to the development of multiple endocrine neoplasia type 2A (MEN 2A) syndrome. MEN 2A has a prevalence rate of 2.5 per 100 000. The clinical manifestations

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DISCLOSURE

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include medullary thyroid cancer (MTC) (>90%), pheochromocytoma (40%-50%), and parathyroid hyperplasia (10%-20%).

Like mutations in the *RET* protooncogene resulting in MEN 2A, mutations in *KIT* and *PDGFRA* (platelet-derived growth factor receptor, alpha polypeptide), both transmembrane tyrosine kinase receptors, have been associated with the formation of gastrointestinal stromal tumors (GISTs) (1). With an estimated incidence of only 11 to 14.4 cases per million persons in northern European populations (2-4), GISTs are the most common sarcoma of the gastrointestinal tract, most frequently involving the stomach (40%-60%) or small intestine (30%-40%) (5). GISTs are believed to originate from the interstitial cells of Cajal that control gut motility. Most GISTs have a gain-of-function mutation in the *KIT* protooncogene (1), while 5% have a constitutive activating mutation in the *PDGFRA* gene (6). Ninety-five percent of GISTs stain positive for CD117 antigen, an epitope of the *KIT* tyrosine kinase (7). Herein, we describe the first known association of MEN 2A and GIST. In addition, this patient had MTC metastasizing to the ovaries and fallopian tubes, highlighting the possibility of the ovary as a metastatic site for MTC.

CASE REPORT

A 57-year-old African woman presented in 1982 with a rapidly enlarging goiter. Fine-needle aspiration showed MTC with positive staining for calcitonin, and she had a concomitant serum calcitonin concentration of 98 000 pg/mL. The patient reported episodes of tachycardia at rest associated with headaches and diaphoresis that had increased in severity over the past year. Ultrasonography performed at admission showed a well-defined, 1.5-cm, spherical mass on the right adrenal gland, and findings from a biochemical workup during an episode of hypertension were consistent with pheochromocytoma. In 1984, she underwent a right adrenalectomy, and pathology confirmed pheochromocytoma.

That same year the patient underwent a total thyroidectomy and central neck node dissection. Pathology findings were consistent with MTC with extensive amyloid and vascular infiltration. Three years later, she had a left adrenal resection for an enlarged adrenal mass, and the final pathology confirmed pheochromocytoma. Intraoperatively, her liver was noted to be studded with lesions that were biopsied and were positive for MTC despite negative preoperative computed tomography and magnetic resonance imaging. After this second resection, the patient was maintained on hydrocortisone and fludrocortisone replacement.

The patient was given the clinical diagnosis of MEN 2A because of the presence of MTC and pheochromocytoma. Although genetic testing for *RET* mutations was not performed in the patient, the MEN 2A diagnosis was confirmed by the presence characteristic features in an older brother and paternal niece. A germline mutation in the *RET* gene (p.Cys634Ser in exon 11) was identified in the niece. The patient's father died at a young age of unknown causes. None of the patient's maternal relatives had any clinical manifestations of MEN 2A. None of her affected family members was known to have a GIST.

The patient was subsequently followed up for 20 years with surveillance imaging, which demonstrated stable metastatic disease to the liver, kidney, and spine. In 2005, a routine computed tomography scan for disease surveillance documented a questionable right lower-quadrant lesion. Follow-up computed tomography, magnetic resonance imaging, and ultrasonography suggested a right adnexal mass growing in size and changing from cystic to solid in nature. In 2007, the patient was taken to the operating room for exploration and anticipated hysterectomy and bilateral salpingo-oophorectomy. Surgical exploration identified a 5-cm, solid, smooth, noncommunicating, pedunculated small-bowel mass approximately 25 cm from the ileocecal junction that did not appear to communicate with the lumen. A small-

bowel resection and a side-to-side anastomosis with the Endo-GIA stapler were performed. Inspection of the pelvis revealed an infantile-appearing uterus and visually normal ovaries that were unusually firm on palpation. Peritoneal surfaces and the capsule of the ovaries demonstrated no evidence of metastases. Because of the firmness of the ovaries and the known history of metastatic MTC, total abdominal hysterectomy and bilateral oophorectomy were performed.

The patient's hospital course was uncomplicated, and she was discharged home on postoperative day 7. Anatomic pathology findings of both ovaries and fallopian tubes were positive for metastatic MTC (Fig. 1). The tumor cells in the ovary stained positive for amyloid with Congo red and were positive for synaptophysin, chromogranin, and calcitonin, and negative for inhibin, desmin, smooth muscle actin, and estrogen receptor. Pathology of the small-bowel mass showed a 5-cm GIST of uncertain malignant potential (Fig. 2) with a mitotic rate of 1/50 per high-power field. Immunohistochemistry demonstrated positive staining for c-KIT (CD117) and smooth muscle actin, which stains positive in 30% to 40% of GISTs. The tumor was negative for CD34 (a sialylated transmembrane glycoprotein found in hematopoietic progenitor cells and endothelial cells, which is expressed in 70% of GISTs) and S-100 (a neural cell marker, which is negative in 95% of GISTs).

DISCUSSION

To our knowledge, we are reporting the first association of MEN 2A and GIST. Recently, GISTs have been associated with other hereditary neoplasia and paraganglioma syndromes (8-11). For example, patients with neurofibromatosis may have a higher risk of GIST than the general population. One autopsy series identified GISTs in up to one-third of patients with neurofibromatosis type 1 (8). However, tumor tissue from these GISTs often lack both *KIT* and *PDGFRA* mutations (9,12), and these tumors are distinguished by their unique phenotype of multicentricity, location in the small intestine, morphology, and nonaggressive behavior (9).

GISTs have also been identified in paraganglioma syndromes. Carney triad occurs primarily in young women and is characterized by pulmonary chondroma, extra-adrenal paraganglioma, and gastric GISTs (10). The GISTs associated with Carney triad are not as aggressive as sporadic GISTs, with longer disease-free intervals and longer life expectancy (13). They occur exclusively in the stomach and present at a young age (7). In 2002, Carney and Stratakis described a familial paraganglioma and gastric stromal sarcoma syndrome that is distinct from Carney triad (14). This series of 12 patients exhibited either paraganglioma, gastric stromal sarcoma, or both, but did not exhibit pulmonary tumors, and the patients were not predominantly female.

In 2006, Perry et al described 3 cases of nonfamilial occurrences of abdominal paraganglioma and GISTs that did not exhibit the germline *SDHA*, *SDHB*, *SDHC*, *SDHD*, or *KIT* mutations that are generally associated with familial paraganglioma or GIST syndromes (11). Whether these cases are coincidental or could represent a new genetic syndrome or a variation of the Carney triad or the paraganglioma-gastric stromal sarcoma syndrome remains unknown.

The standard treatment of GIST is en bloc surgical resection leaving the pseudocapsule intact and maintaining sufficient resection margins. For metastatic disease, imatinib, a tyrosine kinase inhibitor first approved for treatment of chronic myelogenous leukemia, has become the standard of care. The median time for drug response is 12 to 15 weeks (5), with 65% to 70% of patients achieving partial response (15). In this patient's case, imatinib has not been initiated because of her limited disease with complete surgical resection.

Another interesting observation arising from this case is that metastatic MTC was identified in the ovaries and fallopian tubes. Metastatic tumors to the ovary have been reported in up to 21% of all ovarian malignancies and include lung, breast, renal, cervical, and gastrointestinal sources, among others (16,17). Metastasis of thyroid cancer to the ovary is uncommon; however, a few cases of papillary thyroid cancer have been reported (18,19). We considered MTC to the ovary in our patient because of her extensive metastatic disease. We recognize that this is atypical as only 1 report of metastatic MTC to the ovary has been published. Silverberg et al studied 54 autopsied cases of thyroid cancer and found only 1 medullary and 2 anaplastic thyroid carcinomas in the ovaries (20). We believe the hilar location of the MTC in this case suggests hematogenous dissemination rather than peritoneal or lymphatic spread, as direct extension from the neck seems impossible.

CONCLUSION

In summary, this case raises 2 interesting issues. The first is the ovary as a metastatic site for MTC, which has only been described once before in the literature. The second is whether MEN 2A could be classified as a syndrome that may include GISTs, and thus a new paraganglioma/GIST syndrome. The presence of a *RET* mutation in an affected family member raises the possibility that *RET* mutations may be causal for GIST, although coincidence is also a possibility. It would be of interest to look for similar activating *RET* mutations in other individuals with GISTs, occurring either alone or with paraganglioma syndromes, who do not harbor mutations in *KIT*, *PDGFRA*, or other known genes.

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Abbreviations

GIST, gastrointestinal stromal tumor; MEN 2A, multiple endocrine neoplasia type 2A; MTC, medullary thyroid cancer.

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Fig. 1.

Pathology of ovaries showing well-circumscribed tumors composed of small cells with round nucleoli and eosinophilic cytoplasm within both ovaries. The nuclei have stippled chromatin and small nucleoli. The trabeculae are separated by hyaline stroma, which stain positive for amyloid with Congo red. The tumor cells are positive for synaptophysin, chromogranin, and calcitonin and negative for inhibin, desmin, smooth muscle actin, and estrogen receptor. (Hematoxylin-eosin stain; original magnification $\times 150$.)

Fig. 2. Pathology of the gastrointestinal stromal tumor. *Panel A*, low magnification ($\times 100$). *Panel B*, higher magnification ($\times 150$). Higher magnification shows the tumor to be composed of spindle cells, with eosinophilic cytoplasm and rare mitotic figures. (Hematoxylin-eosin stain.)