Ectopic prolactin secretion is an extremely rare cause of hyperprolactinemia and should be suspected in a patient with severe hyperprolactinemia, negative pituitary magnetic resonance imaging (MRI), and absence of alternative explanations, such as drug-induced prolactin elevation in a setting of renal failure (1, 2). Described sources of ectopic prolactin include ectopic pituitary glands (mainly located in the sphenoid sinus and sphenoid bone) (3, 4) and conceptually similar cases of ectopic development of pituitary tissue within embryologically aberrant teratoma (5) as well as in hematological malignancies (acute lymphoblastic and myeloid leukemias) (6, 7). Two cases of perivascular epithelioid cell tumors (PEComas) with symptomatic hyperprolactinemia have been described previously, but in neither of those cases was ectopic prolactin secretion confirmed with positive immunohistochemistry of the tumor tissue (8, 9). Thus, ectopic production of prolactin by a solid tumor is not currently included in the differential diagnosis of hyperprolactinemia.

We report a first case of PEComa, where ectopic prolactin secretion was proven clinically and biochemically.
The tumor tissue stained positive for prolactin on immunohistochemistry and also expressed the human prolactin gene. Therefore, ectopic prolactin secretion should be considered as a diagnostic possibility in patients with neoplastic prolactin concentrations (>200 ng/mL) and normal pituitary MRI. This constellation of findings requires a search for a nonpituitary source of prolactin synthesis and secretion.

Case Report

A 47-year-old woman presented to our clinic with a 3-year history of amenorrhea, decreased libido, and galactorrhea. She denied any vision changes. The serum prolactin concentration was 1700 ng/mL, and other pituitary hormones and thyroid function tests were normal. Evaluation for macroprolactinemia was negative, and she did not take any medications capable of elevating prolactin concentrations. MRI of her pituitary gland revealed partially empty sella, but no tumor or infiltrative lesion. She was prescribed cabergoline 0.5 mg twice a week, but 1 month later, her prolactin remained high at 1900 ng/mL. Cabergoline was discontinued to look for alternative causes of hyperprolactinemia, and the patient was scheduled for reevaluation in 2 months. In the interim, she developed severe abdominal pain, and she was seen in the emergency department of a local community hospital. A computed tomography scan demonstrated a 17 × 13 × 8-cm right-sided heterogeneous abdominal mass abutting the distal stomach, proximal duodenum, and right colon (Figure 1).

The patient underwent urgent laparotomy with total excision of the mass. Within 1 month after surgery, her galactorrhea had resolved, her libido returned to normal, and she resumed regular menstrual periods. The prolactin level fell to 5 ng/mL and remained normal on follow-up.

We obtained a tissue block from the pathology service of the community hospital where the operation was performed.

Materials and Methods

Prolactin measurements

Serum prolactin was measured by the Ligand Laboratory at the University of Michigan Medical Center using Advia Centaur Prolactin chemiluminometric assay (Siemens Corp).

Immunohistochemistry

Immunohistochemistry was performed in formalin-fixed, paraffin-embedded 5-μm tissue sections, using antibodies against HMB-45 (mouse monoclonal, pH 8.5 antigen retrieval, prediluted; Dako), S-100 (rabbit polyclonal, prediluted; Ventana Medical Systems), MART-1, actin, EMA (mouse monoclonal, pH 8.5 antigen retrieval, prediluted; Ventana Medical Systems), desmin (mouse monoclonal, pH 8.5 antigen retrieval, prediluted; Cell Marque), cytokeratin AE1/AE3 (mouse monoclonal, protease, 1:200; Millipore), CD117 (rabbit monoclonal, pH 8.5 antigen retrieval, 1:100; Millipore), CD34 (mouse monoclonal, pH 8.5 antigen retrieval, 1:100; Dako), and prolactin (rabbit polyclonal, 1:600; Dako). All immunohistochemistry was performed on automated Ventana platform using the Ultraview DAB detection system.

Detection of prolactin expression using PCR

Total RNA was extracted from 3 × 10-μm scrolls of formalin-fixed, paraffin-embedded pituitary, adrenal, and PEComa tumor tissues using miRNeasy FFPE Kit (QIAGEN). The mRNAs were reverse-transcribed to cDNAs with random decamers following the manufacturer’s instructions (AM2043; Ambion). Expressions of the prolactin (PRL) and the internal control glyceraldehyde-3-phosphate dehydrogenase (GAPDH) genes were detected applying gene-specific primers: CATCAACAGCTGCCACACTT and CGTTTGGTTTGCTCCTCAAT (for PRL), and CCATGGAGAAGGCTGGGG and CAAAGTTGTCATGGATGACC (for GAPDH). PCR under went 40 cycles of 30-second denaturing at 95°C, 30-second annealing at 60°C, and 1-minute extension at 68°C. The PCR products were visualized in a 1.2% agarose gel with ethidium bromide staining.

Results

Pathological examination revealed nested epithelioid neoplastic cells with eosinophilic granular cytoplasm. In some areas, the tumor cells were arranged in a concentric fashion around blood vessels. The tumor was strongly positive for HMB45 and weakly positive for CD117, whereas it was negative for S100, MART-1, desmin, actin, EMA, cytokeratin AE1/AE3, and CD34—a pattern consistent with PEComa (10). Between 5 and 10% of the tumor cells were focally but strongly positive for prolactin on immunohistochemistry (Figure 2).
RT-PCR (Figure 3) identified prolactin mRNA in two known prolactin-secreting pituitary tumors (lanes 1 and 2), and there was no prolactin mRNA signal in a control sample from adrenal cortical carcinoma with negative prolactin immunohistochemistry (lane 3). A strong prolactin mRNA signal was identified in the abdominal PEComa from the patient (lane 4).

Equality of mRNA loading in all samples was confirmed by similar intensity of signals for GAPDH (Figure 3, lower panel).

Discussion

The diagnosis of a prolactinoma is usually fairly straightforward: a combination of a radiologically identifiable pituitary tumor and a serum prolactin level above 200 ng/mL establishes the diagnosis with an almost 100% certainty (11). Occasionally, drugs such as risperidone and metoclopramide may cause prolactin elevations above 200 ng/mL in patients with concomitant severe renal failure without evidence of an adenoma (1, 2).

However, there are extremely rare cases of marked hyperprolactinemia in the presence of normal MRI appearance of the pituitary gland. In those cases, ectopic prolactin secretion may be legitimately suspected.

As a rule, ectopic secretion of pituitary hormones (with the exception of ACTH) is very rare and may reflect different pathological processes. By far the most frequent causes are the tumors arising within the ectopic pituitary gland. The so-called “pharyngeal pituitary” is found routinely on autopsy, but these structures are as a rule endocrinologically quiescent (12). Ectopic pituitary glands are the remnants of anterior pituitary tissue left behind along the embryological migration of the Rathke’s pouch and can be encountered in the posterior pharynx, sphenoid sinus, or sphenoid bone (13). Prolactinomas located in the sphenoid sinus were reported in several patients, and some of them were described as being asymptomatic and discovered at autopsy, whereas others presented with classical symptoms of hyperprolactinemia and imaging showing a mass in the sphenoid sinus or sphenoid bone (3, 4, 14). Similarly, some teratomas and dermoid cysts were shown to contain aberrant pituitary tissue within their solid component, and the magnitude of hyperprolactinemia may be substantial, up to 1000 ng/mL, and accompanied by oligomenorrhea and galactorrhea (5). Several cases of lymphoma or acute lymphoblastic leukemia were reported to be accompanied by hyperprolactinemia, but in most cases, this finding could be attributed to stalk/hypo-
thalamic infiltration or involvement of the anterior chest (15–17). Only one case of acute lymphoblastic leukemia (6) and one documented case of acute myeloid leukemia with prolactin-producing blast cells have been described (7). The rarity of ectopic somatotrophinotropic hormone production is further exemplified by the paucity of cases of ectopic acromegaly. Melmed et al (18) provided conclusive evidence of ectopic GH secretion by a malignant pancreatic tumor, but this is the only example described thus far. Similarly, only one case of GH production by a lymphoma has been encountered (19).

Several earlier reports claimed the description of true ectopic prolactin secretion, but the diagnosis was not substantiated by evidence. Normalization of hyperprolactinemia after excision of renal cell carcinoma (20) was not confirmed by the demonstration of prolactin in the tumor cells, whereas immunohistochemical demonstration of prolactin synthesis and secretion by a gonadoblastoma was not accompanied by even a mild degree of hyperprolactinemia (21). Several reports suggested a high incidence of ectopic prolactin secretion by cervical and colon adenocarcinomas (22, 23), but subsequent studies failed to confirm even the occasional presence of such a phenomenon in these tumor types (24, 25). Two cases of PEComa, one with circulating prolactin of 269 ng/mL and another of 1239 ng/mL, have been reported, but surprisingly, neither tumor was positive for prolactin immunohistochemically (8, 9). Thus, the present case is the first documented instance of ectopic prolactin secretion by a solid extrapituitary malignant tumor.

The patient presented here exhibited the classic clinical syndrome of hyperprolactinemia: amenorrhea and galactorrhea. Analogous to the patient with ectopic GH secretion (18) who did not respond to classical central modulators of GH secretion (GHRH and TRH), our patient was completely insensitive to the central suppressor of prolactin secretion, the dopamine receptor agonist cabergoline. However, her hyperprolactinemia cleared rapidly after resection of an abdominal PEComa, and the clinical manifestations of hyperprolactinemia, ie, amenorrhea and galactorrhea, abated in parallel. The tumor contained prolactin-producing cells and expressed the human prolactin (PRL) gene. Thus, our data fulfill the main criteria defining ectopic hormone production and secretion. Because the tumor was excised urgently and in another hospital, we could not sample its blood vessels in search of the arteriovenous gradient or perform in vitro studies demonstrating prolactin synthesis by the neoplastic cells.

Immunohistochemical analysis of the tumor detected prolactin staining in 5–10% of the cells. Even if one assumes the lower estimate of prolactin-secreting cells in this tumor, ie, 5%, the total volume of “lactotrophs” in a $13 \times 8$-cm tumor would be equivalent to a 2-cm pure lactotroph neoplasm, in good agreement with 1700–1900 ng/mL concentrations of circulating prolactin. In the other two PEComas described earlier (8, 9), the tumors were labeled “prolactin-negative” by immunohistochemistry. The authors of one report postulated ectopic production of a prolactin-releasing or antidopaminergic substance (9). However, there might be alternative, simpler explanations to the reported immunonegativity of those tumors: assay performance or only focal expression of prolactin-producing cells. Also, the proportion of prolactin-secreting cells in these tumors might have been below the visual threshold for a pathologist to call them “prolactin-positive,” but sufficient to result in hyperprolactinemia of approximately 300 and 1200 ng/mL. Indeed, even if the proportion of prolactin-producing cells in the second case (9) was only 1%, the total mass of lactotrophs would be equivalent to an approximately 1.6-cm solid tumor. Re-evaluation of the original pathological material might be the only way to answer this question. If this finding is confirmed in a larger sample of PEComas, prolactin might be a circulating marker for these tumors.

In conclusion, we have presented the first fully documented case of ectopic prolactin production and secretion by a solid tumor. The cumulative clinical, biochemical, immunohistochemical, and molecular data strongly suggest that ectopic prolactin secretion does exist (25, 26) and that this diagnosis should be actively pursued in patients with neoplastic levels of circulating prolactin and a negative pituitary MRI.

Acknowledgments

We thank Michelle Vinco of the Molecular Pathology Research Laboratory (Department of Pathology, University of Michigan) for tissue procurement, RNA extraction, and cDNA preparation.

Address all correspondence and requests for reprints to: Ariel Barkan, MD, University of Michigan, 24 Frank Lloyd Wright Drive, G-1500, Ann Arbor, MI 48106. E-mail: abarkan@med.umich.edu.

Disclosure Summary: The authors have nothing to disclose.

References


