We report a case of gallbladder paraganglioma that was discovered during nonrelated surgery. Retrospective study disclosed a family history of pheochromocytoma. The occurrence of gallbladder paraganglioma in the presence of family history of endocrine neoplasia supports that gallbladder paraganglioma may indeed occur as a part of the multiple endocrine neoplasia syndrome. Gallbladder paraganglioma is a rare tumor, and so far to our knowledge only 6 cases have been reported in the literature. Three cases were discovered incidentally during cholecystectomy for cholelithiasis, 2 presented with right upper quadrant pain, and 1 manifested with gastrointestinal bleeding. We herein review all reported cases of paraganglioma of gallbladder and biliary system.

(Arch Pathol Lab Med. 2005;129:523–526)

During embryogenesis, neural crest cells migrate to diverse locations in the body and differentiate into chief and sustentacular cells, which are designated as paraganglia.

Paragangliomas are rare extra-adrenal tumors of the paraganglia, and they are found in association with sympathetic and parasympathetic nerves. Paragangliomas in the head, neck, and mediastinum are usually associated with the parasympathetic system and are chromaffin negative and nonfunctional. Extra-adrenal retroperitoneal paraganglia are usually associated with the sympathetic system and are chromaffin positive and functional.1 No difference in survival is noticed in functional versus nonfunctional paragangliomas. However, extra-adrenal tumors are more likely to be malignant than adrenal tumors.2,3

Paragangliomas can occur in a variety of locations including the orbit, nose, ear, carotid area, vagus nerve, larynx, mediastinum, retroperitoneum, organ of Zuckerkandl, urinary bladder, cauda equina, duodenum, prostate, cheek, and thyroid. Among the reported cases of gallbladder paraganglioma,4–7 the association with other endocrine neoplasias has not been well documented.

REPORT OF A CASE

A 36-year-old man was admitted for a Roux-en-Y gastric bypass procedure for morbid obesity. His medical history was significant for hypertension, obstructive sleep apnea, hypothyroidism, asthma, and depression. He had a history of cocaine intake and smoking in the past but denied any alcohol abuse. Physical examination was unremarkable except for morbid obesity. Results of routine admission laboratory tests, including liver function profile, were unremarkable. Two months prior to admission, the patient had experienced vague right upper quadrant discomfort. An ultrasound of the gallbladder at that time did not demonstrate stones or mass.

At operation, a round mass of 1.5-cm diameter was noted in the wall of the gallbladder. The gallbladder was otherwise normal in appearance. Cholecystectomy was performed, and frozen section of the mass demonstrated gallbladder paraganglioma and extensive cholesterolosis. Permanent sections confirmed the diagnosis of gallbladder paraganglioma. His pre-operative blood pressure was 170/98 mm Hg, and postsurgical blood pressure remained in a range of 134/76 to 142/78 mm Hg. This suggested that his hypertension might be related to the tumor. However, there was no record regarding changes in blood pressure postprandially or during the operation. Because the tumor was found incidentally during the gastric bypass surgery, serum norepinephrine or urinary vanillylmandelic acid levels were not measured. The patient’s postoperative course was uncomplicated, and he was discharged on the 6th day after admission. No further therapy was thought to be indicated. Retrospective follow-up study revealed no other tumor but disclosed a family history of pheochromocytoma in one of the patient’s siblings.

PATHOLOGIC FINDINGS

Grossly, the gallbladder measured 10.5 cm in length and 4.5 cm in maximum diameter. The serosal surface was smooth, shiny, and congested. A mass of 1.5 cm in diameter was palpable at the fundus of the gallbladder. On opening the gallbladder, the mucosa revealed diffuse cholesterolosis, and there was a well-circumscribed round intramural mass. The cut surface of the mass was tan-red and focally hemorrhagic, and it appeared to be situated within the wall without involving mucosal or serosal surfaces.

Microscopically, the tumor was highly vascular and completely surrounded by a thin fibrous capsule. The tumor cells were arranged in small islands formingzellballen nests (Figure 1, a). The alveolar nesting pattern is accentuated by reticulin stain (Figure 1, b). Individual cells were round to polygonal, with finely granular eosinophilic to amphophilic cytoplasm and centrally located nuclei. The cytoplasm was amphophilic to acidophilic, and there was variably accentuated periodicity. The nuclei were round to indented, with evenly distributed chromatin. The nuclei of the chief cells were centrally located, with eosinophilic cytoplasm. The sustentacular cells were oval to round, with eosinophilic cytoplasm and centrally located nuclei. A number of small veins were present within the tumor, and there was marked stromal fibrosis. The tumor cells were chromafin positive and immunohistochemically positive for synaptophysin. There was focal positivity for NSE and Chromogranin. The tumor cells were negative for S100, CD34, and CD31.
ovoid nuclei with stippled “salt and pepper” chromatin and small inconspicuous nucleoli. Grimelius stain demonstrates many distinct fine cytoplasmic argyrophilia. Occasional tumor cells contain globules positive for periodic acid–Schiff in the cytoplasm (Figure 1, c). There was no tumor necrosis or cellular pleomorphism, and the mitotic activity was very low. In addition to extensive cholesterolesis, chronic cholecystitis was present. The immunohistochemical stains for chromogranin and synaptophysin were strongly positive in the tumor cells (Figure 2, a), and stain for S100 was positive only in sustentacular cells (Figure 2, b). Stain for CD34 was positive only in vascular channels, and stains for keratin and smooth muscle actin were negative. On the basis of typical histopathologic and immunohistochemical findings, a diagnosis of gallbladder paraganglioma was made. There was no vascular or lymphatic invasion, and the serosal and surgical resection margins were free of the tumor.
and symptoms related to obstruction. Instead, this patient had jaundice, whereas the third case did not have any signs and symptoms related to gallbladder disorder (Table 1). Three of these 7 cases presented with signs and symptoms related to gallbladder paraganglioma, indicating that all 6 cases except Wolff’s reported tumors were nonfunctioning. Two of these cases presented with obstructive jaundice, whereas 1 tumor was located in the submucosa. In 2 cases, the tumor was present subserosally, whereas 1 tumor was located in the neck of the gallbladder. The authors attributed the absence of obstructive features to the early stage of the tumor. Farrell et al reported a nonfunctioning paraganglioma simultaneously involving the liver, gallbladder, common bile duct, celiac, and portal lymph nodes. The features of all these tumors are summarized in Table 2.

Biliary system paragangliomas are predominantly seen in females and are discovered in the fifth to sixth decade of life. Although they are usually small in size, the largest reported tumor was 5 cm in diameter. Because these tumors are nonfunctioning, they are typically discovered secondary to their complications, such as obstructive jaundice, right upper quadrant pain, and gastrointestinal bleeding, or incidentally during gallbladder or unrelated surgery. When found in the gallbladder, they are most commonly located in subserosa. Interestingly, all these tumors are nonfunctioning. Thus, they mimic chromaffin-negative extra-adrenal tumors found in the head, neck, and mediastinal region, as opposed to the extra-adrenal retroperitoneal paragangliomas.

So far, no familial association has been reported in any of the paragangliomas of the biliary system. To our knowledge, our patient is the first case of biliary system paraganglioma with a family history of multiple neuroendocrine neoplasms. Hereditary paraganglioma is a rare genetic disease characterized by development of mostly benign tumors in the head and neck regions. Familial paragangliomas may occur in the absence or presence of other familial disease syndromes such as multiple endocrine neoplasia (MEN), type 2A (most common); MEN, type 2B; von Recklinghausen disease; and von Hippel-Lindau disease. However, no other endocrine tumor or family history was described in any of the reported cases.

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**COMMENT**

Review of all 7 reported cases (including our case) of gallbladder paraganglioma indicates that all 6 cases except ours presented with signs and symptoms related to gallbladder disorder (Table 1). Three of these 7 cases presented with cholelithiasis, and paraganglioma was an incidental finding. Two cases presented with upper abdominal pain, and a mass was seen on radiologic investigation. The sixth case presented with recurrent hematemesis from a cholecystoduodenal fistula, which resulted from scarring secondary to their complications, such as obstructive jaundice, right upper quadrant pain, and gastrointestinal bleeding, or incidentally during gallbladder or unrelated surgery. When found in the gallbladder, they are most commonly located in subserosa. Interestingly, all these tumors are nonfunctioning. Thus, they mimic chromaffin-negative extra-adrenal tumors found in the head, neck, and mediastinal region, as opposed to the extra-adrenal retroperitoneal paragangliomas.

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pel-Lindau syndrome.\textsuperscript{11} They are most commonly observed after the third decade of life, although they can be seen in the early teen years. Another characteristic feature of familial tumors is multicentricity and bilaterality. A peculiar pattern of inheritance called \textit{genomic imprinting} has been seen in Dutch families. The disease gene is mapped to approximately 6Mb critical region on chromosome band 11q23 (\textit{PGL1}) and has shown deletion at the involved site.\textsuperscript{12}

Because extra-adrenal tumors are more commonly malignant than adrenal tumors, gallbladder paraganglioma should not be misinterpreted as a secondary deposit, specifically in the setting of MEN syndrome, where multiple tumors are present. Distinguishing malignant tumors from benign paraganglioma is not histologically easy. None of the suggested histologic features can independently predict the biological behavior of tumors. However, coarse nodularity, absence of hyaline globules positive for periodic acid–Schiff, and an extra-adrenal location are known to be suggestive of a malignant nature. Other features suggestive of malignant behavior are alveolar pattern, decrease in sustentacular cells, extra-adrenal location, high mitotic count (3/30 per high-power field), large size of the tumor, hemorrhage and tumor necrosis, male sex, local aggressiveness, multicentricity, bilaterality, pleomorphism, and capsular and vascular invasion. Distant metastasis is the most reliable and definitive indicator of malignancy.\textsuperscript{3,13} DNA ploidy studies have suggested that benign tumors can be euploid or aneuploid, whereas malignant tumors are aneuploid.\textsuperscript{14}

Primary gallbladder paragangliomas theoretically arise from primordia of hepatic plexus, which innervates the gallbladder, and are formed from sympathetic and parasympathetic fibers of the left vagus nerve and celiac plexus.\textsuperscript{4} It is important to realize that primary gallbladder paraganglioma, although rare, may occur, and it should be considered in the differential diagnosis of gallbladder lesions. A careful search should be carried out, as in this case, for the possible association with MEN syndrome.

\textbf{References}
\begin{enumerate}
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