A Case of Hemorrhagic Gallbladder Paraganglioma Causing Acute Cholecystitis

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Gallbladder paraganglioma is a very rare tumor and so far only a few cases have been reported. Most of these were asymptomatic and were found incidentally during operation. Recently, we experienced a gallbladder paraganglioma that gave rise to hemorrhage, which in turn caused acute cholecystitis. Our case involved a 45 year-old female patient complaining of an intermittent right upper abdominal pain. After a preoperative evaluation, cholecystectomy and lymphadenectomy were performed under the impression of gallbladder cancer with acute cholecystitis. Postoperative pathologic examination revealed a hemorrhagic gallbladder paraganglioma accompanied by acute cholecystitis. Immunohistochemical staining of the chief cells for neuron specific enolase, chromogranin and synaptophysin were positive. Sustentacular cells also stained positively for S100 protein.

Key Words: Paraganglioma, gallbladder, acute cholecystitis

INTRODUCTION

The paraganglion system, which executes neuroendocrine functions in association with sympathetic or parasympathetic system, is composed of neuroepithelial cell collections. The most representative organ is the adrenal medulla, and extra-adrenal paraganglion cell nests are distributed in the head, neck, mediastinum and retroperitoneum along the aorta. Histologically, round or polygonal epithelioid cells form small nests in Zellballen patterns, which characteristically appear to be encircled by supporting sustentacular cells and elaborate vasculature. Paraganglioma is a tumor arising from the paraganglion cells and includes pheochromocytoma, which occurs in the adrenal medulla. Some paragangliomas are functional and induce clinical symptoms by secreting hormones, such as catecholamines. Paraganglioma in the gall bladder is extremely rare and only few cases have been reported. All reported cases were discovered incidentally and had no particular symptoms or signs. Interestingly, our case gave rise to hemorrhage into the gallbladder, which in turn caused acute cholecystitis.

CASE REPORT

A 45-year-old female patient was admitted to our hospital complaining of an intermittent abdominal pain in the right upper quadrant, which began one month prior to admission. There were no remarkable signs or symptoms related to hypertension in the past. At admission, the patient did not present symptoms, such as jaundice, nausea or fever. Physical examination showed a blood pressure of 100/70 mmHg, a pulse rate of 70/minute, and a body temperature of 36.5°C. There was a tenderness, but no rebound tenderness, in the right upper quadrant of the abdomen. The results of laboratory test were WBC 9200/µm³, hemoglobin 8.8 g/dl, total serum bilirubin 0.8 mg/dl, AST/ALT 361/183 IU/L, ALP 817 IU/L and CEA 1.52 ng/ml. An enhanced mass on the wall of the gallbladder and diffuse thickening of the gallbladder wall were observed by abdominal computed tomography (Fig. 1), and endoscopic ultrasound examination showed a slightly hyperechoic solid mass in the fundus of the gallbladder (Fig. 2). Under the suspicion of a
gallbladder cancer accompanied by acute cholecystitis, exploratory laparotomy was performed. The gallbladder was 13.5 × 4.5 × 3.0 cm in size and the serosal surface was pinkish tan and focally hemorrhagic. On opening the gallbladder, it was found to be filled with concentrated bile juice and blood and there was a well-demarcated round tumor (2.5 cm in diameter) arising from the wall. It had a lobular, beefy, red to brown spongy appearance with a necrotic and hemorrhagic surface on the luminal side. The remaining mucosa of gallbladder was greenish yellow and slightly atrophic, the wall of the gallbladder was thickened and edematous (Fig. 3), and there were multiple stones within the gallbladder. The common bile duct was compressed due to gallbladder distention but it was patent and without stones. Histological examination of a frozen slice was carried out after performing cholecystectomy. With a report of suspicious malignancy, additional lymphadenectomy around the hepatoduodenal ligament was performed. However, permanent pathological examination revealed a gallbladder paraganglioma accompanied by cholecystitis. On microscopic study, round or polygonal epithelioid tumor cells were observed arranged in small nests surrounded by delicate vasculature (Fig. 4). The nuclei were centrally located and had finely clumped chromatins, and the cytoplasm had either an amphophilic or eosinophilic appearance. Focal nuclear atypia and vascular invasions were occasionally seen and the periphery of the tumor showed an infiltrative growth pattern (Fig. 5 and

Fig. 1. Abdominal CT showed an eccentric, highly enhanced mass (arrows) in the wall of the gallbladder and diffuse thickening of the gallbladder wall.

Fig. 2. Endoscopic ultrasonography showed an intraluminal hyperechoic solid mass (arrows) in the wall of the gallbladder.

Fig. 3. Cut section of the gallbladder showed a well-defined tumor in the wall (P, paraganglioma.).

Fig. 4. Microscopic findings of the tumor showing a Zellballen pattern (H & E, ×40).
6). It was difficult to determine malignancy potential of the tumor, and clinical follow-up was believed necessary. To further confirm the neuroepithelial origin of the tumor, immunohistochemical staining was performed upon its major cellular components using antibodies against neuron specific enolase (1:50, DAKO, CA, USA), chromogranin (1:100, DAKO, CA, USA) and synaptophysin (predilution, DAKO, CA, USA) (Fig. 7). All proved positive. The sustentacular cells also stained positively for S100 protein, using anti-S100 antibody (1:500, ZyMed, CA, USA) (Fig. 7). These findings firmly establish the diagnosis of gallbladder paraganglioma. In order to determine tumor multiplicity and the presence of metastasis, a 123I-MIBG study was performed but findings were negative. Her postoperative course was uneventful and the patient has been under observation on an outpatient basis.

**DISCUSSION**

Paraganglioma is a tumor that arises from the paraganglion where there are collections of neural crest cells. These are related to autonomic nervous system, which is found ubiquitously in the body. The tumors are subdivided into pheochromocytoma, which develops in the adrenal gland, and paraganglioma, which occurs in the extra-adrenal paraganglion system. It is known that paragangliomas occur mainly in the carotid body, vagus nerve, mediastinum and the retroperi-

toneum around the organ of Zuckerkandl, and rarely in the nasopharynx, orbit, thyroid, duodenum, cauda equina, urinary bladder and so on.\(^{12}\) Gallbladder paraganglioma was first reported by Miller et al.\(^{3}\) in 1972. In this particular case, a 3 cm-sized gallbladder paraganglioma was discovered during an operation on refractory duodenal ulcer. Since then, Freschi and Sassi\(^{3}\) reported an incidental gallbladder paraganglioma, and Ferrell et al.\(^{5}\) reported upon non-functioning paragangliomas simultaneously involving the liver, gallbladder, common bile duct and the celiac and portal lymph nodes. Hitanant et al.\(^{6}\) discovered and reported a paraganglioma of the common hepatic duct in a patient admitted with a complaint of obstructive jaundice. The majority of reported gallbladder paragangliomas were found incidentally during operations for other diseases, rather than because of symptoms arising from the paragangliomas. Our case was discovered during a preoperative diagnostic study undertaken to find the cause of a right upper abdominal pain. As for the cause of cholecystitis, it seemed that hematoma arising from tumor bleeding led to a cystic duct obstruction and acute cholecystitis. The tumor was initially suspected as a carcinoma because frozen biopsy section showed cellular atypia, focal vascular invasion and peripheral invasive tumor growth. Moreover, gallbladder paraganglioma was not expected, because it is a very rare tumor arising from the gallbladder. Although the functionality of our case was not ascertained by biochemical study, the fact
that there were no remarkable symptoms before the surgery and no fluctuation of blood pressure during operation indicated that it was a non-functional paraganglioma. Paraganglioma has unique pathological features wherein the tumor has well-defined nests made up of round or polygonal epithelioid cells. These are arranged in a 'Zellballen' pattern and surrounded by sustentacular cells with delicate fibrovascular stroma. Compared to normal paraganglion, paraganglioma has a larger 'Zellballen' pattern and its constitutional cells are larger and atypical. The criteria of malignancy are controversial to the extent that the only clear basis for malignancy is metastasis. Although malignancy in pheochromocytoma is known to be about 10%, several studies conducted over a long-term follow-up have actually reported higher incidences. Also, a higher incidence of malignancy or a more aggressive clinical course has been reported in extra-adrenal paraganglioma than in pheochromocytoma. Linnola et al. reported that extra-adrenal location, coarse nodularity, confluent necrosis, the absence of hyaline globules and decreased expression of neuropeptides, could give a preview of malignancy. The paraganglioma in our case was well encapsulated and well-differentiated, and it positively reacted immunohistochemically to stains for neuron specific enolase, chromogranin, synaptophysin and S100. On the other hand, focal tissue necrosis, infiltrative growth and vascular invasion, which are suggestive of malignancy, were also shown. Thus, it could not be pathologically determined whether the tumor was benign or malignant. Further follow-up studies and observations were thought to be necessary. At least, the possibility of multiple lesions could be excluded, since there were no positive findings in the postoperative ¹¹¹-MIBG study.
REFERENCES


