

Case Report



Gallbladder Paraganglioma

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Abstract

A 34-years-old married middle-class housewife without diabetes, hypertension or betel-nut- chewing hailing from Manikganj, Dhaka; came with the outside diagnosis as neuroendocrine tumor of the gallbladder to the Oncology Department of Khwaja Yunus Ali Medical College and Hospital (KYAMCH). She was admitted in the hospital with complaints of upper abdominal pain, abdominal bloating, weakness, anorexia, nausea and heartburn while taking fatty food. According to her Ultrasonography (USG) of the abdomen, a soft tissue mass was found in the gallbladder with unremarkable routine blood examination including tumor markers. She underwent open cholecystectomy with the suspicion of cancer. Grossly, gallbladder measures 7.0x 5.0 cm with 0.3 cm wall thickness and on opening a polypoid nodule is found. Before treatment on request from the Oncology Department of KYAMCH, all slides were reviewed and a histopathological diagnosis of paraganglioma was made on the basis of organoid, nested or lobules (Zellballen pattern) of tumor cells in the lamina propria surrounded by a prominent fibrovascular stroma. Atypical mitoses, tumor necrosis, lymphovascular or perineural invasion was not found. The IHC reveals diffuse and strong positive reactions to NSE and CD56 for chief cells and strong positive reaction to S-100 protein for sustentacular cells. The epithelial tumor was ruled out by CK negative reaction. Therefore, the diagnosis of paraganglioma of the gallbladder was established. Because of the positive reaction to sustentacular cells, the neuroendocrine tumor has been excluded. To our knowledge, this type of case has not been reported in our country. On clinical follow-up the patient was found healthy.

Keywords: Gallbladder, Neuroendocrine tumor, Paraganglioma, Sustentacular cells, Zellballen pattern

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Introduction

Paraganglia differentiate from neural crest cells during the embryonic period. Paragangliomas are unusual neoplasms originating from paraganglia. The paraganglion system consists of two cell types, they are chief cells and sustentacular cells.¹ Paragangliomas are subdivided into adrenal (pheochromocytoma) and extra-adrenal. Extra-adrenal paragangliomas are rare tumors of extra-adrenal paraganglion system and they are found in association with sympathetic and parasympathetic nerves. It 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.²

Primary gallbladder paraganglioma (GP) 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.³ Paragangliomas are very rare in the gallbladder. Only 13 cases of GP have been reported in the literature so far.¹⁻¹¹ We aimed to present a non-functional gallbladder paraganglioma.

Case Presentation

A 34-years-old woman without diabetes and hypertension was admitted in the Oncology Department of Khwaja Yunus Ali Medical College with the outside diagnosed as a case of neuroendocrine tumor of gallbladder. Her chief complaints were upper abdominal pain, bloating and heartburn during taking fatty food. Her medical history and physical examinations were uneventful. Results of routine blood tests including tumor markers were unremarkable. The USG of the abdomen reveals a soft tissue mass in gallbladder. Then she had undergone open cholecystectomy with the suspicion of cancer.

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Macroscopically, the gallbladder measured 7.0X5.0 cm with wall thickness of 0.3 cm. On opening, it showed a 3.5 cm polypoid nodule protruding from the mucosa into the lumen which was 2.0 cm away from resection margin. The remaining mucosa was unremarkable. Microscopically, the submucosal tumor was highly vascular and completely surrounded by a thin fibrous capsule. The tumor cells were arranged in organoid, nested or lobules of small islands forming Zellballen pattern. Individual cells were round to polygonal with finely granular eosinophilic to amphophilic cytoplasm and centrally located ovoid nuclei with stippled "salt and pepper" chromatin. There were no tumor necrosis, cellular pleomorphism, lymphovascular and perineural invasion or atypical mitosis. The overlying mucosa was unremarkable. In addition to this tumor, feature of chronic cholecystitis was present.

Histologically, the tumor was diagnosed as paraganglioma of the gallbladder (Figure: 1 & 2).

To further confirm the neuroepithelial origin of the tumor, immunohistochemical staining was performed. NSE and CD-56 revealed strong and diffuse positive reaction to chief cells (Figure: 3 & 4) and S-100 showed strong positive reaction to sustentacular cells (Figure: 5). Epithelial tumor was ruled out by CK negative reaction (Figure: 6). These findings firmly established the diagnosis of gallbladder paraganglioma. On clinical follow up at 8 weeks, patient was found healthy.

Discussion

Paragangliomas are subdivided into adrenal that is pheochromocytoma and extra-adrenal paraganglioma developing in the extra-adrenal paraganglion system. Extra - adrenal paragangliomas are rare tumors of the paraganglion system 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.¹²

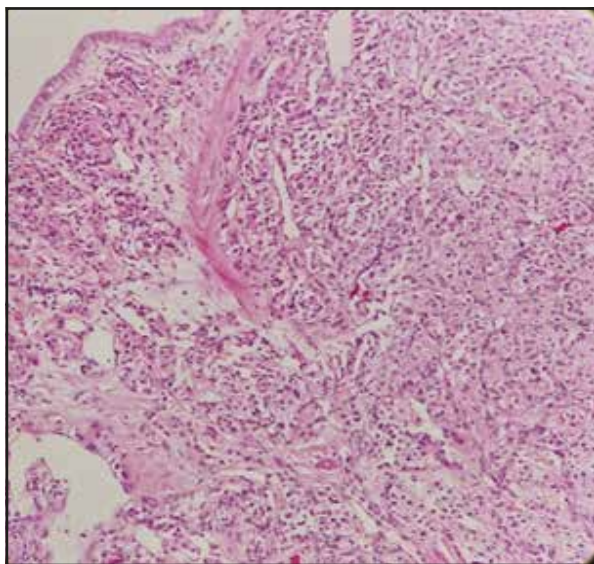


Fig. 1: Organoid proliferation arranged in nests and lobules with prominent vascular network X10.

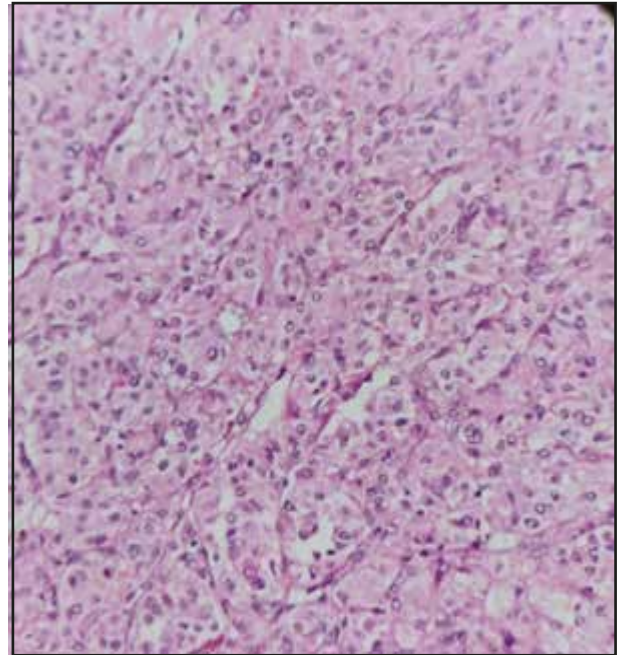


Fig. 2: Presence of two cell types: Chief cells and sustentacular cells X 40.

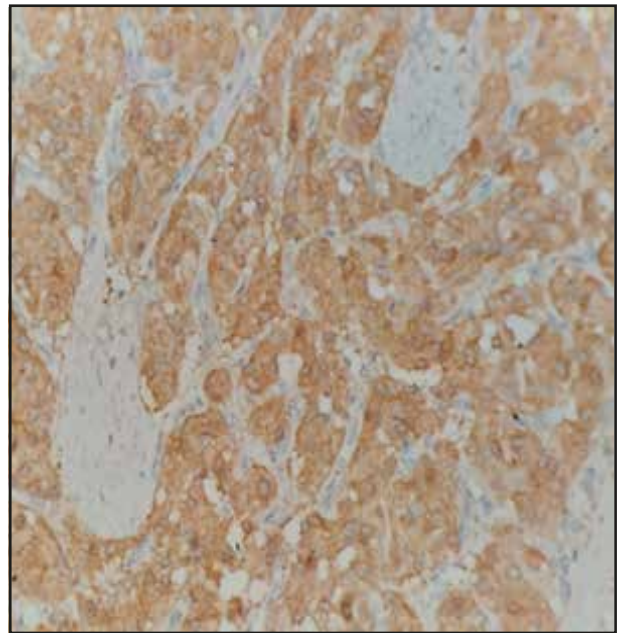


Fig. 3: Chief cells showing prominent immunostaining for NSE X 40.

No difference in survival is noticed in functional versus nonfunctional paragangliomas. However, extra-adrenal tumors are more likely to be malignant than adrenal tumors.³

Paraganglioma rarely occurs in the biliary system. Only 13 cases of GP have been reported in the literature so far (Table: I). In 1972, Miller et al. reported the first case of GP.⁴

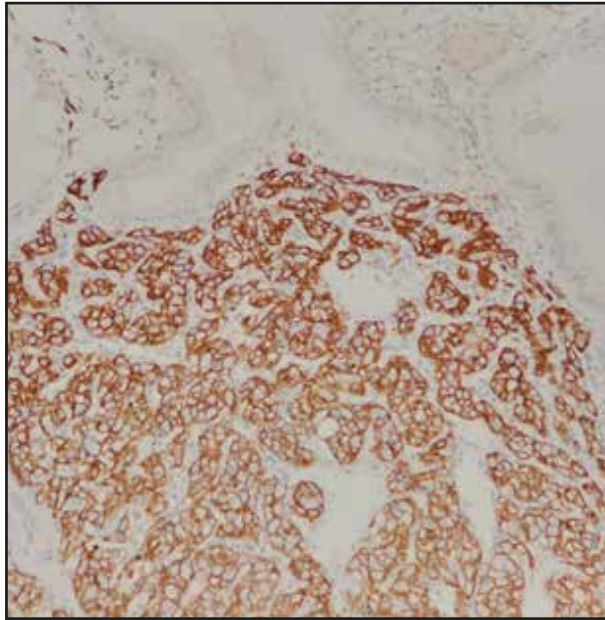


Fig 4: Chief cells showing prominent immunostaining for CD56 X 40.

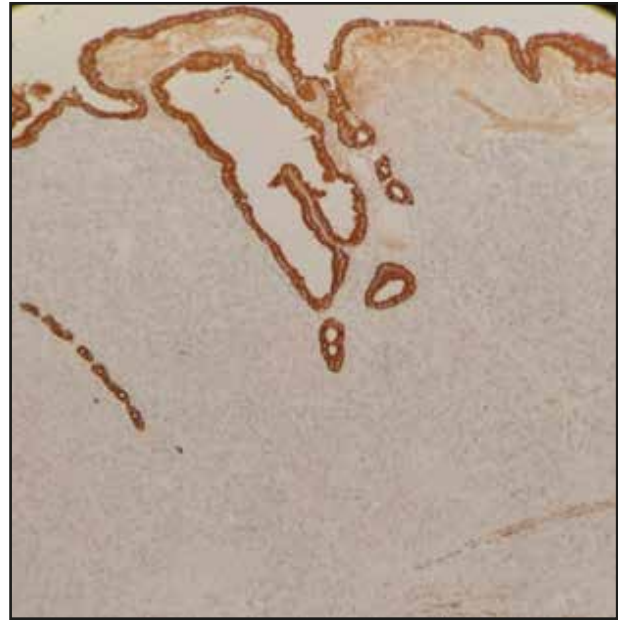


Fig. 6: Lining epithelium showing prominent immunostaining for Cytokeratin and tumor cells are negative X 20.

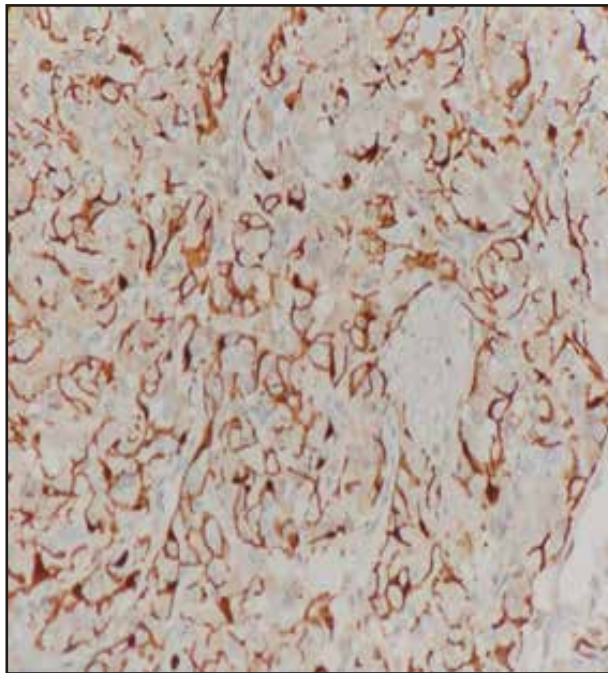


Fig. 5: Sustentacular cells were immunoreactive for S100 protein X 40.

Most of the cases including our case were present with upper abdominal pain associated with cholelithiasis or chronic cholecystitis except three cases, those were in addition to pain have features of recurrent hematemesis and tumor bleeding.

According to the literature, gallbladder paraganglioma is more common in females than in males (10 females vs. 3 males). It usually occurs in middle- aged patients (range: 32–67 years) (Table 1). In terms of tumor size, it is usually small, measuring 3.5 cm in diameter (range: 0.25–3.5 cm). Our case fulfilled all the criteria.

In 7 cases tumor were located in the subserosal region and 3 cases location were unknown. Only 2 cases and in our case tumor is located in the submucosal region.

Mehra and Chung-Park have reported a case of GP with a family history of pheochromocytoma and they suggest that it might occur as a part of multiple endocrine neoplasm syndrome.⁸ However, other cases of GP including our case were not associated with multiple endocrine neoplasm syndrome.

Laboratory examinations and imaging studies such as abdominal USG, CT, and MRI are usually unhelpful because GP presents no specific findings. Therefore, almost all GP cases were diagnosed incidentally based on histopathological and IHC findings after cholecystectomy.

In immunohistochemical staining, paraganglioma is positive for neuroepithelial markers (NSE, CD-56, Synaptophysin, Chromogranin).

Table 1. Summary of reported cases of gallbladder paraganglioma

Case no	Reference	Age /sex	Clinical findings	Imaging study	Size	Location	Treatment
1	Miller et al. (1972) [4]	67/ M	Recurrent hematemesis, tumor bleeding, cholecystoduodenal fistula	Duodenal ulcer	3	-	Cholecystectomy
2	Wolff (1973) [5]	32/ F	Cholelithiasis/CC	NM	NM	Subserosal	Cholecystectomy
3	Wolff (1973) [5]	52/ F	Cholelithiasis/CC	NM	NM	Subserosal	Cholecystectomy
4	Wolff (1973) [5]	59/ F	Cholelithiasis/CC	NM	NM	Subserosal	Cholecystectomy
5	Hirano (2000) [6]	58/ F	Right hypochondrial pain	Mass in the neck of GB	1.3X 0.9	Submucosal	Cholecystectomy
6	Cho et al. (2001) [7]	45/ F	Right hypochondrial pain, tumor bleeding, CC	Mass in the fundus of GB	NM	-	Cholecystectomy
7	Mehra and Chung - Park (2005) [8]	36/ M	None/ CC	Normal	1.5	Subserosal	Cholecystectomy
8	Ro dríguez - Merchán et al. (2006) [9]	50/ F	Right hypochondrial pain. CC	Intra and extra - hepatic biliary dilatation	1.0	Subserosal	Cholecystectomy
9	Ece et al. (2014) [1]	57/ F	Right hypochondrial pain	Solid mass in the neck of GB	1.8	Serosa & muscularis propria	Cholecystectomy
10	AlMarzooqi et al. (2018) [10]	-	Right hypochondrial pain	Early cholecystitis	0.25	Cystic duct	Cholecystectomy
11	Abdul Sater et al. (2019) [11]	36/ M	HTN, tinnitus, bilateral carotid mass	T2 hypertense lesion with arterial enhancement	2.2	Submucosa & muscularis propria	Cholecystectomy
12	D'John and Jabbar (2020) [3]	63/ F	Recurrent biliary colic exacerbation	Mildly dilated GB	<1.0	Subserosal	Cholecystectomy
13	Song SH et al. (2021) [2]	48/ F	Intermittent abdominal pain	Hemorrhage within the GB	1.6	-	Cholecystectomy
14	Present case	34/ F	Upper abdominal pain	Soft tissue mass within the gallbladder	3.5	Submucosal	Cholecystectomy

Cholecystectomies were performed for all reported cases including our case of GP. No tumor recurrence or metastasis was noted at eight weeks after operation.

However, further clinical studies with a large number of GPs are needed in the future.

Conclusion

Gall bladder paraganglioma is a rare tumor that is difficult to diagnose before surgery. It can be diagnosed based on histopathological and immunohistochemical findings. Simple cholecystectomy is suggested as an appropriate treatment. It should be considered in the differential diagnosis of gallbladder lesions.

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References

1. Ece İ, Alptekin H, Celik ZE, Şahin M. Gallbladder paraganglioma. *Ulus Cerrahi Derg* 2014; 31: 244-46.
2. Song SH, Cho CK, Park EK, Kim HJ, Hur YH, Koh YS, Lee YH. Gallbladder paraganglioma with hemorrhage: A case report and literature review. *Ann Hepatobiliary Pancreat Surg*. 2021 Nov 30; 25(4): 566-70.
3. D'John M, Jabbar F. Primary gallbladder paraganglioma: a case report and review of literature. *Int J Surg Case Rep* 2020; 75: 451-53.
4. Miller TA, Weber TR, Appelman HD. Paraganglioma of the gallbladder. *Arch Surg* 1972; 105: 637-39.
5. Wolff M. Paraganglioma of the gallbladder. *Arch Surg* 1973; 107: 493.
6. Hirano T. Paraganglioma of the gallbladder: report of a rare case. *Am J Gastroenterol* 2000; 95: 1607-8.
7. Cho YU, Kim JY, Choi SK, Hur YS, Lee KY, Kim SJ, et al. A case of hemorrhagic gallbladder paraganglioma causing acute cholecystitis. *Yonsei Med J* 2001; 42: 352-56.
8. Mehra S, Chung-Park M. Gallbladder paraganglioma: a case report with review of the literature. *Arch Pathol Lab Med* 2005; 129: 523-26.
9. Rodriguez-Merchan B, Lozoya R, Allende E, Mesa J. Paraganglioma of the gallbladder. *Med Clin (Barc)* 2006; 127:58.
10. AlMarzooqi R, AlJaberi L, Rosenblatt S, Plesec T, Berber E. A rare case of paraganglioma of the cystic duct. *Int J Surg Case Rep* 2018; 52:16-19.
11. Abdul Sater Z, Jha A, Mandl A, Mangelen SK, Carrasquillo JA, Ling A, et al. Gallbladder paraganglioma associated with SDHD mutation: a potential pitfall on 18F-FDOPA PET imaging. *Nucl Med Mol Imaging* 2019; 53:144-47.
12. Rajabi M, Rajabi P, Helarpour M, Raanai M. Paraganglioma of gallbladder: a case report. *The American Journal of Case Reports*. 2008; 9: 220-23