A rare case of paraganglioma of the cystic duct

Raha AlMarzoqi a,⁎, Loay AlJaberi a,⁎, Steven Rosenblatt a, Thomas Plesè c, Eren Berber d

a Department of General Surgery, Cleveland Clinic, 9500 Euclid Ave., Cleveland, Ohio, 44195, United States
b Al-Quds University School of Medicine, East Jerusalem, Palestine
c Department of Pathology, Cleveland Clinic, 9500 Euclid Ave., Cleveland, Ohio, 44195, United States
d Department of Endocrine Surgery, Cleveland Clinic, 9500 Euclid Ave., Cleveland, Ohio, 44195, United States

A R T I C L E   I N F O

Article history:
Received 2 September 2018
Received in revised form
19 September 2018
Accepted 22 September 2018
Available online 1 October 2018

Keywords:
Case report
Cystic duct
Neuroendocrine tumor
Paraganglioma

A B S T R A C T

INTRODUCTION: Biliary system paragangliomas are rare neuroendocrine tumors of embryonic neural crest origin. The majority is asymptomatic and incidentally found due to gallbladder functional disorders. Herein, we present a non-functional, 2.25 mm focus in the cystic duct, which to our knowledge, is the first reported paraganglioma of the cystic duct.

PRESENTATION OF CASE: The patient presented to the Emergency Department complaining of a sudden-onset, right upper abdominal and epigastric pain. Ultrasound and Computed Tomography were both consistent with signs of early cholecystitis. Laparoscopic cholecystectomy was performed without major complications. In addition to cholelithiasis and chronic cholecystitis, pathological examination reported a neuroendocrine proliferation in the cystic duct measuring 2.25 mm favoring paraganglioma. Incidentally, the patient is unique in that they were also found to have an adrenal nodule and a normocalcemic primary hyperparathyroidism that raised suspicion for an underlying endocrinopathy. Nevertheless, genetic testing was negative.

DISCUSSION: Extensive literature review demonstrates only nine cases of gallbladder paraganglioma, and three cases of hepatic ducts paraganglioma, but no cases of paraganglioma occurring at the cystic duct. Although a gene mutation and syndrome was not identified in the patient, the fact that an adrenal nodule and normocalcemic primary hyperparathyroidism were present, suggests that a complete hormonal workup should be obtained in these patients.

CONCLUSION: It is important to realize that biliary system paragangliomas, although rare, may occur. As they have an association with multiple endocrine neoplasia syndrome, a thorough endocrine investigation should be made.

Published by Elsevier Ltd on behalf of IJS Publishing Group Ltd. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

1. Introduction

Paragangliomas are rare neuroendocrine tumors of neural crest origin that arise from chromaffin cells. Paragangliomas can be potentially found anywhere along the paravertebral axis from their predominant location at the base of the skull and neck to the pelvis [1]. Pheochromocytoma and carotid body tumor are the two most common types of paragangliomas, which occur in the adrenal medulla and at the bifurcation of the carotid artery, respectively; however, remaining paragangliomas are usually retroperitoneal in origin, and found in the sympathetic or parasympathetic ganglia [1,2]. Most paragangliomas are asymptomatic and present as a painless mass [1]. While all can potentially secrete hormones such as catecholamines due to their origin from chromaffin cells, only a small percentage of cases are clinically significant and evoke systemic symptoms [1]. Biliary system paragangliomas are predominantly seen in females in the fifth to sixth decade of life [3]. These tumors are typically discovered incidentally during gallbladder or unrelated surgery, or secondary to complications such as obstructive jaundice, right upper quadrant pain, and gastrointestinal bleeding [3]. Herein, we present a non-functional, 2.25 mm focus in the cystic duct, which to our knowledge, is the first reported paraganglioma of the cystic duct. This work has been reported in line with the SCARE criteria [4].

2. Presentation of case

A patient with a past medical history of atrial fibrillation, hypertension, and hyperlipidemia and no past surgical history walked into the Emergency Department of an academic institute complaining of a sudden-onset, sharp, right upper abdominal and epigastric pain radiating to the back. Family history was negative and social history did not include any tobacco, alcohol, or drug misuse. On physical examination, the patient was tender in the right upper quadrant. On imaging, a right upper quad-

* Corresponding author at: Apartment 522, 10001 Chester Ave., Cleveland, Ohio, 44106, United States.
E-mail address: rahaalnlive.com (R. AlMarzoqi).
rant ultrasound showed signs of early cholecystitis (Fig. 1) and computed tomography of the abdomen showed gallstones and distended liver bile ducts, distended gallbladder with wall thickening, edema, and a mild surrounding inflammation consistent with the ultrasound findings (Fig. 2). Anti-coagulation was held and the patient underwent an uncomplicated laparoscopic cholecystectomy two days after presentation by the general surgery team. Intra-operatively, an inflamed appearing gallbladder was noted. The patient was discharged on the second postoperative day and recovered uneventfully.

On pathology, routine hematoxylin and eosin-stained sections revealed a relatively well-circumscribed 2.25 mm lesion adjacent to the cystic duct. The lesion was composed of nests of monomorphic cells containing pale-to-eosinophilic foamy cytoplasm. The nuclei were round, with granular chromatin and lacked significant mitotic activity. No necrosis was identified. On immunohistochemical studies, the specimen showed diffuse positivity for synaptophysin and focal positivity for chromogranin, supporting neuroendocrine differentiation. SOX-10 highlighted a few cells at the periphery of the nests, consistent with sustentacular cells. In all, the morphologic and immunophenotypic findings were most consistent with an incidental paraganglioma (Fig. 3a–c).

Based on this pathology report, in the follow-up appointment a few weeks later, the patient was referred to an endocrine surgeon. The patient had blood and urine work-up including a plasma catecholamine panel showing epinephrine levels of 20 pg/mL (10–200), norepinephrine levels of 492 pg/mL (80–520), and dopamine of <20 pg/mL (0–20), all within normal levels. The patient also had
Table 1
Paragangliomas of the Gallbladder.

| Clinical Presentation     | Imaging Findings              | Location          | Size     |
|---------------------------|-------------------------------|-------------------|----------|
| Miller et al. [5]         | Recurrent hematemesis         | Duodenal ulcer    | Unknown  | 3 cm     |
| Wolff [6]                 | Cholelithiasis                | Unknown           | Subserosal | Unknown  |
| Wolff [6]                 | Cholelithiasis                | Unknown           | Subserosal | Unknown  |
| Hirano [7]                | RUQ pain                      | Mass at the neck of the gallbladder | Submucosal | 1.3 cm  |
| Cho et al. [8]            | RUQ pain                      | Mass at the fundus of the gallbladder | Unknown | 2.5 cm   |
| Mehra et al. [3]          | Asymptomatic                  | None              | Subserosal | 1.5 cm   |
| Rodriguez-Merchan et al. [9] | RUQ pain                  | Intra and extra-hepatic biliary dilation | Subserosal | 1 cm     |
| Ece et al. [10]           | RUQ pain                      | Mass at the neck of the gallbladder | Serosa and muscularis propria | 1.8 cm  |

Table 2
Paragangliomas of the Hepatic Duct.

| Clinical Presentation     | Imaging Findings              | Location          | Size     |
|---------------------------|-------------------------------|-------------------|----------|
| Sarma et al. [11]         | Obstructive jaundice          | Mass at the hepatic duct | Hepatic duct | Unknown  |
| Hitanant et al. [12]      | Obstructive jaundice          | Extrahepatic biliary dilatation | Hepatic duct | 5 x 2 x 1.8 cm |
| Carceres et al. [13]      | RUQ pain                      | Unknown           | Hepatic duct | Unknown  |

Fig. 4. Non-contrast CT showing a 1.5 cm nodule involving the adrenal gland with a Hounsfield unit density of 14. On MRI, this was interpreted as a benign adenoma.

A 24 h urine metanephrine panel showing metanephrine levels of 169 ug/24 h (52–341), and normetanephrine levels of 333 ug/24 h (88–444), all within normal levels. Chromogranin A level was 181 ng/ml, which was high, normal less than 95 (ranging from 0 to 95).

As a part of the patient’s investigations, computed tomography scan of the chest, abdomen, and pelvis was ordered. The scan demonstrated a 1.5 cm right adrenal mass with a Hounsfield unit of 14 (Fig. 4). The left adrenal gland was normal. MRI revealed a benign adenoma. The patient subsequently underwent blood and urine work-up including plasma ACTH and cortisol, as well as 24 h urine cortisol which were all normal at 8 pg/ml (<47), 10.3 ug/dl (AM = 5.3–22.5, PM = 3.4–16.8), and 23 ug/d (<45) respectively. In addition, the patient underwent a plasma renin and 24 h urine aldosterone work-up, which were also normal at 10.4 pg/ml (Upright: 3.6–8.6 pg/ml, Supine: 2.5–45.1 pg/ml) and 13 ug/24 h (3–25) respectively, with a 24 h urine sodium of 171 mmol/24 h (40–220) and potassium of 52 mmol/24 h (30–99). Finally, her work-up included a 24 h urine catecholamine panel showing epinephrine levels of 5 ug/d (1–7), norepinephrine levels of 37 ug/d (16–71), and dopamine levels of 140 ug/d (77–324).

Work-up for primary hyperparathyroidism was also initiated in the next few months. Labs showed calcium of 9.5 mg/dl (8.5–10.2) with a PTH of 73 pg/ml (15–65), and a 25 hydroxyvitamin D level of 32.9 ng/ml (31–80).

Finally, a hereditary paraganglioma-pheochromocytoma panel and evidence genes through Invitae was performed. Genetic testing did not reveal any mutations of EGLN1, FH, KIF1B, MAX, MEN1, NF1, RET, SDHA, SDHAF2, SDHB, SDHC, SDHD, TMEM127, or VHL genes.

3. Discussion

A literature review demonstrates nine cases of gallbladder paraganglioma [3,5–10], with the first reported case in 1972 by Miller et al [5], and three cases of hepatic paraganglioma [11–13], with the first reported case in 1980 by Sarma et al [11]. All reported paraganglioma cases were non-functional. Further features of these paragangliomas are summarized in the tables below (Tables 1 and 2).

However, extensive literature review revealed no cases of paraganglioma occurring at the cystic duct. In this case report, the patient presented with classical signs and symptoms of acute cholecystitis. Pre-operatively, the patient had no symptoms indicating a paraganglioma and the focus of the tumor was too small to be seen on imaging. It was only on pathological review of the specimen that a neuroendocrine proliferation measuring 2.25 mm in size at the cystic duct was noticed, which further stains favored a paraganglioma. Incidentally, the patient is unique in that they were also found to have an adrenal nodule, and a mild normocalcemic primary hyperparathyroidism that raises suspicion for an underlying endocrinopathy, despite a negative gene panel.

Although a gene mutation and syndrome was not identified in this patient, the fact that an adrenal nodule and normocalcemic primary hyperparathyroidism was present, suggests that a complete hormonal workup should be obtained in patients that present with paragangliomas.

4. Conclusion

It is important to realize that biliary system paragangliomas, although rare, may occur. Paragangliomas should be considered in the rare differential diagnosis of gallbladder, cystic duct, and hepatic duct lesions. Paragangliomas of the biliary system have been reported to be benign, malignant, and to have an association with multiple neuroendocrine neoplasia (MEN) syndrome [1]. Therefore, a thorough endocrine investigation to rule out this association should be made.

Conflicts of interest

The authors have no conflicts to declare.

Funding

There was no source of funding.
Ethical approval

This is case report is exempt for ethical approval in our institute.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-chief of this journal on request.

Author contribution

Raha AlMarzooqi, Loay AlJaberi: Wrote and revised manuscript. Thomas Plesec, Steven Rosenblatt, Eren Berber: Reviewed manuscript.

Registration of research studies

Not applicable.

Guarantor

Eren Berber.

Provenance and peer review

Not commissioned, externally peer-reviewed.

References

[1] S.E. Rha, J.Y. Byun, S.E. Jung, et al., Neurogenic tumors in the abdomen: tumor types and imaging characteristics, Radiographics 23 (January–February (1)) (2003) 29–43.
[2] D. Erickson, Y.C. Kudva, M.J. Ebersold, et al., Benign paragangliomas: clinical presentation and treatment outcomes in 236 patients, J. Clin. Endocrinol. Metab. 86 (November (11)) (2001) 5210–5216.
[3] S. Mehra, M. Chung-Park, Gallbladder Paraganglioma: a case report with review of the literature, Arch. Pathol. Lab. Med. 129 (April (4)) (2005) 523–526.
[4] R.A. Agha, A.J. Fowler, A. Saetta, I. Barai, S. Rajmohan, D.P. Orgill, SCARE Group, The SCARE statement: consensus-based surgical case report guidelines, Int. J. Surg. 34 (October) (2016) 180–186.
[5] T.A. Miller, T.R. Weber, H.D. Appelman, Paraganglioma of the gallbladder, Arch. Surg. 105 (October (4)) (1972) 637–639.
[6] M. Wolff, Paraganglioma of the gallbladder, Arch. Surg. 107 (September (3)) (1973) 403.
[7] T. Hirano, Paraganglioma of the gallbladder: report of a rare case, Am. J. Gastroenterol. 95 (June (6)) (2000) 1607–1608.
[8] Y.U. Cho, J.Y. Kim, S.K. Choi, et al., A case of hemorrhagic gallbladder paraganglioma causing acute cholecystitis, Yonsei Med. J. 42 (June (3)) (2001) 352–356.
[9] B. Rodríguez-Merchán, R. Lozoya, E. Allende, et al., Paraganglioma of the gallbladder, Med. Clin. (Barc) 24 (June (4)) (2006) 158.
[10] I. Ece, H. Alptekin, Z.E. Çelik, et al., Gallbladder paraganglioma, Ulus. Cerrahi Derg. 31 (4) (2015) 244–246, http://dx.doi.org/10.5152/UCD.2014.2691, 2014 Sep 8.
[11] D.P. Sarma, F.H. Rodriguez Jr., E.O. Hoffmann, Paraganglioma of the hepatic duct, South. Med. J. 73 (December (12)) (1980) 1677–1678.
[12] S. Hitamant, S. Srumpai, S. Na-songkla, et al., Paraganglioma of the common hepatic duct, Am. J. Gastroenterol. 79 (June (6)) (1984) 485–488.
[13] M. Caceres, L.F. Mosquera, J.A. Shih, et al., Paraganglioma of the bile duct, South. Med. J. 94 (May (5)) (2001) 515–518.