Primary hepatic paraganglioma with megacolon: A case report

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Abstract. Primary hepatic paraganglioma (PGL) is a rare neuroendocrine tumor characterized by clinical manifestations including paroxysmal hypertension, palpitation, abdominal pain and constipation. In the present study, the case of a 21-year-old woman with pathologically confirmed hepatic PGL with megacolon following surgery is reported. The patient initially visited Beijing Tiantan Hospital (Beijing, China) for hypoferric anemia. A triple-phase CT scan of the whole abdomen showed a large hypodense mass with a solid periphery and strong arterial enhancement of the peripheral solid portion of the liver. The sigmoid colon and rectum were obviously distended, filled with gas and intestinal contents. The patient was preoperatively diagnosed with iron deficiency anemia, liver injury and megacolon and then underwent partial hepatectomy, total colectomy and enterostomy. Microscopically, the liver cells exhibited an irregular zellballen pattern. In addition, immunohistochemical staining revealed that liver cells were positive for CD56, chromogranin A, vimentin, S-100, melan-A and neuron-specific enolase. Therefore, the diagnosis of primary PGL of the liver was confirmed. These findings suggested that primary hepatic PGL should not be excluded when megacolon occurs and comprehensive imaging evaluation is of great importance for its diagnosis.

Introduction

Paragangliomas (PGLs) are rare vascular, neuroendocrine tumors of paraganglia cell clusters originating from the neural crest tissue of the autonomic nervous system (1). According to the World Health Organization (WHO) 2017 classification, tumors arising from the adrenals are considered pheochromocytomas, while those associated with extra-adrenal sympathetic tissue are considered as paragangliomas (1). PGLs are accompanied by catecholamine oversecretion-related symptoms such as hypertension, palpitations and headache. In addition, several patients with PGLs suffer from abdominal discomfort (2,3).

Arising from paraganglionic tissue that runs along the axis of the body that is distributed in areas from the base of the skull to the pelvis, the most common site of PGLs is the retroperitoneal space (55.2%) and head and neck regions (25.6%). Occasionally, PGLs develop in the bladder and mediastinum (2). The incidence of PGLs is 2-10 per million people. Surgical resection of the tumor is the main therapy. However, primary hepatic PGL, and gastrointestinal disease-related primary hepatic PGL, is very rare (2,4-12). To the best of our knowledge, the present case report is the first to describe a female patient with primary hepatic PGL accompanied by megacolon in terms of clinical, radiological and histopathological features.

Case report

A 21-year-old female patient was referred to Beijing Tiantan Hospital (Beijing, China) with hypoferric anemia during September 2021. The patient was referred to another local hospital due to bilateral lower limb swelling. The patient did not complain of dizziness and weakness, but described symptoms of abdomen distension. After the diagnosis of anemia, the patient was treated with iron supplements. The patient exhibited a complicated medical history that included constipation, with an average defecation of once every 5 days to 1 month, weight loss of 5 kg over a period of 3 months and intestinal obstruction that improved following 3 years of conservation treatment.

Physical examination revealed microcytic hypochromic anemia, blood pressure of 75-120 mmHg and an abdomen circumference of up to 100 cm. Laboratory tests showed mild anemia with hemoglobin levels of 96 g/l. The values for carcinoembryonic antigen, neuron-specific enolase (NSE) and CYFRA 21-1 were 8.92, 27.59, and 5.79 ng/ml, respectively. The levels of urinary vanillylmandelic acid were not determined since the patient had no symptoms of a functional tumor.

Following admission, ultrasound examination showed a solid-cystic mass with a size of 11.4x10.2 cm in the right lobe of the liver, which was considered benign disease. A CT scan of the entire abdomen showed a large, round, hypodense mass with a solid and well-marginated periphery. A contrast-enhanced CT scan revealed that the solid portion of the abdominal circumference displayed strong enhancement in the arterial phase. In addition, several tortuous blood

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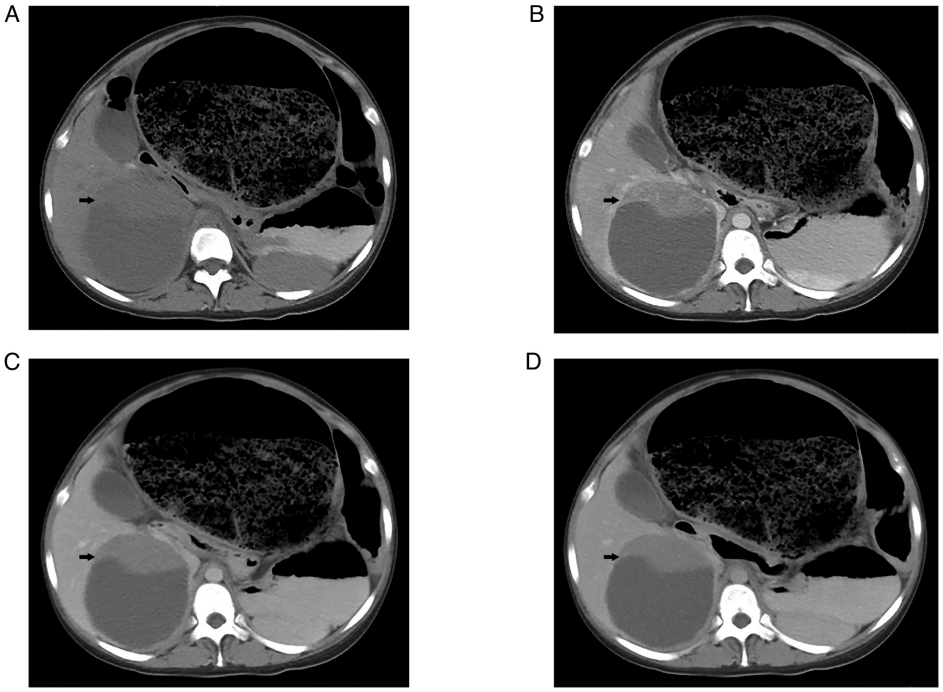

Figure 1. Preoperative abdominal and contrast-enhanced CT images. (A) Abdominal CT scan revealed a large, round and hypodense mass with a solid and well marginated periphery (arrow). (B) Abdominal contrast-enhanced CT images revealed that the solid portion displayed intense enhancement in the arterial phase (arrow). Enhancement was also observed (arrow) at the (C) portal and (D) delayed phases. The sigmoid colon and rectum were well distended and expanded and filled with gas and intestinal contents.

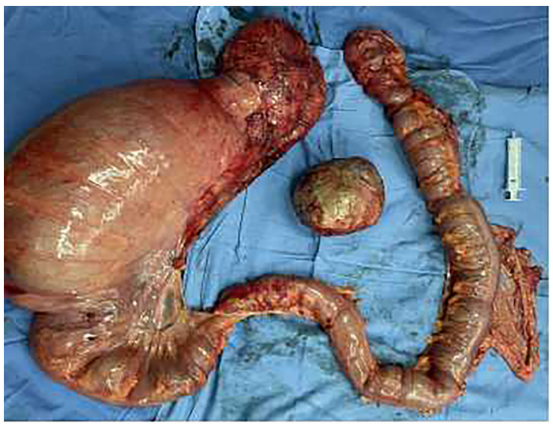

Figure 2. Intraoperative image of round hepatic paraganglioma and expanded colon.

vessels were observed (Fig. 1). The sigmoid colon and rectum were obviously distended and expanded, filled with gas and intestinal contents. The maximum diameter of the colon was 20 cm. The patient did not undergo MRI examination. In addition, gastrointestinal angiography and colonoscopy were not performed due to intestinal contents. Finally, the patient was diagnosed with iron-deficiency anemia, liver damage and megacolon.

The patient was transferred to the General Surgery Department of Beijing Tiantan Hospital and was routinely administered an enema while fasting. Following symptomatic treatment for 15 days, the patient underwent partial hepatectomy, total colectomy and enterostomy. Intraoperative examination revealed a huge sigmoid colon with a diameter of 15 cm. The rest of the colon was dilated with a mean diameter of 6 cm. A hard mass with a diameter of 10 cm and a smooth surface was found in the right posterior lobe of the liver (Fig. 2). The surgical procedure was completed without any complications based on detailed preoperative planning.

Pathological examination following surgery showed that the mass had a nested and trabecular architecture with a prominent vascular network. In addition, tumor cells with pleomorphic morphology were present (Fig. 3). Giant tumor cells were also observed, while mitotic cells were rare. For light microscope, 4 um sections were routinely mounted. The tissues were use formalin-fixed, paraffin-embedded (FFPE) and use 10% neutral buffer formalin fixed for 12-24 h. We used DAB for color development (DAB staining kit, ZLI-9019, Beijing Zhongshan Jinqiao Biotechnology Co., Ltd.). Immunohistochemical staining of the resected liver tissues revealed that liver cells were positive for CD56, chromogranin A, vimentin, S-100, melan-A and NSE. However, liver cells were negative for hepatocyte paraffin-1, α fetoprotein, arginase-1, cytokeratin, HMB-45, CD68, epithelial membrane antigen, desmin and smooth muscle actin. The Ki-67 labeling index was <5% (Fig. 3). The patient was postoperatively followed-up for 6 months and no evidence of recurrence or metastasis was recorded.

Discussion

PGLs are rare neuroendocrine tumors arising from the autonomic nervous system and are classified into functional and non-functional PGLs based on secretion levels of catecholamine. Catecholamine levels in patients with functional PGL are commonly 4x higher than normal level (10). These patients

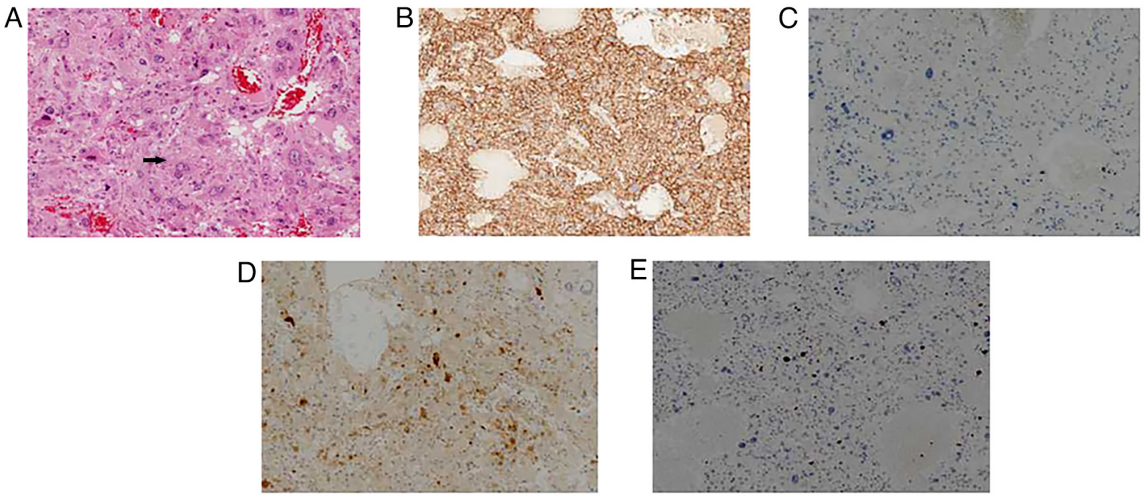

Figure 3. Pathological examination. (A) Hematoxylin and eosin staining showed that the mass exhibited a nested and trabecular architecture with prominent vasculature (arrow). The pleomorphism of the tumor cells is obvious. Giant tumor cells are shown, while mitotic cells were rare (magnification, x40). Immunohistochemical staining demonstrated that the tumor cells were positive for (B) CD56 and negative for (C) hepatocyte paraffin-1. (D) Sustentacular cells expressing S-100 protein are shown. (E) Ki-67 index was <5%. Magnification, x40.

commonly present characteristic symptoms, such as hypertension, palpitations and headache (10). A total of 10-15% of patients with PGLs are asymptomatic and the painless mass is identified on abdominal imaging (13).

In the present case report, the patient did not display typical symptoms associated with catecholamine secretion and only experienced hypoferric anemia. This indicated that the accurate diagnosis of primary hepatic PGL is difficult when relying only on age, medical history and symptoms.

PGLs are accompanied by several clinical symptoms associated with the secretion of catecholamines. Catecholamines act on α, β and dopaminergic receptors to modulate processes including heart rate, blood pressure and myocardial contractility (14). In addition to effects on the cardiovascular system, catecholamines affect the gastrointestinal system via stimulating smooth muscle α-1, α-2 and β-2 adrenergic receptors (3). Sustained secretion of high catecholamine levels may result in intestinal smooth muscle relaxation (15). Furthermore, prolonged vasoconstriction of the gastrointestinal tract leads to intestinal wall ischemia, which further contributes to decreased gastrointestinal motility (3). Clinically, patients with PGLs may initially experience intermittent constipation followed by intestinal obstruction and megacolon for a long period (16).

Megacolon, a rare complication of PGL, consists of three types, namely congenital Hirschsprung's disease, idiopathic Hirschsprung's megacolon and acquired megacolon (AMC). Hirschsprung's disease is caused by intestinal ganglion cell dysplasia, while AMC is associated with secretion of catecholamines that affect the gastrointestinal system via stimulating smooth muscle receptors (16).

In the present case report, the initial symptoms of the patient were associated with the gastrointestinal system, including anemia and abdomen distension. The patient's condition was not obviously relieved following symptomatic treatment. In addition, the patient had a medical history of intestinal obstruction 3 years before the final hospital admission. However, the patient had not undergone imaging examination during the aforementioned period.

Imaging examination serves a critical role in the management of PGLs and commonly guides clinical treatment. PGL is commonly present as a homogenous mass with a soft tissue density >10 Hounsfield units and uniform contrast enhancement on CT images (17). However, larger PGLs undergo hemorrhage and necrosis, thus resulting in areas of lower density. On an MRI scan, this tumor type commonly appears as a free-fat mass on chemical shift with high signal on T2 sequences. In previous studies, the tumor might display high signal intensity on T2-weighted images, while increased necrosis within the contrast enhanced tumor could be observed (14,17,18). Anatomical imaging, such as CT and MRI scanning, show excellent sensitivity, are helpful in delineating anatomic significance, but less helpful in metastatic disease. Therefore, positron emission tomography may be more useful in evaluating PGLs (17).

Distinguishing PGLs from other liver tumors via imaging examination is difficult. Previous studies have suggested that primary hepatic PGLs could initially be misdiagnosed as hepatocellular carcinoma (HCC) (5,6,8,12), fibrolamellar HCC (FHC) (4,7) or cavernous hemangioma of the liver (CHL) (9). However, HCC is typically characterized by arterial enhancement followed by portal venous phase washout. Additionally, FHC commonly presents with enhanced central scar on delayed-phase images. CHL is commonly characterized by contrast enhancement at the periphery of the mass in the early phase. In the present case study, the mass presented with delayed persistent enhancement and a massive cystic change. Given the rarity of primary hepatic PGLs and their non-specific imaging features, it is difficult to make an accurate diagnosis of this disease without pathological examination and laboratory tests.

Surgical resection is considered the optimal treatment approach for primary hepatic PGL. However, surgery may lead to massive release of catecholamines and is therefore a major mortality risk factor (19). Furthermore, previous studies have reported extreme fluctuations in blood pressure following surgery-mediated tumor induction (5,12). Therefore, it is important for the preoperative diagnosis of PGLs to be

accurate to avoid perioperative complications and to improve surgical safety.

Primary hepatic PGL is commonly considered a benign disease. To the best of our knowledge, however, currently, there is no available reliable pathological or imaging method to clarify whether a tumor is benign or malignant (20). A previous case report showed hepatic PGL metastasis in the spleen and liver after surgical treatment with a 3-year follow-up (12). In the present case report, recurrence or metastasis was not observed. However, a long-term follow-up period is required.

PGLs usually occur sporadically and ~10% of cases are hereditary (13). Multiple genes are associated with PGL and up to 40% of patients exhibit a disease-causing germ-line mutation (21). Classic tumor syndromes such as neurofibromatosis type 1 (NF1), multiple endocrine neoplasia type 2 and Von-Hippel Lindau syndrome (VHL) are associated with a germ-line mutation in the tumor suppressor gene NF1, proto-oncogene RET and tumor suppressor gene VHL, respectively (22). Hereditary PGLs usually develop at a younger age and more frequently grow bilaterally (19).

PGLs have a genetic predisposition. Once diagnosis is established, genetic testing is recommended for all patients. The specific gene may guide the imaging observation and subsequent treatment (23). The first-degree relatives of a mutation carrier should be offered predictive testing to make a diagnosis in the early stages and to provide a targeted preventive therapy (23). In the present case report, the patient had no family history of similar disease. In addition, the monitoring and treatment of helicobacter pylori and physical examinations using gastroscopy and colonoscopy are important methods for early detection of digestive cancer. Prophylactic probiotics may help digestion of food and absorption of nutrients to alleviate the burden of the intestine and colon (24).

In summary, primary hepatic PGL is rare type of tumor. It less commonly causes intestinal obstruction and megacolon compared with common catecholamine secretion-associated symptoms, such as hypertension, palpitations and headaches. The present case report described the complex course of pathological changes involved in the development of megacolon. Overall, the results suggested that comprehensive imaging evaluation may be of significance for the diagnosis and treatment of non-hypertensive hepatic PGLs. Medical and surgical teams may be able to treat the perioperative condition and decrease complication rates of this rare neoplasm.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

JZ contributed to the conception and design of this study. JPB discovered this case in clinical work and summarized the case. JPB collected clinical information and performed the literature review. JPB and JZ wrote and revised the manuscript. MXS performed the pathological examination. NZ collected imaging data and revised the content of imaging examination. JZ, JPB, MXS and NZ confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Informed consent was obtained from the patient.

Patient consent for publication

Informed consent was obtained from the patient.

Competing interests

The authors declare that they have no competing interests.

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