Non-functional paraganglioma: A case report

ZHENG LIU[1], YANG ZHANG[1], XINGYUAN ZHANG[1] and LINGQUN KONG[2]

[1]Department of Hepatobiliary Surgery, Binzhou Medical University Hospital; [2]Department of Hepatobiliary Surgery, Binzhou People's Hospital, Binzhou, Shandong 256603, P.R. China

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Abstract. Paraganglioma (PGL) usually presents as the elevation of blood pressure and metabolic changes in patients, and its common symptoms are persistent or paroxysmal hypertension. However, some patients have no typical clinical symptoms, such as patients with non-functional PGL. Therefore, the present study reviewed the literature and summarized the present rare case to provide more accurate and in-depth help for clinical diagnosis and comprehensive treatment. The case was a 64-year-old female with epigastrium malaise for 1 year and aggravation for 7 days. Contrast-enhanced CT revealed that the soft tissue of the irregular mass was in the front of the kidney on the right abdomen with a clear boundary and the size was ~6.5x5.4x6.6 cm. Large vessels were observed in the interior and edge of the lesion. The present study prepared for retroperitoneal tumour resection according to the diagnosis of PGL. After the operation, the patient recovered smoothly and was discharged from the hospital. As of March 2023, the general condition of the patient is good.

Introduction

Pheochromocytomas/paragangliomas (PPGL) are rare neuroendocrine tumours (1). A previous study of patients with PPGL from various countries, including the United States, Canada, Denmark, the Netherlands, Australia, Spain and Sweden, reported that between 1949 and 2019 the incidence of PPGL ranged from 0.04-0.95 cases per 100,000 per year (2). Approximately 85-90% of PPGL are localized in the adrenal glands and 10-15% are extra-adrenal and are called paraganglioma (PGL) (1). PGL, originating from the autonomic nervous system ganglia and its accompanying neural regions, was first described by Fränkel in 1886 (3,4). Most of PGLs are functional and can secrete catecholamines. Its common clinical symptoms are headaches, heart palpitations and sweating (1,3). Only 10% of PGL cases are clinically silent (non-functional PGL) and are observed incidentally via imaging (5). Non-functional PGL is mostly located in the neck and rarely in the abdomen (6). PGL is most common in adults between the ages of 20 and 40 years, and there is no significant difference in sex in its occurrence (7). The incidence of PGL has been increasing gradually, as confirmed by Berends *et al* in 2018 (8). This previous study reported that the age-standardized rate for PGL among patients from the Netherlands increased from 0.08 (95% CI: 0.06-0.10) to 0.11 (95% CI: 0.09-0.13) per 100,000 person-years in the periods 1995-1999 and 2011-2015, respectively (8).

Once PGL is diagnosed, surgical resection is the only curative treatment and the mortality rate of patients for PGL resection from the United States has decreased from ~40% in the 1950s to 0-3% over the last four decades (9,10). However, recurrence after resection has been reported to occur in 3-16% of patients (11,12). Due to the risk of local recurrence, metastasis and a new PGL, surgical resection cannot guarantee a complete cure (9,12). Recurrence of PGL can be difficult to treat. Cui *et al* (11) reported that 47% of patients with recurrence had multiple tumours at the site of recurrence and 58% had metastases (11). However, as treatment significantly decreases the risk of metastases and mortality, patients should be treated promptly after detection of recurrence (12). Thus, long-term follow-up is essential (13).

Case report

Patient information. The patient, a 64-year-old female, was admitted to Binzhou Medical University Hospital (Binzhou, China) in August 2022 for 'Epigastrium malaise for 1 year with aggravation for 7 days'. The patient presented with upper abdominal distension accompanied by nausea and chest tightness. Physical examination showed abdominal tenderness that was mainly on the right side. There was a palpable mass in the right upper quadrant of the abdomen with a hard texture and clear boundary and other significant abnormalities were not observed. In August 2021 the patient had abdominal discomfort without obvious cause, mainly in the upper abdomen, with a feeling of stuffiness and distension, accompanied by a poor appetite. There were no abnormalities, such as nausea

Correspondence to: Dr Lingqun Kong, Department of Hepatobiliary Surgery, Binzhou People's Hospital, 515 Huanghe 7th Road, Binzhou, Shandong 256603, P.R. China
E-mail: konglingqun2014@163.com

Abbreviations: PGL, paraganglioma; PPGL, Pheochromocytomas/paragangliomas; CT, computed tomography; CA, catecholamine; E, epinephrine; NE, norepinephrine; DA, dopamine; GIST, gastrointestinal stromal tumour

Key words: paraganglioma, retroperitoneal tumour, diagnosis, treatment, case report

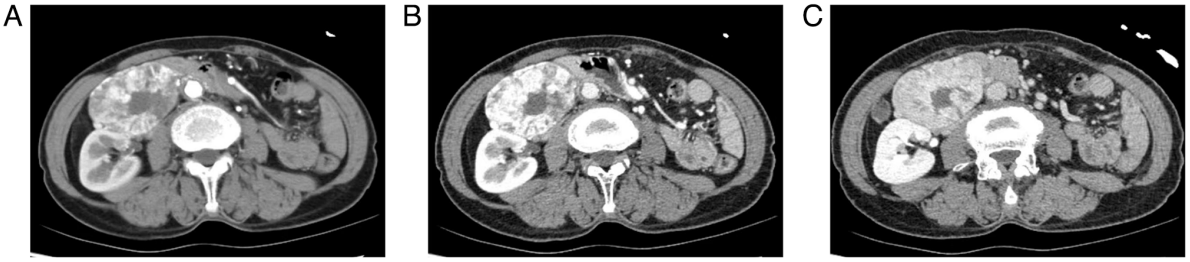

Figure 1. Preoperative contrast-enhanced CT. (A) Arterial phase, (B) venous phase and (C) delayed phase.

and vomiting, and the patient's feeling of abdominal distension persisted, so she went to the local hospital. After treatment with oral Chinese medicine and infusion, the symptoms still occurred intermittently. Approximately 7 days before admission to Binzhou Medical University Hospital, the patient experienced aggravated abdominal distension accompanied by nausea and chest tightness, and thus immediately went to Huimin People's Hospital (July 2022; Binzhou, China). After abdominal ultrasound examination, routine biochemical examinations and gastrointestinal barium meal examinations, the patient was diagnosed with an abdominal tumour. After 7 days, the patient was admitted to Binzhou Medical University Hospital with an 'abdominal tumour'. The patient had been constipated since the onset of the disease in August 2021 and urinated normally. In the past, the patient had a history of tracheitis for >30 years without regular treatments. She had a history of surgery for haemorrhoids 3 years ago.

Imaging findings. After admission, the patient underwent relevant examinations. Abnormalities were not found in routine blood and biochemical examinations. Other laboratory examinations showed that the level of carcinoembryonic antigen was 7.33 ng/ml (reference value 0-3.4 ng/ml), aldosterone was 52.81 pg/ml (reference value 70-300), methoxyepinephrine was 265.7 pg/ml (reference value 0-145 pg/ml) and norepinephrine was 212.8 pg/ml (reference value 217-1109 pg/ml). On a CT scan of the whole abdomen, a mass-like soft tissue shadow was seen in the lower part of the gallbladder fossa with a clear boundary, measuring ~6.5x5.4x6.6 cm. A low-density area and punctate high-density shadow were seen in the mass against the adjacent tissue, and the partial lesions were close to the intestinal tract. (Fig. 1) On whole abdominal CT enhancement, irregular masses of soft tissue with a clear boundary were seen in the front of the kidney on the right abdomen, and the size was ~6.5x5.4x6.6 cm. On the contrast-enhanced CT scan, the lesions were obviously enhanced inhomogeneously, and there were low-density areas and punctate high-density shadows in the lesions without enhancement. Large vessels were observed in the inside and edge of the lesion, which pushed against the descending and horizontal parts of the duodenum. The anterior margin of the right kidney, the head of the pancreas and the uncinate process were compressed, and the systems of the pancreatic duct and bile duct were slightly dilated.

Therapeutic interventions and histopathological findings. After oral administration of phenoxybenzamine and intravenous infusion for 1 week, the present study performed the elective operation of laparoscopic exploration. After inserting the laparoscope, there were no obvious abnormalities observed in the stomach, small intestine, colon, peritoneum or pelvic cavity. Then, the lateral membrane of the duodenum was opened and a tumour with a hard texture and clear boundary was visible in the back of the pancreas, the abdominal aorta and the anterior part of the inferior vena cava. During the operation, removal of the tumour was attempted. Because the base of the tumour was closely involved with the abdominal aortic sheath and it was difficult to turn completely freely under the laparoscope, we decided to perform open surgery. A longitudinal incision around the umbilicus ~20 cm long was made in the upper abdomen and continued to expose the retroperitoneal tumour. Since the right margin of the tumour was free and the peritoneum of the duodenum was fully opened, we disconnected the tumour from the inferior vena cava after breaking off two branches of the venous reflux. We further severed the connection between the tumour, the abdominal aortic sheath and the tumour basilar artery. The retroperitoneal tumour was resected. Postoperative pathology showed that the surface of the grey-white and grey-red nodular tumour with a volume of 8.5x7x4.5 cm was completely encapsulated. The tangential section of the tumour was greyish red with a soft texture, and another section was greyish white with a hard texture. Then immunohistochemistry was performed on the tumour tissue. The immunohistochemistry protocol included the following indicators: Synaptophysin (Syn), Chromogranin A (CgA), CD56, S-100, epithelial membrane antigen (EMA), cytokeratin (CK), Vimentin, Melan-A, paired box 8 (PAX-8) and Ki-67. Immunohistochemical staining used the following primary antibodies (ZSGB-Bio): Anti-Syn (cat. no. ZM0246), anti-CgA (cat. no. ZM0076), anti-CD-56 (cat. no. ZM0057), anti-S-100 (cat. no. ZM0224), anti-EMA (cat. no. ZM0095), anti-CK (cat. no. ZM0067), anti-Vimentin (cat. no. ZM0260), anti-Melan-A (cat. no. ZM0398), anti-PAX-8 (cat. no. ZM0468) and anti-Ki-67 (cat. no. ZM0167). The following are details of the immunohistochemistry: Tissues were embedded after fixing with 4% paraformaldehyde at room temperature for 48 h and the thickness of sections was ~5-μm. Peroxidase was inactivated by incubating sections with 3% H_2O_2 for 10 min at room temperature. Normal goat serum working fluid (cat. no. ZLI9022; OriGene Technologies, Inc.) was used to incubate the sections for 15 min at room temperature. Subsequently, the aforementioned primary antibodies were used at a dilution of 1:100 and incubated at 4˚C for 12 h. Next, the sections were incubated with biotin-labelled goat anti-mouse/rabbit IgG secondary antibodies (ZSGB-Bio; cat. no. SAP-9100) at a dilution of 1:500 for 30 min at room temperature. After, images were

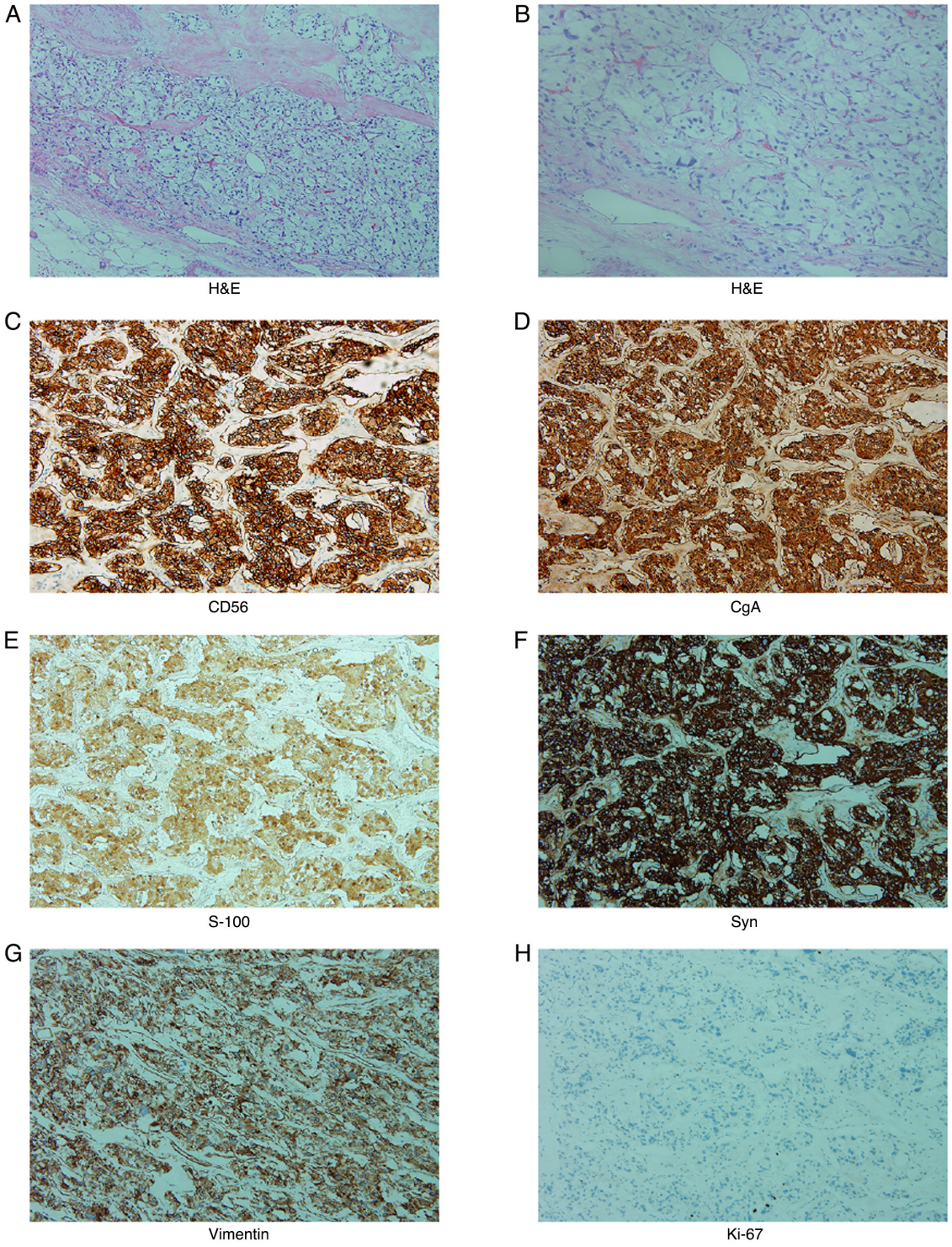

Figure 2. Pathological examination. H&E staining at magnification (A) x100 and (B) x200. Immunohistochemical staining for (C) CD56(+), (D) CgA(+), (E) S-100(+), (F) Syn(+), (G) Vimentin(+), (H) Ki-67 (the proliferation index was ~1%) (all magnification, x100).

captured using a fluorescent microscope. The results of H&E staining are shown in Fig. 2A and B. The immunohistochemistry results were as follows: Syn(+), CgA(+), CD56(+), Vimentin(+), S-100(+), the proliferation index of Ki-67 was ~1% and the others were negative (Fig. 2C-H).

Follow-up and outcomes. After the operation, anti-infection, antithrombus and rehydration treatment were actively performed, and the blood pressure of the patient was monitored closely. There was no obvious abnormality on contrast-enhanced CT after the operation. The patient recovered successfully and was discharged. As of March 2023, the general condition of the patient during follow-up is good.

Discussion

Predominantly located in the abdomen, PGLs are found mostly in the confluence of the inferior vena cava and the renal vein or

in the organ of Zuckerkandl, directly above the aortic bifurcation and near the origin of the inferior mesenteric artery (7,14). Other rare areas are the renal hilum, suprarenal pole, hepatic hilum, between the liver and inferior vena cava, near the head of the pancreas, the iliac fossa or tissues near the iliac fossa blood vessels, such as the ovary, bladder and rectum (15,16).

Originating from the sympathetic trunk, PGL mainly synthesizes, secretes and releases large amounts of catecholamines (CA), such as epinephrine (E), norepinephrine (NE) and dopamine (DA). Therefore, the clinical manifestations of PGL is mostly similar to those of pheochromocytoma, such as the elevation of blood pressure and metabolic changes in patients (14). Its common symptoms are persistent or paroxysmal hypertension, and it is characterized by a triad of headache, palpitations and hyperhidrosis or a triad of tremor, facial pallor and dyspnoea (3,14,17). Nausea and vomiting, abdominal pain, constipation, intestinal obstruction and other symptoms of the digestive system are also observed (16). However, some patients have no typical clinical symptoms, such as patients with non-functional PGL.

Non-functional PGLs, which are mostly located in the neck and rarely in the abdomen, represent ~10% of all PGLs (5,6). Non-functional tumours in abdomen are usually large when they are found, and therefore patients usually present with abdominal or back pain and a palpable mass (18,19). Due to their similar symptoms, PGL is often misdiagnosed as a gastrointestinal stromal tumour (GIST). They can be differentiated by enhanced CT and MRI. PGL exhibits an enhanced vessel shadow on CT and a vascular flow empty signal on T2WI of MRI, and DWI mostly shows a high signal (20). GISTs usually present as an exophytic growth mass with a clear boundary on CT or MRI, uneven internal density of the tumour, and a visible liquefied necrotic area (20). T1WI shows a mostly heterogeneous low or equal signal, and T2WI shows an uneven high signal (21).

The diagnosis of PGL can be missed for a lifetime, so the most important step in diagnosing PGL is to be aware of the possibility of the tumour (17). When PGL is suspected, the levels of CA and its metabolite are determined first. Preferred laboratory tests include the concentration determination of free plasma or urine methoxyepinephrine or methoxyadrenalin (3,8,16), and the concentration of NE, E, DA and other metabolites such as 3-methoxytyramine, vanillylmandelic acid and homovanillic acid in blood or urine can also be detected simultaneously to aid in diagnosis (11). When a qualitative diagnosis of PGL is established, CT is the preferred imaging examination for the localization of the tumour (8,15,16); in addition, the tumour body, which can be enhanced by contrast medium, is shown on CT as a circular or quasicircular soft-tissue shadow with uneven density (16,22-27).

PGL is a complicated and difficult endocrine disease that involves numerous subjects (3,16). It should be resected as soon as possible after localization and qualitative diagnosis. Before surgery, the patients should first be administered an α-receptor blocker (15,16). At the same time, they should be treated with venous dilatation therapy, and open surgery is recommended (28). Postoperative blood pressure and heart rate are closely monitored (8).

After admission, the present patient underwent an enhanced CT scan, which indicated a retroperitoneal occupying lesion. The contrast-enhanced CT scan revealed a marked heterogeneous enhancement of the lesion. The relevant examinations showed that the level of methoxynorepinephrine was significantly elevated. The diagnosis of PGL was made on the basis of the patient's imaging findings and elevated methoxyepinephrine in laboratory examinations. At the same time, the present study excluded the diagnosis of GIST based on laboratory and imaging findings. The patient, having no typical symptoms such as blood pressure changes and only manifesting with upper abdominal distension and accompanied by nausea and chest tightness, was diagnosed with nonfunctional PGL. Therefore, the present study prepared for surgery according to the diagnosis of paraganglioma. Phenoxybenzamine was provided orally in addition to an intravenous infusion. At 1 week later, the present study performed the retroperitoneal tumour resection. According to the history and relevant examination results of the patient, the final diagnosis was non-functional PGL.

After the operation, the present patient recovered smoothly. No significant blood pressure abnormality was observed after the operation. The patient recovered well and was discharged from the hospital. Based on the present case, accurate and timely diagnosis of the disease is essential. At present, the patient's general condition is good after 6 months of follow-up. Because of its highly local recurrence, the short follow-up time for the present study is a limitation and we will follow up the patient for a longer period of time in the future.

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Availability of data and materials

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

Authors' contributions

ZL and LK drafted the manuscript and conceived the study. YZ provided the relevant images. XZ, ZL and YZ contributed to collecting clinical data and confirmed the authenticity of all the raw data. LK and ZL corrected the manuscript and prepared histopathological results. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Competing interests

The authors declare that they have no competing interests.

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