Unclear Retroperitoneal Tumors, an Interdisciplinary Challenge – A Case Report and Review of the Literature

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Case report

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Abstract

Background

Unclear retroperitoneal tumors still impose major challenges for clinicians. Tumors can originate primarily from retroperitoneal tissue or secondarily invade into the retroperitoneal space. While benign lesions also occur, malignant tumors are far more common. Clinical presentation often depends on replacement or invasion of other organs and is therefore highly variable. The heterogeneous tumor composition makes a definitive preoperative diagnosis difficult. Nevertheless, surgical resection is the gold standard for treatment but often proves challenging due to frequent involvement of large retroperitoneal vessels.

Case presentation

We present a case report of a 70-year old woman diagnosed with a large, unclear retroperitoneal tumor. Initial clinical symptoms were increasing dyspnea and dysphagia in our clinic. Gastroenterologic and cardiologic workup was unremarkable. Computed Tomography (CT) revealed a large retroperitoneal mass in the right upper abdomen with severe displacement of the inferior vena cava and renal veins. Without signs of irresectability, the patient was scheduled for tumor resection. The procedure was challenging due to the vessel involvement and large blood pressure alterations during tumor mobilization. The post-operative pathologic workup then revealed the rare finding of a completely resected paraganglioma. The post-surgical course was uneventful. One year after diagnosis, the patient is relapse-free.

Conclusion

This case impressively shows the challenges of retroperitoneal tumors and the importance of interdisciplinary work in these cases.

Background

The unclear retroperitoneal tumor remains a major diagnostic and therapeutic challenge for clinicians of multiple disciplines. The majority of these lesions are malignant tumors and their clinical presentation is dependent on involvement of surrounding organs. Paraganglioma and Pheochromocytoma are rare tumors of the sympathetic nervous system that can occur in the retroperitoneum. They can be silent or endocrinologically active. Preoperatively asymptomatic tumors can prove challenging for the OR team of surgeons and anesthesiologists due to intraoperative catecholamine release. The prognosis is dependent on complete tumor resection and the presence or absence of metastases. This report offers a complete clinical workup of a large paraganglioma including a review of the literature.

Case Presentation

A 70-year old female (BMI 23 kg/m²) was admitted to our surgical clinic with the diagnosis of an unclear right-sided retroperitoneal tumor. The patient initially presented to her general physician with exercise-

related dyspnea, retrosternal pain, and dysphagia.

Initial cardiologic (ECG, long-term blood pressure (BP) measurement, echocardiography) and gastroenterologic (gastroscopy) workup was without pathologic finding. Contrast-enhanced Computed Tomography (CT) of the abdomen revealed an unclear subhepatic retroperitoneal tumor of 15 x 12 x 14 cm. The tumor showed displacing growth without signs of infiltration into adjacent organs or metastatic spread. Importantly, the inferior vena cava (IVC) and left renal vein were stretched by the tumor.

At the time of presentation in our clinic, the patient was in good physical shape (WHO performance status 0). Medical history only included a hemithyroidectomy in 2013 for thyroid follicular carcinoma in 2013 with regular follow-up. Long-term BP workup was already without pathological findings in the outpatient setting and the patient did not report any clinical signs indicative of a pheochromocytoma. Echinococcus serology was negative.

Radiologic workup

In the given scan the origin of the mass remained unclear. However, it showed expansive growth from between the aorta and the IVC while displacing the IVC, suggesting that the lesion likely arose from this location. It could not be clearly separated from the right adrenal gland, so an adrenal tumor was unlikely but not excluded. The mass appeared predominantly cystic with arterial hyperenhancing septa and solid components, non-typical for hematoma or infectious diseases. Lacking highly invasive growth patterns, the leading differential diagnosis were sarcoma, retroperitoneal paraganglioma, retroperitoneal mucinous cystadenoma/cystadenocarcinoma, and retroperitoneal cystic teratoma (Fig. 1A-D) (1, 2).

Treatment

As there were no signs for irresectability, the patient was scheduled for primary resection. Due to the size of the tumor and the complex vessel involvement, a minimally invasive approach was not feasible. Exploratory laparotomy showed the large tumor in the lesser sac, compressing the pylorus, pushing the liver upwards, and with extended compression of the IVC and hepatoduodenal ligament. The surgical situs after exploration is shown in Fig. 2A. First, the hepatoduodenal ligament was secured with a vessel loop. Next, the liver was completely mobilized with exposure of the hepatic veins and the IVC subdiaphragmatically in order to achieve control over venous backflow. Both renal veins were exposed and secured with vessel loops, as was the IVC distal of the renal vein confluence. Following this, the IVC was dissected from the tumor. The tumor was freed from attachments on the left side of the IVC with the upper margin of the pancreas and the retroperitoneum under careful preparation of the left renal artery and the celiac axis. After complete mobilization, the tumor could be removed *in toto*. The situs after tumor resection is shown in Fig. 2B, the tumor itself in Fig. 2C.

Due to the tumor location, control over hemostasis was crucial and all involved vessels were exposed and secured with vessel loops.

Macroscopically, the tumor had a benign appearance. Given the long attachment of the IVC to the tumor, a safety margin as required for malignant lesions was not achievable and a microscopically positive resection margin (R1) could not be ruled out during surgery.

During the operation, the patient showed extensive alterations in systolic BP ranging from 220mmHg to 60mmHg, requiring extensive pharmacological BP management. There were no bleeding complications during the surgery to explain the BP alterations. Additional compression of the IVC was avoided by lifting the liver upwards during preparation of the IVC. Due to this clinical presentation, the right adrenal gland was removed together with the tumor despite the absence of clinical signs for a pheochromocytoma preoperatively. After tumor removal and repositioning of the IVC in the anatomically correct position, no more BP alterations occurred.

Pathologic workup

The surgical specimen was intact and consisted of an unifocal, well-circumscribed tumor measuring 15 x 14.5 x 9.5 cm that adhered firmly to the right adrenal gland. The tumor's cut surface demonstrated extensive hemorrhagic and cystic degeneration. Microscopic examination revealed a slowly proliferating, pseudo-encapsulated, non-invasive neuroendocrine neoplasm with small to pleomorphic chief cells that were surrounded by sustentacular cells and arranged in sclerotic, trabecular, and organoid patterns (Fig. 3). This led to the diagnosis of a completely excised extra-adrenal sympathetic paraganglioma. Histological grading and risk stratification according to the Grading System for Adrenal Pheochromocytoma and Paraganglioma (GAPP) (3) revealed a low metastatic risk.

Outcome

The postoperative course was uneventful and the patient was discharged on day 11. Follow-up over one year was without complications and a control MRI was without signs of recurrence.

Discussion

Differential diagnosis and management of unclear retroperitoneal tumors. Solid neoplastic masses in the retroperitoneum must be distinguished between primary retroperitoneal tumors and neoplasms originating in retroperitoneal organs or secondarily invading the retroperitoneal space (4). The latter include tumors arising in the adrenal glands, kidneys, and excretory system, secondary retroperitoneal organs (pancreas, colon), and systemic dissemination of neoplasms (metastases, lymphomas). These account for the majority of soft tissue retroperitoneal masses (5). Diagnosis and treatment are based on the guidelines for the respective disease.

The WHO classifies soft tissue tumors by their tissue of origin: Lipomatous, fibrous (Fibroblastic and Fibrohistiocytic), smooth and skeletal muscle, vascular and perivascular, chondro-osseous, and tumors of uncertain differentiation (6). All entities include benign and malignant lesions, but malignant lesions are four times more common (5). Symptoms are usually nonspecific and patients often present late due to

compression of the gastrointestinal or urinary tract (5). Consequently, the recent phase III STRASS trial reported a median tumor size in retroperitoneal sarcomas of 16.7 cm (7).

Cross-section imaging is key in the diagnostic workup. CT and magnetic resonance imaging (MRI) can differentiate between primary and non-primary retroperitoneal tumors by identifying or excluding a specific organ of origin (8). CT of the thorax, abdomen, and pelvis is usually preferred for retroperitoneal masses and can offer an estimate of tumor differentiation (9, 10).

Suspected resectable soft tissue sarcomas should undergo upfront surgery due to the risk of track implantation. In other cases, diagnostic material can be gained through surgical incision biopsy or, preferably, core needle biopsy (9). In this case, a soft tissue sarcoma could not be ruled out so primary resection was scheduled.

Surgical excision remains the only curative approach for most retroperitoneal tumors (11). Complete macroscopic tumor resection and histologic grading are important predictors for recurrence-free survival in the case of retroperitoneal sarcomas (12).

Paraganglioma and Pheochromocytoma. Paraganglioma (PGL) and the closely related pheochromocytoma (PCC) (described together as PPGL) arise from chromaffin cells in neural ganglia and are therefore not considered primary retroperitoneal tumors (4, 13). As they are histologically indistinguishable, the WHO uses the anatomical location for classification: While pheochromocytomas arise from the adrenal medulla, paragangliomas, also called extra-adrenal pheochromocytomas, arise from extra-adrenal paraganglia (14). Both tumors are rare with an incidence of about 0.6 cases per 100,000 person-years and pheochromocytomas are at least 4 times more common (15, 16). Both entities are endocrinologically active tumors that commonly secrete a variation of catecholamines (13).

PGL can arise from parasympathetic and sympathetic ganglia. As parasympathetic PGL most commonly arise in head & neck, the WHO classifies PGLs into 1) head & neck PGL and 2) sympathetic PGL (17). Head & neck PGL are rarely endocrinologically active and usually present as slowly growing masses e.g. as carotid body tumors (16). Sympathetic PGL are located below the diaphragm in the vast majority of cases and are usually endocrinologically active (13).

Genetic susceptibility is a major component of PPGL pathogenesis. More than 20 genes are known to be associated with PPGL development (18). Over 40% of all tumors are hereditary, making PPGL the most common human hereditary tumor (19). The first identified risk factor was the RET proto-oncogene, responsible for the MEN-2 syndrome (20). Other PCC / PGL associated syndromes include the von Hippel-Lindau disease (mutant VHL tumor suppressor), Neurofibromatosis Type 1 (mutant NF1 tumor suppressor), and paraganglioma syndromes (mutations in the succinate dehydrogenase genes) (16).

Clinical presentation is dependent on endocrine activity. The classical symptom triad due to catecholamine release consists of headaches, palpitations, and sweating. A recent meta-analysis of clinical symptoms reported a likelihood ratio of + 6.312 (95 % CI 0.217–183.217) in diagnosing PPGL for

patients with the classic triad (21). However, distinguishing PPGL patients from the general population based solely on clinical symptoms is often not possible (22). Alternatively, PGL and PCC are commonly diagnosed as incidental findings in cross-section imaging and in screenings of genetically susceptible individuals (16). In a prospective study, PPGL-related symptoms, incidental findings, and screens due to past history or genetic risk were each responsible for about a third of PPGL diagnoses (22).

Free plasma levels of metanephrines had the highest sensitivity of 99% of biochemical tests for PCC in a multicenter cohort study of 858 patients (23). In CT diagnostics, chromaffin tumors present as tumors with low lipid content. Further diagnostics can use functional imaging, especially in the metastatic setting or with expected multiple neoplasms. A recent meta-analysis showed superiority of ^{68}Ga -DOTA-conjugated somatostatin receptor-targeting peptide PET-CT over other functional imaging methods with a combined detection rate of 93% (24).

Biopsies of PPGLs can be associated with a high risk of complications and are not included in current recommendations of clinical practice (19, 25).

The only curative approach for PPGL is surgical resection, ideally minimally invasive (16). Excessive intraoperative catecholamine release can cause severe hemodynamic instabilities and associated complications (26). The Endocrine Society Guidelines therefore recommend premedication with α -adrenergic receptor blockade for patients with hormone-active PPGLs (27). A few groups have challenged this approach in order not to delay surgery (28). Groeben and colleagues published an observational study involving 266 patients with similar outcomes with and without premedication (29) so upfront surgery may be an option in asymptomatic patients (30).

A patient's prognosis after PPGL resection is dependent on a number of variables. Amar and colleagues reviewed 38 studies on PPGL (Head & Neck PGL excluded) and identified syndromic diseases and PGL as risk factors for recurrence (31). The biological aggressiveness of a single tumor cannot be determined by histologic parameters and only the presence of metastases serves as proof for malignant behavior (16). The WHO therefore refrains from the use of "malignant PPGL" and instead classified them as "metastatic PPGL" (17). Scoring systems like the Grading System for Adrenal Pheochromocytoma and Paraganglioma (GAPP) based on histologic features and catecholamine secretion have been developed to predict metastatic potential (3). *In toto* tumor resection without capsule rupture is important for reducing risk of metastatic spread (32). Management of metastatic disease is based on surgical metastasectomy, local ablation techniques, systemic chemotherapy, and irradiation techniques (16).

Our case combines the rare combination of a retroperitoneal paraganglioma that is not endocrinologically active. This allowed the tumor to reach an impressive size and only became symptomatic after displacement of adjacent organs. Definite preoperative diagnosis by cross-section imaging was not possible and histologic confirmation was avoided due to the risk of track metastasis in case of a sarcoma. Nevertheless, tumor mobilization intraoperatively triggered catecholamine release and resulted in severe blood pressure alterations. The successful complication-free treatment of the patient

was only possible in the hands of experienced clinicians in their fields of surgery and anesthesiology in addition to diagnostic workup in radiology and pathology.

Conclusion

Management of retroperitoneal tumors is challenging and involves a multidisciplinary approach. Paragangliomas and Pheochromocytomas are rare tumor entities. Asymptomatic, sporadic disease is hard to identify preoperatively and can cause unexpected complications in the OR. An experienced team is crucial in achieving best short- and long-term outcomes.

Abbreviations

Blood pressure (BP)

Computed tomography (CT)

Grading System for Adrenal Pheochromocytoma and Paraganglioma (GAPP)

Inferior vena cava (IVC)

Magnetic resonance imaging (MRI)

Paraganglioma (PGL)

Pheochromocytoma (PCC)

Paraganglioma and Pheochromocytoma described together (PPGL)

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

The patient presented has given written consent on publication of the case

Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

DHB, MW and BT performed the surgery, BT and JL wrote the report, BH performed the radiologic workup, LB performed the pathologic workup

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Figures

Figure 1

Pre-operative CT-scan. Native (A) and contrast-enhanced scans (B-D) in transversal (A-C) and coronar (D) sections. Asterix marks the predominantly cystic tumor, the white arrow marks the severely displaced IVC.

Figure 2

Surgical tumor resection. A: Situs after explorative laparotomy reveals a large tumor in the lesser sac with displacement of liver, stomach and duodenum, hepatoduodenal ligament, and IVC (*). B: Situs after tumor resection with the IVC repositioned in its original position. IVC (1) and renal veins (2, 3) are secured with vessel loops. C: Tumor after resection, contact with IVC is marked with white dashed line.

Figure 3

Pathological workup. Hematoxylin-eosin staining (A) and immunohistochemical staining (B-D) of the excised extra-adrenal sympathetic paraganglioma (magnification 400x). Polygonal medium sized and larger pleomorphic chief cells arrange in an organoid pattern (A). Chief cells stain for the neuroendocrine marker chromogranin-A (B). Sustentacular cells surrounding the chief cells stain for S100 protein (C). Tumor cells show a low proliferative activity in the Ki-67 staining (D).