CASE REPORT

UROLOGICAL ONCOLOGY

Diagnosis of extra-adrenal phaeochromocytoma after nephrectomy

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This case describes a 50–yr–old man who was admitted to the Urology Ward upon the suspicion of a left kidney tumor. As part of the pre–operative check–up, an ultrasound and computed tomography of the kidneys were conducted. The results confirmed the initial diagnosis. The postoperative diagnosis was extra-adrenal pararenal phaeochromocytoma (ePCC) with succinate dehydrogenase complex, subunit B (*SDHB*) gene mutation. During the follow–up, a second tumor was detected by 3,4–dihydroxy–6–F–18–fluoro–L–phenylalanine positron emission tomography/computed tomography F–DOPA–PET CT that resulted in another surgery with complete resection of the tumor. The patient and his family were counseled by a genetic laboratory and remain under surveillance.

Key Words: extra-adrenal phaeochromocytoma ‹› diagnosis ‹› therapy ‹› surgery

CASE DESCRIPTION

In February 2009, a 50–yr–old man in good general health complaining of left upper abdominal pain, excessive sweating and fever was presented in our outpatient department. The patient reported an occasional heart rhythm disorder with ventricular arrhythmias and was treated for several years with three different medicaments for severe arterial hypertension. He was also treated for diabetes mellitus type II with oral medication for several years. His family history concerning tumor diseases was negative. Sonographic imaging revealed tumor formation of the left kidney. A computed tomography scan (Figure 1) revealed a 9–cm tumor of the upper pole of the left kidney with suspected infiltration of the adrenal gland, renal fascia, left renal vein, and artery. Increased retroperitoneal lymph nodes were described, but no distant metastases were detected. Urine and labor analysis, especially the tumor markers [*Lactate dehydrogenase (LDH), Human chorionic gonadotropin (βHCG), Alpha–fetoprotein (AFP), Prostate–specific antigen (PSA), Cancer antigen (CA19–9), and Carcinoembryonic antigen (CEA)*] were normal. A malignant renal cell carcinoma was suspected and a retroperitoneal radical nephrectomy with adrenalectomy was performed. Intraoperatively, the tumor mass was detected in the upper pole of the kidney, attached to the pancreas and neighbor tissue. Its knotty growth without capsule or limits was highly atypical for renal cell carcinoma and the preparation was difficult. During the operation, the patient experienced hemodynamic fluctuation with tachycardia and fluctuations of blood pressure. The tumor mass, including the left kidney and the adrenal gland, was resected. Histological and immunohistochemical analysis revealed a 6 cm, partially necrotic, extra-adrenal phaeochromocytoma in the area of the renal hilus with marked blood vessel invasion, spreading directly to the kidney and adrenal gland, but not infiltrating them (Figure 2). No precise statement on the malignant potential could be done. The

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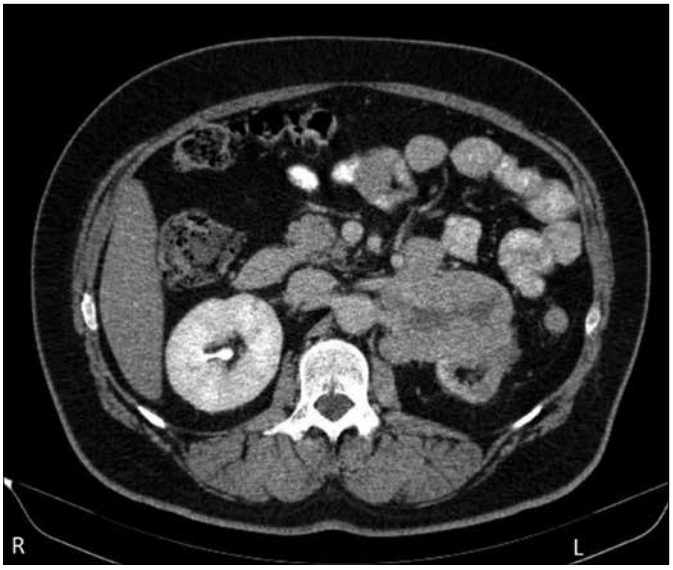

Figure 1. *Computed tomography: transversal view of a 9–cm tumor in the upper pole of the left kidney.*

immunohistochemistry detected positive staining for cytokeratin, vimentin and synaptophysin and the results were confirmed by the reference pathologist. Postoperatively, fasting as well as transient drainage were needed for about two weeks because of a pancreatic fistula. The patient recovered quickly and all the drains could be removed. The postoperative urine tests (24h collection) were analyzed and normal levels of metanephrine, normetanephrine, dopamine, adrenaline, and noradrenaline were detected. Genetic testing for Von Hippel–Lindau (*VHL*), succinate dehydrogenase complex, subunit B (SDHB), succinate dehydrogenase complex, subunit C (SDHC) and succinate dehydrogenase complex, subunit D (SDHD) including polymerase chain reaction (PCR) and deoxyribonucleic acid (DNA)–sequencing were performed (Department of Nephrology, University Hospital of Freiburg, Germany). A single mutation in Exon 7 of *SDHB* was detected. The patient was identified as a carrier of *SDHB*–mutation, which predisposes him for phaeochromocytoma (ePCC). A few weeks after the operation, blood pressure normalized and medication could be gradually stopped. Postoperatively, he was not dependant on steroid medication. Six months later, the patient presented a mild form of hypertonia (systolic pressure 150–160 mmHg without medication). A follow–up restaging with Fluorine–18–L–dihydroxyphenylalanine (^{18}F–DOPA) positron emission tomography (PET) was performed. A 3.5 x 5 cm second tumor was detected paraaortalally to the left with possible infiltration of the pancreas and spleen (Figure 3). A reoperation was performed in a specialized department of surgery. Preoperatively, blood pressure was lowered by a ß–blocker and the catecholamine urine test was slightly positive. Because of the location and the adhesions of the tumor, the initially planned minimally invasive operation was converted to open surgery with partial pancreatectomy and splenectomy needed. The histology and immunohistochemistry confirmed the previous diagnosed of phaeochromocytoma with active proliferation. Postoperatively, the patient developed a pancreatic fistula and pneumonia with respiratory insufficiency. Temporary treatment in the intensive care unit was necessary and the patient recovered after two weeks. Blood pressure medication could be reduced gradually and stopped after four weeks. Genetic counseling for the patient and his 20–yr old son were conducted. Clinical follow–ups and annual catecholamine controls in urine were recommended. The follow–ups two years after the second operation were unsuspicious.

DISCUSSION

Phaeochromocytoma is a rare tumor entity, which can be located retroperitoneal. Sometimes, the tumor grows nearly asymptomatically and reaches considerable size as shown in the presented case. The key message is to think about phaeochromocytoma in patients presenting hypertonia. Clinicians should be aware of the possible rise of blood pressure during the operation. An experienced anesthetist is required to handle the operation [1]. The metanephrines were measured only after the operation; the levels were not elevated in 24–h urine and therefore not useful in the presented case. DOPA–PET/CT showed a high sensitivity and confirmed the second tumor of ePCC [2]. One of the challenges was the detection of the second tumor after an open surgery with a major complication. A standard operative approach for treatment of PCC is a laparoscopic resection [3, 4]. However, a retroperitoneal endoscopic approach was not possible because of the localization of the tumor retropancreatic, paraaortal with adhesions to the pancreas and spleen. In preoperative assessment it is obligatory to monitor arterial blood pressure, heart rate and arrhythmias, to restore the blood volume to normal and to exclude cardiomyopathy. The intense perioperative management decreased morbidity and mortality significantly [5]. Preoperative medical setting of blood pressure and intraoperative support are important to reduce the risks for complications from hemodynamic instability and hypertensive crises. Different treatment strategies for used medication are available. Before surgery, the patient is conventionally prepared with α–adrenergic blockade (over 10–14 days) and, subsequently, additional β–adrenergic blockade is required to treat any asso-

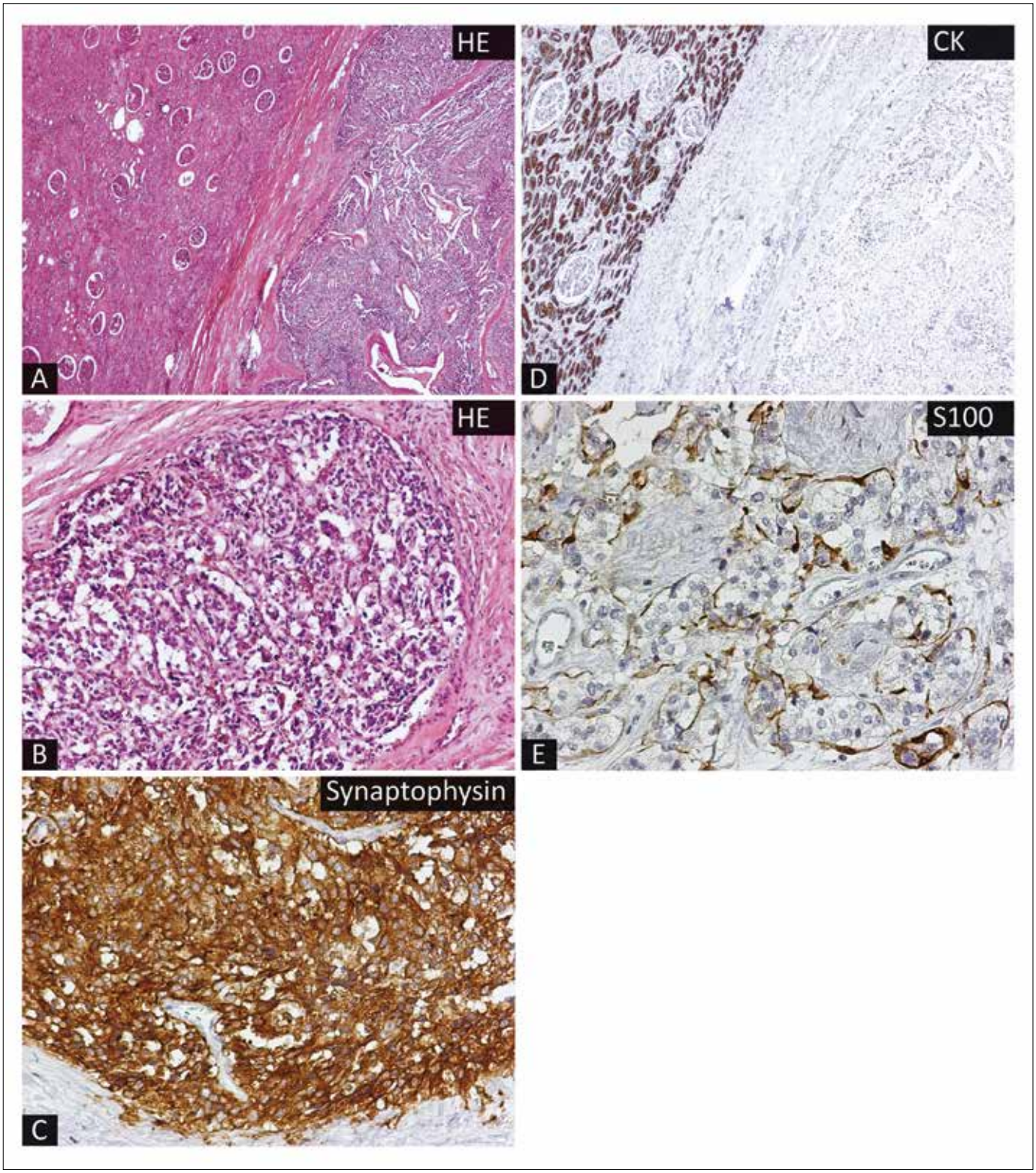

Figure 2. *HE–morphology and immunohistochemical analysis of the paraganglioma A Normal renal parenchyma on the left hand side and paraganglioma on the right hand side are separated by a thick layer of connective tissue (HE, 20x magnification). B The paraganglioma (right) shows no positivity for cytokeratin (CK) in contrast to the renal tubules (left) (20x magnification). C HE–morphological assessment revealed a tumor grown in trabecules with relatively monomorphous tumour cells (100 x magnification). D Immunohistochemistry against the S100 protein demarks a layer of sustenticular cells (200x magnification). E The majority of tumour cells is positive for synaptophysin (200x magnification).*

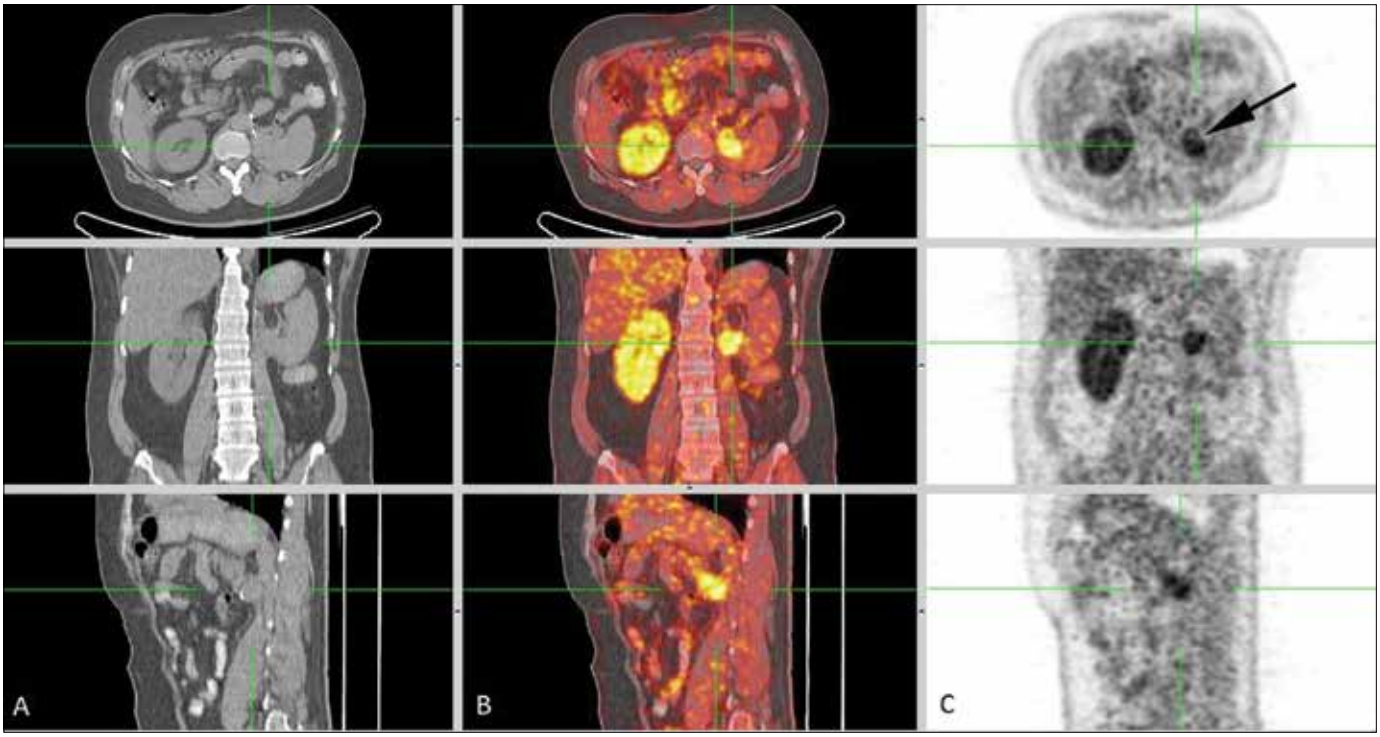

Figure 3. *F–18–DOPA PET–CT: 3–axial view of the F–DOPA positive, recurrent tumor in the left paraaortal region with a maximum diameter of 5 cm. A: CT, B: PET–CT, C: DOPA–CT.*

ciated tachyarrhythmias [6]. Other authors showed safe perioperative outcomes without an α–receptor blockade before resections of catecholamine–producing tumor [7].

Another problem is the prediction of the malignancy after the short termed relapse without metastases. The pathological prediction is impossible because of the lack of histological features. Only the presence of metastases establishes the definite diagnosis. Detection of germline mutations is the crucial step for further monitoring of patients. A genetic analysis and counseling of our patient and his family were performed. Autosomal–dominant *SDHB*–mutation was detected with the malignant potential of about 30%, so the complete resection of the tumor was of compelling necessity. The son of the patient has a probability of about 30% to develop phaeochromocytoma and he should be controlled regularly [1, 8, 9]. In order to provide the correct treatment and counseling of patients with PCC, a referral to a specialized center or receiving a second opinion from a specialist is important. Cooperation with a genetic laboratory is necessary. For all laboratories that provide genetic testing, quality assurance mechanisms must exist, including inter–laboratory comparison of reference samples, standardization of test reports and proficiency testing [10]. A possible solution can be a national or even international database providing the standardization and quality of genetic testing. The main problems are still the availability of the specialized genetic counseling and the costs of genetic analyses. In Germany there are only a few specialized endocrinologic laboratories and the only database with a trial on phaeochromocytoma is managed by the Department of Nephrology, University Hospital of Freiburg, Germany.

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