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Case Report

Pancreatic neuroendocrine tumor with solitary splenic metastasis and synchronous renal cell carcinoma: A rare case report ☆

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ABSTRACT

Synchronous pancreatic neuroendocrine tumors and renal cell cancer are extremely rare. Von-Hipple-Landau syndrome is a major association. A 43-year-old male patient with left upper quadrant pain and significant weight loss was diagnosed with a synchronous pancreatic tail neuroendocrine tumor with solitary splenic metastasis and a clear-cell renal cell carcinoma of the left kidney. Sonography and a computed tomography scan of the abdomen showed a complex exophytic left renal mass and a necrotic lesion limited to the spleen. Although not apparent on preoperative imaging, distal pancreatic mass was also discovered intraoperatively. Subsequently, left radical nephrectomy, splenectomy, and distal pancreatectomy were performed, and the synchronous primaries and splenic metastasis were confirmed histopathologically. This case is unique in that it demonstrates multiple extremely rare events occurring simultaneously, namely pancreatic and kidney primaries, as well as solitary splenic metastasis.

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Introduction

Simultinous pancreatic neuroendocrine tumors (NETs) and renal cell carcinoma (RCC) are extremely rare, with the small number of similar case reports available attesting to this fact [1]. von Hippel-Lindau (VHL), a hereditary cancer syndrome, is implicated in the majority of the cases reported so far [2]. Pancreatic NETs and RCC generally occur at a relatively younger age, and they tend to be multifocal when associated with VHL

Abbreviations: NET, pancreatic neuroendocrine tumor; RCC, renal cell carcinoma; VHL, von Hippel-Lindau; CT, computed tomography; MRI, magnetic resonance imaging.

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[3]. There is radiological and cytopathological confusion when RCC metastasis to the pancreas is considered a possible diagnosis because both lesions are highly vascular on cross-sectional imaging. Suggested computed tomography (CT) findings in favor of NETs include larger size, being solitary, more heterogeneity, and the presence of calcifications. Immunohistochemistry also plays a crucial role in their differentiation [2]. Most patients undergo renal surgery for RCC [4]. Pancreatic NETs over 2 cm are also resected as they present an increased risk of metastasis [5].

Splenic metastasis is very rare. According to autopsy results, splenic metastasis occurs in only 3% of cases, with even lower rates detected clinically [6,7]. Metastasis from pancreatic primaries has occurred, but only in a handful of reports [8]. Researchers have suggested multiple immune-related and mechanical factors to explain the rarity of splenic metastasis [7–10]. The effectiveness of splenectomy for metastatic disease is variable, and a confident recommendation is lacking due to the rarity of the condition [8].

Case presentation

A 42-year-old male patient without previously recognised tumor syndrome or a family history of genetic disease presented with progressively worsening left upper abdominal pain of 3 months duration, which eventually precluded him from his daily activities. Over the same period, he unintentionally lost 5 kg. He has a history of tobacco smoking (1 pack-year for 20 years), but quit when his illness began. He has no history of hematuria or other lower urinary tract symptoms. His past medical history is unremarkable. On physical examination, he is obese, with a body mass index of 34 kg/m^2. He had normal vital signs with a pulse rate of 70/min, a respiratory rate of 20/min, a blood pressure of 110/80 mmHg, and a temperature of 36.7°C. Abdominal examination showed splenomegaly, which was tender to deep palpation. The rest of his physical examination was non-revealing. Laboratory examinations, including complete blood count, electrolyte panel, liver function tests, and urine analysis, were normal. His renal function was also unaffected; creatinine was normal at 0.7 mg/dL, and BUN was 18 mg/dL. He underwent abdominopelvic CT and abdominal ultrasound afterwards. The abdominal ultrasound (Fig. 1) showed a large lesion confined to the splenic hilar region. It had a central necrotic component with no internal blood flow. The spleen also showed enlargement. There was also a complex left renal mass. The abdominopelvic CT (Figs. 2 and 3) better defined the nature of these lesions. The splenic lesion predominantly exhibited irregular rim enhancement. The left renal mass was round and exophytic, with heterogeneous enhancement. There was no evidence of abdominal lymphadenopathy or liver lesions. A chest CT was also negative (not presented).

Given the above imaging findings, the initial consideration was a left renal cell cancer with splenic metastasis. Radical nephrectomy and splenectomy were planned, and the patient underwent surgical exploration. Intraoperatively, a 3 cm

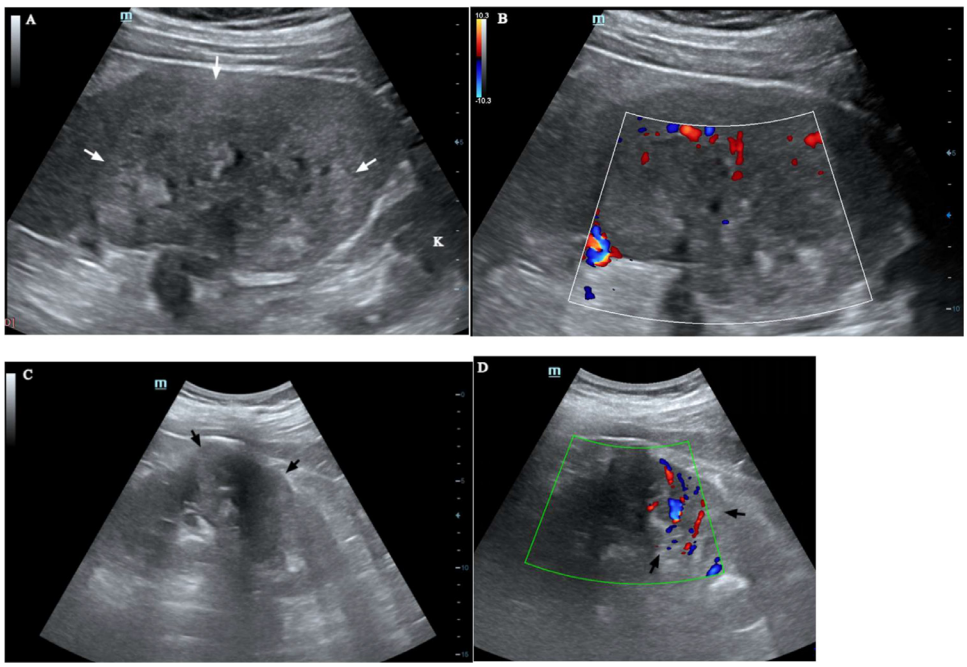

Fig. 1 – Transverse Gray (A) and doppler (B) mode sonography of the spleen and longitudinal Gray (C) and doppler (D) mode sonography of the left kidney: A relatively hyperechoic splenic hilar lesion (white arrows in A) with heterogeneous central echo-content. Upper pole of left kidney (k) is seen in the left lower corner of the image. There is paucity of flow in the center of the lesion (B). The renal lesion is heterogeneously hypoechoic and deforms the left renal contour (black arrows on C). Although there is some bowel gas shadowing on the color doppler (D), the visible part of the lesion shows significant flow (black arrows in D).

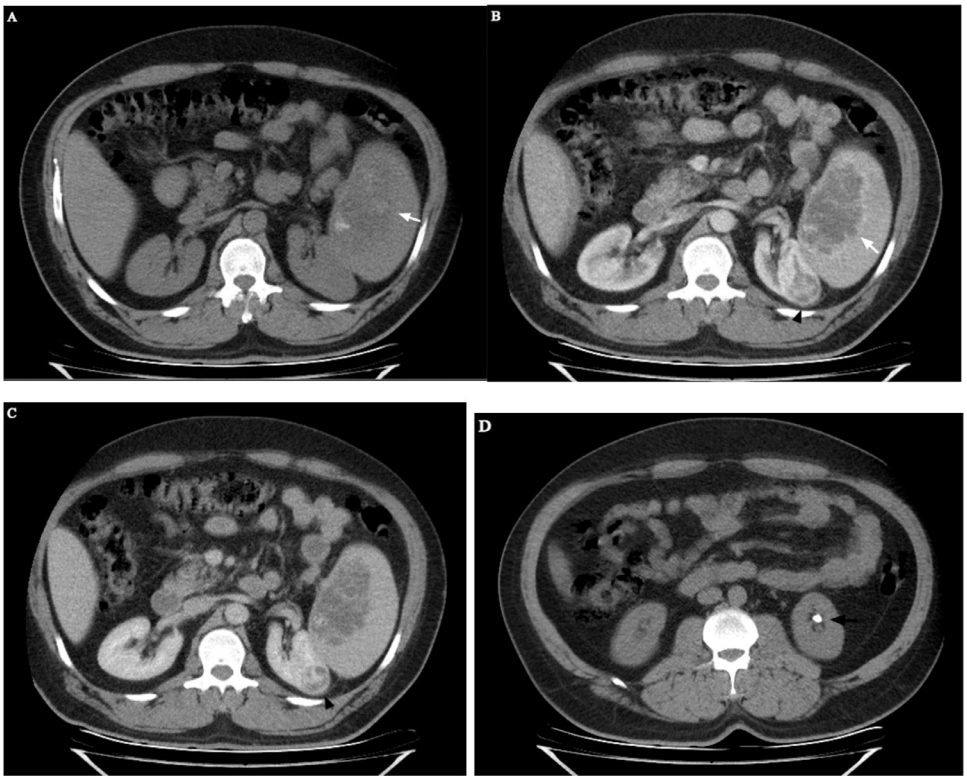

Fig. 2 – Triphasic abdominal CT in pre-contrast (A, D), arterial (B) and portal (C) phases at the level of the spleen: A 9 x 6.6 x 8 cm (AP x TR x CC) irregularly marginated splenic hilar lesion (white arrows) seen. It is only faintly visualized in the precontrast (A) phase, but shows circumferential rim enhancement and some dispersed central enhancing regions in the arterial phase (B) which subsequently fade in the portal phase (C). On the same planes, there is a 2.8 x 3 x 3.5 cm (AP x TR x CC) left posterosuperior relatively well-defined round or ball shaped renal contour deforming and heterogeneously enhancing renal mass (black arrowheads). Incidental note is made of a small left lower pole stone without causing calicyal dilation (black arrow D).

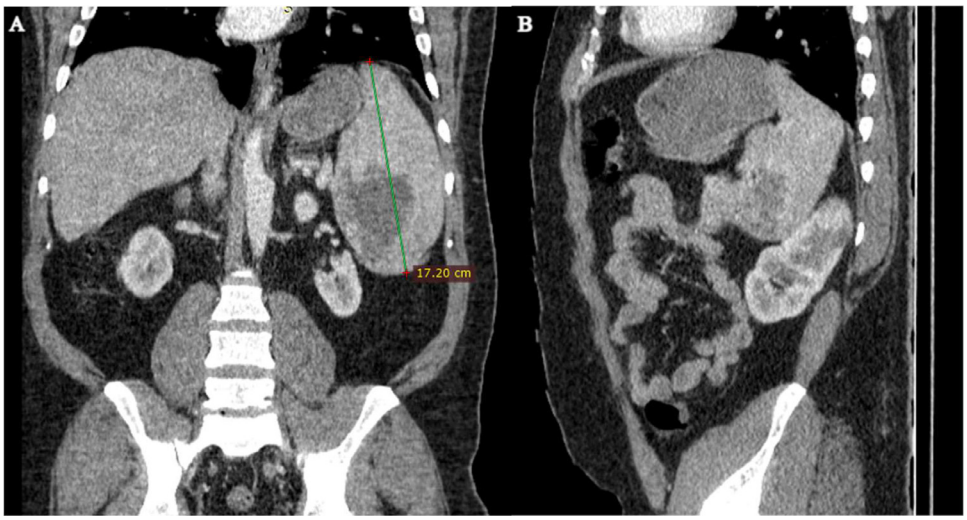

Fig. 3 – Reconstructed coronal (A) and sagittal (B) portal phase CT: The splenic lesion is causing splenomegaly, which measures 17 cm. The sagittal view depicts the relative positions of the splenic and left renal masses.

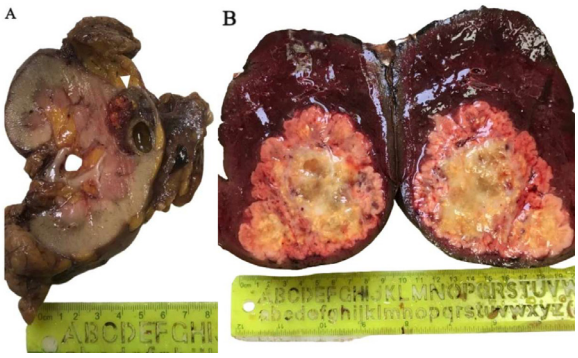

Fig. 4 – Cut sections of the left kidney (A) and spleen (B): The left kidney shows a circumscribed mid pole mass (arrowhead in A). (B) reveals a large gray white solid area with cystic and necrotic foci within the spleen.

(longest axis) hard pancreatic tail mass was discovered (not detected on preoperative imaging), necessitating distal pancreatectomy. The splenic lesion remained entirely within the splenic parenchyma and did not connect with either the pancreatic tail or left renal masses. Abdominal lymphadenopathy was not found. Post-operatively, the patient had a smooth course and was discharged on the eighth postoperative day.

Gross pathologic examination of the specimens (Fig. 4) revealed a 3 × 2.5 × 2 cm midpole circumscribed variegated renal mass with a cystic component as well as an 8 × 8 × 4 cm grey-white splenic solid mass with necrotic and myxoid changes. In addition, multiple grey-white pancreatic nodules ranging from 1.5–3 cm were also received (not shown).

On microscopy, representative sections through the kidney showed a circumscribed mass composed of polygonal cells with round nuclei, inconspicuous nucleoli, and abundant clear cytoplasm arranged in a tubular and microcyst pattern separated by thin fibrovascular septae, consistent with clear cell renal cell carcinoma, WHO/ISUP grade 1 (Figs. 5A and B). Sections through the distal pancreatic mass revealed relatively monotonous cells with salt and pepper chromatin arranged in an organoid and trabecular pattern, with areas of oncocytic cells having prominent nucleoli and abundant eosinophilic cytoplasm. About 7 mitosis/2 mm^2 was counted, and no necrosis was noted (Figs. 5C and D). Similar cells also infiltrated the spleen. This was consistent with the pancreatic neuroendocrine tumor, grade 2, with splenic secondaries (Figs. 5E and F).

During his 2-month postoperative appointment, no signs of late surgical complications were detected. Afterwards, the patient was linked to the oncology service for further follow-up, and a decision to put the patient on active surveillance was made using an annual abdominal CT. Immunotherapy management was impossible because they are not currently available in our setting.

Discussion

We presented a male adult with synchronous pancreatic NET that metastasized to the spleen only and clear cell carcinoma of the left kidney. To the best of our knowledge, this is the first case report in the English medical literature of simultinious RCC and pancreatic NET with splenic secondaries from the latter. Multiple primary tumors are rare, occurring in only 1%-3% of cases [11]. Simultinous renal and pancreatic neoplasms are ever rarer and can represent primary neoplasms originating from both organs or a primary neoplasm with metastasis to the other organ [2]. Renal tumors consist of RCC and angiomyolipoma, whereas pancreatic tumors include both exocrine and endocrine neoplasms, and include NETs, ductal adenocarcinoma, and intraductal papillary mucinous tumors Tobacco smoking is a common environmental risk factor for both and approximately doubles their relative risk [12,13]. Synchronous pancreatic and renal tumors can be a coincidence or related to a common genetic predisposition, namely VHL [1]. VHL is a rare autosomal dominant tumor syndrome with a prevalence rate of 1/36,000–50,000 live births. In 20% of cases, it occurs *de novo* [1,3]. It has high penetrance, with over 90% of patients becoming symptomatic by the age of 65 [3]. From 2001 to 2021. Persano et al. [2] identified 13 reports of concurrent pancreatic NETs and RCC cases. Out of these cases, 9/13 had been diagnosed with VHL, while the remaining cases were not tested. The majority of the patients were female, with a median age of 49 years. The clear cell variant of RCC occurred in 6 cases. The pancreatic NETs were mostly located in the head, followed by the tail regions. About 6/13 were >2 cm in size. Although the cohort size in this review was small, it still shows the central role VHL plays. Unfortunately, due to financial reasons, we did not test the patient for VHL in our case.

RCC is the second-commonest cancer of the urinary tract, accounting for 2.4% of all cancers [12,14]. Clear-cell RCC is the major histologic subtype, causing 80%-90% of RCC [15]. Locally advanced RCC is present in 20% of patients, and 18%-30% of patients would have had a metastasis at the time of their diagnosis [16]. Currently, the established risk factors for sporadic RCC are cigarette smoking, obesity, and hypertension [17]. Our patient has 2 of these, namely, smoking and obesity. Clear-cell RCC is present in 25%-45% of VHL patients and tends to develop at a mean age of 39 years. In fact, the diagnosis of clear-cell RCC below the age of 50 is an indication for VHL screening [3].

Pancreatic NETs are rare and account for 1%-2% of all pancreatic tumors. Patients typically receive a diagnosis during their fourth to sixth decades. As only a quarter of pancreatic NETs are hormonally active, most patients remain asymptomatic. When symptoms arise, they mainly consist of abdominal pain and weight loss [18]. About 30%-70% of pancreatic NETs are metastatic at diagnosis and have a 28% overall 5-year survival rate [18,19]. Patients with VHL have a 15% chance of developing pancreatic NETs, and more than half of these lesions will be multiple [3].

Metastasis to the pancreas is very rare (2%-4% of all pancreatic masses), but RCC is among the most common tumors to do so, occurring in 10% of RCC patients [20,21]. Moreover, RCC metastasis to the pancrease can often be solitary [22]. Because both pancreatic NETs and metastatic RCC in the pancreas are typically hypervascular, imaging differentiation can be particularly difficult [2,22]. Suggested CT features in favor of pancreatic NETs are larger size, solitariness, a more heterogeneous appearance, and calcification. In addition, RCC

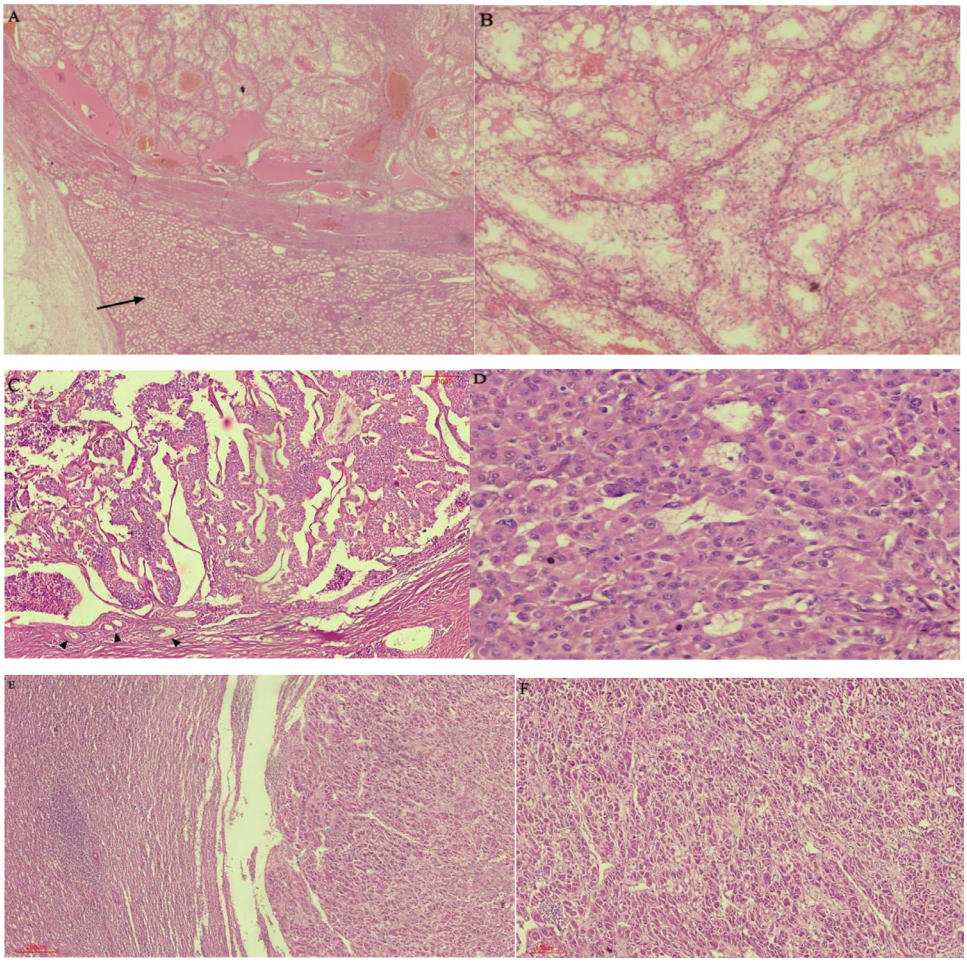

Fig. 5 – Photomicrographs at low (A, C, E) and high (B, D, F) power magnifications of the left kidney (A and B), pancreatic (C and D), and splenic (E and F) specimens: A low-power (2x) photomicrograph of the left kidney shows a circumscribed mass with adjacent normal renal parenchyma (arrow in A). At a higher power (20x), the left kidney shows clear cells with small nucleoli arranged in tubes with fine fibrovascular septae, which is consistent with clear cell renal cell carcinoma. The pancreatic tail mass at 20x magnification reveals monomorphic cells with stippled chromatin arranged in an organoid pattern adjacent to the pancreatic duct marked with an arrowhead, indicating features consistent with NET. At 40x magnification, D depicts the intermingled areas of oncocytic NET in the pancreas, which are composed of relatively monotonous cells with central nucleoli and ample eosinophilic granular cytoplasm. At 10x magnification, microscopy reveals a circumscribed splenic mass consisting of sheets of polygonal cells with ample eosinophilic cytoplasm, alongside normal splenic tissue visible on the left. High-power (40x) magnification of splenic mass composed of similar cells as depicted on D, with more dyscohesive growth.

metastasis is associated with less pancreatic ductal dilation, vascular invasion, and peripancreatic nodal involvement. Furthermore, histologically, a clear cell variant of NETs exists and can mimic clear cell RCC. In such cases, immunohistochemistry plays a crucial role [7]. In our case, the preoperative CT was intended to assess renal and splenic lesions and included only late arterial and portal phases. This is the probable reason for the failure to detect the pancreatic tail NET, which would have required an early arterial phase when pancreatic NETs ordinarily show peak contrast enhancement. Ultrasound also failed due to the patient's difficult body habitus.

Overall, metastasis to the spleen is rare, with rates largely established by autopsy studies. One such study from 2006 found the rate to be 3%, with lung cancer (24.6%), cutaneous malignant melanoma (15.8%), and breast cancer (12.3%) being the top 3 primaries [7]. Sauer et al. [8] assessed the clinical prevalence and outcome of 6137 patients with splenic metastases, of whom only 59 (0.96%) had splenic metastases. Only 6 cases of pancreatic carcinoma (type not specified) metastasized to the spleen, and 3 occurred synchronously.

The pathophysiologic reasons for the rarity of splenic metastases are multiple, and both lymphatic and mechanical reasons are considered. The former is due to the splenic parenchyma's inherent inhibitory effect (through phagocytic and humoral factors) on metastatic tumor cell growth. Mechanical factors include a tough splenic capsule, regular diaphragmatic contractions inhibiting implantation, a sharp angle and tortuous course of the splenic artery, splenic blood flow towards the portal vein, constant intraparenechymal

blood flow with a washout effect, and a lack of afferent lymphatic vessels [7–10,23]. Spread to the adjacent splenic lymph nodes is unfavourable as it signifies effective tumor cell infiltration from within the splenic parenchyma or retrogradely from efferent retroperitoneal lymphatics [23]. The majority (60%) of splenic metastases are clinically silent [24]. Radiologic investigations performed in the course of cancer staging are becoming the dominant diagnostic tools. An ultrasound series [24] that described isolated splenic metastases found lesions can be solid, cystic, or a mix with variable echogenicity. CT is more sensitive but non-specific. Jang et al. [25] found that absence of splenomegaly, absence of calcification, ill-defined margin, absence of wall, solid nature, presence of contrast enhancement, and lymph node enlargement occurred more in malignant than benign lesions. They also identified the solid nature of lesions, LN enlargement, and the presence of underlying malignancy as statistically significant predictors of malignancy. In our case, the splenic lesion had aggressive features, consisting of an irregular border as well as necrotic and ehnacing components.

Splenectomy continues to be offered in cases of splenic metastasis albeight for different indications. It is appropriate for pain palliation and for emergent complications such as splenic hemorrhage. When the intention is to cure, the outcome is variable. Furthermore, the low incidence of splenic secondaries and the infrequency of surgical procedures limit the ability to determine the effectiveness of splenectomy for metastatic disease [8]. For some tumors such as ovarian malignancies, splenectomy as part of debulking surgery together with chemotherapy has resulted in a good outcome in terms of achieving a long disease-free interval [26].

In conclusion, synchronous primaries of the pancreas and kidneys are an extremely rare occurrence and should lead to VHL screening. Although rare, solitary splenic metastasis should be considered in the presence of a known primary.

Patient consent

Written informed consent was obtained from the patient for anonymized information to be published in this article.

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