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Case Report

Metachronous Malignancy (Pancreatic Endocrine Neoplasm And Renal Cell Carcinoma): Case Report.

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Abstract

Pancreatic neuroendocrine tumors (PNET) are rare neoplasms that comprise 1-2% of all pancreatic tumors. However, they are the second most common solid pancreatic neoplasms. They have a wide range of imaging appearances, but most of the time they are solitary well-marginated enhancing solid masses (1). We present a 61year old male with multiple comorbidities, who was evaluated in the ER for suspected pulmonary embolism ; with incidental findings of right renal mass on CT angiogram of the chest. Further studies were done; including CT abdomen and pelvis with contrast. CT guided biopsy and FNAB of the pancreas and thyroid revealed a well- differentiated pancreatic endocrine neoplasm (PEN) and benign follicular neoplasm respectively. Pathology specimen showed right kidney renal cell carcinoma (RCC). Subsequent evaluation for Von Hippel-Lindau (VHL) disease was negative.

Despite significant increase in the incidence of PNETs in the United States, this disease remains an understudied and underfunded area of research. Our review intends to discuss the major challenges associated with the management of PNETs (2). The patient discussed in this case report may be one of the first cases reported of concomitant PEN and RCC in the same patient.

CASE REPORT

Index patient is a 61 year old African American male, with a past medical history (PMHx) of morbid obesity (BMI = 73), osteoarthritis (bilateral knees), venous stasis dermatitis, Obstructive sleep apnea (OSA) on CPAP, HTN, and NIDDM .Patient underwent right nephrectomy following an incidental finding of right renal mass on evaluation in the Emergency Room (ER) for chest pain and shortness of breath (SOB). A CT chest with contrast done to evaluate for pulmonary embolism in the ER revealed a 5.3cm right thyroid lobe mass; an indeterminate partially imaged right renal mass and an indeterminate hyper enhancing mass adjacent to the pancreatic neck.

Subsequently; a CT abdomen and pelvis with contrast demonstrated a 2.6 x 2.5 cm pancreatic soft tissue attenuation (figure 2) with centrally increased attenuation and a solid heterogeneous exophytic mass of the anterior upper right kidney, measuring 5.4 x 4.8 cm with multiple lobulations. On discharge, patient underwent a CT guided biopsy of the pancreatic body with pathology significant for well- differentiated PEN. He was then scheduled for a right nephrectomy and pancreatectomy. Unfortunately, surgery was aborted after the right nephrectomy was undertaken, secondary to patient's body habitus.

Pathology specimen showed right kidney renal cell carcinoma (RCC) measuring 6.8 x 4.5 x 2.4 cm (of the clear cell type) and limited to the kidney with no invasion of the renal capsule (Figure 2). All surgical resection margins were negative for carcinoma. Patient was discharged on post-operative day 6. He then underwent genetic evaluation for possible Von Hippel-Lindau (VHL) disease; results were negative. Following a post-nephrectomy CT Abdomen/Chest with contrast which showed hyper vascular metastatic liver lesions; 6months later, patient underwent a biopsy of the liver that revealed metastatic well differentiated neuroendocrine tumor.

He subsequently underwent hormonal therapy with lanreotide monthly infusions (x 12 infusions). A repeat CT Abdomen/

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pelvis showed an unchanged 2.6cm lesion within the neck/body of the pancreas, and multiple vague arterially enhancing liver lesions, compatible with known metastatic liver-pancreatic endocrine neoplasm. There was no metastasis to the chest or pelvis. He was seen by the Otolaryngology service, following complaints of difficulty in swallowing, and subsequently underwent right sided thyroidectomy. Pathology report showed Multinodular goiter. He is currently stable, and has seen a decrease in weight from 555lbs to 469lbs.

Patient was subsequently seen in the hospital for worsening renal function, associated with recurrent abdominal pain, nausea, vomiting, and diarrhea. He was noted to be positive for Clostridium Difficile colitis and placed on oral Vancomycin. He had a repeat computed tomography (CT) Abdomen/pelvis which demonstrated a poorly evaluated mass of the right hepatic lobe measuring 3.6 x 2.3 cm. He was discharged to a nursing home and died at the facility secondary to a fall at the facility.

Figure 1. CT abdomen and pelvis with contrast showing Left renal cyst.

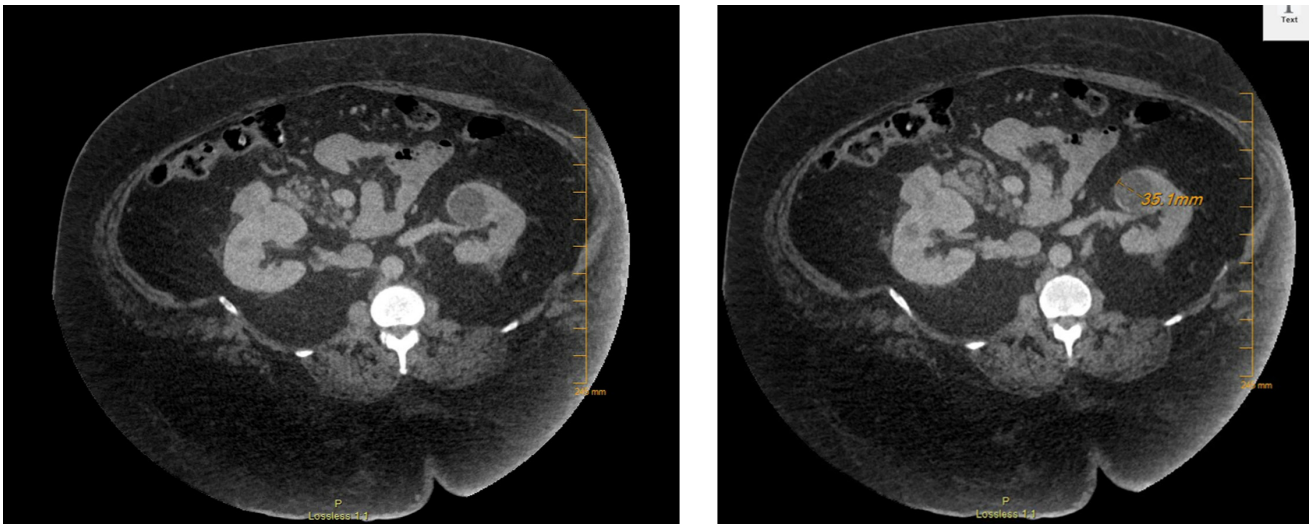


Figure 2. CT abdomen and pelvis with contrast showing Right Renal Cell Carcinoma.

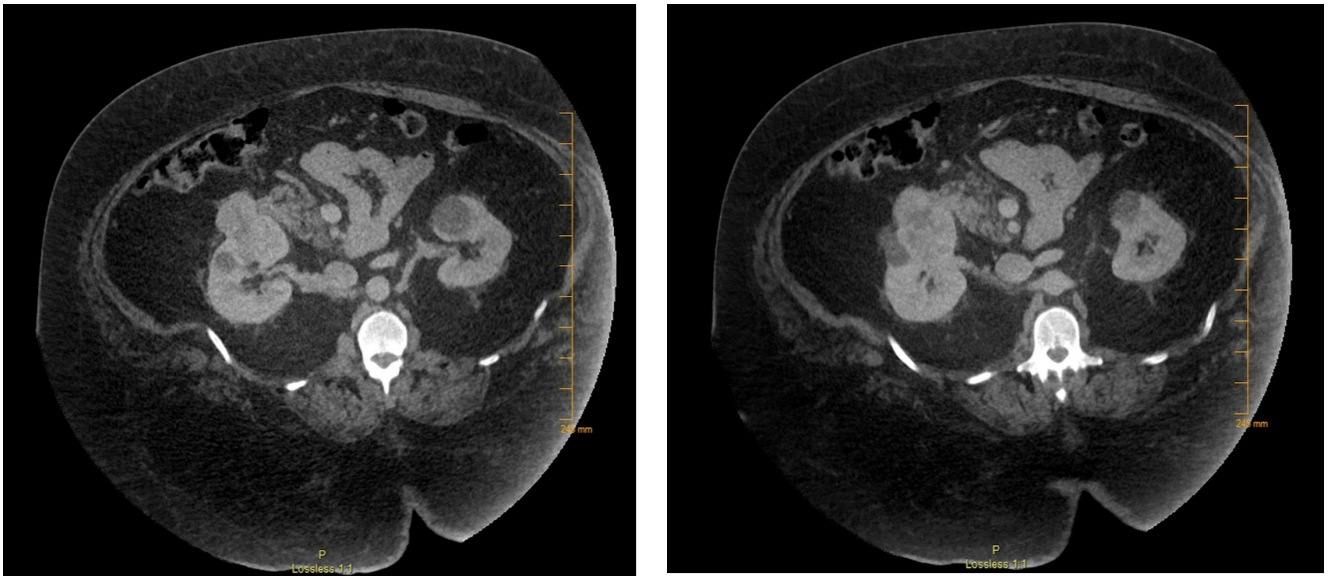


Figure 3. Pancreatic Endocrine Neoplasm.

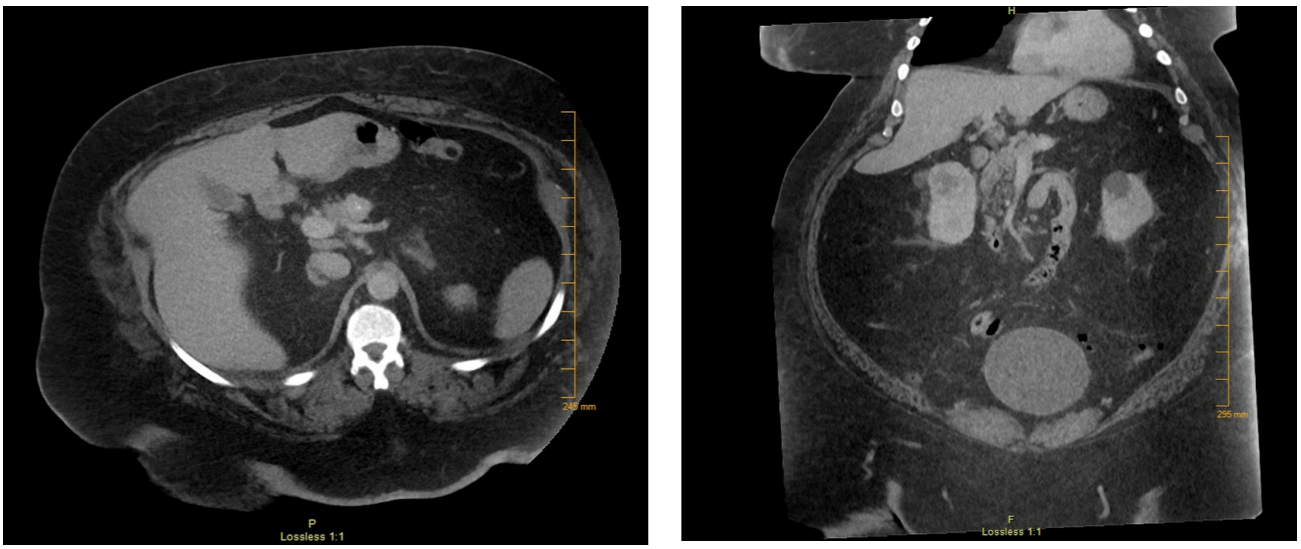


Figure 4. Von Hippel Lindau- Right Renal Cell Carcinoma.

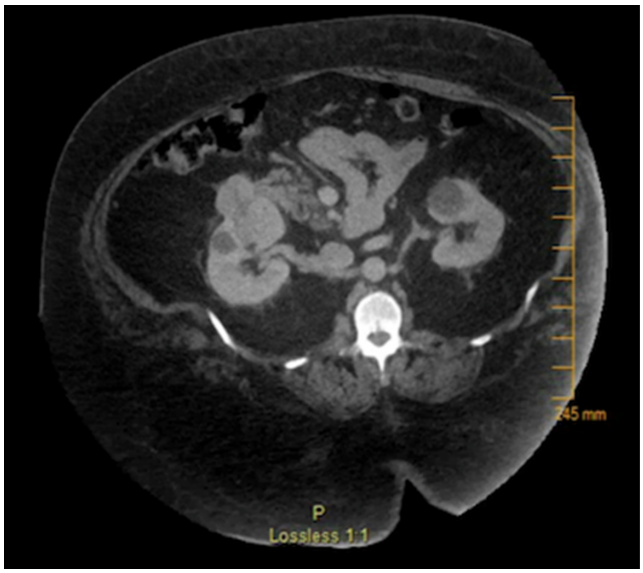
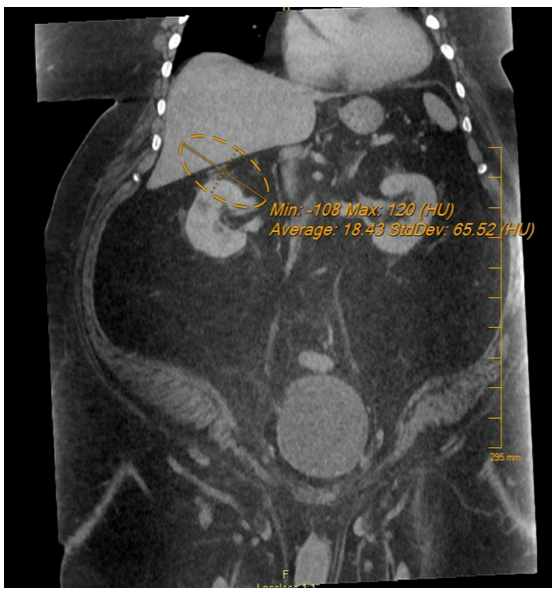


Figure 5. Adrenal Tumor



DISCUSSION

Neuroendocrine tumors (NETs) are a heterogeneous group of neoplasms originating from neuroendocrine cells. Although NETs are slow-growing, they have malignant potential(1). PNETs are rare neuroendocrine neoplasms with a reported incidence of <1 per 100,000 and account for about 1–2% of all pancreatic neoplasms. However, they are the second most common solid pancreatic neoplasm after pancreatic ductal adenocarcinoma. The incidence increases with age and peaks in the sixth and seventh decade (3).

PNETs are classified into functional and non-functional tumors, based on the presence or absence of symptoms. In recent studies, non-functional PNETs (NF-PNETs) comprise approximating 80% of all cases. Due to advances in imaging techniques , accidental detection of asymptomatic PNETS may have a contributory role in this relative increase(3). According to the National Cancer Institute registry, the incidence of PNETs is estimated at 1000 new cases every year in the United States (2). Although the majority of PNETs are sporadic, they may also arise in the context of familial syndromes (less than 10% of all cases). Cancer predisposition syndromes are frequently characterized by an inherited deleterious germline mutation in a tumor suppressor gene that leads to increased tumor susceptibility in the pancreas and in other neuroendocrine organs, leading to the development of multiple tumors. These syndromes include multiple endocrine neoplasia type 1 (MEN1), von Hippel–Lindau disease (VHL), neurofibromatosis type 1 (NF1), and tuberous sclerosis complex (4).

PNETs develop in 10% to 17% of VHL patients. They are almost exclusively non-functional and are frequently detected incidentally during follow up for other extra-pancreatic tumors associated with the syndrome(4). In addition to pancreatic neoplasms, patients with VHL often develop a variety of benign and malignant neoplasms, including clear-cell RCC, pheochromocytomas, paragangliomas, hemangioblastomas, retinal angiomas, endolymphatic sac tumors of the middle ear, and papillary cystadenomas of the epididymis and broad ligament(4) Although the precise mechanism that leads to the development of PNETs is unknown, the mutated VHL protein results in a lack of degradation of the hypoxia-inducible factors (HIF) and ultimately in an uncontrolled production of factors promoting angiogenesis and tumor growth (4).

The family history of our patient was significant for pancreatic malignancy in the mother; which emphasizes the importance of obtaining a detailed family history from patients.

Our patient denied use of cigarettes, and/or alcohol. Smoking or alcohol consumption does not appear to increase the risk of NENs. GI NETs are more common in African Americans than whites, while bronchial carcinoids predominantly affect Caucasians (5).

The diagnoses of our patient's RCC and PEN masses was incidental. However, when symptoms such as abdominal pain, weight loss or abdominal mass are present, they are typically as a result of mass effect(1). Incidentally identified masses is common in the literature(6). The masses were found on a CT Chest Pulmonary embolism protocol. The most common diagnostic tools for the dual diagnoses of RCC and PEN are dynamic CT scans(7). Other diagnostic tools include ultrasonography, MRI, octreotide scintigraphy and PET-scans with 5-hydroxytryptophan or L-dopa(8). Endoscopic Ultrasound (EUS) is an excellent modality useful for the detection of PNETs, especially small tumors that are not detectable by CT or MRI. EUS also offers the additional benefit of obtaining biopsies for diagnosis. Nuclear medicine imaging including SPECT or PET scan could be useful for localizing functioning PNET and searching for metastatic disease or recurrence. (1) PNETs cannot be visualized on PET scan with 18F-FDG because a majority of them are well differentiated. However, PET with 68-Ga DOTATATE has improved sensitivity (9). The size of the PEN mass in our patient was 2.5-2.6cm and it is in the moderate risk category for metastatic PEN disease(10). The frequency of metastatic disease at the time of diagnosis is reported as 60%–80%(1) .Compared with pancreatic adenocarcinoma and functional PNETs, non-functional PNETs have an aggressive ability. They usually invade the surrounding organs and blood vessels and most of the patients are discovered with liver metastases. (1)

The Criteria for metastases in PEN include tumor size above 3 cm, increased tumor doubling time of less than 500 days and mutation on exon 3(10). It was no surprise, that in a space of two months the PEN in our patient had metastasized to the liver and developed into a metastatic PNET Generally; most PNETs are indolent, and a "wait-and-see" approach has historically predominated. However, an "aggressive" approach now predominates and consist of 4 components: surgery, locoregional therapy, systemic therapy, and complication control. Surgical removal of primary, non-metastatic PNET is the only clinical cure, and surgical debulking of liver PNET metastases reduces the hormone secretion from functioning PNETs and the tumor mass effects of all PNETs. Locoregional therapy of liver metastases is indicated for most patients with liver metastases. Systemic therapy is required for patients with residual disease after surgery and locoregional therapy(11). PNETs tend not to respond well to chemotherapy and targeted drugs; therefore treatment of choice is surgical resection with curative intent (1). New advances in treatment have introduced innovative techniques like PRRT (Peptide receptor radionuclide therapy. (2)

The RCC in our index patient was contained in the kidney and did not penetrate the gerota fascia; as such, surgical excision was definitive in the treatment of his RCC .Survival outcomes of curative surgery are better than those of loco-regional therapies, such as liver chemoembolization. Elias

et al. reported detecting a 5-year survival rate of 71% for 47 patients who underwent partial hepatectomy versus 31% for 65 patients treated with chemoembolization .Furthermore, Tao et al. demonstrated that debulking surgery improves the effect of subsequent loco-regional treatment. In cases of synchronous metastases, simultaneous resection of the primitive tumor and hepatectomy has been reported, with acceptable postoperative morbidity and mortality(12). However, surgical resection is controversial in patients with a tumor size smaller than 2 cm; tumors having a benign appearance and tumors showing slow progression.(13)

One debated point is the indication for primary tumor resection in patients with unresectable metastatic disease. The meta-analysis by Zhou and colleagues included 10 studies, with a total of 1226 patients undergoing primary tumor resection and 1623 patients who did not have surgery. Results showed a significantly longer survival in patients who had surgical resection of the primary tumor (35.7–83% surviving patients in the surgical group versus 5.4–50% in the non-surgical group at 5years). (12).

Our Patient was managed on monthly Lanreotide 120mg SC. There are no definitive treatment plans for PNETs that present with a diffuse infiltration of the pancreas(1). More than 80-90% of pancreatic islet tumors express somatostatin receptors (SSTRs). The somatostatin receptor analogs (SSRA) Octreotide and Lanreotide are commonly used for initial treatment of advanced stage well-differentiated grade 1 or 2 PNETs(2). In addition, SSRA are also used as palliative treatments to slow down progression and stabilize the disease burden (13). Biological response to SSRAs depends on distribution and level of expression of SSTRs subtypes in tumors, and the expression of selective somatostatin receptor-signaling pathway molecules (14).

In a randomized, double-blind, placebo-controlled study on patients with GEP-NET, the SSRA octreotide-LAR delayed tumor progression compared to placebo (14.3 months versus 6 months). Following 6 months of therapy, progression-free disease was observed in 66.7% of the therapy group compared to 37.2% of the placebo group (13).

Rinke et al performed a placebo-controlled, double-blind, phase IIIB study in 85 patients with well-differentiated metastatic midgut NETs using octreotide-LAR. Median time to tumor progression in the treatment and placebo groups was 14.3 and 6 months, respectively. After 6 months of treatment, stable disease was observed in 66.7% of patients in the treatment group and 37.2% of patients in the placebo group. Functionally active and inactive tumors responded similarly(14).

Since, somatostatin analogs do not cause tumor shrinkage; Peptide Receptor Radionuclide Therapy (PRRT), everolimus (mTOR inhibitor), chemotherapy or sunitinib (multi RTK inhibitor) are used to manage well-differentiated PNETs that have progressed on SSRA. PRRT is also relevant for metastatic disease (2). However; most of the treatment strategies used by GI oncologists to overcome tumor burden lack objective response. At most, these therapies stabilize the tumors but do not enhance the overall survival of patients (2).

Nevertheless; a randomized clinical trial with 410 patients who had advanced, low-grade or intermediate-grade PNET, compared Everolimus with placebo. Everolimus significantly prolonged progression-free survival compared to placebo (11.0 versus 4.6 months) (14). Similarly; In a phase III trial of 171 patients with advanced, well-differentiated, progressive PNET, Sunitinib improved investigator-assessed progression-free survival versus placebo (11.4 versus 5.5 months) (15).

NF-PNETs have a poor prognosis, with a 5-year survival of 60%–100% in cases of localized disease, 40% for regional, and 29% for distant metastases (1) . In a retrospective series including 72 patients with liver invasive PNET, the morbidity and mortality rates following surgery was found to be 50% and 0% respectively. One and five year survival rates was found to be 97.1% and 59.9% respectively (13) .

PNET are frequently diagnosed at a late stage, with approximately 65% of patients presenting with unresectable or metastatic disease; as a result, these patients have poor prognosis. The median survival time for patients with distant metastasis is 24 months and limited treatment options are available for this population(16). However; prognosis following diagnosis of RCC and PEN is good. Death rate for metastatic PEN in VHL patients was 0.3% (10) and for RCC, its overall incidence-based mortality rate was5.3 per 100,000 person years from 1992 to 2015 (17).

In a large multi-center study to assess the prognosis of sporadic nonmetastatic sNF-PNETs; the tumor was resected in 210 patients, (median tumor size was 15 mm). Postoperative mortality was 0.5% . Severe morbidity rate was 14.3% and 10.6% of patients had metastatic lymph nodes. The 1, 3 and 5 year disease-free survival rates were 95.1%, 91.0%, and 87.3%, respectively (18).

CONCLUSION

The incidence of PNETs is vastly increasing worldwide; therefore, novel strategies to manage this specific neoplasia is urgently needed. Several factors contribute to the management failure of PNETs. PNET is characterized by significant heterogeneity which is the major challenge associated with the management of this neoplasia. Also, the majority of PNET therapeutics only stabilize the disease. Furthermore, Immunotherapy does not work in this patient population. Our patient's unique presentation, with two concomitant but metachronous tumors, highlights the importance of evaluating for multiple tumors when treating a patient with morbid obesity and a positive family history.

Conflict of Interest

The authors declare that there are no conflicts of interest to disclose regarding the publication of this paper. This manuscript is original and has not been published by any other journal. Neither is the manuscript under consideration for publication elsewhere.

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