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PANCREATIC METASTASES FROM UROTHELIAL CANCER

Maria Kyrkasiadou[1], Ioannis S. Papanikolaou[1], Ekaterini Politi[2], Vasiliki Nikolaidou[1], Konstantina Kakogianni[1], Keisi Mara[1], Aristotle Bamias[1]

[1] 2nd Propaedeutic Dept of Internal Medicine, National & Kapodistrian University of Athens, Attikon University Hospital, Chaidari, Greece
[2] Cytopathology Department, National and Kapodistrian University of Athens, Aretaieion University Hospital, Athens, Greece

Corresponding author's e-mail: v.k.nikolaidou@gmail.com

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ABSTRACT

Background: Urothelial carcinoma (UC) is a common malignancy that rarely metastasizes to the pancreas. Pancreatic masses in patients with UC present significant diagnostic challenges.

Case report: An elderly man with a history of nephroureterectomy for UC of the renal pelvis presented with lower back pain, nausea, and constipation. Imaging revealed local relapse and a solitary pancreatic mass. Endoscopic ultrasound-guided fine needle biopsy (EUS-FNB) confirmed the diagnosis of metastatic UC. The patient was treated with carboplatin and gemcitabine and subsequently with pembrolizumab but experienced rapid progression and succumbed to his disease.

Conclusion: Pancreatic metastases from UC are extremely rare. Accurate diagnosis requires histological confirmation, and EUS-FNB provides a minimally invasive and effective method. Management should be individualized, and the role of multidisciplinary team involvement is critical.

KEYWORDS

Urothelial carcinoma, pancreatic metastasis, endoscopic ultrasound, fine needle biopsy

LEARNING POINTS

- In patients with a history of advanced urothelial carcinoma, the possibility of a pancreatic mass being metastatic, though uncommon, should always be considered in the differential diagnosis.
- Multidisciplinary team involvement is crucial for optimal diagnostic and management decisions.
- Histological confirmation is mandatory, and endoscopic ultrasound-guided fine needle biopsy is the most accurate and minimally invasive approach for obtaining tissue.

INTRODUCTION

Urothelial cancer (UC) is the 9th most common cancer worldwide, accounting for 3% of all newly diagnosed cancers, with a higher incidence in developed countries[1]. Around 80% of UCs arise from the bladder but the entire urinary tract (renal pelvis, ureter, urethra) may be involved. Amongst risk factors tobacco smoke is the leading cause of UC, followed by exposure to environmental and occupational chemicals[1]. Most UCs do not invade the muscle layer at diagnosis and can be managed with surgical

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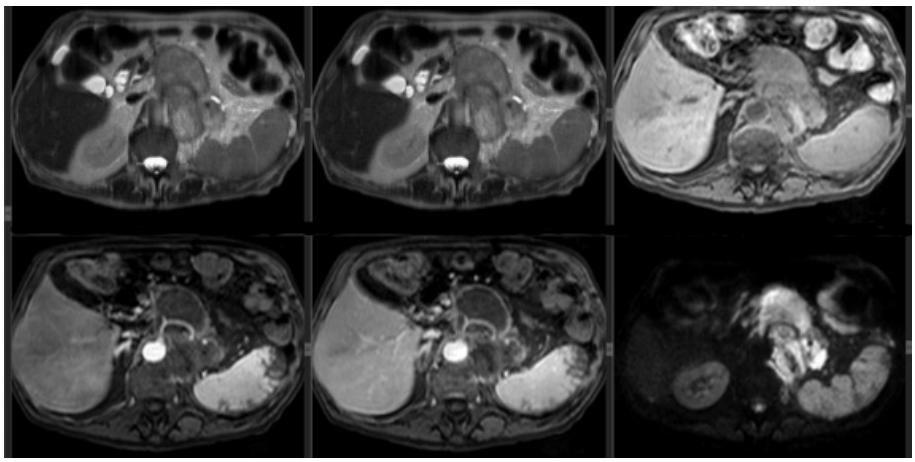


Figure 1. Magnetic resonance imaging of the abdomen showing a 4.3 × 3 cm mass of the pancreatic body, (MRI-T2W sequence: upper middle/CM T1 sequence: lower middle). There is evidence of invasion of the splenic artery, the superior mesenteric artery and the splenic vein.

removal of the tumour, with intravesical chemotherapy or Bacillus Calmette-Guérin (BCG) reserved for cases with high probability to progress to muscle-invasive disease. Although only 5% of patients have metastatic disease at diagnosis, about 50% of patients with non-metastatic, muscle-invasive disease will develop metastases. Despite significant recent progress in the treatment of metastatic disease, prognosis remains poor with only around 20% of patients living beyond 3 years[2]. Most common sites of metastasis include lymph nodes, bones, lungs and liver.

The pancreas is a rare site of metastasis from other solid tumours. Roughly 2-5% of pancreatic masses are secondary carcinomas, although autopsy series suggest that clinically silent cases may be more frequent[3,4]. Lung, gastrointestinal and renal cell carcinomas are the most frequent primaries metastasizing to the pancreas. In contrast to its neighbouring renal-cell carcinoma, UC rarely metastasizes to the pancreas. Consequently, the presence of a pancreatic mass in the context of UC is a considerable diagnostic and therapeutic challenge.

We present a rare case of solitary pancreatic metastasis from urothelial carcinoma of the renal pelvis, diagnosed via endoscopic ultrasound guided fine needle biopsy (EUS-FNB). Our case underlines the importance of including metastatic disease in the differential diagnosis of pancreatic masses in a patient with another active malignancy, despite the rarity of such metastatic manifestation and the importance of swift and accurate diagnosis through multidisciplinary (MDT) involvement to avoid unnecessary major surgery.

CASE DESCRIPTION

An 81-year-old male presented with lower back pain, nausea and constipation. The patient had undergone a left nephro-ureterectomy 8 months previously, for a high-grade urothelial cancer of the renal pelvis (pT3NxM0).

His past medical history was significant for hypertension, and a surgically removed meningioma with no sequelae. Regular medication included phenytoin, amiloride, furosemide, olmesartan and simvastatin. Social history was positive for 40 pack-year smoking, while the patient denied alcohol consumption. Family history was insignificant.

Physical examination was unremarkable with only mild tenderness of the epigastrium. There was no tenderness of bony areas and no palpable lymph nodes.

Laboratory studies, including complete blood cell count, glucose level, metabolic panel, electrolyte levels, lactate dehydrogenase level, and coagulation studies, were within normal ranges. Magnetic resonance imaging (MRI) of the abdomen revealed a hypovascularized mass (4.3 × 3 cm) of the pancreatic body, with involvement of the splenic artery, the superior mesenteric artery and splenic vein, local relapse of his primary tumour and abdominal wall implants *(Fig. 1)*. Since, differential diagnosis of the pancreatic mass between primary or metastatic tumour could not be made, based on radiological criteria, we performed an endoscopic ultrasound guided fine-needle biopsy (EUS-FNB) of the pancreatic mass. EUS confirmed the presence of a mass of mixed echogenicity in the body of the pancreas. The mass seemed to compress the splenic vessels, however without any definite criteria of vessel invasion; no pathological lymph nodes were noted. EUS-FNB was performed using a 22-gauge FNB-needle (Acquire, Boston Scientific, USA) *(Fig. 2)*. According to our protocol, two needle passes were performed, yielding macroscopically adequate material. No early adverse events were noted, and the patient was discharged. Cytological examination of the FNB-specimen revealed very atypical epithelial cells lying singly and in clusters in a necrotic background.



Figure 2. Endoscopic ultrasound showing a pancreatic mass of mixed echogenicity. Fine-needle biopsy (FNB) using a 22-gauge FNB-needle was performed.

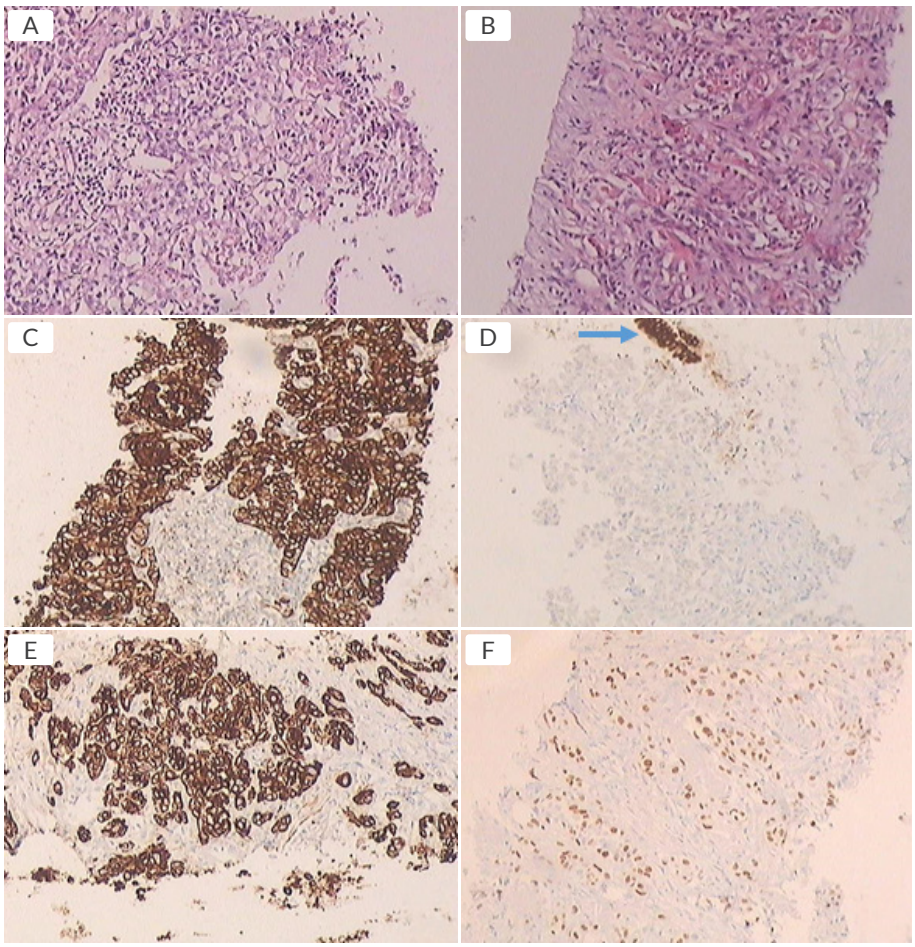


Figure 3. A, B) Hematoxylin ad eosin-stained cell block; C) Strong positive membranous immunostaining of CK34βE12 in neoplastic cells; D) Tumor is MUC5AC-negative. There is positive cytoplasmic immunostaining of MUC5AC in normal pancreatic tissue (positive internal control) (arrow); Tumor cells display strong membranous CK7 (E) and intense nuclear p63 staining (F).

According to the past medical history of the patient a panel of immunocytochemical stains were performed on the cell-block in order to confirm or exclude a metastatic urothelial carcinoma *(Fig. 3)*. Immunostaining was positive for cytokeratin-7 (CK7), CK 34βE12, CK AE1/AE3, CK20, p63 and negative for Mucin 5AC (MUC5AC), Vimentin and Paired-box gene 8 (PAX8). The diagnosis was consistent with metastasis favouring UC origin.

After the diagnosis, his case was discussed in our institutional multidisciplinary Oncology Board. Taking into consideration the multiple sites of disease, the short interval from initial surgery and the non-resectability of the pancreatic mass, a decision for systemic therapy was made.

According to international guidelines at the time of diagnosis[5], the patient was evaluated for eligibility to receive cisplatin. He was deemed ineligible based on an Eastern Cooperative Oncology Group performance status (ECOG PS) of 2. Therefore, he received chemotherapy consisting of the combination carboplatin and gemcitabine administered every 2 weeks. Patient received 3 cycles of chemotherapy. During this period, his symptoms deteriorated with an increase in back pain, limitation of his daily activities, nausea and weight loss. Radiological tumour assessment was performed earlier than planned and revealed increase in the size of the pancreatic mass (6 × 4.3 cm). Treatment with pembrolizumab, an anti-programmed cell death-1 (PD-1) immune checkpoint inhibitor was planned. Unfortunately, the patient deteriorated rapidly and died from his cancer, 4 months after the diagnosis of pancreatic metastasis.

DISCUSSION

Metastases to the pancreas from UC are exceptionally rare, with only a limited number of cases reported in the literature[5-10]. These reported cases are summarized in *Table 1*. Most of these cases were diagnosed within the first year after the initial diagnosis of the primary tumour, highlighting the aggressive biology of UC when the pancreas is involved. In contrast to more common sites of UC spread, such as lymph nodes, liver, or lung, pancreatic involvement is not typically considered in routine clinical practice, which makes timely recognition particularly challenging.

Our case aligns with the few previous reports in demonstrating that diagnosis cannot rely solely on imaging findings, as radiological features often overlap with primary pancreatic tumours[6,7]. In this context, histological confirmation becomes essential. EUS-FNB offers a minimally invasive, highly accurate method, as supported by large single-centre series and recent meta-analyses. In our patient, EUS-FNB allowed for rapid confirmation of metastatic UC and avoided unnecessary surgical exploration.

Management strategies for pancreatic metastases from UC remain heterogeneous. Some authors have reported curative resections in highly selected oligometastatic

Reference	Year	Primary tumour		Diagnosis of pancreatic metastases		Other disease sites	Treatment	Follow up
		Site	Stage	Time from primary	Method			
Shinagare et al.[3]	2004-2009	Bladder	>II	NR	Imaging	NR	NR	NR
Canter et al.[5]	2012	Bladder	I	concurrent	Laparotomy	Bladder	Chemotherapy	NR
Park et al.[6]	2021	Bladder	IIIA	7 months	Surgery (pancreaticoduodenectomy)	Regional LNs	Surgery + chemotherapy	Disease-free for 16 months
Smith et al.[7]	2000-2014	NR	NR	NR	EUS-FNB	NR	NR	NR
Koyuncuer et al.[8]	2022	Renal pelvis	IVB	12 months	EUS-FNB	Lung	None	Died 2 months after pancreatic M
El Hajj et al.[9]	2005-2019	Renal pelvis, bladder	NR	NR	CT-FNB MRI-FNB EUS-FNB	NR	NR	NR
Hou et al.[10]	1998-2010	Bladder						
Our case	2022	Renal pelvis	IIIB?	8 months	EUS-FNB	Local relapse, abdominal implants	Chemotherapy	Rapid deterioration

Table 1. *Reported cases of metastases to the pancreas from urothelial cancer. Staging according to American Joint Committee on Cancer (AJCC) 8th edition.*

Abbreviation: NR, not reported; EUS, endoscopic ultrasound; FNB, fine-needle biopsy; CT, computed tomography; MRI, magnetic resonance imaging; LNs, lymph nodes.

patients with favourable outcomes. However, most cases—including ours—were treated with systemic therapy, in line with current international guidelines. Despite treatment with carboplatin–gemcitabine, our patient experienced rapid progression, which is consistent with previously described poor prognoses[2]. The advent of immunotherapy has reshaped the therapeutic landscape, and PD-1/PD-L1 inhibitors may provide benefit in selected cases, though robust evidence in the setting of pancreatic metastases remains lacking. Our patient received pembrolizumab following progression on chemotherapy with no meaningful response of his disease. Although, experience with UC metastasis to the pancreas is extremely rare, outcome in our case is in sharp contrast to the favourable natural history of pancreatic metastases from the anatomically neighbouring clear-cell renal carcinoma.

In our case, establishing the urothelial origin of the pancreatic mass was crucial, as the therapeutic implications differ substantially from those of a primary pancreatic carcinoma. While histological confirmation is generally required for metastases in other sites as well, in this context it was particularly important to avoid a potential misdiagnosis that could have led to unnecessary major pancreatic surgery and to ensure the patient received the appropriate systemic treatment for advanced UC.

In summary, our case emphasizes three important messages: first, pancreatic metastases, though rare, should be included in the differential diagnosis of pancreatic masses in UC patients; second, EUS-FNB is the diagnostic method of choice, ensuring accuracy and preventing unnecessary surgery; and third, treatment decisions should be individualized within a multidisciplinary framework, based on the results of contemporary systemic therapy.

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