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Multiple Pancreatic Metastasis of Clear Renal Cell Carcinoma Associated with Neuroendocrine Tumor

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Rezumat

Metastaze pancreatice multiple de carcinom renal cu celule clare asociate cu tumoră neuroendocrină

Introducere: Tumorile metastatice ale pancreasului sunt mai puțin frecvente, carcinomul renal cu celule clare fiind unul dintre puținele tipuri de cancer cunoscute ce pot metastaza la acest nivel. Puține cazuri au fost raportate în literatură ca fiind cu metastaze metacrone multicentrice ale pancreasului, după cunoştințele noastre, niciunul fiind asociat cu o tumoră neuroendocrină pancreatică.
Prezentare caz: Descriem cazul unei femeie în vârstă de 66 de ani care a fost diagnosticată cu metastaze pancreatice multicentrice de carcinom renal cu celule clare, asociate cu tumoră neuroendocrină pancreatică concomitentă, după 14 ani de la diagnosticul inițial de cancer renal. Datorită rezultatelor bune şi supraviețuirii prelungite, rezecția chirurgicală este recomandată pentru metastazele pancreatice solitare şi multiple, precum şi pentru tumorile neuroendocrine pancreatice.
Concluzii: Diagnosticul diferențial pentru tumorile pancreatice multiple este important, chiar dacă nu ar fi influențat major indicația preoperatorie a pacientei noastre. Pacienții cu carcinom renal cu celule clare trebuie să urmeze o supraveghere pe termen lung, cu examinări regulate şi investigații imagistice, astfel încât eventualele metastaze să poată fi detectate precoce şi tratate corespunzător.

Cuvinte cheie: carcinom renal cu celule clare, metastaze pancreatice, tumori neuroendocrine pancreatice

Abstract

Introduction: Metastatic tumors of the pancreas are uncommon, but renal cell carcinoma is one of the few known cancers that can metastasize to the pancreas. Few cases have been reported as being metachronous multicentric metastases to the pancreas, but none associated with a pancreatic neuroendocrine tumor and reported in literature, to our knowledge.

Case presentation: We describe a case of 66-year-old woman who was diagnosed with multicentric pancreatic metastases from clear renal cell carcinoma associated with concomitant pancreatic neuroendocrine tumor, after 14 years from the initial diagnosis of kidney cancer. For this patient, the symptoms were unspecific for neoplastic disease, she had multiple pancreatic metastases which is an uncommon finding, but even rarer was the association of metastases with neuroendocrine tumor in the pancreas. Because of the good outcome and survival, surgical resection is recommended for solitary and multiple pancreatic metastases, as well as for pancreatic neuroendocrine tumors.

Conclusion: Differential diagnosis for multiple pancreatic tumors is undisputedly important, even though it would not have changed anything in our patient's preoperatively course. Patients with renal cell carcinoma must follow long-term surveillance with regular examination and imaging investigation so that any possible metastases can be detected early and treated properly.

Key words: clear renal cell carcinoma, pancreatic metastases, pancreatic neuroendocrine tumors

Introduction

Clear renal cell carcinoma (cRCC) is the most common subtype of renal cancer and studies show that one third of the patients have metastases on the diagnosis (1). Approximately 20% to 50% of patients with RCC will probably develop metastasis after radical nephrectomy, usually located in the lung, liver, bone, brain, and adrenal gland or anywhere else in the body (2). Pancreatic solid tumors are more frequently primary tumors, mainly adenocarcinomas and represent 70% to 95% of all pancreatic solid tumors. The pancreas is an uncommon site for metastases, accounting for only 2% to 5% of all malignancies of the pancreas (3,4). If metastasis is suspected, it has probably spread from renal cell carcinoma, melanoma, colorectal carcinoma, breast carcinoma or sarcoma (5). RCC typically spreads to the pancreas after many years, tumors being found through imaging methods in follow-up period or incidentally for other reasons. Treatment of metastatic RCC to the pancreas is surgical if complete resection can be performed, being associated with a long-term survival period, even if there are metastases present in other sites or multiple pancreatic metastases (6,7). For multicentric pancreatic metastases, total pancreatectomy can be the best treatment option.

Pancreatic neuroendocrine tumors (pNETs) develop from endocrine islet cells of the pancreas and are rare, accounting for less than 2% of all pancreatic tumors (8). They are mostly asymptomatic (from 60 to 90% of cases) and can remain undetectable for years (9). PNETs have a slower growth rate compared to exocrine tumors or metastases and have a variable range of malignant potential. Functioning pNETs include insulinoma, gastrinoma, VIPoma, glucagonoma and somatostatinoma, while non-functioning pNETs are more common and include tumors

that rather cause morbidity and mortality by invading surrounding tissues and metastasizing (10-12). After proper diagnosis of pNETs, the two most common staging systems of these types of tumors are European Neuroendocrine Tumor Society's (ENETS) guidelines and one other proposed by the American Joint Committee on Cancer (AJCC). The guidelines recommend surgical treatment as the only potentially curative treatment for all functioning and non-functioning pNETs (13).

Following the protocol for diagnosing and staging of pancreatic tumors, appropriate clinical evaluation and critical interpretation in a multidisciplinary team lead to the optimal treatment of the disease.

Case Report

We present a rare case of multiple pancreatic metastases of renal cell carcinoma associated with a neuroendocrine pancreatic tumor in a 66-year-old female, who initially presented for progressive hard-to-control glucose levels. The medical history of this patient includes grade IV obesity, type 2 diabetes insulin dependence for 7 years and clear renal cell carcinoma of the left kidney. RCC was diagnosed and surgically treated 14 years prior to presentation, when the patient underwent total left nephrectomy without other oncologic treatment. The patient has no family history of malignancies. On admission, the patient complained about progressive hard-to-control blood glucose levels that appeared progressively for 3 months. Laboratory tests showed CA19-9 within normal levels and high glucose levels 223 mg/dL. Ultrasound and CT scans were performed and 4 pancreatic tumors were detected, located in the uncinate process, the body of the pancreas and two in the caudal process measuring 25 mm, 7 mm, 30 mm, and 17 mm respectively. Imaging characterised the pancreatic masses as hypervascular in the arterial phase, with an intense homogenous contrast enhancement when compared to normal pancreas parenchyma. The multidisciplinary board (MDT) met, differential diagnosis was discussed and concluded that, most probably, the tumors are metastases from renal cell carcinoma and the best treatment option would be surgical resection. The MDT concluded that no biopsy was needed due to the fact that the surgical indication would not have been changed by the histopathological result. Intraoperatively, the presence of the pancreatic tumors and one suspicious hepatic artery lymphadenopathy were confirmed. The patient underwent total duodenopancreatectomy with en-bloc splenectomy and hepatic artery lymph node dissection. The patient had normal postoperative evolution, without events, being discharged 10 days after surgery. A histological examination revealed 3 pancreatic metastases of RCC and 1 benign neuroendocrine tumor located in the pancreas tail. The resected lymph nodes were negative for malignancy. The patient has been followed up first at 3, 6, 9 and 12 months postoperatively and then from 6 months to 6 months (by abdominal ultrasound, CT scans and CA 19-9 levels) with no signs of recurrence being detected 4 years after the surgery. The exocrine and endocrine functions of the pancreas were managed by the diabetologist and the gastroenterologist, by administration of insulin and per os pancreatic enzyme. Due to the long period of time from the renal surgery and R0 resection margins, MDT did not prescribe any oncologic adjuvant treatment.

Discussion

We report a rare case of multicentric pancreatic metastases of renal cell carcinoma synchronous with pancreatic neuroendocrine tumor, as we did not find other reported cases in the literature. Generally, metastatic tumors to the pancreas are rare, but renal cell carcinoma metastases to the pancreas are more frequently reported. PNETs are much less common than pancreatic exocrine tumors, but those tumors have a better prognosis. These tumors are usually diagnosed at ages from 30 to 60, while mRCC typically occur in the seventh decade of life.



Figure 1. Surgical specimen. Needles shows the topography of the tumors

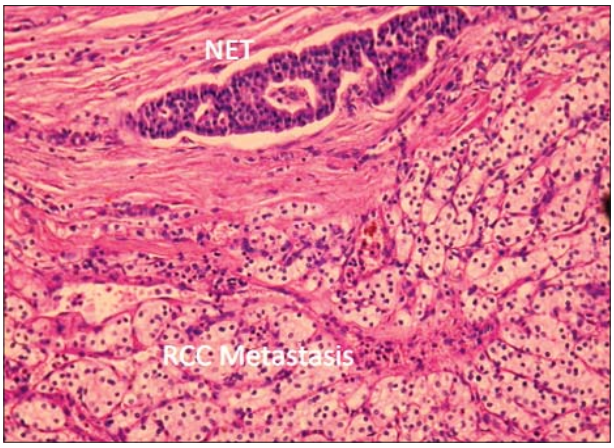


Figure 2. Histopathological examination - microscopy.

Diagnosis of these two types of tumors is challenging, being mostly asymptomatic and often found incidentally or during the follow-up surveillance. Patients with mRCC can sometimes experience weight loss, non-specific abdominal pain, jaundice or gastro-intestinal bleeding, symptoms on diagnosis being predictive factors for a worse survival rate (14-16). Our patient had high blood glucose levels for the last 3 months, a rare and unspecific sign.

RCC is the primary cancer that metastasises to the pancreas after such a long disease-free interval. This makes long-term surveillance essential for these patients. Another common situation is that in many cases there is a tendency of multiple metastases in the pancreatic tissue, frequency ranging from 27% to 39% in reported case series or literature reviews (6,17). Reported intervals between RCC diagnosis and nephrectomy until pancreatic metastasis detection is often more than 10 years, but there have been reported cases with up to 25 years of free disease intervals (17) (18). Diagnosis of pNETs is often difficult for non-functioning tumors and should include detailed past medical history of the patient and family history followed by a complete physical examination. Further biochemical and imaging tests must be performed and are uttermost important for treatment strategy. Serum PNETs biomarkers include general (Chromogranin A, neuron-specific enolase, progastrin-releasing peptide, pancreatic polypeptide) and specific (insulin, glucagon, VIP, gastrin, and somatostatin) biomarkers (19). High-resolution computerised tomography (CT) scan is the most used tool in order to evaluate pancreatic tumors even though magnetic resonance imaging (MRI) has the advantage of non-ionized radiation and some studies reported superiority over CT in detecting smaller pancreatic lesions and liver metastases (20,21). PET CT imaging techniques exceed the result brought by Octreoscan, showing a significantly higher detection rate and accuracy, for the detection of the somatostatin receptor expressing tumors (22).

Diagnosis for mRCC is mainly radiological and the use of CT in the periodic follow-up of oncological patients can be the most valuable tool in order to detect small pancreatic metastases early and compare with previous images, giving the chance to the clinician to make the correct diagnosis. Both types of tumors have similar radiological characteristics: well-circumscribed hypoechoic masses on ultrasound and homogenous hypervascular tumors on CT (23-25). All the tumors of our patient had similar radiological signs, without rising any suspicion of being different types. We considered up the possibility of other tumors in differential diagnostic and

hypothesised neuroendocrine tumors, acinar cell carcinoma, accessory spleen, solid serous adenoma, solitary fibrous tumor, and pancreatic hamartoma (26). But given the multifocality, we assumed there were all metastases from RCC.

A systematic review and meta-analyses showed that EUS can detect pNETs in 97% of cases, but the most important benefit is that adding the FNA biopsy can lead to a pre-operative diagnosis that many clinicians attempt to have before surgery (27,28). EUS is sometimes required to evaluate the relation of the tumor with the vessels and for tissue acquisition. There is still controversy regarding the utility of the routine EUS-FNA with biopsy for small solid pancreatic tumors in order to get a preoperative diagnosis since many clinicians think that the risks of the procedure complication outweigh the benefits while others believe that routine biopsy is needed for characterising and grading the tumor. Supporting the importance of pre-operative diagnosis of pancreatic small tumors (≤15 mm), Dietrich et al (29) conducted a retrospective study which included 394 patients included and had a preoperative imaging-guided biopsy or surgery diagnosis. Among these patients, approximately 40% had pancreatic ductal adenocarcinoma and 60% had neuroendocrine tumors, metastases or other tumors, thus they avoided a radical pancreatic resection and exposing the patients to important morbidity and mortality.

Surgical resection is the only potentially curative treatment for both these types of tumors. The surgical options depend on the localisation of the tumor and consists of enucleation, central pancreatectomy, distal pancreatectomy with or without splenectomy, and pancreatoduodenectomy. For pNETs, tumor size is a significant predictor for malignancy, being also correlated with Ki67 (30). Tumors above 2 cm are associated with a higher malignant potential and frequently with positive regional lymph nodes, thus it is recommended to include a lymph node dissection in this situation. ENETS first presented in 2012 a potentially better option for tumors under 2 cm, the conservative "watch-and-wait" treatment, but this is still controversial (31). A novel strategy is a histopathologic diagnostic obtained through EUS and FNA, thus choosing the treatment option according to the histopathological grading system as follows: for small WHO grade 3 tumors, surgical resection is the best option, due to its malignant potential, while for WHO grade 2 and 1 conservative treatment with periodical imaging and serum biomarkers level are recommended (32-34). Guidelines recommend surgical resections for all functioning pNETs and localised non-functioning pNETs. Although, many studies suggest and support surgical therapy as the best option therapy for localised as well as for metastatic pNET, a recent systematic review and meta-analysis on 1542 patients says that 1-, 3-, and 5-year survival rates for patients undergoing hepatectomies for pNETs metastases are significantly higher than for those who did not have surgery (35,36). Furthermore, in selected cases, enucleation may be oncologically equivalent to resection (8).

Pancreatic metastases from cRCC should be managed aggressively with complete surgical resection when possible. It was believed that RCC was resistant to chemo-therapy and radiation therapy, but recent research has shown that tyrosine kinase inhibitor-targeted therapy improves their prognosis.

Simultaneous sites of other metastases that were concomitantly resected were liver, thyroid, and skin (18,37). Studies showed a good 5-year survival rate ranging from 78% to 88% with a median disease-free survival of 44 months for patients who had pancreatic resection for mRCC. Even patients with multiple pancreatic metastases who underwent total pancreatectomy, showed a good survival rate, supporting thus the aggressive surgical intervention (37). On the other hand, patients who did not undergo surgery had a lower 5-year survival rate of 47%, with a median survival time of 27 months (6).

Both types of tumors are rare, frequently asymptomatic and found mainly incidentally,

with similar radiologic characteristics, both having a surgical curative treatment with a good survival rate.

Conclusion

Patients with a history of renal cell carcinoma should have a long-term and meticulous follow-up and we must keep in mind also to check up on the less frequent sites of metastases like the pancreas. Pancreatic resection for renal cell metastases is safe and effective, it may confer a survival benefit and should be considered in patients for whom no contraindication for surgery exists.

With this article, we would like to emphasize the importance of differential diagnosis in pancreatic tumors, multidisciplinary teams (surgeon, oncologist, radiologist, anatomopathologist) and long-term surveillance in oncologic patients.

Conflict of Interest: None declared.

Informed Consent

The patient has provided a written consent for this case report.

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