

LATE ONSET OF PANCREATIC METASTASES FROM RENAL CELL CARCINOMA. A CASE REPORT

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ABSTRACT

Metastasis of renal cell carcinoma (RCC) to the pancreas is a rare entity accounting only 0.25–3% of all pancreatic tumors. We present a rare case of isolated three focal pancreatic metastases from RCC, occurring 15 years after the left nephrectomy. The majority of the pancreatic metastases are asymptomatic, as it was in case of our patient excluding the weight loss for the last three months. We demonstrate the importance of the medical history, radiological examinations, histological and immunohistochemical analysis in making a definitive diagnosis.

Keywords: Renal cell carcinoma, Metastasis; Pancreas, Late onset

Abbreviations: RCC: renal cell carcinoma; Cytokeratin: CKAE1/AE3: CK 7: PMs: pancreatic metastases, CT: Computed Tomography

INTRODUCTION

Secondary pancreatic tumors are rare malignancies, with estimated frequency from 2% to 5% [1-3]. Renal cell carcinoma (RCC), followed by malignant melanoma, lung, colon and breast carcinoma, are among the few malignancies that are known to metastasize to the pancreas [1, 3]. Metastases occur in 30-50% of RCC cases, but only 1–2% of RCC metastasis occur in pancreas [2, 4].

It is considered that RCC is the most common primary cancer leading to isolated pancreatic metastasis, and the metastases usually occur many years after nephrectomy. The late onset of RCC metastases

is reported in a disease-free interval from 2 to 32.7 years [3, 5, 6].

We present a case of organ-isolated multifocal (three-focal) pancreatic metastasis from RCC occurring after 15 years disease-free interval.

CASE REPORT

A 66-year-old female with a history of left nephrectomy, 15 years ago due to a clear cell renal cell carcinoma, visited her physician for an annu-

al follow up. She has lost 8 kilograms in the last three months but she did not pay attention to it. Her medical history was significant for type 2 diabetes mellitus, treated with insulin and metformin, also. The operated tumor of the left kidney was classified as pT1b, G2, according to the TNM staging system classification and the Fuhrman grading system, as it was reported in the histopathology report.

Her 5-year postoperative follow-up period was uneventful, so she underwent an annual medical examination for the last 10 years period. Her blood glucose was high (12.1mmol/l) upon the hospital visit. All other blood parameters including alpha amylase level were normal.

The physical examination did not reveal any pathological signs.

A routine abdominal ultrasound examination revealed an abnormal mass with hypoechoic center in the pancreatic head. Consecutively, contrast-enhanced computed tomography (CT) of the abdomen revealed three focal masses in the pancreas: a 36 mm hyper vascular lesion with central hypodensity, which extended to the pancreatic duct and caused its consecutive dilatation. This lesion was located in the pancreatic body. The two other lesions (measuring 29 mm and 21 mm) with similar CT characteristics were detected in the pancreatic head and at the projection of duodenojejunal junction, respectively (Figure 1).

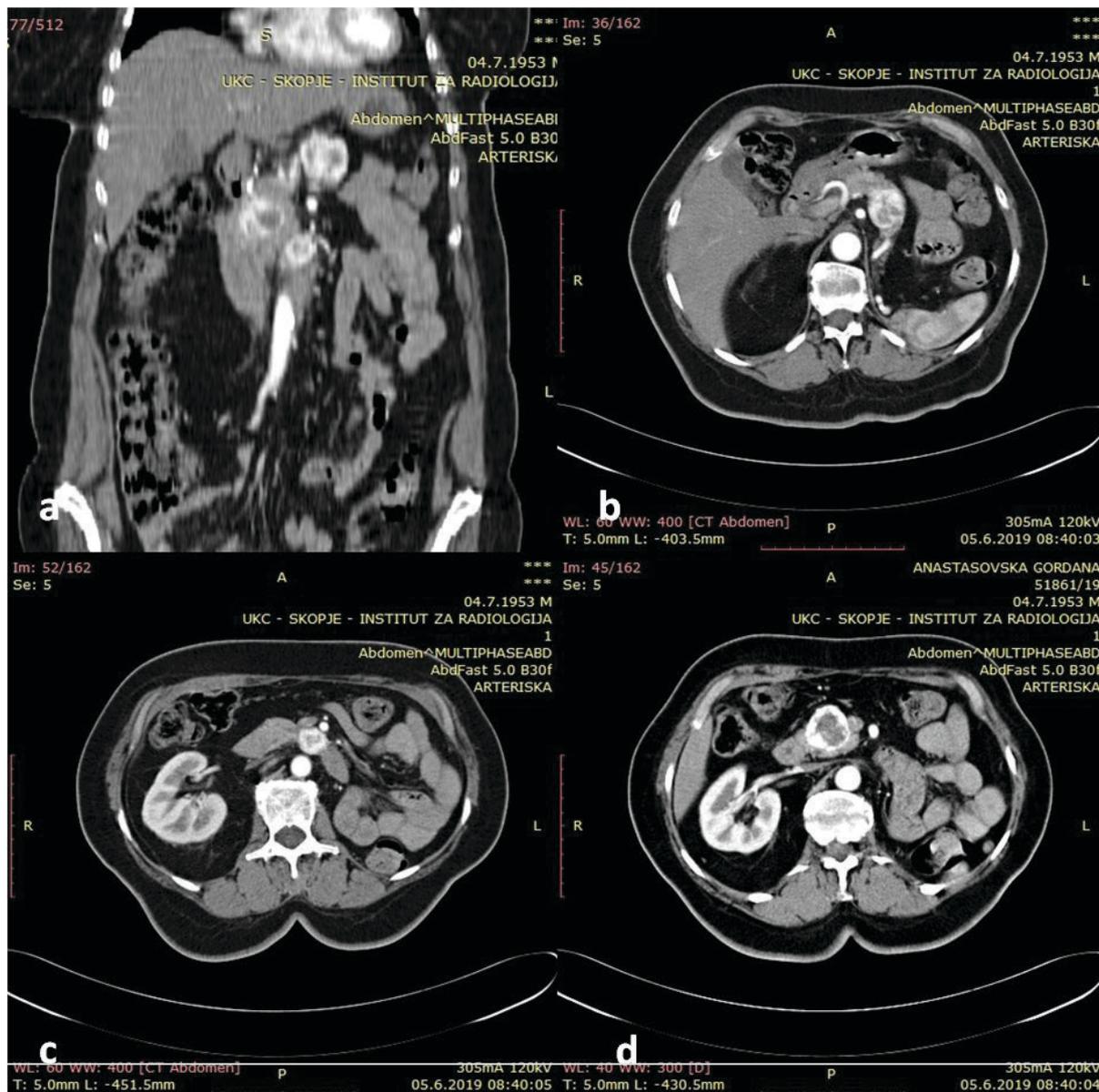


Figure 1. Multiphase CT scans, arterial phase. a) Scan in coronal plane, where 3 different sized tumor masses are clearly visible b, c, d) Well demarcated heterodense, with peripheral post contrast enhancement, predominantly solid nodular masses, located in the pancreatic body and head are visible

A positron emission tomography (PET) scan showed no other lesions in the body except the lesions located in the pancreas.

An ultrasound guided biopsy of one of the lesions was performed and the pathological report relieved pancreatic metastases from previously treated clear cell renal clear cell carcinoma. The patient underwent subtotal duodenopancreatectomy (with blind stump) at the University Clinic for Abdominal Surgery in Skopje.

The postoperative period was without any complications and the patient was released 7 days after the operation. She is in good health and without any symptoms 6 months after the operation.

The further examination of the operative material was performed at the Institute of Pathology in Skopje.

Gross examination of the operative material revealed three well demarcated white-yellowish

colored lesions with central hemorrhage, located in the body, head and uncinata process of the pancreas, measuring 3.5 cm, 3 cm and 1.3 cm, respectively.

The microscopic examination confirmed the diagnosis reported on the biopsy material in all three pancreatic nodes. The neoplastic tissue was composed of epithelial cells with clear cytoplasm, well-defined cell margins and centrally positioned nucleoli arranged in alveolar, glandular, tubular and cystic formations, some of them with papillary projections. A reach network made of small thin vessels was visible in tumor tissue. Areas of hemorrhage were found in all three tumors. Additional immunohistochemical analyzes were made with CD 10, Vimentin, CKAE1/AE3 and CK 7 antibodies. The neoplastic cells were positive for CD10 and Vimentin diffusely and partially for AE1/AE3. They were negative for CK7 antibody (Figure 2).

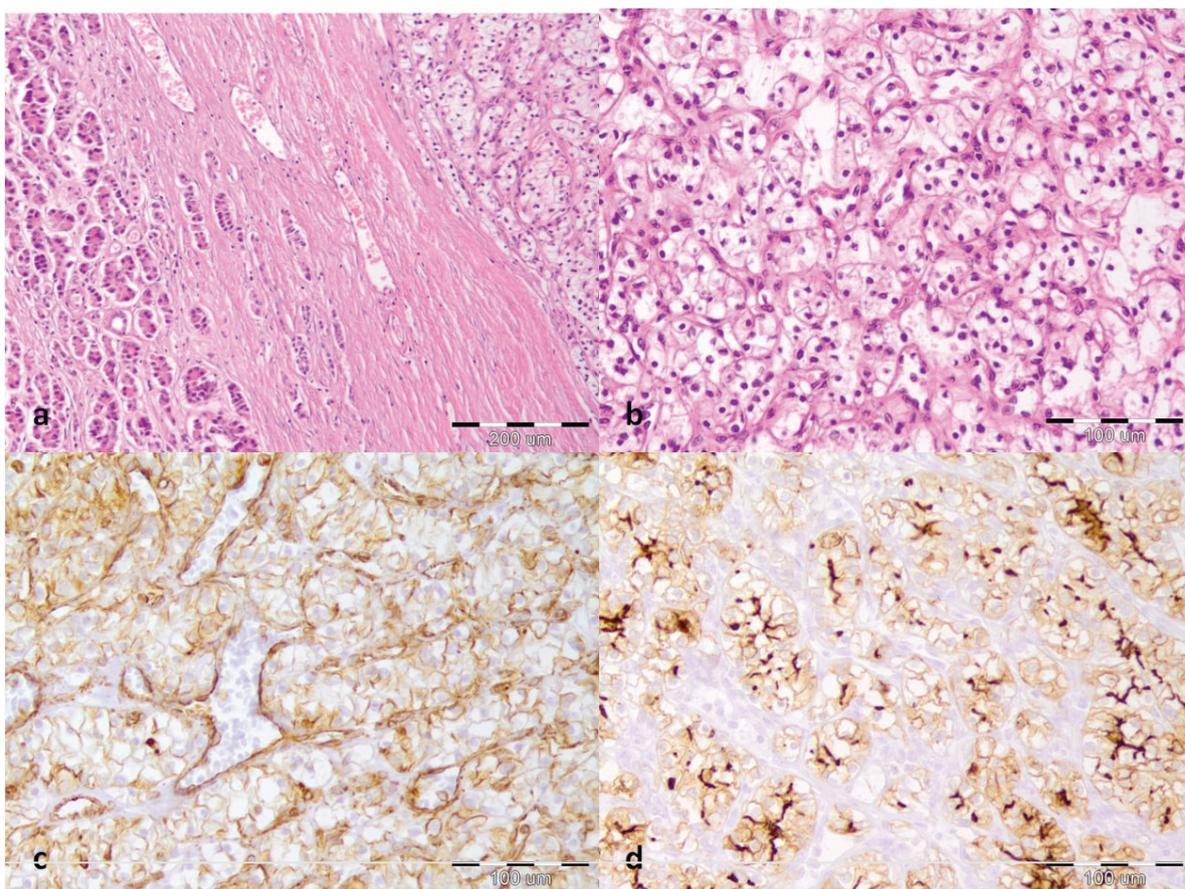


Figure 2. Microphotographs of RCC pancreatic metastasis. a) The metastasis was separated from pancreatic tissue with fibrous pseudo capsule (H.E. x 100) b) Morphological features characteristic for RCC. Clear cells with distinctive borders in alveolar arrangements (H.E. x 200) c) Tumor cells were positive for Vimentin (x 200) d) CD10 positivity in tumor tissue (CD10 x 200)

DISCUSSION

RCC is considered as a tumor with a high metastatic potential: one third of the cases already have synchronous metastases at the time of diagnosis, and another 30% will develop metachronous disease, in some cases, more than a decade after the nephrectomy [7, 8]. According to some authors, the most common distant sites for RCC metastases are the lungs, bones, liver, lymph nodes, adrenal gland and the brain [7, 9, 10]. In addition, pancreas, thyroid, skeletal muscle, skin, or soft tissue are potential rare sites for RCC metastases [3, 11].

RCC metastases to the pancreas are rare entity and only 0.25–3% of all resected pancreatic specimens are counted into this group [5, 12, 13]. It is considered that RCC more often lead to isolated pancreatic metastases, as sole site of systemic dissemination [3, 8]. However, 12% of the patients with pancreatic metastases have synchronous extrapancreatic metastases which are associated with poor prognosis [8, 14].

Pancreatic metastases are a fairly rare condition, however, of those detected in daily practice, the largest percentage originate from RCC [2, 3].

According to Shaun Kian Hong C. et al multifocal pancreatic involvement is more commonly reported in patients with metastatic RCC, compared with other primary tumors, ranging between 20% and 45% of the patients [6]. Wentz MN et al. also reported that 30% of patients have multifocal lesions, and even so nearly 80% of cases are resectable [13].

Sellner et al. through a literature search analyzed 236 cases of pancreatic metastases (PMs) and found that 39% of the metastases to the pancreas were multiple. They did not find any predictive parameter for pancreatic localization of the metastasis [14].

The interval between nephrectomy and the occurrence of pancreatic metastases can be over a decade, and this is a well-known feature of RCC [6, 8, 13, 14]. Wentz MN et al. in a series of 15 patients, reported that the median interval between nephrectomy and occurrence of pancreatic metastasis was 86 months [13]. In a review of 23 patients, Ghavamian R et al. [14] reported a mean interval of 116 months. According to the literature, the longest disease-free interval is 32.7 years [6, 8].

The patients with pancreatic metastasis from RCC could be presented with variety of non-specific gastrointestinal symptoms. In a review of 236

cases of PMs, both solitary and multiple, Sellner et al. [14] reported that more than one third of the patients were asymptomatic, abdominal pain and gastrointestinal bleeding occurred in 20% of patients, whereas obstructive jaundice, pancreatitis or diabetes mellitus were less common. On the contrary, all 5 patients with solitary metastatic renal cell carcinoma to the pancreas reported by Kassabian A et al. were symptomatic at presentation [11].

The preoperative differential diagnosis between the primary pancreatic tumors and the secondary metastatic deposits can be challenging, especially when there is a long disease-free interval, as it was in our case. Some authors [3, 8] point to some radiological features that are highly specific for RCC and can help in distinguishing metastases from primary adenocarcinoma of the pancreas. Due to the hypervascular nature of RCC, on CT scan the metastases are identified as hyper-enhancing, most pronounced in the early arterial phases of enhancement, in contrary to non-enhancing appearance of primary adenocarcinoma [3]. Yoshinori Hoshino et al. [8] reported a highlighted rim with non-enhancing internal zone as second most common CT scan pattern associated with RCC that completely correspond with the description of the CT finding in our case.

Although the radiologic features, complemented by medical history of the patient, are strongly suggestive, the final diagnosis is made with pathohistological examination [3, 8].

The most common procedure for treating pancreatic metastasis is the surgical resection. In contrast, other modalities such as chemotherapy, radiotherapy, and immunotherapy have not been shown to be effective. However, to date, there isn't a recommended pattern of treatment for patients with isolated RCC metastases, whether it's solitary or multifocal [1, 2, 4, 5, 8, 10, 17].

The choice between pancreatoduodenectomy, middle-segment or distal pancreatectomy depends on the location of the tumor/tumors within the pancreas [5, 15]. The presence of metastatic deposits in body, head and uncinate process of the pancreas, as in our case, imposed the need of pancreatoduodenectomy performing.

After surgical resection, five year survival varies from 29% to 81% [1, 2, 5, 16]. Kalra S et al. [16] demonstrated higher overall survival in the patients with pancreatic metastases from RCC compared with patients who had metastases to other sites (39 months and 26 months, respectively). According to this fact, it is believed that some host or

tumour features associated with PMs may lead to less aggressive tumor phenotype [16]. Additionally, it has been observed that the peripancreatic lymph node involvement is uncommon, which could partly explain the more favorable survival rate [15].

Patients with multiple pancreatic lesions have worse prognosis than patients with solitary metastasis (54% vs. 29%, respectively) [5].

In our case, the patient presented with a non-specific abdominal pain that lasted for several months. The pancreatic lesions were detected by ultrasound and CT and a suspicion for metastatic disease was made, while the accurate diagnosis was achieved by biopsy.

CONCLUSION

We presented a rare case of multifocal pancreatic metastases originating from RCC, 15 years after nephrectomy. The late onset of metastasis from RCC in solid organs should be always taken in consideration when dealing with treated patients with RCC. The symptoms may be nonspecific, but imaging techniques and biopsy should achieve the diagnosis. Surgical treatment, as our patient has undergone, is the best choice for these patients.

Compliance with Ethical Standards: Authors declare that they have no conflict of interest.

All procedures performed in this studies were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards..

REFERENCES

1. Katsourakis A, Noussios G, Hadjis I, Alatsakis M, Chatzitheoklitos E. Late Solitary Pancreatic Metastasis from Renal Cell Carcinoma: A Case Report. *Case Rep Med.* 2012; 2012: 464808 doi:10.1155/2012/464808
2. Sanghwa K, Sungpil Y, Suk K, Tae-nam K, Hyung-II S. Pancreatic resection for renal cell carcinoma metastasis: a case review. *Ann Hepatobiliary Pancreat Surg.* 2017; 21(3): 176–179. doi: 10.14701/ahbps.2017.21.3.176 PMID: 28990007 PMCID: PMC5620481
3. Thadani A, Pais S, Savino J. Metastasis of Renal Cell Carcinoma to the Pancreas 13 Years Post-Nephrectomy. *GastroenterolHepatol (N Y).* 2011; 7(10): 697–699. PMID: 22298966 PMCID: PMC3265015
4. Kling SM, Tannouri S, Jiang W, Yeo CJ. Pancreatic Mass in a Patient with a History of Resected Renal Cell Carcinoma and Resected Adenocarcinoma of the Ampulla of Vater: A Case Report. *J Pancreat Cancer.* 2018; 4(1): 41–44. doi: 10.1089/pancan.2018.0001. eCollection 2018
5. Sotiropoulos G, Lang H, Liu C, Brokalaki E, Molmenti E, Broelsch C. Surgical Treatment of Pancreatic Metastases of Renal Cell Carcinoma. *JOP. Journal of the Pancreas.* 2005; 6(4): 339–343.
6. Shaun Kian Hong C, Khoon Leong C. Metastatic Renal Cell Carcinoma to the Pancreas A Review. *Arch Pathol Lab Med.* 2016; 140(6): 598–602. doi: 10.5858/arpa.2015-0135-RS.
7. Alves Ribeiro M, Petersen da Costa Ferreira C, de Lucia Hernani B, Arnaldo Szutan L, Galli Mortati M, Toledo Bueno Pereira F et al. Uncommon site of metastasis from renal cell carcinoma: Case report. *Int J Surg Case Rep.* 2019; 56: 45–48. doi: 10.1016/j.ijscr.2019.02.013 PMID: 30849687 PMCID: PMC6406048
8. Hoshino Y, Shinozaki H, Kimura Y, Masugi Y, Ito H, Terauchi T et al. Pancreatic metastases from renal cell carcinoma: a case report and literature review of the clinical and radiological characteristics. *World J Surg Oncol.* 2013; 11: 289. doi: 10.1186/1477-7819-11-289 PMID: 24209713 PMCID: PMC3835140
9. Boscà Robledo A, Barber Millet S, Orbis Castellanos J, Montalvá Orón E, Salom Fuster J, De Juan Burgueño M. Metastasis of the gallbladder in clear cell renal carcinoma. *Oncol Lett.* 2012; 3(5): 1136–1138. doi: 10.3892/ol.2012.616 PMID: 22783406 PMCID: PMC3389630
10. Sand M, Bechara F, Kopp J, Krins N, Behringer D, Mann B. Gallbladder metastasis from renal cell carcinoma mimicking acute cholecystitis. *Eur. J. Med. Res.* 2009; 14: 90–92.
11. Kassabian A, Stein J, Jabbour N, Parsa K, Skinner D, Parekh D et al. Renal cell carcinoma metastatic to the pancreas: a single-institution series and review of the literature. *Urology.* 2000; 56: 211–215.
12. Ghavamian R, Klein KA, Stephens DH, Welch TJ, LeRoy AJ, Richardson RL et al. Renal cell carcinoma metastatic to the pancreas: clinical and radiological features. *Mayo Clin. Proc.* 2000; 75: 581–585.
13. Wente MN, Kleeff J, Esposito I, Hartel M, Müller MW, Fröhlich BE et al. Renal cell metastasis

- into the pancreas: a single-center experience and overview of the literature. *Pancreas*. 2005; 30: 218–222.
14. Sellner F, Tykalsky N, De Santis M, Pont J, Klimpfnger M. Solitary and multiple isolated metastases of clear cell renal carcinoma to the pancreas: an indication for pancreatic surgery. *Ann Surg Oncol*. 2006; 13: 75–85. doi: 10.1245/ASO.2006.03.064.
 15. Lavu H, Yeo JC. Metastatic Renal Cell Carcinoma to the Pancreas. *Gastroenterol Hepatol (N Y)*. 2011; 7(10): 699–700. PMID: 22298967 PMCID: PMC3265016
 16. Strobel O, Hackert T, Hartwig W, Bergmann F, Hinz U, Wente MN, et al. Survival data justifies resection for pancreatic metastases. *Ann Surg Oncol*. 2009; 16(12): 3340–9. doi: 10.1245/s10434-009-0682
 17. Kalra S, Atkinson B, Matrana M, Matin S, Wood C, Karam J et al. Prognosis of patients with metastatic renal cell carcinoma and pancreatic metastases. *BJU Int*. 2015; 117(5): 761–765. doi: org/10.1111/bju.13185

Резиме

ДОЦНА ПОЈАВА НА ПАНКРЕАСНИТЕ МЕТАСТАЗИ ОД БУБРЕЖЕН КАРЦИНОМ. ПРИКАЗ НА СЛУЧАЈ

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Метастазите од бубрежен карцином во поджелудечната жлезда се ретки и на нив отпаѓаат 0,25–3% од сите панкреасни тумори. Прикажуваме редок случај на орган изолирани 3 панкреасни метастази по потекло од бубрежен карцином, кои се јавуваат 15 години по нефректомија. Повеќето метастази во поджелудечната жлезда се асимптоматски, како што беше и во случај на нашата пациентка, со исклучок на губиток на телесната тежина за период од последните три месеци. Во трудот ја потенцираме важноста на медицинската историја, радиолошките испитувања, хистолошките и имунохистохемиските анализи за поставување дефинитивна дијагноза.

Клучни зборови: бубрежен карцином, метастаза, панкреас, доцна појава