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Case Report / Приказ болесника

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Recurrent epistaxis as manifestation of renal cell carcinoma sinonasal metastasis

Понављајуће крварење из носа као манифестација синоназалне метастазе карцинома бубрега

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Recurrent epistaxis as manifestation of renal cell carcinoma sinonasal metastasis

Понављајуће крварење из носа као манифестација синоназалне метастазе карцинома бубрега

SUMMARY

Introduction Renal cell carcinoma is the most frequent infraclavicular primary tumor metastasising in sinonasal region, although those metastases are not common. We present an unusual case of recurrent epistaxis as initial sign of renal carcinoma sinonasal metastasis and discuss about diagnostic and treatment options.

Case outline A 66-year-old patient was admitted to the hospital due to recurrent and severe epistaxis. Patient underwent nephrectomy due to renal cell carcinoma, with no signs of relapse during 3-year follow-up. Nasal endoscopy and computed tomography revealed large mass in nasal cavity, spreading to the anterior and posterior ethmoid cells, sphenoid sinus, orbit and anterior cranial fossa. Definite diagnosis of renal cell carcinoma metastasis in sinonasal region was made by pathologist after biopsy and further radiological examination showed no signs of malignant disease in abdomen, thorax or pelvis. Although patient had received 50 Gy of radiation therapy, malignant disease was evaluated as progressive with furter extension in anterior cranial fossa and maxilla and patient died 5 months after occurrence of epistaxis.

Conclusion In patients with recurrent epistaxis that also had a history of renal carcinoma, endoscopic finding of tumefaction in nasal cavity should raise a suspicion of sinonasal metastasis. In such cases biopsy is mandatory to differentiate a metastasis from primary sinonasal tumors. Histological confirmation should be followed by radiological examination of abdomen, thorax and pelvis to evaluate the possibility of renal cell carcinoma recurrence or metastatic dissemination elsewhere.

Keywords: epistaxis; renal cell carcinoma; neoplasm metastasis; nasal cavity

САЖЕТАК

Увод Карцином реналних ћелија је најчешћи инфраклавикуларни тумор који метастазира у синоназални регион, мада ове метастазе нису толико честе. Представљамо необичан случај пацијента код кога је крварење из носа било први знак синоназалне метастазе реналног карцинома и дискутујемо о дијагностичким и терапијским могућностима.

Приказ болесника Шездесетшестогодишњи болесник је примљен на болничко лечење због понављајућег, интензивног крварења из носа. Пацијенту је претходно, због карцинома одстрањен бубрег и током трогодишњег праћења није имао знакове релапса малигне болести. Ендоскопским прегледом и компјутеризованом томографијом утврђена је велики израштај у носној шупљини, који се шири у предње и задње етмоидне ћелије, сфеноидни синус, очну дупљу и предњу мождану јаму. Биопсијом је постављена дијагноза метастазе карцинома бубрега, а даља радиолошка испитивања у искључила постојање релапса малигне болести у малој карлици, абдомену или грудном кошу. Иако је пацијент примио радиотерапију, тумор је испољио даљу прогресију у предњој можданој јами и максили, а пацијент је преминуо 5 месеци након појаве крварења из носа.

Закључак Код болесника са понављајућим крварењем из носа, који у личној анамнези имају податак о карциному бубрега и код којих је ендоскопским прегледом виђен тумефакт у носној шупљини, требало би посумњати на могућност синоназалне метастазе. У таквим случајњвима обавезна је биоспија како би се разликовао примарни тумор од метастазе. Након патохистолошке потврде метастазе карцинома бубрега потребно је спровести радиолошко испитивање мале карлице, абдомена и грудног коша како би се искључила даља дисеминација малигне болести.

Кључне речи: епистакса; карцином бубрега; метастаза тумора; носна шупљина

INTRODUCTION

Nasal cavity and paranasal sinuses are very rare site of metastatic disease. Renal cell carcinoma (RCC) is the most common malignant renal tumor with unpredictable course that develops extranodal metastases of head and neck in 1.1% of cases [1]. It is reported to be the most frequent infraclavicular primary tumor metastasising in sinonasal region, although those metastases are not common [2].

We present an unusual case of recurrent epistaxis as initial sign of RCC sinonasal metastasis and discuss about diagnostic and treatment options. Patient's written consent was obtained and publication conforms to the ethical standards.

CASE REPORT

A 66-year old male was admitted to the hospital due to recurrent and severe epistaxis. Patient had a medical history of hypertension and cardiac arrhythmia regulated with standard medications prescribed by cardiologist and pacemaker implanted 4 years earlier. Patient underwent nephrectomy due to RCC, with no signs of relapse during 3-year follow-up. Also, he had a sigmoid colon carcinoma resected 13 years earlier, with no signs of recurrence.

The initial laboratory testing excluded a coagulopathy or high blood pressure as a direct cause of bleeding (prothrombin time 10.7 seconds, activated partial thromboplastin time 31.7 seconds, international normalized ratio 1.1, platelet count 210 x 10^3/mL, blood pressure 110/80 mm Hg).

During endoscopic examination, a large hypervascular outgrowth in nasal cavity was determined as the source of the bleeding. CT scan showed soft-tissue-density mass in nasal cavity, spreading to the anterior and posterior ethmoid cells, sphenoid sinus, orbit and anterior cranial fossa (Figure 1). Despite the CT scan finding, patient had no visual impairments or neurological deficits, except hyposmia. During hospital treatment, patient complained of frontal headaches which were treated with standard analgesic therapy.

Definite diagnosis of RCC metastasis in sinonasal region was made by pathologist after endoscopic biopsy (Figure 2). Haematoxylin and oesin staining showed a tumor composed of

large clear cells organized in acini. The cells showed immunohistochemical positivity for renal cell carcinoma antigen, vimentin and CD10, but were negative for CK7 and CK20.

Further radiological examination with computed tomography showed no signs of malignant disease in abdomen, thorax or pelvis. Finding of the neck ultrasound was normal with no enlarged lymph nodes or signs of neoplastic disease in thyroid gland.

Althought patient had received 50 Gy od radiation therapy, malignant disease was evaluated as progressive with furter extension in anterior cranial fossa and maxilla. The patient with incurable RCC sinonasal metastasis died 5 month after the epistaxis appearance.

DISCUSSION

Nasal secretion, stuffy nose and epistaxis are very common complaints in otorhinolaryngology practice. In such cases, detection of hypervascular tumefaction in the nasal cavity found during clinical examination should raise a suspicion for primary sinonasal tumor, such as hemangiomas, hemangiopericytomas, adenocarcinomas or melanomas. Infrequently, those patients are diagnosed with metastatic sinonasal tumor spreading from distant primary sites. Primary and metastatic sinonasal tumors are difficult to differentiate by clinical and radiological examination, therefore the biopsy is recommended.

Sinonasal metastases are quite rare; however, RCC is the most common malignancy that metastasizes to this area [3]. Common sites of RCC metastases are lungs, liver, adrenal glands, brain and bones. Most of the patients develop multiple RCC metastases, such as in the lung and liver; on the other hand sinonasal metastases are commonly solitary.

Hematogenous spread of RCC tumor cells to the sinonasal region is carried out by two routes; one is responsible for the dissemination through the inferior vena cava, heart, lungs and maxillary artery and the other leads to head and neck region via Batson's paravertebral venous plexus, bypassing the lungs. Therefore, caval route could be responsible for the concurrent lung or brain metastases and retrograde venous route could explain uncommon presentation of sinonasal metastasis without evidences of malignant tumor elsewhere. Another explanation for solitary sinonasal metastasis of RCC could be lymphatic spread of tumor cells via thoracic duct.

Today, RCC is often asymptomatic and is generally detected incidentally. One-third of newly diagnosed RCC patients have a distant metastasis as the initial presentation; another one-third of RCC patients develop a metastasis during follow-up [4]. In our case, patient underwent curative nephrectomy 3 years before the appearance of recurrent nasal bleeding and has been disease-free during regular follow-up. Radiological examination showed solitary sinonasal metastasis with no metastatic spreading elsewhere. The long latency interval may be attributed to the slow-growing characteristic of renal cell carcinoma and the fact that RCC is under the influence of host immunity. Were there any metastasis elsewhere undetected by radiological examination or RCC developed a solitary sinonasal slow-progressive metastasis, is the question that need to be addressed.

The common presentation of RCC sinonasal metastasis comprises nasal obstruction, swelling and pain. Approximately 46% of those patients complained of recurrent epistaxis due to highly vascular nature of RCC and its metastasis [5]. Identification of von Hippel-Lindau tumor suppressor (pVHL) considerably improved understanding of the RCC molecular biology. pVHL is a component of E3 ubiquitin ligase complex that targets α units of hypoxia-inducible factors (HIF-1, HIF-2) for proteasomal degradation in environment with normal oxygen concentration. In hypoxic conditions, HIF-1α is stabilized and induces the transcription of a number of downstream genes involved in pathogenesis of head and neck squamous cell carcinoma. HIF-1α significantly contributes to carcinogenesis by inducing angiogenesis through the synthesis of VEGF. HIF is known to be upregulated by VHL gene, which functional loss is identified in majority of clear cell RCCs. This sequence of events is responsible for increased vascularity of RCC sinonasal metastases and epistaxis as major sign of disease.

Histopathological confirmation of sinonasal metastatic RCC should be followed by the evaluation of the possible recurrence of primary tumor or distant spreading elsewhere. PET/CT has a high sensitivity and specificity in detecting RCC recurrence and results are in correspondence with conventional radiological examination with CT and MRI [6]. On the other hand, PET/CT is more powerful in detection of early metastatic disease, especially in bones and muscles [7]. High level of false positive results due to inflammation or scaring should raise carefulness with clinician during RCC evaluation on PET/CT.

Metastatic renal carcinoma has a poor prognosis due to chemotherapy and radiotherapy resistance and silent growth. Surgical treatment is considered optimal choice for patients with

single resectable sinonasal metastasis. 5-year survival of 35 % is reported with such patients after radical excision and nephrectomy [5]. Treatment modalities such as radiotherapy, chemotherapy or immunotherapy are reserved for the patients with unresectable metastatic disease. In last decade, numerous molecular-targeted agents were approved with positive impact on survival of patients with metastatic RCC [8]. Antiangiogenic therapy with VEGF inhibitors is considered the first-line of targeted therapy, comprising a great variety of novel agents [9]. Generally, chemotherapy is used with patients who didn't respond to immunotherapy. Patients with metastasis in multiple organs have a very poor prognosis, with 5-year survival below 7 % [10]. Our patient had a nonresectable metastasis and radiotherapy didn't achieve any benefit, which can be explained with tumor biology and volume.

In patients with recurrent epistaxis that also had a history of renal carcinoma, endoscopic finding of tumefaction in nasal cavity should raise a suspicion of RCC sinonasal metastasis. In such cases biopsy is mandatory to differentiate a metastasis from primary sinonasal tumors. Histological confirmation should be followed by radiological examination of abdomen, thorax and pelvis to evaluate the possibility of RCC recurrence or metastatic dissemination elsewhere.

Conflict of interest: None declared.

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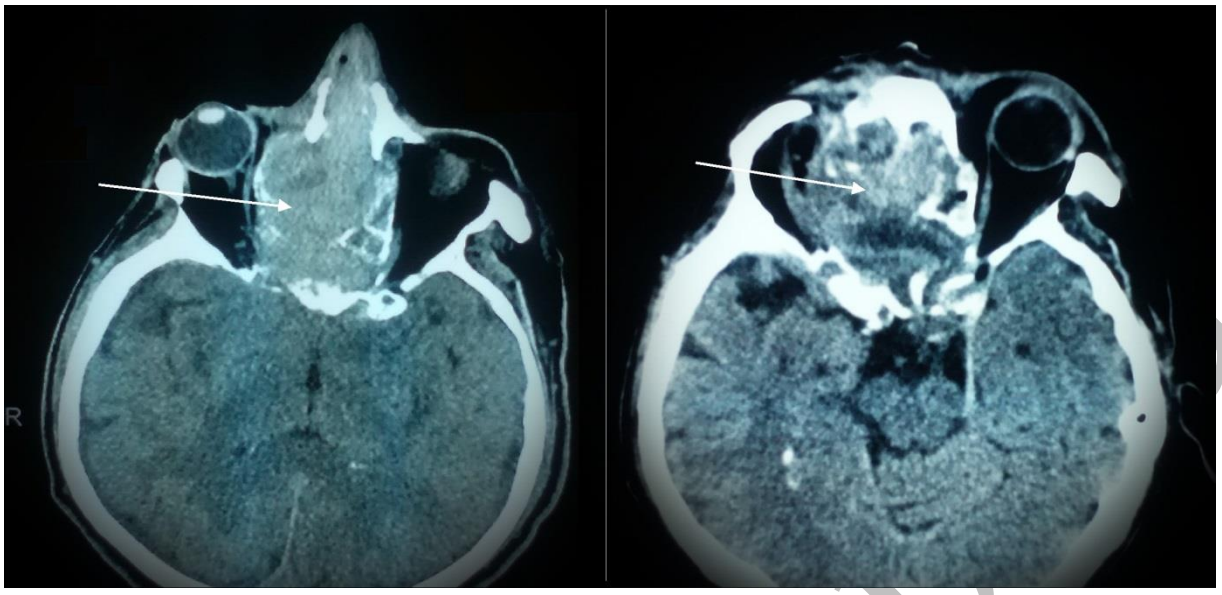

Figure 1. The 66-year old male with recurrent and severe epistaxis and history of colon carcinoma resection and nephrectomy due to renal cell carcinoma; CT scan of the paranasal sinuses: axial views; arrows point to renal cell carcinoma sinonasal metastasis with orbital and anterior cranial fossa extension

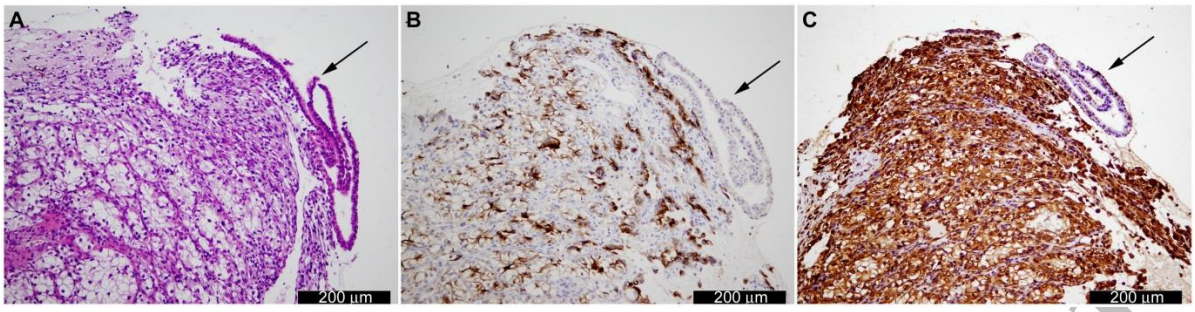

Figure 2. Histopathological finding after endoscopic biopsy of sinonasal tumor in 66-year-old male; A) tumor is under the strip of flattened pseudostratified epithelium (arrow) (H&E); tumor is composed of large clear cells organized in acini; B) tumor is positive for renal cell carcinoma antigen; C) tumor is positive for vimentin; pseudo-stratified epithelium is negative (arrow)

