



## CASE REPORT / ПРИКАЗ БОЛЕСНИКА

# Recurrent epistaxis as a manifestation of renal cell carcinoma sinonasal metastasis

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## SUMMARY

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

**Case outline** A 66-year-old patient was admitted to the hospital due to recurrent and severe epistaxis. The patient underwent nephrectomy due to renal cell carcinoma, with no signs of relapse during a three-year follow-up. Nasal endoscopy and computed tomography revealed a 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 a pathologist after biopsy and further radiological examination showed no signs of malignant disease in the abdomen, thorax, or pelvis. Although the patient had received 50 Gy of radiation therapy, the malignant disease was evaluated as progressive with further extension in anterior cranial fossa and maxilla, and the patient died five months after the occurrence of epistaxis.

**Conclusion** In patients with recurrent epistaxis who also had a history of renal carcinoma, endoscopic finding of tumefaction in the 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 the 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

## INTRODUCTION

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

We present an unusual case of recurrent epistaxis as the initial sign of RCC sinonasal metastasis and discuss the diagnostic and treatment options.

The 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. The patient had a medical history of hypertension and cardiac arrhythmia regulated with standard medications prescribed by the cardiologist and pacemaker implanted four years earlier. The patient underwent nephrectomy due to RCC,

with no signs of relapse during a three-year follow-up. Also, he had 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  $210 \times 10^9/\text{mL}$ , blood pressure 110/80 mmHg).

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

Definite diagnosis of RCC metastasis in the sinonasal region was made by a pathologist after an endoscopic biopsy (Figure 2). Hematoxylin and eosin staining showed a tumor

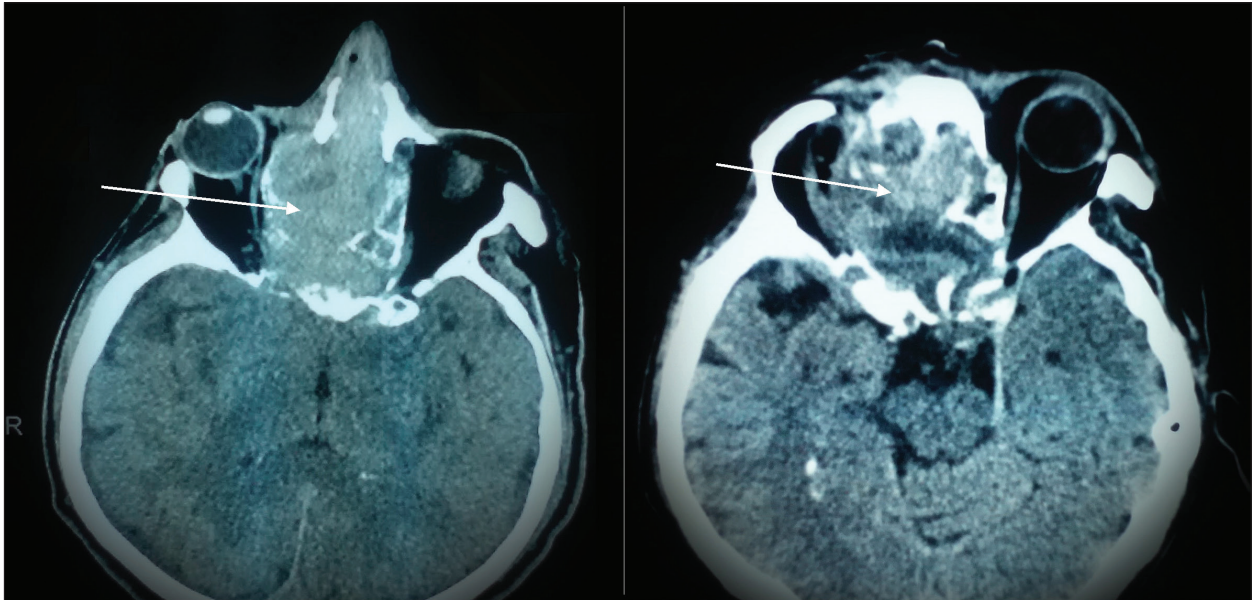
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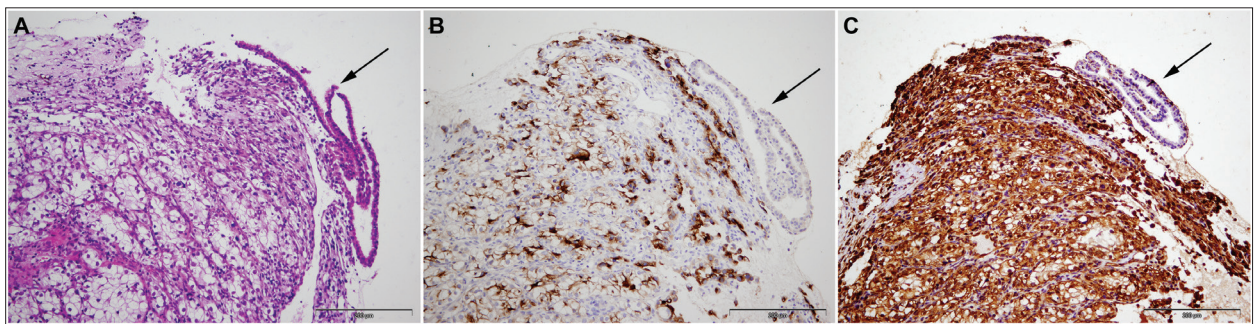
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**Figure 1.** The 66-year-old male patient with recurrent and severe epistaxis and a history of colon carcinoma resection and nephrectomy due to renal cell carcinoma; CT scan of the paranasal sinuses: axial views; arrows point to a renal cell carcinoma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



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

composed of large clear cells organized in acini. The cells showed immunohistochemical positivity for the RCC antigen, vimentin, and CD10, but were negative for CK7 and CK20.

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

Although the patient had received 50 Gy of radiation therapy, malignant disease was evaluated as progressive with further extension in the anterior cranial fossa and the maxilla. The patient with incurable RCC sinonasal metastasis died five months 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 suspicion

about 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, 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 the lungs, the liver, the adrenal glands, the brain, and bones. Most of the patients develop multiple RCC metastases, such as in the lung and the 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, the heart, the lungs, and maxillary artery, and the other leads to the head and neck region via Batson's paravertebral venous plexus, bypassing the lungs. Therefore, the caval route could be responsible for the concurrent lung or brain metastases, and the retrograde venous route could

explain uncommon presentation of sinonasal metastasis without evidence of malignant tumor elsewhere. Another explanation for solitary sinonasal metastasis of RCC could be lymphatic spread of tumor cells via the 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 third of RCC patients develop a metastasis during the follow-up [4]. In our case, the patient underwent curative nephrectomy three years before the appearance of recurrent nasal bleeding and had been disease-free during the 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 RCC and the fact that RCC is under the influence of the host immunity. Were there any metastasis elsewhere undetected by the radiological examination or did RCC develop a solitary sinonasal slow-progressive metastasis is the question that needs to be addressed.

The common presentation of RCC sinonasal metastasis comprises nasal obstruction, swelling, and pain. Approximately 46% of these 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 the understanding of RCC molecular biology. pVHL is a component of E3 ubiquitin ligase complex that targets  $\alpha$  units of hypoxia-inducible factors (HIF-1, HIF-2) for proteasomal degradation in the environment with a normal oxygen concentration. In hypoxic conditions, HIF-1 $\alpha$  is stabilized and induces the transcription of a number of downstream genes involved in pathogenesis of head and neck squamous cell carcinoma. HIF-1 $\alpha$  significantly contributes to carcinogenesis by inducing angiogenesis through the synthesis of vascular endothelial growth factor (VEGF). HIF is known to be upregulated by the VHL gene, whose functional loss is identified in the majority of clear cell RCCs. This sequence of events is responsible for increased vascularity of RCC sinonasal metastases and epistaxis as a major sign of the disease.

Histopathological confirmation of sinonasal metastatic RCC should be followed by the evaluation of the possible recurrence of the primary tumor or distant spreading elsewhere. Positron emission tomography – computed tomography (PET-CT) has high sensitivity and specificity in detecting RCC recurrence and results are in correspondence with conventional radiological examination with CT and magnetic resonance imaging [6]. On the other hand, PET-CT is more powerful in detecting early metastatic disease, especially in bones and muscles [7]. High level of false positive results due to inflammation or scarring should raise caution with clinicians 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 the optimal choice for patients with single resectable sinonasal metastasis. Five-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 patients with unresectable metastatic disease. In the 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 did not respond to immunotherapy. Patients with metastasis in multiple organs have a very poor prognosis, with five-year survival below 7% [10]. Our patient had a nonresectable metastasis and radiotherapy did not achieve any benefit, which can be explained by tumor biology and volume.

In patients with recurrent epistaxis that also had a history of renal carcinoma, endoscopic finding of tumefaction in the nasal cavity should raise 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 the abdomen, the thorax, and the pelvis to evaluate the possibility of RCC recurrence or metastatic dissemination elsewhere.

**Conflict of interest:** None declared.

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## Понављајуће крварење из носа као манифестација синоназалне метастазе карцинома бубрега

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### САЖЕТАК

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

**Приказ болесника** Шездесет шестогодишњи болесник је примљен на болничко лечење због понављајућег, интензивног крварења из носа. Болеснику је претходно због карцинома одстрањен бубрег и током трогодишњег праћења није имао знакове релапса малигне болести. Ендоскопским прегледом и компјутеризованом томографијом утврђен 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 испи-

тивања су искључила постојање релапса малигне болести у малој карлици, абдомену или грудном кошу. Иако је болесник примио радиотерапију, тумор је испољио даљу прогресију у предњој можданој јами и максили, а болесник је преминуо пет месеци после 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 случајевима обавезна је биопсија како би се разликовао примарни тумор од метастазе. После 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