# Metastatic renal cell carcinoma presenting as a paranasal sinus mass:

the importance of differential diagnosis Short title: Renal Cell Carcinoma and Paranasal Sinus Mass Ralli Massimo <sup>a</sup>, Altissimi Giancarlo <sup>b</sup>, Turchetta Rosaria <sup>b</sup>, Rigante Mario <sup>c</sup> a) Department of Oral and Maxillofacial Sciences, Sapienza University of Rome, Italy. b) Department of Otorhinolayngology, Audiology and Ophtalmology, Sapienza University of Rome, Italy. c) Department of Otorhinolayngology, Catholic University of Sacred Heart, Rome, Italy **Corresponding Author:** Massimo Ralli, MD, PhD Address: Department of Oral and Maxillofacial Sciences, Sapienza University of Rome. Viale del Policlinico 155, 00186, Rome Italy. Email: massimo.ralli@uniroma1.it Conflicts of interest: none Sources of Funding: The Authors have not received financial support for this research and work.

## 26 Abstract

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Metastasis in the paranasal sinuses are rare; renal cell carcinoma is the most common cancer that metastasize to this region. We present the case of a patient with a 4-month history of a rapidly growing mass of the nasal pyramid following a nasal trauma, associated to spontaneous epistaxis and multiple episodes of hematuria. Cranial CT scan and MRI showed an ethmoid mass extending to the choanal region, the right orbit, the right frontal sinus with an initial intracranial extension. Patient underwent surgery with a trans sinusal frontal approach using a bicoronal incision combined with an anterior midfacial degloving; histological exam was compatible with a metastasis of clear cell renal carcinoma. Following histological findings, a total body CT scan showed a solitary 6 cm mass in the upper posterior pole of the left kidney identified as the primary tumor. Although rare, metastatic renal cell carcinoma should always be suspected in patients with nasal or paranasal masses, especially if associated to symptoms suggestive of a systemic involvement such as hematuria. A correct earlystage diagnosis of metastatic RCC can considerably improve survival rate in these patients; preoperative differential diagnosis with contrast-enhanced imaging is fundamental for the correct treatment and follow up strategy.

## Introduction

Renal cell carcinoma (RCC) is the most common kidney cancer, with approximately 35,000 new cases in the US each year [1]; RCC mainly affects male patients between 40 and 60 years old [2]. Common presentation symptoms include hematuria (40%), flank pain (40%), and a palpable abdominal mass (25%) [3]. Approximately 30% of patients with renal cell carcinoma present with methastatic disease [4]; target organs are lung (75%), soft tissues (36%), bone (20%), liver (18%), cutaneous sites (8%) and central nervous system (8%) [5, 6]. Metastasis in the paranasal sinuses are rare [7]; however, RCC is the most common cancer that metastasize to this region. Prognosis of metastatic RCC is poor [8]; the survival rate ranges between 15-30% at 5 years [9] in case of a single metastasis and between 0 and 7% in patients with multiple metastases [10]. Metastatic RCC is often resistant to chemotherapy and radiotherapy [11]; numerous agents targeting VEGF and non-VEGFR pathways have been proposed during the last decade for the treatment of advanced RCC [12-18].

We present the case of a patient with a single, rapidly growing mass in the upper portion of the nasal pyramid, with late, post nasal surgery histological diagnosis of renal cell carcinoma that allowed primary tumor identification.

#### **Case Presentation**

A 72-year-old man was referred to our institution with a 4-month history of a voluminous mass in the upper portion of the nasal pyramid following a nasal trauma. He had been treated a few weeks earlier at a different ENT service for a massive spontaneous epistaxis. The patient also reported a long history of hematuria, previously attributed to renal tuberculosis occurred over 40 years before. At admission, a cranial CT scan showed a large soft tissue ethmoid mass extending to the

right and left choanal region, the right orbit, the right frontal sinus and an initial intracranial extension with partial erosion of the crista galli. MRI confirmed the evidence found at computed tomography (Fig. 1). Fine needle aspiration showed typical epithelial tissue and clear-cytoplasm cells interpreted as pericytes. Preoperative local biopsy was not performed due to the history of severe epistaxis and the high risk of massive bleeding during the procedure.

The patient underwent surgery with a trans sinusal frontal approach using a bicoronal incision combined with an anterior midfacial degloving to excise the mass; however, the right orbital and especially the initial intracranial extension did not allow a complete removal of the neoplasm. Considerable bleeding occurred during surgery. The histological exam revealed a clear cell renal carcinoma (*Fig. 2*). Based on these findings, the patient underwent a total body CT scan that showed a solitary 6 cm mass in the upper posterior pole of the left kidney. Bone scintigraphy also revealed increased uptake in the ethmoid and orbital region. Due to the poor general conditions, no surgery was performed to remove the primary tumor; the patient died 4 months later.

## Discussion

Nasal cavity and paranasal sinus cancers are usually primary tumors. Metastasis to the paranasal sinuses are rarely found; among them, renal cell carcinoma is the most common cancer to metastasize to this region (49%) followed, respectively, by bronchus, urogenital ridge, breast and gastrointestinal tract. [19,20]. RCC can metastasize to any region of the body, with a prevalence for lungs (75% of cases), regional lymph nodes (65%), bone (40%), and liver (40%) [21]. Metastasis to the head and neck regions account for about 15% of the cases, targeting in order of

frequency the paranasal sinuses, the larynx, jaws, temporal bones, thyroid and parotid glands [22].

RCC tumor cells can reach the sinonasal region via two routes: the first includes inferior vena cava, lungs, heart and the maxillary artery; the second involves the communication of the avalvular vertebral venous plexus and the intracranial venous plexous [23]. Maxillary sinuses are the most commonly involved sinuses by metastatic tumors (36%), followed by the ethmoid (25%), frontal and sphenoid sinuses (17%) and nasal cavity (11%) [24,25]. One of the first reports available in recent literature to describe a renal clear cell carcinoma metastatic to the paranasal sinuses has been published by Matsumoto in 1982 [26]; afterwards several Authors described case reports of RCC presenting as metastatic diseases in the paranasal sinuses. Available literature describes presentation of RCC metastasis as a solitary periorbital [27] and orbital mass [28], as a frontal sinus mass [29], as an ethmoid sinus mass [30,31], in the nasal cavity [32-33], in the maxillary [34,35] and sphenoid sinus [36-38]. In some cases, the extension of the metastasis to the skull base has been described [39].

Metastatic RCC to the sinonasal district has been reported as the presenting sign of this disease in a few cases [29,34], while in others followed or occurred simultaneously to primary cancer diagnosis. Presentation symptoms are often limited to recurrent epistaxis [40-43] and the presence of a primary renal cell carcinoma is recognized only after surgical removal of the metastatic tumor via histologic examination supported by immunohistochemical staining of the specimen [5]. Rarely, metastasis in the sinunasal cavities followed RCC diagnosis and treatment [44-46]; cases of post surgery metastasis in the head and neck district have been described up to 12 years after surgery [47].

The key point in RCC presenting with a sinonasal metastasis is differential diagnosis with primary tumors such as adenocarcinomas, angiofibromas, hemangiopericytomas, melanomas, hemangiomas, metastatic tumors from the breast and lungs and, more rarely, systemic diseases such as Wegener's and midline granulomas [48]. In fact, in such cases diagnostic delays, misdiagnosis, undertreatment and mismanagement could occurr due to 1) the attribution of the mass to a primary sinonasal cancer given the rare nature of sinonasal metastasis, or 2) to the overlook of presenting symptoms such as recurrent epistaxis, swelling, pain and nasal obstruction. Haematuria can be considered as an indicator of RCC; it has been reported that about 10% of patients with RCC with distant metastasis exhibit massive haematuria. However, intermittent haematuria may be present in 90% of cases [3]. For this reason, patients presenting with nasosinusal tumors also reporting hematuria should always undergo systemic evaluation. Radiological examination with CT scan and, secondly, MRI and angiography are necessary in assessing the extent of the metastatic lesion. However, it should be considered that RCC metastasis have similar radiological appearances to primary malignant lesions of sinunasal cavities; some indicators of renal origin at CT scan are enhancement, destruction, and lack of tumoral calcification [6]. In this case, CT scan allowed the identification of a neoformed paranasal sinus

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mass; however, only histological exam identified the mass as a metastasis of RCC and led to the execution of total body CT scan to identify primary tumor. Although difficult, differential preoperative diagnosis is fundamental for the correct treatment and follow up strategy; contrast-enhanced imaging plays a central role since a preoperative biopsy of the nasal mass may be difficult in these patients due to massive recurring bleeding and, in some cases, may result in only necrotic tissue inconclusive

on histopathology [42]. The ENT specialist, therefore, should always suspect metastatic disease from primary sites external to the head and neck region in patients with hypervascular mass in the nasal cavity or paranasal sinuses and a history of massive nasal bleeding and should complete preoperative workup with total-body CT scan. Furthermore, it is important to remark that metastatic tumours originating from primary kidney masses are highly vascularized and surgeons should expect significant haemorrhage during surgical removal. One of the main advantages of a preoperative diagnosis of RCC when approaching a patient with sinonasal mass is the preparation for management of severe perioperative bleeding, thus implementing strategies to optimise the patient's tolerance to bleeding and to reduce the amount of bleeding morbidity and mortality.

Prognosis of metastatic RCC is poor; however, a correct early-stage diagnosis of metastatic disease can considerably improve survival rate: literature reports that excision of solitary metastatic lesion of renal cell carcinoma following nephrectomy results in a 41% survival at 2 years and 13% survival at 5 years [48]. The sole excision of the metastatic lesion, instead, significantly lowers survival rate [49]; patients with multiple metastases have a 5 year survival rate between 0 and 7% [10].

Although metastatic RCC is often resistant to chemotherapy and radiotherapy, numerous agents targeting VEGF and non-VEGFR pathways should be taken into account for the treatment of advanced RCC. Multitargeted VEGF tyrosine kinase inhibitors (TKIs) include sorafenib [12], sunitinib [13], pazopanib [14] and axitinib [15], bevacizumab [16]; mTOR inhibitors include temsirolimus [17] and everolimus [18]. Unfortunately, especially in cases of advanced neoplasms, benefits are still time-limited and treatment decisions should be based not only on guidelines but also on clinical considerations, such as patient comorbidities, treatment toxicity, prognostic

factors and molecular aspects of disease. In this case, the poor general conditions of the patient prevented additional treatment except for palliative pain management.

In conclusion, metastatic renal cell carcinoma should always be suspected in patients with nasal or paranasal masses, especially if associated to symptoms suggestive of a systemic involvement such as hematuria; early-stage diagnosis of metastatic disease can considerably limit perioperative complications and improve survival rate.

#### 177 References

- 178 1. JemalA, Tiwari RC, Murray T, et al. Cancer statistics, 2004. CA Cancer J Clin
- 179 2004; 54: 8–29
- 180 2. Lim R. Y., Bastug D.F., Caldwell B.L. Metastatic renal cell carcinoma of the
- nasal septum. WV Med J. 1989. 85: 143-145.
- 3. Skinner DG, Vermillion CD, Pfister RC, Leadbetter WF. Renal cell
- carcinoma. Am Fam Physician. 1971;4:89–94
- 4. Flamigan RC, Campbell SC, Clark JI, Picken MM. Metastatic renal cell
- carcinoma. Curr Treat Options Oncol. 2003;4:385–390.
- 5. Singh J, Baheti V, Yadav SS, Mathur R. Occult renal cell carcinoma
- manifesting as nasal mass and epistaxis. Rev Urol. 2014;16(3):145-8.
- 6. Som PM, Norton KI, Shugar JM, et al: Metastatic hypernephroma to the head
- and neck. AJNR Am J Neuroradiol 8:1103–1106, 1987.
- 7. Ziari M, Shen S, Amato RJ, Teh BS. Metastatic renal cell carcinoma to the
- nose and ethmoid sinus. Urology. 2006 Jan;67(1):199.
- 8. Ather MH, Masood N, Siddiqui T. Current management of advanced and
- metastatic renal cell carcinoma. Urol J. 2010;7:1-9.
- 9. Torres Muros B, Bonilla Parrilla R, Solano Romero JR, Rodríguez Baró JG,
- 195 Verge González J. Metastasis in maxilar sinus as only manifestation of
- disseminate renal adenocarcinoma. An Otorrinolaringol Ibero Am.
- 197 2007;34(3):231-6.
- 198 10. Cheng ET, Greene D, Koch RJ. Metastatic renal cell carcinoma to the nose.
- Otolaryngol Head Neck Surg 2000;122:464.
- 200 11. Motzer RJ, Russo P, Nanus DM, Berg WJ. Renal cell carcinoma. Cur Probl
- 201 Cancer 1997;21:185–232.

- 202 12. Escudier B, Lassau N, Angevin E, Soria JC, Chami L, Lamuraglia M,
- Zafarana E, Landreau V, Schwartz B, Brendel E, Armand JP, Robert C. Phase
- I trial of sorafenib in combination with IFN alpha-2a in patients with
- 205 unresectable and/or metastatic renal cell carcinoma or malignant melanoma.
- 206 Clin Cancer Res. 2007 Mar 15;13(6):1801-9.
- 207 13. Motzer RJ, Michaelson MD, Rosenberg J, Bukowski RM, Curti BD, George
- DJ, Hudes GR, Redman BG, Margolin KA, Wilding G. Sunitinib efficacy
- against advanced renal cell carcinoma. J Urol. 2007 Nov;178(5):1883-7.
- 210 14. Sternberg CN, Davis ID, Mardiak J, Szczylik C, Lee E, Wagstaff J, Barrios
- 211 CH, Salman P, Gladkov OA, Kavina A, Zarbá JJ, Chen M, McCann L, Pandite
- L, Roychowdhury DF, Hawkins RE. Pazopanib in locally advanced or
- 213 metastatic renal cell carcinoma: results of a randomized phase III trial. J Clin
- 214 Oncol. 2010 Feb 20;28(6):1061-8.
- 215 15. Rini BI, Melichar B, Ueda T, Grünwald V, Fishman MN, Arranz JA, Bair AH,
- Pithavala YK, Andrews GI, Pavlov D, Kim S, Jonasch E. Axitinib with or
- without dose titration for first-line metastatic renal-cell carcinoma: a
- randomised double-blind phase 2 trial. Lancet Oncol. 2013 Nov;14(12):1233-
- 219 42.
- 220 16. Escudier B, Pluzanska A, Koralewski P, Ravaud A, Bracarda S, Szczylik C,
- Chevreau C, Filipek M, Melichar B, Bajetta E, Gorbunova V, Bay JO,
- Bodrogi I, Jagiello-Gruszfeld A, Moore N; AVOREN Trial investigators...
- Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell
- carcinoma: a randomised, double-blind phase III trial. Lancet. 2007 Dec
- 225 22;370(9605):2103-11.

- 226 17. Hudes G, Carducci M, Tomczak P, Dutcher J, Figlin R, Kapoor A,
- Staroslawska E, Sosman J, McDermott D, Bodrogi I, Kovacevic Z, Lesovoy
- V, Schmidt-Wolf IG, Barbarash O, Gokmen E, O'Toole T, Lustgarten S,
- Moore L, Motzer RJ; Global ARCC Trial.. Temsirolimus, interferon alfa, or
- both for advanced renal-cell carcinoma. N Engl J Med. 2007 May
- 231 31;356(22):2271-81.
- 18. Motzer RJ, Escudier B, Oudard S, Hutson TE, Porta C, Bracarda S, Grünwald
- V, Thompson JA, Figlin RA, Hollaender N, Urbanowitz G, Berg WJ, Kay A,
- Lebwohl D, Ravaud A; RECORD-1 Study Group.. Efficacy of everolimus in
- advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled
- phase III trial. Lancet. 2008 Aug 9;372(9637):449-56.
- 237 19. Sountoulides P, Metaxa L, Cindolo L. Atypical presentations and rare
- 238 metastatic sites of renal cell carcinoma: a review of case reports. J Med Case
- 239 Rep. 2011;5:429.
- 20. Evgeniou E, Menon KR, Jones GL, Whittet H, Williams W. Renal cell
- carcinoma metastasis to the paranasal sinuses and orbit. BMJ Case Rep. 2012
- 242 Mar 27;2012. pii: bcr0120125492.
- 21. Lang EE, Patil N, Walsh RM, Leader M, Walsh MA. A case of renal cell
- carcinoma metastatic to the nose and tongue. Ear Nose Throat J 2003;82:382–
- 245 3.
- 22. Dinçbas FO, Atalar B, Oksüz DC, Aker FV, Koca S. Unusual metastasis of
- renal cell carcinoma to the nasal cavity. J Buon. 2004 Apr-Jun;9(2):201-4.
- 248 23. Gottlieb MD, Roland JT Jr. Paradoxical spread of renal cell carcinoma to the
- 249 head and neck. Laryngoscope. 1998;108:1301–1305

- 24. Kovačić M, Krvavica A, Rudić M. Renal cell carcinoma metastasis to the
- sinonasal cavity: case report. Acta Clin Croat. 2015 Jun;54(2):223-6.
- 25. Bernstein J.M., Montgomery W. Bologh K. (1966) Metastatic tumors to the
- 253 maxilla, nose and paranasal sinuses. Laryngoscope 76: 621-650.
- 26. Matsumoto Y, Yanagihara N. Renal clear cell carcinoma metastatic to the nose
- and paranasal sinuses. Laryngoscope. 1982 Oct;92(10 Pt 1):1190-3.
- 27. Homer JJ, Jones NS. Renal cell carcinoma presenting as a solitary paranasal
- 257 sinus metastasis. J Laryngol Otol. 1995 Oct;109(10):986-9.
- 28. Jung JW, Yoon SC, Han DH, Chi M. Metastatic renal cell carcinoma to the
- orbit and the ethmoid sinus. J Craniofac Surg. 2012 Mar;23(2):e136-8.
- 29. Ikeuchi T, Asai N, Hori T, Hirao N, Tozawa K, Yamada Y, Kori K. Renal cell
- carcinoma detected by metastasis to the frontal sinus: a case report. Hinyokika
- 262 Kiyo. 1998 Feb;44(2):89-92.
- 30. Maheshwari GK, Baboo HA, Patel MH, Usha G. Metastatic renal cell
- carcinoma involving ethmoid sinus at presentation. J Postgrad Med. 2003 Jan-
- 265 Mar;49(1):96-7.
- 266 31. Terada N, Hiruma K, Suzuki M, Numata T, Konno A. Metastasis of renal cell
- cancer to the ethmoid sinus. Acta Otolaryngol Suppl. 1998;537:82-6.
- 268 32. Vreugde S, Duttmann R, Halama A, Deron P. Metastasis of a renal cell
- carcinoma to the nose and paranasal sinuses. Acta Otorhinolaryngol Belg.
- 270 1999;53(2):129-31.
- 271 33. Nason R, Carrau RL. Metastatic renal cell carcinoma to the nasal cavity. Am J
- 272 Otolaryngol. 2004 Jan-Feb;25(1):54-7.

- 34. Torres Muros B, Solano Romero JR, Baró Rodriguez JG, Bonilla Parrilla R.
- 274 Maxillary sinus metastasis of renal cell carcinoma. Actas Urol Esp. 2006
- 275 Oct;30(9):954-7.
- 35. He YF, Chen J, Xu WQ, Ji CS, Du JP, Luo HQ, Hu B. Case report. Metastatic
- 277 renal cell carcinoma to the left maxillary sinus. Genet Mol Res. 2014 Sep
- 278 12;13(3):7465-9. doi: 10.4238/2014.September.12.12.
- 36. Koscielny S. The paranasal sinuses as metastatic site of renal cell carcinoma.
- Laryngorhinootologie. 1999 Aug;78(8):441-4.
- 37. Simo R, Sykes AJ, Hargreaves SP, Axon PR, Birzgalis AR, Slevin NJ,
- Farrington WT. Metastatic renal cell carcinoma to the nose and paranasal
- 283 sinuses. Head Neck. 2000 Oct;22(7):722-7.
- 38. Pereira Arias JG, Ullate Jaime V, Valcárcel Martín F, Onaniel Pérez VJ,
- Gutiérrez Díez JM, Ateca Díaz-Obregón R, Berreteaga Gallastegui JR.
- Epistaxis as initial manifestation of disseminated renal adenocarcinoma. Actas
- 287 Urol Esp. 2002 May;26(5):361-5.
- 288 39. Parida PK. Renal cell carcinoma metastatic to the sinonasal region: Three case
- reports with a review of the literature. Ear Nose Throat J. 2012
- 290 Nov;91(11):E11-6.
- 40. Szymański M, Szymańska A, Morshed K, Siwiec H. Renal cell carcinoma
- metastases to nose and paranasal sinuses presenting as recurrent epistaxis.
- 293 Wiad Lek. 2004;57(1-2):94-6.
- 41. Lee HM, Kang HJ, Lee SH. Metastatic renal cell carcinoma presenting as
- epistaxis. Eur Arch Otorhinolaryngol. 2005 Jan;262(1):69-71. Epub 2004 Feb
- 296 19.

- 297 42. Nayak DR, Pujary K, Ramnani S, Shetty C, Parul P.Metastatic renal cell
- carcinoma presenting with epistaxis. Indian J Otolaryngol Head Neck Surg.
- 299 2006 Oct;58(4):406-8.
- 300 43. Kumar R, Sikka K, Kumar R, Chatterjee P. Nephrogenic epistaxis. Singapore
- 301 Med J. 2014 Jul;55(7):e112-3.
- 44. Montoro Martínez V, López Vilas M, Gurri Freixa M, De Dios Orán E,
- Montserrat Gili JR, Fabra Llopis JM. Nasal sinus metastasis of renal
- 304 carcinoma. A case report. Acta Otorrinolaringol Esp. 1999 Nov-
- 305 Dec;50(8):653-6.
- 45. Sawazaki H, Segawa T, Yoshida K, Kawahara T, Inoue T, Soda T, Kanba T,
- Yoshimura K, Takahashi T, Nakamura E, Nishiyama H, Ito N, Kamoto T,
- Ogawa O. Bilateral maxillary sinus metastasis of renal cell carcinoma: a case
- 309 report. Hinyokika Kiyo. 2007 Apr;53(4):231-4.
- 46. Hong SL, Jung DW, Roh HJ, Cho KS. Metastatic renal cell carcinoma of the
- posterior nasal septum as the first presentation 10 years after nephrectomy. J
- 312 Oral Maxillofac Surg. 2013 Oct;71(10):1813.e1-7.
- 47. Fyrmpas G, Adeniyi A, Baer S. Occult renal cell carcinoma manifesting with
- epistaxis in a woman: a case report. J Med Case Rep. 2011;5:79.
- 48. Dineen MK, Pastore RD, Emrich LJ, Huben RP. Results of surgical treatment
- of renal cell carcinoma with solitary metastasis. J Urol 1988;140:277–279
- 49. Skinner DG, Colvin RB, Vermillion CD, Pfister RC, Leadbetter WF.
- Diagnosis and management of renal cell carcinoma. A clinical and pathologic
- 319 study of 309 cases. Cancer 1971;28:1165–1177.

321 Figures

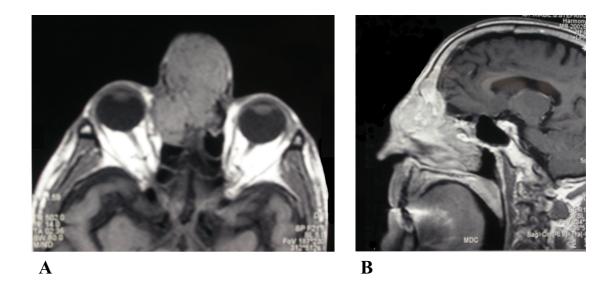


Fig. 1: MRI in the axial (A) and sagital (B) planes showing a soft tissue ethmoid mass extending to the right and left choanal region, the right orbit, the right frontal sinus and an initial intracranial extension with partial erosion of the crista galli.



Fig 2: the excised mass; histological exam was consistent with a clear cell renal carcinoma.