



Metastatic Renal Cell Carcinoma: An Enigmatic Nasal Mass

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Abstract Metastatic Renal Cell Carcinoma rarely presents in head and neck and is even rarer in the sinonasal region. However, a sinonasal metastatic mass is usually of RCC origin. These metastases may present prior to the renal symptoms or may appear after primary treatment. Report a 60-year lady with epistaxis due to metastatic RCC. Calculate total published cases of sino-nasal metastasis of RCC. Classify according to sequence of primary and metastatic presentation. A computer aided search of PubMed and Google scholar databases was done using pertinent combinations of the keywords “renal cell carcinoma”, “nose and paranasal sinus”, “metastasis”, “delayed metastasis” and “unusual presentation”, revealing 1350 articles. 38 relevant articles were included in the review. Our case presented with epistaxis 3 years after primary RCC. She had a vascular left sided nasal mass which was excised enblock. Immunohistochemistry confirmed metastatic RCC. She is on oral chemotherapy and asymptomatic 1 year post excision. Literature search revealed 116 such cases. 19 patients presented within 10 years of RCC while 7 more were delayed metastasis. 17 cases presented primarily with nasal symptoms with subsequent incidental renal mass. Chronology of presentation was unavailable in the rest 73 cases. We recommend to consider the diagnosis of sinonasal metastatic RCC in a patient presenting with epistaxis or nasal mass, particularly with a past history of RCC. Also, any person with known diagnosis

of RCC should undergo regular ENT examination for early diagnosis of sinonasal metastasis.

Keywords Metastatic RCC · Sinonasal metastasis · Delayed metastasis · Epistaxis in RCC

Introduction

Metastatic renal cell carcinoma (RCC) may present with diverse range of clinical manifestations and becomes a diagnostic dilemma with its unusual presentations. Approximately 25% of patients have distant metastases upon the first diagnosis and about 20–50% of RCC patients will eventually develop metastasis after nephrectomy [1]. If metastasis develops after 10 years of primary tumor diagnosis, it is classified as delayed metastasis [2].

The most common sites of metastasis are the lungs (75%), regional lymph nodes (65%), bones (40%), and liver (40%). Of the 15% of RCCs metastasizing to the head and neck region, it is the paranasal sinuses, larynx, jaws, temporal bones, thyroid gland, and parotid glands which are mostly involved. The most common metastasis reported in the paranasal sinuses is from RCC [3] & represents < 1% of sinonasal masses [4]. Metastatic RCC to the Sino nasal cavity presents as an intranasal mass causing recurrent epistaxis, nasal obstruction, facial pain and may extend as an orbital mass. The overall prognosis of a renal metastatic disease to the nose and paranasal sinuses is very poor [1].

RCC metastasize to the Sino nasal cavity via two potential routes, either through the inferior vena cava, lungs, heart, and maxillary artery or through the Batson venous plexus.

Treatments of metastases are variable and must be individualized according to the histology, location and extent of metastasis, primary tumor control, coexistence of other

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metastases and the patient's desire. It is aimed at improving survival and patients quality of life [5].

Aims

1. To report a case of a 60-year lady with epistaxis and left sided vascular nasal mass of metastatic RCC origin.
2. To calculate total published cases of sino-nasal metastasis of RCC.
3. To classify cases of sino-nasal metastatic RCC according to sequence of primary RCC and metastatic presentation.

Material and Methods

Renal cell carcinoma (RCC) metastasises to different regions of body but rarely to head and neck. Nasal and paranasal metastasis occurs in < 1% of systematic metastasis. Our patient presented with nasal metastasis, 3 years after primary RCC. A computer aided search of PubMed and Google scholar databases was done using pertinent combinations of the keywords “renal cell carcinoma”, “nose and Paranasal sinus”, “metastasis”, “delayed metastasis” and “unusual presentation”, which revealed 1350 articles. Publications were analysed and 38 relevant articles were included in the review which yielded 116 cases. The chronology of presentation was noted. This review of Literature includes all accessible data till date (Table 1).

Case Report

A 60-year-old female patient presented to our OPD 1 year back with complaints of multiple episodes of unprovoked left sided epistaxis since last 2 months. These were not associated with nasal obstruction, craniofacial swelling or pain. There were no complaints of recurrent upper respiratory infections or any other symptoms. She had developed pain in right flank 3 years back for which CT abdomen had been undertaken (Fig. 1). It had revealed a mass in right kidney for which a radical nephrectomy was done. This mass was reported as clear cell variant of renal cell carcinoma grade 3 on histopathology. She had not undertaken any further therapy.

On examination external appearance of nose and face was normal. Anterior rhinoscopy revealed left sided impacting spur which obscured distal visualization. Nasal endoscopy uncovered a reddish mass in left inferior meatus (Fig. 2). This was also visible in nasopharynx from the opposite choana. CECT scan of PNS was suggestive of a hyperdense lobulated soft tissue lesion in left nasal cavity with an avid enhancement. It measured 5 × 1.5 × 2 cm. There was no

involvement of maxillary sinus or pterygopalatine fossa (Fig. 1).

An endoscopic approach was planned with consent of external resection if required. After a wide middle meatal antrostomy, sphenopalatine artery in sphenopalatine foramen was identified. Artery was clipped and cauterized (Fig. 2). The mass was attached to inferior turbinate and both were removed en-block. Histopathology denoted tumor composed of cells arranged in tubules with moderately vesicular nuclei and abundant clear cytoplasm suggesting a differential diagnosis of metastatic RCC and paraganglioma. Immunohistochemistry showed saw tooth pattern positivity for CD10 (Fig. 3). It was also positive for CK, CK7, Vimentin, AMACR and negative for Synaptophysin which thus confirmed metastatic RCC.

She was referred to medical oncologist who on further workup found a subpleural metastatic lesion in left lung 1.2 × 1 cm (Fig. 1) for which oral chemotherapy was advised. She is continuing daily oral chemotherapy since last 10 months (Sunitib 50 mg) and is presently asymptomatic.

Review of Literature

RCC is most commonly seen in the age group of 30–60 years with a male–female ratio of approximately 1.5:1 [6]. It routinely presents with flank pain, palpable abdominal mass, and gross hematuria. It shows a variable growth rate and metastases may be found anywhere in the body [7]. Our patient is a 60 year old lady who had first presented with flank pain 4 years back.

Metastases can occur either hematogenously or lymphatically. The para-spinal Batson's plexus communicates with the deep veins of the pelvis, intercostal veins, inferior vena cava, and the azygos system. Any increase in intra-abdominal pressure can produce retrograde venous out flow and enables tumor cells to reach the head and neck region [5]. Another theory suggests that a solitary metastasis may be produced by the existence of communications between the right and left atrium. Here the neoplastic cells would reach the right atrium through the inferior vena cava, pass through the interatrial communication to the left atrium, and from there via the arterial route they would reach the cavernous sinus and would implant in the paranasal sinuses [5].

Neoplastic cells could have also previously crossed the lungs, leaving behind micro metastases that cannot be diagnosed radiologically. Moreover, lung metastases from kidney cancer could regress due to immunological reactions in 1–5% of cases, before being implanted in nasal cavity or paranasal sinuses [5]. The clinical course of the primary tumour is often unpredictable, with spontaneous regression noted. Metastases may be found at diagnosis in

Table 1 Metastatic RCC as sino nasal mass

Sr. no	Article	Metastasis preceding diagnosis of RCC	Early metastasis (< 10 years)	Delayed metastasis (> 10 years)	Total cases reported
1	Bernstein et al. [11]	NA	NA	NA	36
2	Matsumoto and Yanagihara [12]	2			2
3	Kathuria et al. [13]	1			1
4	Loh [14]		1 (4 years)		1
5	Akdas [15]		1 (6 years)		1
6	Fandella et al. [16]	1			1
7	Pagano et al. [17]	NA	NA	NA	40 (including 3 from sr. 2 and 4)
8	Lynne Lim [18]		1 (1.5 years)		1
9	Lee et al. [19]	1			1
10	Lang et al. [20]		1 (1 month)		1
11	Nason and Carrau [21]		1 (2 years)		1
12	Dincabas et al. [22]		2 (15 days and 1 year)		2
13	Ziari et al. [23]			1 (17 years)	1
14	Zachary et al. [23]			1 (11 years)	1
15	Nasab et al. [24]		1 (4 years)		1
16	Nayak et al. [25]		1 (6 years)		1
17	Sedat et al. [26]		1 (6 years)		1
18	Choong et al. [27]	2	2 (1.5 years and 4 months)		4
19	Pradipta Kumar [28]	3			3
20	Evgeniou et al. [29]			1 (12 years)	1
21	Tadashi Terada [30]		1 (8 years)		1
22	Hong et al. [31]			1 (10 years)	1
23	Remenschneider et al. [32]		1 (3 years)	1 (10 years)	2
24	Kovacic et al. [1]		1 (6 years)		1
25	Mahajan et al. [9]		1 (6 years)		1
26	Ralli et al. [33]	1			1
27	Asher and Ecevit [34]	1			1
28	Dalkoti et al. [35]	1	1 (1 year)		2
29	Zhang et al. [6]		1 (6 years)		1
30	Cui et al. [36]	1			1
31	Petruzzelli et al. [37]		1 (2.5 years)		1
32	Spooner et al. [8]			1 (25 years)	1
33	Joo et al. [4]			1 (12 years)	1
34	Allen et al. [38]	1			1
35	Verma et al. [7]	1			1
36	Patel et al. [10]	1			1

25–30% patients, or after some interval post nephrectomy [3]. Longer intervals up to 25 years have been reported in literature [8].

Nasal cavity and paranasal sinus malignancies are usually primary tumors. This is a rare location of metastasis, RCC being the most common source [7]. The median time before relapse is 15 months while 85% of relapses occur within 3 years. The 5-years survival rate after nephrectomy is approximately 60–75%, falling to 0–5% in case of multiple metastases [9]. Our patient presented with nasal metastasis

3 years after being diagnosed with renal cell carcinoma and is presently asymptomatic, 4 years from primary diagnosis.

Epistaxis is the most common presenting symptom in sinonasal metastatic RCC. This is due to abundant sinusoids causing hypervascularity of the tumour [9]. Our patient also complained of multiple episodes of epistaxis in her primary presentation. Other symptoms are nasal obstruction, orofacial pain, nasal or facial mass, headache, proptosis, diplopia, nasal discharge and in advanced cases, symptoms of cranial nerve impairment. These alarming

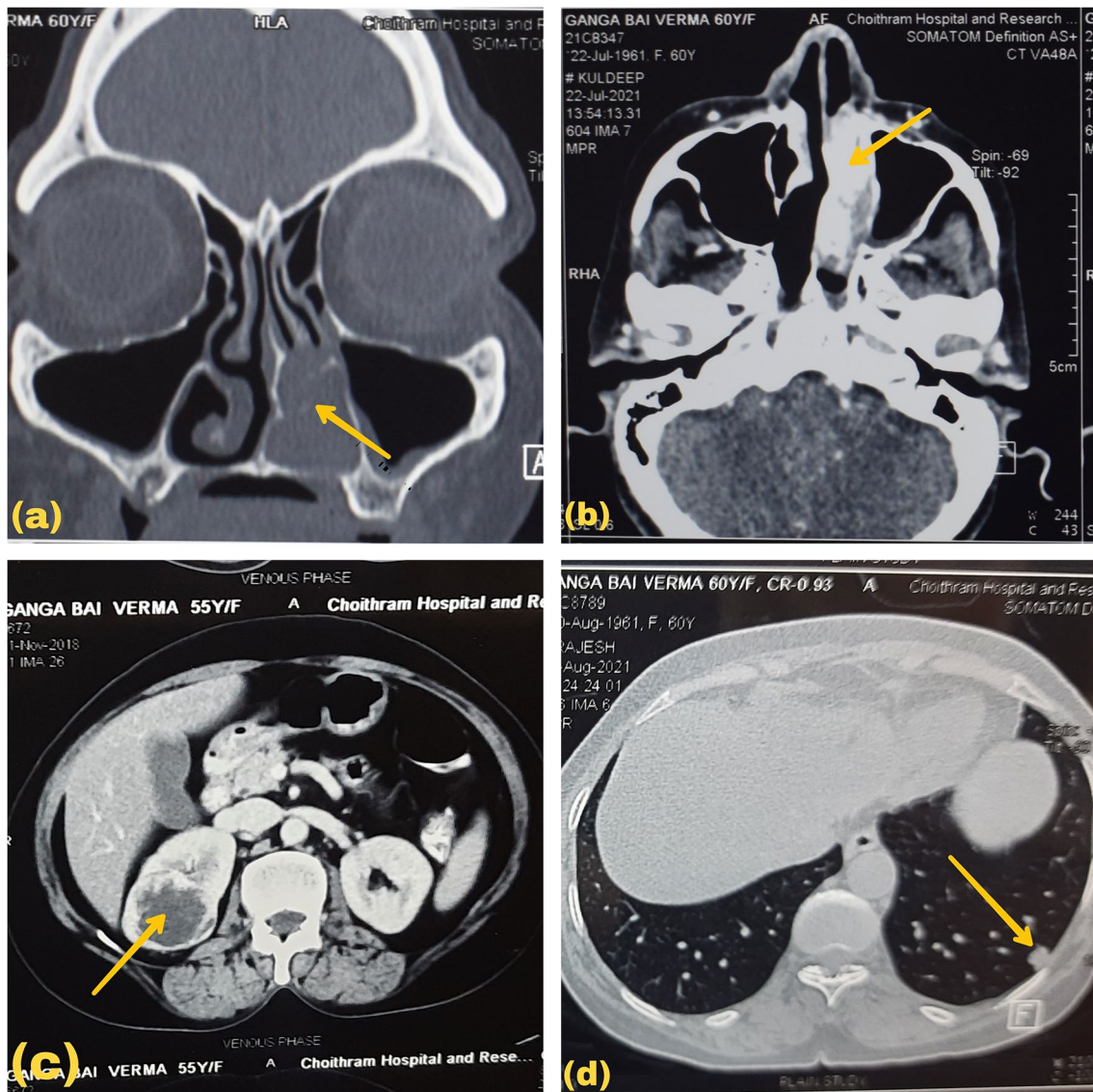


Fig. 1 a CT PNS with spur left & left nasal mass. b CECT PNS with enhancing mass. c CT Abdomen with right RCC renal mass. d CECT Chest with subpleural metastatic lesion in left lung

symptoms should provoke suspicion for underlying malignancy [10]. Our patient did not have any such symptoms.

Treatment of metastatic RCC is palliative in majority of patients and varies by tumor location, number of metastases, and primary tumor status. Most metastatic RCC in nasal cavity or paranasal sinuses are single, unlike in other regions where multiple metastases is the norm. Endoscopic resection is recommended as the gold standard in patients with a single resectable sinonasal RCC. This ensures effective local control and prevents recurrent bleeds [4]. The patient reported here was operated endoscopically and mass with inferior turbinate was removed enblock after clipping sphenopalatine artery.

The first Literature review was given by Bernstein et al. in 1966, where they have mentioned 36 cases of metastatic renal cell carcinoma to nose and paranasal sinuses. They found the most common site to be maxilla. 1 of these patients had developed delayed metastasis, 13 years post nephrectomy and 1 patient developed metastasis within 8 years [11].

Matsumoto and Yanagihara reported 2 cases in 1977 of metastatic RCC where nasal symptoms preceded renal signs. In the 1st case, they found bilateral involvement of maxilla which was treated surgically followed by radiation. Second case required multiple surgeries for local recurrence [12].

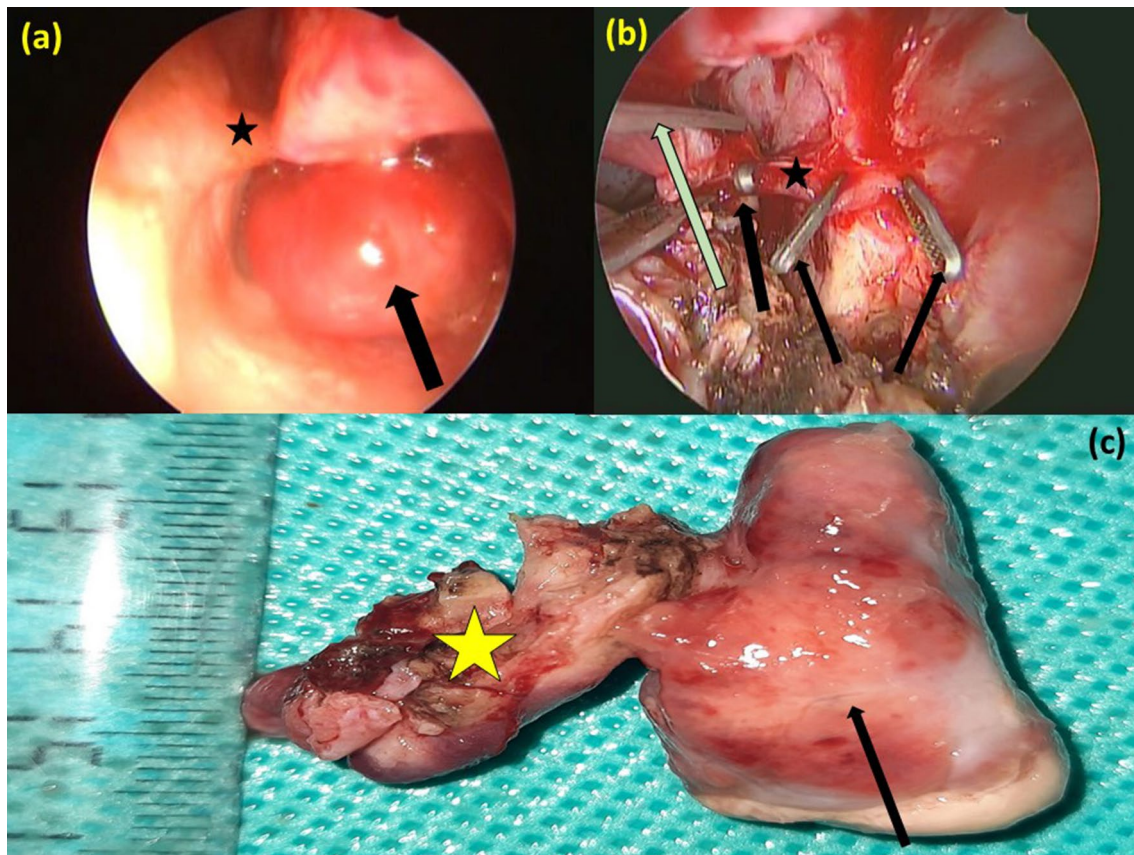


Fig. 2 **a** DNE picture of left nasal mass (black arrow) and impacting spur (star). **b** Intra-op photo of Left Sphenopalatine artery (star) Clips (black arrows) and bipolarisation (green arrow). **c** Resected enblock mass (black arrow) with its attachment to inferior turbinate (star)

Kathuria et al. [13] also reported a case of metastatic RCC as initial presentation. In this case, RCC initially manifested as nosebleed due to a highly vascular metastasis in the nasal cavity.

Loh reported a case in 1986, who had metastatic RCC 4 years after nephrectomy. According to him, 80% of metastatic tumours in the nose and sinuses arise from a renal carcinoma and in the majority they are clear cell carcinoma [14].

Akdas et al. [15] published a case of a 55-year-old male with recurrent metastasis in the oral cavity and maxillary sinuses, as well as other organs 6 years after nephrectomy. They treated the lesions by local excision, hormonal therapy and palliative measures.

Fandella et al. in 1991 reported a case of metastatic RCC to the nose and paranasal sinuses where the patient presented primarily with nasal symptoms. Later on he was diagnosed to have a 3 cm tumour in the right kidney [16].

Pagano et al. [17] wrote a review of literature on “Unusual clinical metastases, metastatic modes and patterns and comparison between clinical and autopsy metastatic series”. They found that out of total of 1451 metastases, 40 had metastasised to nose and paranasal sinuses. Three of these

40 cases have been noted separately while calculating the total number of cases [12, 13].

Lynne Lim found a case of Sino nasal metastasis of RCC in 2000. The patient had a nasal mass of 2 cm at the dorsum of the right side of nose. It was painless, fluctuant, and not tender. This patient had undergone nephrectomy for clear cell RCC 19 months back [18].

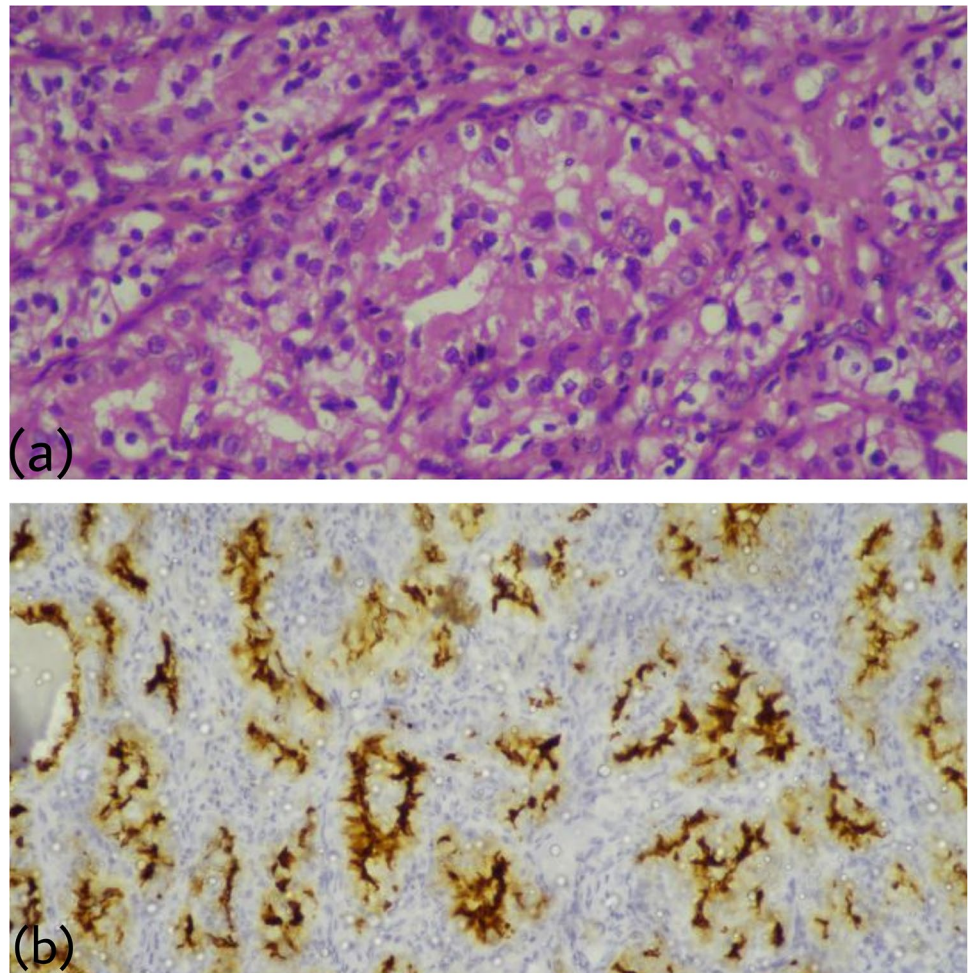
Lee et al. [19] reported a case of a 73-year-old male presenting with repeated episodes of massive epistaxis and no urinary symptoms. After resection of nasal lesion, HPE was suggestive of metastatic RCC. Further work up showed a $8 \times 8 \times 7$ cm mass in left kidney [19].

Lang et al. in 2003 published a case of a 45-year-old male with RCC who later presented with epistaxis. He developed nasal metastasis within 1 month of diagnosis primary RCC. It grew rapidly and was treated with radiotherapy. Subsequently, a rapidly enlarging tongue metastasis developed which was removed via laser excision [20].

Nason and Carrau [21] reported a case of metastasis of RCC, where a 56 year old male had developed nasal symptoms 2 years after nephrectomy.

Dincbas et al. [22] published 2 case reports of metastatic RCC. 1st patient had presented with nasal symptoms 15 days

Fig. 3 **a** 400 ×, H & E staining showing nests of cells with vesicular nuclei & clear cytoplasm. **b** 200 × saw tooth pattern positivity for CD10, Immunohistochemistry



post nephrectomy and 2nd patient had epistaxis 1 year after surgery for RCC.

Ziari et al. [3] reported a case of delayed nasal metastasis of RCC 17 years post nephrectomy. According to our literature search, this is the 2nd most delayed presentation of metastasis.

Zachary et al. (2007) reported a case of multiple metastases over a period of 6 years after patient being asymptomatic for 11 years post nephrectomy. He developed metastasis to gastrointestinal tract, thyroid and later in nose [23].

Nasab et al. in 2008 also published a case of metastasis of RCC to nose and paranasal sinuses 4 years after nephrectomy [24].

Nayak et al. [25] from Manipal documented a 56-year-old male patient with history of left sided epistaxis, facial pain and headache of ten days duration. Seven years prior to this, the patient had undergone left radical nephrectomy for RCC. CECT Scan of PNS revealed an enhancing soft tissue mass involving the sphenoid sinus with destruction of the roof and extension of the soft tissue lesion into the sella and laterally to cavernous sinus with compression of ICA. Lung metastasis was also found. He was treated

with palliative radiotherapy [25]. Similarly Sedat et al. [26] reported a 45-year old female patient, who presented with metastasis of RCC, 6 years post nephrectom.

Choong et al. (2011) did a retrospective study of 10 years and found 4 cases of nasal and paranasal metastasis of renal cell carcinoma. They utilized the Memorial Sloan Kettering Cancer Center (MSKCC) risk classification for metastatic RCC. All 4 patients were classified as MSKCC poor prognosis by this risk criteria. Two of these patients had precedence of nasal symptoms and 2 patients developed metastasis within 2 years [27].

Pradipta Kumar [28] from JIPMER, Puducherry reported 3 cases of bilateral renal cell carcinoma with large metastases to the frontonasal region that produced unusual symptoms before the primary lesion could be detected.

Evgeniou et al. [29] published a case of RCC metastasis to the left paranasal sinuses and orbit with cranial nerve involvement 12 years after treatment for the primary tumour. Patient had RCC in 1998, which was treated with nephrectomy and had incidentally undergone right eye enucleation for melanoma in 1967.

Tadashi Terada wrote about a 76-year-old male presenting with nasal symptoms in 2012, 8 years after treatment of renal cell carcinoma [30].

Hong et al. [31] reported 1 case of delayed metastasis of metastatic RCC to nose and paranasal sinuses who presented 10 years post nephrectomy. Remenschneider et al. [32] documented 1 patient who presented 10 years after nephrectomy and 1 patient who presented 3 years post nephrectomy.

Kovacic et al. [1] also reported a case of nasal and paranasal metastasis of RCC along with metastasis to liver, pancreas and vertebrae after receiving treatment for renal cell carcinoma. In the same year Mahajan et al. [9] from Bangalore reported 1 patient of metastasis of RCC to nose and paranasal sinuses 6 years post-nephrectomy.

Ralli et al. (2017) published a case of 72 year-old male with a 4-month history of a large mass in the upper portion of the nasal pyramid following a nasal trauma. He had history of massive epistaxis. He also had hematuria which was attributed to a 40-year-old history of renal tuberculosis. The nasal mass was excised and histopathology reported it to be metastatic RCC. Later-on a 6 cm tumour was found in left kidney [33]. Similarly Ashier and Ecevit [34] reported a case where nasal symptoms preceded the urinary symptoms of RCC [34].

Dalakoti et al. (2018) from Manipal, reported 2 cases of metastatic RCC, wherein the 1st patient developed metastasis of renal cell carcinoma to nose and paranasal sinuses within 1 year of diagnosis of primary tumor. The 2nd case primarily presented with complaints of epistaxis and a nasal mass was found for which maxillectomy was done. The histopathology of mass was consistent with metastatic RCC. On workup CT scan abdomen showed a large mass of $13 \times 9.2 \times 7.7$ cm replacing the right kidney [35].

Zhang et al. [6] reported a case regarding a 62-year-old male, who developed metastasis thrice in the nose and paranasal sinuses, over a period of 9 years. Cui et al. [36] also reported a case of metastatic RCC, who had presented primarily with nasal symptoms. He was treated with Sunitib 50 mg/day followed by Axitinib at a dose of 5 mg twice daily.

Petruzzelli et al. (2019) documented a 60-year-old man who presented for the evaluation of right-sided facial asymmetry, severe hemifacial pain and right-side nasal airway obstruction. CT scan revealed a right maxillary mass filling the antrum with bony destruction. This was resected. Histopathology reported it as metastatic RCC. He was previously operated for RCC 2.5 years back [37].

Spooner et al. [8] reported about an 88-year-old male, who had developed delayed metastasis over his tip of nose. He had undergone nephrectomy for clear cell RCC 25 years back. According to our review this is the longest time post nephrectomy when patient developed secondary metastasis [8].

Joo et al. 4 published about a 64-year-old man presenting with left nasal obstruction. He had undergone right nephrectomy for RCC 12 years prior. PNS Combiscan revealed a 4.6-cm-diameter mass exhibiting delayed contrast enhancement in left maxillary sinus and the nasal cavity. On resection, histopathology was suggestive of metastatic RCC [4].

In 2020, Ruggerui et al. wrote an article “Nasal cavity and paranasal sinus metastasis” and found 8 cases of metastatic RCC. In six patients the metastases were located in the paranasal sinuses and in two in the nasal cavity [5]. All of these 8 cases have been noted separately in Table 1 [3, 9, 22, 29, 33].

Allen et al. [38], Verma et al. [7] and Patel et al. [10], each reported 1 case of metastasis of RCC to nose and paranasal sinuses. All these patients primarily presented with nasal symptoms. When these patients were evaluated, an incidental renal mass more than 3 cm in size was noted in all the cases. This is consistent with Verma’s explanation of primary size more than 3 cm predisposing to metastasis.

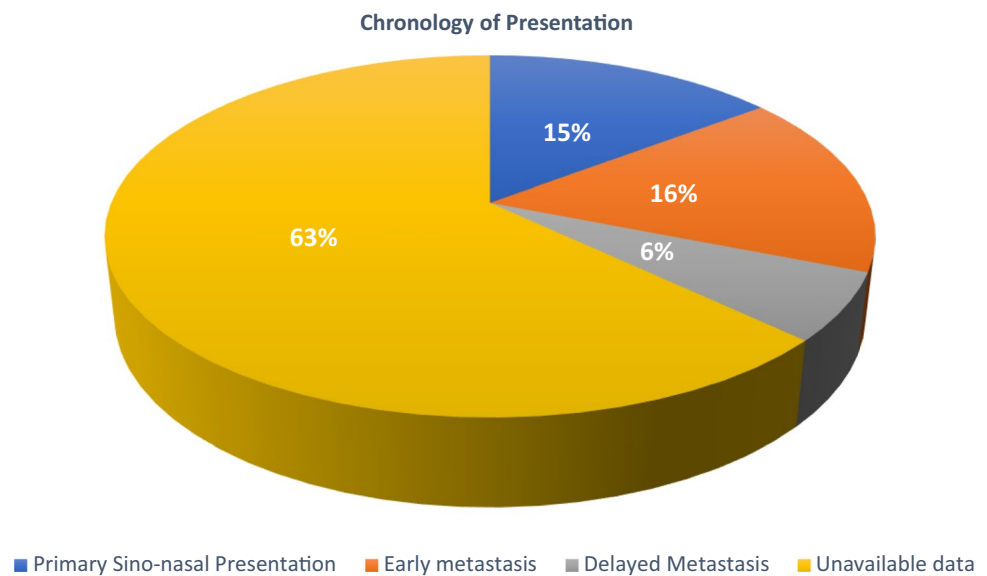
The application of FDG (18F-fluoro-2-deoxy-2-d-glucose) PET/CT is limited for RCC, mainly due to the physiological excretion of FDG from the kidneys, which decreases contrast between renal lesions and normal tissue, and may obscure or mask the lesions of the kidneys. The role of PET/CT in staging and metastatic workup in RCC is evolving as it has the advantage in detection of early metastatic disease and identification of musculoskeletal metastases, which are difficult to assess on CT and MRI [39]. The results of Wang et al. showed that FDG-PET is better able to detect extra-renal rather than renal RCCs, as extra-renal lesions are not obscured by urinary FDG activity. However, FDG-PET may not localize a small lesion as accurately as a larger one [40].

Results

Literature search revealed 116 such cases. 19 patients presented within 10 years of RCC while 7 more were delayed metastasis. 17 cases presented primarily with nasal symptoms with subsequent incidental renal mass. Chronology of presentation was unavailable in the rest 73 cases (Fig. 4). Thus, of all the 43 cases in which chronology of presenting symptoms were documented 17 (39.53%) presented primarily with sinonasal metastasis.

Conclusion

Nasal masses being of metastatic origin is rare. Nose is an unlikely site for RCC to metastasise, however RCC is the commonest primary of metastatic nasal mass. Sometimes such metastasised patients present primarily with symptoms of epistaxis, nasal obstruction and nasal discharge. Afterwards patients may develop renal symptoms or a silent

Fig. 4 Chronology of presentation of sino-nasal metastasis

kidney mass may be discovered incidentally. Our review of literature found 116 patients of sinonasal metastatic RCC till date. Majority of patients presented within 10 years of surgery for primary tumor, while a few presented after 10 years [2]. Maximum duration of delayed metastasis was found to be 25 years.

To summarize, we recommend to keep the differential diagnosis of metastatic RCC in mind when a patient presents with a vascular mass and history of epistaxis, especially if he has been previously treated for Renal cell carcinoma. Also, any person who has been diagnosed with Renal cell carcinoma should undergo periodic ENT examination as nasal metastasis is known to occur even after years of primary therapy.

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Declarations

Conflict of interest The authors declare they have no financial interests.

Human or Animal Rights No Research involving human participants or animals.

Informed Consent Informed consent taken from the patient.

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