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OTHER ARTICLES

Metastasis in Sinonasal Region Revealing a Silent Primary: A Series of 2 Cases with Review of Literature

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Abstract Metastasis to the nasal cavity and paranasal sinuses are very rare and only few cases have been reported so far. Metastatic nasal mass with silent primary renal cell carcinoma (RCC) is even rarer. So are giant cell tumors which rarely affects soft tissues whether superficial or deep. These rarely occur in nasal cavity. We would like to discuss 2 cases—one being a 74 year old female with a solitary asymptomatic extensive metastatic lesion in sinonasal area of silent primary renal cell carcinoma and other being a 38 year old female multiple lytic expansile lesions in facial and skull bones who was previously treated for giant cell tumor of long bone-tibia. We aim to bring their occurrence to notice as they are rare, to highlight importance of these tumors in differential diagnosis of sinonasal masses and treatment options for the same.

Keywords Renal cell carcinoma (RCC) · Giant cell tumors (GCT) · Sinonasal metastasis

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Introduction

Nasal cavity and paranasal sinus cancers are usually primary tumors and metastatic deposits to this region is rarely known. Though rare, renal cell carcinoma is the most common cancer to metastasize to this region (49%). Others include tumors of bronchus, urogenital ridge, breast, and gastrointestinal tract [1, 2]. The other entity that is giant cell tumours which we discuss here more commonly metastasize to lung. Other reported sites to which metastasis occur include lymph nodes (mediastinum, paraaortic), bone, skin, and breast [3]. These giant cell tumors rarely occur in nasal cavity and the exact incidence is not yet recorded in the literature [4].

Renal cell carcinoma (RCC) accounts for approximately 3% of all adult malignancies and 85% of primary renal tumors [5]. It is an aggressive tumor with usual sites of metastasis being lungs (75%), regional lymph nodes (65%), bone (40%), liver (40%), and brain (5%) [5]. Unusual presentation, multiple metastasis, and high vascularity of the tumour make it difficult for the clinician to diagnose and intervene and hence has a poor prognosis.

Giant cell tumors on the other hand constitute about 4–5% of all primary bone tumors [6], are usually benign and occasionally malignant. Most common site of giant cell tumors is the epiphysis of long bones around the knee [7]. Giant cell tumors of head and neck are very rare and constitute about 2% of all giant cell tumors [8]. Giant cell

tumor is rare in soft tissues. Though benign, they have been reported to have metastatic potential to distant sites.

Case Report 1

A 74 year old female presented in emergency room with head injury following road traffic accident. Her CT scan of head incidentally detected polypoidal thickening in bilateral frontal sinuses, left ethmoid and left maxillary sinus with suspicious breach in posterior wall of frontal sinus. She had no previous nasal complaints of epistaxis. She had type 2 diabetes well controlled on oral hypoglycaemic agents.

On examination she had hypertension, telecanthus, pulsatile soft tissue swelling in superomedial aspect of left eye with non axial proptosis (Fig. 1a). Diagnostic nasal endoscopy showed pulsatile hypervascular mass in left nasal cavity in region of middle meatus and ethmoids which bled on touch (Fig. 1b). Her routine blood and urine investigations were normal. Differential diagnosis as per CT features were fungal sinusitis, benign tumors including angiogenic lesions and sinonasal primary malignancy were considered.

To work up the nasal mass, a contrast enhanced MRI scan of brain, nose and paranasal sinuses (Fig. 1c, d) were performed which showed a heterogeneously enhancing mass, occupying the left nasal cavity and maxillary sinus, bilateral frontal sinus with anterior cranial fossa involvement. Ethmoid sinus component caused bulge in sinus wall encroaching into left orbit with no involvement of intraorbital structures.

Biopsy of the nasal mass was taken. The mass was friable and bled profusely. However, bleeding got controlled after repeated nasal packing. Histopathology was reported as metastatic renal cell carcinoma-clear cell type (Fig. 2c, d), further immunohistochemistry strongly positive for RCC antigen and vimentin (Fig. 2e, f).

We started our further work up. CT urography (Fig. 2a, b) revealed left renal ill defined heterogeneously enhancing neoplastic mass 7 × 3 × 4.5 cm in size with large exophytic component and internal nonenhancing necrotic areas, left renal vein tumor thrombus, and locoregional lymphadenopathy. Metastatic work up including bone scan and CECT thorax showed no other metastasis. Patient was planned for cytoreductive renal surgery and radiotherapy for the sinonasal mass.

Case Report 2

A 38 year old female presented to the ENT OPD with a swelling over the medial canthus of right eye for 6 months (Fig. 3a), with watering from right eye and generalized headache for 3 months. She was a known case of Giant cell tumor of right proximal tibia who underwent wide local excision and limb reconstruction with alcohol inactivated autograft and knee arthrodesis on March 2016 (Fig. 4a). She was on follow up thereafter. Patient did not have any nasal complaints.

Non Contrast Computed Tomography of the paranasal sinuses revealed multiple lytic expansile lesions in facial and skull bones reported as metastatis of giant cell tumour (Fig. 3b, c). Incisional biopsy confirmed the presence of giant cells (Fig. 4b). Medical oncology reference was obtained and therapy with denosumab was advised.

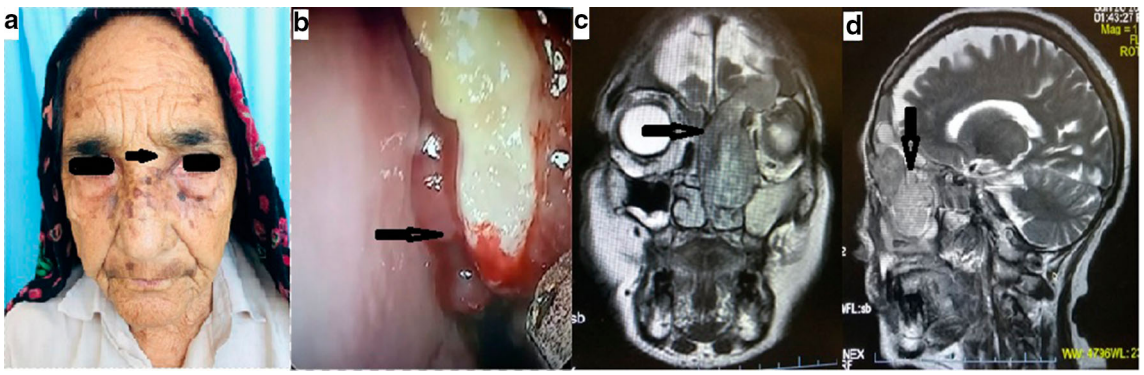

Fig. 1 **a** 74 year female with telecanthus and pulsatile soft tissue swelling in superomedial aspect of left eye.(black arrow) **b** DNE image showing pulsatile bleeding from mass in left middle meatus (blue arrow) **c** & **d** coronal and sagittal views, T2W1 CEMRI showing heterogeneously enhancing mass, in left nasal cavity and maxillary sinus and frontal sinus with anterior cranial fossa involvement

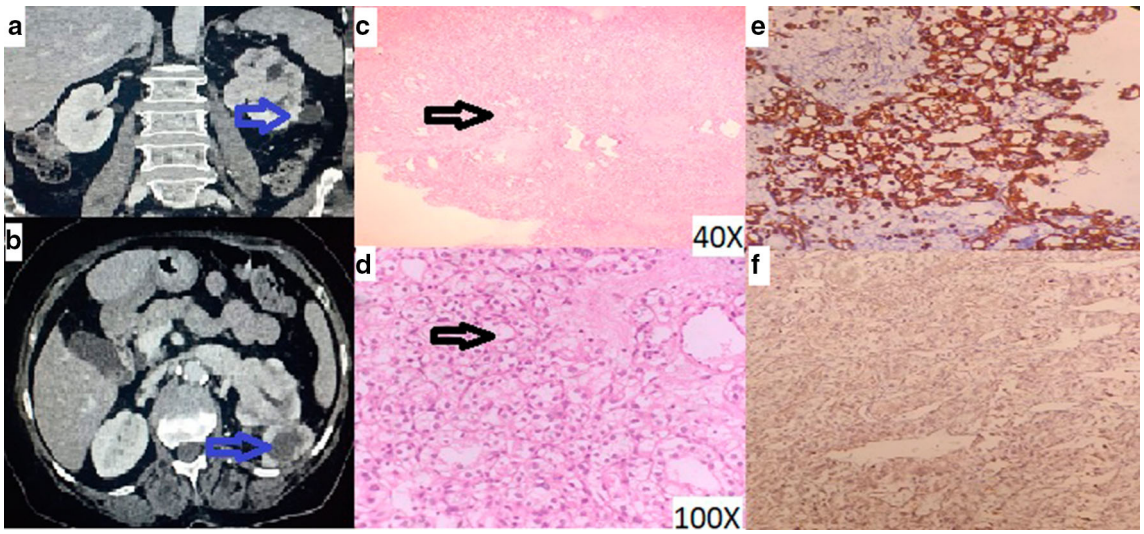

Fig. 2 **a** Enhancing left renal mass **b** Enhancing left renal mass with left renal vein invasion **c** 40X image showing tumour cells arranged in diffuse sheets **d** 100X Image showing large tumor cells with clear and vacuolated cytoplasm, round to oval nucleus and prominent nucleolus **e** Tumor cells positive for Vimentin on IHC **f** Tumor cells showing positivity for RCC antigen on IHC

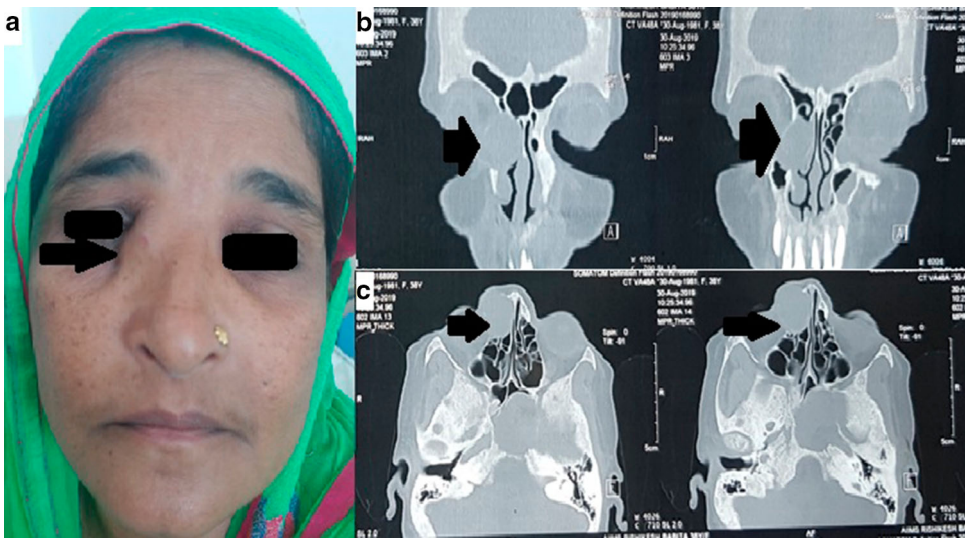

Fig. 3 **a** clinical image showing 38 year old female with a swelling over the medial side of right eye **b** NCCT Nose & PNS coronal view showing multiple lytic expansile lesion with areas of cortical breech on facial and skull bones **c** axial view of same lesion (black arrows marks the lesion)

Discussion

The clinical course of RCC is unpredictable, ranging from aggressive nature to spontaneous regression. Metastasis may be found at the time of diagnosis in 25–30% of the patients and upto even 17 years after nephrectomy [9]. Unusual sites of metastases are characteristic of RCC and virtually any organ site can be involved. Metastasis to the head and neck regions account for about 15% of the cases, the paranasal sinuses being highest in the order of frequency [10]. Maxillary sinuses are the more commonly involved (36%), followed by ethmoid (25%), frontal and sphenoid sinuses (17%), and nasal cavity (11%) [11, 12].

RCC mainly affects males between 40 and 60 years [13]. Common presenting symptoms include haematuria (40%), flank pain (40%), and a palpable abdominal mass (25%) [14]. This triad is seen only in 10% of patients. Sinonasal mass as initial presentation has been reported in a few cases [15, 16], while in others it occurred concurrently with renal mass as in our case or occurred years after nephrectomy. Hypervascularity of tumor explains the massive epistaxis which is the most common symptom. Mutation of the VHL gene causes upregulation of hypoxia-induced factor 1a and leads to angiogenesis through VEGF upregulation [17].

In case 1, patient is an elderly female with absence of classical triad of RCC and sinonasal mass which was

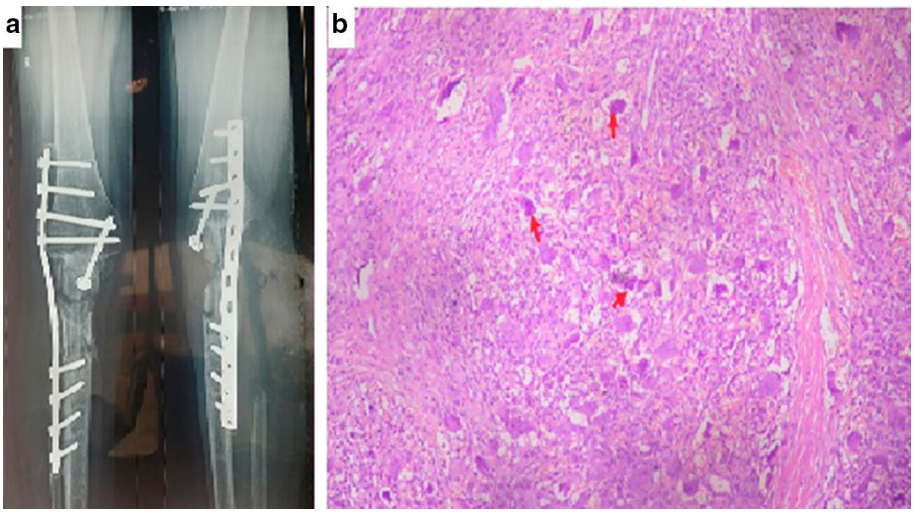

Fig. 4 **a** Giant Cell Tumor—Post-operative X-ray Knee **b** On HPE numerous osteoclasts like giant cells (red arrow) are seen uniformly distributed throughout the tumor in a background of monomorphic mononuclear cells population. The cells are round to spindled with bland nucleus

detected incidentally during a screening CT for head injury. Patient neither had previous episodes of spontaneous epistaxis nor symptomatic nasal obstruction which was surprising after seeing the extent of disease. Clinical suspicion and adequate preoperative haemostatic precautions helped us to control the massive pulsatile bleed which occurred during biopsy and debulking.

In RCC, tumor cells can reach the sinonasal region via two ways: (a) through the great vessels inferior venacava, and subsequently into lungs, heart, and the maxillary artery, (b) through the valveless vertebral venous plexus and intracranial venous plexus.

In the present case, metastasis might have occurred through the second route which by passes the lungs and explains the solitary sinonasal metastatic lesion. In general, work-up for a sinonasal mass should include endoscopic examination, followed by a contrast enhanced CT scan, prior to considering biopsy. This is the imaging test of choice considering its ability to delineate vascularity and skull base involvement. CT angiography and preoperative embolization may be considered which can significantly reduce intraoperative bleeding from external carotid system and internal carotid arteries to some extent. Ultrasound screening for abdominal organs in case of clinical suspicion can detect renal lesions. In CT scan, radiological appearances of metastasis from RCC has similarities to primary malignant lesions of sinonasal cavity. Some indicators of renal origin are enhancement, destruction, and lack of calcification in tumor [18].

Metastatic clear cell RCC on microscopy shows clear cell borders, eosinophilic cytoplasm, round or oval nuclei, and tumor cells arranged in nests with capillaries in between. Immunohistochemical staining for vimentin, EMA, CD10, CA IX, and PAX8 is done for tumor differentiation [19].

Treatment modalities include radiotherapy and immunochemotherapy for metastatic diseases. RCC is considered both radio- and chemo-resistant because of the inability to obtain high doses of radiation in the retroperitoneum, but in the nose and paranasal sinuses effective dose of radiation can be given. Now endoscopic surgery as either complete excision or cytoreduction is gaining more importance as it reduces bleeding in the course of treatment. Two reports describe the successful endoscopic resection of localized disease in the paranasal sinuses with greater 5 year survival [20]. Adjuvant treatment options include anti–vascular endothelial growth factor (VEGF) and mTOR pathway inhibitors, which may improve progression free survival in advanced RCC [21]. Prognosis of metastatic RCC is poor [22]; the survival rate ranges between 15 to 30% at 5 years [23] in case of a single metastasis and upto 7% in patients with multiple metastases [24].

Giant cell tumors commonly present during third and fourth decades in the epiphyseal region of long bones [25]. It can also involve the metaphysis of skeletally immature patient. Distal femur, proximal tibia, distal radius and sacrum are the other commonly involved sites. Other less common sites include proximal fibula, proximal femur, and proximal humerus. Multicentric and synchronous occurrence is rare [26, 27]. GCTs are benign tumors with metastatic potential. Though rare, they may be associated with destruction of local bony architecture. 1 to 9% of cases can show metastasis to distant sites [28].

Pain and soft tissue mass are the common presentation. Pathological fracture may be the presentation in 12% of the cases which indicates more aggressive disease and poor prognosis [27]. On radiography, it has a radiolucent geographical appearance with narrow zone of transition at the margin of the lesion lacking a sclerotic rim. Brown tumor of hyperparathyroidism, aneurysmal bone cyst,

telangiectatic osteosarcoma, and malignant fibrous histiocytoma are the differential diagnosis considered [29, 30].

Based on radiographic appearance, GCTs were classified by Enneking and later by Campanacci. They described three stages depending on the aggressiveness and local recurrence: Stage I—latent, Stage II—active and Stage III—aggressive. Radiologically, they are graded as Grade 1, Grade 2 and Grade 3. 20–30% of the cases show local recurrence. Recurrence after three years is less common. Grade 3 has shown to have an increased rate of recurrence [27, 31, 32].

GCT with pulmonary metastasis shows poor prognosis which is seen in 3% of cases [28]. Mean interval noted between the primary tumor and lung metastasis was approximately 18 to 24 months [33]. Giant cell tumors of head and neck are very rare and constitute about 2% of all giant cell tumors [8]. These giant cell tumors rarely occur in nasal cavity and the exact incidence is not yet recorded in the literature [4]. The natural history of metastatic lesions is unpredictable. However, if completely excised, they show good prognosis. Surgery is the mainstay of treatment. Hence, if possible metastatic lesions should be dealt surgically.

Radiotherapy and chemotherapy are of limited value in case of metastasis. At present no effective chemotherapeutic agents are available. Radiotherapy is recommended for unresectable cases like that of spine or sacrum. There have been reports of sarcomatous changes in giant cell tumors following Radiotherapy [34]. In unresectable cases, steroids are also a good option.

There have been reports of topical or systemic use of bisphosphonates as adjuvant therapy: pamidronate or zoledronate. Bisphosphonates targets osteoclast like giant cells and thus results in apoptosis which limits progression of tumor [35, 36]. The giant cells overexpress RANK receptor which plays an important role in osteoclast genesis. The RANK receptor is stimulated by cytokine RANKL. The RANK/RANKL interaction is predominantly responsible for the extensive bone resorption by the tumour. Hence anti-RANKL therapy is the other modality which can be used in giant cell tumors that cannot be surgically excised.[27]. Denosumab, a monoclonal antibody approved by United States Food and Drugs Administration (US FDA) binds to RANKL and has resulted in dramatic responses.[37, 38].

Conclusion

These case reports revealed a silent primary with metastasis to rare distant sites. Histopathology and immunohistochemistry are the mainstay for diagnosis. In both the cases the final diagnosis was surprising and hence sinonasal masses especially those with unusual morphology and hypervascular nature, should undergo a detailed work up. A proper clinical evaluation, radiological correlation and biopsy under precautions are necessary to establish the diagnosis.

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Compliance with Ethical Standards

Conflict of interest None.

Informed Consent Informed consent was obtained from both the participants included in the case report for publishing the details.

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