OPEN ACCESS – CASE REPORT

Atypical Metastatic Presentation of Sporadic Clear Cell Renal Cell Carcinoma: An Indolent Unilateral Intranasal Mass in a 60-year-old Male with Recurrent Epistaxis

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ABSTRACT

Renal cell carcinoma (RCC) is notorious for its propensity to metastasize even after a prolonged period of remission following nephrectomy. The metastatic spread can occur months or even years after initial treatment, which necessitates a heightened level of clinical awareness and vigilance in patients with a history of renal malignancy, particularly who present with new or unexplained nasal symptoms. Although RCC most commonly metastasize to the lungs, bones and liver, its involvement in the nasal cavity is exceedingly rare, posing significant diagnostic challenges due to the non-specific nature of symptoms. We describe a case of metastatic renal cell clear cell carcinoma presenting with recurrent epistaxis and unilateral nasal obstruction. Immunohistochemistry studies play a crucial role in confirming the diagnosis and ruling out potential differential diagnoses, along with a comprehensive clinical history of the patient.

Key words: clear cell renal cell carcinoma, metastasis, nasal cavity, epistaxis, intranasal mass

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INTRODUCTION

Metastatic renal cell carcinoma (RCC) is a malignant tumor that originates in the kidneys and is known for its propensity to spread to distant sites, often involving the lungs, bones, liver, and less commonly, the head and neck region. However, metastasis to the sinonasal cavity region is exceedingly rare and presents significant diagnostic challenges due to its indolent growth and non-specific symptoms, which may mimic benign sinonasal pathology. This case highlights the insidious nature of metastatic RCC, where misdiagnosis can result in delay and suboptimal treatment and management.

CASE REPORT

This is a case of a 60-year-old male who presented with a 6-year history of non-foul- smelling, unilateral rhinorrhea in the left nasal cavity, without accompanying symptoms such as epistaxis, nasal congestion, fever, cough, headache, anosmia or nasal obstruction. The patient tolerated the condition over time. However, 2 years before admission, symptoms persisted and were now associated with epistaxis occurring twice a month. Each episode involved approximately three cotton balls soaked in blood, but the patient continued to tolerate his condition. Symptoms persisted until 1 year before admission, the patient sought consult with an otorhinolaryngologist. Nasal endoscopy with punch biopsy was done which noted a friable, ill-defined, reddish to purple intranasal mass with whitish discharges obstructing the entire left nasal cavity (Figure 1).

Paranasal sinus CT scan was requested which revealed a solid mass in the left nasal cavity, measuring at least 3.0 x 2.1 x 4.3 cm. The mass deviated the nasal septum to the right and laterally obstructed the left ostiomeatal unit. Fluid densities were in the left ethmoid, sphenoid and maxillary sinus (Figure 2). However, the result of the initial

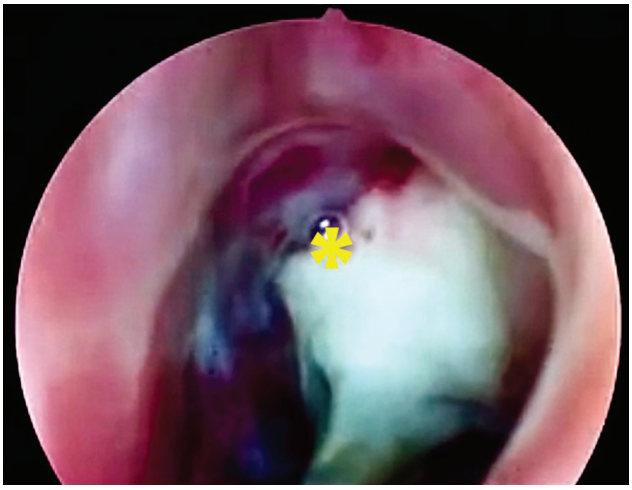

Figure 1. Nasal endoscopy findings showing a reddish intranasal mass (*) with whitish discharges.

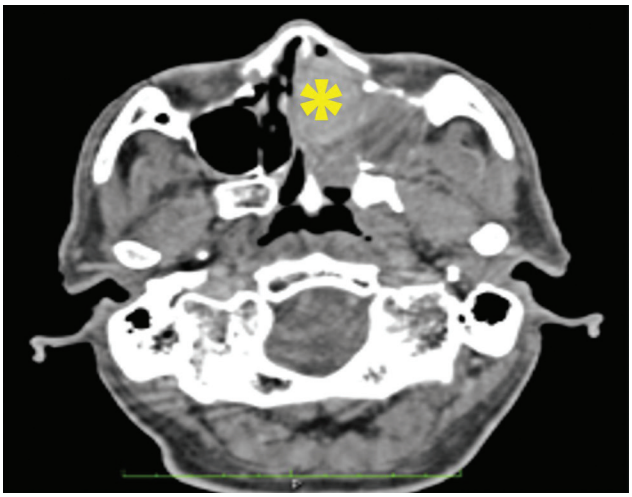

Figure 2. Paranasal sinus CT scan findings showing a solid mass in the left nasal cavity (*), deviating the nasal septum and obstructing the left ostiomeatal unit.

biopsy was non-diagnostic, which revealed only extensive necrosis with acute and chronic inflammation.

Repeat punch biopsy was done. The specimen submitted for pathology consists of three, minute, tan cream, irregular tissue fragments which measured 2.0 x 1.1 x 0.7 cm. Histopathologic examination showed tumor cells predominantly in tubular and microcystic architecture and some in an acinar pattern intervened by fibrous stroma (Figure 3 and 4). The tumor cells were relatively large, having irregularly ovoid, hyperchromatic, centrally located nuclei with inconspicuous nucleoli and abundant clear cytoplasm. Luminal polarization of nuclei was absent. The tumor cells in acinar pattern were separated by fibrotic stroma, characteristically endowed with a prominent network of small and thin-walled blood vessels (Figure 5). No areas demonstrated papillary or alveolar architectural patterns. Keratinization was not observed in any area.

Based on the histomorphologic features, main differential diagnoses include primary clear cell carcinoma of the

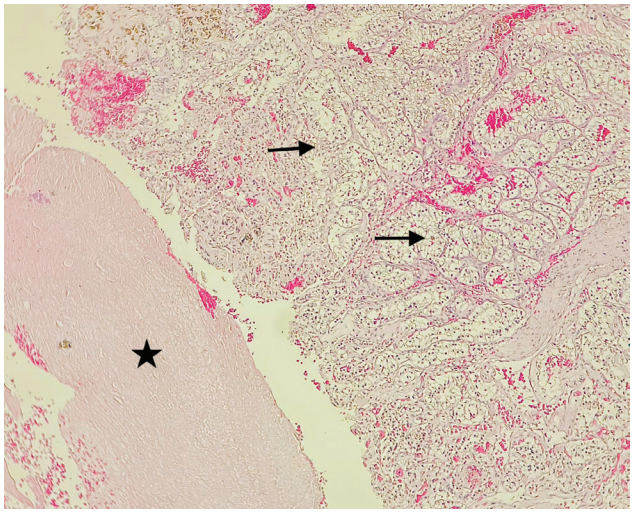

Figure 3. Tumor cells *(black arrows)* in tubular, microcystic and acinar architecture with extensive necrosis *(black star)* (H&E, 40x).

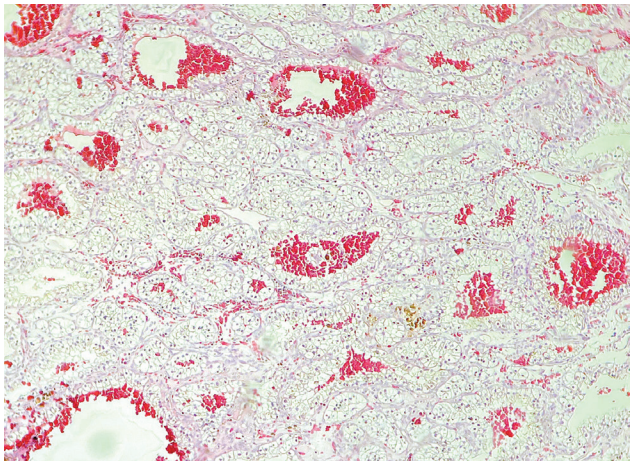

Figure 4. Tumor cells in prominent acinar growth pattern intervened with extravasated blood (H&E, 100x).

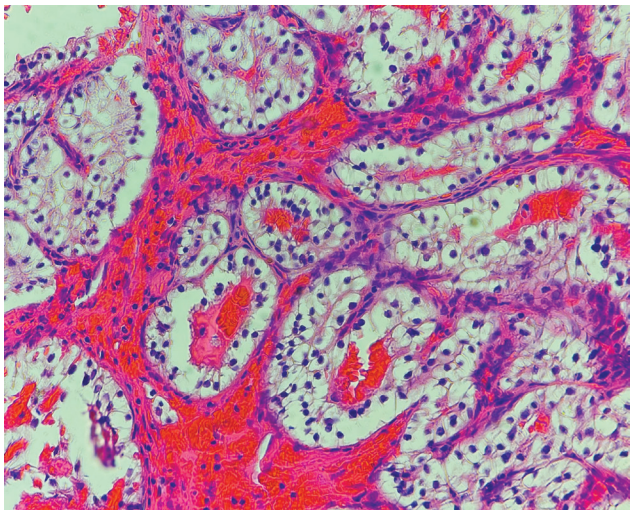

Figure 5. Tumor cells with centrally located nuclei and abundant clear cytoplasm (H&E, 400x).

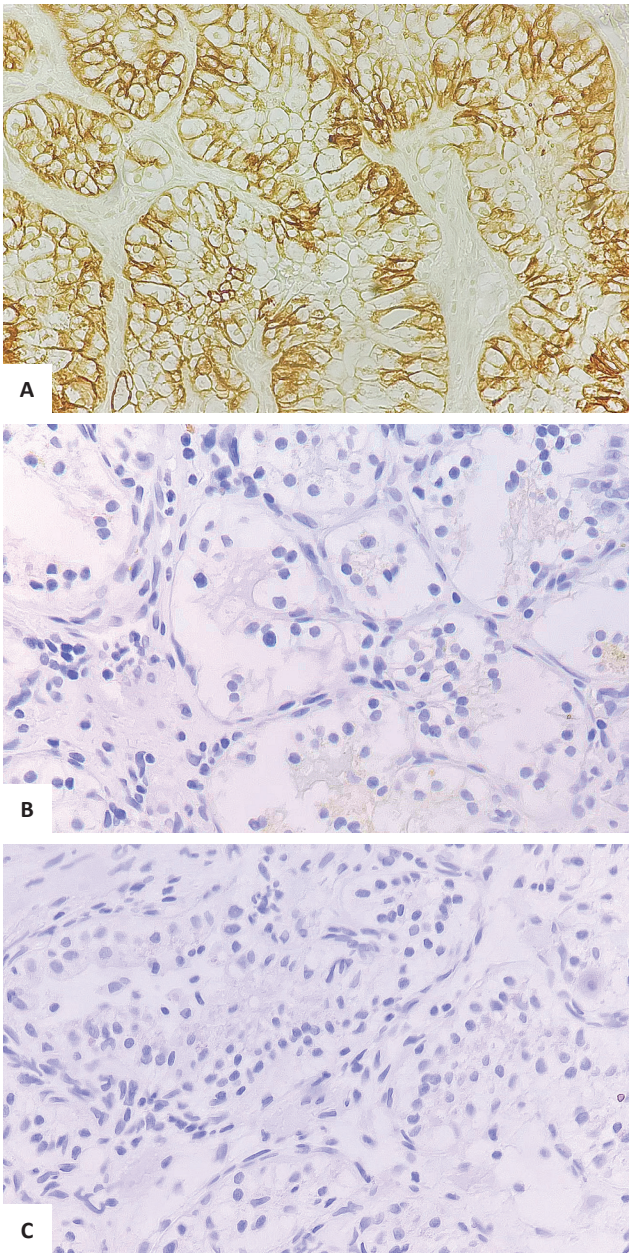

Figure 6. Immunohistochemistry showing strong and diffuse, **(A)** membranous staining for CK7; **(B)** negative for CK20 and **(C)** PSA.

nasal cavity, metastatic carcinoma from the prostate and thyroid (papillary carcinoma), and non-intestinal type, adenocarcinoma of clear-cell variant.

Initial panel of immunohistochemistry studies revealed negative for CK20 (Figure 6B), and PSA (Figure 6C). Tumor cells were positive for CK7 (Figure 6A). CK7 positivity and CK20 negativity suggested a primary of the lung, salivary gland, breast, or head and neck.

Additional immunohistochemical staining was performed, including S100, TTF-1, p63 and CD117. Negative staining for S100 (Figure 7A) and TTF-1 (Figure 7B) ruled out sinonasal mucosal malignant melanoma and metastatic papillary thyroid carcinoma respectively. The absence of p63 expression ruled out both squamous cell carcinoma

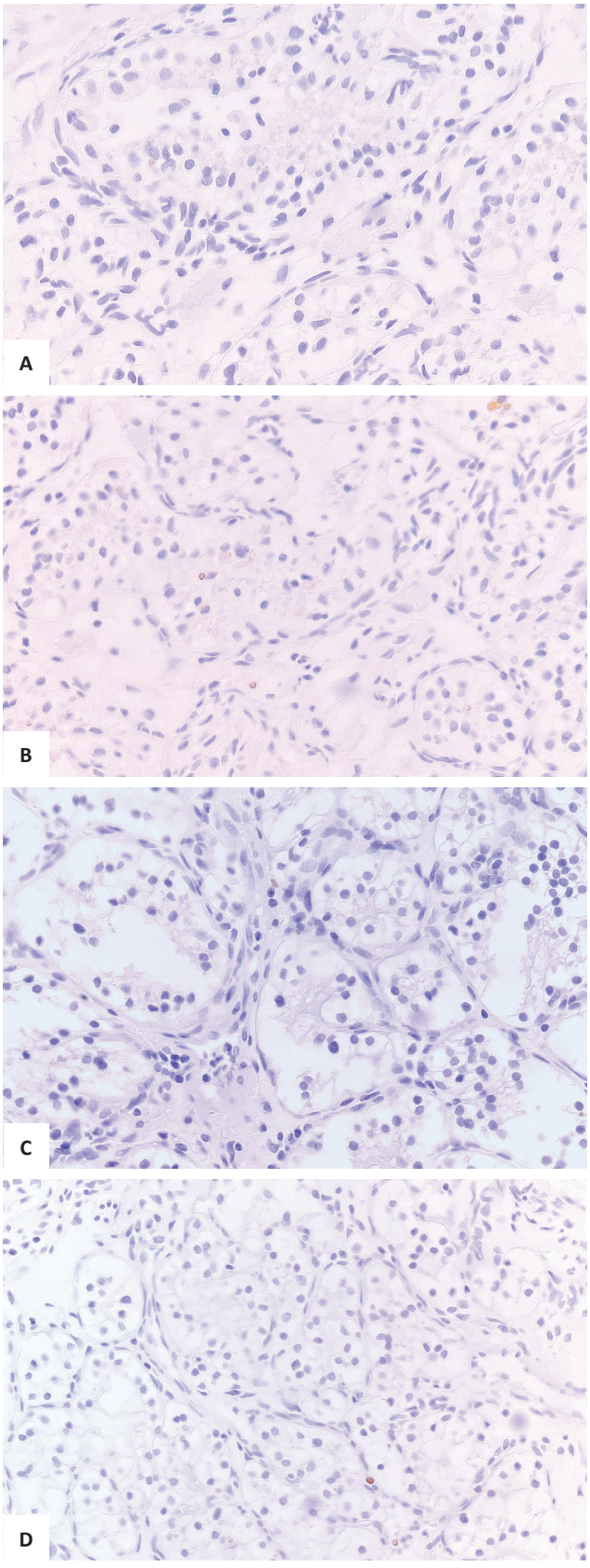

Figure 7. Immunohistochemistry showing negative expression for **(A)** S100, **(B)** TTF-1, **(C)** p63 and **(D)** CD117.

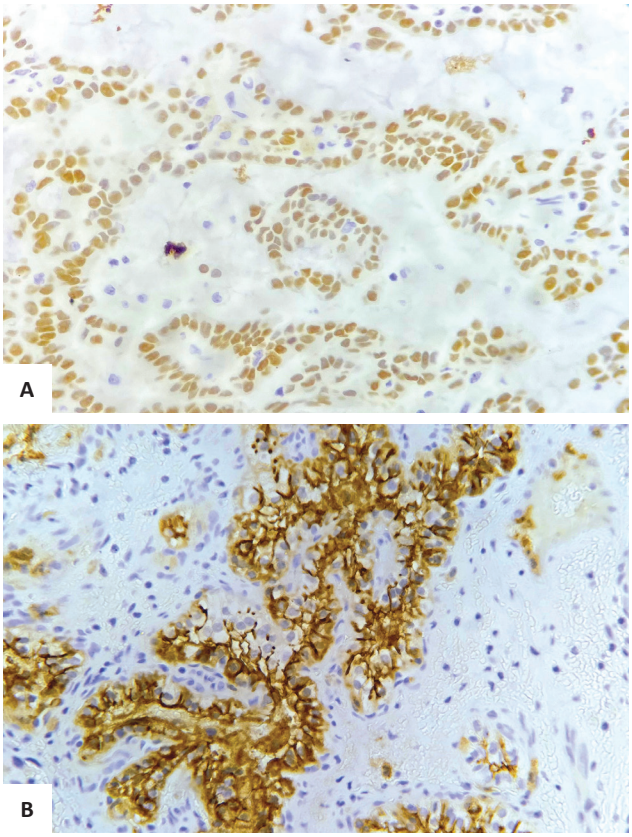

Figure 8. Immunohistochemistry showing strong and diffuse, **(A)** nuclear staining for PAX8 and **(B)** membranous staining for CD10.

of clear cell variant as well as mucoepidermoid carcinoma with clear cell changes (Figure 7C). Clear-cell predominant acinic cell carcinoma is also ruled out because of the absence of CD117 expression (Figure 7D).

Negative staining for S100 also ruled out myoepithelioma and myoepithelial carcinoma as potential diagnoses. Hence, the most likely remaining differential diagnosis is a metastatic lesion from a renal malignancy, which would typically exhibit CK7 positivity and CK20 negativity. While the immunoprofile is compatible with metastatic papillary renal cell carcinoma, it is not aligned with its histomorphologic characteristics. Hallmark features of papillary renal cell carcinoma such as presence of papillary architecture of tumor cells, clear and glycogenated cytoplasm, and 'piano key' appearance of aligned nuclei are absent.

A final panel of immunostains was performed such as PAX8 (Figure 8A) and CD10 (Figure 8B), showing strong nuclear and membranous positive staining, respectively. Upon reviewing the clinical history of the patient, he had undergone radical nephrectomy last 2014 at a private institution. CT urography confirmed a surgically absent right kidney, with no other significant findings. According to the patient, he had been diagnosed with Stage I, Renal Cell Carcinoma. Considering the histomorphologic features and immunoprofile in conjunction with the patient's clinical history, the case was signed out as Metastatic Clear Cell Carcinoma of the Kidney.

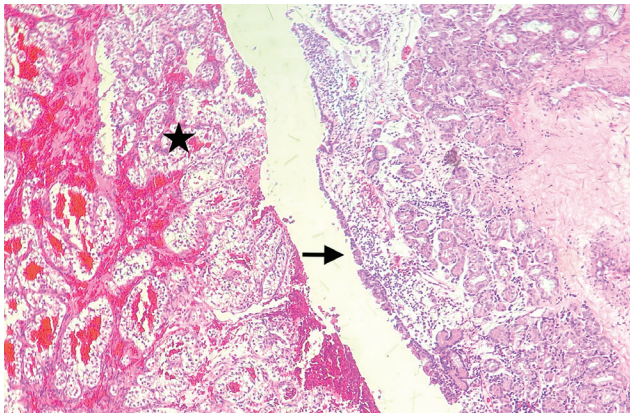

Figure 9. Tumor cells in prominent microcystic architecture intervened with extravasated blood *(black star)* and normal respiratory epithelium of the nasal cavity with mucosal glands *(black arrow)* (H&E, 40x).

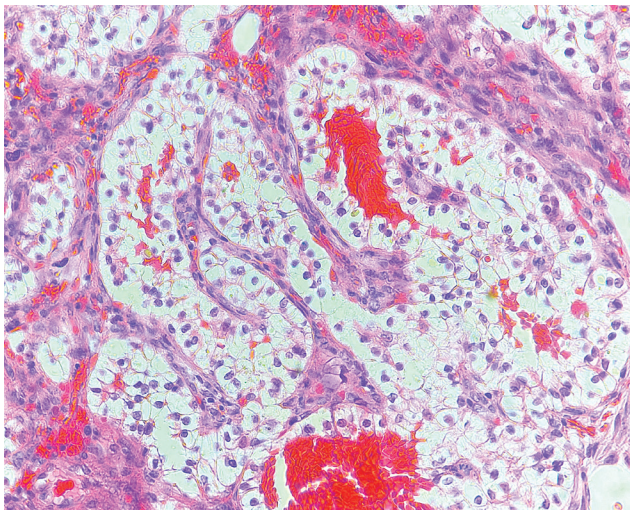

Figure 10. Tumor cells with centrally located nuclei and abundant clear cytoplasm (H&E, 400x).

The patient was advised for surgery but did not comply due to financial limitations. Approximately four months prior to admission, an increase in episodes of epistaxis was noted and prompted the patient to consult at our institution. The patient underwent endoscopic sinus surgery to excise the intranasal tumor. The specimen submitted for pathology consists of several, tan to dark brown, rubbery to firm, smooth to rough, irregular tissue fragments measuring 8.0 x 6.0 x 1.5 cm. Histopathologic examination revealed tumor cells in prominent microcystic architecture intervened by fibrous stroma and extravasated blood (Figure 9) with extensive necrosis (Figure 11). The tumor cells have centrally located nuclei with abundant clear cytoplasm (Figure 10). These findings were consistent with the previous punch biopsy of the nasal cavity. Immunostaining with CD10 on the received specimen was done to support the previous diagnosis of Metastatic Clear Cell Renal Cell Carcinoma, demonstrating strong positivity (Figure 12).

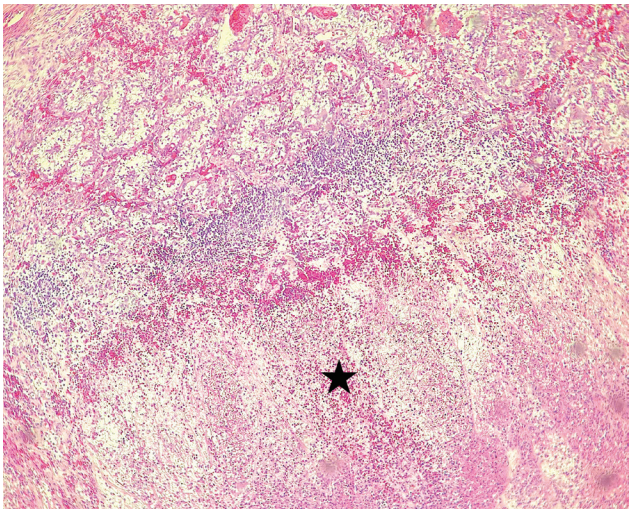

Figure 11. Tumor cells in a background of extensive necrosis *(black star)* (H&E, 100x).

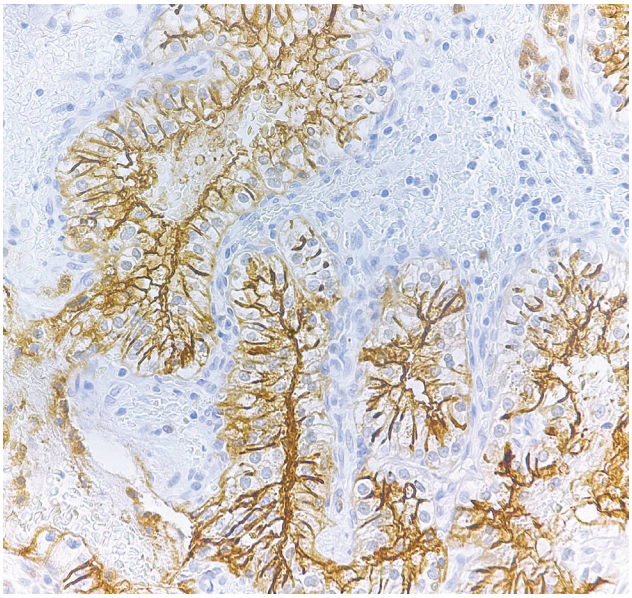

Figure 12. Immunohistochemistry showing strong, membranous staining with CD10.

DISCUSSION

Worldwide, renal cell carcinoma (RCC) represents the sixth most frequently diagnosed cancer in men, accounting 5% of all malignancies.[1] In the Philippines, a total of 2, 916 new cases of renal malignancy were recorded with a mortality of 1.3% last 2022. The 5-year prevalence of renal malignancy was 7.4 per 100, 000 population, highlighting its significant impact on the global burden of cancer. Approximately 30% of patients with renal cell carcinoma present with metastatic disease primarily in the lungs (75%), soft tissues (36%), bone (20%), liver (18%), cutaneous sites (8%) and CNS (8%). Metastasis to the paranasal sinuses and intranasal cavity is exceedingly rare.[2] This atypical site of metastasis is believed to occur through either hematogenous or lymphatic spread, although the exact mechanism remains uncertain.[3] Hematogenous dissemination is considered the most common route and may follow one of two pathways. The first pathway involves the renal vein, inferior vena cava, heart, lungs, and maxillary artery. This route is supported by the frequent presence of simultaneous lung and/or brain metastases in reported cases of RCC with sinonasal involvement.[4] The second and less common route is through the Batson's paravertebral venous plexus, which allows tumor cells to bypass filtration through the lungs, liver and brain.[5] Lymphatic spread is via the regional lymphatics and the thoracic duct.[6]

However, RCC is the most common cancer metastasizing to these regions based on published case reports.[7] Metastasis to these regions often presents with recurrent epistaxis. No published case report has been documented in the Philippines up to this date. Unfortunately, the prognosis of metastatic RCC is poor and often resistant to chemotherapy and radiotherapy.[8] Thus, immediate diagnosis is of great importance for better treatment outcomes. For isolated sinonasal metastasis from RCC, surgery is generally regarded as the treatment of choice. Endoscopic resection is appropriate for localized lesions. In cases of extensive sinonasal involvement, a maxillectomy may be warranted.[9] Others recommend the addition of radiotherapy to surgical management, though its efficacy has been reported with variable outcomes. It reduces the tumor burden and provides symptomatic relief.[10]

Immunohistochemistry studies are typically required to confirm the diagnosis. For this case, several immunostains such as CK7, CK20, PAX8, CD10, TTF-1, S100, PSA, p63 and CD117 were performed. Potential differential diagnoses must be ruled out such as primary clear cell carcinoma of the nasal cavity, squamous cell carcinoma of clear cell variant, clear cell-predominant acinic cell carcinoma, sinonasal mucosal malignant melanoma, mucoepidermoid carcinoma with clear cell changes, myoepithelioma, myoepithelial carcinoma, metastatic carcinoma from thyroid and kidney, as well as non-intestinal type adenocarcinoma of clear cell variant.

The prognosis for metastatic renal cell carcinoma remains poor; however, early and accurate diagnosis of metastatic disease can substantially improve the patient's survival rate. According to the existing literature, surgical excision of a solitary metastatic lesion following nephrectomy has been associated with a 41% survival rate at 2 years and a 13% survival rate at 5 years.[11] These findings highlight the potential benefit of early intervention in selected cases. In contrast, survival outcomes are notably worse when only the metastatic lesion is removed, as this approach alone significantly reduces long-term survival rates. Furthermore, patients with multiple metastatic lesions face a bleak prognosis, with reported five-year survival rates ranging from 0% to 7%. These statistics underscore the critical importance of early detection, accurate staging, and appropriate treatment strategies to improve outcomes for patients with metastatic RCC.[12]

CONCLUSION

The clinical progression of renal cell carcinoma (RCC) is highly variable, exhibiting a spectrum that ranges from an aggressive, rapidly advancing course to instances of

spontaneous regression. The metastatic potential of RCC is a significant concern, as metastasis may be detected in 25-30% of patients at the time of initial diagnosis. This can metastasize even years after nephrectomy, emphasizing the unpredictable nature of the disease. This delayed metastatic spread presents a challenge in monitoring patients' post-treatment, as metastases may emerge long after apparent clinical remission, underscoring the need for long-term surveillance and ongoing vigilance in managing patients with a history of RCC. Reporting these uncommon occurrences enhances clinical understanding, aids in the recognition of unusual metastatic patterns, and contributes valuable insights to the literature. This, in turn, helps refine diagnostic approaches and treatment strategies for similar future cases, fostering improved patient outcomes.

ETHICAL CONSIDERATIONS

Patient consent was obtained before the submission of the manuscript.

STATEMENT OF AUTHORSHIP

All authors certified fulfillment of ICMJE authorship criteria.

AUTHOR DISCLOSURE

The authors declared no conflict of interest

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