Clinical Case Report

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Sinonasal renal cell-like adenocarcinoma, a unique variant of primary clear cell carcinoma of the head and neck

The first reported case in Korea

Nah-Ihm Kim, MD[a], Jung-In Yang, MD[a], Sung-Sun Kim, MD, PhD[a], Ji-Shin Lee, MD, PhD[a], Sang-Chul Lim, MD, PhD[b], Shin Jung, MD, PhD[c], Jae-Hyuk Lee, MD, PhD[a], Kyung-Sub Moon, MD, PhD[c,*], Kyung-Hwa Lee, MD, PhD[a,*]

Abstract

Rationale: Primary sinonasal renal cell-like adenocarcinoma (SNRCLA) is a rare and unique neoplasm.

Patient concerns: A 63-year-old man presented with repeated epistaxis, nasal obstruction and hyposmia of 2-month duration. Radiological studies revealed a mass of the left ethmoid sinus involving anterior skull base.

Diagnosis: The patient was treated with craniofacial resection, bifrontal craniotomy combined with an endonasal endoscopic approach. Intraoperatively, a hypervascular paranasal mass invading the dura mater was removed *en block*. Histologically, the tumor resembled a clear cell renal cell carcinoma, with cuboidal shaped cells having clear cytoplasm. The tumor cells were positive for CK7, S100, vimentin and PAX-8 and negative for CD10 and PAX-2 by immunohistochemistry. No evidence of renal malignancy was found by radiological and clinical examinations.

Interventions and outcomes: Following local radiation therapy, the patient was in good health without recurrence for 15 months after the operation.

Lessons: To the best of the authors' knowledge, this is the first reported case of SNRCLA in Korea. Because of its histological feature of clear cytoplasm, SNRCLA needs to be differentiated from clear cell renal cell carcinoma and other salivary clear cell carcinomas. The prognosis of SNRCLA is generally favorable as shown in the previously reported cases. Considering the limited number and follow-up periods of the cases, however, delayed recurrence should be kept in mind for clinicians.

Abbreviations: RCC = renal cell carcinoma, SNRCLA = sinonasal renal cell-like adenocarcinoma.

Keywords: immunohistochemistry, paranasal sinus neoplasm, prognosis, sinonasal renal cell-like adenocarcinoma

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[a] Department of Pathology, [b] Department of Otolaryngology-Head and Neck Surgery, [c] Department of Neurosurgery, Chonnam National University Hwasun Hospital and Medical School, Hwasun, Jeollanamdo, South Korea.

[*] Correspondence: Kyung-Hwa Lee, Department of Pathology, Chonnam National University Hwasun Hospital and Medical School, 322 Seoyang-ro, Hwasun-eup, Hwasun-gun, Jeollanam-do 519-763, South Korea (e-mail: mdkaylee@jnu.ac.kr); Kyung-Sub Moon, Department of Neurosurgery, Chonnam National University Hwasun Hospital and Medical School, 322 Seoyang-ro, Hwasun-eup, Hwasun-gun, Jeollanam-do 519-763, South Korea (e-mail: moonks@chonnam.ac.kr).

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1. Introduction

Primary sinonasal renal cell-like adenocarcinoma (SNRCLA) is a very rare tumor. Since its first description,[1,2] SNRCLA has been reported in only 15 patients.[1–12] Histologically, SNRCLA and clear cell renal cell carcinoma (RCC) share the characteristic feature of a translucent cytoplasm. In the head and neck region, primary clear cell carcinoma originated mainly either in the salivary glands or in the thyroid gland.[2] Because of its rare occurrence and impressive resemblance to clear cell RCC, SNRCLA may be misdiagnosed or overly treated.

Recently, we treated a man with an ethmoidal tumor diagnosed as SNRCLA. After reviewing hematoxylin-and-eosin (H&E) stained slides, we also considered the tumor as metastasis of RCC to the sinonasal tract. However, primary renal malignancy was not detected by radiological and urological work-ups. Immunohistochemistry undertaken to distinguish RCC and SNRCLA revealed the tumor as SNRCLA. To the best of our knowledge, this report presents the first case of SNRCLA in Korea.

2. Case presentation

The patient was a 63-year-old male who presented with 2-month duration of repeated left-sided epistaxis. He also complained of nasal obstruction, impaired olfaction, and sleep apnea. Nasopharyngoscopy showed a polypoid mass in the lateral and posterior portion of the middle turbinate. Review of systems and

laboratory findings were not instructive to the diagnosis. Lymphadenopathy and any palpable mass were not detected by physical examination. Computed tomography scans and magnetic resonance images showed a 2.6×2.1 cm, heterogeneously enhanced irregular mass with bony erosion in the left ethmoid sinus. Destruction of the ethmoidal roof with enhancement of the thickened dura was also evident, suggesting primary paranasal sinus tumor with invasion into the anterior skull base (Fig. 1A–C). A preoperative biopsy led to diagnosis as malignant epithelial tumor, such as metastatic clear cell RCC or other sinonasal clear cell carcinoma. To exclude metastatic RCC, the patient underwent renal imaging studies including abdominal computed tomography scans. However, no primary renal malignancy was identified (Fig. 1D). The patient was treated with craniofacial resection, bifrontal craniotomy combined with an endonasal endoscopic approach for tumor removal. Intraoperatively, a hypervascular paranasal mass invading the dura mater was evident. The lesion was removed en block. Histology of the tumor revealed compactly arranged glands composed of a single row of cuboidal to columnar cells. The tumor glands were tightly packed in a back-to-back arrangement with little luminal spaces within the dura (Fig. 2A). The compact tubules were closely intermingled with the collagenous dural tissues, displaying deeply dissecting extension. The tubular structures varied in size with irregular large glandular spaces near the mucosal surface, showing rather loosely infiltrating features (Fig. 2B). Centrally located nuclei were surrounded by abundant clear cytoplasm with distinct cytoplasmic membranes, but no cytoplasmic granularity (Fig. 2C). The nuclei were uniform and round with minimal pleomorphism. Tumor necrosis was present, but the change seemed to be associated with the previous excision biopsy procedure. Perineural invasion was identified, while mitotic figures were almost absent. Numerous calcospherules with concentric laminar structures were placed within the luminal spaces. No bimodal myoepithelial pattern or stromal hyalinization was seen. Initial immunohistochemistry revealed strong cytoplasmic positivity for cytokeratin (CK), CK7, epithelial membrane antigen (EMA), S-100, CD56 and vimentin, and weak luminal positivity for carcinoembryonic antigen (CEA) and calponin (Fig. 2D–E). Tumor cells were negative for CK20, CD10, p63, and synaptophysin. Additional stains for differential diagnosis displayed nuclear positivity for PAX-8 and negative staining for PAX-2 (Fig. 2F). Periodic acid Schiff (PAS) stain was positive for intracytoplasmic material, but PAS stain after digestion using diastase was negative, indicative of glycogen accumulation. Although the histopathological features of the tumor were highly reminiscent of those of clear cell RCC, immunonegativity of PAX-2 was indicative of nonrenal primary. Also negative imaging findings of the abdomen made the possibility of a renal primary ruled out. The final pathological

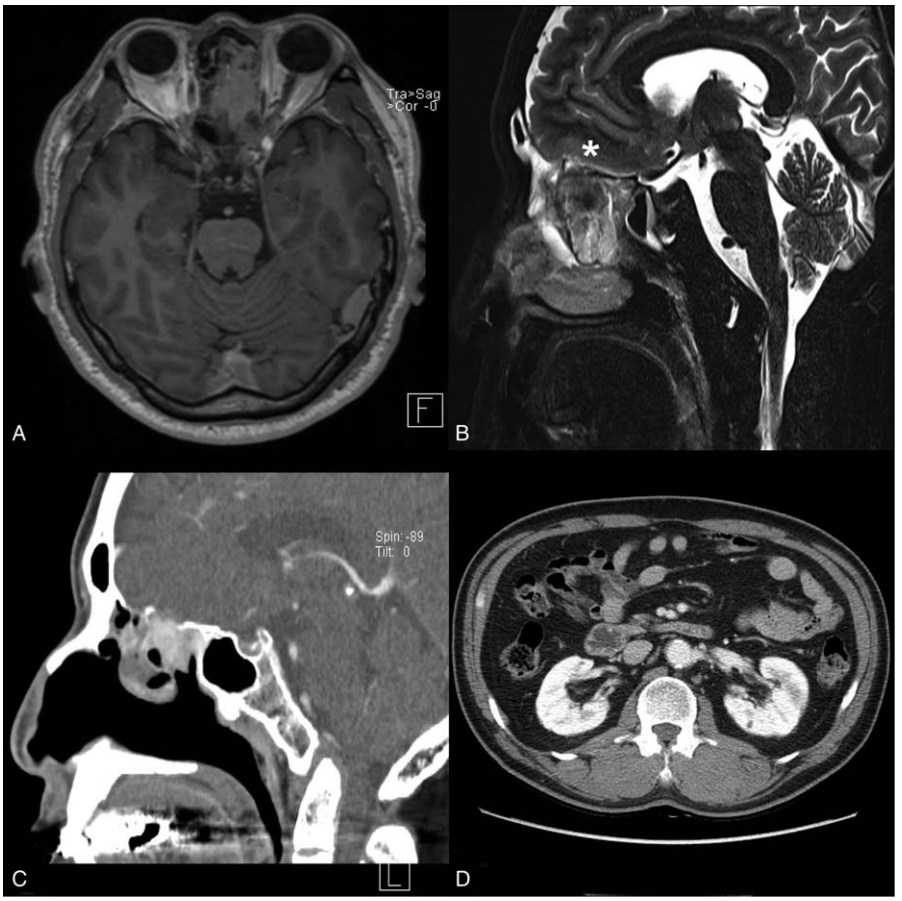

Figure 1. Radiological findings. Preoperative T1-weighted axial MRI with gadolinium enhancement (A) and T2-weighted sagittal MRI (B) demonstrated a heterogeneously enhanced mass in the paranasal sinus with invasion of the dura mater of the anterior skull base (asterisk). A bony destruction of the anterior skull base was also observed on sagittal CT scan (C). Note that enhanced abdominal CT scan (D) demonstrated no mass lesion in both the kidneys. CT = computed tomography, MRI = magnetic resonance imaging.

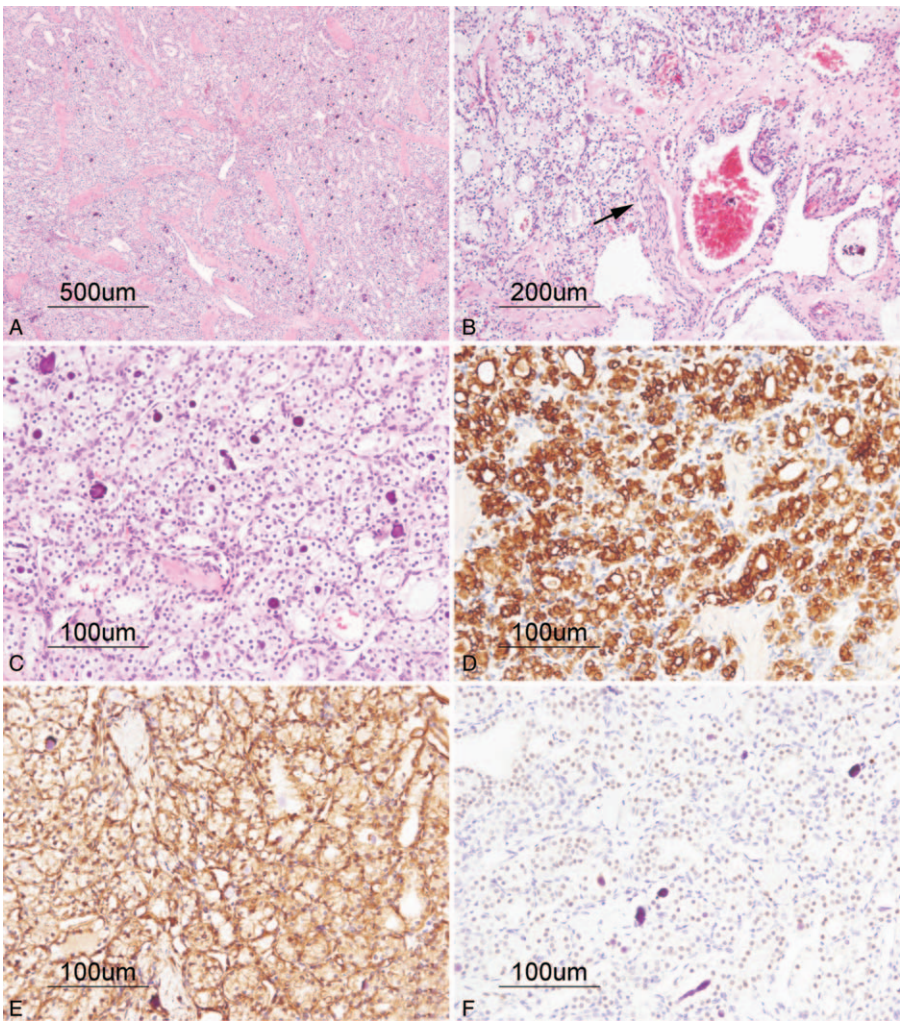

Figure 2. Features of tumor cells. (A) The tumor was composed of regularly spaced tubules that showed invasive growth dissecting the dural tissue in this field. (B) Some areas displayed variable-sized tubules and rarely perineural invasion by tumoral glands (black arrow). (C) At a higher magnification, tumor cells were shown to have small round nuclei, abundant clear cytoplasm, and distinct cytoplasmic borders in back-to-back appearances. Calcospherules mimicking psammoma bodies were also frequently identified. (A–C, hematoxylin-and-eosin [H&E] stain, original magnification, ×40, ×100, and ×200, respectively) (D) Immunohistochemistry revealed strong positivity for CK7 in tumor cells. (E) Tumor cells were also diffusely positive for vimentin. (F) The tumor nuclei were weakly stained with PAX-8 antibody. (D–F, immunohistochemistry, original magnification, ×100).

diagnosis was primary SNRCLA. Postoperatively, the patient underwent fractionated radiotherapy of 5600 cGy for 6 weeks. The patient was in good health without recurrence for 15 months after the operation. The patients provided signed, informed consent, and the study was approved by the Institutional Review Board of the Chonnam National University Hwasun Hospital.

3. Discussion

SNRCLA is an extremely rare neoplasm. The first reports[1,2] led to the recognition of prior possible cases of SNRCLA.[4,7,9] The descriptive term, "renal-cell like," was originally proposed by Zur et al,[1] the authors pointed out that the major differential diagnosis of their index case was a metastatic clear cell RCC because the 2 neoplastic entities looked very similar. Histologically, SNRCLA displays a remarkable resemblance to RCC. The tumor cells have a cuboidal to columnar cell shape with an abundant clear cytoplasm and distinct cytoplasmic borders. The cytoplasm of the tumor cells may be predominantly clear or slightly eosinophilic, but can be exceptionally basophilic in a localized pattern. The nucleus tends to be low-grade; small, round, and monotonous. The tubular structures are round and regular in a back-to-back arrangement, but the tubule sizes may be variable. However, no high-grade features have been described in SNRCLA including marked nuclear pleomorphism, high mitotic activity, hemorrhage, and necrosis.[1–3,8,11] Nevertheless, some tumors reportedly display infiltrative growth; the current case also showed deeply invasive growth within the dura. Compared to SNRCLA, neoplastic cells in clear cell RCC are arranged in solid nests separated by an intervening vascular network and may show high-grade Fuhrman nuclear features, frequent mitoses, and necrotic changes. Strikingly, in the current case there were numerous calcospherules within the luminal spaces. The concentric calcified materials resembled psammoma bodies. Finally, the most recent edition of World Health Organization classification of Head and Neck tumors included this rare tumor as a morphologically unique entity of low-grade sinonasal nonintestinal-type adenocarcinomas.[13]

Table 1

Summary of the previously reported SNRCLA cases with differential immunohistochemical findings in comparison with clear cell RCC.

	Age/sex	Location	CK7	CK20	EMA	CEA	S100	Vimentin	CD10	Calponin	PAX2	PAX8	Treatment	Clinical outcome
Heffner, 1982[4]	62/F	Nasal	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Resection, RT	Recurrence at 3 and 5 y. AWD at 7.5 y
Moran, 1991[7]	67/M	Sinonasal	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Follow-up lost
Newman, 1993[9]	77/M	Nasal	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Resection, RT	Recurrence at 7 mo
Zur, 2002[1]	50/F	Nasal	+	–	+	+	+	–	–	–	NA	NA	Resection, RT	NED 8 y
Moh'd Hadi, 2002[2]	22/F	Nasal	+	–	NA	NA	–	–	NA	–	NA	NA	Resection	NED 5 y
Stork, 2008[11]	36/F	Nasal	+	+	+	+	–	–	+	NA	NA	NA	Resection, RT	NED 4 y
Storck, 2008[11]	69/M	Nasopharynx	+	–	NA	NA	–	–	NA	NA	NA	NA	RT	NED 2 y
Cheng, 2008[3]	63/F	Nasopharynx	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Resection, RT	NED 1 y
Negahban, 2009[8]	52/F	Nasal, paranasal sinuses	+	–	+	–	–	NA	NA	NA	NA	NA	Resection	NA
Huang, 2011[6]	54/F	Nasal	NA	NA	+	NA	NA	–	+/–	NA	NA	NA	Resection	NED 1 y
Suzuki, 2012[12]	59/F	Sphenoid skull base	–	–	+	NA	+	+	–	–	NA	NA	RT	NED 2 y
Hong, 2013[5]	34/M	Nasal	+	NA	+	NA	+	–	–	NA	NA	NA	ChemoRT	NED 1 y
Shen, 2015[10]	56/F	Nasal, skull base	+	+	NA	NA	+	+	NA	NA	NA	–	Resection, RT	NED 22 mo
Shen, 2015[10]	89/F	Sinonasal	+	–	NA	NA	–	–	NA	NA	NA	–	Resection	NED 4 mo
Shen, 2015[10]	73/M	Nasal	+	–	NA	NA	+	+	–	NA	NA	NA	Resection, RT	NED 20 mo
Present case	63/M	Paranasal sinus	+	–	+	+	+	+	–	+	–	+	Resection, RT	NED 15 mo
Clear cell RCC			–	–	+	–	+	+	+	–	+	+		

AWD = alive with disease, F = female, M = male, NA = not available, NED = no evidence of disease, RT = radiotherapy, RCC = renal cell carcinoma, SNRCLA = sinonasal renal cell-like adenocarcinoma.

Clear cell RCC is usually negative for both CK7 and CK20 and shows positive expression for vimentin, CD10, RCC antigen, and CA9.[8] Also, the majority of clear cell RCC cases express nuclear PAX-2 and PAX-8. As summarized in Table 1, most of the previously reported SNRCLA cases were positive for CK7 (9/10) and negative for vimentin (7/10). Contrary to our hypothetical prediction, the current case was positive for vimentin and PAX8; these markers have not been thought to be positive in SNRCLA. Recent studies reported positive vimentin expression in SNRCLA.[10,12] Although PAX-8 positivity for tumors of urogenital tract origin has been described, the current case showed weak nuclear positivity for PAX-8. To exclude the possibility of a renal primary origin, the current case needed to be tested for PAX-2, a more specific marker of urogenital origin. The staining result was negative. We cautiously suggest that CK7 and PAX2 are the most useful marker to rule out metastatic RCC, although the specificity of PAX-2 as a negative marker of SNRCLA needs to be tested further in additional cases. Scrupulous radiological studies should be carried out to exclude primary renal malignancy. One recent study reported strong carbonic anhydrase expression in SNRCLA and suggested the idea that SNRCLA may originate in the seromucinous glands.[10]

The top differential diagnosis for primary sinonasal neoplasm would be a salivary hyalinizing clear cell carcinoma (HCCC). Histologically, strand-like growth and stromal hyalinization are typically identified in HCCC, while as gland formation and expression of EMA, CEA, and S100 protein by IHC supports SNRCLA.[11] In addition to HCCC, epithelial-myoepithelial carcinoma, squamous cell carcinoma, mucoepidermoid carcinoma, and acinic cell carcinoma should be considered as differential diagnoses. Epithelial-myoepithelial carcinoma is a malignant neoplasm composed of biphasic tubular patterns. Inner ductal cell layers are surrounded by outer myoepithelial layers containing clear cytoplasm. Immunohistochemistry findings and the absence of bilayered patterns of ductal differentiation can be valuable for the differentiation of SNRCLA from epithelial-myoepithelial carcinoma.[9] Squamous cell carcinoma (SCC) is the most common form of malignant tumor in the sinonasal tract. Clear cell changes can be observed due to glycogen accumulation or artifactual cytoplasmic clearing in SCC. It can be distinguished from SNRCLA by apparent keratinization and intercellular bridges.[1,11] Mucoepidermoid carcinoma (MEC) is the most frequent malignant epithelial neoplasm in the minor salivary glands, but primary sinonasal MEC is relatively uncommon.[1] The epidermoid and intermediate cell component of MEC can change into clear cells. MEC can be ruled out by lack of mucus cell and intermediate or epidermoid cells.[2,9] Most acinic cell carcinomas occur in the parotid gland and represent 0.2% to 1.3% of the sinonasal tumors. Acinic cell carcinoma features serous acinar cell differentiation with zymogen granules in the cytoplasm. This carcinoma is different from SNRCLA by the lack of fine-to-coarse secretory granules.[1]

Although metastatic tumors rarely occur in the sinonasal tract, the possibility of RCC should be clinically ruled out for diagnosis of SNRCLA. Among tumors metastasizing to the head and neck region, RCC is the 3rd most common following lung and breast carcinomas.[4,14] One third of patients with RCC may present with metastases to the lung, liver, bones, and brain. Although the overall incidence of RCC metastasizing to the head and neck is as low as 6% of cases, symptoms in metastatic lesions may be the only initial manifestation.[15] The Armed Forces Institute of Pathology assembled 53 cases; 20% featured a nasal tumor as initial presentation.[16] A review of 50 sinonasal adenocarcinoma cases chronicled presenting symptoms including nasal obstruction, epistaxis, and pain.[4] As in the present case, epistaxis, nasal obstruction, and pain have been described for SNRCLA patients.[1,2]

The biological behavior of SNRCLA appears to be favorable. Patients diagnosed as SNRCLA do not display distant metastases to the lymph nodes or other organs. Of the previously reported cases, 14 patients (including ours) had follow-up examinations. Only 2 patients showed local recurrence. One patient developed 2-time recurrences at 3 and 5 years after the operation.[4] The other patient developed recurrence at 7 months.[9] The remaining 12 patients were free of disease after primary treatment (ranging from 4 months to 8 years; mean 2.4 years). Metastasis of RCC to the

head and neck region heralds a poor outcome, whereas primary SNRCLA carries a favorable prognosis. Primary salivary clear cell carcinoma is regarded as a low grade tumor and is associated with an even better outcome than other clear cell carcinomas of the salivary gland. The most effective treatment is surgical resection of tumor. Yet, there have been no published studies on the effect of adjuvant chemoradiation therapy, and the role of adjuvant treatment is still contentious. Our patient was treated by craniofacial resection, bifrontal craniotomy combined with an endonasal endoscopic approach for complete tumor removal.

Although the clinical progression of SNRCLA is generally favorable, delayed recurrence should be reminded for clinician, considering the limited number and follow-up periods of the reported cases. Further studies on clinical behaviors, risk factors, and other relevant information are necessary for better identification of SNRCLA.

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