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Original contribution

# Sinonasal renal cell–like adenocarcinomas: robust carbonic anhydrase expression☆,☆☆

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**Summary** We report 3 new patients with sinonasal renal cell–like adenocarcinoma (SNRCLA). One case submitted in consultation demonstrated robust carbonic anhydrase IX (CA-IX) expression, leading us to a broader inquiry of CA-IX and carbonic anhydrase II (CA-II) expression in other SNRCLA, Schneiderian tissues, and histologic mimickers. Robust cytoplasmic and membranous CA-IX expression is demonstrated in 6 of 7 SNRCLAs; CA-II expression was demonstrated in 2 of 5 cases. Robust, diffuse CA-II expression is demonstrated throughout sinonasal seromucinous glands in all 10 normal Schneiderian samples. CA-IX is also expressed in all normal sinonasal samples, albeit focally. The closest salivary mimic to SNRCLA is hyalinizing salivary clear cell carcinoma; only focal CA-IX expression was demonstrated in 1 of 2 cases studied. Carbonic anhydrase expression in Schneiderian tissue speaks to its role in regulating the ion concentration of sinonasal secretions and may also explain the origin of this rare tumor.


## 1. Introduction

Sinonasal renal cell–like adenocarcinoma (SNRCLA) is an extremely rare neoplasm that mimics the clear cell variant of renal cell carcinoma. In 2002, 2 independent publications described this unique, low-grade, sinonasal neoplasm with clear cytoplasm that did not fit any known diagnostic category [1,2]. In 2008, we reported 2 additional patients and updated follow-up on the index patients [1-3]. Nine additional patients have been identified in the published literature [4-13]. Here, we report 3 new SNRCLA patients, for a total of 16 reported cases.

Histologically, SNRCLA is composed of monomorphous cuboidal to columnar glycogen-rich clear cells lacking mucin production. The cellular cytoplasm may be "crystal clear" or slightly eosinophilic. SNRCLA is less vascular and pleomorphic, compared to the clear cell variant of renal cell carcinoma. The overall histologic impression is that of a

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**Table 1** Three patients with SNRCLA

| Age, sex | Tumor site | Treatment | Follow-up |
|---|---|---|---|
| 56 F [4] (Fig. 2) | Nasal, skull base | Surgery, adjuvant radiotherapy | Recurrence free at 22 mo |
| 89 F (Fig. 3) | Sinonasal | Surgery | Recurrence free at 4 mo |
| 73 M (Fig. 4) | Nasal | Surgery, adjuvant radiotherapy | Recurrence free at 20 mo |

low-grade neoplasm. To date, no patient developed metastatic disease or local recurrence, and renal carcinoma has not been identified in any of these patients [4].

## 2. Materials and methods

### 2.1. Samples

Seven SNRCLA cases were studied; 3 new cases were seen in consultation in the past 2 years. We also studied normal Schneiderian tissues from 10 patients. Other clear cell neoplasia, which might mimic SNRCLA, was also studied: 2 cases each of hyalinizing salivary clear cell carcinoma, mucoepidermoid carcinoma clear cell variant, epithelial-myoepithelial carcinoma, and 1 endolymphatic sac tumor. This study was exempted from institutional review board.

### 2.2. Immunohistochemical

Studies were performed according to manufacturer's protocols. Briefly, 4-$\mu$m sections were obtained from

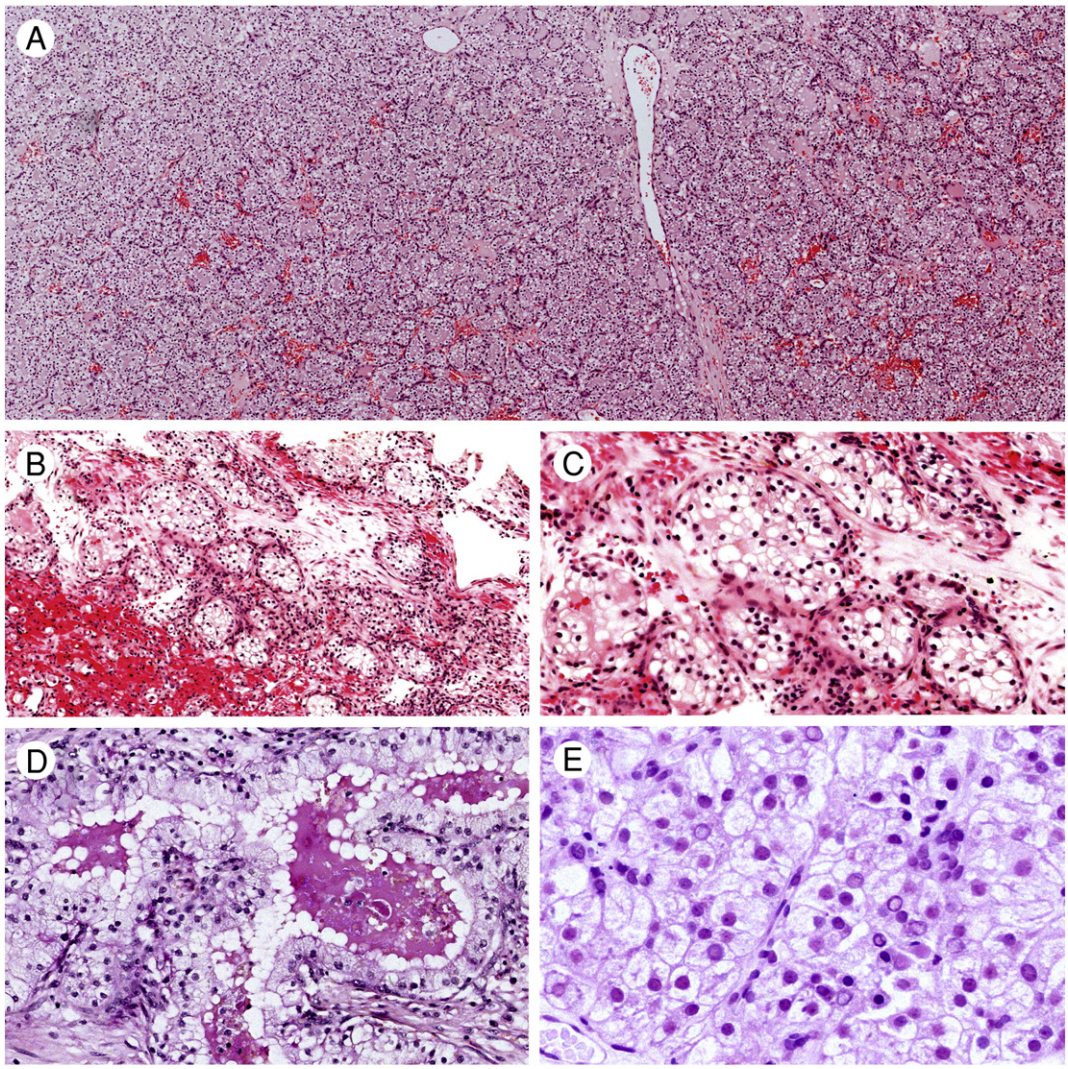


**Fig. 1** Sinonasal renal cell–like adenocarcinoma. A to C, This clear cell neoplasm with a hemorrhagic background is quite reminiscent of metastatic renal cell carcinoma. D, Follicular and glandular structures. E, Cuboidal tumors cells with rounded nuclei, fine chromatin, prominent nucleoli, and occasional intranuclear holes.

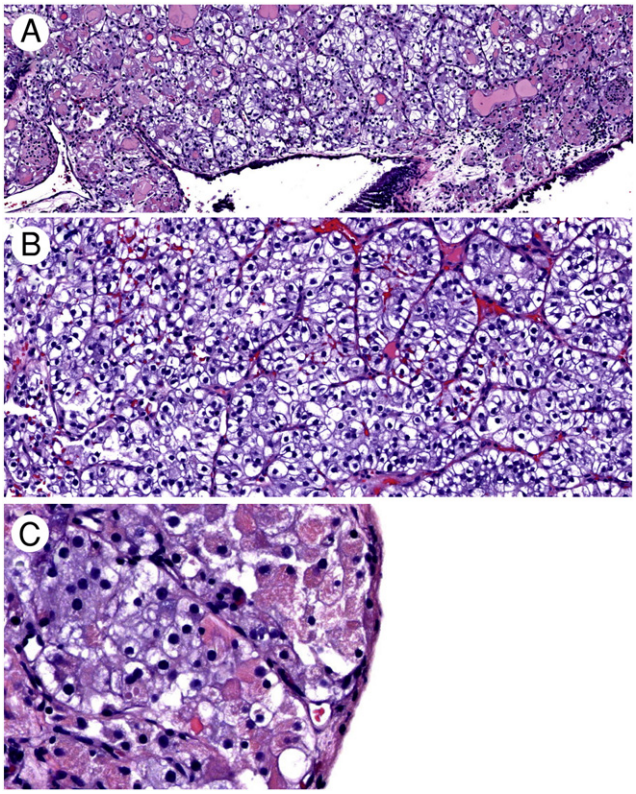


**Fig. 2** Sinonasal renal cell–like adenocarcinoma in a 56-year-old woman (Table 1). This tumor is remarkable for thyroid-like follicular structures containing dense eosinophilic material (A) and foci of tumor cells with either oncocytoid or basophilic cytoplasm (B and C). This particular tumor expressed AE1/AE3, Cam 5.2, and CA-IX; there was focal expression of CK7, CK20, and S-100. See Table 2 for remaining immunohistochemical studies. There was no clinicoradiographic evidence of renal neoplasia. The patient received adjuvant radiotherapy and remains disease free after 17 months.

formalin-fixed, paraffin-embedded block preparations. Heat-induced epitope retrieval with 0.02 mol/L concentration of citrate buffer (pH 9.0) in a heater at 97°C for 20 minutes was applied. The sections were incubated for 20 minutes at room temperature with a dilution of 1:800 of either mouse anti–carbonic anhydrase IX (CA-IX) monoclonal antibody (Cell Marque, Rocklin, CA) or rabbit anti–carbonic anhydrase II (CA-II) monoclonal antibody (Abcam, Cambridge, MA). Immunostaining was accomplished with a semiautomated immunostainer (Dako Autostainer Link 48, Carpinteria, CA) and an Envision FLEX HRP system. Fifteen-minute incubation with Envision FLEX Link (mouse or rabbit) was used as an enhancer. The chromogen diaminobenzidine tetrachloride was used to visualize the antibody-antigen complex. The tissue was counterstained with hematoxylin. Clear cell variant of renal cell carcinoma was used as positive control for optimizing mouse anti–CA-IX monoclonal antibody, and normal renal tissue was used as positive control for optimizing rabbit anti–CA-II monoclonal antibody. The negative control slides consisted of tissue sections of each case processed without the addition of primary antibody.

## 3. Results

### 3.1. Patient demographics

Table 1 details the 3 new SNRCLA patients; the latter patient was previously illustrated [4]. One tumor was confined to the nasal cavity; the other 2 extended to paranasal sinuses or skull base. All were treated by primary surgery; 2 received adjuvant radiotherapy.

**Table 2** Sinonasal renal cell–like adenocarcinomas: reported immunohistochemical data

| Study | Age (y), sex | Site | Cytokeratin | CK7 | CK20 | CK5/6 | P63 | Cam 5.2 | AE1/3 | EMA | S-100 | Vimentin | CEA | Calponin |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Moh'd Hadi et al 2002 [1] | 50 F | Nasal | + | + | − | | | | + | + | + | − | + | − |
| Zur et al 2002 [2] | 22 F | Nasal | | + | − | | | + | | | − | − | | − |
| Storck et al 2008 [3] | 36 F | Nasal | | + | + | | | | | + | − | − | + | |
| Storck et al 2008 [3] | 69 M | Nasopharynx | | + | − | | | | | | − | − | | |
| Present report | 56 F | Nasal, skull base | + | + | + | | | + | + | | + | + | | |
| Present report | 89 F | Sinonasal | | + | − | − | − | | | | − | − | | |
| Present report | 73 M | Nasal | | + | − | − | − | | + | | + | + | | |
| Suzuki et al 2012 [11] | 59 F | Sphenoid skull base | + | − | − | | | | | + | + | + | | |
| Huang et al 2011 [7] | 54 F | Nasal | + | | | | | | | + | | − | | |
| Li et al 2011 [8], Hong et al 2013 [12] | 34 M | Nasal | + | + | | | | | | + | + | − | | |
| Cheng et al 2008 [5] | 63 F | Nasopharynx | + | | | | | | | | | | | |
| Negahban et al 2009 [13] | 52 F | Sinonasal | + | + | − | | | | | + | − | | − | |

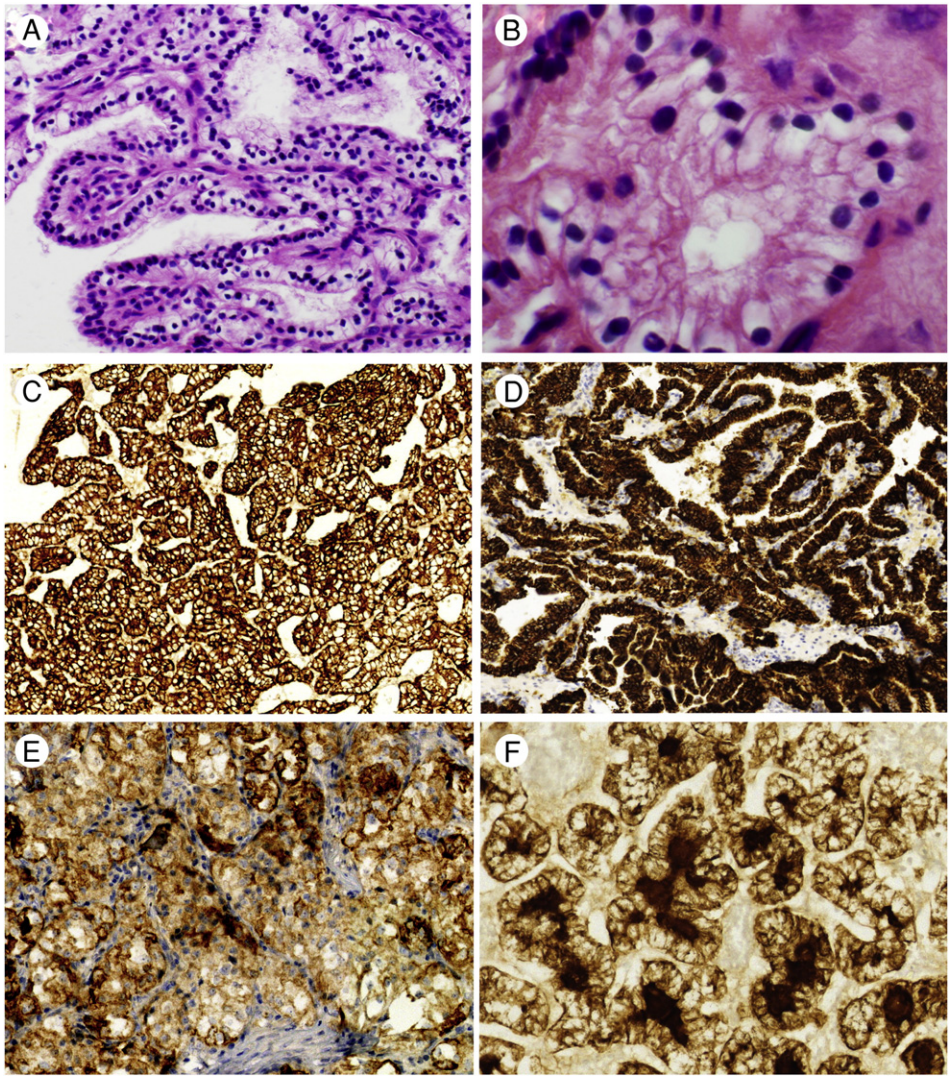


**Fig. 3** Sinonasal renal cell–like adenocarcinoma in an 89-year-old woman (Table 1). A and B, This tumor is remarkable for its prominent papillary architecture, reminiscent of endolymphatic sac tumor. C and D, Robust cytoplasmic and membranous CA-IX expression in this case. This particular tumor also expressed CK7 and CA-II. See Table 2 for remaining immunohistochemical studies. There was no clinicoradiographic evidence of renal neoplasia. The patient remains disease free after 4 months. E and F, CA-IX expression in 2 other previously reported SNRCLA.

| SMA | Desmin | CD10 | GFAP | RCC | PAX8 | TTF1/ thyroglobulin | HMB45 | Melan A | Chromo granin | Synap tophysin | CA-IX | CA-II | Estro gen | Proges terone | PSA | Mamma globin | DOG1 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| – | | – | | – | | | | | | | + | | | | | | |
| – | | | | | | | | | | | + | | | | | | |
| | | + | | – | | – | – | | | – | – | – | | – | | | |
| – | – | | | – | – | – | – | – | – | – | + | – | – | – | | – | – |
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### 3.2. Histology

SNRCLA is composed of uniform low-grade clear tumor cells; a hemorrhagic background can be seen, which brings to mind metastatic renal cell carcinoma (Fig. 1). SNRCLA typically forms follicular/glandular structures; 2 tumors were entirely solid and nonglandular. Cytologically, tumor cells are cuboidal, with round nuclei, fine chromatin, prominent nucleoli, and occasional intranuclear holes. Cell cytoplasm is typically "crystal clear" or contains fine, flocculent eosinophilic material (Fig. 1). One case of SNRCLA was remarkable for prominent foci of oncocytoid and basophilic tumor cells (Fig. 2). True oncocytic differentiation was excluded by phosphotungstin acid hematoxylin. Immunohistochemistry for Discovered on GIST1 (DOG1) was negative, ruling out acinar differentiation. Another case was noteworthy for its prominent papillary architecture (Fig. 3), reminiscent of endolymphatic sac tumor. Mitotic activity was sparse in all tumors; no necrosis, perineural invasion, or lymphovascular tumor emboli were seen.

### 3.3. CA-IX and CA-II expression in SNRCLA

Table 2 summarizes the CA-IX and CA-II results. Robust cytoplasmic and membranous CA-IX expression was seen in 6 of 7 SNRCLAs (Fig. 3). Only 5 SNRCLAs could be studied for CA-II due to sample limitations. Two cases demonstrated cytoplasmic and membranous CA-II expression (Fig. 4); 3 cases were negative.

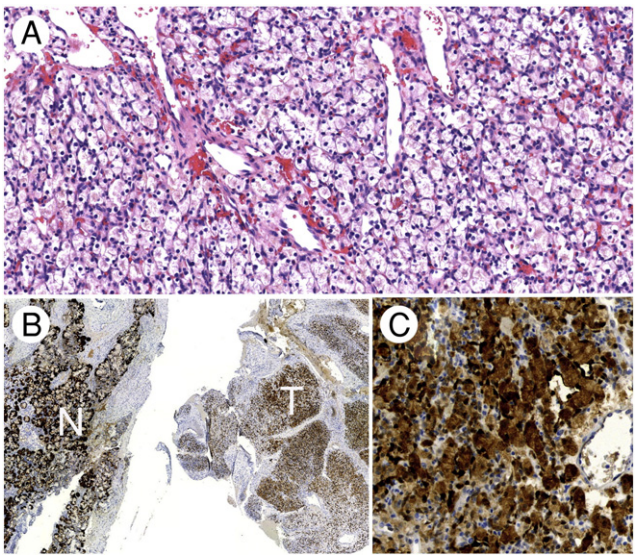


**Fig. 4** Sinonasal renal cell–like adenocarcinoma in a 73-year-old man (Table 1). A, This particular tumor is solid and non–gland forming. Robust CA-II expression in normal seromucinous glands (B [N]) and tumor (B [T] and C). This particular tumor also expressed AE1/AE3, CK7, CA-IX, and vimentin. There was cytoplasmic tumor expression of S-100, with intensity of 2+/3+. See Table 2 for remaining immunohistochemical studies. There was no clinicoradiographic evidence of renal neoplasia. The patient received adjuvant radiotherapy and remains disease free after 20 months.

### 3.4. CA-IX and CA-II expression in Schneiderian mucosa

Only focal CA-IX expression was observed in respiratory epithelium and occasional seromucinous ducts. In contrast, robust diffusely CA-II expression was seen throughout usual seromucinous glands. No CA-II expression was seen in the surface respiratory epithelium (Fig. 5).

### 3.5. CA-IX and CA-II expression in other clear cell neoplasia

We also studied some potential SNRCLA mimics. Focal CA-IX expression was seen in only one of two hyalinizing salivary clear cell carcinomas (Fig. 6). Both mucoepidermoid carcinomas demonstrated robust expression of CA-IX and CA-II. CA-IX was also expressed in both epithelial-myoepithelial carcinomas and one endolymphatic sac tumor (Fig. 7).

## 4. Discussion

Sinonasal renal cell–like adenocarcinoma is a rare, low-grade neoplasm that bears no resemblance to any other sinonasal primary tumor. Previously, we reported the lack of Renal Cell Carcinoma (RCC) antigen expression in SNRCLA, which is typical of conventional renal cell carcinomas [3,4]. Here, we demonstrate the novel finding of CA-IX and CA-II expression in this enigmatic tumor. CA-IX is a member of the carbonic anhydrase family; this transmembrane protein catalyzes the conversion of carbon dioxide to bicarbonate and protons. Thus, CA-IX is crucial to ion transport, pH maintenance, and cell survival during hypoxia [14-16]. Hypoxia activates hypoxia-inducible factor-1, which upregulates CA-IX [14-17]. CA-IX overexpression is common to various different malignancies, (eg, renal, uterine, colonic, and pulmonary carcinomas) [18-22]. Accumulating data support its importance to tumor growth, survival, and invasion; the latter is facilitated by decreasing extracellular matrix pH [14-17]. On the other hand, CA-II is a cytosolic isoenzyme highly expressed in normal renal tubules, brain, and endothelial cells; it is not overexpressed in malignant cells [20-25].

Interestingly, the nasal salt glands, which enable marine birds and reptiles to tolerate high salt concentrations, are considered "sinonasal auxiliary kidneys" and contain high concentrations of carbonic anhydrases; their secretions are instantaneously blocked by acetazoleamide, a specific inhibitor [26]. Carbonic anhydrase has also been detected in mammalian sinonasal mucosa, which lacks nasal salt glands [27-29]. Carbonic anhydrase VI transcripts and protein have been demonstrated in canine sinonasal tissue [28]. It has been suggested that carbonic anhydrases play a

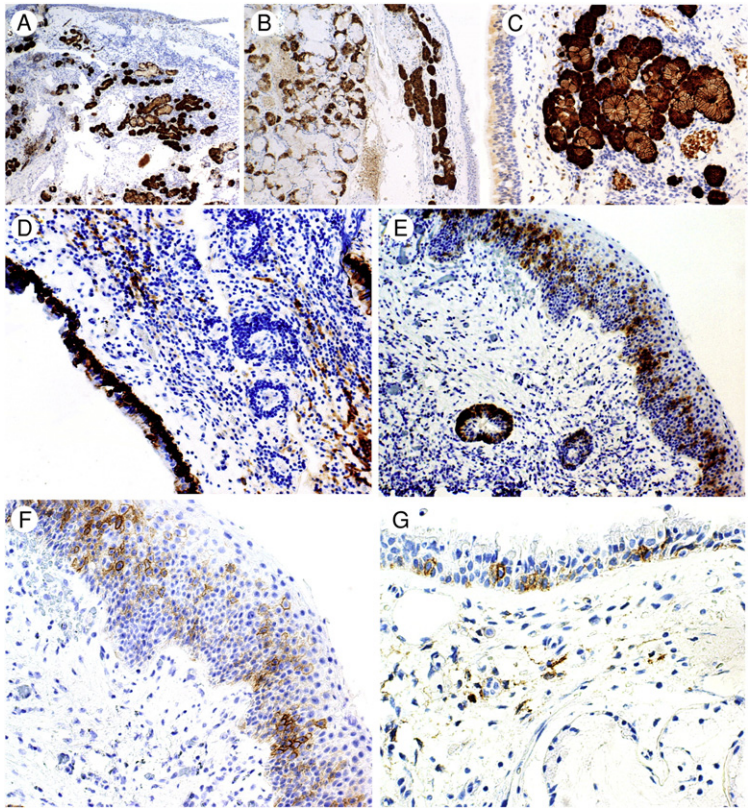


**Fig. 5** CA-IX and CA-II in human sinonasal mucosa. A to C, Robust, diffuse CA-II expression in seromucinous glands. D to G, Focal cytoplasmic and membranous CA-IX expression in respiratory epithelium and occasional seromucinous gland ducts.

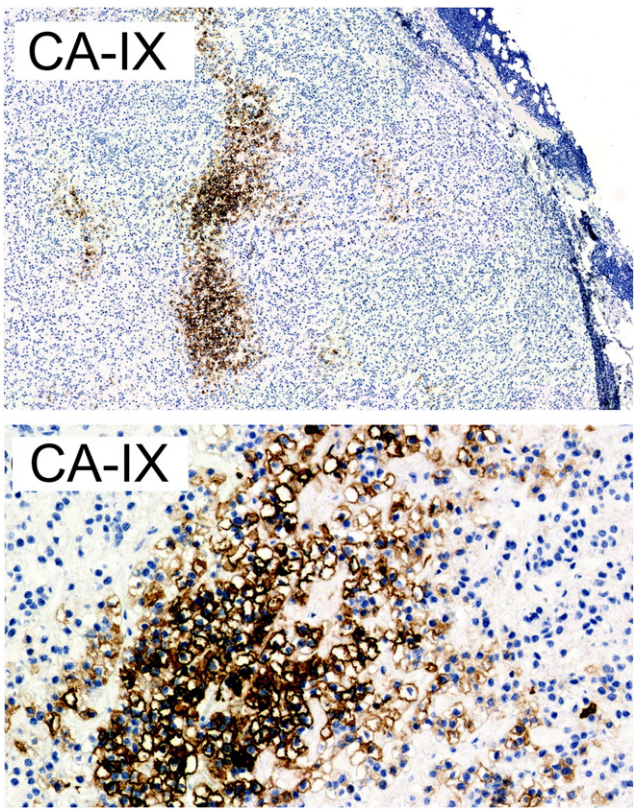


**Fig. 6** Focal CA-IX expression in hyalinizing salivary clear cell carcinoma.

protective role in mammals by maintaining the physiological pH of sinonasal secretions. Little is known about human sinonasal carbonic anhydrase activity and function. Multiple isoenzyme transcripts are present in human sinonasal tissue; CA-II expression is greater than CA-IX [29]. Kim et al demonstrated intense immunohistochemical CA-IX expression in human Schneiderian tissues [30]. In contrast, we find only focal CA-IX expression; this discordance may be explained by our use of a monoclonal antibody to CA-IX, which is likely more specific than the polyclonal antibody used by Kim et al [30]. Our finding of robust CA-II expression in sinonasal mucosa is similar to previous reports [30]. We emphasize that CA-II was diffusely expressed throughout the usual Schneiderian seromucinous glands and not limited to a subset of glands. Thus, the pattern of carbonic anhydrase expression (robust CA-II and limited CA-IX) mirrors that seen in normal renal tissue; this supports the idea that these enzymes regulate ion concentration in Schneiderian mucosal secretions.

The average pathologist is much more likely to encounter sinonasal metastatic renal cell carcinoma than SNRCLA. Up to one-third of patients with renal cell carcinoma are diagnosed after biopsy of metastatic disease. Presentation with head and neck metastases represents 6% of this group; sinonasal involvement comprises 20% of head and neck metastatic presentations [2]. SNRCLA and renal cell carcinoma can be easily distinguished by histology and

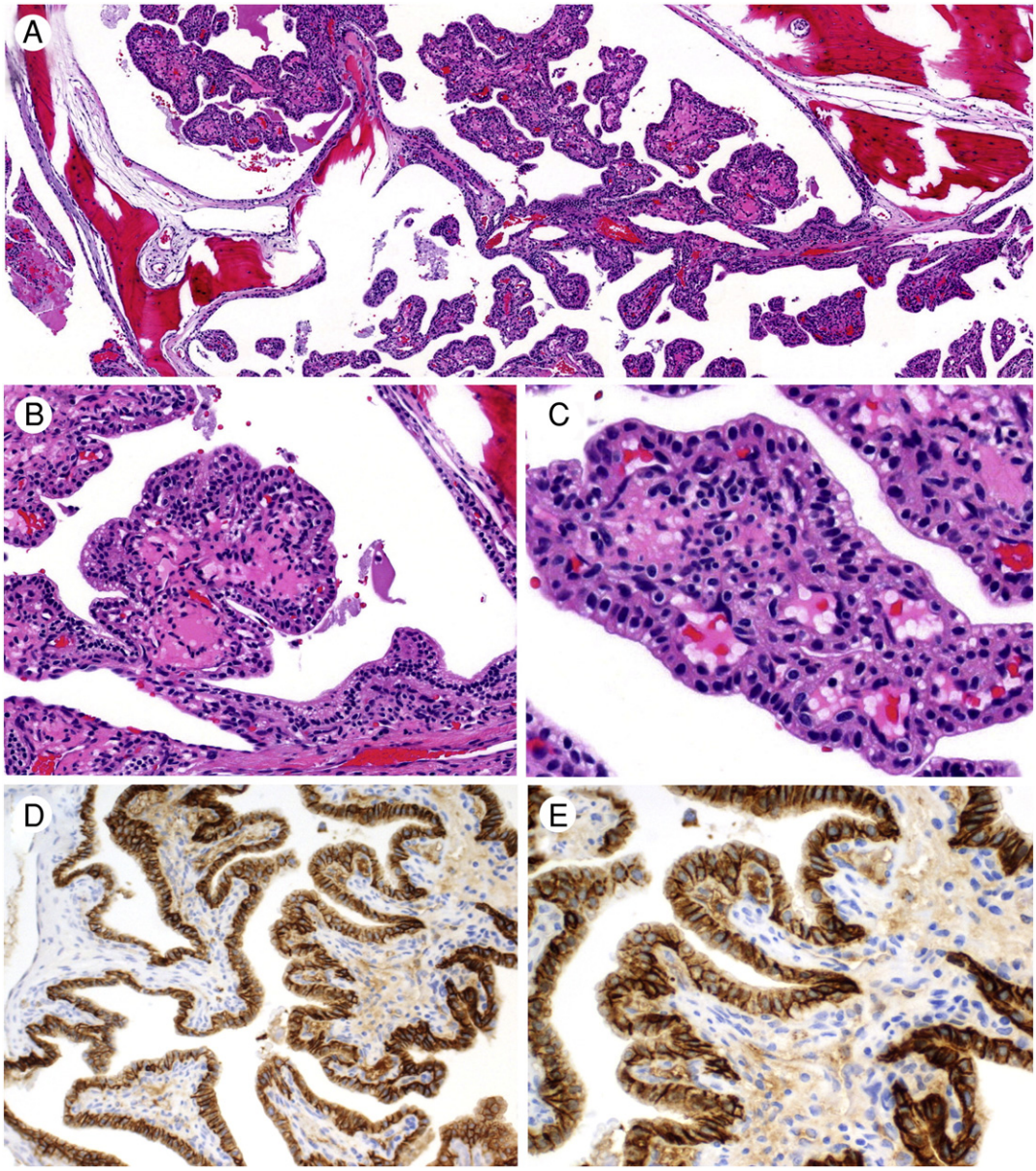


**Fig. 7** Endolymphatic sac tumor (courtesy of Dr Rong Li, Children's Hospital, Birmingham, AL). A to C, Cytologically, this clear cell papillary neoplasm is reminiscent of SNRCLA. D and E, Strong CA-IX expression.

immunohistochemistry, despite the commonality of robust CA-IX expression. Nuclear pleomorphism is typical for clear cell variant of renal cell carcinoma; necrosis and rich vascularity are common. SNRCLA is composed of monomorphic bland cuboidal to columnar clear cells; necrosis is absent but a hemorrhagic background may be present. Clear cell variant of renal cell carcinoma commonly expresses RCC antigen (72%-85%) and vimentin (87%) and is usually negative (or only focally positive) for Cytokeratin (CK) [31]. By contrast, SNRCLA characteristically expresses CK7; vimentin expression is variable. Table 2 details all SNRCLA immunohistochemical data for our cases, plus those reported in the literature. Although the CK7+/CA-IX+ immunophenotype is also characteristic for the clear cell papillary variant of renal cell carcinoma, it is highly unlikely to be a diagnostic consideration in the sinonasal tract, as distant metastasis has not been observed in this variant [32].

Other entities to consider in the differential diagnosis of SNRCLA include clear cell variant of follicular thyroid carcinoma, melanoma (balloon cell variant), Perivascular epithelioid cell tumor (PECOMA), and salivary tumors with clear cell features (ie, mucoepidermoid carcinoma, hyalinizing salivary clear cell carcinoma, etc). SNRCLA is Thyroid transcription factor1 (TTF1) negative,i and S-100 expression is variable (Table 2). All SNRCLAs examined for Human melanoma black-45 (HMB45), Melan A, and smooth muscle actin (SMA) are negative, thus excluding balloon cell variant of melanoma and PEComa, respectively. Clear tumor cells can be commonly seen in squamous cell carcinomas, either as a primary or posttherapeutic change. Lastly, sinonasal

nonintestinal adenocarcinomas are high-grade adenocarcinomas, not otherwise specified, which lack CK20/CDX2 expression. Sinonasal nonintestinal adenocarcinomas with prominent clear cell features have been described but are distinguished from SNRCLA by the presence of pleomorphism [33]. Hyalinizing salivary clear cell carcinoma is the closest histologic mimicker of SNRCLA; it rarely arises in the sinonasal track [34]. Both have low-grade nuclei, clear cytoplasm, and well-defined cell borders. Histologically, hyalinizing salivary clear cell carcinoma is predominantly solid and nonglandular, although occasionally, it may form glandular structures. By contrast, SNRCLA characteristically forms glandular/follicular structures but may occasionally be entirely solid. Robust CA-IX expression in SNRCLA contrasts to the focal CA-IX expression seen in 1 of 2 hyalinizing salivary clear cell carcinomas studied.

In conclusion, SNRCLA is a distinct neoplasm remarkable for its resemblance to grade I renal cell carcinoma, clear cell variant. Here, we report 3 new cases seen in consultation. Although classified as a carcinoma, thus far, SNRCLA appears to have no malignant potential. Adjuvant radiotherapy and cervical neck dissection do not appear to be warranted. Robust carbonic anhydrase expression is demonstrated in SNRCLA and Schneiderian seromucinous glands. This speaks to the role of seromucinous gland carbonic anhydrase in regulating the ion concentration of sinonasal secretions. It also supports the idea that SNRCLA may arise from these seromucinous glands.

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