CERRAHİ BİLİMLER / *SURGICAL SCIENCES*
Olgu Sunumu / Case Report

Sinonasal Low Grade Adenocarcinoma; A case report and the analysis of its histochemical and immunohistochemical characteristics

Sinonazal Düşük Dereceli Adenokarsinoma; Bir olgu sunumu ve histokimyasal / immünohistokimyasal özelliklerin analizi

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Sinonasal adenocarcinomas (SAs) are local aggressive tumors and occur in middle and advanced aged male patients.

A polypoid mass involving to the left nose and paranasal sinuses was determined in endoscopical examination of a 57-year-old female patient admitting with epistaxis. Punch biopsy revealed a low grade adenocarcinoma. The mass was totally excised and its histopathological features were similar to punch biopsy. Glandular epithelium was positive for EMA, CK7, CK19, LMWCK and S-100. The findings were concordant with a low grade adenocarcinoma originating from sinonasal mucosa. No recurrence was determined 20 months after total excision.

SAs are a heterogenous group of neoplasms characterizing by variable clinical behavior and different epidemiological features. In the differential diagnosis, many tumoral and tumor like lesions should be considered. The differential diagnosis is very important because of the risk of recurrence.

Key Words : ***Adenocarcinoma, Sinonasal Region.***

Sinonazal adenokarsinomalar (SA) lokal agresif tümörlerdir ve çoğunlukla orta ve ileri yaştaki erkeklerde görülür.

Burun kanaması şikayeti ile başvuran 57 yaşındaki kadın hastanın endoskopik muayenesinde sol burun boşluğu ve paranazal sinüsleri tutan polipoid kitle lezyonu saptandı. Punç biyopsi düşük dereceli adenokarsinoma ile uyumluydu. Kitle total olarak çıkarıldı ve histopatolojik özellikleri punç biyopsininki ile benzerdi. Glandüler epitel hücreleri EMA, CK7, CK19, LMWCK ve S-100 için pozitifdi. Bulgular, sinonasal mukozadan kaynaklanan düşük dereceli adenokarsinoma ile uyumluydu. Total eksizyon sonrası 20. ayda hastada nüks gelişmedi.

SA değişken klinik davranış ve farklı epidemiyolojik özellikler ile karakterli heterojen bir grup neoplazmdır. Ayırıcı tanıda, bir çok tümor ve tümor benzeri lezyon hesaba katılmalıdır. Bu lezyonlar arasındaki ayırıcı tanı nüks riski nedeniyle önemlidir.

Anahtar Sözcükler: ***Adenokarsinoma, Sinonazal Bölge.***

Tumors of nasal and paranasal sinuses account for 0.4% of all human neoplasms (1). Sinonasal adenocarcinomas (SAs) are the third most frequent malignancies following squamous carcinoma and lymphoma, respectively (1). Dulgerov et al (2) reported that SAs had a rate of 11.4% in all tumors of this region. If salivary gland type adenocarcinomas are excluded, SAs can be broadly classified into enteric and nonenteric subtypes based on their histopathological resemblance to intestinal and submucosal seromucinous glands, respectively (3). The World Health Organization (WHO) classification recognizes four major categories of primary SAs; low grade adenocarcinoma, papillary adenocarcinoma, intestinal type adenocarcinoma (ITAC) and polymorphous low grade adenocarcinoma (4).

SAs are clinically local aggressive tumors and predominantly occur in middle and advanced aged male patients. The ethmoid sinus, maxillary sinus and nasal cavity are the most common sites of origin (1). Nasal obstruction, epistaxis and rhinorrhoea are the most common symptoms. Probable effects of some factors such as wood and leather dust

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are suggested for the development of SA (1,5). This occupational relationship is valid for especially ITAC and elderly men are chiefly involved and ethmoid sinus is the site of origin (1). Sporadic SAs often affect women and occur in the maxillary sinus (1).

In here, we present a 57-year-old female patient with low grade SA that showed tubulopapillary growth pattern and argue its differential diagnosis, including immunohistochemical characteristics, in accompanying of the literature.

Case history

A 57-year-old female patient was admitted with intermittent epistaxis from left nose and nasal obstruction for last 10 days. The patient was a housewife and the medical history of the patient was unremarkable. General physical examination was normal and there was no abnormal finding of hemogram and blood chemistry. In the endoscopical view of nose and paranasal sinuses, a polypoid mass originating from the ostium of sphenoid sinus and at the posterior of lower concha was determined. The polypoid lesion extended to nasopharynx.

Histopathological findings

Punch biopsy revealed a polypoid lesion consisting of very crowded glandular structures with back to back pattern. Most glands had papillary structures (Figure 1A). Although cytologically bland and uniform appearance was dominant, nucleomegaly and mild pleomorphism were noticed in some areas. Lining epithelium of the glands was columnar or cuboidal with rare intraepithelial cyst formations Mitosis was very rarely observed. The nuclei with inconspicuous nucleoli were basally located (Fig. 1B). Elongated and distorted glandular structures resembling stromal invasion were noticed in the central of the lesion (Fig. 1C). On the basis of these findings, we diagnosed the case as a low grade adenocarcinoma originating from sinonasal mucosa and favored total excision of the mass. The histopathological findings of resected polypoid mass were similar to those of previous punch biopsy. Polypoid lesion was covered with respiratory type epithelium. More advanced cytological and architectural atypia were not determined according to previous punch biopsy.

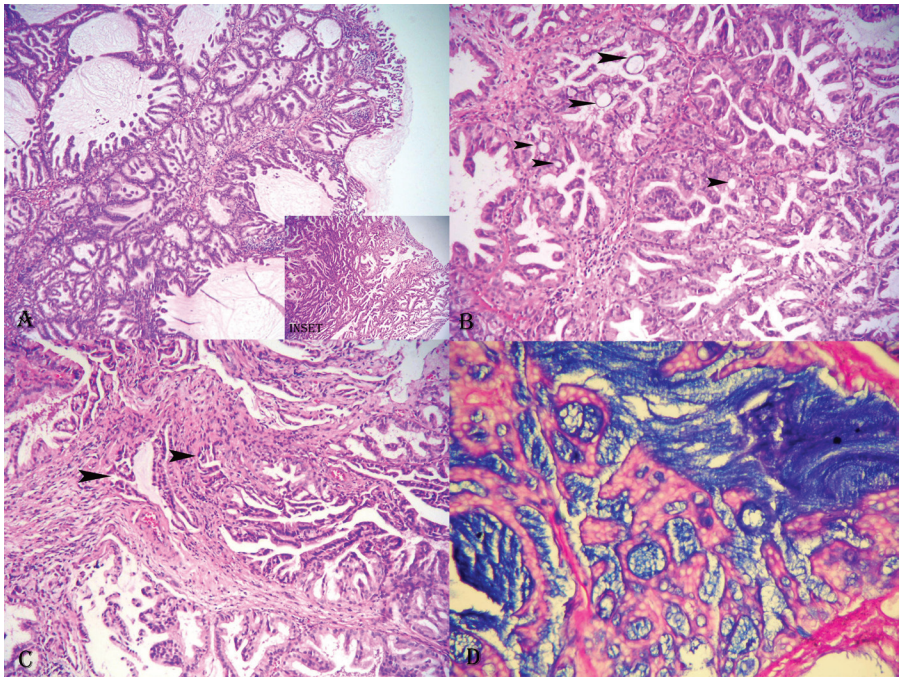

Figure 1 A: Polypoid tumoral lesion consisting of crowded tubulopapillary structures with back to back pattern (HE, X10). Inset shows a more crowded area of glands in the tumoral lesion.
Figure 1 B: Intraepithelial microcysts (arrow heads) in the lining epithelium of tubulopapillary structures (HE, X20).
Figure 1 C: Stromal invasion area consisting of distorted glandular structures (HE, X20).
Figure 1 D: Intraluminal and intracystic material positive with alcian blue in pH2.5 (Periodic acid Schiff-alcian blue, X30).

Histochemical and immunohistochemical findings

Cystic dilated glands and microcysts were filled by deep blue staining material with Periodic acid-Schiff (PAS)-Alcian blue (AB) at pH 2.5 (Fig. 1D). This material was diastase resistant and showed a weak staining with mucicarmen. Histochemical findings pointed out acidic type mucin. The features of antibodies used in the current study and the immunohistochemical results are shown in Table 1. Glandular epithelium for EMA, CK7, CK19, LMWCK and S-100 was focally positive (Fig. 2). Covering respiratory epithelium showed also focal staining for CK7 and CK19.

All these findings were concordant with a low grade adenocarcinoma originating from sinonasal mucosa. After the diagnosis, the patient is closely followed-up with routine clinical, endoscopical and radiological examinations. No recurrence was determined 20 months after total excision.

Discussion

SAs are a heterogenous group of neoplasms characterized by variable clinical behavior and different epidemiological features. SAs, especially the group of low grade adenocarcinoma have been poorly characterized from the histopathological point of view (5). Basic histopathological features of low grade SAs are cystically dilated glands and tubulopapillary structures lined by bland cuboidal and/or columnar epithelial cell with intraepithelial cyst formation. In our case, all these findings were present and a focus of nuclear/ar-

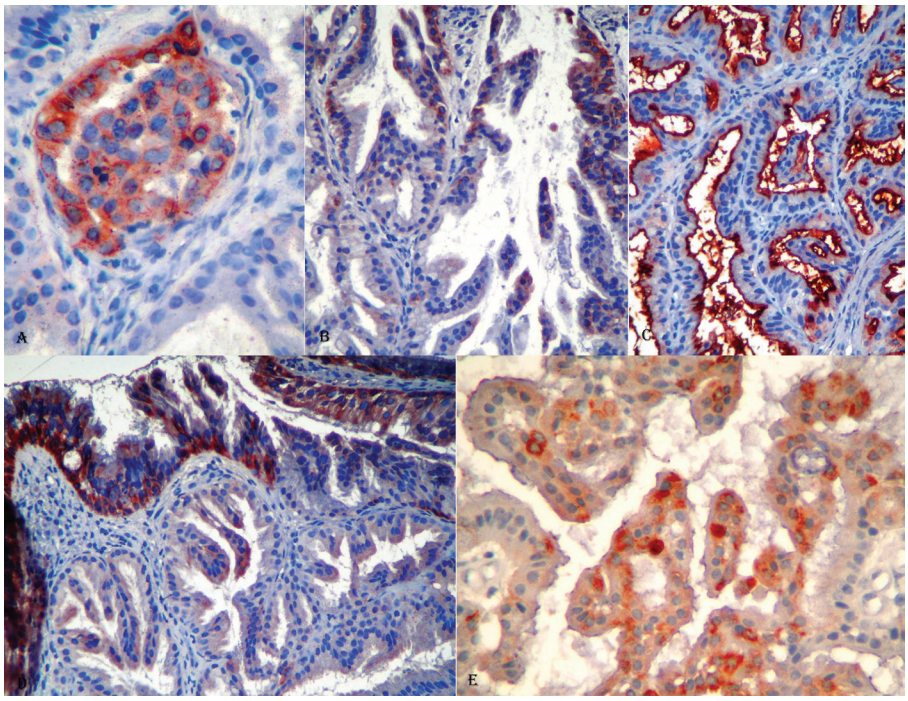

Figure 2: Focal cytoplasmic staining for LMWCK (A), CK 7 (B), CK 19 (D) and S-100 (E) on the lining epithelium of tubulopapillary structures. Pseudostratified epithelium covering the surface of polypoid tumoral lesion shows also cytoplasmic staining for CK 19 (D), (AEC, X40, X20, X20 and X40, respectively).
Diffuse membranous positivity with EMA (C) on the lining epithelium (AEC, X20).
Abbreviations: HE; hematoxyline-eosin, LMWCK; low molecular weight cytokeratin, CK; cytokeratin, EMA; epithelial membrane antigen, AEC; amino ethyl carbazole.

chitectural atypia favoring the stromal invasion was also noticed. Intraluminal spaces and intraepitelial microcysts were filled with positive material for diastase resistant PAS, AB at pH 2.5 and mucicarmine. Intraluminal material was acidic type mucin. Similar histochemical findings were reported by Skalova et al (4) and Franchi et al (6). Sinonasal ITACs and low grade SAs have some similar histopathological features. The distinction between low grade SAs and ITACs may be easy in many cases. Evident nuclear pleomorphism and architectural characteristics reminiscent of a colonic neoplasm are very helpful for this discrimination. But, especially low grade ITACs with papillary configuration may be very similar to low grade SAs. However, distinction between these is very important because ITACs have an aggressive behavior characterized by repeated local recurrences and poor outcome (7). However, low grade SAs have a more indolent clinical course (4). Immunohistochemically, some distinctive characteristics may be suggested for the differential diagnosis. CK7 and CK20 antibodies may be useful for this aim. CK7+/CK20- immunophenotype is the phenotype of normal upper respiratory mucosa. Low grade SAs show also this immunophenotype. CK7-/CK20+ immunophenotype shows intestinal differentiation and this phenotype is seen in sinonasal ITACs (8). In our case, both of histopathological and immunohistochemical findings favored to low grade SA. Immunophenotype of our case was CK7+/CK20-. In addition, other epithelial markers (LMWCK, EMA and CK19) and S-100 were also positive in the present case, while neuroendocrine markers, p53, c-myc, CA19-9, CD10 and CEA were negative. Some authors have reported that expressions of p53, c-myc and CA19-9 have been found in malignant tumors of salivary gland and other organs (especially gastrointestinal tract) more commonly than their benign counterparts or lesions (9, 10). However, some myoepithelial markers (such as alpha-SMA, CD10) showed stronger staining in benign myoepithelial cells surrounding the malignant epithelial cells than those surrounding benign cells in salivary gland (11). Our case was negative for all of these antibodies.

Table 1: The features of the antibodies and the results of immunohistochemical staining.

Antibodies	Clone	Dilution	Result
CK7	Clone OV-TL 12/30	1/200	Focally positive
CK19	Clone BA17	1/50	Focally positive
CK20	Clone Ks20.8	1/50	Negative
LMWCK	AE1	1/200	Focally positive
EMA	GP1.4	1/1000	Diffusely positive
NSE	E27	1/200	Negative
ChA	Clone SP12	1/200	Negative
Synp	Polyclonal	1/300	Negative
CEA	COL-1	1/100	Negative
p53	D07	1/100	Negative
S-100	Polyclonal	1/200	Focally positive
SMA	Polyclonal	1/100	Negative
CD10	56C6	1/60	Negative
CA19-9	121SLE	1/100	Negative
c-myc	9E10	1/60	Negative

Abbreviations: CK; cytokeratin, LMWCK; low molecular weight cytokeratin, EMA; epithelial membrane antigen, NSE; neuron specific enolase, ChA; chromogranin A, Synp; synaptophysin, CEA; carcino embryonic antigen, SMA; smooth muscle antigen.

The differential diagnosis of low grade SAs includes also columnar cell papilloma (Schneiderian papilloma) and polymorphous low grade adenocarcinoma of minor salivary glands. Columnar cell papilloma has several histological features similar to those of low grade SAs, such as cytologically bland appearance, epithelium with eosinophilic staining cytoplasm, intraepithelial microcysts containing mucin, regular simple papillary structures. The dis-

tinguishing features of papilloma include stratified epithelium and lack of true glandular formation. However, a characteristic feature of low grade SAs is a true stromal invasion (4). Another important differential diagnosis is polymorphous low grade adenocarcinoma of minor salivary glands in the sinonasal tract (12). This neoplasm is cytologically uniform and bland but it shows considerable morphological variability, frequent perineural invasion and clinically more aggressive behavior. Mucin production is not present. True stromal invasion and mucin production were present in our case. However, co-expression of CK7 and CK19 was remarkable in the present case. CK19 is more frequently positive in salivary gland tumors. This may point out to a mixed origin of the present tumor at the level of immunophenotype. Another differential diagnosis is papillary cystic variant of acinic cell carcinoma which is a type of minor salivary gland neoplasm that is rarely seen and has a papillary-cystic morphology (13). Bland cytology, S-100 expression and intraepithelial microcysts are similar features for both neoplasms. However, basophilic staining of cytoplasm and more aggressive behavior are characteristic features for papillary cystic variant of acinic cell carcinoma (13). A basophilic staining of cytoplasm was not present in the tumor of the present case and our case has a clinically indolent course. No recurrence was determined at postoperative 20 months.

Another lesion which should be considered in the differential diagnosis is sinonasal polyp (antrocoanal polyp). Sinonasal polyps may include foci of glandular proliferations reminiscent of a glandular neoplasm in the edematous loosely stroma. Papillary configuration, true stromal invasion and higher degrees of cellularity and nuclear pleomorphism are distinguishing features for low grade SAs. Our case also showed similar areas as sinonasal polyp. Areas of higher cellularity, complexity of glandular structures and true invasion foci are important in the differential diagnosis.

In conclusion, low grade SA is a poorly defined neoplasm of sinonasal tract and only a few small series of the cases are present in the literature. Its bland morphological features constitute the basis of difficulty in the differential diagnosis with other similar neoplasms of sinonasal tract. Although they have a lower risk for recurrence than sinonasal ITACs, low grade SA should be distinguished from other lesions of sinonasal tract, especially benign neoplasms such as columnar cell papilloma and cellular sinonasal polyp.

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