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Review Article

Diagnostic traps awaiting the head/neck pathologist: "Cytoplasm-poor" neoplasms

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ABSTRACT

Context: Beyond squamous carcinoma, a variety of diagnostically challenging neoplasms arise within various head and neck sites. This is particularly the situation with neoplasms where little cellular cytoplasm is present to assist the pathologist in categorizing such lesions.
Objective: To highlight diagnostic pitfalls that accompanying neoplasms composed primarily of 'cytoplasmically-poor' cells. These pitfalls include morphologic and immunohistochemical traps that emerge from this class of neoplasms.
Data sources: Selection of pathologic specimens from the author's personal files, and literature review.
Conclusions: Interpretative pitfalls regarding the histopathology and immunophenotype of small 'cytoplasmically-poor' neoplasms are a diagnostic hazard in head and neck surgical pathology practice, and require knowledge of histomorphologic plasticity and aberrant immunophenotyping.

1. Introduction

The potential for diagnostic error, sometimes minor and occasionally major, constantly awaits the head and neck surgical pathologist. As part of this Midwestern Conference, I chose to illustrate a series of cases that fit into the category of 'cytoplasmically poor' head and neck neoplasms that I have encountered over the past several years where diagnostic error occurred for a variety of reasons including unfamiliarity with aberrant morphologic features, as well as misuse, non-use, and misinterpretation of ancillary immunohistochemical (IHC) stains. Errors in this series of four cases show a failure to order or even consider the use of IHC, over reliance of weak IHC staining as being definitive, failure to order the appropriate IHC stain by not establishing a proper differential diagnosis, and failure to appreciate that aberrant IHC staining is not a rare phenomenon in this category of neoplasms.

2. HPV-related non-keratinizing squamous cell carcinoma, basaloid variant

2.1. Clinical history

A 57 year old man presented to an outside hospital with a right neck mass. Mass size, duration, and exact location within the neck were undocumented. A core needle (CN) biopsy was performed and a pathologic diagnosis of adenoid cystic carcinoma (AdCC) was made. The patient and his slides were subsequently referred to our medical center. After examination of hematoxylin and eosin (H&E)-stained slides, a request was made to the outside hospital for the paraffin block in order to perform IHC staining as none was previously done. However, prior to receipt of the outside block, the patient appeared in our clinic where a fine-needle aspiration (FNA) biopsy of the mass was performed. Final cytopathologic diagnosis from that FNA biopsy was also AdCC. After some delay, the outside paraffin block from the CN biopsy was subsequently received, a series of IHC stains were performed, and the correct diagnosis of human papilloma virus (**HPV)-related non-keratinizing squamous cell carcinoma, basaloid variant (BSqCC)** was issued. Subsequent hospital course showed a right tonsillar mass and no evidence of a salivary gland (SG) mass.

2.2. Pathologic findings

The outside specimen consisted of a single 1.2 long tissue core. A small cell neoplasm arranged in an irregularly configured insular pattern contained a variable amount of eosinophilic hyalinized stroma. In areas, the stroma was somewhat plentiful and globular imparting a cribriform-like appearance to cell nests (Fig. 1). Isomorphic basaloid cells had round to oval nuclei, indistinct nucleoli, and minimal visible cytoplasm. Focal palisading of cells was present at the periphery of

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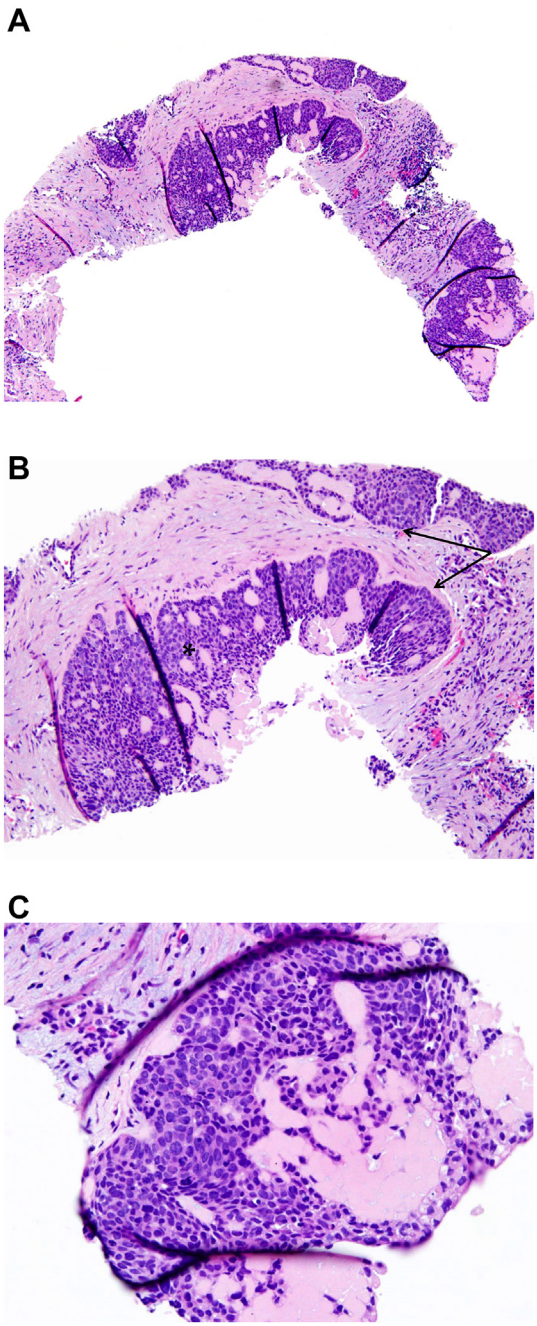

Fig. 1. A. Several misshapen cell nests are scattered in this core of fibrous tissue. Hyalinized stroma is visible within most cell nests. B. Cribriform-like foci (asterisk) and focal peripheral nuclear palisading (arrows) are seen. C. Higher power shows a uniform small cell population minus a population of peripherally-oriented myoepithelial cells. H&E stain.

some cell aggregates. No myoepithelial cell component was present. FNA smears and cell-block from our hospital contained numerous clusters of basaloid cells and occasional glassy globular matrix with background necrosis (Fig. 2). After receipt of the outside block, IHC staining revealed positive staining of basaloid cells with p16, p40, p63, and cytokeratin 5; staining was negative with smooth muscle actin (Fig. 3). Right tonsillectomy subsequently revealed a primary HPV-related BSqCC (Fig. 4).

2.3. Comment

Originally described by Wain et al. as an unusual form of carcinoma involving the tongue, larynx, and hypopharynx [1], the basaloid variant of squamous cell carcinoma (BSqCC) is one of several squamous cell carcinoma (SqCC) histologic subtypes. It affects a wide variety of sites within the head and neck, as well as other regions of the body [2-5]. Though not restricted to the oropharynx, BSqCC is one of several HPV-related variants in this site [6,7]. In a study of over 400 oropharyngeal SqCC, the basaloid variant constituted 3.4% of cases, of which 87% were p16 positive [8]. Architectural patterns for BSqCC are variable adding to potential diagnostic difficulty. Solid, trabecular, cystic, lobular and cribriform patterns have all been described, and mixed patterns are not uncommon. Of these, one of the more diagnostically troublesome is the cribriform pattern, also known as a 'jigsaw' pattern of growth due in large part to the variable, sometimes abundant amount of hyalinized stroma which can create a strong resemblance to the cribriform pattern commonly seen in AdCCA [9]. Presumably, the presence of this bulbous hyaline stroma coupled with a basaloid cell population in both CN and FNA cell-block slides is the primary reason that led two separate pathologists to an incorrect diagnosis of AdCCA.

Another critical factor that led to diagnostic error is failure to correlate both the tissue core specimen and the cytologic specimen with the patient's clinical history. Perusal of his clinical record showed that he did not even have a SG mass, and thus a failure to correlate histopathology with the clinical situation ensued. For a primary SG AdCCA to remain clinically occult and yet metastasize to regional nodes is exceedingly uncommon. Large studies of SG AdCCA show cervical metastasis in16%–19% of patients, but nearly always in those with stage T3 or T4 primary tumors [10-12]. Additionally, the absence of a peripheral myoepithelial cell population when hyalinized foci are present should have alerted both pathologists that this finding is exceedingly unusual for the cribriform pattern of AdCCA. Finally, as basaloid head and neck neoplasms are among the more difficult to segregate from one another, particularly with limited sampling (as in this patient), they nearly always require one to establish a proper differential diagnosis and perform a cogent battery of IHC markers which was not done on either specimen [13]. As this case emphasizes, the mere presence of stromal hyalinosis, globular or otherwise, is not intrinsically diagnostic of a specific entity.

3. Clear cell carcinoma

3.1. Clinical history

A 60 year old woman presented to our hospital with a clinical history of tonsillitis and a left neck mass. FNA of the neck was diagnosed at an outside hospital as 'carcinoma' only. Endoscopic examination showed asymmetry of her tongue base with a small lesion that appeared 'concerning' to the surgeon. Multiple small biopsies of this area were performed. Initial pathologic interpretation was invasive SqCC based on positive IHC staining of malignant cells with cytokeratin AE1/AE3, p63 and p40. p16 staining was not performed. Subsequent pathologic review of the case showed a single focus of clear cell change within malignant cells prompting the pathologist to order fluorescence in-situ hybridization (FISH) testing for *EWSR1* rearrangement. After receiving a positive FISH result, the pathologic diagnosis was changed to **Clear Cell Carcinoma (CCC)**.

3.2. Pathologic findings

The specimen consisted of a 1.2 cm. aggregate of tissue fragments. Nearly all fragments contained a proliferation of uniform basaloid cells arranged in linear cords and vague cell nests. (Fig. 5) Cells possessed a minimal amount of pale eosinophilic cytoplasm, and stained with pankeratin, p40, p63, keratin 34βE12, and low-molecular weight cytokeratin; staining was negative smooth muscle actin, calponin, S-100, and smooth muscle myosin. Slight myxoid change was seen within stroma, but no fibrosis or stromal hyalinization was present. Mitotic figures

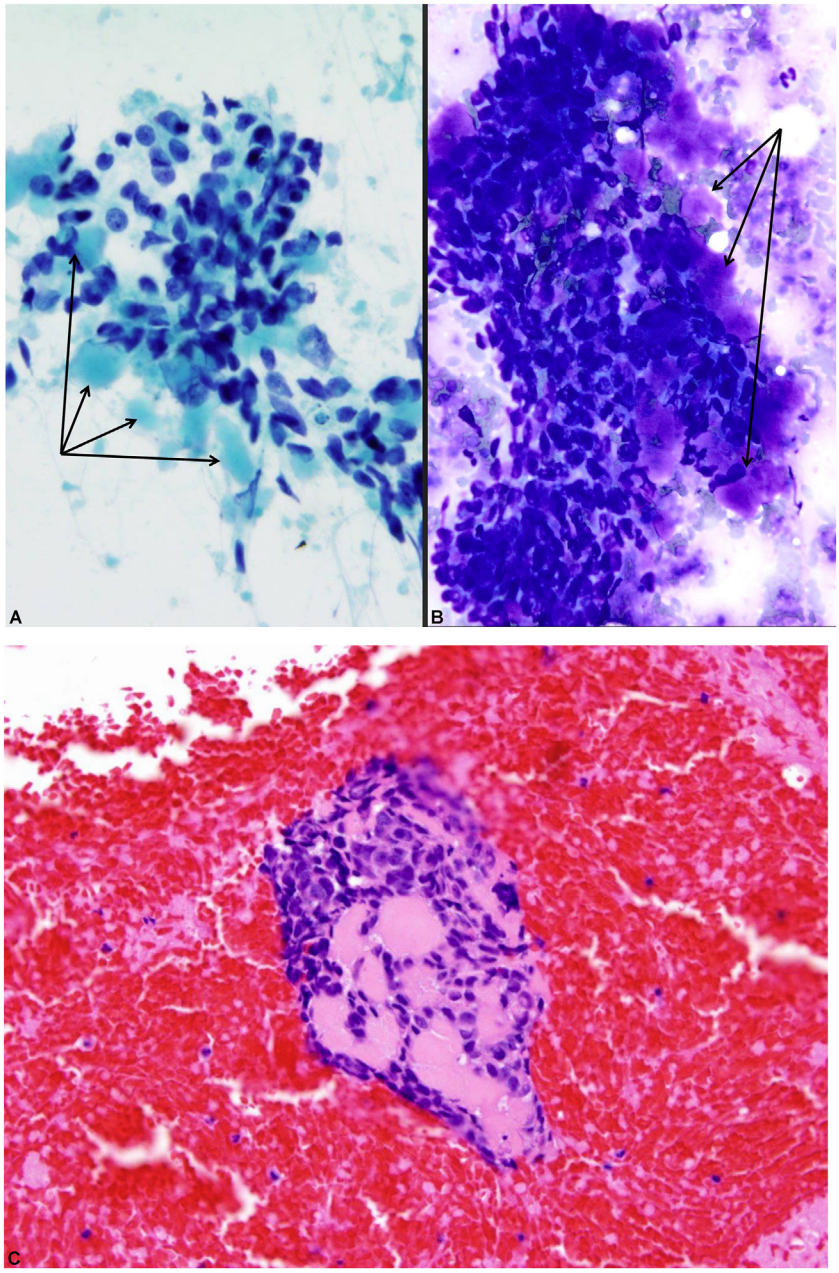

Fig. 2. A. FNA smears highlighting a small cell neoplasm admixed with slightly rounded glassy matrix (arrows). Papanicolaou stain. B. Romanowsky stain. C. Cytology cell block exemplifies a cribriform-like pattern. H&E stain.

were exceptionally infrequent, and necrosis absent. In the single focus with clear cell change, cells had isomorphic nuclei and optically clear cytoplasm with sharp cell borders mixed with non-clear cells (Fig. 6).

3.3. Comment

CCC is a low-grade SG malignancy initially named 'hyalinizing clear cell carcinoma' due to the abundance of fibrotic, hyalinized stroma that characterized this neoplasm along with cells containing noticeable optically clear cytoplasm [14]. Re-named CCC in the World Health Organization (WHO) classification of head and neck tumors, it is characterized as a low-grade malignancy with a 5 year disease-specific survival of 81% [15]. Having a female predominance, most examples arise from minor salivary glands of the oropharynx and oral cavity from patients in their sixth decade of life. Comprehensive literature reviews find the palate and base of tongue as the most common sites with the maxilla, floor of mouth, and parotid also involved [16,17]. Because clear cell change is ubiquitous in salivary gland tumors [18], CCC was often considered a diagnosis of exclusion [19]. IHC staining mimics that of SqCC with strong diffuse nuclear staining for p63 and p40, and negative staining for myoepithelial markers smooth muscle actin, S-100, and glial fibrillary acidic protein; mucin staining is rare [17,20]. Indeed, ultrastructural features originally highlighted by Dardick concluded that CCC is a squamous lesion [21]. A major advance occurred with the discovery that most CCCs (unlike other 'clear cell' SG neoplasms) show positive *EWSR1* gene rearrangement by FISH [22-24]. In addition to the more common *EWSR1-ATF1* gene fusion, a novel one, *EWSR1-CREM*, has recently been identified using next-generation sequencing [25]. Bilodeau et al. have shown that CCC essentially cannot be separated reliably from clear cell odontogenic carcinoma (CCOC) except by location of the latter within the mandible [26,27].

Initial diagnostic error in this case was due to several factors

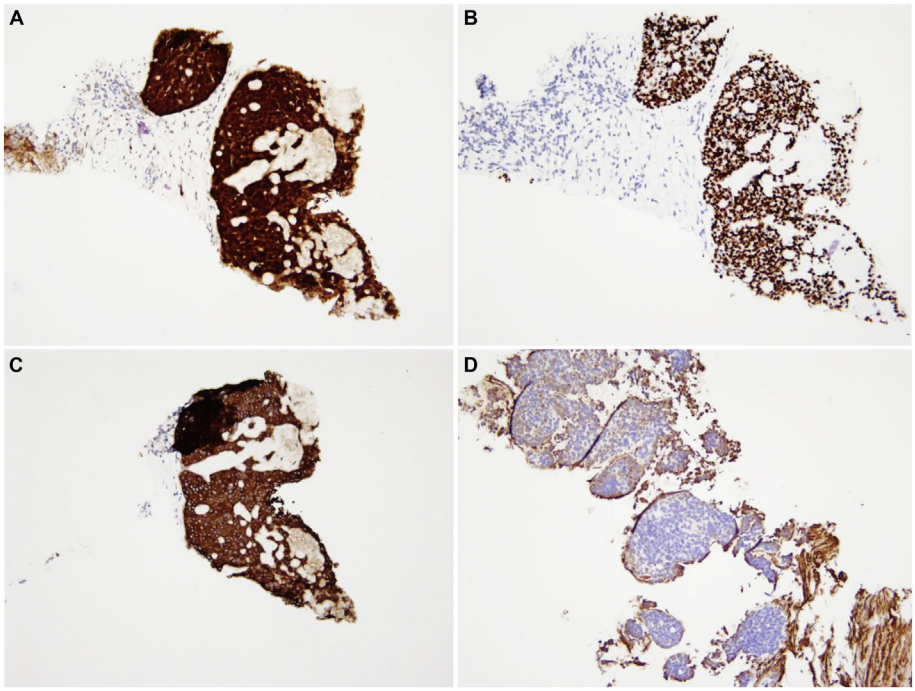

Fig. 3. Immunoprofile. Positive staining of carcinoma occurs with p16 (A), p40 (B), and cytokeratin 5 (C), while staining with smooth muscle actin fails to identify a myoepithelial cell component (D).

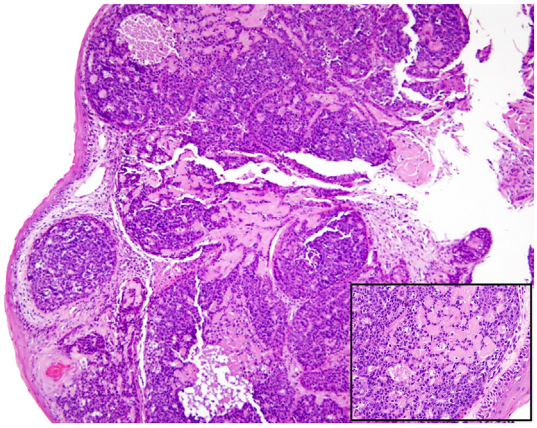

Fig. 4. Tonsil. Resection of the primary carcinoma shows a non-keratinizing basaloid squamous cell carcinoma situated just below unremarkable squamous mucosa. Stromal hyalinosis producing a cribriform-like pattern is readily evident (inset). H&E stain.

including near absence of clear cell cytoplasm within the carcinoma, failure to recognize clear cell change in a single microscopic focus among multiple tissue fragments, and an IHC profile identical to conventional SqCC. As Weinreb has emphasized, even though conventional SqCC can have sclerosis and thin cords of tumor cells, it is invariably associated with some degree of nuclear enlargement and mitotic activity which was lacking in this case [19]. The absence of mucosal intraepithelial dysplasia is another clue that would argue against a diagnosis of conventional SqCC. Although p16 staining was not performed in this case, Bishop et al. have emphasized that since CCC is invariably p16 positive, this could have further added to a mistaken diagnosis of HPV-related oropharyngeal SqCC [28]. Despite its name, prior reports of CCC have emphasized that so-called 'hyalinizing' CCC may actually lack dense hyalinization altogether, and can have minimal to absent clear cell differentiation [19,22,23]. Additional anomalous features of CCC that one needs to be cognizant of, and that may hinder recognition of CCC, include reports showing areas with myxoid stroma, perineural invasion, cribriform growth pattern, and polygonal cells having high-grade nuclei [19,20].

4. Sinonasal undifferentiated carcinoma

4.1. Clinical history

An 80 year old man presented to an outside hospital with the clinical diagnosis of chronic sinusitis. Computerized tomography/positive emission tomography (PET/CT) showed a hypermetabolic (standard uptake value [SUV] of 31) osseous-destroying mass involving the ethmoid sinus, cribriform plate, medial wall of the right maxillary sinus, middle/inferior nasal turbinates, and destruction of the anterior skull base. PET/CT also noted a large hypermetabolic right parapharyngeal lymph node and hypermetabolic cervical lymph nodes. Multiple biopsies performed at the outside hospital were diagnosed as a poorly-differentiated neoplasm favored to be compatible with high-grade olfactory neuroblastoma (ONB). Per the outside report, this interpretation was made 'due to the focal strong staining with synaptophysin and CD56'. The patient and patient's slides were transferred to our medical center where an identical pathologic interpretation of consistent with ONB was issued.

However, clinicians' skepticism regarding the diagnosis of ONB, and subsequent internal disagreement among pathologists regarding that diagnosis led to expert review at an outside institution where a diagnosis of **Sinonasal Undifferentiated Carcinoma** (SNUC) was made. The diagnosis was then amended. The patient was sent for hospice care where he expired shortly afterward.

4.2. Pathologic findings

Submitted tissue consisted of multiple fragments, some polypoid, of sinonasal mucosa from both left and right nasal sinuses. These harbored a neoplastic proliferation of polygonal cells arranged in both lobular nests and as single infiltrating strands of cells. Malignant features appreciated at high power consisted of large cells with enlarged nuclei,

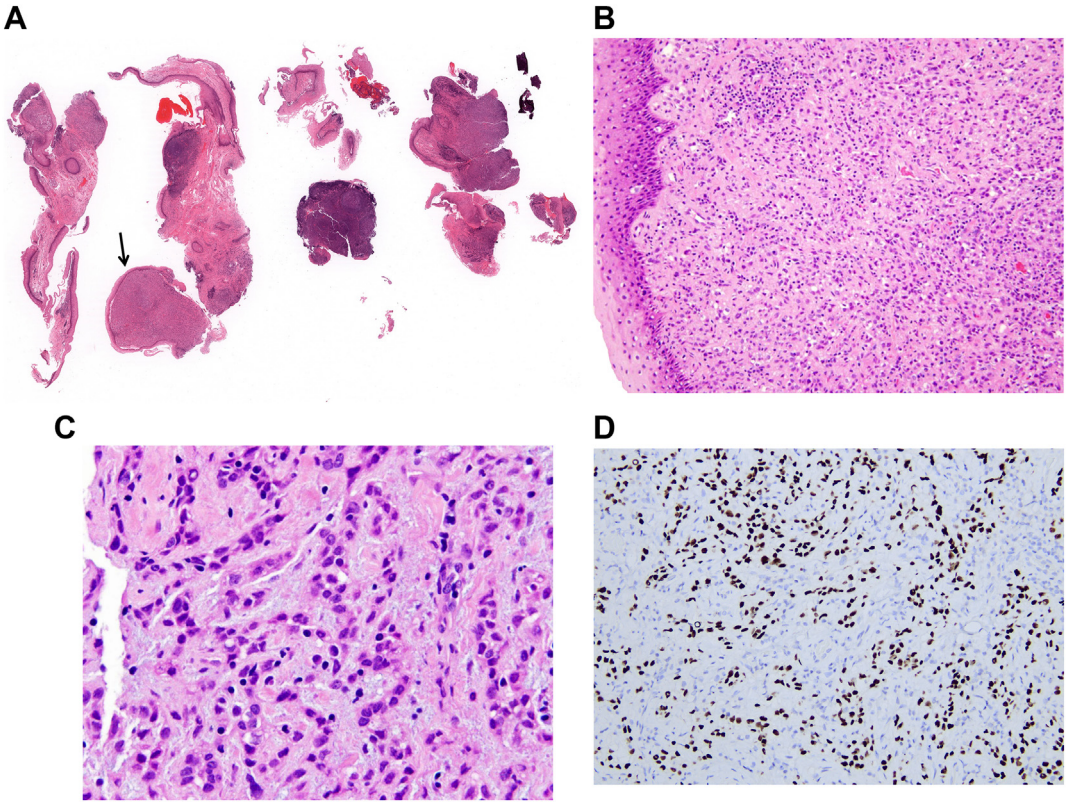

Fig. 5. A. Multiple fragments from the base of tongue showing benign squamous mucosa and lymphoid tissue at low magnification. The arrow points to a fragment which on medium power (B) shows a solid proliferation of innocuous appearing basaloid cells. Note the absence of involvement of the overlying mucosa. H&E stain. C. Some foci showed short linear tumor cell cords and scattered lymphocytes. Isomorphic tumor cell nuclei are oval to rounded with slightly wrinkled contours, and retain meager amounts of pale, eosinophilic cytoplasm. H&E stain. D. p40 immunostain is expressed in most tumor cell nuclei.

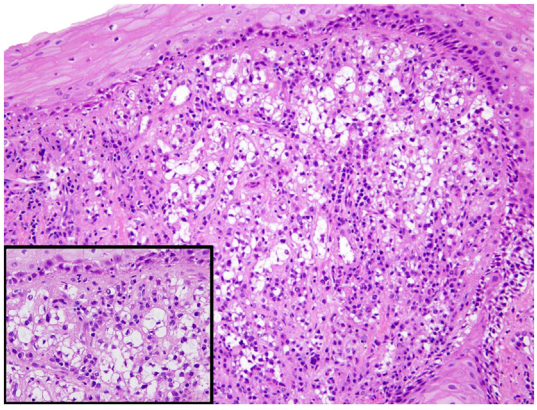

Fig. 6. Clear cell change is evident in many cells in this field. Most of these vacuolated cells exhibit discrete cell borders (inset). H&E stain.

many with acidophilic macronucleoli, and only a modest amount of eosinophilic cytoplasm (Fig. 7). Mitotic figures (3–4 per high power field) and individual cell necrosis was commonplace. IHC stains performed at the outside hospital and reviewed by us showed focal, but real staining with synaptophysin, CD56, and dot-like staining with cytokeratin AE1/AE3. (Figs. 8A–D) Staining with CAM 5.2 was diffuse in most areas, but also patchy in others. (Fig. 8E) Negative IHC stains included chromogranin, CD99, p63, p40, cytokeratin 7, cytokeratin 20, cytokeratin 5, p16, S-100, EBER, TTF-1, desmin, CD20, and CD45. Tissue sent for flow cytometry was also negative.

4.3. Comment

It has been stated that per cm^3 the sinonasal tract gives rise to a greater diversity of neoplasms than any other site in the human body [29]. Poorly-differentiated sinonasal malignancies, particularly those that fit into the 'small rounded cell tumor' category are among the most difficult to segregate as they encompass a wide spectrum of neoplasms ranging from sarcomas (e.g. alveolar rhabdomyosarcoma, adamantinoma-like Ewing sarcoma) [30-33], to melanoma, neural neoplasms (ONB), non-Hodgkin lymphomas (e.g. extranodal NK/T-cell lymphoma, nasal type), and a list of long-established carcinomas such as SNUC [34], small cell and large cell neuroendocrine carcinoma, lymphoepithelial carcinoma, and the solid variant of AdCC. Along with these previously known entities, several newly characterized poorly-differentiated carcinomas with overlapping morphologic features have been 'chipping away' at the broader category of SNUC. Among these are NUT carcinoma [35,36], SMARCB-1 (INI-1) deficient sinonasal carcinoma [37-39], SMARC4 deficient sinonasal carcinoma [40], high-grade myoepithelial carcinoma, [41] and HPV-related multiphenotypic sinonasal carcinoma [42,43]. With this broad differential list, ancillary IHC is imperative, and should be extensive enough to cover a number of these entities.

As currently defined by the WHO classification, SNUC remains largely a diagnosis of exclusion due to its completely undifferentiated nature showing no evidence of glandular or squamous differentiation and not classifiable into any other category [34,36]. Isocitrate dehydrogenase 2 mutations have been recently identified in some cases of SNUC suggesting the existence of other genomically defined subsets within the spectrum of this neoplasm.[44,45]. A recent review of over 300 SNUC cases showed an age-adjusted incidence rate of 0.2 per million, a male to female ratio of 2:1 to 3:1, and an overall median

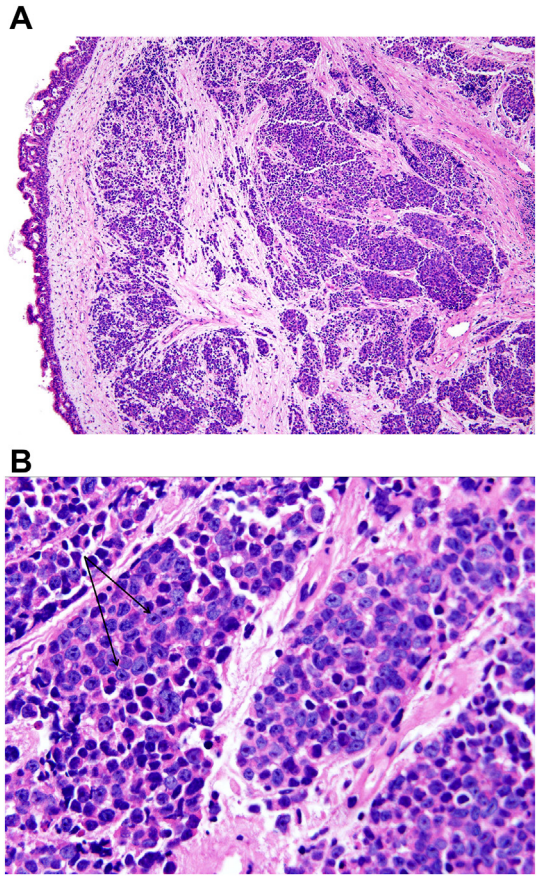

Fig. 7. A. Low power image showing misshapen islands and infiltrating threads of malignant cells. B. Lobules of large cells with high N/C ratios. Note the markedly enlarged acidophilic nucleoli (arrows). H&E stain.

survival of 22.1 months [46,47]. Typical clinical presentation for SNUC is the rapid development of a midline sinonasal mass affecting multiple adjacent sites with extensive local invasion, and involvement of the skull base and orbit as seen in this patient. Clinical signs and symptoms are non-specific and overlap with ONB including headache, epistaxis, proptosis and diplopia among others [48-50].

ONB is also a relatively rare tumor, and as such can be a challenging diagnosis, particularly for the general pathologist. At one major cancer hospital, in only two of twelve patients was the referral pathologic diagnosis of ONB confirmed; eight of these individuals required significant alteration in the initially proposed treatment plan due to misdiagnosis [51]. A major pitfall in this case was placing an undue amount of reliance on the diagnostic specificity of neuroendocrine markers CD56 and synaptophysin. ***Focal*** staining with these markers is insufficient to issue a diagnosis of high-grade ONB. Although publicized that neuroendocrine differentiation should be absent in SNUC, subsequent literature has documented that patchy expression of neuroendocrine markers can be seen, and should not be taken as unequivocal evidence of a neuroendocrine neoplasm. Numerous reports have documented that *focal* staining with synaptophysin, CD56, neuron-specific enolase, and chromogranin can be seen in SNUC as well as in a variety of other non-neuroendocrine neoplasms [29,34,48-50,52-55]. Furthermore, in reading the outside pathologist's note, a phrase mentions the presence of 'cytoplasmic dot-like keratin staining that is consistent with a neuroendocrine tumor'. Dot-like staining also is morphologically non-specific and it too should not per se be considered indicative of neuroendocrine differentiation. Clinically, destructive involvement of multiple sites within the head and neck including the skull base as occurred in this patient is unusual for ONB, but highly characteristic of SNUC. PET/CT showed enlarged lymph nodes in additional to his sinonasal mass. Approximately 10–20% of SNUC patients will have evidence of cervical nodal metastases at the time of presentation [56]. Pathologists can also take advantage of PET/CT scanning values to help distinguish between ONB and SNUC. Maximum standard uptake value (SUV_{max}) from PET/CT scans are markedly elevated in SNUC

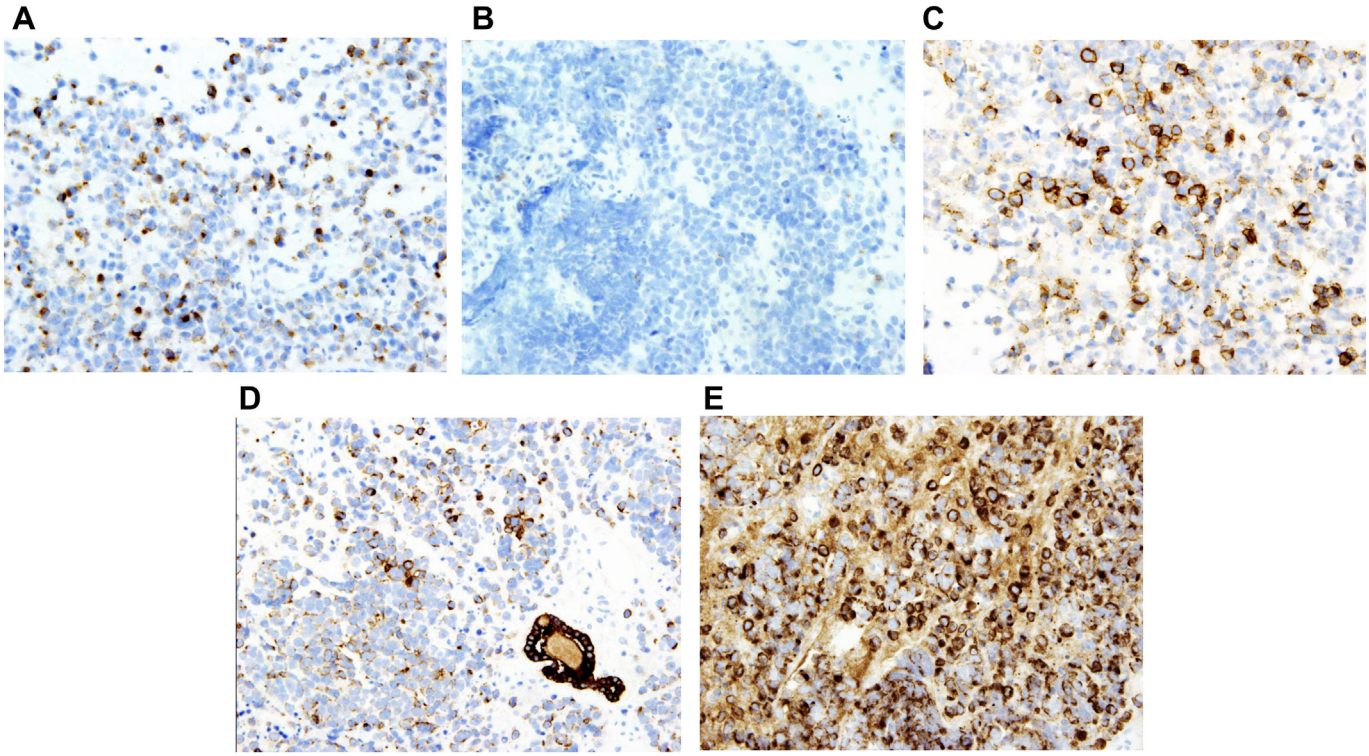

Fig. 8. A. Most intense area of synaptophysin staining. B. Negative synaptophysin staining that was present in about 90% of the specimen. C. Patchy staining seen with CD56 and (D.) cytokeratin AE1/AE3. E. CAM 5.2 stain. Though not diffuse, much of the tumor showed this strong degree of staining.

(sometime double) when compared with those of ONB [57,58]. Mistaking SNUC for high-grade ONB is not an innocuous error as there are major differences in management as well as prognosis [48].

5. Malignant melanoma, small cell variant

5.1. Clinical history

An 81 year old woman was seen by her dentist for poor fitting dentures. Oral examination revealed an exophytic mass bulging into the gingivobuccal sulcus. CT scan showed a 6 cm. mass centered in the left maxillary sinus. Small biopsies were submitted for pathologic examination and a preliminary diagnosis of 'poorly-differentiated epithelioid neoplasm' was made at an outside hospital. Slides and blocks were then submitted to us for consultation. Subsequent IHC testing results by us (see below) confirmed a diagnosis of **Malignant Melanoma (MM), small cell variant**, of the maxillary sinus. The originating pathologist was unsure of a specific diagnosis for this malignancy because of negative staining for epithelial markers, desmin, neuroendocrine markers, lymphoid markers, and S-100. Regarding the latter stain, the comment was made in the outside pathology report that "no evidence of a neural tumor or melanoma is identified with an S-100 immunostain." Several months later she developed a chest wall mass that was diagnostic of metastatic MM.

5.2. Pathologic findings

The gingivobuccal specimen consisted of several small tissue fragments that in aggregate measured only 0.8 cm. in maximum dimension. Deep to an unremarkable squamous mucosa, a population of uniformly-sized, mitotically active malignant small cells had polygonal and angulated nuclei, inconspicuous nucleoli, and minimal cytoplasm (Fig. 9A, B). No cytoplasmic pigment was seen. S-100 stain showed only a rare cell with nuclear staining (Fig. 9C). Remaining IHC stains from the outside hospital showed no expression for CAM 5.2, cytokeratin 5, cytokeratin 7, desmin, CD43, CD45, and synaptophysin. Repeat staining for desmin and S-100 performed in our laboratory was interpreted as negative also, as was added staining for cytokeratin AE1/AE3, myogenin, ERG, and tyrosinase. However, unequivocal positive staining was present with the insertion of additional melanoma markers Melan-A, HMB-45, and SOX-10 (Fig. 10). Subsequent IHC staining of her chest wall metastasis also demonstrated unequivocal expression of HMB-45, SOX-10, Melan-A, and vimentin, but once again weak to absent staining with S-100.

5.3. Comment

MM is aptly regarded by pathologists as the great masquerader due to its morphologic and immunophenotypic diversity [59]. The upper aerodigestive tract is the most common site of mucosal melanoma; sinonasal and oral cavities being most often afftected [60,61]. Sinonasal MM represents about 5% of neoplasms from this site. They have a broad age range, nearly equal gender distribution, and a heteromorphic appearance comprising epithelioid, spindle, small cell, rhabdoid, and pleomorphic shapes in both pigmented and non-pigmented forms [62].

S-100 protein has withstood the test of time as a reliably sensitive, though certainly not entirely specific IHC marker for the recognition of MM [63]. Because of this high sensitivity, many pathologists use it as the sole IHC stain to consider or exclude MM when confronted with an undifferentiated malignancy, as occurred in this example. Yet, the literature has shown that singular reliance on negative S-100 staining to exclude MM may lead to diagnostic error [63]. Though not specifically addressing the sinonasal region, a Mayo Clinic study showed that 9% of epithelioid MM and 5% of spindle cell MM were S-100 negative [54]. Absence of S-100 staining is recognized to not be a rare event in desmoplastic [64] or rhabdoid variants [65,66]. Undifferentiated sinonasal

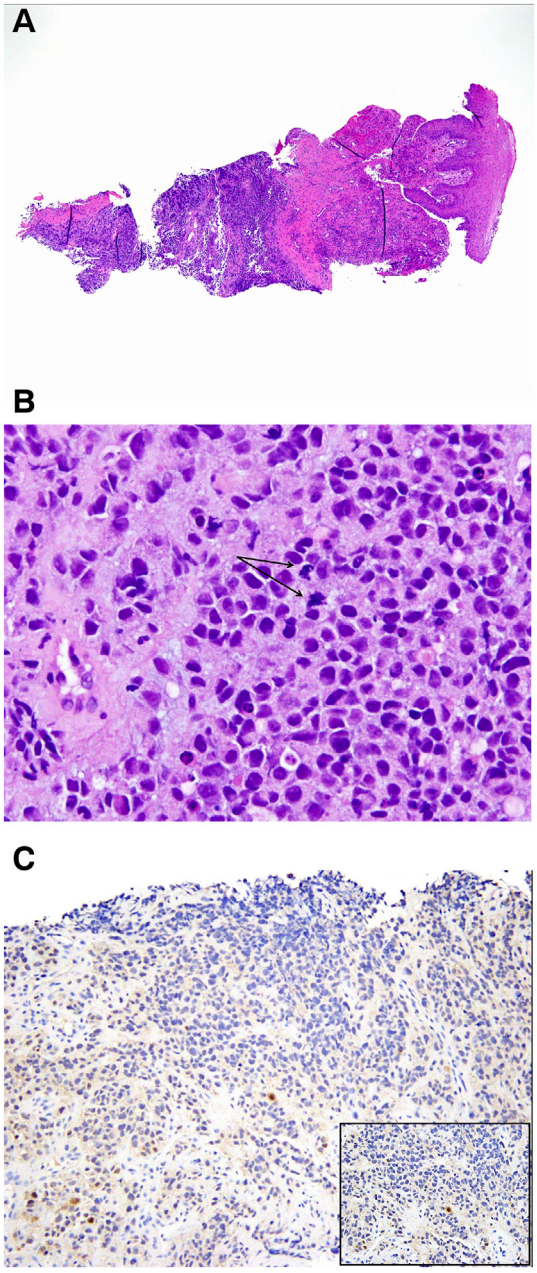

Fig. 9. A. Conical shaped fragment of unremarkable mucosa (right) and a population of basaloid cells occupying the submucosal region. H&E stain. B. High power from the specimen base shows a sheet of relatively monotonous small cells with minimal cytoplasm, smudged nuclei, and spotty individual cell necrosis. Arrows highlight two mitotic figs. H&E stain. C. S-100 stain is nearly completely negative with the exception of a rare cell exhibiting nuclear staining; high power (inset).

neoplasms are an added category where reliance on negative S-100 staining alone can lead to a false negative impression; small biopsies specimens being prone to this phenomenon. Reghauer et al. found that although S-100 was expressed in all examples of sinonasal MM, those tumors composed of undifferentiated small blue cells (similar to this case) showed only isolated foci of cytoplasmic and nuclear staining adjacent to many completely negative tumor cells [67]. Large series have found a small number of S-100 negative sinonasal cases ranging from 3%–9%, and though positive, a larger number of melanoma cases were described in these reports as having S-100 staining in < 5% of cells [62,68]. Five sinonasal MM cases from Lee et al. found S-100 to be negative or present only in a few scattered cells in 80% of cases; again,

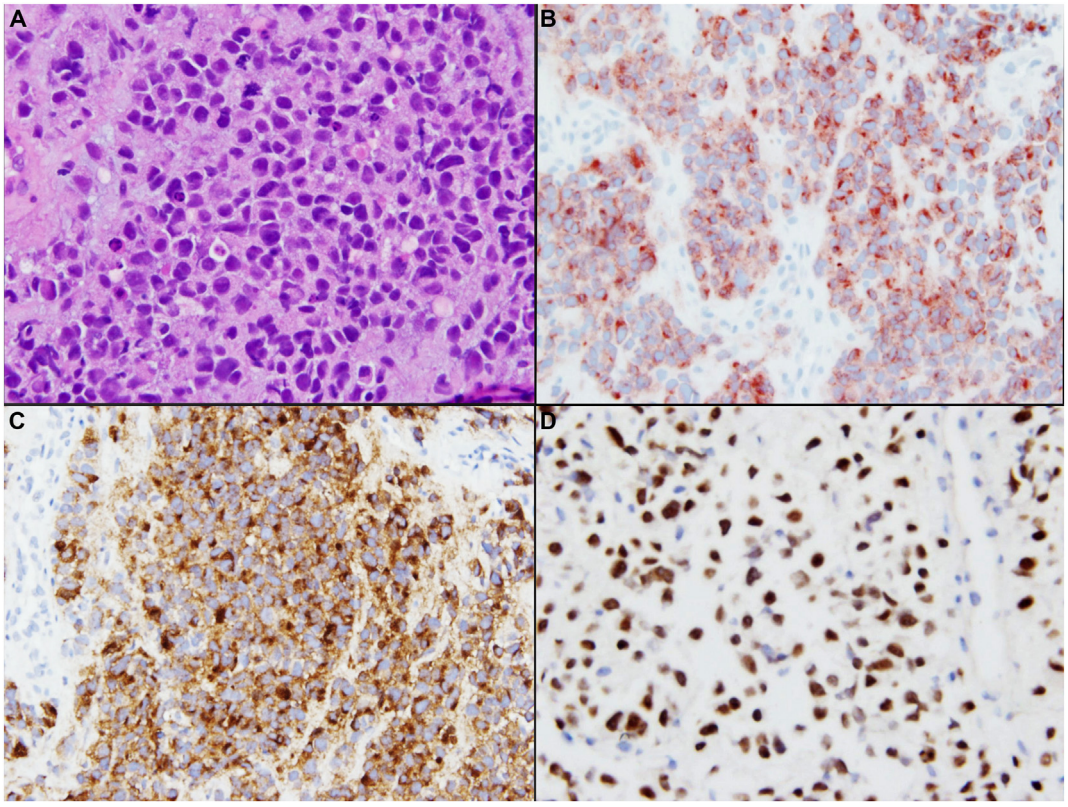

Fig. 10. Immunoprofile showing malignant cells (A.) with positive staining for melan-A (B), HMB-45 (C), and SOX-10 (D) stains.

three of these tumors were examples of the small cell variant of MM [69]. Of forty-three spindle-cell sinonasal MM from a large study, only 84% were immunoreactive with S-100 protein, but 96% from the undifferentiated group were S-100 positive [62]. Recently, Agaimy et al. published a series of fourteen examples of molecularly confirmed metastatic MM cases designated 'undifferentiated/dedifferentiated MM' because all immunohistochemical evidence of their true nature was lost (using five well known melanoma markers) [70].

As discussed in the example of SNUC, small cell 'cytoplasm-poor' malignancies of the head and neck usually require broad IHC panels to achieve diagnostic specificity. Thus, in retrospect, the immunoprofile requested for this patient's tissue was incomplete.

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