Case Report

Paucilymphoid non-keratinizing nasopharyngeal carcinoma with prominent stromal desmoplasia – an unusual case reported with brief comments on uncommon histological variants

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Abstract: We present a case of de novo non-keratinizing carcinoma of the nasopharynx (NK-NPC) with an unusual combination of histological features: (1) a minimal associated component of reactive lymphoplasmacytic cells and (2) a prominent desmoplastic stromal response. Apart from the unusual histologic features, this case did not display any unusual clinical or radiological features. On immunohistochemistry the tumor cells were strongly positive for cytokeratins (AE1-3 and 5/6) and p63 and there was strong and diffuse nuclear positivity for EBV on in situ hybridization. Since no external factor could be attributed to the conspicuous paucity of associated lymphoid cells, we feel that this may be due to inherent features of the neoplasm itself. This case highlights the histomorphological variability of NK-NPC. Awareness of the histological spectrum of NK-NPC is important in clinical practice and this is not always adequately highlighted in currently used standard textbooks of head and neck pathology.

Keywords: Nasopharynx, carcinoma, fibrosis, fibroplasia, desmoplasia

Introduction

A desmoplastic stromal reaction, e.g. fibrosis and myofibroblastic proliferation is exceedingly rare in de novo non-keratinizing nasopharyngeal carcinoma (NK-NPC). Stromal changes are more frequently seen in cases of recurrent NK-NPC that have been subjected to radiotherapy with or without concomitant chemotherapy and in primary keratinizing NPC. The majority of NK-NPCs are associated with a heavy (reactive) lymphoplasmocytic infiltrate which is significantly less frequently encountered in the keratinizing NPC. We herein report a patient with a de novo NK-NPC, where the tumor featured the highly unusual combination of both a conspicuous paucity of reactive lymphoplasmacytic cells and a prominent desmoplastic stromal reaction.

Case report

A previously healthy 48 year old male presented with a right neck mass of two months duration. The patient had no history of previous or concurrent steroid- or any other immunosuppressive therapy. On clinical examination, a tumorous mass was found in the right nasopharynx. There were enlarged right sided neck nodes in levels II and V. There was no cranial nerve palsy and no abnormalities in the ear. Magnetic resonance imaging (MRI) showed a tumorous mass arising from the nasopharynx, affecting the infratemporal region and the cavernous sinus (Figure 1). There were bilateral neck nodes which showed enhancement.

Material and methods

The biopsy measured 4x3 mm and the tissue was fixed in formalin and embedded in paraffin. Four-micron thick sections (from multiple levels) were cut and stained with Hematoxylin and Eosin (H&E). An immunohistochemical study was performed with commercial antibodies accord-
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According to the manufacturers’ protocols: Cytokeratins (CK, AE1-3, CK5/6) and p63. Periodic acid Schiff (PAS) stains with and without diastase digestion were performed.

Epstein-Barr virus (EBV) early RNA (EBER) was detected using an EBER peptide nucleic acid probe and in situ hybridization detection kit (DAKO).

Results

The biopsy was well preserved and revealed small nests separated by abundant stroma. The neoplastic epithelial cells displayed a high nuclear-cytoplasmic ratio, mitotic activity and moderate to prominent nucleoli. The cytoplasm was not well delineated and featured a pale, slightly vacuolated character (Figure 2). Despite cutting sections from multiple levels, there was no light microscopical evidence of bona fide squamous differentiation (e.g. keratinization or intercellular bridges). Only few lymphoid cells were identified, sprinkled in the stroma and around the small groups of neoplastic epithelial cells. The stroma was prominent and showed desmoplastic features, i.e. proliferation of spindle-type stromal cells with bland nuclear features in a myxocollagenous background. No foreign body-type giant cells with associated keratinous debris were identified. The neoplastic cells contained no intracellular glycogen or mucin.

The immunohistochemical study showed that the neoplastic cells were strongly positive for cytokeratins (AE1-3, 5/6) and p63 (data not shown). In addition, all neoplastic cells displayed strong nuclear positive reaction for EBV (Figure 3).

Figure 1. An MRI-scan shows a tumor mass arising from the right nasopharynx depicted by arrows.

Figure 2. Hematoxylin and esoin stained sections from the nasopharyngeal biopsy (A) showing nests of neoplastic epithelial cells surrounded by a desmoplastic stroma with a mild sprinkling of mononuclear inflammatory cells (B). The tumor cells show a syncytial arrangement, slightly vacuolated cytoplasm, moderately pleomorphic nuclei with moderate to prominent nucleoli. A mitotic figure is seen (arrow; C).
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Discussion

We present a case of a de novo nasopharyngeal non-keratinizing carcinoma (NK-NPC) from Singapore, a high incidence ("endemic") area for NPC, with an unusual histologic pattern that included a paucity of reactive inflammatory (lymphoplasmacytic) cells and a marked stromal desmoplastic response. The clinical and radiological features of this case were characteristic for NPC and, as expected, there was a strong positive nuclear reaction for EBV on in situ hybridization (EBER). We could not identify any clinical factors that could account for the conspicuous absence of lymphoid tissue. In addition, there were no radiological clues as to the unusual histological pattern that this tumor displayed.

WHO classifies nasopharyngeal carcinoma (NPC) into keratinizing, non-keratinizing (including differentiated and undifferentiated variants) and basaloid types of squamous cell carcinoma. This is not a pure "histological" classification system, but in addition to morphology, it also embraces epidemiological, virological and prognostic/therapeutic aspects[1]. The remarkably higher incidence of NPC among the Chinese, especially in south China and South Eastern Asia is mainly attributed to the non-keratinizing subtype which has a virtually 100% association with EBV and is characterized by its marked sensitivity to radiotherapy. Among pathologists in China and South East Asia, the substantial histological diversity of NK-NPC is well known. In fact, before the first (1978) WHO attempt to rationalize and simplify the classification of NPC (spearheaded by Professor Shangmugaratnam from the National University of Singapore), there was a plethora of terms and several classification systems pertaining to NPC in Asia [2-4]. Uncommonly encountered morphological variants of NK-NPC include the spindle cell-, clear cell-, pleomorphic and papillary types which together constitute less than 10% of all cases of NK-NPC[5]. NK-NPC characteristically harbours a prominent, although infrequently sparse reactive lymphoplasmocytic infiltrate. When this is especially prominent and the neoplastic epithelial cells display a nested or individual cell (Régaud-) pattern, diagnostic difficulties may ensue and immunohistochemistry is frequently needed to highlight the epithelial component. On the contrary, when NK-NPC shows the sheet-like (Schminke) pattern composed of large undifferentiated neoplastic cells, the possibility of an aggressive lymphoma needs to be ruled out.

Figure 3. In situ hybridization for EBV (EBER). The nested appearance and the paucilymphoid desmoplastic stroma is appreciated on low and medium power magnification (A,B). There is strong nuclear positivity for EBV in the nuclei of the tumor cells (B,C).
A more detailed characterization is entertained phological variability that may be encountered. desmoplasia in NPC or the spectrum of cytomor-
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With regards to the histological variability of NK-
Although the (reactive) lymphoplasmacytic infiltrate may vary, the presence of a desmoplastic type stromal response to a NK-NPC is very rarely encountered. A stromal reaction is more frequently seen with keratinizing squamous cell carcinoma of the NP and in post treatment recurrences of NK-NPC that are not infrequently associated with ulceration, acute inflammation with accompanying granulation tissue and “radiation-type” hyaline fibrosis in the surrounding soft tissue/stroma.

With regards to the histological variability of NK-NPC in general and the occurrence of a desmoplastic stromal response in particular, this is variably covered in currently used standard text-books of head and neck pathology. For example, in Gnepp’s Diagnostic Surgical Pathology of the Head and Neck[12], there is no mention at all of the cytomorphological variability or the rare occurrence of desmoplasia of NPC. However, there is a brief sentence on the fact that these neoplasms may display papillary features. Likewise, in the Armed Forces Institute of Pathology (AFIP) Atlas of Tumor Pathology, Tumors of the upper aerodigestive tract and ear[13], the authors do not mention anything about stromal desmoplasia in NPC or the spectrum of cytomorphological variability that may be encountered. A more detailed characterization is entertained in Wenig’s Atlas of Head and Neck Pathology [14]. The author mentions that undifferentiated NPCs may show “a relative absence of an associated lymphoplasmocytic cell infiltrate” and states that desmoplasia is commonly seen in keratinizing NPC. It is also stated that “typically, there is an absence of a desmoplastic response to invasive growth” (non-keratinizing carcinoma, differentiated) and “infiltrative growth of this tumor generally does not produce a host desmoplastic response” (non-keratinizing carcinoma, undifferentiated). Table 8.13 (p.333) highlights the possibility of “limited to absent desmoplastic response to invasion” in non-keratinizing differentiated carcinoma. The cytomorphological variability, eg. clear cell-, spindle cell-, and pleomorphic variants are also recognized. Similarly, the WHO (“blue book”) presents an even more detailed picture of the histomorphology of NPC. The authors acknowledge the rare possibility of a desmoplastic stromal reaction in NPC. The highly variable presence of reactive inflammatory cells is highlighted: “At one extreme, there are no or few lymphocytes within the tumor islands, although some lymphoid cells are present in between”. The cytomorphological variability is appreciated and in addition to spindle shaped cells, clear cell and the occurrence of significant cellular pleomorphism (“some tumor cells can resemble Reed-Sternberg cells”), the presence of spherical amyloid globules (in reality keratin), papillarity and the presence of intracellular mucin in very rare cells are also mentioned. The authors of this excellent chapter also state that epithelioid granulomas (which even may show necrosis) are not uncommonly associated with NPC and that, very rarely, NPC may display a reticulated pattern secondary to extracellular edema and/or stromal accumulation myxoid substances.

When faced with a limited nasopharyngeal biopsy showing an epithelial/epithelioid neoplasm with a nested pattern, a few differential diagnostic possibilities, in addition to a NPC, need to be entertained. Rarely, primary salivary gland carcinomas such as mucoepidermoid carcinoma [15], polymorphous low-grade adenocarci-
while the NP may develop cystic lesions of this type. In both primary and secondary adenocarcinoma, the situation is quite different: for example, the nasopharynx may be affected by adenoid cystic carcinoma [17] and adenocystic carcinoma [18] that may arise in the NP. More commonly encountered neoplasms in the NP are ectopic pituitary adenoma and meningioma, either ectopic or invading from an intracranial site. Also rare, but well documented cases of primary NP neuroendo-
crine tumor and carcinoma (both small and
non-small cell types), synovial sarcoma, NUT midline carcinoma, paraganglioma and gangliocytic paraganglioma are on record [18-31]. The presence of a myxocollagenous cellular stroma with nests of neoplastic cells may be reminiscent of a desmoplastic small round cell tumor, which have been recorded in the head and neck region [32], but has yet to be described in the NP. With more extensive disease (also involving the nasal cavity), olfactory neuroblastoma, sinonasal undifferentiated carcinoma and sinonasal mucosal melanoma are further differential diagnostic possibilities. Hence, the differential diagnostic spectrum is wide. Paying close attention to histomorphological details and performing a broad enough immunohistochemical study should allow for making the correct diagnosis. Regarding the case presented herein (and all cases of NK-NPC with unusual histological features), it is most important to perform in situ hybridization for EBV, which would be negative in all of the above mentioned differential diagnostic alternatives.

In summary, we present a case of de novo non-keratinizing carcinoma of the nasopharynx with a highly unusual combination of histological features; (1) a minimal associated component of reactive lymphoplasmacytic cells and (2) a prominent desmoplastic stromal response. Since no external factor could be attributed to the conspicuous paucity of associated lymphoplasmacytic cells, we feel that this may be due to inherent immunological features of the neoplastic cells. Apart from the unusual histologic features, this case did not display any unusual clinical, radiological or other features, including strong and diffuse nuclear positivity for EBV. This case highlights the histomorphological spectrum/variability of NPC that is possibly less well known among diagnostic histopathologists in areas where this malignant neoplasm is not endemic.

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References


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