Reticular and Myxoid Non-keratinizing Nasopharyngeal Carcinoma: An Unusual Case Mimicking a Salivary Gland Carcinoma

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Abstract We present a case of non-keratinizing carcinoma of the nasopharynx (NK-NPC) with an unusual histopathological pattern. The neoplastic cells were arranged in anastomosing cords embedded in a stroma which contained a significant component of alcian blue-positive myxoid substance forming a reticular pattern. These histopathological features gave an initial impression of a salivary gland-type carcinoma. On immunohistochemistry the tumor cells were strongly and diffusely positive for cytokeratins (AE1-3 and 5/6) and p63 and there was strong and diffuse nuclear positivity for Epstein–Barr virus-encoded small RNA on in situ hybridization. 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 · Reticular · Myxoid · Salivary gland carcinoma · Epstein–Barr virus

Introduction

The vast majority (>90 %) of non-keratinizing carcinomas of the nasopharynx (NPC) display, in addition to nuclear presence of Epstein–Barr virus-encoded small RNA (EBER), a spectrum of characteristic histomorphological patterns. This includes at one end, tumor cells arranged in syncytial sheets (Regaud-pattern), variably sized nests to isolated malignant epithelial cells (Schmincke-pattern), admixed with abundant reactive lymphocytes and plasma cells. The individual tumor cells display obvious features of malignancy; enlarged nuclei, prominent nucleoli and limited amount of cytoplasm. However, in a significant minority (up to 10 % of cases), NPC may show a variety of uncommon histopathological patterns, including spindle cells, clear cells, presence of bizarre tumor cells, non-caseating granulomas, papillarity, a desmoplastic stromal reaction frequently with paucity of reactive mononuclear inflammatory cells [1]. Extremely rarely, NPC may display a cord-like arrangement of tumor cells associated with significant myxoid substances in the stroma. This latter pattern differs significantly from the classic appearances of NPC and mimics a salivary gland-type carcinoma. We herein report a patient with such a histopathological variant of NPC.

Case Report

A previously healthy 46 year-old Chinese female presented with 3-month history of left-sided neck masses. On clinical examination, left-sided cervical lymphadenopathy was present. CT-scan of the neck revealed enlarged left-sided level II and level V lymph nodes with necrosis (Fig. 1a). The right side of the upper nasopharynx was thickened and

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Fig. 1 A CT-scan showed enlarged left-sided neck nodes with central necrosis (**a**, *arrow*). The right side of the upper nasopharynx was thickened and there was irregularity of the corresponding fossa of Rosenmuller and torus tubarius (**b**, *arrow*)

there was irregularity of the corresponding fossa of Rosenmuller and torus tubarius (Fig. 1). A bone scintigraphy study revealed hot spots in the body of the L1 vertebra, left proximal humerus and supra-acetabular region of the right iliac bone, highly suspicious of bone metastases. Fine needle aspiration cytology of an enlarged left cervical lymph node showed features of a high-grade carcinoma. A biopsy of the nasopharynx was performed.

Materials and Methods

The biopsy material was composed of fragments of tissue measuring 2–3 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 according to the manufacturers' protocols: cytokeratins (AE1-3 and CK5/6), CD 117 (C-kit), synaptophysin and p63. Periodic-acid Schiff (PAS) stains with and without diastase digestion and Alcian Blue were performed.

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

Results

Histopathology

Already on low-power examination a significant component of the tumor displayed a pattern of anastomosing cords of tumor cells giving rise to a reticular appearance (Fig. 2a). This arrangement of the malignant cells was even more

apparent on higher magnification where also a stroma rich in mucosubstances with a vague bluish character on H&E was identified (Fig. 2b,c). On high-power examination, the neoplastic cells showed obvious malignant cytological features, including irregular, moderately pleomorphic nuclei, significantly sized nucleoli, limited cytoplasm and readily identified mitotic figures (Fig. 2d). There was no formation of true luminal/glandular structures, no lobular configuration with peripheral palisading of tumor cells, necrosis, reduplicated basement membrane material or keratinization seen. The stroma was intensely positive for alcian blue, but negative when stained with PAS subjected to diastase digestion. Also, no intracellular PAS-positive, diastase resistant material was identified. Limited amounts of PAS-positive substance (likely glycogen) was seen in a minority of the tumor cells. Mild focal sprinkling of lymphocytes and some plasma cells were present in the stroma.

Immunohistochemistry

The immunohistochemical study showed that the neoplastic cells were strongly and diffusely positive for cytokeratins (AE1-3) and p63 (Fig. 3a). No “bilayering” or any pattern indicative of a dual neoplastic (“p63-positive and p63-negative”) cell population was seen. Virtually all neoplastic cells displayed strong nuclear positive reaction for EBV (EBER-ISH; Fig. 3b). The neoplastic cells did not express CD 117/C-kit or synaptophysin.

Discussion

We present a case of a nasopharyngeal non-keratinizing carcinoma from Singapore, a high incidence (“endemic”) area for NPC, with an unusual histologic pattern that

Fig. 2 Low-power magnification of a hematoxylin and eosin stained section from the nasopharyngeal biopsy shows a tumor with a reticular appearance composed of anastomosing cords of tumor cells set in a fibromyxoid stroma (a). The reticular pattern/anastomosing cords of neoplastic epithelial cells with a myxoid stromal reaction is

reminiscent of a salivary gland-type carcinoma (b, c). Some of the neoplastic cells display a ring-like arrangement mimicking luminal structures (b). The tumor cells show obvious cytomorphological features of malignancy including several mitotic figures (d)

Fig. 3 The tumor cells are diffusely positive for p63 (a) and there is strong nuclear positivity for EBV in the nuclei of the tumor cells (b; EBER-ISH)

included a reticular arrangement of tumor cells associated with a significant amount of alcian blue-positive mucosubstances in the stroma. This combination of histological features initially gave us the impression of a salivary gland-type carcinoma, e.g. adenoid cystic carcinoma (ADCCA) or polymorphous low-grade adenocarcinoma (PLGA). Given the reticular/trabecular arrangement of tumor cells, we also considered the possibility of a neuroendocrine carcinoma. However, the clinical and radiological features of this case were characteristic for NPC. In addition, the degree of nuclear atypia and mitotic activity exceeded that of both ADCCA and PLGA (with no high-grade transformation). Also, the multitude of patterns regularly exhibited by PLGA was not present. The absence of a dual population (of which one is positive for p63) and a complete absence of expression of CD117/c-kit strongly argue against ADCCA. Given the complete absence of synaptophysin expression, the likelihood of a neuroendocrine carcinoma is low. In addition, there was a strong positive nuclear reaction for EBER-ISH which also argues against the above mentioned diagnostic alternatives.

WHO classifies NPC into keratinizing (K-NPC), non-keratinizing (including differentiated and undifferentiated variants; NK-NPC) and basaloid types of squamous cell carcinoma (BSCC). This is not a pure “histological” classification system, but in addition to morphology, it also embraces epidemiological, virological and prognostic/therapeutic aspects [2]. 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. The substantial histological diversity of NK-NPC is well known among pathologists in China and South East Asia and perhaps less so in the west where the incidence of NK-NPC is significantly lower. Before the first (1978) WHO attempt to rationalize and simplify the classification of NPC (headed by Professor Shanmugaratnam from the National University of Singapore), there was a plethora of terms and classification systems pertaining to NPC in Asia [1, 3, 4]. Uncommonly encountered morphological variants of NK-NPC include the spindle cell-, clear cell-, pleomorphic and papillary types which together constitute <10 % of all cases of NK-NPC [5]. NK-NPC characteristically harbours a prominent, although infrequently sparse reactive lymphoplasmacytic infiltrate. When this is especially prominent and the neoplastic epithelial cells show a nested or individual cell (Schminke-) 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 (Régaud) pattern composed of large undifferentiated neoplastic cells, the possibility of an aggressive lymphoma

frequently needs to be ruled out with the assistance of an immunohistochemical study.

Although the (reactive) lymphoplasmacytic infiltrate may vary, the presence of a desmoplastic type stromal response to a NK-NPC is very rarely encountered [6]. A desmoplastic 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 reticular/myxoid appearance in particular, this is not very well covered in currently used standard textbooks of head and neck pathology. For example, in Gnepp’s Diagnostic Surgical Pathology of the Head and Neck [7], there is very limited information on the cytomorphological and architectural variability that may be encountered in NPC. There is a brief sentence mentioning that NPC 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) [8], the authors do not mention anything about the spectrum of cytomorphological variability that may be encountered in NPC. A somewhat more detailed characterization is entertained in Wenig’s Atlas of Head and Neck Pathology [9] where the rare occurrence of NK-NPC displaying a stromal desmoplastic response with relative paucity of reactive lymphoplasmacytic cells is acknowledged. Moreover, the cytomorphological variability, e.g. clear cell-, spindle cell-, and pleomorphic variants is recognized. However, the exceedingly rare occurrence of NK-NPC with a reticular-myxoid appearance, as exhibited in the case presented herein, is not mentioned. The WHO- (“blue book”) presents a detailed picture of the histomorphology of NPC. In addition to acknowledging the rare possibility of a desmoplastic stromal reaction in NPC, the authors state that, very rarely, NPC may display a reticular pattern secondary to extracellular edema and/or stromal accumulation of myxoid substances, i.e. the features of our case. However, no references are given in conjunction to this statement. The highly variable presence of reactive inflammatory cells is also highlighted. Moreover, 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, the presence of intracellular mucin in very rare cells and that NPC may be associated with non-infectious epithelioid granulomas (which even may show necrosis) are mentioned.

When faced with a limited nasopharyngeal biopsy showing an epithelial neoplasm with a reticular/myxoid

pattern, the most crucial differential diagnosis is a salivary gland-type neoplasm. Uncommonly, primary salivary gland carcinomas such as mucoepidermoid carcinoma [10], PLGA [11] and ADCCA [12] may arise in the NP. As stated above, in our case, the degree of nuclear atypia and the presence of rather brisk mitotic activity would not be compatible with a benign neoplasm, but a carcinoma and exceeds that of both ADCCA and PLGA. Also rare, but well documented cases of primary nasopharyngeal neuroendocrine tumors and carcinomas (both small and non-small cell types) and NUT translocated carcinomas are on record [13–18]. BSCC may be associated with EBV [19] and frequently harbors small foci of alcian blue-positive mucosubstances in the stroma. However, our case did not display the lobularity, peripheral palisading, comedo-type necrosis, reduplicated basement membrane material and focal keratinization which typify BSCC.

In summary, we present a case of a non-keratinizing carcinoma of the nasopharynx with a highly unusual combination of histological features; (1) a reticular arrangement of tumor cells and (2) a myxoid character of the stroma, which mimicked a salivary gland-type carcinoma. 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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