Non-Keratinizing Nasopharyngeal Carcinoma with Adenomatous Differentiation

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Abstract

A case of non-keratinizing, EBV-positive (EBER-in situ hybridization), carcinoma with adenomatous differentiation is presented. The patient is a 40 year old male with T2N2M0 disease who received standard combined chemo- and radiotherapy with complete resolution of all tumor. The tumor cells were strongly positive for low-molecular weight cytokeratins (AE1–3) and scattered cells expressed cytokeratin 20. No expression of cytokeratin 5/6, 7, p63, TTF-1, CDX2 or androgen receptor was detected. There was no evidence of recurrence or disease progression on follow-up after 19 months, which included post treatment MRI and PET–CT scans.

Keywords Nasopharynx · Carcinoma · Adenocarcinoma · Epstein–Barr virus

Introduction

The majority (> 90%) of non-keratinizing carcinomas of the nasopharynx (NPC) display, in addition to nuclear presence of Epstein Barr virus RNA (EBER), a spectrum of classical histomorphological patterns. This includes at one end, tumor cells arranged in syncytial sheets (Regaud-pattern) to at the other end small nests and isolated malignant epithelial cells (Schmincke-pattern), admixed with a variable number of reactive lymphocytes and plasma cells. However, NPC may show a variety of uncommon histopathological patterns, including spindle cells, clear cells, presence of bizarre (Reed–Sternberg-like) tumor cells, non-caseating granulomas, papillarity, with eosinophilia, amyloid and eosinophilic cytoplasmic globules [1]. Very rarely, NPC may display a cord-like, reticular arrangement of tumor cells associated with significant myxoid substances in the stroma [2]. Extremely rarely NPC may exhibit adenomatous differentiation [3]. This report presents a case of NPC with a component of the tumor where adenomatous structures were formed. Awareness of this phenomenon should help facilitate establishing the correct diagnosis when faced

with a limited biopsy specimen in NPC with this uncommon pattern.

History/Clinical Findings

The patient is a previously healthy male who was diagnosed with stage T2N2M0 nasopharyngeal carcinoma (NPC) (Fig. 1a, b). He was treated with a standard combination of concurrent chemo- and radiotherapy. There has been no evidence of recurrence or disease progression on follow-up after 19 months, which included post treatment MRI and PET–CT scans.

Histopathology, Immunohistochemistry and In-Situ Hybridization

The biopsy material consisted of three fragments of tissue ranging from 0.2 to 0.4 cm. Two of these fragments contained tumor, which were composed of variably sized nests of neoplastic cells set in a fibrous stroma with a heavy lymphocytic component. On medium power magnification one could note that the tumor displayed luminal structures (Fig. 2a). On higher power magnification this impression was confirmed and it was also evident that the luminal structures were lined by neoplastic epithelial cells where the nuclei were polarized away from the luminal structure, i.e. filling the criteria for true lumen formation (Fig. 2b). The tumor cells had enlarged, moderately pleomorphic nuclei

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with prominent nucleoli. The amount of cytoplasm was limited and mitotic figures were easily detected. There was no necrosis and no high-grade dysplasia was seen in the lining surface epithelium, which was squamous.

On immunohistochemistry the tumor cells revealed strong labelling for broad spectrum cytokeratins (CK; AE1/3). A few sporadic tumor cells expressed CK20.

There was no expression of CK7, CK5/6, CDX2, TTF-1, p63 and androgen receptor.

On in-situ hybridization for EBV (EBER) with 3,3'-Diaminobenzidine (DAB) as chromogen, there was diffuse strong positive nuclear signal which highlighted the luminal structures (Fig. 3a, b).

Fig. 1 Magnet resonance imaging study from the patient with non-keratinizing nasopharyngeal carcinoma with adenomatous differentiation showing a locally advanced tumor with parapharyngeal extension (a) and bilateral nodal metastatic disease (b)

Fig. 2 Photomicrographs from hematoxylin and eosin stained sections revealed already on medium power magnification presence of luminal structures (a). High power magnification showed true luminal structures with neoplastic cell nuclei polarized away from the luminal aspect (b)

Fig. 3 The tumor cells were diffusely and strongly positive for EBV on in situ hybridization for EBV (a). High power magnification highlighted the formation of true lumina (b)

Diagnosis

Non-keratinizing carcinoma with adenomatous differentiation.

Discussion

Non-keratinizing NPC may show a range of uncommon histopathological features. In this report a case of NK-NPC with adenomatous differentiation is presented. WHO classifies NPC into keratinizing (squamous cell), non-keratinizing (including differentiated and undifferentiated variants) and basaloid (squamous) types of carcinoma. This is not a pure “histological” classification system, but in addition to morphology, it also embraces epidemiological, virological and prognostic/therapeutic aspects [4]. The remarkably higher incidence of NK-NPC among the Chinese, especially in south China and south eastern Asia is mainly attributed to the non-keratinizing type which has an almost 100% association with EBV and is characterized by its marked sensitivity to radiotherapy [1]. NK-NPC characteristically harbors a prominent reactive lymphoplasmacytic infiltrate and as long as the tumor is confined to the lymphoid compartment of the nasopharynx, the malignant cells do not usually elicit a desmoplastic stromal response. When the lymphoplasmacytic infiltrate is especially prominent and the neoplastic epithelial cells display a small nested or individual cell distribution it has been labelled as the Régaud-pattern. At the other end of the classical spectrum of NK-NPC, the malignant cells are arranged in syncytial sheets and this has historically been attributed to Schminke. However, NK-NPC may exhibit light microscopic features that radically deviate from this standard “text book appearance”. The substantial histological diversity of NK-NPC is well known among pathologists in China and Southeast Asia. In fact, before the first (1978) WHO attempt to rationalize and simplify the classification of NPC, there was a plethora of terms and several classification systems pertaining to NPC in Asia [5–7]. Uncommonly encountered morphological variants of NK-NPC include tumors with spindle cells, clear cells, pleomorphic (Reed–Sternberg like) cells, desmoplastic stroma, a granulomatous component, eosinophilic cytoplasmic globules, marked stromal eosinophilia, amyloid, and also prominent papillarity [1]. Very rarely, a reticular myxoid pattern may be encountered [2]. To the best of my knowledge, there has only been one previous report on two patients with NK-NPC showing adenomatous, “glandular” differentiation [3]. This study included two male, Caucasian patients—one 58 years-old, the other 56. Both had cervical lymph node metastases. One of the patients was treated with combined radio- and chemotherapy and was alive with no evidence of disease at 3 years follow-up. The other patient was treated only with

radiotherapy to the nasopharynx and neck. He developed lung metastases and succumbed to disease 2 years after presentation. The tumor tissue from both patients contained two different patterns, each affecting approximately 50% of the tumor volume. These two different components were (1) a component of conventional undifferentiated carcinoma and (2) a lumen/gland forming component with malignant cell nuclei polarized away from the lumina. Based on the description and illustrations, there appeared to be no significant difference in the cytomorphological features between the two components. Both tumors contained a prominent lymphocytic infiltrate. Both components in both tumors were positive for EBV (EBER) on *in situ* hybridization. The authors also provided electron microscopy support to the light microscopic impression of true adenomatous differentiation. The neoplastic cells lining the lumina had more of the cytoplasm towards the luminal aspect, displayed microvilli with a fine granular glycocalyx and a terminal web of microfilaments and junctional complexes between adjacent cells were identified in the apical portion of the cytoplasm. With the exception that the adenomatous component made up of more than 50% of the tumor volume in the case presented herein, there are significant similarities between the actual case and the previously reported tumors. All tumors were EBV-positive, contained a significant lymphocytic component and when treated adequately, i.e. with combined chemo- and radiotherapy responded favorably with resolution of all tumor including the nodal neck disease. This treatment response was also seen in the patient presented herein who also had bilateral and prominent metastatic disease to the cervical nodes. Except for the polarization away from the luminal aspect, the cytological features in the case presented herein were within the spectrum of those seen in conventional non-keratinizing NK-NPC; high nuclear to cytoplasmic ratio, enlarged moderately pleomorphic nuclei and prominent nucleoli. In addition, in the cases reported by Jain et al. there appeared to be no significant light microscopic difference between the cells in the adenomatous and undifferentiated components.

On immunohistochemistry most NK-NPCs exhibit a squamous phenotype with expression of p63/p40 and CK5/6. Those markers were not studied in the cases reported by Jain et al. However, in the case presented herein there was no expression of p63 or CK5/6. There was focal expression of CK20, but not of CK7. Speculatively, whatever the mechanism may be behind the “phenotypical drift” towards an adenomatous morphology, this is likely associated with lack of expression of squamous markers. Given the treatment response stated above, this is likely not relevant for the tumor biological properties of NK-NPC with adenomatous differentiation.

Interestingly, in a study from Taiwan, an endemic region for NPC, the presence of EBV (EBER-ISH) in what the

authors labelled as nasopharyngeal salivary gland type carcinomas has been investigated [8]. The authors identified 15 cases among 1193 NPCs diagnosed during a period of 5 years. Of these cases 15 were mucoepidermoid carcinomas (MEC), of which five were EBV-positive, two adenoid cystic carcinoma, both EBV-negative, four adenocarcinomas, of which three were EBV-positive and one composite tumor (undifferentiated/adenocarcinoma). The composite tumor bears a striking resemblance to the tumors presented by Jain et al. The pure adenocarcinomas are not described in detail and not illustrated. Hence, it is thus possible that the three EBV-positive cases may represent examples of the tumor presented herein, i.e. that they may be non-keratinizing carcinomas with adenomatous differentiation rather than bona fide salivary gland-type adenocarcinomas. Of note is that the EBV-negative adenocarcinomatous case contained papillary structures, which was not seen in the three EBV-positive tumors and not in the actual case. In contrast, based on the description and illustrations, the MECs appear to be genuine examples of this tumor and not NK-NPC with unusual light microscopic appearances. However, no molecular genetic data, e.g. CRTC1/3/MAML2 translocations was presented. Interestingly, none of the patients with follow-up suffered any tumor recurrence and/or progression.

In conclusion, a patient with an EBV-positive non-keratinizing NPC with adenomatous differentiation is presented. The tumor showed both radiological and clinical features typical for NPC, including complete resolution of all tumor with standard combined chemo- and radiotherapy, despite locoregionally advanced disease.

Compliance with Ethical Standards

Conflict of interest The author has no conflict of interest.

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