EBV-Associated Non-keratinizing Nasopharyngeal Carcinoma with Prominent Spindled Cell and Whorling Patterns: A Previously Unreported Histological Variant in a Patient Presenting with Dermatomyositis

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Abstract

A case of non-keratinizing, EBV-positive (chromogenic EBER-in situ hybridization), carcinoma with a hitherto undescribed nodular whorling architecture is presented. The patient is a 55 year old male with 2 months history of dermatomyositis who was diagnosed with T1N0M0 non-keratinizing nasopharyngeal carcinoma. The patient received radiotherapy with complete response. The tumor cells predominantly displayed spindle cell morphology, strongly expressed low-molecular weight cytokeratins (AE1-3), p63 and p40. There was no evidence of recurrence or disease progression on follow-up after 16 months which included post treatment biopsy, MRI and PET-CT scans.

Keywords Nasopharynx · Carcinoma · Whorling · Epstein–Barr virus

Introduction

The majority (> 90%) of non-keratinizing carcinomas of the nasopharynx (NK-NPC) display, in addition to nuclear presence of Epstein Barr virus RNA (EBER), a range of classical histomorphological patterns. This includes at one end of the spectrum, tumor cells arranged in syncytical sheets (Regaud-pattern), and at the other end, small nests and isolated malignant epithelial cells (Schmincke-pattern). Most often there is a significant component of reactive lymphocytes and plasma cells. At times the inflammatory cells may be so abundant that the malignant epithelial are obscured and may require an immunohistochemical study for cytokeratins for definitive identification.

In endemic regions approximately 10% of cases of NPC exhibit uncommon histopathological patterns and/or cytomorphological features. These include tumors with spindle cells, clear cells, presence of bizarre (Reed-Sternberg-like) tumor cells, non-caseating granulomas, papillarity, with

abundant eosinophils or neutrophils, a desmoplastic stromal reaction, 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]. Another very uncommon histological pattern in NPC is adenomatous/glandular differentiation [3]. This report presents a patient with a non-keratinizing NPC which predominantly was composed of neoplastic spindle cells which were organized into whorls, frequently around small caliber blood vessels. Awareness of this phenomenon should help facilitate establishing the correct diagnosis when faced with a limited biopsy specimen in NPC with this uncommon pattern in relation to other neoplasms that may exhibit a whorling architecture.

History/Clinical Findings

The patient is a 55 year old male of Chinese ethnicity who was diagnosed with stage T1N0M0 NK-NPC. Prior to the diagnosis of NPC he had suffered from skin rashes (face, fingers, and upper back), myalgia and muscle weakness for 2 months. He also had experienced hair loss and some dysphagia. On the clinical dermatological examination there were photodistributed confluent erythema on the

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sun-exposed surfaces of the face and upper back, scalp erythema with reduced hair density, few pink-violaceous papules on the dorsa of the fingers and dilated capillaries were seen at most of the proximal nail folds of the fingers. The muscle power was reduced. Skin punch and deltoid muscle biopsies supported the clinical diagnosis of dermatomyositis. A positron emission tomography (PET) scan revealed an FDG-avid focus in the left lateral wall of the nasopharynx (Fig. 1a). No other FDG-avid foci were detected. The patient was referred to the ENT clinic and endoscopic examination of the nasopharynx showed no obvious tumor mass, but an area of increased vascularity and nodularity in left foss of Rosenmuller. A biopsy was performed.

A subsequent magnetic resonance imaging (MRI) scan showed subtle asymmetry and mild mucosal thickening with increased signal in the left fossa of Rosenmuller and left lateral wall of the nasopharynx (Fig. 1b). No enlarged neck nodes were identified. The patient was treated with standard radiotherapy with complete resolution of the tumor. Post treatment, the patient has suffered from bilateral chronic sinusitis involving maxillary and sphenoid sinuses and left mastoiditis. Post treatment MRI and PET-CT scans have

shown signal abnormality and soft tissue enhancement in the left clivus down to the occipital condyle and petrous temporal bone with soft tissue surrounding the left petrous internal carotid artery as well as hypermetabolic lesions seen in the left central skull base and carotid space. These findings are favored to represent early inflammatory changes related to radionecrosis rather than recurrence. Hence, there has been no definitive evidence of recurrence or disease progression on follow-up after 16 months.

Histopathology, Immunohistochemistry and In-Situ Hybridization

The biopsy material consisted of two fragments of tissue measuring 0.5 and 0.7 cm. Both of these fragments contained tumor which were composed of neoplastic cells with spindle cell features admixed with a mild infiltrate of lymphocytes and plasma cells. The malignant cells exhibited a striking tendency to form round whorling nests (Fig. 1c, d). The tumor cells had enlarged, moderately pleomorphic nuclei with prominent nucleoli and mitotic

Fig. 1 After the diagnosis of dermatomyositis a PET scan revealed an FDG-avid focus in the left lateral wall of the nasopharynx (a). A subsequent MRI scan showed subtle asymmetry and mild mucosal thick-

ening with increased signal in the left fossa of Rosenmuller and left lateral wall of the nasopharynx (b). The biopsy revealed a tumor predominantly composed of spindle cells forming nodular whorls (c, d)

figures were easily detected (Fig. 2a). Frequently these whorls of neoplastic cells appeared centered around small caliber blood vessels. This was especially apparent on an immunohistochemically cytokeratin stained section and in the center of some of these vasculocentric whorls, there were frequent aggregates of neutrophilic granulocytes. There was no necrosis identified and no high-grade dysplasia was seen in the lining surface epithelium.

On immunohistochemistry the tumor cells revealed strong expression of broad spectrum cytokeratins (CK; AE1/3), which highlighted the whorling architecture of the tumor and small caliber vessels within the center of several of the whorls. (Fig. 2b, c). Both p63 and p40 were strongly expressed by the majority of the neoplastic cells.

On in-situ hybridization for EBV (EBER) with 3,3'-Diaminobenzidine (DAB) as chromogen, there was diffuse strong positive nuclear signal which also highlighted the whorling features (Fig. 2d).

Diagnosis

Non-keratinizing nasopharyngeal carcinoma predominantly composed of spindle cells and with a whorling architecture presenting with paraneoplastic dermatomyositis.

Discussion

In this report a patient with NK-NPC predominantly composed of spindle cells and with a whorling architecture is presented. This is to the best of my knowledge a hitherto undescribed pattern/architecture in NPC and is not mentioned in the 2017 WHO classification of NPC [4]. NK-NPC classically harbors a prominent reactive lymphoplasmacytic infiltrate and the malignant epithelial cells display either a small nested or individual cell distribution (Régaud-pattern), or syncytial sheets (Schminke-pattern). However, NK-NPC may show a range of uncommon histopathological features that deviate from the standard “text book appearance” referred to above. Uncommon morphological variants of NK-NPC include tumors with spindle cells, clear

Fig. 2 The neoplastic cells displayed malignant cytomorphological features and mitotic figures were easily discerned (a; circles). In the immunohistochemical study the neoplastic cells strongly expressed cytokeratins (AE1-3) which highlighted the nodular whorling architecture (b). On high-power light microscopical examination, small

caliber vessels were identified in some of the nodular whorls (c; arrow), occasionally with small aggregates of neutrophils (c). The neoplastic cells showed strong nuclear positivity for EBV (EBER-CISH), which also highlighted the nodular whorling architecture (d)

cells, pleomorphic (Reed-Sternberg like) cells, desmoplastic stroma, a granulomatous component, eosinophilic cytoplasmic globules, associated abundant eosinophilic or neutrophilic granulocytes, amyloid, and prominent papillarity [1]. Very rarely, a reticular myxoid pattern or adenomatous differentiation may be encountered [2].

When faced with a limited biopsy sample from the nasopharynx containing a spindle cell neoplasm with a whorling component, a wide range of neoplasms with meningeal, peripheral neural- or mesenchymal differentiation could be contemplated as differential diagnoses. Many spindle cell neoplasms may exhibit a component of whorling architecture and may occur in the head and neck region. These include meningioma (either ectopic or downgrowth from intracranial primary), dedifferentiated liposarcoma with meningotheelial whorls, low-grade fibromyxoid sarcoma, interdigitating reticulum cell-/follicular dendritic cell sarcoma, myofibroma, myopericytoma, perineurioma, vascular leiomyoma, cellular schwannoma and malignant peripheral nerve sheath tumor. To separate these entities from a NPC predominantly composed of spindle cells with a whorling architecture is easily done by IHC for cytokeratins and in-situ hybridization for EBV. The difficulty lies primarily in the awareness of that NPC rarely may show this histopathological pattern.

The patient in this report presented with symptoms of dermatomyositis (DMS) preceding the diagnosis of the carcinoma for two months. DMS is an idiopathic inflammatory demato-myopathy with a range of systemic and cutaneous manifestations that leads to significant variability in clinical presentation. The original DMS classification criteria were limited to muscle involvement and a limited number of cutaneous manifestations [5, 6], but the significant heterogeneity among DM patients is now recognized and amyopathic DM is now included as a defined subgroup [7]. The reported incidence of malignancy in patients with DTMS ranges from less than 7 to over 30% [8]. Worldwide, it appears that ovarian and breast cancer in females and lung cancer in males are common types of malignant tumors that are associated with DMS [8]. However, a wide variety of malignant tumor have shown association with DMS [9].

In Singapore, the most common malignant tumor associated with DMS is non-keratinizing NPC, accounting for at least 50% of cases [10, 11]. Similar findings have been reported from Malaysia, a country with a significant component of ethnic Chinese [12, 13], Hong Kong [14], Guangzhou in Southern China [15] and Taiwan [16]. Also the amyopathic variant of DMS may be associated with NPC [11, 17]. Therefore, in Singapore, a diagnosis of DMS immediately initiates examination of the nasopharynx including biopsy, which was the case in the patient presented herein. It is in this context important to be aware of that NPC may present, not only with regional but also metastatic disease, with

an endoscopically normal appearance of the nasopharynx, so called non-exophytic (“submucosal”) NPC [18]. Elevated plasma or serum levels of EBV DNA is highly indicative of the presence of NK-NPC [19, 20] and is an important piece of information pointing to the correct diagnosis in this group of patients, who require a deep nasopharyngeal biopsy under general anesthesia.

The risk of malignancy is highest within the first year of diagnosis and diagnosis of DMS and declines thereafter. However, reportedly, although rare, DMS may precede the NPC with several years and may then present with clinical exacerbation of the DMS [17]. This potential time lag between the diagnosis of DMS and malignancy is not specific for NPC, but has been reported for a wide variety of tumor types and the risk of developing a malignancy is increased until 5 years after a diagnosis of DMS [9].

In conclusion, a patient with an EBV-positive non-keratinizing nasopharyngeal carcinoma predominantly composed of spindle cells and with a hitherto undescribed whorling architecture is presented. The patient presented with symptoms of paraneoplastic dermatomyositis 2 months prior to the diagnosis of the nasopharyngeal carcinoma. The tumor was low stage (T1N0M0), partly due to rapid clinical investigation for nasopharyngeal carcinoma after the diagnosis of dermatomyositis was established. This procedure is based on the statistically strong association between dermatomyositis and nasopharyngeal carcinoma in patient of Chinese ethnicity.

Compliance with Ethical Standards

Conflict of interest The author has no conflict of interest. No funding was received.

Ethical Approval It is my institution’s policy not to require formal ethical approval for reports on up to two patients.

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