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EDITORIAL

Basaloid squamous cell carcinoma of the upper aerodigestive tract: a single squamous cell carcinoma subtype or two distinct entities hiding under one histologic pattern?

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Recent advances in our understanding of the etiology and biology of malignant epithelial neoplasms together with more sophisticated diagnostic techniques mean that a pathological diagnosis of squamous cell carcinoma (SCC) without any other specifications is now inadequate, even for incisional biopsy specimens. Invasive SCC can be graded into well, moderately and poorly differentiated. Verrucous carcinoma, a non-metastasizing variant of SCC, was described in 1948 [1], and since then, at least seven more variants or subtypes of SCC have been described and assigned specific ICD-O codes; together these variants account for around 15% of all SCCs [2]. Basaloid squamous cell carcinoma (BSCC) is one of the more common subtypes with several series reported [3–10] since the original description of ten cases by Wain et al. [11] in 1986. BSCC is defined by the World Health Organization (WHO) [12] as "an aggressive, high-grade variant of SCC composed of both basaloid and squamous components".

The histopathology of BSCC is characteristic [12]. The cells of the basaloid component are small with round, hyperchromatic nuclei that usually lack nucleoli, and are arranged in lobules with prominent peripheral palisading

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and frequent comedo-type necrosis. Small cystic spaces containing basophilic PAS- and Alcian blue-positive material and stromal hyalinization are the additional features that help us to differentiate BSCC from poorly differentiated conventional SCC [12]. An additional architectural finding that has been emphasized by some, on low magnification, is a "jigsaw puzzle" arrangement of the tumor nests whereby they appear to mould to each other, being separated only by thin, regular lines of hyalinized, eosinophilic stroma. There are abundant apoptosis and mitotic activity. The maturing squamous component may be in situ, or frankly invasive keratinizing type SCC, or more often, is seen only as abrupt, focal keratinization within the basaloid tumor nests. Metastatic deposits may consist of one or both components [12].

In addition to poorly differentiated conventional SCC, the differential diagnosis of BSCC includes neuroendocrine carcinoma, adenoid cystic carcinoma, adenosquamous carcinoma and adenocarcinoma, not otherwise specified (NOS). Immunohistochemically, BSCC has an expression profile identical to the typical keratinizing-type SCC, characterized by positive anti-cytokeratin 34 betaE12 and cytokeratin CK5/6 staining of the basaloid cells and the absence of neuroendocrine markers such as chromogranin, synaptophysin and glial-fibrillary acidic protein [2, 13–15]. The absence of myoepithelial cells and the presence of dot-like vimentin expression in BSCC aids in the differentiation from adenoid cystic carcinoma [12]. Additionally, different staining patterns with p63 also are of aid in excluding solid (grade III) adenoid cystic carcinoma. BSCC will consistently have strong, diffuse p63 expression whereas solid adenoid cystic carcinoma has patchy staining with areas where staining is limited to a few nuclei at the periphery of the nests (this staining pattern represents myoepithelial differentiation) [16, 17].

Electron microscopy shows desmosomes and tonofilaments in both the basaloid and the squamous components of BSCC but no secretory or neurosecretory granules and no myofilaments [12]. True ducto-glandular differentiation and intracellular mucins are seen only in adenosquamous carcinoma and adenocarcinoma NOS and are, therefore, useful distinguishing features [12]. The latter two tumors rarely have a solid carcinoma component that is as distinctly basaloid as BSCC.

It is thought that BSCC originates from totipotent primitive cells within the basal layer of the surface epithelium or the proximal ducts of minor salivary glands [3, 11]. Ereño et al. [18] speculated that BSCC originates from tissues derived from the primitive digestive tube, where endodermal and ectodermal field meet. Most BSCCs arise within the oropharynx, especially the base of tongue, the pyriform sinus of the hypopharynx and the supraglottic larynx [11]. The oral cavity is less commonly affected [9] and lesions arising within the nasopharynx, nasal cavity, and paranasal sinuses are rare [19].

Aggressive, high-grade behavior forms part of the WHO definition of BSCC [12], and is based on several reports of advanced stage at presentation, high rates of regional and distant metastases, and poor outcomes [3, 6, 9, 13, 20]. However, reports of aggressive behavior have been disputed by some authors; indeed, several studies [8, 21, 22] matching BSCC with moderately or poorly differentiated conventional SCC of similar site and stage have demonstrated similar biologic courses and outcomes among the two groups of patients. Recently, Thariat et al. [2] reported similar or better locoregional control rates and a relatively better radiosensitivity for BSCC than for conventional SCC and suggested that BSCC exhibits a dual behavior based on etiology.

When first described, the typical patient with BSCC was an elderly male with a history of heavy tobacco and/or alcohol use [11]. More recently, BSCC is increasingly seen in younger age groups and females without a history of tobacco or heavy alcohol use. Instead, infection with human papillomavirus (HPV), particularly type 16, is emerging as an important etiological factor [2, 10, 23]. Viral access to basal mucosal cells in the tonsillar crypts is easy and either palatine or lingual tonsils have an apparent predilection to transformation by HPV, analogous to the cervical transformation zone [24].

HPV-associated carcinomas affect predominantly the oropharynx, have a poorly differentiated, non-keratinizing morphology with basal/basaloid cell features, and have a high rate of cervical lymph node metastases, often with cystic change [25, 26]. Increased radiosensitivity and better prognosis among HPV-associated tumors have been widely reported [27–30].

As HPV is an important etiological and prognostic factor in a subset of BSCC, this very likely explains the inconsistencies in clinical outcome among the reports in the literature. Series that included a high proportion of oropharyngeal cases seem to have had a more favorable outcome due to the inclusion of more HPV-associated tumors. The series of Thariat et al. [8] is a classic example with 85% oropharyngeal SCCs and no HPV testing. Begum and Westra [23] identified HPV-16 by in situ hybridization in 76% of 21 oropharyngeal BSCCs and only 1 (6%) of 32 BSCCs at non-oropharyngeal sites. They confirmed that patients with HPV-positive carcinomas were more likely to present with lymph node metastases, yet showed a better overall survival. Chernock et al. [10] identified high-risk HPV by in situ hybridization in 9 of 12 oropharyngeal BSCCs but in none of the 16 non-oropharyngeal BSCCs. Prognosis was distinctly better for the HPV-positive BSCCs than for the HPV-negative ones [10]. Interestingly,

the three oropharyngeal BSCCs in their series which were HPV-negative, although a very small group, had poor clinical outcomes.

Current evidence suggests that despite the similar morphological features, oropharyngeal BSCCs can be separated into two groups not on the basis of light microscopy, but rather as a function of HPV status. The distinction is important since HPV-16 (or other high risk HPV) positivity in SCC of the head and neck is a powerful indicator of sensitivity to radiotherapy and improved survival, regardless of the treatment type. HPV-negative BSCC is associated with a high rate of systemic metastases and poor outcome. A thorough imaging workup at primary diagnosis and more aggressive multimodality therapy, in the absence of apparent distant metastasis, may be warranted [10, 23]. Screening for HPV, by immunohistochemical staining for p16, is becoming increasingly common in the workup of oropharyngeal cancers, with positive cases demonstrating improved outcomes with almost all having detectable high risk HPV by whatever testing method chosen, most frequently by in situ hybridization.

So, recent findings show that BSCC is not a uniform entity. Oropharyngeal BSCC, which constitutes the majority of cases, appears to be divisible into better and worse prognostic groups by HPV status. We feel that these tumors should be divided into two groups: (1) HPV-positive oropharyngeal BSCC and (2) HPV-negative oropharyngeal BSCC plus non-oropharyngeal BSCC. Practically speaking, this means performing p16 and/or HPV-specific testing on all oropharyngeal BSCC. Emphasis must be placed on the fact that despite the morphology, when arising in the oropharynx and HPV-positive, BSCC has a biology and prognosis apparently equivalent to typical HPV-positive oropharyngeal SCC. For simplicity, such tumors could be grouped simply with all other "HPV-positive" oropharyngeal SCC. This would simplify the management to identify the best therapeutic strategies, allow for patient stratification in clinical trials and provide accurate, meaningful outcome data.

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