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■ REVIEW ■

Basaloid Squamous Cell Carcinoma of the Upper Aerodigestive Tract

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Basaloid squamous cell carcinoma (BSCC) is an uncommon variant of squamous cell carcinoma (SCC), usually occurring in the larynx, hypopharynx, oropharynx and esophagus. BSCCs have been reported from various geographic areas, but esophageal BSCCs are more prevalent in Asia. The morphology of BSCC is quite characteristic, but BSCC occasionally needs to be differentiated from neuroendocrine carcinoma or adenoid cystic carcinoma. Human papillomavirus16-associated oropharyngeal SCC with poorly differentiated or basaloid features has recently been recognized as a new clinical entity with a different etiology and prognosis. Nonoropharyngeal BSCC appears to share etiologic factors, genetic alterations and an immunoprofile with conventional SCC of the upper aerodigestive tract. However, the divergent differentiation of BSCC into various non-basaloid, epithelial or mesenchymal elements suggests the participation of more mulipotential cells than in SCC. The biologic behavior of BSCC has been reported to be worse than or equal to that of SCC, yet the data including the increasing numbers of human papillomavirus-associated cases now require reanalysis. It is presently uncertain whether BSCC is a histogenetically or clinically unique disease entity.

Key Words : Carcinoma, basaloid squamous cell; Head and neck neoplasms; Esophagus

Basaloid squamous cell carcinoma (BSCC) is an uncommon variant of squamous cell carcinoma (SCC), first described in 1986 by Wain *et al.*[1] It is now listed as a subtype of SCC in the World Health Organization (WHO) classification of tumours of the nasal cavity/paranasal sinuses, nasopharynx, hypopharynx/larynx/trachea, oral cavity/oropharynx and esophagus.[2,3] Awareness of its distinct morphology has enabled the diagnosis of BSCC to be made without much difficulty, yet the histogenesis, histological diversity and biologic behavior of BSCC are still being actively investigated. Moreover, the recent recognition of human papillomavirus (HPV)16-associated oropharyngeal SCC with poorly differentiated or basaloid features as a different clinical entity has brought considerable confusion to the true identity of BSCC.[4] This paper focuses on covering the current knowledge on traditional BSCC of the head and neck (HN) and the esophagus through a literature review, along with briefly discussing the HPV16-associated oropharyngeal carcinomas, which deserve examination in a separate review.

Epidemiology and localization

BSCC of the upper aerodigestive tract (BSCCUADT) have been reported from various countries in North and South America, Western Europe, the Mediterranean area and East Asia.[5-9] It may seems that there is a global distribution of BSCCUADT, but different trends are present when the location of this cancer is divided into the HN and the esophagus. Among the approximate 500 reported cases of HN BSCC, more than 80% were from western countries including the USA, France, Italy, Spain, and Germany,[10-14] while more than 80% of approximate 200 reported cases of esophageal BSCC were from East Asia, including Japan, Korea, China, and Hong Kong,[15-18] where the incidences of esophageal cancers are relatively high. BSCC of both the HN and esophagus usually occurs in aged men. According to 15 studies that have available data, the male to female ratio is reported to be 5 : 1, and the mean age is 62.3 years with narrow deviations.[6,9,12,14,19-21] Esophageal BSCC has shown stronger male preponderance (8 : 1),[16-18] and white males are more predominant than black males, as reported by the papers from the USA.[21-22]

The first report by Wain *et al.*[1] included 4 hypopharyngeal (pyriform sinus), 3 laryngeal (supraglottic) and 3 oral (base of tongue) BSCCs, and those three are the most commonly involved HN sites to date. Aside from HPV-associated oropharyngeal carcinomas, the most frequently reported single site for BSCC is the esophagus (more than 200 cases),[15-18,22-27] followed by the

larynx (about 140 cases),[13,14,19,21,28-30] the hypopharynx (about 100 cases),[5,9,12,21,31,32] the oral cavity (about 80 cases)[7,9,21,33] and the nasopharynx/sinonasal tract (about 30 cases).[20,31,34]

Etiology and the genetic background

Many of the risk factors for BSCCUADT are shared with conventional SCC of the UADT. Histories of tobacco and alcohol abuse were recorded for many patients with BSCC.[6,9,22,28,30] A few cases with histories of radiation or chemical exposure have also been reported.[20,34]

Among the oncogenic viruses, HPV has long been studied as a causal agent of HN SCC. Since the first description by Brandsma and Abramson in 1989,[35] the predilection of HPV, and especially type 16, for SCC of the oropharyngeal location has been confirmed by many researchers. HPV16-associated oropharyngeal SCC has recently been recognized as a new clinical entity with characteristics that distinguish it from HPV-negative HN SCC.[4] This subset has disordered the identity of BSCCUADT because the HPV16-associated oropharyngeal carcinomas tend to show a poorly differentiated or basaloid morphology.[36] To avoid confusion, Begum and Westra[31] have suggested classifying these tumors as 'nonkeratinizing SCC' and to suspend use of the term 'basaloid' to the comment section. However, much of the data on BSCC still include the oropharyngeal cases. BSCCs of the nonoropharyngeal sites and esophagus have shown zero or very low positivity rates for HPV DNA, as assessed in situ hybridization (ISH) and/or polymerase chain reaction.[6,22,31]

Besides HPV, Wan *et al.*[34] reported that nasopharyngeal BSCCs were associated with Epstein-Barr virus (EBV), as assessed by ISH for EBV-encoded small nuclear RNA, while the BSCCs of other sites were not. The presence of human herpes virus in BSCC has also been reported.[5]

p53 is the most commonly altered oncogene in HN SCC, and p53 is reported to be overexpressed in 40-80% of the cases of BSCCUADT.[7,10,14,16,19,37,38] Many studies have tried to explore the differences in the p53 status of BSCC as compared to that of conventional SCC. The results have been variable, with higher,[25] equal[23] or lower expression rates in BSCC as compared to those in SCC.[22,33] However, the differences were mostly insignificant, suggesting a major role of p53 mutation in the pathogenesis of BSCC, like that in the pathogenesis of conventional HN SCC. The loss of heterozygosity (LOH) on chromosome 9p was also reported to be equal to or more frequent in BSCC as compared with that of SCC.[10,39] LOH on 9q, 11q, chromosome 17, the adenomatous polyposis coli gene and the mutated in colorectal cancer gene was detected in some cases.[10,25,39]

A small number of studies on other cell cycle-related genes have been carried out, and they have shown relatively low expression rates for p16 (0-33%), p27 (19%) or cyclin D1 (37%), and the loss of Rb (9-50%).[10,16,19,22,25] A few cases with p16 methylation were also recorded.[10] Sarbia *et al.*[40] showed a higher rate of c-myc amplification (48%) in BSCC than that in typical SCC (26%). They also found a bcl-2 expression significantly more often in BSCC (87%) than that in SCC (17%), indicating the coactivation of c-myc and bcl-2 is the molecular pathogenesis of esophageal BSCC. The relatively high expression rates (50-100%) of BSCC for bcl-2 were reported in other papers as well, with this being interpreted that BSCC has a high proliferative activity or a basal cell character.[29,40,41]

Pathologic aspects

More often than conventional SCC, BSCCUADT tends to grow exophytically and and present as fungating or polypoid masses (Fig. 1). Histologically, BSCC is a biphasic tumor that generally consists of monotonous small undifferentiated cells. These basaloid cells form well demarcated large lobules or smaller nests with smooth rounded margins (Fig. 2A). The inner parts of the large lobules commonly show extensive comedo-type necrosis (Fig. 2B) or cribriform-like pseudoacini formation (Fig. 2C), which are diagnostic for BSCC, but these features are also reminiscent of ductal carcinoma or adenoid cystic carcinoma. The smaller nests tend to be solid in texture (Fig. 2A). Abrupt central foci of keratin pearl formation were described in the earlier reported cases.[1,21,30] The occasionally seen festoon- or

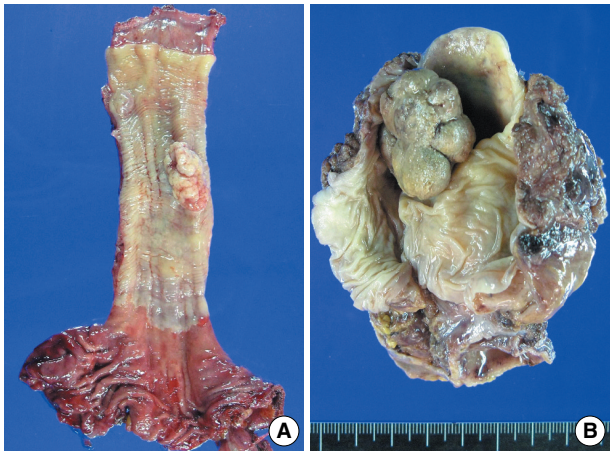

Fig. 1. Basaloid squamous cell carcinomas of the esophagus (A) and the hypopharynx (B) show intraluminally protruding gross features.

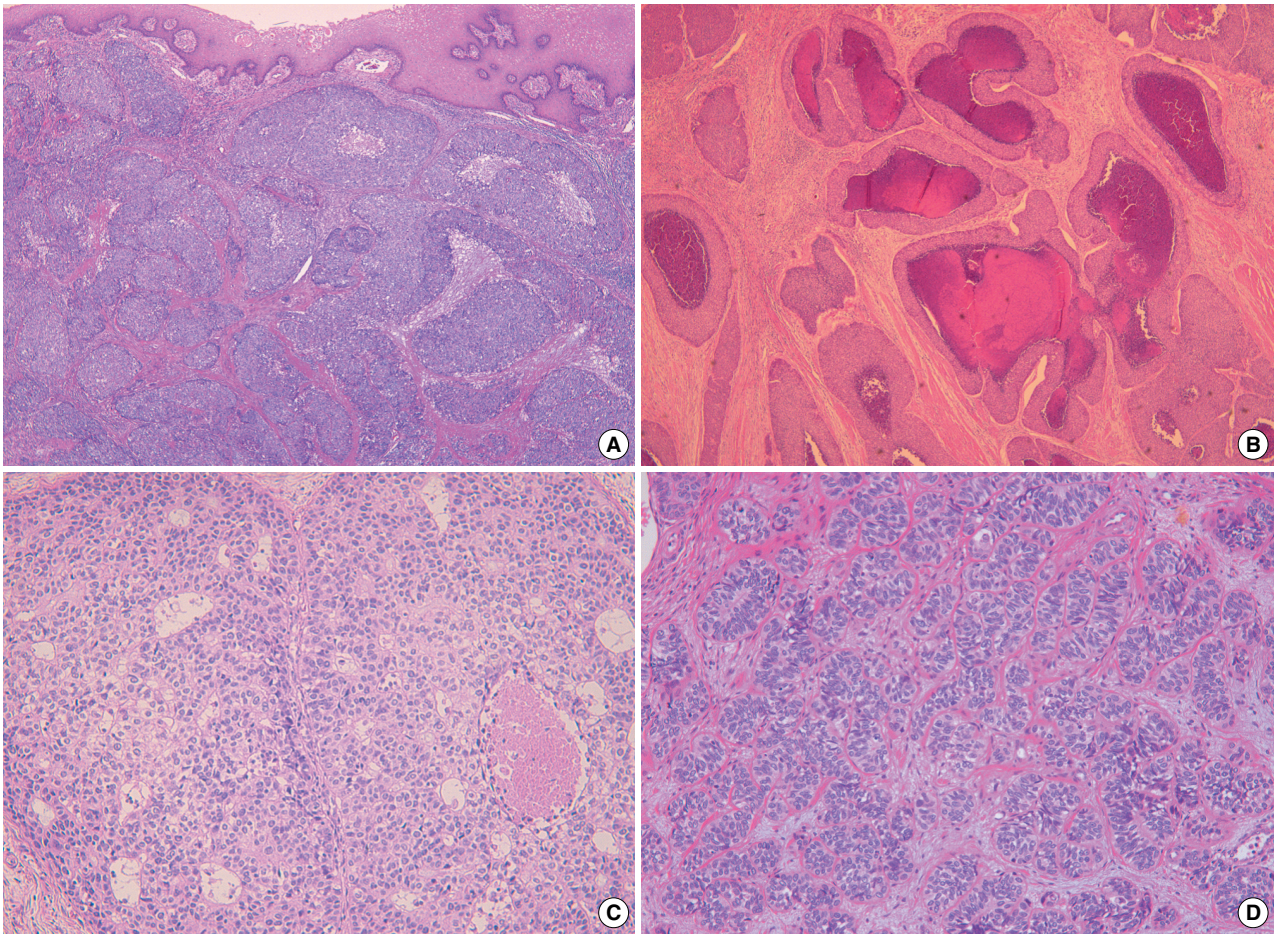

Fig. 2. Basaloid squamous cell carcinomas miscroscopically consist of smooth-margined cellular nests and lobules (A). The small nests are solid, but the large lobules commonly show comedo-type necrosis (B) or a cribriform pattern (C). The tumor cells are often arranged in a ribbon-like pattern (D).

ribbon-like arrangement of tumor cells can resemble neuroendocrine carcinoma (NEC) (Fig. 2D). The individual cells are small to medium-sized with hyperchromatic round to oval nuclei and a small amount of cytoplasm (Fig. 3A). The nuclei show finely granular chromatin, small nucleoli and mild pleomorphism, but the mitotic activity can be brisk (Fig. 3B). The cell membranes are distinct and they are tightly opposed each other. The cytoplasm is usually pale, eosinophilic and granular, but it may be clear or mucinous (Fig. 3B, C). The stroma is usually rich and desmoplastic, and it is often hyalinized along the cell border like a basement membrane (Fig. 3C). Nuclear palisading can occasionally be seen at the periphery of cell nests (Fig. 3D).

The second component of BSCC is concomitant typical SCC. The SCC components are adjacent to, but distinct from the basaloid areas without transitional zones. They are variable in amount, in the form of invasive carcinoma (Fig. 4A), carcinoma in situ (Fig. 4B) or both. The absence of squamous components does not exclude the diagnosis of BSCC if the above mentioned features of BSCC are present. Since the SCC areas can be very small, they might have escaped being sampled.

BSCCUADT infrequently harbors non-basaloid components other than SCC. The presence of spindle cell components (Fig. 4C) could cause diagnostic difficulty.[42] Interestingly, the spindle cell components of HN BSCC have mostly proved to be spindle cell carcinoma on the basis of their expression of epithelial markers,[42] but in esophageal BSCC, true sarcomas with specific differentiation, including osteosarcoma, rhabdomyosarcoma, and chondrosarcoma, have been recognized.[43-45] The reports on coexistent small cell neuroendocrine,[16,27] adenocarcinomatous (Fig. 4D),[16,27,38,44] or myoepithelial differentiation have also been restricted to the esophageal cases.[44,46] These findings could lead to a hypothesis that BSCCUADT are tumors of multipotential cells that display multidirectional differentiation, but their plasticity may vary according to the anatomic sites.

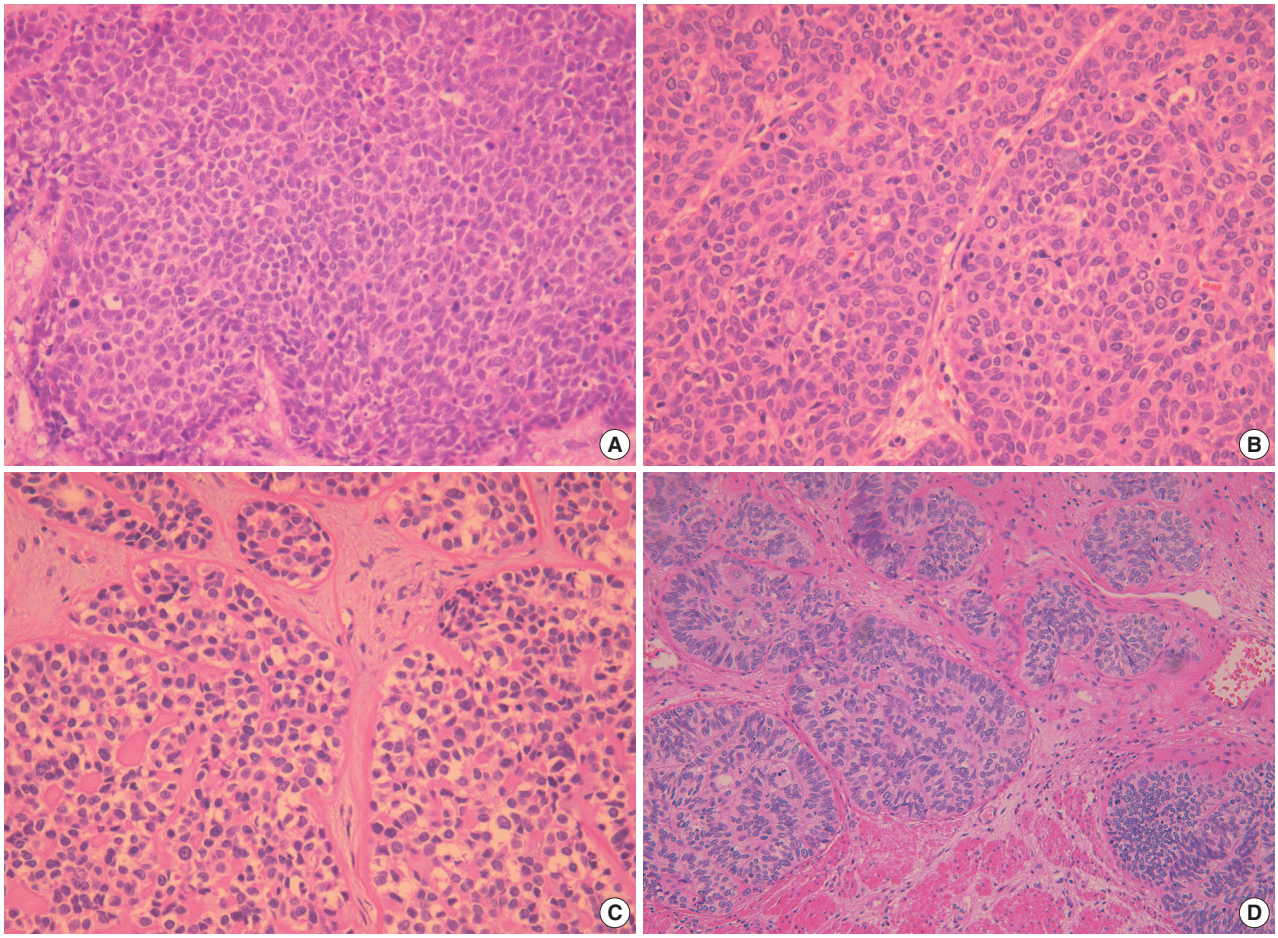

Fig. 3. The basaloid tumor cells are small and monotonous with round to oval nuclei, mild pleomorphism and scanty cytoplasm (A). Frequent mitotic figures and focal mucin-containing cells are seen (B). The basement membrane-like hyalinized stroma is bordering the tumor cells that have clear cytoplasm (C). The tumor cells occasionally show nuclear palisading at the periphery (D).

Immunoprofiles and differential diagnoses

Many investigators have performed immunohistochemical studies on BSCCUADT to search for characteristics that are different from those of conventional SCC or for making the differential diagnosis from NEC or adenoid cystic carcinoma (ACC).

The labeling indices of BSCCUADT for proliferative activity markers such as proliferating cell nuclear antigen or Ki-67 were generally high (50-100%). When compared with those of matched SCC, the labeling indices of BSCC were either equal[23,29,33,37] or higher[7,15,17]. Most authors have failed to find any clinical significance of the labeling indices for the proliferative activity of BSCC.[29,33] Vague association between a lower Ki-67 labeling index and better survival or better clinicopathologic data has been reported.[14,19]

Among the cytokeratins (CK) of various molecular weights, BSCCAUDT has shown high positivity rates for the high molecular weight and basal type CK, including 34βE12, CK5/6, CK14, and CK19.[6,23] 34βE12, which is a cocktail antibody for CK1, 5, 10, and 14, demonstrated immunostaining in 95-100% of BSCCs.[21,32,47] Serrano *et al.*[32] showed that all 18 HN BSCCs were positive for CK5/6, and our similar study showed positivity for CK5/6 in 14 out of 18 HN BSCCs (data not published). The CK14 and CK19 positivity has tended to be restricted to the periphery of the solid nests.[18,38] The absent or infrequent expression of CK1, CK4, CK7, CK8, and CK18 has been described,[7,15,26] but CK7 was detected in 4 of the 18 BSCCs in our study (data not published). The expression of CK13, which labels differentiating squamous cells, was reported to be less extensive in BSCC than that in SCC.[7] Overall, the CK subtype expression patterns of BSCC did not greatly differ from those of SCC, but these expression patterns are rather useful for making the differential diagnosis from NEC or ACC.

BSCCUADT may look like NEC because of their undiffer-

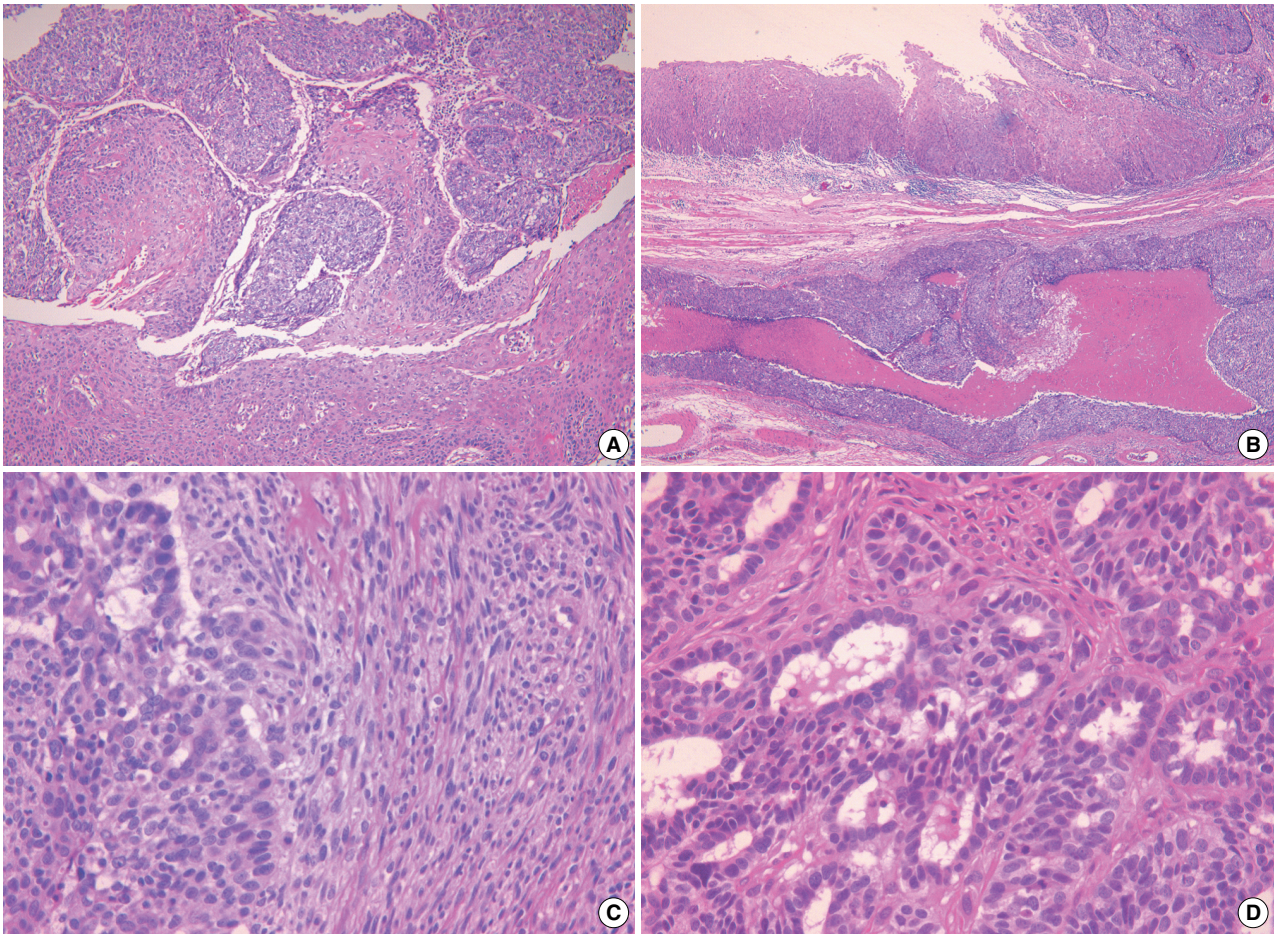

Fig. 4. Concomitant invasive squamous cell carcinoma nests (lower area) are distinguishable from the basaloid nests (upper areas) (A). Squamous cell carcinoma in situ is neighboring the basaloid components (B). Spindle cells (C) and glandular differentiation (D) are observed.

entiated nature, their relatively monotonous nuclear features, their rounded or festoon-like organoid pattern, or their peripheral palisading. Especially, esophageal BSCC might be confused with small cell carcinomas, which rarely occur in the esophagus, and are occasionally accompanied by SCC components. In the larynx, BSCC may be mistaken for large cell NEC, which shares the supraglottic predilection with BSCC. Unfortunately, making the differential diagnosis between BSCC and NEC may not be aided by immunohistochemical study. Since variable reactivities of BSCC for neuroendocrine markers, including neuron-specific enolase, chromogranin and synaptophysin, have been described,[21,28,32] the expression of these markers cannot exclude BSCC. Morice and Ferreiro[47] suggested that 34βE12 immunostaining was more useful than the neuroendocrine markers for distinguishing BSCC from small cell carcinoma. Serrano *et al.*[32] also mentioned the diffuse positivity of BSCC for 34βE12 and CK5/6 in comparison with the absent or only focal positivity of NEC. Nevertheless, there also are many studies that have reported negative reactions of BSCC to synaptophysin, chromogranin or CD56.[6,15,16,20] Careful interpretation of both the histologic and immunohistochemical findings can provide enough differential points between those two tumors.

The cribriform pattern of BSCC had led to the misdiagnoses of ACC in the past.[48] For making the differential diagnosis between these two categories, the immunostaining may again not be of great help. Smooth muscle actin (SMA) positivity is highly suggestive of ACC, but BSCC has also been reported to show an infrequent SMA expression.[15,18,20,32] SMA was not detected in BSCC by many other papers.[21,27,47] 34βE12 was diffusely positive in both BSCC and solid ACC.[32] p63, which is a member of the p53 tumor suppressor family and is expressed in the nuclei of basal cells, was also positive in both tumors, but with different patterns.[32,49] While all the BSCC cases show diffuse p63 positivity, the p63 staining in ACC is restricted at the periphery of

cell nests. On E-cadherin immunostaining, BSCC showed a reduced expression,[14] and a decreased E-cadherin and α-catenin expression was more frequent in BSCC than that in ACC.[26] With or without immunohistochemical study, ACC can be differentiated from BSCC by its bland nuclear morphology and the absence of comedo-type necrosis.

Biologic behavior and prognostic factors

There have been different points of view regarding the biologic behavior of BSCCUADT. Since BSCC was initially known to be a very aggressive tumor,[21,30] many clinical studies were conducted with matched SCC patients. Their results showed that the prognoses of BSCC appear to be the same as[11,17,29,33] or worse than those of SCC.[7,12] However, the recognition of HPV16-associated oropharyngeal carcinoma, which is believed to be less aggressive with higher radiosensitivity, and its inclusion in BSCCUADT have been blurring the true clinical significance of BSCC. Recent studies from France and USA with 62 and 51 patients with BSCC, respectively, resulted in different conclusions. The former group (the 62 BSCC patients from France) demonstrated significantly higher mortality for the BSCC patients who were treated by various modalities in comparison with 62 patients with SCC,[12] while the latter group (the 51 BSCC patients from the USA) failed to confirm a worse prognosis for the BSCC patients after radiotherapy, compared with the prognosis of 431 poorly differentiated SCC patients and 525 well or moderately differentiated SCC patients.[11] The latter group included more oropharyngeal cases (43 of 51) than the former group did (19 of 62), and the latter group's results might have benefited from the better outcomes of the oropharyngeal BSCC patients. According to Begum and Westra,[31] 76% and 86% of 21 oropharyngeal BSCCs and 5% and 28% of 32 nonoropharyngeal BSCCs were positive for HPV16 and p16, respectively, and the absence of HPV16 was significantly associated with decreased overall survival. There have been additional opinions that the p16 status of oropharyngeal carcinoma is a more important prognostic factor than HPV16.[50] It seems that at this moment, the clinical significance of BSCC cannot be determined before reanalyzing all these recent findings.

Aside from HPV, Salerno *et al.*[19] reported that low levels of a p27 expression were significantly correlated with a poor prognosis for 16 patients with BSCC of the larynx. Marioni *et al.*[13] reported that a high nuclear expression of survivin is associated with disease recurrence and a poor prognosis in 9 patients with laryngeal BSCC. Koide *et al.*[41] reported that esophageal BSCCs with distant metastasis showed a strong expression of vascular endothelial growth factor, but the number of cases was limited. Lam *et al.*[17] studied the telomerase activity of 20 esophageal BSCCs, and they showed correlation of high telomerase activity with shorter survival.

Summary

BSCCUADT is a morphologically distinct neoplasm that has a predilection for the esophagus, larynx, hypopharynx and oropharynx. The cases of oropharyngeal BSCCs have recently been separated on the basis of their association with HPV16 and a better prognosis. The basaloid morphology and divergent differentiation of BSCC suggest participation of multipotential cells. It is presently uncertain whether the BSCC is a histogenetically or clinically unique disease entity.

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