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Submucosal gland differentiation and implications in esophageal basaloid squamous cell carcinomas

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Keywords: basaloid squamous cell carcinoma, esophagus, lymph node metastasis, classification, differentiation.

Short title: SGD in esophageal BSCC

Abbreviations:

SCC, squamous cell carcinoma; BSCC, basaloid squamous cell carcinoma; SGD, submucosal gland differentiation; LNM, lymph node metastasis; IHC, Immunohistochemical; HPV, human papillomavirus; CK, cytokeratin.

Abstract

Esophageal basaloid squamous cell carcinoma (BSCC) is a heterogeneous entity with multilineage differentiation. It lacks systematical analysis on submucosal gland differentiation (SGD) due to the histological diversity and low incidence of esophageal BSCC. This study aims to find the correlation of SGD and clinicopathological features. A total of 152 esophageal BSCCs were separated into three histological groups: pure, mixed, and borderline group. The clinicopathological features were compared between different groups. The prevalence of SGD was also compared between cases of different groups. A panel of antibodies were used to identify SGD. The pure group differed from the mixed and borderline groups in many aspects, lymph node metastasis (LNM), cancer embolus, perineural invasion, and advanced stage occurred less frequently in the pure group ($P<0.01$). The pure group had a better but statistically insignificant overall survival ($P=0.097$). The squamous cell carcinoma (SCC) component or focal squamous differentiation was present in metastatic lymph node in almost all mixed BSCCs (95.7%, 22/23) with LNM. The LNM rate of superficial (T1b) BSCCs (17.6%, 6/34) was comparable to that of superficial (T1b) SCCs (18.5%, 57/308). However, LNM exclusively occurred in superficial mixed (3/5) and borderline (3/10) BSCCs. The IHC results demonstrated a prevalence of SGD in pure group (77%, 43/56). SGD is considered to be a favorable
factor, while the squamous differentiation or invasive SCC component is an adverse factor in esophageal BSCCs. Refinement of classification is a promising way to improve patient management.

Introduction

Previous pathological analyses demonstrated that basaloid squamous cell carcinoma (BSCC) is a distinct neoplasm with multipotential differentiation, and most cases show squamous and/or submucosal gland differentiation (SGD) (Cho et al., 2000; Li et al., 2004; Kobayashi et al., 2009). The histological features of BSCC can be further divided into several specific patterns: solid nest with or without central necrosis, microcyst and/or trabecular nest, invasive squamous cell carcinoma (SCC), duct, and cribriform pattern. Solid nest, microcyst and/or trabecular nest, and invasive SCC are the most common elements. Immunohistochemical (IHC) results demonstrate a prevalence of SGD in esophageal BSCCs (Kobayashi et al., 2009). Adenoid cystic carcinoma-like features are detected in more than half of cases (Li et al., 2004). However, analysis on SGD is rare due to the histological diversity and low incidence of esophageal BSCC.

The prognosis of esophageal BSCC is generally comparable to or worse than that of common SCC (Sarbia et al., 1997; Zhang et al., 1998; Lam et al., 2001; Salami et al., 2018). To be specific, the clinical outcome is similar to that of poorly and moderately differentiated SCC but worse than that of well differentiated SCC (Chen et al., 2012; Imamhasan et al., 2012; Xu et al., 2021). Most reported esophageal BSCCs are advanced cases, only a few studies focus on superficial cases (Tauchi et al., 1990; Ohashi et al., 2003; Oguma et al., 2017). In these studies, superficial BSCCs show an unexpectedly similar or better prognosis compared to superficial SCCs. Superficial BSCCs display a lower rate of lymph node metastasis (LNM) than superficial SCCs and mixed carcinomas, as well as the frequency of lymphatic invasion (Oguma et al., 2017). The underlying mechanism of the discrepancy has not been elucidated.
In this study, esophageal BSCCs were divided into three histological groups, and the frequency of metastasis and other clinicopathological features were compared between these groups. In addition, IHC examination was performed to identify the frequency of SGD in different groups.

Materials and Methods

Case selection

A total of 2699 surgically resected and 961 endoscopically resected cases of esophageal SCC were archived in Nanjing Drum Tower Hospital between January 2006 and April 2021. The cases with a diagnosis of BSCC were retrieved. The clinical records, pathological characteristics and survival information of these cases were analyzed.

Microscopic examination

Esophageal BSCCs can be separated into three histological groups: pure, mixed, and borderline group. Pure BSCCs showed tumor nests with solid, microcystic, trabecular, cribriform, and ductal patterns. Comedonecrosis can be seen in solid tumor nests. Palisade structure and well-demarcated outline were essential characteristics of pure BSCC and the major distinctions from borderline BSCC. Typical invasive SCC component and/or focal or patchy squamous differentiation were characteristics of mixed BSCCs. Borderline BSCCs consisted of solid tumor nests without conspicuous characteristics of basal (palisade structure, well-demarcated outline), glandular (ductal, microcystic, and cribriform structure) or squamous (keratin pearl) cells. SGD, lymph node and distant metastasis, tumor deposit, perineural invasion, and cancer embolus were compared between different histological groups. The intramucosal SCC components were excluded from histological analysis.

IHC analysis

IHC examination was performed in cases with sufficient tumor tissue. For BSCCs with heterogeneous morphology, sections harboring the characteristic component
were chosen. The used antibodies were P53 (DO7, dilution 1:150; ZSGB-BIO, Beijing, China), Ki67 (MIB-1, dilution 1:300; Dako, Glostrup, Denmark), P16 (1C1, dilution 1:150; ZSGB-BIO, Beijing, China), MYB (EP769Y, dilution 1:200; Abcam, Cambridge, UK), SOX10 (EP268, ready-to-use; ZSGB-BIO, Beijing, China), P63 (4A4, dilution 1:150; Abcam, Cambridge, UK), CK5/6 (D5/16B4, dilution 1:200; Dako, Glostrup, Denmark), S100 (Z0311, dilution 1:1000; Dako, Glostrup, Denmark), Calponin (CALP, dilution 1:200; Dako, Glostrup, Denmark), CK8/18 (B22.1&B23.1, ready-to-use; ZSGB-BIO, Beijing, China), CK7 (OV-TL12/30, dilution 1:150; Dako, Glostrup, Denmark). The EnVision+ method was used according to the vendor’s protocol. Appropriate positive and negative controls were conducted. The MYB was regarded as positive when strong nuclear staining was present. P53 staining was graded as negative (wild type, weak or uneven staining intensity), and positive (mutational type, diffusely strong positivity or absence of staining). Other markers were scored according to the proportion of cells staining negative (0% to 5%), positive (5% to 60%), and diffusely positive (60% to 100%).

The submucosal gland of the esophagus consists of intralobular and extralobular sections, and SGD can be specified as acinar and/or ductal differentiation. The positivity of SOX10, S100 or Calponin was assumed to be evidence of acinar differentiation, and heterogenous positivity of CK7, CK8/18, CK5/6, and P63 was evidence of ductal differentiation. We considered SGD when the acinar and/or ductal staining patterns appeared.

Statistical analysis
The categorical variables were analyzed using the $\chi^2$ or Fisher exact test. Continuous data were analyzed using $t$ test or the Mann-Whitney U test. The survival analysis was performed using the Kaplan-Meier method, and differences between survival curves were determined using log-rank tests. Results were regarded as significant when the $P$-value was less than 0.05. The software GraphPad Prism 6.0 (GraphPad Prism Software Inc, San Diego, CA) was used.
Results

Clinicopathological features

A total of 156 cases with a diagnosis of BSCC were retrieved. Four cases were excluded from further analysis because they harbored a synchronal SCC or adenocarcinoma (AC) that hampered further clinicopathological analysis. The clinical and pathological features of the remaining 152 cases were summarized (Table 1). Fifteen patients received endoscopic submucosal dissection (ESD), and the other patients received esophagectomy. Tumor residual was found in 18 cases. Two patients with ESD therapy later received additional esophagectomy. Because most older cases were lost to follow up, the survival information was only collected from cases that occurred after the year 2012. The pure group showed a better overall survival (Fig. 1), but the difference was not statistically significant ($P=0.097$).

The pure BSCCs consisted of basaloid cells arranged as solid, ductal, microcystic, and cribriform patterns. The palisade structure was apparent, forming a well-demarcated outline (Fig. 2). Mixed BSCCs were divided into combined and intermingled type based on the mixing pattern. The combined type exhibited a combination of discriminable pure BSCC and typical SCC component (Fig. 3), and the intermingled type showed focal or patchy squamous cell differentiation in tumor nests of pure BSCC. The indicators for squamous differentiation included abundant clear or eosinophilic cytoplasm, clear cell boundary, intercellular bridges, and presence of dyskeratosis and/or keratin pearls (Fig. 4). The borderline BSCCs were composed of solid tumor nests without conspicuous palisade structure and well-demarcated outline, the basaloid tumor cells lacked clear histological lineage differentiation. Irregular infiltration and stromal fibrosis were easily observed (Fig. 5).

There was no significant difference in gender and age of the patients, and tumor deposit between histological groups. Distant metastasis was rare in all groups. The only difference between mixed and borderline group was that the former group had a
smaller tumor size \((P=0.03)\). In contrast, the pure group differed from the mixed and borderline group in many aspects, LNM, cancer embolus, perineural invasion, and advanced stage occurred less frequently in the pure group \((P<0.01)\). For the tumor size, pure BSCCs were smaller than borderline BSCCs \((P<0.01)\), but there was no statistical difference between pure and mixed BSCCs. LNM \((2\%, 1/48)\) was rare in the pure group. However, LNM was present in most cases \((62\%, 23/37)\) of the mixed group. The SCC component or focal squamous differentiation in the metastatic lymph node was detected in almost all mixed BSCCs \((96\%, 22/23)\) with LNM. The risk of LNM was not much different between the combined \((65\%, 13/20)\) and intermingled type \((44\%, 10/23)\).

As for the superficial \((T1b)\) BSCCs, the rate of LNM \((18\%, 6/34)\) was comparable to that of superficial \((T1b)\) SCCs \((19\%, 57/308)\) in the same period. However, LNM was exclusively detected in superficial mixed \((3/5)\) and borderline \((3/10)\) group, it was not revealed in the 19 pure BSCCs. These 19 cases all showed deep submucosal invasion \((\text{depth of } 0.45\text{ to } 17\text{ mm})\).

IHC results

Four cases were exempted for IHC examination due to improper storage of the paraffin blocks or lack of sufficient tumor tissue. The IHC results of pure, mixed, and borderline group are displayed in Table 2. SGD was displayed in most pure BSCCs \((77\%, 43/56)\) and BSCC components in mixed BSCCs \((74\%, 31/42)\). Only a minority of borderline BSCCs \((6\%, 3/50)\) showed SGD. Generally, the pure group and the BSCC component in the mixed group showed similar IHC staining patterns, which was a higher positive rate of Calponin, S100 and SOX10. Significant difference was not observed in the positive rates of CK7, CK5/6 and CK8/18 between different histological groups. However, the staining pattern was different, and these markers were generally patchy or scattered positive in pure BSCC and the BSCC component in mixed group (Fig. 6, 7, and 8). The positive rate and staining pattern for P53 and P16 were not much different between groups. MYB was strongly positive in focal
area of one pure BSCC, although the diagnosis of adenoid cystic carcinoma was not established because of the negative result of the subsequent fluorescence in situ hybridization.

Discussion

The concept of SGD is broad and ambiguous because the submucosal gland consists of intralobular and extralobular sections, and the lining epithelial cells vary in different parts of submucosal gland (Nie et al., 2020). We further define the acinar and ductal differentiation according to the expression patterns of the IHC markers. Generally, SOX10 is the marker of acinar and intercalated (intralobular) ductal differentiation (Ohtomo et al., 2013). S100 and Calponin are myoepithelial cell markers, while CK7 and CK8/18 are epithelial cell markers. CK5/6 and P63 are positive for myoepithelial, basal, and squamous cells (Zhu et al., 2015). CK7, CK8/18, CK5/6, and P63 can be expressed in the SCC component, but these markers commonly display a uniform staining pattern, which is different from that of pure BSCC. It is worth noting that myofibroblasts and dendritic cells are positive for Calponin and S100, respectively. These distractors need to be excluded from the evaluation of IHC markers.

The positivity of SOX10 has been proven in most BSCCs of head and neck (Rooper et al., 2019). They can be divided into basal, ductal, and mixed subtype (Cho et al., 2017). The ductal subtype has a better but statistically insignificant short-term prognosis. Similarly, the ductal differentiation in esophageal BSCCs is reported to be associated with significantly better survival (Imamhasan et al., 2012).

A high prevalence of human papillomavirus (HPV) infection (86%) has been demonstrated in BSCCs of head and neck. Subgroup analysis shows a better survival of HPV positive cases (Jacobi et al., 2015). However, esophageal BSCCs show less immunoreactivity for P16 and negativity of high-risk HPV by in situ hybridization.
More immunoreactivity for P16 has been observed in poorly differentiated SCCs and small cell carcinomas. In these high-grade esophageal carcinomas, P16 is considered to be induced through inactivation of the RB1 signaling pathway. Overexpression of P16 in esophageal high-grade carcinomas is not a indicator of favorable clinical outcome (Ishida et al., 2021). Diffuse positivity of P16 is only detected in a small percentage of esophageal BSCCs. Esophageal BSCCs are less likely to be related to HPV infection. Mutations of p53 indicate a worse patient survival, and equal or less immunoreactivity of P53 has been observed in the present and previous series (Huang et al., 2001; Bellizzi et al., 2009; Imamhasan et al., 2012; Xu et al., 2021; Yanai et al., 2022).

The impact of invasive SCC component has almost been ruled out according to the rigorous definition of pure BSCCs. Instead, SGD is common in pure BSCCs, and it is thought to be a favorable factor. Pure BSCCs have a lower frequency of LNM, cancer embolus, perineural invasion, and advanced stage. In contrast, no matter the proportion and mixed pattern of SCC component in the mixed BSCCs, the metastatic components always display a squamous differentiation. Compared with mixed and borderline group, more cases are at early stage in the pure group. Tumor stage is an independent prognostic factor for disease free and overall survival in both BSCC and common SCC (Jiang et al., 2023). According to esophageal cancer practice guidelines, esophageal carcinomas with deep (>200µm) submucosal invasion, even if they are superficial, should be treated in the same manner as advanced carcinomas (Kitagawa et al., 2019). In the present study, all superficial (T1b) pure BSCCs showed deep submucosal invasion, but no LNM was detected. Due to the rarity, expanding the ESD indications for superficial (T1b) pure BSCC still needs further validation. However, ESD is probably a good therapeutic option for the patients intolerant to surgical operation.

Survival analysis has demonstrated a better but statistically insignificant overall survival of the pure group. However, the tumor stages do not match between groups,
and early stage case is rare in the borderline group, which is a flaw in the survival analysis. In a recent multi-omics study, esophageal BSCCs displayed distinct RNA expression pattern and immune characteristics but not specific genetic mutations (Li et al., 2023). Two major clusters were yielded by clustering analysis with different pathway scores. The patients in the first cluster had longer relapse free survival and overall survival. The representative morphology of the first cluster was similar to that of pure BSCC (Li et al., 2023). A similar subdivision scheme for esophageal BSCCs has been reported in another study. The pure group also displayed a better but statistically insignificant disease free and overall survival. Similarly, pure BSCCs showed a significantly lower rate of LNM (Jiang et al., 2023). Esophageal BSCC is currently regarded as a distinct histological variant of SCC or SCC with basaloid features (Sauer et al., 2022). However, it is a separate entity, basaloid carcinoma, in Japan (Japan Esophageal Society, 2017; Watanabe et al., 2022). Refinement of the classification of BSCC seems to be inevitable. BSCCs with exclusive SGD differ from common SCCs in many aspects and may qualify as a separate entity.

In summary, esophageal BSCC is a rare and heterogeneous entity. Compared to mixed and borderline group, the pure group displays a higher frequency of SGD, and a lower rate of LNM, cancer embolus, perineural invasion, and advanced stage, as well as a relatively better prognosis. Considering the heterogenous nature, refinement of the classification of esophageal BSCC is a promising way to improve patient management.

Conflicts of interest

The authors have no conflicts of interest to disclose.
**Funding**

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**Ethics approval**

This study was approved by the Committee on Medical Ethics of Nanjing Drum Tower Hospital (IRB number: 2020-254-02)). Informed consent was obtained from all patients for participating and publication.

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and electron microscopic study of sixteen cases. World J. Gastroenterol. 4, 397-403.


**Figure Legends**

**Fig. 1** The survival information of different histological groups of esophageal BSCC.

**Fig. 2** The histological features of pure BSCC. Pure BSCC consisted of basaloid cells arranged as solid (A), cribriform (B), microcystic and/or trabecular (C, and D), and ductal (E) patterns. The tumor nests generally showed a well-demarcated outline. Comedonecrosis (A) and stromal hyalinization (F) can be observed.

**Fig. 3** The histological features of mixed BSCC. A combined type mixed BSCC invaded submucosal layer and showed an invasive SCC component at the left side (A). There was clear boundary between pure BSCC and invasive SCC component (B). The majority of the tumor was composed of basaloid cells arranged as trabecular and solid nests (C). Prominent SGD was observed in focal area at the right side of the tumor (A), the tumor cells forming acinar and ductal structures, resembling the surrounding submucosal glands (D).
Fig. 4 The various SCC components in mixed BSCCs. The invasive SCC component was either separate (A) or intermingled (B-F). The indicators for squamous differentiation included keratin pearls (B) and dyskeratosis (C), abundant clear or eosinophilic cytoplasm (D, and E), and the presence of clear cell boundary and/or intercellular bridges (D, E, and F).

Fig. 5 The histological features of borderline BSCC. Borderline BSCCs were composed of basaloid cells without prominent squamous or glandular differentiation (A, C). Demarcated outline and suspected palisade structure can be observed in high power figures (A, C), but irregular tumor infiltration and significant stromal fibrosis presented in low power figures (B, D).

Fig. 6 The IHC results of invasive SCC component (Fig. 3B). The invasive SCC component in a mixed BSCC (A) showed a diffuse positivity of P63 (B) and CK5/6 (C), and negativity of CK8/18 (D), S100 (E), and SOX10 (F). Note that the S100 positive cells were not tumor cells (E).

Fig. 7 The IHC results of typical BSCC component (Fig. 3C). The typical BSCC component (A) showed weak to moderate positivity of P63 in partial tumor cells (B). CK8/18 (C) and CK5/6 (D) were patchy positive. The staining of S100 (E) was weak and almost unidentifiable, while SOX10 (F) was diffusely positive.
Fig. 8 The IHC results of BSCC component with significant SGD (Fig. 3D).

Heterogenous positivity of P63 (B), CK5/6 (C), and CK8/18 (D) was observed in BSCC component with significant SGD (A). Both S100 (E) and SOX10 (F) were strongly positive. The IHC results demonstrated both ductal and acinar differentiation.

Note that normal submucosal glands located at the upper right area can be regarded as internal controls.

464 Tables

465 Table 1. The clinicopathological features of different histological groups of esophageal BSCC.

466 BSCC, basaloid squamous cell carcinoma.

467 * Lymph node metastasis and tumor deposit were evaluated in cases received esophagectomy.

<table>
<thead>
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<th>Pure group</th>
<th>Mixed group</th>
<th>Borderline group</th>
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<tr>
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<td>43</td>
<td>52</td>
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<tr>
<td>Gender (male/female)</td>
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<td>35/8</td>
<td>46/6</td>
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<tr>
<td>Median age (range, year)</td>
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<td>66 (52-78)</td>
<td>64 (47-82)</td>
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468
Table 2. The immunohistochemical results of different histological groups of esophageal BSCC.

BSCC, basaloid squamous cell carcinoma

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<tr>
<th>Markers</th>
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<th>Borderline group (n=50)</th>
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