Abstract

In the recent years, basaloid squamous cell carcinomas (BSCCs) have gained attention because of (1) observation of a relative increase in the number of tumors arising particularly in head and neck sites, (2) identification of human papillomavirus (HPV) in BSCCs arising predominantly in the oropharynx, and (3) controversies that exist regarding the biological aggressiveness of the tumor. The objective of the present review was to address the issues mentioned above by focusing primarily on oral BSCCs, using literature that has been published in the English language up to 2013. According to the literature review, oral BSCCs were found to be relatively more common in elderly patients with a mean age of 64 years. A male predominance with a male/female ratio of 3:1 was observed. The predominant site was the tongue, with almost half of the reported cases occurring at this site, followed by the floor of the mouth and palate. With reference to habit history, majority were found to be tobacco and alcohol users. However, only 3 studies revealed data on HPV status of purely oral BSCC, and according to the results of these studies, of […]

Reference


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A literature review on oral basaloid squamous cell carcinomas, with special emphasis on etiology

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A B S T R A C T
In the recent years, basaloid squamous cell carcinomas (BSCCs) have gained attention because of (1) observation of a relative increase in the number of tumors arising particularly in head and neck sites, (2) identification of human papillomavirus (HPV) in BSCCs arising predominantly in the oropharynx, and (3) controversies that exist regarding the biological aggressiveness of the tumor. The objective of the present review was to address the issues mentioned above by focusing primarily on oral BSCCs, using literature that has been published in the English language up to 2013. According to the literature review, oral BSCCs were found to be relatively more common in elderly patients with a mean age of 64 years. A male predominance with a male/female ratio of 3:1 was observed. The predominant site was the tongue, with almost half of the reported cases occurring at this site, followed by the floor of the mouth and palate. With reference to habit history, majority were found to be tobacco and alcohol users. However, only 3 studies revealed data on HPV status of purely oral BSCC, and according to the results of these studies, of the 17 tumors tested, 4 had harbored high-risk HPV. Furthermore, most oral BSCCs were in an advanced clinical stage, namely, stage III or IV with T3 or T4 lesions and cervical lymph node metastasis at initial presentation, whereas 41% of patients had presented with local recurrences and 45% had died of the disease. In conclusion, although, the present literature review found enough evidence to consider tobacco and alcohol as risk factors for the development of oral BSCC, steps should be taken to fill the gap in our knowledge that exist with reference to contribution of oncoviruses, particularly HPV in the etiology of oral BSCC.

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1. Introduction
Basaloid squamous cell carcinoma (BSCC) was originally described as a malignant tumor composed of cells showing a basaloid pattern and intimately associated with squamous cell carcinoma, carcinoma in situ, or focal squamous differentiation, by Wain et al [1] in 1986. Basaloid squamous cell carcinoma is considered as a tumor that predominantly arises in elderly men. In addition, these tumors have been identified in numerous head and neck sites including oral cavity [2-18], oropharynx [1,6,19-23], hypopharynx [16,24-26], esophagus [27-29], and sinonasal region [30]. Basaloid squamous cell carcinomas are also considered as more aggressive tumors showing a poorer survival compared with squamous cell carcinoma by some authors [15,21,31], whereas others disagree with this observation [12,16,18,27]. In recent years, BSCCs have gained attention owing to observation of a relative increase in the number of tumors arising particularly at head and neck sites, identification of human papillomavirus (HPV) in BSCCs arising predominantly in the oropharynx [8,10,29,32] and its correlation to etiopathogenesis of the tumors, and controversies that exist regarding the biological aggressiveness of the tumor [12,15,16,21,27,31,32].

Because these tumors occur in multiple head and neck as well as non–head and neck sites, it is difficult to assess the tumor characteristics for a given site because most articles focusing on the subject of BSCCs have included tumors from several sites [1,19,24]. This same difficulty also arises when focusing on other characteristics...
such as contribution of different etiological factors toward the development of tumors and biological aggressiveness. Therefore, the present review will primarily focus on oral BSCCs, with special emphasis given to the etiopathogenesis, using literature that has been published in the English language up to 2013.

2. Materials and method

2.1. Literature review

Initially, a literature review of “head and neck BSCC” was performed via either Hinari, PubMed, or PubMed Central Web sites to obtain all full-text articles provided free of charge on the aforementioned subject. All articles thus acquired were screened to obtain clinicopathologic data on oral BSCC. Based on the literature review [2-16], 15 full-text articles including case reports were found to contain data on oral BSCC (Table 1). These publications were used to gain knowledge on the clinicopathologic characteristics of oral BSCC.

3. Results

Table 2 shows the summary of the clinicopathologic features of oral BSCC. Based on the literature review, habit history was available in less than half of the patients included in the sample, and evaluation of it resulted in identifying more than two-thirds of the patients as tobacco and alcohol users. Only 3 studies revealed data on HPV status of purely oral BSCC, and according to the results of these studies, of the 17 tumors tested, 4 had harbored high-risk HPV. Furthermore, the authors of the present study performed immunohistochemical investigations using p16 antibody, considered as a surrogate marker for HPV16, on 6 oral BSCC samples. However, none of the samples showed p16 positivity (unpublished data).

Furthermore, the literature review also revealed the biological aggressiveness of the tumor, with 41% presenting with local recurrences and 45% dying of the disease. In addition, most oral BSCCs were in an advanced clinical stage, namely, stage III or IV with T3 or T4 lesions and cervical lymph node metastasis at initial presentation.

4. Discussion

Basaloid squamous cell carcinoma is a distinct subtype of squamous cell carcinoma with a characteristic clinical and histopathologic profile (Figs. 1 and 2). Furthermore, the tumors show a high proliferative activity (Fig. 3). Immunohistochemically, the tumors express both low- and high-molecular-weight cytokeratins (Figs. 4 and 5). Owing to the rarity of the tumor, most investigators who have studied the clinicopathologic characteristics of BSCCs, especially with reference to head and neck BSCCs, have used tumors that occurred in multiple sites [1,19,24]. Therefore, difficulties were encountered when compiling clinicopathologic characteristics based on literature review of primarily oral BSCC for the present study. Separating purely oral cavity BSCCs from oropharyngeal tumors was also problematic because lesions occurring at the base of the tongue and palate were considered as belonging to the oropharynx by some, whereas others have included these tumors as arising from the oral cavity [32,33]. However, subsequently, a review article based on 92 cases of purely oral BSCCs was also identified [17]. Most findings of this study corresponded with the findings of the present study, except for the commonest site of occurrence.

Tobacco use in the form of either smoking or betel chewing, together with alcohol, is considered the main etiological agents responsible for the development of most variants of oral squamous cell carcinoma (OSCC) including oral BSCC. However, recent evidence

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**Table 1**

Summary of publications from which data on oral BSCCs were obtained

<table>
<thead>
<tr>
<th>No.</th>
<th>Authors of the study</th>
<th>No. of cases studied</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mane et al [2]</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>Choussy et al [3]</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>Rachel et al [11]</td>
<td>1</td>
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<tr>
<td>4</td>
<td>Satsish and Kumar [4]</td>
<td>1</td>
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<td>5</td>
<td>Friedrich et al [5]</td>
<td>7</td>
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<td>6</td>
<td>Hira et al [6]</td>
<td>2</td>
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<tr>
<td>7</td>
<td>Ereno et al [7]</td>
<td>10</td>
</tr>
<tr>
<td>8</td>
<td>Begum and Westra [8]</td>
<td>6</td>
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<tr>
<td>9</td>
<td>Jayasooriya et al [9]</td>
<td>9</td>
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<td>10</td>
<td>Cabanillas et al [10]</td>
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<td>11</td>
<td>De sampao Goes et al [12]</td>
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<td>12</td>
<td>Ide et al [13]</td>
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<td>13</td>
<td>Paulino et al [14]</td>
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<td>14</td>
<td>Coppola et al [15]</td>
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<tr>
<td>15</td>
<td>Luna et al [16]</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
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<td>119</td>
</tr>
</tbody>
</table>

* Although, the literature review [13] is based on 46 oral BSCCs, the total sample is considered as 30 because reference nos. 13 to 15 included in the study of Ide et al is considered separately.
Human papillomavirus is a double-stranded DNA virus that, upon integration into the host genome, is capable of interfering with the host p53 and retinoblastoma gene activities. Most OSCCs harboring HPV DNA are reported to show characteristic microscopic features such as lack of keratinization with basaloid morphology. Although, tumors showing the above microscopic description are considered as such as lack of keratinization with basaloid morphology. Although, tumors showing the above microscopic description are considered as such as lack of keratinization with basaloid morphology. Although, tumors showing the above microscopic description are considered as such as lack of keratinization with basaloid morphology.

Literature review revealed only a very few studies with HPV status for oral BSCC. Polymerase chain reaction, in situ hybridization, and immunohistochemical techniques have been used to determine the presence or absence of HPV in relevant tumor samples [3,10,36]. Recent data suggest the possibility of using immunohistochemical detection of p16, as a surrogate marker for HPV16 [36]. However, in contrast, Begum and Westra [8] have shown p16 overexpression in 26% of HPV-negative tumors, after excluding the presence of high-risk HPV other than HPV16. According to the present literature review, only 4 tumors of 17 oral BSCCs analyzed had harbored HPV [2,8,10]. Furthermore, the authors’ own experience with p16 antibodies have also given negative results (unpublished observations). However, in contrast, studies have demonstrated high-risk HPVs in oropharyngeal BSCCs [8,10,29,32]. Considering the fact that some oropharyngeal tumors are lesions that arose at the base of the tongue, it is extremely difficult to conclude on the HPV status of oral BSCC using available literature.

At present, no conclusive evidence exists to point toward an oncovirus-based etiopathogenesis for oral BSCC. However, the contribution of HPV to the development of oral BSCC cannot be totally dismissed because of the current evidence showing a relationship between BSCC of oropharynx and HPV [8,10,29,32]. Therefore, further investigations should be undertaken to identify HPV status on larger samples of oral BSCC from different geographic regions before concrete conclusions are made. In addition, although no studies exist to date demonstrating epstein-barr virus or herpes simplex virus status in oral BSCC, such an analysis would also be useful to make a definite statement regarding the etiopathogenesis of oral BSCC.

However, the present literature review found enough evidence to show the contribution of tobacco and alcohol in the pathogenesis of oral BSCC (Table 2). Therefore, while acknowledging the contribution of tobacco and alcohol as risk factors for the development of oral BSCC, steps should be taken to fill the gap in our knowledge that exist with reference to contribution of oncoviruses in the etiology of oral BSCC.

The present literature review based on 119 oral BSCCs revealed essentially similar overall presentation as previously reported and could be considered as a tumor of old age occurring predominantly in men and showing a predilection to the tongue and floor of the mouth (Table 2) [17]. Furthermore, it could also be characterized as a tumor showing an aggressive clinical course, with approximately half of the patients developing local metastasis and slightly more than half the patients dying of the disease (Table 2). However, in contrast, Ide et al [13], in their review, have shown no sex predilection for oral BSCC. Furthermore, the most recent review on oral BSCC has shown no significant differences in the survival rates between oral BSCC and oral squamous cell carcinomas [17].

According to the 2005 World Health Organization classification [37], BSCC is described as a tumor containing variable proportions of basaloid and squamous components. Basaloid component is composed of small monomorphic cells showing a lobular configuration, with frequent central comedo-type necrosis (Figs. 1 and 2). The squamous component is made of large cells with well-defined borders and occasional keratinized cytoplasmic. Traditionally, solid-type adenoid cystic carcinoma and small cell neuroendocrine carcinoma...
have been considered in the histopathologic differential diagnosis [38]. P63 immunostaining is useful to differentiate BSCC from solid-type adenoid cystic carcinoma (Fig. 6). However, in addition, recently described nonkeratinizing squamous cell carcinoma [34,35] should also be considered in the histopathologic differential diagnosis. Although, in 1 article, nonkeratinizing squamous cell carcinoma was considered as a synonym for BSCC [8], the tumors should be considered as 2 distinct entities because BSCC usually contains a squamous component, whereas nonkeratinizing squamous cell carcinoma is devoid of a squamous component. Therefore, steps should be taken to clarify this controversy because the latter tumors have been shown to harbor high-risk HPV and are associated with better prognosis, as most tumors are radiosensitive.

From the very early reports, BSCCs were considered as more aggressive tumors compared with OSCCs. However, few studies that compared survival status of BSCC with OSCC have given controversial results, with some showing worse prognosis for BSCC compared with OSCC, whereas others indicating no prognostic differences between the 2 tumors [12,15,16,21,24,27,31,32]. In addition, particularly with reference to oropharyngeal BSCC, prognosis is thought to depend on the presence or absence of a squamous component. For example, patients presenting with high-risk HPV have shown better survival compared with HPV-negative BSCC [8,10]. However, further research is necessary to determine the prognostic relevance of HPV-positive and HPV-negative oral BSCCs. In addition, some authors consider the presence of the basaloid component itself as a criterion for poor prognosis [24].

Therefore, it would be worthwhile to apply the classification proposed by Soriano et al [24], which is based on the percentage of basaloid component present in the tumors to oral tumors, as well and to compare it with the overall survival in future studies.

References


