Hybrid Verrucous Carcinoma: A Wolf in Sheep’s Clothing
Case Report and Integrative Review of 280 Cases

ABSTRACT: Hybrid verrucous carcinoma (HVC) is defined as a rare neoplasm in which there is histopathological evidence of verrucous carcinoma and microscopic foci of squamous cell carcinoma, synchronously in the same site, affecting behavior and prognosis. This study aimed to present a new case of HVC in the mouth, and critically and comparatively analyze the cases reported in literature, to better understand the biological behavior and contribute to diagnostic precision. A review was performed using six databases, and the gray literature. Twenty-two articles were selected, with a total of 280 cases. The most frequent clinical appearance was verrucous carcinoma which included benign lesions. This implies that the potential for aggressive behavior can be detected microscopically, in the form of a ruptured basement membrane, which visualization can be facilitated by the use of some immunohistochemical markers discussed here. This is important for the diagnosis of HVC and adequate treatment. Hybrid verrucous carcinoma is what can be thought of as “a wolf in sheep’s clothing.” When analyzing cases with clinical suspicion of verrucous carcinoma microscopically, great attention is recommended, since they may be HVC and can recur, metastasize, and lead to death.

KEY WORDS: carcinoma, verrucous; carcinoma, squamous cell; mouth; basement membrane.

INTRODUCTION

Verrucous carcinoma (VC) is a rare, well-differentiated variant of squamous cell carcinoma (SCC) of the skin and mucosa. It exhibits a low degree of malignancy, indolent biological behavior, and favorable prognosis. It was first described in 1948 by Dr. Lauren V. Ackerman (Ackerman, 1948) and has since been referred to as “verrucous carcinoma of Ackermann,” “Ackermann’s tumor,” “Bruschke-Loewenstein tumor,” “florid oral papillomatosis,” “epithelioma cuniculatum,” and “carcinoma cuniculatum” (Asthana & Singh, 2014). The epithelial ridges of this tumor are rhomboid and there is hardly any rupture of the basement membrane. This represents a low metastasis risk. However, VC could be locally invasive, as the number of cells is greatly increased; these masses can enter the connective tissue by pushing (Patel et al., 2013).

There have been cases of dissemination, suggesting the possibility of existing invasive variants. The first case series was published in 1984 by Medina et al. (1984). In this study, 104 cases of VCs were evaluated, and it was found that in 20% of them, there were interspersed foci of invasive SCC. Since then, several cases of VC have been reviewed and their diagnoses have changed (Medina et al., 1984; Depprich et al., 2006; Kolokythas et al., 2010; Patel et al., 2015; Cunha et al., 2017). A recent study by Elhassan et al. (2019) reported that 47% of VC were compatible with this invasive variant. It is called “hybrid
Hybrid verrucous carcinoma (HVC) is an even rarer entity. It is defined as a neoplasm with histopathological evidence of the coexistence between VC and one or more microscopic foci of SCC, with different degrees of differentiation, synchronously, at the same site (Medina et al., 1984; Batsakis et al., 1999; Gokavarapu et al., 2014).

Although infiltrative behavior implies the potential for regional and distant metastases, the clinical aspect and the dominant histological features remain the same as those of a pure VC. The hybrid variant needs to be identified because it demands a therapeutic approach distinct from that used for VC (Medina et al., 1984; Depprich et al., 2006; Kolokythas et al., 2010; Patel et al., 2013; Pires et al., 2013; Asthana & Singh, 2014; Candau-Alvarez et al., 2014; Gokavarapu et al., 2014; Emanverdyade et al., 2015; Gokavarapu et al., 2015; Patel et al., 2015; Cunha et al., 2017; Franklyn et al., 2017; Surana et al., 2018).

This study aimed to present a new case of HVC in the mouth, and to critically and comparatively analyze the cases reported in literature. The authors will discuss the precise diagnosis and contribute to a better understanding of the lesion, especially its behavior and prognosis, using the extreme entities within this spectrum (VC and SCC).

MATERIAL AND METHOD

A. Case report. A 71-year-old man visited the dental clinic of the State University of Maringá, complaining of a “small ball on the tongue.” The patient reported having noticed it 6 months prior and denied any associated deleterious habits. No abnormalities were observed during the extraoral physical examination. The intraoral examination revealed a white nodular mass, located on the right lateral margin of the tongue, measuring approximately 3 cm. The lesion was dome-shaped, with a sessile base, verrucous surface, and well-defined limits. There was also a well-circumscribed white plaque, measuring about 3 cm, that was not removable by scraping. The white plaque extended laterally to the nodule (Fig. 1) and was contiguous to it.

A careful microscopic analysis of the region revealed concomitant characteristics of both SCC and VC (Fig. 2). There were fragments of mucosa covered by hyperparakeratinized stratified squamous epithelium, with numerous prominent superficial digitiform projections. In some areas, the epithelium was proliferative and advanced in depth, pushing the underlying connective tissue. However, in other areas, infiltration was observed. Several neoplastic islands permeated by significantly inflamed stroma were noted. Their cells presented pleomorphism, hyperchromatism, and mitotic figures. There were also corneal pearls and dyskeratotic foci.

The patient was diagnosed with SCC on June 12, 2019, after an incisional biopsy of the tongue lesion. Histopathological examination also indicated that it was a well-differentiated lesion with a 5 mm-depth of invasion. The clinical stage at that time was T2N0M0. The patient was referred to the oncology local service where he received the first surgical treatment on September 12, 2019. After 2 months, he returned to the hospital because of severe pain and dysphagia. This was a neoplastic recurrence. A major surgery was performed (glossomandibulectomy with cervical lymphadenectomy, and tracheostomy), and the reconstruction was conducted using the pectoralis major flap on December 12, 2019. During the second microscopic examination, a well-differentiated epidermoid carcinoma, yet verrucous in appearance, was observed, with an invasion depth of 1.5 cm, compromising deep surgical margins. Only one of the level II, III, and V cervical lymph nodes had metastasized. Thus, the disease was staged as T2N1M0.
From February to April 2020, the patient underwent concomitant chemotherapy and linear accelerator radiotherapy. During the outpatient follow-up, the patient exhibited treatment sequelae, such as difficulty in eating and speaking. In October 2020, after CT scans, the patient was diagnosed with advanced recurrence of the neoplasm in the neck and metastases in the lungs. With clinical staging IV-C (T3N1M1), a palliative chemotherapy protocol with carboplatin, paclitaxel, and zoledronic acid was initiated. The patient developed low back pain and presented with difficulty breathing due to the worsening oral and metastatic lesions. He passed away on January 6, 2021, 18 months after the initial diagnosis.

B. Critical literature review: A critical literature review was performed using the PubMed/Medline, Virtual Health Library, Embase-via Elsevier, Scopus, Web of Science, and Cochrane Library databases, as well as gray literature (Google Academic, Open Grey, and Brazilian Digital Library of Theses Dissertations-BDTD). The search was complemented by manual screening of the previously selected articles. All the references found were exported to EndNote Web® (Thomson Reuters, New York, USA). As a search strategy, we chose the modified PICO, as detailed in Table I. Inclusion criteria were: case reports and descriptive observational studies, histologically confirmed diagnosis of HVC, and involvement of the mouth or maxillary bones. Microscopically, a large amount of keratin with rhomboid epithelial ridges without invasion characteristic of VC, together with areas of neoplastic infiltration compatible with SCC should also be observed (Medina et al., 1984; Kolokythas et al., 2010; Cunha et al., 2017). The articles had to be in Portuguese, English, Spanish, French, or Italian languages and without restrictions on the year of publication. The following exclusion criteria were used: a) articles without the full version being available, b) HVC in other regions, and c) abstracts published in event annals.

C. Data extracted from each study and its analysis. The following information was extracted from each study and is available in Table II: author, patient profile (sex, age), location of the lesion, evolution time, smoking load (if present), clinical appearance, symptomatology, lymph node features, imaging appearance, diagnostic hypothesis, biopsy type, histopathological features, depth of invasion, metastasis (if present), treatment, and outcome.

Fig. 2. Photomicrographs of the lesion on the tongue. A, Neoplastic epithelium with prominent superficial digitiform projections (H&E; original magnification x 4). B, Parakeratin plugs, partially filling the spaces between the projections (H&E; original magnification x 4). C, Advancement of the neoplastic epithelium, in depth, but “en bloc”, in a “push” pattern of the underlying tissue (H&E; original magnification x 4). D, Section showing infiltrative behavior, with numerous small islands of neoplastic epithelium in the midst of the connective stroma (H&E; original magnification x 4). E, Horny pearls and dyskeratotic foci (H&E; original magnification x 4). F, Pleomorphism and hyperchromatism cellular (H&E; original magnification x 10).
Table I. Search strategy.

| Data base                  | Search: 08/12/2020                                                                 |
|----------------------------|------------------------------------------------------------------------------------|
| Pubmed/Medline             | (hybrid verrucous carcinoma OR (hybrid verrucous-squamous carcinoma)) AND (Mouth [Mesh] OR (Oral Cavity) OR (Cavity, Oral) OR (Cavitas Oris) OR (Vestibule of the Mouth) OR (Vestibule Oris) OR (Oral Cavity Proper) OR (Mouth Cavity Proper) OR (Cavitas oris propri)) |
| Virtual Health Library     | “hybrid verrucous carcinoma” OR (hybrid verrucous-squamous carcinoma) AND mouth OR (Oral Cavity) OR (Cavity, Oral) OR (Cavitas Oris) OR (Vestibule of the Mouth) OR (Vestibule Oris) OR (Oral Cavity Proper) OR (Mouth Cavity Proper) OR (Cavitas oris propri)) |
| Embase                    | (’hybrid verrucous carcinoma’ OR (((hybrid/exp OR hybrid) AND verrucous AND (carcinoma/exp OR carcinoma))) AND (mouth/exp OR mouth)) TITLE-ABS-KEY (”hybrid verrucous carcinoma” OR “hybrid verrucous-squamous carcinoma”) AND (mouth OR “Oral Cavity” OR “Cavity, Oral” OR “Cavitas Oris” OR “vestibule off the mouth” OR “Vestibule Oris” OR “Oral Cavity Proper” OR “Mouth Cavity Proper” OR “Cavitas oris propri”) hybrid verrucous carcinoma* OR hybrid verrucous-squamous carcinoma AND Mouth* |
| Scopus                    | hybrid verrucous carcinoma AND mouth                                                 |
| Web of Science             | hybrid verrucous carcinoma                                                           |
| Cochrane Library           | hybrid verrucous carcinoma                                                           |
| Google scholar             | hybrid verrucous carcinoma                                                           |
| Brazilian Digital Library of Theses Dissertations-BDTD | hybrid verrucous carcinoma |
| Open Grey                  | hybrid verrucous carcinoma                                                           |

To facilitate the analysis of the eventual relationship between clinical and microscopic variables, another table was presented (Table III), with the following information extracted from each study: author, histological grade, depth invasion, TNM staging, and prognosis/survival. Descriptive data analysis among variables was performed, as other types of analysis of association could not be performed.

Fig.3. Prisma fluxogram.
Table II. Data from case reports and observational studies.

| Author | Sex | Age | Location/ Evolution time | Habit/Time | Clinical appearance | Symptomatology | Lymph nodes | Imaging appearance | Diagnosis/patchwork | Biopsy type/ Histopathological result | Diameter of invasion | Metastasis | Treatment and outcome |
|--------|-----|-----|--------------------------|------------|---------------------|----------------|-------------|-------------------|---------------------|----------------------------------------|---------------------|------------|----------------------|
| Ahmad and Singh, 2014 | M | 60 | Buccal mucosa | Chewing tobacco | White exfoliative lesion, pain, swelling, difficulty in swallowing, and in eating | N.I | Verrucous carcinoma, leukoplakia, papilloma, verrucous carcinoma | Radiograph and CT-Infiltration in the maxillary sinus and destruction of the alveolar arcus and osseous destruction. CT-Enhancement of the bone erosion- Enlarged cervical lymph node | Verrucous carcinoma/ Leukoplakia N.I | N.I | No lymph node metastasis | N.I | N.I/NI |
| Banerjee et al., 2015 | F | 65 | Buccal mucosa | Chewing tobacco | Verrucous leukoplakia, 4.0 cm, asymptomatic | Radiograph-lytic | N.I | Submucosal lymph nodes were enlarged and tender on palpation | Radiograph-lytic | Indolent or biopsy/HVC | Less than 2 mm | No lymph node metastasis | Resection, neck dissection and radiotherapy | N.I |
| Choudhury et al., 2010 | F | 30 | Buccal mucosa | No | Soft tissue lesion | Painful | N.I | Verrucous carcinoma, squamous cell carcinoma | Radiograph and CT-Enhancement of the bone erosion- Enlarged cervical lymph node | Verrucous carcinoma/ Leukoplakia N.I | N.I | No lymph node metastasis | N.I | N.I/NI |
| Curta et al., 2017 | M | 78 | Floor of the mouth | Tobacco/N.I | Exophytic tumor | Painless | N.I | Verrucous carcinoma | Radiograph-clasping of the maxillary sinus and destruction of the alveolar bone- CT-Enlarged cervical lymph node | Verrucous carcinoma | N.I | No lymph node metastasis | N.I | N.I |
| Deshpande et al., 2009 | F | 73 | Palate, buccal mucosa, upper lip, lower lip | No detectable habits | Eosinophilic tumor | N.I | Verrucous carcinoma | Radiograph-lytic | Basal proliferative verrucous carcinoma, squamous cell carcinoma | Verrucous carcinoma/ Leukoplakia N.I | N.I | No lymph node metastasis | N.I | N.I |
| Elmamunzy et al., 2014 | F | 44 | Hard palate | N.I.N.I | Multiple sessile exophytic lesions with nodular surface measuring 1.5 x 0.9 cm and without bleeding | Painless | N.I | Verrucous carcinoma | Radiograph and CT-Enlargement of cervical lymph node | Verrucous carcinoma | N.I/HVC | N.I | N.I/N.I |
| Nohra et al., 2015 | M | 48 | Buccal mucosa | Chewing tobacco | Ulceroproliferative growth, with 9 x 6 cm, nodular margins, verrucous pink with corrugated appearance | Tender papillae | N.I | Verrucous carcinoma | Radiograph-lytic | Indolent or biopsy/HVC | N.I | No lymph node metastasis | Resection/HVC | N.I |
| Kohli et al., 2010 | F | 60 | Buccal mucosa and floor of mouth | Tobacco/2 months | Eosinophilic papillary white-striated fleshy mass | Pain | No cervical lymphadenopathy | Radiograph-lytic | Papillar verrucous leukaoplakia and verrucous carcinoma | Verrucous carcinoma | N.I/HVC | Deeply into the surrounding tissue | No lymph node metastasis | Resection and radiotherapy | N.I |
| Oswal et al., 2015 | M | 73 | Buccal mucosa | Non-smoker | White, verrucous lesion | N.I | Verrucous carcinoma | CT-III (malignant) or CT-II (potentially malignant) | Verrucous carcinoma, squamous papillomas, focal epidermal hyperplasia, squamous cell carcinoma and condyloma acuminatum | Verrucous carcinoma | N.I | One lymph node metastasis | Reaction and neck dissection | N.I |
| Sharma et al., 2020 | M | 73 | Buccal mucosa | Whisker-like exophytic sessile growth, 3.8 x 3.5 cm and with well-defined margins | Painless | No cervical lymphadenopathy | CT-III (malignant) or CT-II (potentially malignant) | Verrucous carcinoma, squamous papillomas, focal epidermal hyperplasia, squamous cell carcinoma and condyloma acuminatum | Verrucous carcinoma | N.I | No lymph node metastasis | Reaction and neck dissection | N.I |
| Suresh and Mavoor, 2018 | M | 39 | Buccal mucosa | Chewing tobacco | Eosinophilic papillary white-striated fleshy mass | N.I | Verrucous carcinoma | Perforated succulated venous tumour measuring 1.5 x 1.5 cm | Verrucous carcinoma | N.I/HVC | N.I | N.I | N.I |
| Sukhdev and Mavoor, 2018 | F | 94 | Hard palate | Hard palate | Perforated succulated venous tumour measuring 1.5 x 1.5 cm | Oral discomfort | N.I | Verrucous carcinoma | Biopsy (the HVC) | Verrucous carcinoma | Microinvasion | N.I | N.I | N.I/NI |

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The most commonly reported locations were the oral mucosa (n=85, 30.3 %), followed by the larynx (n=23, 8.2 %), tongue (n=15, 5.3 %), gingiva (n=12, 4.2 %), alveolar mucosa (n=6, 2.14 %), hard palate (n=2, 0.7 %), lip (n=2, 0.7 %), and oropharynx (n=1, 0.3 %). The time of evolution was 2–36 months. Destruction of the underlying alveolar bone was observed in three cases. Of the 12 case reports, the diagnostic hypotheses were VC (n=6, 50 %), SCC (n=3, 25 %), proliferative verrucous leukoplakia (n=2, 16.6 %), papilloma verrucous hyperplasia (n=2, 16.6 %), squamous papilloma (n=1, 8.3 %), epithelial hyperplasia (n=1, 8.3 %), and condyloma acuminatum (n=1, 8.3 %).

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Of the 280 cases, most did not provide important information such as the microscopic features, therapeutic approaches, or follow-up details. In 16 % of the cases, the atypia was mild, and the invasion was minimal (< 2 mm). In another 7.1 % of cases, in which the depth of invasion was available, it exceeded 2 mm. Lymph node metastasis was reported in only 14 cases. This information was absent in 40.7 % of the patients. The most common treatment protocol was surgery alone (n=70, 25 %); followed by surgery and radiotherapy (n=12, 4.2 %); surgery and neck

RESULTS

A total of 114 publications were found (PubMed/ Medline 34; Virtual Health Library 25; Embase 9; Scopus 7; Web of Science 27; Cochrane Library 0; Google Scholar 10; Open gray 0; BDTD 0; and manual search 2). Figure 3 in the Appendix shows the flow chart in detail. After removing duplicate texts, 80 articles were retained. The search was conducted up to November 2020. After applying the eligibility criteria (inclusion and exclusion), we arrived at 22 articles, with 12 case reports and 10 descriptive observational studies, for a total of 280 cases.

Table II in the appendix summarizes the main findings from the HVC literature. Men were more affected than women (n=79, 28.2 % vs. n=68, 24.2 %, respectively), and the highest incidence was in adults, with a mean age of 63.28 years. The most frequent clinical appearance was mass/swelling, with little variation from the classic VC presentation. Symptoms were rarely present. When present, the symptoms ranged from discomfort to pain. Deleterious habits such as cigarette smoking (n=14, 5 %), alcohol (n=6, 2.14 %), and chewing tobacco (n=3, 1.07 %) were also found.

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Due to lack of information, Table III in the Appendix did not present some relevant associations.
between histological grade and the depth of invasion versus clinical staging and prognosis. Of the 31.7 % cases with histological grade, most were well-differentiated (n=57, 63.3 %), followed by moderate (n=11, 12.2 %) and poorly differentiated (n=21, 23.3 %). The depth of invasion, available in only 32.1 % of the cases, was divided into two groups: 1 (n=68, 76.4 %): few infiltrations in the stroma (< 4 mm), and 2 (n=22, 24.7 %), and frank infiltration in the stroma (> 4 mm). The clinical TNM staging, when available (only in 32.85 % of the cases), was predominantly T2 (n=62, 22.1 %) and N0 (n=90, 32.1 %). Recurrence was noted in 33 (11.78 %) cases. A total of 8 (2.86 %) patients died.

**DISCUSSION**

When comparing VC and HVC, both clinically and in relation to the patient’s profiles, both have important similarities and differences. The predilection for males over 60 years of age is similar between both neoplasms. However, VC tended to have a longer evolution time (up to several years), while HVC, as a more aggressive lesion, presented a shorter clinical course (Peng et al., 2016). As reported in the study, cases showed a duration from 2–36 months. Tobacco chewing was the etiological factor most associated with both VC and HVC (Surana et al., 2018). In our review, most cases reported no harmful habits, and alcohol and/or cigarettes were more frequent than chewing tobacco (Table II) (Depprich et al., 2006; Cudney et al., 2010; Owosho et al., 2015).

Clinically, HVC and VC are similar (Medina et al., 1984; Cunha et al., 2017). Both manifest as thick, well-defined, reddish-white plaques, with prominent surface projections, sometimes verrucous, sometimes papillary, as in our case. This emphasizes the importance of including HVC as a differential diagnosis, even in cases with a harmless clinical appearance, as a way to bring this possibility to the attention of the pathologist.

Microscopically, both HVC and VC have areas with large amounts of keratin, as well as long epithelial ridges that seem to “push” the underlying connective tissue. This seemingly benign appearance is misleading, as it may lead to a false diagnosis of VC. As we have seen in our case, invasive neoplastic foci with cells exhibiting dyskeratosis and atypical mitoses, as in SCCs, may be evident. This combination of features defines the HVC and explains its ability to disseminate (Oliveira et al., 2006; Gokavarapu et al., 2014; Patel et al., 2015; Cunha et al., 2017; Sharma et al., 2020), especially because of the rupture of the basement membrane (BM).

In SCC, the basement membrane appears thin, discontinuous, and lightly stained. The disruption of this barrier by tumor cells occurs by induced failure in synthesis, secretion, and assembly, or even by active degradation (Arduino et al., 2010). In VC, when markers for BM are used, it appears well expressed and more continuous and regular, when compared to the BM of SCC (Arduino et al., 2010). It is logical to infer that the detection of BM rupture can help distinguish HVC from VC, as well as SCC from carcinomas in situ.

Table IV in the Appendix shows a comparative evaluation of HVC, and SCC versus VC. Many studies have mentioned that proteolytic enzyme production and the presence (or absence) of intercellular adhesion receptors are capable of explaining the microscopic differences (Impola et al., 2004; Arduino et al., 2010; Odar et al., 2012). In the study by Odar et al. (2012), for example, using immunohistochemistry and RT-PCR, the expression pattern of desmosomes (plakophilin 1, desmogleins 2 and 3, and desmoplakin) in VC and normal tissue was similar. In contrast, the expression pattern of SCC and HVC differed significantly. This is likely due to the altered components, which seems to contribute to tumor progression by compromising cell-cell adhesion and altering signaling mechanisms, thereby influencing the potential for invasion and metastasis (Shinohara et al., 1996; Kurzen et al., 2003; Papagerakis et al., 2004; Chidgey & Dawson, 2007; Wong et al., 2008; Brennan & Mahoney, 2009).

Fibronectin, a glycoprotein of the extracellular matrix that binds to membrane integrins, showed differential expression in SCC, compared to VC, and can aid in this differential diagnosis (Arduino et al., 2010). The accumulation of fibronectin in the basement membranes of SCC was stronger and seemed to be a compensatory attempt to keep epithelium and connective tissue together, despite the invasion. Likewise, laminin and type IV collagen are present in malignant lesions as a result of the fragmentation generated by proteolytic matrix degradation during migration through surrounding tissues (Arduino et al., 2010).

In the study by Impola et al. (2004), also presented in Table IV, the immunohistochemical
Table IV. Immunohistochemistry and RT-PCR analysis between verrucous carcinoma, hybrid verrucous carcinoma, and squamous cell carcinoma.

| Author | Technique | Molecular marker | Expression | Intensity | Location |
|--------|-----------|-----------------|------------|-----------|----------|
| Arduino et al., 2009 | Monoclonal antibodies (MAbs) directed against rabbit polyclonal antibodies to laminin | Monoclonal antibodies (MAbs) directed against human fibronectin | VC- Positive | SCC- Positive | VC- Defined (p=0.017) S CC- Less defined VC- BM |
| | | | Type IV Collagen | VC- Positive | SCC- Positive | VC- Same intensity S CC- Same intensity VC- BM S CC- BM |
| | | | Laminin | VC- Positive (10 %) | SCC- Positive (50 %) | VC- Same intensity S CC- Same intensity VC- BM S CC- BM |
| | | | Laminin - VC | VC- Negative | SCC- Negative | VC- Same intensity S CC- Same intensity VC- BM S CC- BM |
| | | | | VC- Positive | SCC- Positive | VC- Same intensity S CC- Same intensity VC- BM S CC- BM |
| Elhassan et al., 2019 | Paraffin block specimens | Syndecan-1 (CD138) | VC- Negative | VC with micro-invasive-Positive | VC- Moderate to mild VC with micro-invasive-Mild VC- BM S CC- BM |
| | | | MMP-2 | VC- Negative | SCC- Negative | VC- None | SCC- None VC- BM S CC- BM |
| | | | MMP-3 | VC- Negative | SCC- Positive | VC- (50 %) | SCC- (90 %) VC- BM S CC- BM |
| | | | MMP-7 | VC- Positive | SCC- Positive | VC- Only one sample | SCC- (under 50 %) VC- BM S CC- BM |
| | | | MMP-9 | VC- Positive | SCC- Positive | VC- (under 50 %) | SCC- (90 %) VC- BM S CC- BM |
| | | | MMP-10 | VC- Positive | SCC- Positive | VC- (50 %) | SCC- (90 %) VC- BM S CC- BM |
| | | | MMP-12 | VC- Positive | SCC- Positive | VC- Only one sample | SCC- (under 50 %) VC- BM S CC- BM |
| | | | MMP-13 | VC- Positive | SCC- Positive | VC- (under 50 %) | SCC- (90 %) VC- BM S CC- BM |
| | | | MMP-19 | VC- Positive | SCC- Positive | VC- (50 %) | SCC- (under 50 %) VC- BM S CC- BM |
| | | | v_5 Integrin | VC- Positive | SCC- Positive | VC- Some cells | SCC- Strong VC- BM S CC- BM |
| | | | Laminin-5 | VC- Positive | SCC- Positive | VC- N I | SCC- NJ VC- BM S CC- BM |
| | | | | | HVC- Positive | VC- N I | HVC- Desmosomes S CC- Desmosomes |
| Impola et al., 2004 | Formalin-fixed, paraffin embedded samples | MMP-1 | VC- Negative | SCC- Negative | VC- None | SCC- None VC- BM S CC- BM |
| | | | MMP-2 | VC- Positive | SCC- Positive | VC- (50 %) | SCC- (90 %) VC- BM S CC- BM |
| | | | MMP-3 | VC- Negative | SCC- Positive | VC- None | SCC- (50 %) VC- BM S CC- BM |
| | | | MMP-5 | VC- Positive | SCC- Positive | VC- (50 %) | SCC- (90 %) VC- BM S CC- BM |
| | | | MMP-6 | VC- Positive | SCC- Positive | VC- (50 %) | SCC- (90 %) VC- BM S CC- BM |
| | | | MMP-7 | VC- Positive | SCC- Positive | VC- (under 50 %) | SCC- (90%) VC- BM S CC- BM |
| | | | MMP-9 | VC- Positive | SCC- Positive | VC- (under 50 %) | SCC- (90%) VC- BM S CC- BM |
| | | | MMP-10 | VC- Positive | SCC- Positive | VC- (50 %) | SCC- (90%) VC- BM S CC- BM |
| | | | MMP-12 | VC- Positive | SCC- Positive | VC- (under 50 %) | SCC- (90%) VC- BM S CC- BM |
| | | | MMP-13 | VC- Positive | SCC- Positive | VC- (under 50 %) | SCC- (90%) VC- BM S CC- BM |
| | | | MMP-19 | VC- Positive | SCC- Positive | VC- (50 %) | SCC- (under 50 %) VC- BM S CC- BM |
| | | | _v_5 Integrin | VC- Positive | SCC- Positive | VC- Some cells | SCC- Strong VC- BM S CC- BM |
| | | | Laminin-5 | VC- Positive | SCC- Positive | VC- N I | SCC- NJ VC- BM S CC- BM |
| | | | | | HVC- Positive | VC- N I | HVC- Desmosomes S CC- Desmosomes |

**KIMURA, T. C.; SCATOLIM, D. B.; HENSCHEL, F. A. N. & VELTRINI, V. C.** Hybrid verrucous carcinoma: A wolf in sheep’s clothing. Case report and integrative review of 280 cases. Int. J. Odontostomat., 16(2):202-213, 2022.
expression of metalloproteinases was compared in cases of VC, verrucous hyperplasia, and SCC. These enzymes degrade the interstitial matrix and basement membrane during neoplastic invasion and participate in the release of some growth factors. Paradoxically, VC presented more MMP-7, MMP-9, and MMP-12, when compared to SCC, probably because the MMPs, although related to the process of protein cleavage, would also inhibit angiogenesis and therefore impair tumor growth.

Recently, Elhassan et al. (2019) evaluated Syndecan-1 (CD138), a protein that participates in cell-cell and cell-matrix adhesion. There was an almost complete loss (94.1%) of expression in invasive VC, that is, in VC that could be called HVC. This loss of expression, detectable by immunohistochemistry, facilitates the early identification of microinvasion, compared to HE, and permits the differential diagnosis between VC and HVC.

Considering the natural history of VC and the potential to change biological behavior, for a long time it was thought that it could lose differentiation and invade, but only when submitted to radiotherapy (Perez et al., 1966; Batsakis et al., 1999). Over time, publications began to report that this change occurred in non-irradiated lesions (Kolokythas et al., 2010; Bande et al., 2015; Surana et al., 2018; Sharma et al., 2020).

According to Deprich et al. (2006), the HVC is the concomitance of two distinct entities. In fact, microscopic characteristics of both are present: VC (a lot of keratin, discreet atypia, and no invasion) and SCC (less keratin, more atypia, and invasion), but not in a real hybrid pattern. There are reports of lesions that began as VC, which transformed into HVC, and ultimately became SCC (Terada, 2012; Bande et al., 2015; Patel et al., 2015; Sharma et al., 2020). For VC, there may be a natural tendency for transformation to occur.

The VC has been considered a well-differentiated variant of SCC (Oliveira et al., 2006; Strojan et al., 2006; Terada, 2012; Cunha et al., 2017; Surana et al., 2018). In the light of the above new insight, it is important to understand VC as a well-differentiated variant of an in-situ carcinoma (Shimizu et al., 2006). Due to its high differentiation, its potential for evolution to SCC would be less than that of an in-situ carcinoma. Even if this does occur, it would take more time for such transformation. This justifies the need to consider the detectable transitional lesion, namely, the HVC.

Adequate biopsies are fundamental. In the study by Gokavarapu et al. (2015), 51% of incisional biopsies failed to identify the SCC components of HVC. As lesions are usually extensive, a careful clinical evaluation should guide the choice of the area for incisional biopsy, in the same way that potentially malignant disorders (PMD) are mapped. It is desirable to determine which areas have a greater chance of presenting invasion in VC, just as we try to detect areas with the most intense atypia in PMD. As such, multiple biopsies may even be indicated in heterogeneous lesions (Gokavarapu et al., 2014; Emanverdyzade et al., 2015).

The sectioning of the specimen during macroscopy and subsequent paraffin embedding should always be adequate to analyze the epithelium and connective tissue in a single section plane. VC are usually extensive lesions and the SCC components that give the “hybridity” to the lesion will occur, at first, in small segments of the tumor. A pathologist who receives a specimen for microscopic examination with a clinical diagnosis of VC should be alerted. If microscopic features of VC with discrete foci of invasion are found, it should be reported as HVC, preferably, and not SCC. A diagnosis of HVC would clarify to the clinician that it is an ongoing transformation, or a case of superficially invasive carcinoma. On the other hand, HVC with exuberant SCC components should be diagnosed as SCC because they can recur, metastasize, and lead to death (Medina et al., 1984; Gokavarapu et al., 2014), as observed in this report. There may be a need for adjuvant therapy, with radiation and cervical lymph node dissection, depending on the stage of the tumor (Candau-Alvarez et al., 2014; Patel et al., 2015). Therefore, there is no specific therapeutic protocol (Patel et al., 2015), and in principle, these lesions should all be treated as SCC (Ferlito et al., 1998; Yoshimura et al., 2001; Kang et al., 2003; Shimizu et al., 2006; Kabiraj et al., 2015), close follow-up is also recommended (Emmaverdyzade et al., 2015).

HVC have a better prognosis. The chance of metastasis is approximately 13.5%. In contrast, the metastasis risk of SCC is 30% (Gokavarapu et al., 2014). However, it seems to depend on the depth of the invasion. The prognosis of an HVC worsens as the level of invasion of its SCC component increases. Hybrid tumors with < 4 mm of invasion, for example, have a lower chance of metastasizing and recurring locally, compared to frankly infiltrating ones (Medina et al., 1984; An et al., 2008; Larsen et al., 2009; Cunha
et al., 2017). Therefore, just as pathologists should mention the depth of invasion of an SCC, they should do the same for an HVC.

HVC is what we can call a “wolf (SCC) in sheep's clothing (VC).” Great attention is recommended when analyzing clinical cases that are suspected as VC.

CONCLUSION

We reported a new case and critically analyzed the HVC literature. This study allowed us to develop new perspectives about the nature of this tumor and also led to two recommendations. The first is for clinicians. Awareness of the existence of this transitional lesion is important and HVC should be included in the differential diagnosis, even though its clinical presentation resembles that of VC. The second and the most important recommendation is for pathologists. Faced with the histological characteristics of VC, they should actively search for foci of invasion. In view of their existence and having measured the level, pathologists should ensure that this information is included in the histopathological report. In this way, the critical diagnosis of HVC will not be missed.

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