Epulis-Like Presentation of Gingival Renal Cancer Metastasis

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Abstract
Mouth metastatic cancers are very rare and they usually represent the evidence of a widespread disease. Common primary tumors are lung carcinoma in men and breast carcinoma in women, followed by kidney cancer. In the oral soft tissues, the gingiva is the most common site, suggesting a possible role of inflammation in the attraction of circulating tumor cells. Oral metastasis has a serious prognosis. In this work, we describe the case of a 58-year-old man affected by renal cancer, who was brought to our attention for the appearance of a gingival swelling. Initially, the lesion was excised through a provisional clinical diagnosis of epulis. Subsequently, anatomopathological analysis showed a metastasis compatible with clear-cell carcinoma and specifically its renal origin was confirmed by immunohistochemical techniques.

Introduction
The gingiva is the predominant localization of oral metastatic tumors and in both sexes (male and female), renal cell carcinoma represents the third most common primary cancer. The determination of the primary cancer and the differential diagnosis with benign lesions...
can be quite difficult to establish. Recent improvements in imaging technologies, molecular profiling tools, and immunohistochemical testing have enhanced the identification of the primary lesion sites and influenced the treatment choices. The collaboration between maxillofacial surgeon, dentist, pathologist, and oncologist is essential. The described case is unique for its peculiar localization at the mucosal area underlying the prosthesis, where the absence of specific symptoms and the epulis-like appearance may have played a fundamental role in the onset of the lesion.

Case Presentation

The case has been followed in our center for 2 years. A 58-year-old nonsmoking man, affected by clear-cell renal cancer of 5 cm of greater axis with invasion of the perirenal fat (macroscopic lymphatic and microscopic venous invasion), Führman nuclear grade 3, stage cT3aN1M1, with pulmonary and bone metastases, treated with radical nephrectomy and sunitinib – and in clinical response – reported the presence on the gingival edge of a small painful reddish indurated swelling (not ulcerated or with any bleeding) in correspondence to a removable prosthetic device at the level of +13/+14 (Fig. 1).

Suspecting a fibrous epulis, the patient was subjected to a complete surgical resection. Surprisingly, histopathology revealed a highly vascular tumor with a trabecular growth pattern and immunohistochemical analysis showed vimentin and carbonic anhydrase positivity and cytokeratin 7 negativity, confirming the diagnosis of metastasis of the clear-cell cancer of the kidney (Fig. 2). Computerized tomography and magnetic resonance excluded soft tissue and maxillary bone invasion. Similarly, positron emission tomography, done at an interval of 3 weeks, excluded uptake in the oral cavity highlighting the presence of edema and two metastases in the left occipital site, confirmed also by nuclear magnetic resonance imaging (Fig. 3). Noting an appearance of metastasis during treatment with sunitinib, it was decided to treat the cerebral metastasis surgically and to start immunotherapy with nivolumab.

Discussion

Oral metastatic cancers are rare and among them, only 1% is metastatic [1]. They are more frequent in the jaws than in the soft tissue, respectively 2:1, tending to occur predominantly in males between the 40s and 60s [2]. Nevertheless, the incidence of metastatic tumors in the jaws is probably higher than suggested. Micrometastatic foci in the jaws were found in 16% of autopsied carcinoma cases despite the absence of radiologic findings [3]. Two-thirds of the cases suggest that the primary cancer is known and the oral metastasis is an anatomical seat of a widespread disease. Meanwhile, one-third of the cases point out that the primary cancer is unknown and it represents its first clinical manifestation [4]. The most common primary sites in men are the lungs, kidney, liver, and prostate, while in women, they are the breast, female genital organs, lungs, and kidney. In a Korean study, the liver was the most common primary site in males [5]. Oral metastasis was found to be the first sign of stage IV disease in approximately 25% of cases. Clear-cell renal carcinoma has a higher preference for vascular invasion than for lymphatic invasion, in consideration of the higher incidence of renal vein involvement. The most common metastatic sites include lung (33–72%), infra-abdominal lymph nodes (3–35%), bone (21–25%), brain (7–13%), and liver (5–10%)
In the jawbones, the mandible was more frequently involved than the maxilla, with the molar area being the most frequent site (50%) followed by the premolar area (38%) and the angle (29%) [7]. In the oral soft tissues, the gingiva is the most commonly affected site (60%) followed by the tongue (18%) [8]. Gingival localization has long been known [9, 10].

A literature analysis has recently found a significant association between gingival metastasis and the presence of teeth or periodontitis, suggesting the possible role of inflammation in the distribution of metastatic deposits to the gingiva. The microenvironment in a chronically inflamed gingiva may provide a favorable niche for circulating tumor cells to colonize and proliferate [11]. Soluble cytokines such as IL-1 and TNF-α in the chronically inflamed tissues are known to facilitate metastatic progression through the stimulation of angiogenesis and tumor-associated macrophages. In the described case, we believe that the prosthetic mucositis could play an important role in the development of the metastasis. In the involvement of the oral cavity, lung metastasis is usually already present, although it is described as direct metastasis to the oral cavity through the vertebral venous plexus. Gingival metastasis usually looks like rapidly progressive hyperplastic growths of an exophytic polypoid tumor, with or without ulceration and undefined margins. Radiolucent undefined areas are possible in bone involvement. Histologic assessment by biopsy becomes essential, though a severe postbiopsy hemorrhage has been reported in some cases, especially in metastatic hepatocellular carcinoma. Immunohistochemical techniques during the anatomopathological studies are essential to confirm the primary or metastatic origin of the tumor [12]. Early lesions, mainly those located in the gum, may resemble hyperplastic or reactive lesions, such as pyogenic granuloma, peripheral giant cell granuloma, hemangioma, or fibrous epulis [13]. The prognosis of a patient with oral metastasis is serious with an average survival rate of 7 months. The best treatment approach will depend on the stage of the disease or other tumors and patient-related factors. Many authors believe local excision (when possible) to be the best treatment regardless of the disease stage [14]. Indeed, when the oral lesion was found to be the only metastatic lesion, resection seemed to result in an improved prognosis. Renal cell carcinoma is known to be largely radioresistant. The usefulness of radiotherapy in the management of intraoral renal metastasis is not fully established. Additional therapeutic options, including immunotherapy, tyrosine kinase inhibitors and clinical trial participation, should be discussed with the patient despite the poor prognosis.

**Take-Home Messages**

- Oral cavity metastatic cancers are very rare and renal cell carcinoma is believed to be the third most common primary cancer.
- Renal cell carcinomas metastasizing to the head and neck region represent 15% of the cases where the gingiva in particular is the most common oral site.
- Chronic gingival inflammation is an important cofactor in the attraction of circulating tumor cells.
- The prognosis is serious and depends on the stage of the disease.
- Local excision is believed to be the best treatment of choice offering both disease volume reduction and potential of cure in the case of oligometastasis.
Statement of Ethics

The authors have no ethical conflicts to declare.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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Fig. 1. Macroscopic appearance.

Fig. 2. Microscopic appearance.
Fig. 3. Positron emission tomography.