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Up-to Date Review and Case Report

Oral metastasis of pulmonary adenocarcinoma: diagnosis and treatment

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Abstract – Introduction: Oral metastases are rare and represent 1% oro-facial neoplasms. The lung is the most common primary site for oral metastatic tumors. The diagnosis is based on histological analysis. Oral metastases have been associated with poor prognosis and is no longer a proven treatment. It was found in a 58-year old man diagnosed with lung cancer with a voluminous mandibular tumefaction following dental avulsion. The panoramic X-ray showed an area of osteolysis compared to the extraction site. The histological and immunohistochemistry of the lesion showed a positivity of the marker CK7 and a negativity of TTF1, in favor of a lung origin. The biomolecular analysis revealed a mutation on the BRAF gene confirming the metastasis primitive origin. Treatment by surgical resection was performed palliatively. **Comments**: The diagnosis of an oral metastasis remains difficult and is based on the histological analysis and finding immune markers. Molecular biology is sometimes required for theranostics. Treatment options include surgical resection, radiotherapy, and/or chemotherapy. They are sometimes limited to preserve the quality of life. The prognosis of patients with oral metastases is very poor. **Conclusion**: Oral metastases are rare, and the diagnosis remains difficult.

Introduction

Oral metastases remain relatively rare and mark a turning point in patient management. It is generally accepted that about 1% neoplasms affecting the orofacial sphere are of metastatic origin [1].

In 25% cases, they come from an unknown primary cancerous source [2].

Oral soft-tissue metastases are less common than bone metastases, and mainly affect the gingiva and tongue [3,4].

Primary pulmonary origin remains the most common source of oral soft-tissue metastases [3].

The discovery of an oral metastasis has a poor prognosis and its management is not yet standardized.

Observation

A 58-year-old patient presented for a consultation in March 2018 with the appearance of a mandibular tumefaction occurring 1 month after the completion of dental avulsion for chronic periodontitis. The history was mainly marked by the absence of healing of the dental avulsion site associated with asthenia and weight loss of 3 kg in 15 days.

The patient's primary history was lung cancer discovered in March 2017 following emphysema–fibrosis syndrome. The chest CT scan and the PET scan initially revealed a hyperintense nodule in right upper lobe, along with increased uptake range at the level of the lower right lobe associated with voluminous mediastinal ipsilateral hyperintense adenopathy in Barety space. Needle aspiration under ultrasound endoscopy was performed to establish the histological diagnosis. It showed a poorly differentiated adenocarcinoma (non-small cell bronchial cancer). Further evaluations did not reveal any remote metastasis. After a multidisciplinary consultation meeting and taking into account the locally advanced stage of pulmonary pathology, an initial chemotherapy treatment was set up with a course of Permetrexed (Alimta®) and Cisplatine (Cisplatin®). Faced with the poor clinical and biological tolerance, two courses of monotherapy by Permetrexed (Alimta®) were subsequently performed and were moderately tolerated as well. The patient refused to continue the chemotherapy. A therapeutic break of 4 months and a radiological follow-up were therefore arranged. The various follow up scans performed from October 2017 showed a slight increase in the number of pulmonary lesions. The patient still did not want to resume treatment despite a proposal for

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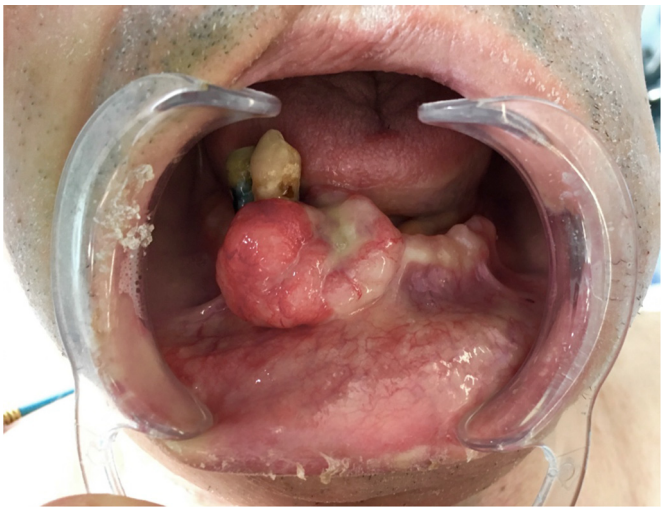

Fig. 1. A burgeoning painful and ulcerated mandibular intraoral lesion.

second-line treatment with Paclitaxel (taxol®); Bevacizumab (avastin®). Simple monitoring was thus put in place until this mandibular swelling first appeared.

The intraoral clinical examination revealed the presence of a voluminous intraoral lesion of about 2 cm in size. It was ulcerated, painful, and nodular lesions were observed in the mandibular area 4 (Fig. 1). The ganglionic areas were unaffected.

The orthopantomogram showed the presence of an osteolytic zone opposite the remaining teeth (Fig. 2). A new evaluation was then performed before the appearance of this lesion. The thoracoabdominopelvic CT scan showed the progression of pre-existing lesions and the appearance of right adrenal metastasis. A bone scan revealed hyperfixation foci in the scapula and right femur.

A biopsy of the mandibular lesion was performed, directing the diagnosis in favor of oral metastasis of bronchial adenocarcinoma. Indeed, the histological analysis found a submucosal capsulated lesion massively invaded by poorly differentiated carcinomatous proliferation, forming small clusters or spans of medium-sized cells with basophilic or clear cytoplasm whose nuclei were atypical chromatic and nucleated. Alcian Blue staining revealed very small vacuoles of intracytoplasmic mucus secretions that showed that it was more than just adenocarcinoma. The immunohistochemical study was negative for P40 and P63 (eliminating the possibility of a squamous cell carcinoma) thyroid transcription factor 1 (TTF1), whereas it was positive for cytokeratin 7 (CK7 +).

This morphological and immunohistochemical profile was that of CK7+, TTF1−adenocarcinoma, which did not correspond to a lesion of primary gingival origin.

A pulmonary origin was strongly suspected considering the clinical context.

A biomolecular study was therefore conducted to investigate lung biomarkers for theranostic purposes and to confirm

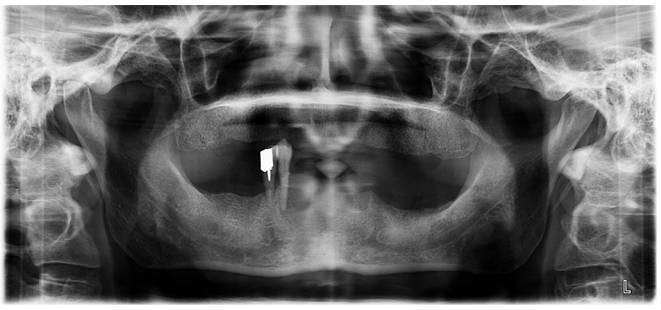

Fig. 2. An orthopantomogram showing signs of osteolysis around the teeth 43/44.

the pulmonary origin of this metastasis. A BRAF gene mutation was detected.

After multidisciplinary consultations, it was decided metastatic resection surgery should be performed given the progression of its neoplastic pathology and the patient's severe dysphagia. Palliative radiotherapy was planned for the postoperative phase.

A segmental mandibulectomy was thus performed in the operating room under general anesthesia, allowing lesion excision (Fig. 3).

Immediately after surgery, the patient was afebrile, had no more oral pain, and was able to resume normal nutrition. Biomolecular studies eventually revealed a BRAF gene mutation in the resected specimen, and targeted therapy was considered.

The patient died before treatment was started, 2 months after his first visit.

Comments

Oral metastases are relatively rare. They represent about 1% neoplasms affecting the orofacial sphere [1]. The discovery of an oral metastasis takes place before the primary tumor is detected in 25% cases; on the other hand, oral metastasis is the first sign of the extension of the neoplastic pathology in 23% cases [2,5].

The lung is the most common primary site for oral metastatic tumors in humans [2,6].

Several cases of lung cancer being diagnosed after the appearance of an oral metastasis have been reported [7,8].

In our case, the pulmonary origin had been diagnosed initially.

The localization of metastases in the oral soft tissue is approximately half as frequent as that in the bone [2]. Among the oral soft tissues, the attached gingiva is the most frequently affected site (60%) with the tongue (18%) [6]. In this case, the involvement was mixed since there were signs of osteolysis on the orthopantomogram.

The pathophysiological mechanisms of metastatic dissemination in the oral cavity are not fully understood. In the literature, it appears that dental avulsions are factors favoring metastatic dissemination [9]. Indeed, the resulting local gingival inflammation would allow the attraction of metastatic

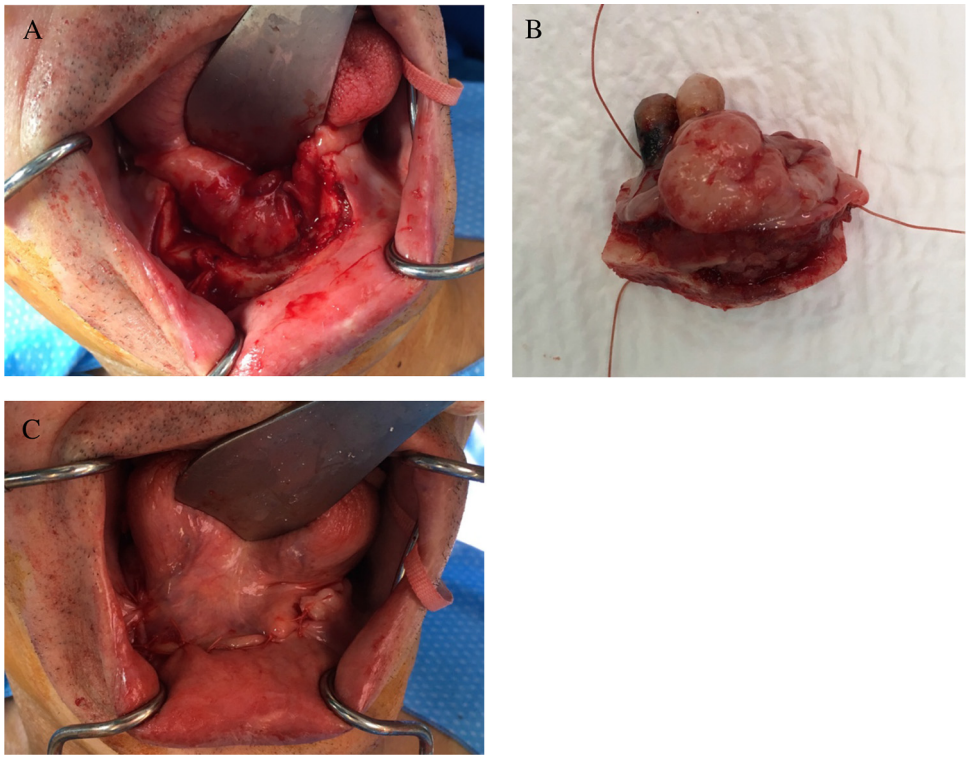

Fig. 3. Metastatic excision surgery. (A) Perioperative view of an uninterrupted partial mandibulectomy with preservation of the inferior alveolar nerve. (B) View of the excised section. (C) Post-operative view immediately after excision and closure of the site.

cells [6,10]. The avulsion, performed sometime before the appearance of the lesion in this patient, has probably played a role in the development of this metastatic tumor lesion.

Clinically, gingival metastases have a fast, painful, hyperplastic mass appearance and has a single lesion in most cases [11]. Multiple lesions are rare [12].

The diagnosis of the primary origin of the cancer is primarily based on histological and immunohistochemical studies [13]. In fact, in the context of a known cancer, the goal is to find a concordance in the expression of the markers of the primary and metastatic tumor [14].

Low-molecular weight cytokeratins (CK7 and CK20) are of primary importance and are routinely used to determine the origin of adenocarcinoma. The CK7+/ CK20− profile is strongly suggestive of a pulmonary, mammary, thyroid, biliary, pancreatic, or ovarian origin [14].

The main specific marker of pulmonary origin of adenocarcinoma is the TTF1 antigen, also expressed in thyroid tumors [15].

In our case, the immunohistochemical profile was that of a CK7+, TTF1− adenocarcinoma, which allowed us to exclude a lesion of primary gingival origin. But the pulmonary origin could only be evoked but not confirmed, considering the TTF1− status.

Immunohistochemical tests have a modest specificity and sensitivity [16]. The use of molecular biology for diagnostic and therapeutic purposes is therefore necessary in certain cases. Indeed, the metastatic tumors have a molecular signature allowing us to determine their primary origin.

The mutations most frequently found in pulmonary adenocarcinoma affect KRAS (25%), EGFR (24%), ALK (6%), and BRAF (3%) genes [15]. A BRAF gene mutation (relatively rare) was found in our case.

The therapeutic strategy for the onset of oral metastasis depends on the primary tumor but is not yet standardized [7]. It is often limited to palliative treatments to improve the quality of life [6,17].

Palliative metastatic surgery, used in our case, prevents pain while eating [18].

Radiotherapy combined with chemotherapy has shown the efficacy in the case of oral metastasis from gastric adenocarcinoma with disease stabilization [19].

The prognosis of patients with oral metastasis is poor with a median survival of about 7 months [6]. For patients with primary pulmonary cancer, the median survival is only 4 months [20].

Conclusion

Gingival metastases are relatively rare. The diagnosis is essentially based on histology as well as immunolabeling. The use of molecular biological examinations is sometimes necessary for theranostics. The treatment is not yet standardized but is often limited to palliative care to improve the quality of life of patients. Once discovered, the prognosis for oral metastasis remains poor.

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