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Medication-related osteonecrosis of the jaw related to epacadostat and pembrolizumab.

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Abstract

MRONJ is a well-known side effect of various medications, such as antiresorptive drugs, anti-angiogenic agents, immunomodulators and immunosuppressants. MRONJ related to immunotherapy is rarely described, with only one case related to ipilimumab. The interaction between the immune system and osteoclast lineage cells is well known. T cells release factors and cytokines that control osteoclastogenesis, and osteoclasts produce factors with an action on T cells. We attempted to explain how immunotherapy could cause MRONJ through the case report of a young patient with metastatic melanoma who developed maxilla MRONJ after pembrolizumab and epacadostat treatment.

Keywords: osteonecrosis, jaw, epacadostat, pembrolizumab, immunology, immunotherapy

Introduction

Medication-related osteonecrosis of the jaw (MRONJ) is a well-known and severe side effect that was first related to the use of bisphosphonates.

The number of MRONJ cases is increasing constantly due to the introduction of new drugs mainly in cancer treatment, such as targeted therapies. The incidence of MRONJ is probably underestimated in these patients due to their short survival.

Only one case of MRONJ associated with immunotherapy (ipilimumab) has been described in the literature [1].

This case illustrates maxillary osteonecrosis in a 28-year-old woman with metastatic melanoma treated with pembrolizumab and epacadostat at the time of osteonecrosis. She never received other medications that could cause MRONJ. We suggest in this case that osteonecrosis is related to pembrolizumab and epacadostat.

Case report

A 28-year-old non-smoking woman was referred by her periodontologist to the maxillofacial department in June 2017 with a 5-month history of pain and infection in the posterior right side of the maxilla. Her past medical history was uneventful except for a surgically treated nodular melanoma on the back in August 2014. Since inguinal sentinel lymph node biopsy was positive, she underwent regional lymph node dissection (1/4 lymph nodes positive for melanoma). The tumour was staged as pT4bpN1acM0 (stage IIIB).

She started adjuvant subcutaneous treatment with interferon for one year from November 2014 until November 2015.

She then presented with a right paralumbar subcutaneous nodule for which she underwent surgery in May 2016. Pathological examination showed transit metastasis expressing BRAF WT, NRAS WT, and cKIT WT. A follow-up was proposed.

PET/CT in November 2016 showed 2 pulmonary suspected nodules in the middle lobe and in the inferior right lobe, and a follow-up was proposed. The control lung CT scan performed 2 months later showed an increase in the size of the middle lobe nodule, compatible with metastasis.

She started 200 mg iv pembrolizumab and 100 mg per os epacadostat every 3 weeks for a total of 4 doses from January 18, 2017 until March 22, 2017.

Four weeks later, she complained of pain and bleeding around the first right maxillary molar (tooth n°16). Intraoral examination by her general dentist revealed good oral hygiene without dental predisposing factors. There was no associated tooth mobility. There was slight swelling and inflammation of the gingiva around this molar. Mild bleeding was described after probing. There was no cold perception on tooth 16. Intraoral X-ray was not specific. A diagnosis of necrotizing ulcerative gingivitis and pulpal necrosis was suggested. She first received a course of 875 mg amoxicillin and 125 mg clavulanic acid for one week without improvement. She underwent root canal treatment with placement of a rubber dam clamp and root planning in March 2017. She did not take any other medication at the time of the oral lesion.

The periodontologist detected bone exposure two weeks later. The patient described exacerbation of the pain and a bad taste in the mouth and received a new course of 875 mg amoxicillin and 125 mg clavulanic acid for 6 weeks. She was also using interdental brushes and chlorhexidine alternately

with 3% hydrogen peroxide mouthwashes without resolution. Gingivitis progressed up to the second molar (tooth n°17).

New melanoma staging with PET/CT in April 2017 demonstrated disease progression with new multiple hepatic and pulmonary metastases. Due to progressive metastatic disease, pembrolizumab and epacadostat were stopped and substituted by ipilimumab (3 mg/kg iv) and nivolumab (1 mg/kg iv) every 3 weeks from April 2017 until June 2017.

Unfortunately, a thoracoabdominal CT scan in June 2017 showed an increase in the size and number of hepatic and lung metastases.

She was referred to the maxillofacial department at that time (June 2017). She still presented with pain and bleeding and felt something rough in the cheek. She described no abscess.

Intraoral examination revealed vestibular necrotic bone exposure 2x1 cm around the first and second right maxillary molars (teeth n°16-17) with mild vestibular root exposure on these 2 teeth (Fig.1). Slight mucosal swelling and light dental mobility were present. Purulent discharge was observed by palpation around the 2 teeth. An orthopantomogram showed a loss of bone around the upper right molars, with right sinusitis.

A CT scan revealed right maxillary sinusitis and osteolysis of the bone around the right maxillary molars, with osteolysis consistent with osteonecrosis (Fig.2).

At follow-up, bone exposure had progressed with large root denudation of the 2 molars, with swelling and erythema of the surrounding gingiva. A vestibular bone sequestrum 7x5 mm in size was easily removed around the first molar without bleeding in July 2017. Histopathological examination showed osteonecrosis and actinomyces associated with inflammatory cells. The final diagnosis was stage 2 MRONJ.

Due to her rapidly evolving metastatic disease, no oral surgical treatment was proposed. She continued with mouth rinses and received morphine to treat the pain caused by the metastases. Immunotherapy was stopped, and treatment was proposed. She died of her disease in October 2017.

Discussion

In this case, the findings were consistent with a diagnosis of MRONJ: exposed bone or bone that could be probed through an intraoral or extraoral fistula in the maxillofacial region that had persisted for longer than 8 weeks, with no history of radiation therapy of the jaw or obvious metastatic disease of the jaw [2], although the medication the patient received at the time of bone exposure was a combination of pembrolizumab and epacadostat. Local symptomatology began 4 weeks after initiation of this treatment. A combination of ipilimumab and nivolumab was started 2 months after the onset of the symptoms.

In most cases, tooth extraction or any dentoalveolar surgery or infection or local trauma represent the triggering factor for MRONJ, even if some cases are spontaneous.

In this case, pulp necrosis and periodontitis could have been the triggering factors of MRONJ and were probably worsened using the rubber dam clamp, which could cause mucosal, periodontal and alveolar bone trauma.

The pathogenesis of MRONJ remains unclear, but decreased bone turnover by changes in osteoclast function, inhibition of angiogenesis, infection, inflammation and soft tissue toxicity have been identified as playing an important role [3].

The treatments implicated are antiresorptive medication (bisphosphonates and denosumab), antiangiogenic agents and, less frequently, immunomodulators and immunosuppressants. MRONJ may also be immune related, as described by Owosho et al [1].

Osteoimmunology focuses on the relationship between the skeletal and immune systems since osteoclasts and T cells share the same bone marrow haematopoietic stem cells [4,5].

The RANK-RANKL-OPG signalling pathway is the most important main regulator of osteoclast proliferation, differentiation and activity. RANKL is expressed by osteoblasts and T cells. RANKL regulates osteoclastogenesis, and T cell activation is one of the most potent triggers of osteoclast differentiation, linking the adaptative immune system and bone resorption [4].

There is intense crosstalk between T cells and osteoclast lineage cells. T cells release factors and cytokines that control osteoclastogenesis, and osteoclasts produce factors with an action on T cells [4,5].

T cells can interact with osteoclasts through cell-to-cell contact or by the production of different cytokines (CKs).

Proinflammatory CKs, such as IL-1, IL-6, IL-7, IL-11, IL-15, IL-17, TNF- α , TNF- β , RANKL, and M-CSF, are pro-osteoclastogenic, as they increase the number and function of osteoclasts directly or induce RANKL expression in osteoblasts. Anti-inflammatory CKs, such as IL-4, IL-5, IL-10, IL-12, IL-13, IL-18, interferon-gamma (IFN- γ), TGF- β and OPG, inhibit osteoclastogenesis by direct or indirect RANKL inhibition. The immune system is thus involved in bone loss and bone regeneration.

All subtypes of T cells can influence bone cell metabolism, especially osteoclast activity [3,5]. *Treg cells*, *Th1 cells*, *Th2 cells*, and *$\gamma\delta$ T cells* can have anti-osteoclastogenic activity, mostly by producing IL-4 and IFN- γ .

Th 17 cells produce IL-17, which is pro-osteoclastogenic. *NK cells* are part of the innate immune response.

NK cells may produce IFN γ to inhibit osteoclastogenesis as well as RANKL and M-CSF to induce osteoclast formation[3].

IFN- γ is produced by various immune cells and is involved in innate and adaptative immune responses, e.g., in the regulation of inflammation. IFN- γ inhibits osteoclastogenesis by promoting TRAF6 degradation in RANKL-induced osteoclast differentiation [5].

Osteoclasts can also act as antigen-presenting cells and stimulate both CD4+ and CD8+ T cells in vitro. Osteoclast precursors proliferate and differentiate in osteoclasts in the presence of different CKs, such as RANKL and M-CSF, produced by stromal cells, osteoblasts and activated T cells [4]. Conversely, bone cells can regulate bone remodelling and immune cells by creating an endosteal niche. On the other hand, immune activation and inflammation induce osteoclast differentiation and rapid bone loss [5].

The question of how epacadostat and pembrolizumab could act on bone metabolism.

Epacadostat is an immunomodulatory drug that inhibits indoleamine-2,3-dioxygenase (IDO1).

IDO1 is the first and rate-limiting catabolic enzyme in the degradation pathway of tryptophan (TRP), which is an essential amino acid. TRP catabolites are kynurenines (KYNs). IDO1 is expressed in all cells

throughout the body and can be locally produced in response to inflammation and infection by cytokines such as IFN γ [6].

Depletion of TRP and increases in KYN induce an immunosuppressive microenvironment; increases in KIN block T cell activation and induce the differentiation and proliferation of Treg cells. Thus, IDO1 downmodulates T cell efficacy [7].

Inhibition of IDO1 by epacadostat increases the efficacy of T cells in the tumour microenvironment.

Epacadostat promotes T cell and NK cell growth with increased production of IFN γ , which inhibits osteoclastogenesis and leads to decreased differentiation of T cells to Treg cells [6].

IDO1 can also promote new blood vessel development, so epacadostat also has antiangiogenic activity [6,8].

Pembrolizumab is an immune checkpoint inhibitor. This anti-PD-1 antibody induces T cell reactivation by preventing the binding of PD-1 with its ligands on the tumour site, thus restoring the immune system [9].

PD-1 is expressed on T-cells, TILs (tumour-infiltrating lymphocytes, mainly CD4+ T cells), B cells, NK cells, monocytes, and dendritic cells. Interaction with its ligands PD-L1 and PD-L2 on tumour cells downregulates T cell activity mostly within peripheral tissues and in the tumour microenvironment, resulting in tumour immune escape [9].

In periodontitis, T cells express higher levels of PD-1. In this case, the blockade of PD-1 results in increased production of IFN γ in the absence of significant T cell proliferation [10].

The side effects of immunotherapy are mostly immune related, occurring via activation of the patient's immune system, and increase with the time of exposure. Immune-related adverse events mainly concern the skin, gastrointestinal tract, liver and endocrine system [9,11]. Concerning the maxillofacial area, Sjögren syndrome, erythema, inflammation, lichenoid lesions, salivary gland dysfunction, and dry mouth are rarely described [12].

How immunotherapy can induce MRONJ is unclear. Activation of T cells usually produces pro-osteoclastogenic cytokines as well as anti-osteoclastogenic cytokines. How osteonecrosis occurs could be through the activation of a subset of anti-osteoclastogenic T cells ($\gamma\delta$ T cells, Treg, Th1, Th2 cells) and NK cells, which induces an increase in the anti-osteoclastogenic CK IFN γ . The anti-angiogenic effect of epacadostat could also be involved.

In this case, the immune stimulation associated with local infection and trauma could have triggered MRONJ.

In conclusion, we described the first case of MRONJ probably associated with immunotherapy (pembrolizumab and epacadostat). A baseline oral examination should be incorporated in the care of cancer patients with immunotherapy. Maintenance of good hygiene and avoidance of invasive oral procedures (tooth extraction, rubber dam clamp position) are necessary to prevent the risk of MRONJ.

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Legends

Figure 1: bone exposure by the 1st and 2d right maxillary molar

Figure 2: CT scan showing right maxillary sinusitis and osteolysis around the 1st right molar



