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Etiologic diagnosis of jaw osteonecrosis, other than bisphosphonate and radiotherapy related osteonecrosis

Diagnostic étiologique des ostéonécroses maxillomandibulaires, ostéonécroses à bisphosphonates et ostéoradionécroses exceptées

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Summary

Our purpose was to highlight the various etiologies of maxillomandibular osteonecrosis, other than radiotherapy and biphosphonate related osteitis that have been abundantly reported. We performed a PubMed search from August 1, 1972 to August 1, 2012 using the following MeSH terms: "osteonecrosis", "bone", "necrosis", "jaw", "maxilla", "mandible", "palate", "oral", "avascular necrosis", NOT "bisphosphonate" NOT "osteoradionecrosis". Most cases of osteonecrosis were iatrogenic. Viral, mycotic, or bacterial infections were less frequent causes. Cocaine abuse, Wegener's granulomatosis, and N/K lymphoma were other etiologies. It is important to identify the various etiologies rapidly to manage this sometimes very mutilating condition adequately.

Keywords: Necrosis, Jaws

Résumé

L'objectif de cette mise au point a été de rechercher les différentes étiologies des ostéonécroses maxillomandibulaires, en dehors des ostéoradionécroses et ostéonécroses sur bisphosphonates faisant l'objet d'une littérature abondante. La recherche a été faite dans PubMed entre le 1er août 1972 et le 1er août 2012 à partir des mots clés du MeSH *osteonecrosis*, *bone*, *necrosis*, *jaw*, *maxilla*, *mandible*, *palate*, *oral*, *avascular necrosis*, *NOT bisphosphonate NOT osteoradionecrosis*. La majeure partie des ostéonécroses sont d'origine iatrogène. Plus rarement des infections virales, mycotiques ou bactériennes peuvent induire une ostéonécrose. L'addiction à la cocaïne, la granulomatose de Wegener et le lymphome N/K peuvent également être mis en cause. L'intérêt est de reconnaître rapidement ces différentes étiologies afin de permettre une prise en charge rapide, l'évolution de certaines de ces ostéonécroses pouvant induire des lésions parfois extrêmement délabrantes.

Mots clés : Nécrose, Mâchoires

Introduction

Maxillo-mandibular osteonecrosis (ON) have been extensively reported since 2003 when bisphosphonates demonstrated to be causative factors for ON. Since then, other agents have been implicated in the genesis of ON, but not all ON are iatrogenic.

Various local or systemic phenomena may take part in ON. "Local factors" may be traumatic, iatrogenic, or related to addictions. "Systemic factors" may be iatrogenic (bisphosphonates, corticotherapy, chemotherapy), hematological disorders (sickle cell anemia, β-thalassemia, coagulation disorders, etc.), metabolic (diabetes, hypercholesterolemia,

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2213-6533/$ - see front matter

hyperlipidemia, Cushing disease, etc.), rheumatologic (disseminated lupus erythematosus, rheumatoid arthritis, etc.), exogenous (alcohol, tobacco) *(fig. 1)*, infectious (viral, bacterial, mycotic), etc. [1,2]. Some genetics factors have been suggested (*CYP2C8* gene polymorphism in bisphosphonate related ON) [3].

ON may be the consequence of direct vascular lesions (traumatic or surgical), or of intrinsic and extrinsic obliterations [2]. "The intrinsic vascular obliteration" may be the consequence of the fat emboli, and/or of gaseous emboli. Sickle cell anemia, hypercoagulability disorders (thrombophilia and hypofibrinolysis, antiphospholipid antibody syndrome, and anticardiolipin syndrome) may also block microcirculation [1,2]. "Extrinsic vascular compression" in the bone marrow may be related to glucocorticosteroid intake or alcohol consumption, which increase bone marrow fat percentage.

Other phenomena may be implicated in ON, besides "mechanical" vascular lesions, including direct toxicity on bone marrow or bone or vascular cells. For example, direct toxicity has been observed on osteocytes after corticosteroids, tobacco, or alcohol intake. Osteoblasts seem to be the most fragile in case of radiotherapy. Osteoclasts are more affected after treatment with bisphosphonate or denosumab [2]. Angiogenesis is inhibited by corticosteroids, interferon, bisphosphonates, and antiangiogenic agents [1].

The specificity of maxillo-mandibular ON is the septicity of the oral cavity; the other localizations of ON are called aseptic necrosis. ON of the mandibular condyle is an aseptic necrosis and shares similar etiological mechanisms with ON of the femoral head. Some isolated cases of mandibular condyle ON have been reported, for example related to trauma, osteotomy, sickle cell anemia, lupus erythematosus, or to corticosteroid therapy (systemic intake or intra-articular injections) [4].

Maxillo-mandibular ON usually presents as an area of exposed bone, often intra-oral, sometimes cutaneous, most of the time infected and painful. The outcome may be relatively destructive.

We had for objective to determine the various etiologies of maxillo-mandibular ON. Osteoradionecrosis and bisphosphonate induced ON have been abundantly reported and were not included in this article.

We performed a PubMed search from August 1, 1972 to August 1, 2012 using the following MeSH terms: "osteonecrosis", "bone", "necrosis", "jaw", "maxilla", "mandible", "palate", "oral", "avascular necrosis", NOT "bisphosphonate" NOT "osteoradionecrosis".

The search included all articles in English, and in any foreign language if an abstract in English was available. We considered only articles concerning humans.

Three etiological groups of osteonecrosis could be determined after this search: iatrogenic ON, ON of infectious origin, and destructive lesions of the mid-face.

Iatrogenic factors

Targeted therapies

Bisphosphonate induced ON was reported in 2003. Since then, other agents used to treat cancer and/or osteoporosis have also been related to the onset of ON. A similar triggering mechanism was described, i.e. local trauma such as oral surgery, or dental infection. The American Association of Oral and Maxillofacial Surgeons' definition of bisphosphonate related ON was also used for targeted therapies, i.e. "exposed bone in the maxillo-facial region for more than 8 weeks, in patients treated or having been treated by bisphosphonate, with no history of head and neck radiotherapy" [5].

Sunitinib

Sunitinib is a tyrosine-kinase inhibitor administrated per os and used most frequently for solid tumors. It is implicated in ON alone or combined with bisphosphonates. Its inhibiting action on the Vascular Endothelial Growth Factor (VEGF) and Platelet-derived Growth Factor (PDGF) receptors induces a modification of angiogenesis, of bone remodeling, and of healing. ON may develop after severe mucitis, a probable triggering factor. Contrary to usual chemotherapy agents, sunitinib may be used over very long periods. The toxic effects could be reversible at treatment interruption or dose reduction [6,7].

Bevacizumab

Bevacizumab, monoclonal antibody inhibiting the Vascular Endothelial Growth Factor (VEGF), is used most often to treat colon and breast cancer. One of its adverse effects is delayed healing of wounds sometimes leading to ON, including by impaired vascularization. An 8 weeks therapeutic window is recommended between treatment by bevacizumab and surgery, or between surgery and bevacizumab initiation to avoid delayed healing of wounds or ON [7,8]. Stopping the treatment could improve healing of the wound.

Denosumab

Denosumab is a monoclonal antibody targeting the Receptor Activator of Nuclear Factor Kappa-B Ligand (RANKL). It is used to treat osteoporosis and bone metastasis. It acts on the differentiation, the survival, and the fusion of osteoclasts by inhibiting their apoptosis, and causes a dysfunction of bone remodelling which could induce ON in case of trauma or of infection. The inhibition of osteoclasts by denosumab could be reversible when stopping the treatment [9].

This type of ON concerns almost exclusively jaws, probably because of their high bone turnover and because of the septicity of the oral cavity. The same pre- and post-dental treatment precautions used for bisphosphonates, are recommended with targeted therapy.