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Case report

Association of osteonecrosis of the jaws and POEMS syndrome in a patient assuming rituximab

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ABSTRACT

POEMS syndrome, is a rare condition characterized by polyneuropathy, organomegaly, endocrinopathy, monoclonal proteinaemia, and skin lesions.

We report a rare case of a patient affected by Waldenström macroglobulinemia, who developed POEMS syndrome and who presented at the time of diagnosis with oral manifestations of the lymphoma and an osteonecrosis of the jaw (ONJ) after rituximab treatment.

Although the etiology of ONJ is not known, it is likely that several factors are at play, including endothelial cell damage, decreased angiogenesis, and microvascular compromise. Our patient was treated with rituximab for a long period, and recent studies have demonstrated the possibility that rituximab, a monoclonal antibody directed against the CD20 can exert part of its anti-tumor action, through its action on angiogenesis.

Although our report does not allow identification of rituximab as a new risk factor for the onset of the ONJ, further studies seem necessary to exclude a role of the antibody in the alterations of angiogenesis that could lead to the development of the syndrome after rituximab treatment.

1. Introduction

POEMS syndrome, is a rare condition characterized by polyneuropathy, organomegaly, endocrinopathy, monoclonal proteinaemia, and skin lesions. It is typically associated with plasma cell dyscrasias and a monoclonal band on serum electrophoresis (Bardwick et al., 1980).

The misdiagnosis of the POEMS syndrome is very common due to its rarity and complicated clinical manifestations, and a delay in diagnosis can lead to serious consequences as, within two years of diagnosis, approximately one-quarter of patients develop respiratory symptoms, which includes restrictive lung disease and pulmonary hypertension, while acute ischemic strokes and myocardial infarcts have occasionally been reported in association with POEMS (Dispenzieri et al., 2003).

The overall median survival of patients with POEMS is 13.7 years, but those with clubbing or extra vascular volume overload had median survivals of 2.6 and 6.6, respectively (Rathore et al., 2011).

There is no standard treatment for POEMS syndrome. Historically, local irradiation and low-dose alkylator along with steroids had been the mainstay of the treatment of POEMS syndrome. Recently, high-dose melphalan with autologous peripheral stem cell transplantation has made impressive progress in the treatment of POEMS syndrome; the response rate of the neuropathy is almost 100% and the response rate of other specific features of POEMS syndrome is also 70%–90%. However, the treatment-related morbidity of transplantation is high, as 50% of patients had engraftment syndrome and 37% of patients required mechanical ventilation. In addition, the transplantation-related mortality is 7.4% (Li et al., 2011).

In recent years, rituximab therapy has been employed in some patients, and Kawano et al. (2010) presented a case report presenting a POEMS syndrome associated with WM treated with rituximab and thalidomide.

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Rituximab is a monoclonal, chimeric (mouse/human) anti-CD20 antibody. CD20 is a molecule only found in most mature B cells, and it is absent from either bone marrow stem cells or pro-B cells.

Anti-CD20 antibodies cause the death of tumor cells through several mechanisms. Binding of antibody to CD20 may activate the complement cascade through C1q, leading to cell death or deposition of complement proteins on the cell membrane, a phenomenon known as complement-dependent cytotoxicity. Antibody-coated cells may be killed by immune cells expressing Fcγ receptors through antibody-dependent cell mediated cytotoxicity. Finally, antibody binding to CD20 may have direct antiproliferative effects or may actively induce apoptosis. These effects appear to be additive and possibly synergistic when anti-CD20 antibody therapy is combined with chemotherapy (Reff et al., 1994).

As with the other biologic agents utilized, rituximab use carries potential risks. The most common side effects include non-life threatening infusion reactions (nausea, hypertension, pruritus, chills, rigors, etc.) in up to a third of patients following their first dose and infections in up to 39% of treated patients. The majority of infections were due to upper-respiratory tract and urinary tract infections, possibly associated with secondary hypogammaglobulinemia. The incidence of serious infections (pneumonia, cellulitis, and sepsis) was reported in approximately 2% of rituximab treated patients.

Much less frequently, although of greater concern, are potential severe infusion reactions (including cardiac arrhythmias, myocardial infarctions, cardiogenic shock, and death), progressive multifocal leukoencephalopathy due to JC virus infection and reactivation of hepatitis B (Beers et al., 2010).

We present a case of a patient affected by Waldenström macroglobulinemia (WM), a lymphoproliferative disorder characterized by the production of serum monoclonal IgM (mIgM) and lymphoplasmacytic bone marrow infiltration, who developed POEMS syndrome and who presented at the time of diagnosis with oral manifestations of the lymphoma and an osteonecrosis of the jaw (ONJ) after rituximab treatment (Morel and Merlini, 2012).

Although previous papers have described cases of ONJ in patients undergoing chemotherapy without a history of BP exposure (Nastro et al., 2009), in our paper we try to explain the possible mechanism of action of rituximab.

2. Case report

The first hematological disease was diagnosed when the patient was 56-year-old. In April 2010 physical examination showed enlarged latero-cervical and axillary lymph nodes. IgM was elevated up to 1117 mg/dl.

Immune fixation showed a monoclonal IgM gammopathy of type kappa.

The other laboratory findings revealed white blood cells, 8.7 × 109/l hemoglobin, 9.2 g/dl; and platelets, 301 × 109/l. ANA was negative (1:50). The serum levels of IgG, and IgA were normal, serum LDH was 438 IU/L.

Serologic tests for hepatitis B virus, hepatitis C virus were negative, and cryoglobulins were absent in the serum.

A bone marrow aspirate and a trephine biopsy specimen showed infiltration by lymphoplasmacytoid cells and immunophenotyping of a bone marrow sample confirmed positive cytoplasmic IgM K expression. A skeletal survey was normal.

Therefore we diagnosed a lymphoplasmacytic lymphoma.

The patient was treated with standard six cycles of R-CVP regimen consisting of 750 mg/m^2 cyclophosphamide intravenously on day 1; 1.4 mg/m^2 of vincristine intravenously, on day 1; and 40 mg of prednisone per day orally on days 1–5. Rituximab at a dose of 375 mg/m^2 was administered the day before the CVP cycle. In January 2011 a bone marrow biopsy revealed a complete remission and the patient was then treated with Rituximab quarterly until March 2012.

At this time he developed a mucosal ulceration localized in the right mandibular edentulous alveolar process.

A tooth extraction was carried out four months before. The patient was initially treated with systemic and locally delivered anti-inflammatory drugs, without success. Subsequently the mucosal lesion enlarged, showing a purulent exudation and the exposure of an underlying alveolar bone sequestrum (Fig. 1a).

Two biopsies from the oral mucosal and from the alveolar bone were performed (Fig. 1b).

Histology revealed oral manifestations of the lymphoma, an abscess in the oral soft tissues, and necrosis of the alveolar bone (Fig. 2a–c).

A mandibular CT confirmed the presence of a large osteonecrotic lesion of the right mandibular body, involving alveolar and basal bone (Fig. 3a,b).

A bone marrow aspirate and a trephine biopsy specimen showed infiltration by lymphoplasmacytoid cells and immunophenotyping of a bone marrow sample confirmed positive cytoplasmic IgM K expression.

On examination, he was pale with peripheral edema, exophthalmos (Fig. 4a), and excess sweating. His liver and spleen were palpable 2 cm below the costal margin, and he presented latero-cervical, and axillary lymphadenopathy. Finally, he presented cutaneous hyperpigmentation of the thorax, thick skin (Fig. 4b), clubbing, hyperhidrosis, and Raynaud phenomenon. He also had symmetrical paresthesias, numbness, weakness, foot drop, abnormal gait and burning pain of the lower limbs. The management of pain required opioid use.

Neurophysiological studies included motor and sensory conduction velocities and EMG examinations of distal arm and leg muscles revealed a sensory-demyelinating polyneuropathy, particularly affecting the legs.

Serum protein electrophoresis revealed the presence of an IgM K monoclonal band.

Blood glucose was 191 mg/dl indicating diabetes mellitus. Serum testosterone, thyroid stimulating hormone, and cortisol concentrations were normal.

Serum anti-MAG IgM/k antibody titer was 144.000 BTU; other antibodies to neuropathy-related-antigens as well as other toxic, metabolic, neoplastic, hereditary and infective causes of neuropathy were excluded.

Our patient fulfilled the diagnostic criteria for POEMS syndrome, and he was treated with standard CHOP regimen consisting of

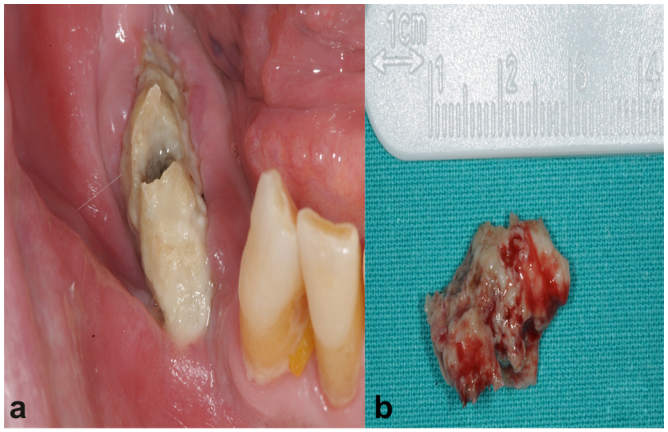

Fig. 1. a) Mandibular lesion showing mucosal ulceration, purulent exudation and bone necrotic exposure. b) Bone sequestrum removed from right mandibular alveolar bone.