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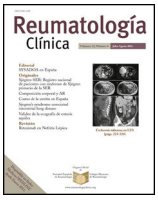

Letter to the Editor

Successful use of azathioprine in glucocorticoid refractory immune amegakaryocytic thrombocytopenia of lupus

El uso exitoso de azatioprina en la trombocitopenia amegacariocítica inmune glucocorticoide refractaria del lupus

Dear Editor:

Amegakaryocytic thrombocytopenia is a rare complication of systemic lupus erythematosus (SLE). Consequently, evidence for its treatment is limited to case reports.[1–3] Here we report successful use of azathioprine in this setting.

A 48-year-old woman presented with polyarthralgia involving bilateral small and large joints, low-grade fever, and easy fatigability of eight years duration. She had Raynaud phenomenon but no skin rashes, oral ulcers, sicca symptoms or photosensitivity. The examination was unremarkable except for minor pedal edema.

For last two months, her creatinine had been elevated (3.3 mg/dL). She had bland sub-nephrotic proteinuria and bilateral shrunken kidneys on sonography. She had been having intermittent thrombocytopenia in the past. Platelet count was 80,000/mm^3 at her first presentation. She had never been worked up for lupus before, given the mild and intermittent nature of her arthralgia, and non-specific symptoms. Anti-nuclear antibody was positive by immunofluorescence in a speckled pattern. Anti-double-stranded DNA antibody was more than 300 IU/mL, complement levels were normal and Direct Coombs test was negative. She was initiated on 0.25 mg/kg prednisone and hydroxychloroquine with a diagnosis of systemic lupus erythematosus. She came back a week later with high-grade fever. This time she had thrombocytopenia of (10,000/mm^3) and lymphopenia (300/mm^3). The diagnostic possibilities considered were lupus disease activity, Macrophage Activation Syndrome (MAS) and viral fever. Serology for Dengue and Epstein–Barr virus were negative, as was polymerase chain reaction for Cytomegalovirus. Hemoglobin of 11.6 g/dL, normal aspartate transaminase (16 IU/L), alanine transaminase (21 IU/L), and coagulation parameters made MAS unlikely. A bone marrow biopsy revealed reduced megakaryocytes with preserved erythroid and myeloid precursors, and plasma cell infiltrate in the interstitium. It ruled out myelophthisis from infiltrative disorders such as myelofibrosis, infections and neoplasia. She was not on any drug that could cause thrombocytopenia, nor had any evidence of exposure to toxins. Thus, with a background of lupus, she was diagnosed as having immune-mediated amegakaryocytic thrombocytopenia. Initially, she was administered intravenous methylprednisolone at a dose of 1 g daily for three days and then, intravenous immunoglobulin at a dose of 1 g/kg daily for two days. The platelet count rose to 80,000/mm^3 over the next seven days, but the rise was ill sustained, necessitating the addition of another immunosuppressant. The literature on therapeutic options in this setting is limited to occasional reports of Cyclosporine, Rituximab, and Eltrombopag. Due to the presence of end-stage renal disease as well as cost considerations, azathioprine (AZA) was considered. The dose was gradually escalated from 25 mg/day to 125 mg/day. Platelet counts stabilized at >100,00/mm^3 by two months. The patient has done well over 3 years after initiating AZA, without further thrombocytopenia or new organ involvement related to lupus.

It has been long believed that bone marrow aplasia in lupus is an exception rather than the rule.[4] Recent series have described aplasia in 10–50% of biopsies from lupus patients, suggesting it may be more common than previously thought.[5,6] In amegakaryocytic thrombocytopenia, the pathogenesis is believed to be immune-mediated. Antibodies to the thrombopoietin receptor (c-Mpl) can block signaling on megakaryocytes, thereby halting maturation of platelets in the bone marrow.[7,8] T-cells in lupus have inhibitory effects on Colony forming unit-Monocyte (CFU-M).[9] Change in T helper to suppressor cell ratio was one of the earliest cited reasons for impaired megakaryopoiesis.[4] The infiltration of plasma cells in the bone marrow in our patient is surrogate for immune-mediated pathogenesis, though we haven't substantiated this by the antibody or in vitro T cell assays.

Since there is evidence of a role of both cell-mediated and humoral factors in the pathogenesis of this entity in lupus, azathioprine may be a good choice when other therapies fail or cannot be used. In our knowledge, literature on the use of AZA in this setting is limited to a single case report.[10] With successful treatment in our patient, we suggest that azathioprine should be added to the armamentarium to treat this rare entity.

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Conflict of interests

None to report.

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Cervical abscess as an exceptional presentation of advance bisphosphonate-related osteonecrosis of the jaw: Case report and review of the literature☆

Absceso cervical como forma de presentación excepcional de osteonecrosis mandibular avanzada inducida por bisfosfonatos. A propósito de un caso y revisión de la literatura

Dear Editor,

Bisphosphonates (BPP) are a group of synthetic analogous drugs of inorganic pyrophosphate used intravenously in the treatment of different oncological processes and in solid tumour bone metastasis (breast, prostate and lung), which do not increase survival but have been demonstrated to raise quality of life.[1] However, they present the serious side effect of inducing osteonecrosis of the jaw (ONJ).

We present the case of a Caucasian woman aged 65 with no toxic substance (tobacco) habits or medical history of interest (diabetes, chronic intake of corticoids, etc.), but with the added risk factor of impaired dental status (many root remnants) and active periodontal disease. She was diagnosed in 2013 with stage IV advanced breast cancer (CT4N2bMx) which required surgical intervention (tumorectomy and axillary node dissection), and treatment was completed with radiotherapy (RT) and polychemotherapy. After successive controls, in 2014 a bone scan detected metastatic foci on the right ala of the sacrum and the spine, with severe pain. Treatment was initiated with intravenous BPP (zoledronic Acid, Zometa® 4 mg/3 weeks). The patient was treated in our unit in 2015 because she spontaneously presented with a right submandibular abscess (Fig. 1) which was initially drained under local anaesthesia, obtaining 150 mL of purulent, cheese-like material, which tested positive for *Actinomyces israelii*. She was subsequently admitted to hospital for examination and treatment with broad spectrum antibiotics for the condition and for pain management. Although the intraoral examination did not reveal any findings of interest, the CAT scan showed the existence of a wide area of osteonecrosis in the right half of the jaw region (Fig. 2). After medical treatment for one week (amoxicillin 1 g/8 h and daily mouthwashes every 8 h with chlorhexidine 2% solution), the patient underwent surgery with a general anaesthesia, with extensive curettage of the wound. Highly favourable medical evolution proceeded until her death in 2017 from the baseline neoplastic process.

BPP-induced ONJ has been widely covered in the scientific literature, but despite the fact there are numerous publications which attempt to explain its aetiopathology, is aetiopathogenic mechanism has not yet been fully defined.[2] At present there are 4 stages to classify ONJ, according to the regulations established by the American Association of Oral and Maxillofacial Surgeons, with the presented case corresponding to the most advanced stage (stage 3).[3] In the case presented zoledronate (Zometa®) is considered to be the most powerful BPP, 100 times superior to pamidronate, having demonstrated with its use that the appearance of ONJ is higher and earlier than that of other BPP, with intravenous administration of them being the main factor of risk for the appearance of ONJ. The most normal form of presentation of ONJ is progressive, both clinically and radiographically and the presented case is therefore exceptional although several authors such as Kaehling et al.[4] and Soda et al.[5] have communicated different case of thromboembolism of the internal jugular vein and subsequent sepsis in the first case and retropharyngeal abscess in the second, as the form of presentation of the ONJ. The explanation lies in super infection of the bone by different pathogenic agents, with the main one being *A. israelii*, and in the action of the BPP on the adjacent soft tissues.

To conclude, the possibility of developing an ONJ has to always be contemplated in patients at risk (oncological patients who have previously been treated with RT), despite its unusual presentation in the form of an abscess, the appearance of it is a relevant data in clinical suspicion of ONJ, requiring personalized treatment, depending on the clinical and radiographic findings of the patient.

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