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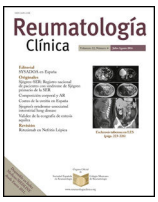

Letter to the Editor

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.

References

1. Fukushima T, Dong L, Sakai T, Sawaki T, Miki M, Tanaka M, et al. Successful treatment of amegakaryocytic thrombocytopenia with anti-CD20 antibody (rituximab) in a patient with systemic lupus erythematosus. Lupus. 2008;17:210–4, http://dx.doi.org/10.1177/0961203307086032
2. Cela I, Miller IJ, Katz RS, Rizman A, Shammo JM. Successful treatment of amegakaryocytic thrombocytopenia with eltrombopag in a patient with systemic lupus erythematosus (SLE). Clin Adv Hematol Oncol. 2010;8:806–9. Available from: https://www.ncbi.nlm.nih.gov/pubmed/21326158
3. Tristano AG. Acquired amegakaryocytic thrombocytopenic purpura: review of a not very well-defined disorder. Eur J Intern Med. 2005;16:477–81, http://dx.doi.org/10.1016/j.ejim.2005.04.014

4. Kuwana M, Kaburaki J, Okazaki Y, Miyazaki H, Ikeda Y. Two types of autoantibody-mediated thrombocytopenia in patients with systemic lupus erythematosus. Rheumatology. 2006;45:851–4, http://dx.doi.org/10.1093/rheumatology/kel010
5. Kuwana M, Okazaki Y, Kajihara M, Kaburaki J, Miyazaki H, Kawakami Y, et al. Autoantibody to c-Mpl (thrombopoietin receptor) in systemic lupus erythematosus: relationship to thrombocytopenia with megakaryocytic hypoplasia. Arthritis Rheum. 2002;46:2148–59, http://dx.doi.org/10.1002/art.10420
6. Nagasawa T, Sakurai T, Kashiwagi H, Abe T. Cell-mediated amegakaryocytic thrombocytopenia associated with systemic lupus erythematosus. Blood. 1986;67:479–83. Available from: https://www.ncbi.nlm.nih.gov/pubmed/3484642
7. Griner PF, Hoyer LW. Amegakaryocytic thrombocytopenia in systemic lupus erythematosus. Arch Intern Med. 1970;125:328–32. Available from: https://www.ncbi.nlm.nih.gov/pubmed/5412024
8. Chalayer E, Costedoat-Chalumeau N, Beyne-Rauzy O, Ninet J, Durupt S, Tebib J, et al. Bone marrow involvement in systemic lupus erythematosus. QJM. 2017, http://dx.doi.org/10.1093/qjmed/hcx102
9. Pereira RM, Velloso ER, Menezes Y, Gualandro S, Vassalo J, Yoshinari NH. Bone marrow findings in systemic lupus erythematosus patients with peripheral cytopenias. Clin Rheumatol. 1998;17:219–22. Available from: https://www.ncbi.nlm.nih.gov/pubmed/9694056
10. Chang H, Tang TC. Successful treatment of amegakaryocytic thrombocytopenia with azathioprine. Acta Haematol. 2011;126:135–7, http://dx.doi.org/10.1159/000328031

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

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

Sr. Editor:

Los bisfosfonatos (BFF) constituyen un grupo de medicamentos análogos sintéticos del pirofosfato inorgánico empleados vía intravenosa en el tratamiento de distintos procesos oncológicos y en metástasis óseas de tumores sólidos (mama, próstata y pulmón), que si bien no inducen un aumento en la supervivencia, han mostrado un incremento en la calidad de vida[1]. Pese a ello, presentan el grave efecto secundario de inducir osteonecrosis maxilar (ONM).

Presentamos el caso de una mujer de raza caucásica de 65 años de edad sin hábitos tóxicos (tabaquismo) ni antecedentes médicos de interés (diabetes, ingesta crónica de corticoides...), con el factor de riesgo añadido de estado dental deficitario (múltiples restos radiculares) y enfermedad periodontal activa, diagnosticada en 2013 de carcinoma mamario avanzado EIV (CT4N2bMx) precisando intervención quirúrgica (tumorectomía y disección axilar), completándose el tratamiento con radioterapia (RT) y poliquimioterapia. Tras sucesivos controles, en 2014 se detecta mediante gammagrafía ósea (GAO) focos metastásicos en ala derecha de sacro y columna vertebral, con clínica de dolor severo iniciando tratamiento con BFF por vía intravenosa (Ac. zoledrónico, Zometa® 4 mg/3 semanas). La paciente es atendida en nuestra unidad en 2015 por presentar de forma espontánea absceso submandibular derecho (fig. 1) que fue drenado bajo anestesia local en primera instancia, obteniéndose 150 mL de material purulento y caseoso, positivo para *Actinomyces israelii*. Posteriormente fue ingresada para estudio y tratamiento con antibioterapia de amplio espectro y control del dolor. Pese a que el examen intraoral no mostró hallazgos de interés, el estudio radiográfico por tomografía axial computarizada (TAC) mostró la existencia de área extensa de osteonecrosis en región hemimandibular derecha (fig. 2). Tras mantener tratamiento médico durante una semana (amoxicilina 1 g/8 h y enjuagues diarios cada 8 h con clorhexidina al 2%), la paciente fue intervenida con anestesia general, practicándose legrado extenso de la lesión. Se constató con posterioridad una evolución clínica muy favorable hasta su fallecimiento en febrero de 2017 por su proceso neoplásico de base.

La ONM inducida por BFF se encuentra ampliamente recogida en la literatura científica, pero a pesar de que hay numerosas publicaciones que tratan de explicar su etiopatología, su mecanismo etiopatogénico no se encuentra aun completamente definido[2]. Actualmente se consideran 4 estadios para las clasificar la ONM según las normas establecidas por la American Association of Oral and Maxillofacial Surgeons, correspondiendo el caso presentado al estadio más avanzado (estadio 3)[3]. En el caso expuesto, el zoledronato (Zometa®), se considera el BFF de mayor potencia, 100 veces superior al pamidronato, habiéndose demostrado que con su empleo la aparición de ONM es superior y más precoz que con respecto a otros BFF, constituyendo la administración intravenosa de los mismos el principal factor de riesgo de aparición de ONM. La forma de presentación más habitual de la ONM es de forma progresiva, tanto clínica como radiográficamente, de ahí que el caso presentado sea excepcional, pese a ello, algunos autores como Kaehling et al.[4] y Soda et al.[5] han comunicado distintos casos de tromboembolismo de la vena yugular interna y posterior sepsis en el primer caso y absceso retrofaríngeo en el segundo, como forma de

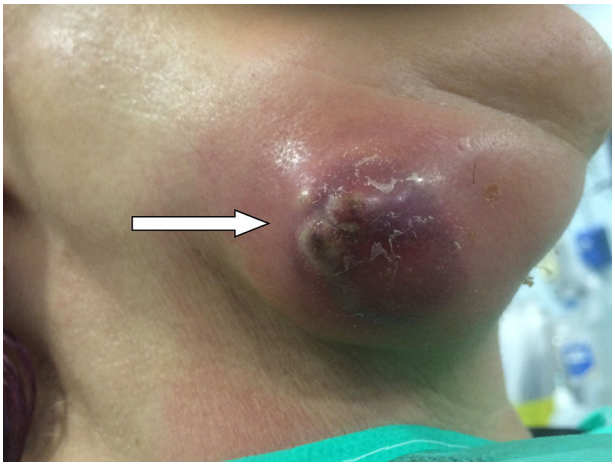

Figura 1. Voluminoso absceso submandibular derecho (flecha blanca).