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# Reumatología Clínica

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## Letters to the Editor

### Macrophage Activation Syndrome: Experience in the Questioned Role of Etoposide<sup>☆</sup>



#### Síndrome de activación macrófágica: experiencia sobre el cuestionado papel del etopósido

To the Editor,

Reactive hemophagocytic lymphohistiocytosis (HLH), or macrophage activation syndrome (MAS), is an unusual complication of systemic inflammatory diseases.<sup>1</sup> Its association with juvenile idiopathic arthritis (JIA) is rare and treatment must be immediate. We report the case of a girl in whom we detected this association and treated it successfully with a drug that is not first-line therapy because of its potential adverse effects.

The patient was a 9-year-old girl who had recently been diagnosed as having JIA. She was admitted to the hospital after a 3-day history of persistent fever (40 °C) and generalized facial edema, presumably associated with methotrexate she was taking, a treatment that was interrupted. At admission, she was pale, had painful hepatosplenomegaly and an increase in the volume of several joints. Laboratory tests showed pancytopenia (hemoglobin 6.4 g/dL; 132,000 platelets/mm<sup>3</sup> and 1080 neutrophils/mm<sup>3</sup>), prothrombin time and partial thromboplastin time were increased (16.8" and 59.2", respectively) and fibrinogen was decreased (164.7 mg/dL).

Treatment was begun with methylprednisolone and paracetamol, but the fever persisted. The suspicion of MAS led to tests that revealed hypertriglyceridemia (291 mg/dL) and elevated ferritin (9579 mg/mL). Myelogram disclosed bone marrow with spicules, activated macrophages with cytophagocytosis of cell debris and erythroblast nuclei (Fig. 1). Bacterial cultures of urine, blood and bone marrow were negative. It was decided to begin treatment with methylprednisolone pulses (1000 mg/day for 3 days) plus cyclosporine A (2 mg/kg body weight [bw]/day). The general status of the patient improved and the fever disappeared; however, the biochemical profile showed no changes. Thus, we started to administer intravenous etoposide (150 mg/m<sup>2</sup>/day), the dose of cyclosporine A was increased (4 mg/kg bw/day) and prednisone therapy was maintained (1 mg/kg bw/day). The patient had a favorable clinical and biochemical course. Twelve days after receiving etoposide, she was asymptomatic and was discharged. Thereafter, we continued monitoring the patient for clinical and biochemical follow-up, which corroborated her improvement through the laboratory results (acute-phase reactants at normal levels).

Macrophage activation syndrome is associated with a high mortality rate (22%).<sup>2,3</sup> For this reason, early diagnosis and proper treatment are essential to ensure the best possible prognosis. Etoposide, also referred to as VP-16, has an accelerated cellular mitosis and induces apoptosis. The cytotoxicity it generates causes alopecia, constipation, nausea, myelosuppression and secondary

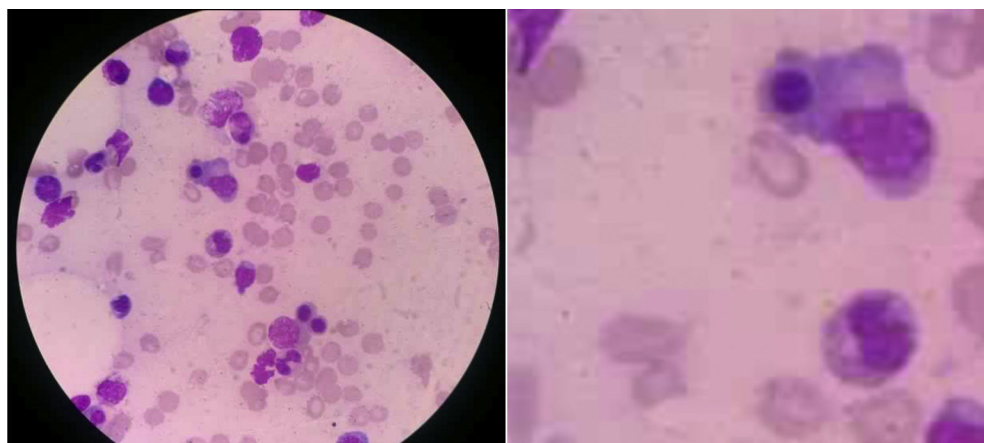


Fig. 1. Bone marrow aspiration. The cytopathology of this tissue shows active hemophagocytosis on the part of macrophages (hematoxylin-eosin staining, 1000×).

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malignancy (leukemia); these effects are potentiated with the simultaneous use of cyclosporine A. For refractory HLH, it is recommended that there be an initial induction phase (2 weeks) with etoposide, cyclosporine A and dexamethasone,<sup>4,5</sup> to be followed by 6 weeks of etoposide, if necessary.<sup>5</sup> The utilization of this medication is still controversial, and there is a lack of consensus as to fully recommending its use because of paradoxical effects involving myelosuppression. This alternative is recommended only in refractory cases.<sup>5,6</sup> Etoposide has been previously utilized in 8 patients with MAS and induced a favorable and rapid response in each case, with no adverse effects.<sup>7–9</sup>

In this instance, etoposide was added because the patient showed resistance to standard therapy. She received only 3 doses because of its high toxicity and the development of pancytopenia. The strategy we employed was successful; however, it proposes a strict control of the etoposide combined with the suggested treatment.

We presented MAS, a condition that is not very common, that was refractory to standard treatment. Thus, we opted for the use of etoposide. The patient we report progressed favorably. Nevertheless, as it is just a single case, we do not recommend generalizing this approach. The outcome can be taken into account in future studies that attempt to establish a complete scheme for the treatment of refractory reactive HLH.

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## Osteoid Osteoma of the Knee Mimicking Juvenile Psoriatic Arthritis<sup>\*</sup>



### Osteoma osteoide de rodilla simulando artritis psoriásica juvenil

To the Editor,

We read very attentively the letter by Moreno-Martinez et al.,<sup>1</sup> who describe a case of pelvic osteoid osteoma (OO), in which the clinical signs and symptoms were compatible with sacroiliitis. We would like to report another OO that developed in knee, that suggested a diagnosis of juvenile psoriatic arthritis (JPA).

A 15-year-old boy presented with an 8-month history of mechanical pain in right knee. It would be intermittent at first and later become continuous, making it difficult for him to walk, and swelling was observed in that area. The treatment consisted of nonsteroidal anti-inflammatory drugs (NSAID), initially ibuprofen, which was replaced by diclofenac, but there was no improvement. He had no history of injury, fever or constitutional symptoms, or manifestations affecting any other peripheral or axial joint or enthesitis. He had been diagnosed with guttate psoriasis at the age of 10 years, with occasional episodes until he was 13, and was treated with topical glucocorticoids; however, he had no family history of psoriasis, psoriatic arthritis, ankylosing spondylitis or inflammatory bowel disease. Physical examination revealed

muscle atrophy in distal thigh and swelling in right infrapatellar region, which was warm, and he had a limitation in last few degrees of flexion, but with no signs of joint effusion. The results of laboratory tests, including biochemical analyses, complete blood count and acute-phase reactants (erythrocyte sedimentation rate 6 mm/h, C-reactive protein 2.31 mg/dL) were normal. Human leukocyte antigen (HLA) typing revealed the presence of Cw6, DR4 and DQ8 haplotypes, but not B27, and the patient was negative for rheumatoid factor and antinuclear antibodies. Plain radiography of the knees showed a sclerotic area in the upper third of right tibia (Fig. 1A and B), which, according to computed tomography (CT), corresponded to an osteolytic lesion measuring 5 mm in diameter in anterior tibial tuberosity, with a “nidus” formed by an ossified matrix, compatible with OO (Fig. 2B and C), with extensive sclerosis of the medullary bone and a solid periosteal reaction in the adjacent cortical bone. Magnetic resonance revealed intense contrast uptake in and around the lesion, as well as in the surrounding bone edema and the Hoffa fat pad (Fig. 2C and D). Bone scintigraphy disclosed hyperemia and a focal increase in the osteogenic response in the proximal epiphysis of right tibia, with no other significant changes. The patient underwent CT-guided radiofrequency ablation, and the pain disappeared a few days after the procedure, and he recovered complete mobility 1 month later, although he had mild persistent muscle atrophy.

Osteoid osteoma is a relatively common, benign bone neoplasm that constitutes between 10% and 12% of benign bone tumors. It usually develops between the ages of 10 and 20 years (although it has been reported in smaller children), and the ratio of males-to-females is 2–3:1.<sup>2,3</sup> It most often affects the lower limbs, and is

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