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Adverse Effects of Immunosuppressive Therapy in Rheumatic Patients: Non-tuberculous Mycobacterial Infection☆

Efectos adversos de terapia inmunosupresora en paciente reumatológico: infección por micobacterias no tuberculosas

To the Editor,

Mycobacterium chelonae is a rapidly growing mycobacterium that causes skin and soft tissue infections after trauma in immunocompetent individuals and in immunocompromised hosts with disseminated disease, especially in patients with rheumatic diseases receiving immunosuppressive therapy.[1–3]

We report the case of a 29-year-old woman whose medical record included systemic lupus erythematosus, sarcoidosis and a 4-year history of sickle cell anemia plus β-thalassemia. At the time of writing, she was being treated with rituximab (she had received 2 cycles of 1 g each), azathioprine 100 mg/day, methylprednisolone 16 mg/day and hydroxyurea 1 g/day. She was admitted to a quaternary care center with a 3-month history of pain in her right hip. Drug treatment with a variety of analgesics and multiple local injections in right hip and gluteus resulted in a partial improvement of her symptoms. One month later, the clinical symptoms returned and she presented with an abscess in right gluteus, with local inflammatory changes. Physical examination revealed the presence of a painful nodule. She underwent surgical drainage of the abscess, and cultures for the usual bacteria, fungi and mycobacteria (auramine–rhodamine stain and culture in Löwenstein–Jensen solid medium) were negative. Antibiotic therapy was initiated with ceftriaxone + vancomycin and ampicillin/sulbactam, with no improvement whatsoever. A biopsy was performed with the drained material, and the latter was analyzed by polymerase chain reaction (PCR) for the detection of mycobacteria, in which *M. chelonae* DNA was isolated. The patient began treatment with clarithromycin 1 g/day and moxifloxacin 400 mg/day in May 2014, with which she continued at the time of writing, with resolution of the clinical condition.

Nontuberculous mycobacteria constitute a group of species that includes *Mycobacterium abscessus* (with 3 subspecies), *M. chelonae* and *Mycobacterium fortuitum*, which are widely distributed in nature.[4]

As a pathogen in humans, *M. chelonae* has a number of clinical forms, the severity of which ranges from frequent mild skin and soft tissue infections to potentially fatal systemic infections.

Skin infection is the most common clinical condition in immunocompetent individuals, and is usually preceded by an injury, open fracture, wound from a sharp, cutting weapon, or a surgical procedure (especially plastic surgery).[5]

In immunocompromised individuals, this pathogen causes disseminated skin infections, and the entry route or route of transmission is generally unidentified. The clinical manifestations consist of infections in organs and skin abscesses that generally affect the lower extremities. Localized injuries can also cause infections (cellulitis, abscesses and osteomyelitis), as can surgical wounds and catheters, although to a lesser degree.

It is important that general practitioners, when treating patients with autoimmune diseases and using biologic therapies, have a high index of suspicion of infection by *M. chelonae*, founded on 3 criteria: (a) a previous skin lesion, mainly from cosmetic or surgical procedures; (b) the presence of painful subcutaneous nodules and abscesses at the site of the lesion; and (c) a poor or inadequate response to the antibiotic therapy received.[6]

The diagnosis starts with the direct observation of mycobacteria in the aspirate of secretions or in the tissue obtained, using Ziehl–Neelsen or auramine–rhodamine stain, plus the performance of special cultures for the diagnosis. The classical Ziehl–Neelsen technique and the fluorescence technique with auramine–rhodamine are equally effective for the diagnosis, but around 30% of the rapidly growing mycobacteria can exhibit negative fluorescence with the auramine-rhodamine technique. Thus, when infection by rapidly growing mycobacteria is suspected, the procedure of choice is the Ziehl–Neelsen stain.

Bacteriological culture enables us to enhance the sensitivity of the diagnosis; even if the result of direct observation is negative, the disease is not ruled out. Therefore, sampling should be carried out for DNA amplification using the PCR technique, to obtain the patterns of sensitivity to first-line and second-line drugs that serve as a guide to the most adequate and effective treatment.[7]

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Uveitis Due to Bisphosphonates: A Rare Side Effect?☆

Uveítis por bisfosfonatos: ¿un raro efecto secundario?

To the Editor,

The use of bisphosphonates has increased in recent years, especially for the treatment of osteoporosis. This circumstance, together with the fact that these treatments are lengthy, has resulted in the development of adverse effects: osteonecrosis of the maxilla, bone and muscle pain, atrial fibrillation, atypical fractures or ocular inflammatory disorders. The latter include conjunctivitis, uveitis (most frequently, anterior uveitis)[1] and episcleritis.[2]

We report the case of a 51-year-old woman with a history of hypothyroidism, tension headache, polymyalgia rheumatica and a posteriori clinical suspicion of temporal arteritis with a negative biopsy, worsening polyarthralgia and back pain. Treatment consisted of an intermittent prednisone regimen with doses ranging between 1 and 2.5 mg/kg/day. She underwent a lateral radiograph of the spine, which focused on thoracic vertebra T8 and lumbar vertebra L2 and, as there was reasonable clinical suspicion of vertebral fracture (back pain of recent onset and height loss of 2 cm in a postmenopausal woman who had received several regimens of glucocorticoids at doses higher than 7.5 mg/kg/day), treatment with ibandronic acid was begun. Approximately 4 months after the initiation of treatment, she presented with ocular discomfort consisting of pain and conjunctival erythema, and was referred to the ophthalmology department, where she was diagnosed with anterior uveitis. Oral glucocorticoid therapy was discontinued and treatment with eye drops containing dexamethasone was begun. The patient was then referred to the rheumatology department, where an autoimmune origin of her condition was ruled out and treatment with bisphosphonates was discontinued, whereas the ophthalmological treatment was maintained. In subsequent visits, a progressive improvement of the anterior uveitis was observed and she chose not to continue with follow-up.

There have been several reports of ocular inflammatory events in patients taking oral bisphosphonates, suggesting that these ocular effects are underdiagnosed.[3] Only 1 epidemiological study has examined the risk of scleritis and uveitis associated with the use of oral bisphosphonates: a 1-year follow-up of a cohort of United States veterans. The relative risk of scleritis and uveitis was 1.23 higher among the users of bisphosphonates, but this finding was not statistically significant. Only 9 cases were recorded among the participants taking these drugs for the first time.[1]

The majority of the cases of scleritis and uveitis developed after use of the bisphosphonate was begun and resolved when it was discontinued,[3] although reports of recurrent uveitis after renewed treatment with pamidronate corroborate the causal relationship, indicating that the use of bisphosphonates, as a class, may increase the risk of uveitis.[4]

Anterior uveitis is usually bilateral and can be associated with fever and flu-like symptoms; it can be mild or severe, and recurs if the use of topical glucocorticoids is reduced. Scleritis may resolve with topical ocular medication, with no need to discontinue bisphosphonate therapy.[5]

Regarding the pathophysiology, inflammatory mediators are thought to play a major role in provoking a mechanism for induction of the inflammatory response,[3] although, in reality, the mechanism is still not clear.

The risk of developing ocular disorders associated with the use bisphosphonates is very low. Patients receiving this treatment should undergo an ophthalmological examination if they note a persistent loss of vision or ocular pain,[3] as both uveitis and scleritis require immediate treatment to prevent additional complications such as cataracts, glaucoma, macular edema and scleral perforation.[3] Clinicians should inform their patients of the signs and symptoms of scleritis and uveitis in order that these diseases be detected and treated rapidly. Patients taking oral bisphosphonates should be aware of these signs and symptoms so that they can be evaluated immediately by an ophthalmologist.

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