Nongranulomatous anterior uveitis associated with alendronate therapy.

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Abstract. We describe a case of acute nongranulomatous anterior uveitis associated with alendronate therapy, in an adult woman, without medical history of previous diseases, except for intercurrent problems of osteoporosis. The symptoms disappeared abruptly after anti-inflammatory therapy and discontinuation of alendronate. Side effects associated with ocular inflammation have been recently documented in 3 patients under alendronate therapy. Clinical and laboratory diagnosis of ocular inflammation syndromes are also reviewed.

Uveitis anterior no granulomatosa asociada a terapia con alendronato.

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Palabras claves: Uveitis, alendronato, inflamación ocular.

Resumen. En este artículo se describe un caso de uveitis anterior no-granulomatosa aguda, asociada a terapia con alendronato, en una mujer adulta, sin historia de enfermedad previa, excepto por osteosporosis intercurrente. Los síntomas desaparecieron abruptamente posterior al inicio de terapia anti-inflamatoria y al descontinuar la terapia con alendronato. La asociación de inflamación ocular a la terapia con alendronato, ha sido recientemente documentado en tres pacientes. Adicionalmente a la descripción del caso, el diagnóstico clínico y de laboratorio de los síndromes de inflamación ocular fueron revisados en este artículo.

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INTRODUCTION

Uveitis is a general term used to define inflammation in the uveal tract. Different types of ocular inflammation syndromes have been described: Anterior segment intraocular inflammation (ASII) is ocular inflammation in the cornea, the iris, and the ciliary body. Posterior segment intraocular inflammation (PSII) is ocular inflammation in the choroids, the retina, and the vitreous (1). Panuveitis is ocular inflammation in both anterior and posterior segments of the eye (2). ASII may be acute (duration <3 months) or chronic (duration >3 months), recurrent (when a new flare appeared following complete resolution of the previous flare), and unilateral or bilateral, sometimes alternating (3). Chronic uveitis is associated with a high incidence of vision threatening complications such as cataract, macular edema, and most importantly, glaucoma, which may cause irreversible visual loss (4). Chronic infections are considered as important causes of PSII. Pathological studies in PSII have shown in toxoplasma choroiditis the presence of tachyzoites in the tissues, in the absence of significant inflammation, and extensive inflammation when the organism is no longer viable. In addition, case reports of infectious PSII in conditions such as cytomegalovirus (CMV) and other infections have shown the value of diagnostic biopsy (1).

Uveitis is a prominent manifestation of several diseases. An underlying systemic disease, often one of autoimmune or infectious origin, can be identified in up to 40% of patients with uveitis (5). Drug-induced uveitis has been reported with several medications (6,7). To establish causality of adverse events by drugs, several criteria mostly related to frequency and documentation of the event, circumstances of occurrence, recovery and coexistence of other factors or medications have been proposed (8). Only systemically administered biphosphonates meet all criteria (9), being upper gastrointestinal symptoms: abdominal pain peptic ulcer and esophageal irritation, the most common adverse effects reported (10). Biphosphonates inhibit bone resorption and increase bone mineral density in postmenopausal women with osteoporosis. Alendronate is a potent amino biphosphonate that increases bone mass and reduces the incidence of vertebral and other bone fractures in postmenopausal women with osteoporosis (11). This is a report about a case of alendronate-associated severe anterior uveitis, in a patient with no previous history of ocular complaints or connective tissue disorders. The symptoms disappeared abruptly after anti-inflammatory therapy and discontinuation of alendronate.

Case report: A 72 y-old woman was admitted to the Immunology clinic at the Institute of Clinical Immunology in Mérida-Venezuela. She complained of 2 weeks history of right ocular pain, exacerbated by extraocular movements, which progressed to conjunctival hyperemia and blurred vision. The left eye was asymptomatic. Her medical and ocular histories were unremarkable except for intercurrent problems of osteoporosis. Although she did not complain of any other symptoms, an exhaustive physical examination was performed and, did not reveal abnormalities that suggested any systemic disorder. Slip-lamp examination of the right eye showed moderately severe peri-keratic injection, the anterior chamber had numerous (3+) cells and a moderately severe flare. Keratic precipitates and posterior synechiae were also present. The intraocular pressure was 13-mm Hg in the right eye and 14-mm Hg in the left eye. Her best-corrected visual acuity was RE (right eye): 20/40 and LE (left eye): 20/20. Laboratory tests included: hemoglobin 12.3

g/dL, hematocrit 25%, white blood cells count 6.800/mm^3, 35 mm/h erythrocyte sedimentation, negative C-reactive protein levels, negative RA-test, negative antinuclear antibodies, activity of antistreptolysin O <200 IU/L, normal classic and alternative complement pathways, negative IgG or IgM anti-toxoplasma serum antibodies, negative PPD test, negative HIV, negative cytomegalovirus, negative VDRL. Chest X-ray was normal and abdominal ultrasound did not show abnormalities in the explored organs.

Because of her previous history of osteoporosis she was under alendronate therapy just 3 weeks before the symptoms appeared. Topical steroid therapy and atropine were initiated and alendronate was discontinued at this stage, remarkably improving both pain and ocular inflammation. Intraocular inflammatory signs resolved completely within 4 weeks. Vision remained normal, without subsequent recurrence of episodes of ocular inflammation, during a following up period of 6 months.

DISCUSSION

In this report we described a case that developed a severe unilateral episode of nongranulomatous anterior uveitis within 3 weeks of alendronate therapy. Side effects associated with ocular inflammation, have been recently documented in 3 patients under alendronate therapy and, iritis has been described as a possible adverse effect of biphosphonates in a few patients (12,13), perhaps secondary to an immunologic mechanism, which has been proposed as a consequence of biphosphonate toxicity. Aminobiphosphonates and related compounds are known to stimulate release of both interleukin 1 and 6 (9,14). Alendronate, belongs to a group of drugs used as potent inhibitors of osteoclast-mediated normal and abnormal bone resorption. They are being used successfully for the management of Paget disease, hypercalcemia associated with malignant neoplasm, painful bone metastases and osteoporosis in postmenopausal women (15).

Uveitis may be categorized into granulomatous and non-granulomatous inflammation. The physical examination in this case showed a process of unilateral non-granulomatous anterior ocular inflammation. Non-granulomatous inflammation can be associated with either acute or chronic inflammation, which may be caused by toxic stimulus, viral infection, or unknown agents. Furthermore, it may be associated with systemic diseases such as ankylosing spondylitis, Reither's syndrome, Bechet's disease, multiple sclerosis, and ulcerative colitis (2).

In our patient a very detailed clinical history including several laboratory tests, were performed to rule out other causes of non-granulomatous inflammation, such as autoimmune and infectious diseases, which represent a high proportion of uveitis-associated systemic disorders. Symptoms and signs improved dramatically once the alendronate was suspended and anti-inflammatory therapy was installed. Although she was not rechallenged with the presumed offending agent (because of the severe symptoms developed at the beginning), the temporal association between alendronate exposure and occurrence of uveitis strongly suggest a causal relationship.

Anterior uveitis has also been reported in association with a variety of topical (phospholine iodine, metipranolol, and dexamethasone phosphate), intraocular (Gentamicin), periocular, an also with intradermal vaccines (Bacille Calmette-Guérin, measless, and influenza), and systemic medications (rifambutin, ibuprofen, diethylcarbamazine, sulfonamides) (9). To many, uveitis is an acute problem that resolves after treatment with topical corticosteroids.

While this may be true for acute anterior uveitis, many forms of uveitis are chronic in nature and often require continuous treatment. Specific infectious causes of chronic uveitis, such as syphilis and viral retinitis, are treated with appropriate antimicrobial therapy and the judicious use of corticosteroids. The long term treatment of patients with non-infectious chronic uveitis is similar in most patients, despite the wide spectrum of possible etiologies, as it is determined by the type of complications. The aims of treatment are to control inflammation, prevent visual loss, and minimize long term complications of the disease (4).

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