Fever with rash following zolendronic acid administration

Dear Sirs,

The amino-biphosphate zolendronic acid is primarily used for the treatment of bone metastases and/or humoral hypercalcemia of malignancy, as well as in the management of Paget’s disease (1). Allergic reactions with skin involvement (mainly pruritus, and hives), fever, and transient hematological changes (mainly leukocytosis with relevant lymphocytopenia) have been described within 3 days after bisphosphonate infusion (2). We describe a patient presenting with protracted fever and a rash 10 days after zolendronic acid administration.

A 64-year-old woman was admitted due to fever and a skin rash. She suffered from neglected rheumatoid arthritis and received methotrexate, prednisone, folic acid, oral calcium and vitamin-D supplements. A dual energy x-ray absorptiometry showed a t-score of -3.5. Ten days prior to admission, while afibrile, she was given zolendronic acid for osteoporosis according to a clinical protocol. Six hours later, the patient experienced fever (39°C) with chills. The fever persisted, and 10 days later she developed a pruritic maculopapular rash in the lower extremities.

The patient was a housekeeper, non-smoker, did not drink alcohol, and recalled no allergic reactions. On admission, her temperature was 38.5°C. Physical examination revealed a confluent maculopapular rash in the medial aspects of both thighs (Fig. 1), and joint deformities of wrists, hands, ankles and knees.

Blood serology, blood and urine cultures and appropriate imaging techniques failed to disclose any infectious causes. Major laboratory findings were: increased C-reactive protein levels (CRP, 61mg/L) and erythrocyte sedimentation rate (48mm/h), while the white blood cell and eosinophil count were normal. The patient was treated with intravenous prednisone 25 mg/day and oral loratadine 10 mg/day. Two days later the rash subsided and the patient was afibrile.

A review of the available literature regarding serious skin reactions associated with bisphosphonate administration discloses discontinuation of bisphosphonate treatment due to fever and a cutaneous rash (3), generalized maculopapular rash with lesions in the buccal and genital mucosa and keratitis (4), superficial gyrate erythema, erythema multiforme and cutaneous rashes (5-7), as well as severe reactions, such as toxic epidermal necrolysis and pancytopenia (8, 9).

It is the first time that zolendronic acid is implicated in a protracted febrile reaction with skin rash. Although the drug was originally given for the treatment of osteoporosis, it is appreciated that the background of rheumatoid arthritis (putatively via cytokine release) may have played a role in the development of this adverse reaction.

E.C. RIZOS, MD
H.J. MILIONIS, MD
M.S. ELISAF, MD, FACA, FRSH, Professor.
Department of Internal Medicine, Medical School, University of Ioannina, Greece.
Address correspondence and reprint requests to: Moses Elisaf, MD, FACA, FRSH, Professor of Medicine
Department of Internal Medicine, Medical School, University of Ioannina, 451 10 Ioannina, Greece.
E-mail: egepi@cc.uoi.gr

References