lium of capillaries caused by angiitis, the deposition of immune complexes, or certain drugs may result in a defective utilization of ADAMTS13 and the subsequent accumulation of unusually-large VWF multimers in the circulation. Since a markedly high level of plasma VWF antigen observed in our study appears to reflect a proportional increase in plasma unusually-large VWF multimers, it is conceivable that a decreased enzyme-to-substrate (ADAMTS13/unusually-large VWF multimers) ratio results in an accumulation of undigested unusually-large VWF multimers, leading to TTP.

T. SATO[1,2], *MD, PHD*
R. HANAOKA[1], *MD, PHD*
M. OHSHIMA[1], *MD*
Y. MIWA[1], MD, *PHD*
Y. OKAZAKI[1], *MD, PHD*
N. YAJIMA[1]*MD*
H. ISHIZASHI[3], *PHD*
M. MATSUMOTO[4], *MD, PHD*
Y. FUJIMURA[4], *MD, PHD*
S. INOKUMA[1], *MD*

[1]Department of Allergy and Immunological Diseases, Tokyo Metropolitan Komagome Hospital, Tokyo; [2]Department of Allergy and Rheumatology, Japanese Red Cross Medical Center, Tokyo; [3]Department of Health Science, Nara Medical University, Nara; [4]Department of Blood Transfusion Medicine, Nara Medical University, Nara, Japan.

Address correspondence and reprint requests to: Dr Takeo Sato, Department of Allergy and Rheumatology, Japanese Red Cross Medical Center, 4-1-22 Hiroo, Shibuya-ku, Tokyo 150-8935, Japan.
E-mail address: satotk-rheumatol@umin.ac.jp

References

1. MOSCHCOWITZ E: Hyaline thrombosis of the terminal arterioles and capillaries: a hitherto undescribed disease. *Proc N Y Pathol Soc* 1924; 24: 21-4.
2. MOAKE JL: Thrombotic microangiopathies. *N Engl J Med* 2002; 347: 589-600.
3. FURLAN M, ROBLES R, GALBUSERA *et al.*: von Willebrand factor-cleaving protease in thrombotic thrombocytopenic purpura and the hemolytic-uremic syndrome. *N Engl J Med* 1998; 339: 1578-84.
4. TSAI H-M, LIAN EC-Y: Antibodies to von Willebrand factor-cleaving protease in acute thrombotic thrombocytopenic purpura. *N Engl J Med* 1998; 339: 1585-94.
5. FESSLER BJ: Thrombotic syndromes and autoimmune diseases. *Rheum Dis Clin North Am* 1997; 23: 461-79.
6. FURLAN M, ROBLES R, SOLENTHALER M, LAMMLE B: Acquired deficiency of von Willebrand factor-cleaving protease in a patient with thrombotic thrombocytopenic purpura. *Blood* 1998; 91: 2839-46.
7. KINOSHITA S, YOSHIOKA A, PARK YD *et al.*: Upshaw-Schulman syndrome revisited: a concept of congenital thrombotic thrombocytopenic purpura. *Int J Hematol* 2001; 74: 101-8.
8. MANNUCCI PM, VANOLI M, FORZA I, CANCIANI MT, SCORZA R: Von Willebrand factor cleaving protease (ADAMTS-13) in 123 patients with connective tissue diseases (systemic lupus erythematosus and systemic sclerosis). *Haematologica* 2003; 88: 914-8.
9. MATSUMOTO M, YAGI H, ISHIZASHI H, WADA H, FUJIMURA Y: The Japanese experience with thrombotic thrombocytopenic purpura-hemolytic uremic syndrome. *Semin Hematol* 2004; 41: 68-74.

Fever with rash following zolendronic acid administration

Dear Sirs,
The amino-biphosphonate 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 biphosphonate 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, and while afebrile, she was given zolendronic acid for osteoporosis according to a clinical protocol. Six hours later, the patient experienced fever (39ºC) 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 sentimentation 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 afebrile.
A review of the available literature regarding serious skin reactions associated with biphosphonate administration discloses discontinuation of biphosphonate treatment due to fever and a cutaneous rash (3), generalized macupopapular 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.

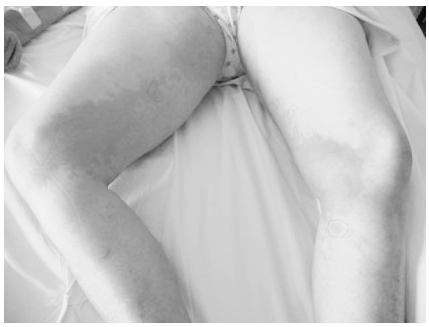

Fig. 1. Rash following zolendronic acid administration.

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

1. PERRY CM, FIGGIT DP: Zolendronic acid: a review of its use in patients with advanced cancer. *Drugs* 2004; 64: 1197-211.
2. ZOJER N, KECK AV, PECHERSTORFER M: Comparative tolerability of drug therapies for hypercalcaemia of malignancy. *Drug Saf* 1999; 21: 389-406.
3. CASCINU S, CASADEI V, DEL FERRO E, ALESSANDRONI P, CATALANO G: Pamidronate in patients with painful bone metastases, who failed initial treatment with hormones and/or chemotherapy. *Support Care Cancer* 1996; 4: 31-3.
4. PAJUS I, LESTANG P, LIOTE F, DRYLL A: Erythroderma after clodronate treatment. *BMJ* 1993; 307: 484.
5. WHITNEY AH, COHEN JB, WETHERINGTON W, COCKERELL CJ: Superficial gyrate erythema as a cutaneous reaction to alendronate for osteoporosis. *J Am Acad Dermatol* 2003; 48: 945-6.
6. BISWAS PN, WILTON LV, SHAKIR SAW: Pharmacovigilance study of alendronate in England. *Osteoporos Int* 2003; 14: 507-14.
7. ELLIOTT AT, MURRAY T, MACKIE RM, HUNTER JA: Severe reaction to diphosphonate: implications for treatment of Pajet's disease. *BMJ* 1988; 297: 592-3.
8. COAKLEY G, ISENBERG DA: Toxic epidermal necrolysis, pancytopenia and adult respiratory syndrome. *Br J Rheumatol* 1995: 34: 798.
9. ROUX C, LISTRAT V, VILLETTE B *et al.*: Long-lasting dermatological lesions after tiludronate therapy. *Calcif Tissue Int* 1992; 50: 378-80.