A Rare Adverse Effect of Montelukast Treatment: Ecchymosis

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Montelukast is a leukotriene receptor antagonist that is effective in the treatment of allergic rhinitis and asthma. We report a rare case of a 31-year-old woman with a history of allergic rhinitis and moderate persistent asthma, who experienced severe bruising on her lower extremities after starting montelukast treatment. Clinicians should be aware of the possibility of unusual bruising during montelukast therapy, and in those patients montelukast should be discontinued. *Key words: montelukast; leukotriene antagonists; adverse effects; bruising.* [Respir Care 2013;58(9):e104–e106. © 2013 Daedalus Enterprises]

Introduction

Asthma is one of the most prevalent long-term diseases; it affects nearly 300 million people, and there may be 100 million new patients by 2025.[1] Allergic rhinitis is also a common disease; it affects 10–40% of the population in the United States.[2,3] Evidence for the association between allergic rhinitis and asthma has been reported frequently in epidemiologic studies.[4,5] Montelukast is a potent and specific cysteinil leukotriene receptor antagonist that possesses bronchodilating and anti-inflammatory properties and is effective in the treatment of both asthma and allergic rhinitis. Montelukast is safe and well tolerated in adults and children,[6,7] and its adverse effects are mostly mild and include headache, gastrointestinal disturbance, fatigue, pharyngitis, upper-respiratory-tract infection, and rash.[6-8]

We present an unusual case of montelukast-induced bruising on the lower extremities of an asthmatic patient.

Case Report

A 31-year-old, female, non-smoker with a 10-year history of allergic rhinitis and moderate persistent asthma presented to our clinic with ecchymosis on her legs. She was taking inhaled budesonide (200 μg twice a day) for asthma, and 1 month before the onset of the ecchymosis she had started montelukast (10 mg once a day), without altering the dose of budesonide. She had no other complaints aside from the bruising on her legs. Her anamnesis was negative for food allergies or other chronic systemic diseases. She had not taken other drugs, over-the-counter medications, or herbal products, nor had she modified her dietary habits. She denied any trauma.

Physical examination showed nothing unusual except for multiple painless ecchymotic lesions, with diameters of 3–5 cm on her lower extremities (Fig. 1). The initial laboratory analyses found: white blood cell 6,000/mL^3, eosinophil count 100/mL^3 (0.1%), hemoglobin 14.1 g/dL, hematocrit 41.8%, platelet count 226,000/mL^3, erythrocyte sedimentation rate 8 mm/h, C-reactive protein 2 mg/L. Immunoglobulin E level was elevated (972 IU/mL). Other biochemical tests, including kidney and liver function tests, bleeding time and blood-clotting tests, hepatitis B and C virus markers, and urinary analysis, were normal. Blood cultures, bacterial (*Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Legionella*), and viral (cytomegalovirus, influenza viruses) serologies were negative. Auto-antibody screening tests yielded negative results for rheumatoid factors, antinuclear antibodies, cryoglobulin, and perinuclear antineutrophil cytoplasmic antibodies (*p*-ANCA). The posteroanterior chest radiograph was normal. Computed tomography of the paranasal sinuses revealed conchal hypertrophy. Food allergies were ruled out by the skin prick test and the radioallergosorbent test for common food allergens. Histology of the affected skin revealed no specific

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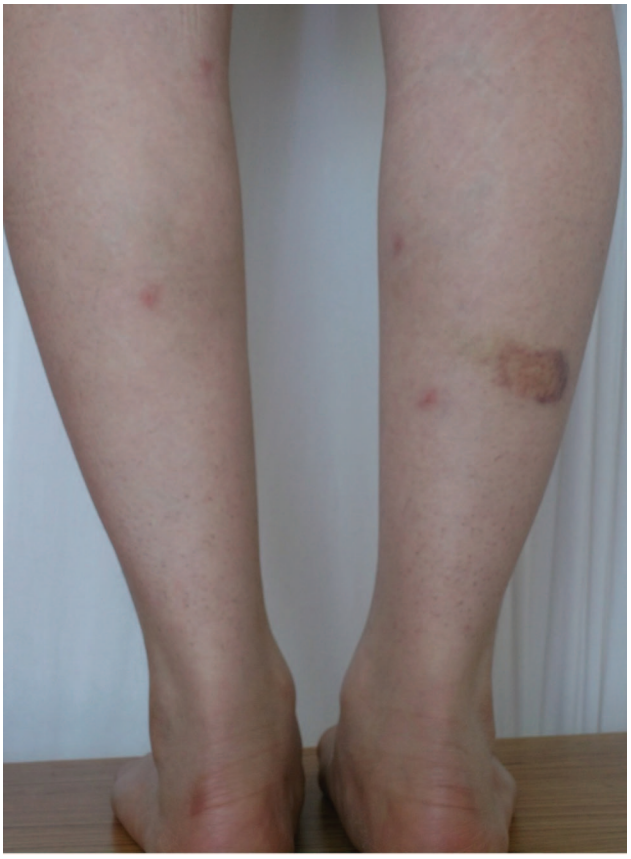

Fig. 1. Ecchymotic lesions (diameters 3–5 cm) on the lower extremities.

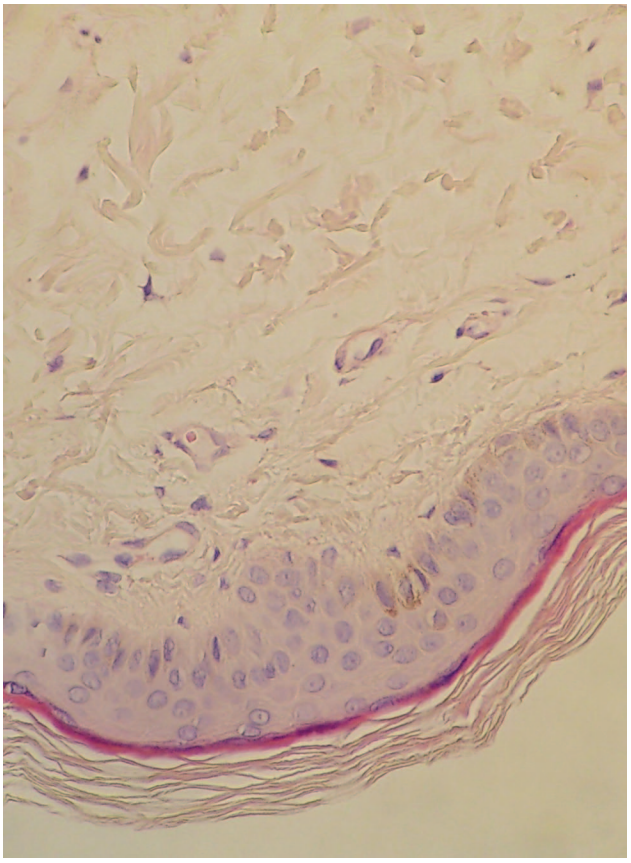

Fig. 2. Histology of the ecchymotic lesions (hematoxylin and eosin stain, magnification 40). There is no vascular inflammation or extravasation of red blood cells around the vessel. There is slight edema in the dermis, but no eosinophils.

pathology. There was no lymphocytic/eosinophilic inflammatory infiltrate, and no extravasation of red blood cells around the vessel. However, there was slight edema in the dermis (Fig. 2).

Montelukast was discontinued on the suspicion that it might have been responsible for the bruising. The bruising resolved within 2 weeks. She continued the inhaled corticosteroid therapy and did not experience any relapses in the following month. Two days after she resumed montelukast she again developed lower extremity bruising. We attributed the adverse reaction to montelukast because of the temporal relationship between use of montelukast and bruising, the positive rechallenge, and the absence of other identifiable causes. We discontinued the montelukast, and she had no relapses in the ensuing 6 months.

Discussion

Initially developed as a treatment for asthma, montelukast also treats allergic rhinitis.[6] Adverse effects include headache, gastrointestinal disturbance, fatigue, pharyngitis, upper-respiratory-tract infection, rash, worsening of asthma, cough, sore throat, hallucinations, depression, suicidal ideation, and tremors.[6-11] A few sporadic cases of mild to moderate acute hepatitis have also been reported.[12–14]

Dermatologic reactions associated with montelukast include unspecified rash, with or without blistering (the most common adverse effect), urticaria, vasculitis, angioedema, erythema nodosum, ecchymosis, skin ulcers, and, rarely, skin nodules.[15] The most serious complication is Churg-Strauss syndrome, a vasculitis, which has been reported in people with asthma who were treated with leukotriene receptor antagonists.[16-18] Common dermatologic manifestations of Churg-Strauss syndrome are palpable purpura, hemorrhagic lesions (ranging from petechiae to extensive ecchymosis), cutaneous and subcutaneous nodules, erythematous maculopapules, and, rarely, ulcers, infarcts, livedo-like eruption and facial edema.[19] It is thought that the decreased corticosteroid dosage needed to control asthma symptoms in patients receiving leukotriene receptor antagonists unmasks an underlying vasculitis that had been controlled previously by the corticosteroids.[17,18,20,21] Our patient was not receiving oral corticosteroid. However, Churg-Strauss syndrome has also been reported after

beginning leukotriene receptor antagonists in asthmatic patients not treated with steroids.[22] The American College of Rheumatology[23] has proposed 6 criteria for the diagnosis of Churg-Strauss syndrome: asthma (wheezing, expiratory rhonchi), eosinophilia of > 10% in peripheral blood, paranasal sinusitis, pulmonary infiltrates (may be transient), histologic proof of vasculitis with extravascular eosinophils, and mononeuritis multiplex or polyneuropathy. The presence of 4 or more of those criteria yields a sensitivity of 85% and a specificity of 99.7%. Our patient exhibited none of the Churg-Strauss syndrome criteria except asthma.

The Naranjo et al criteria[24] classify the probability that an adverse event is related to drug therapy, based on a list of weighted questions that examine factors such as the temporal association of drug administration and the adverse effect, alternative causes for the adverse effect, drug dose, dose/response relationships, and previous patient experience with the medication. Our patient's Naranjo assessment score was 8, which falls into the accepted range for a "probable" relationship to the drug therapy.[24] The complete resolution of the skin lesions after discontinuing montelukast certainly argues in favor of the montelukast causing the bruising.

To our knowledge, bruising caused by montelukast, although listed on the drug package insert, has not been previously described in the literature. Why montelukast causes bruising is not fully understood, but arachidonic acid metabolites may be critical in the process, and montelukast may inhibit platelet aggregation by interfering with platelet-leukocyte cooperation.[25]

This case report highlights the need for vigilance in monitoring for adverse effects of montelukast. Although leukotriene antagonists are believed to be safe drugs and are widely used for asthma and allergic rhinitis, we hope this case raises awareness of potential adverse reactions to montelukast.

REFERENCES

1. Masoli M, Fabian D, Holt S, Beasley R; on behalf of the Global Initiative for Asthma (GINA) Program. The global burden of asthma: executive summary of the GINA Dissemination Committee report. Allergy 2004;59(5):469-478.
2. Marple BF, Fornadley JA, Patel AA, Fineman SM, Fromer L, Krouse JH, et al. Keys to successful management of patients with allergic rhinitis: focus on patient confidence, compliance, and satisfaction. Otolaryngol Head Neck Surg 2007;136(6):107-124.
3. Tripathi A, Patterson R. Impact of allergic rhinitis treatment on quality of life. Pharmacoeconomics 2001;19(9):891-899.
4. Guerra S, Sherrill DL, Martinez FD, Barbee RA. Rhinitis as an independent risk factor for adult-onset asthma. J Allergy Clin Immunol 2002;109(3):419-425.
5. Leynaert B, Neukirch F, Demoly P, Bousquet J. Epidemiologic evidence for asthma and rhinitis comorbidity. J Allergy Clin Immunol 2000;106(5):201-205.
6. Nayak A, Langdon R. Montelukast in the treatment of allergic rhinitis: an evidence-based review. Drugs 2007;67(6):887-901.
7. Lagos JA, Marshall GD. Montelukast in the management of allergic rhinitis. Ther Clin Risk Manag 2007;3(2):327-332.
8. Dempsey OJ. Leukotriene receptor antagonist therapy. Postgrad Med J 2000;76(902):767-773.
9. Jamali AN, Aqil M, Alam MS, Pillai KK, Kapur P. A pharmacovigilance study on patients of bronchial asthma in a teaching hospital. J Pharm Bioallied Sci 2010;2(4):333-336.
10. Malmstrom K, Rodriguez-Gomez G, Guerra J, Villaran C, Piñeiro A, Wei LX, et al; Montelukast/Beclomethasone Study Group. Oral montelukast, inhaled beclomethasone, and placebo for chronic asthma: a randomized, controlled trial. Ann Intern Med 1999;130(6):487-495.
11. Meltzer EO, Lockey RF, Friedman BF, Kalberg C, Goode-Sellers S, Srebro S, et al. Efficacy and safety of low-dose fluticasone propionate compared with montelukast for maintenance treatment of persistent asthma. Mayo Clin Proc 2002;77(5):437-445.
12. Romero-Gómez M, Sánchez-Muñoz D, Castilla L, Castro M. [Acute hepatitis due to montelukast]. Med Clin (Barc) 2003;120(6):239. *Article in Spanish.*
13. Margery J, Dot JM, Bredin C, Bonnichon A, Romand F, Guigay J, et al. Montelukast induced cytolytic acute hepatitis. Gastroenterol Clin Biol 2003;27(1):129-130.
14. Sass DA, Chopra KB, Wu T. A case of montelukast-induced hepatotoxicity. Am J Gastroenterol 2003;98(3):704-705.
15. Litt JZ. Litt's drug eruption reference manual: including drug interactions, 11th edition. London: Informa; 2011:452.
16. UK Medicines and Healthcare Products Regulatory Agency and Committee on Safety of Medicines. Leukotriene receptor antagonists: update on adverse reaction profiles. Curr Probl Pharmacovigilance 1999;25:14.
17. DuMouchel W, Smith ET, Beasley R, Nelson H, Yang X, Fram D, et al. Association of asthma therapy and Churg-Strauss syndrome: an analysis of postmarketing surveillance data. Clin Ther 2004;26(7):1092-1104.
18. Wechsler ME, Finn D, Gunawardena D, Westlake R, Barker A, Haranath SP, et al. Churg-Strauss syndrome in patients receiving montelukast as treatment for asthma. Chest 2000;117(3):708-713.
19. Davis MD, Daoud MS, McEvoy MT, Su WP. Cutaneous manifestations of Churg-Strauss syndrome: a clinicopathologic correlation. J Am Acad Dermatol 1997;37(2):199-203.
20. Katzenstein AL. Diagnostic features and differential diagnosis of Churg-Strauss syndrome in the lung. A review. Am J Clin Pathol 2000;114(5):767-772.
21. Wechsler ME, Garpestad E, Flier SR, Kocher O, Weiland DA, Polito AJ, et al. Pulmonary infiltrates, eosinophilia, and cardiomyopathy following corticosteroid withdrawal in patients with asthma receiving zafirlukast. JAMA 1998;279(6):455-457.
22. Tuggey JM, Hosker HS. Churg-Strauss syndrome associated with montelukast therapy. Thorax 2000;55(9):805-806.
23. Masi AT, Hunder GG, Lie IT, Michel BA, Bloch DA, Arend WP, et al. The American College of Rheumatology 1990 criteria for the classification of the Churg-Strauss syndrome (allergic granulomatosis and angiitis). Arthritis Rheum 1990;33(8):1094-1100.
24. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981;30(2):239-245.
25. Cuchacovich R, Justiniano M, Espinoza LR. Churg-Strauss syndrome associated with leukotriene receptor antagonists (LTRA). Clin Rheumatol 2007;26(10):1769-1771.