

## **A RARE ADVERSE EFFECT OF MONTELUKAST TREATMENT: ECCHYMOSIS**

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**Running Title:** Bruising due to montelukast utilization

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## **Abstract**

Montelukast is a leukotriene receptor antagonist that has been found to be 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, treatment with montelukast should be discontinued.

**Key words:** Montelukast, leukotriene antagonists, adverse effect, bruising

## **Introduction**

Asthma is one of the most prevalent long-term diseases that affects nearly 300 million people in the world and there may be 100 million new patients by 2025.<sup>1</sup> Allergic rhinitis (AR) is also a common disease that affects up to 10-40% of the population in the United States (U.S.).<sup>2,3</sup> Evidence for the association between AR and asthma has been reported frequently among epidemiologic studies.<sup>4,5</sup> Montelukast is a potent and specific cysteinil leukotriene receptor antagonist that possesses bronchodilating and anti-inflammatory properties and is found to be effective in the treatment of both asthma and AR. In the studies, montelukast appears to be safe and well-tolerated in adults and children.<sup>6,7</sup> Adverse effects are described as mild and most often include headaches, gastrointestinal disturbances, fatigue, pharyngitis, upper respiratory tract infections and rashes.<sup>6-8</sup>

In this report, 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 located on her legs. She was receiving inhalant budesonide 200 µg bid for her asthma treatment. One month before the onset of skin lesions, montelukast treatment (10 mg once daily) had been initiated 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 and 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 incidence of trauma.

Physical examination showed nothing unusual except for multiple painless, ecchymotic lesions with diameters of 3-5 cm on the patient's lower extremities (Figure 1). The initial laboratory analyses yielded the following results: white blood cell, 6000/mm<sup>3</sup>;

eosinophil count, 100/mm<sup>3</sup> (0.1%); hemoglobin, 14.1 g/dL; hematocrit, 41.8%; platelet count: 226.000/mm<sup>3</sup>; erythrocyte sedimentation rate, 8 mm/hour; 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. Autoantibody 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 (CT) of the paranasal sinuses revealed conchal hypertrophy. The possibility of food allergies was eliminated using the skin prick test and radioallergosorbent test for common food allergens. A histological examination of affected skin revealed no specific 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 (Figure 2).

Montelukast was discontinued on the suspicion that it might have been responsible for the bruising. The bruising resolved within two weeks. The patient continued the inhaled corticosteroid therapy and did not experience any relapses in the following month. Two days after she resumed treatment with montelukast, she immediately developed lower extremity bruising again. 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 causative factors.

We decided to follow the patient without montelukast treatment. The patient did not experience any relapses in the ensuing 6 months.

## Discussion

Initially developed as a treatment for asthma, montelukast has also been found to be helpful in the treatment of AR.<sup>6</sup> Several adverse effects of montelukast therapy have been described, including headaches, gastrointestinal disturbances, fatigue, pharyngitis, upper respiratory tract infections, rashes, worsening of asthma, coughing and sore throats, hallucinations, depression, suicidal ideation, and tremors.<sup>6-11</sup> A few sporadic cases of mild to moderate acute hepatitis have also been reported.<sup>12-14</sup>

Different types of dermatologic reactions associated with montelukast utilization have been reported to the U.S. Food and Drug Administration (FDA) (<http://www.fda.gov/>, Accessed September 12, 2012). These include unspecified rashes, with or without blistering (the most common manifestations reported), urticaria, vasculitis, angioedema, erythema nodosum, ecchymosis, skin ulcers, and rarely, skin nodules.<sup>15</sup> Among all these adverse reactions, the most serious complication was Churg-Strauss Syndrome (CSS) and this vasculitis has been reported in people with asthma who were treated with leukotriene receptor antagonists.<sup>16-18</sup> Common dermatologic manifestations of CSS 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.<sup>19</sup> 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.<sup>17,18,20,21</sup> Our case was not receiving oral corticosteroid and the dose of inhaled corticosteroid was not tapered off during montelukast treatment. However, CSS has also been reported after beginning leukotriene receptor antagonists in asthmatic patients not treated with steroids.<sup>22</sup> The American College of Rheumatology (ACR) has proposed 6 criteria for the diagnosis of CSS.<sup>23</sup> The presence of 4 or more criteria yields a sensitivity of 85% and a specificity of

99.7%. These criteria include (1) asthma (wheezing, expiratory rhonchi), (2) eosinophilia of more than 10% in peripheral blood, (3) paranasal sinusitis, (4) pulmonary infiltrates (may be transient), (5) histological proof of vasculitis with extravascular eosinophils, and (6) mononeuritis multiplex or polyneuropathy. We did not diagnose our patient with CSS because she did not meet any other criteria other than having asthma.

Naranjo criteria classify the probability that an adverse event is related to drug therapy based on a list of weighted questions. These questions examine factors such as the temporal association of drug administration and event occurrence, alternative causes for the event, drug levels, dose – response relationships and previous patient experience with the medication. According to the Naranjo’s probability scale, we calculated an assessment score of 8, which falls into the accepted range for the bruising’s “probable” relation to drug therapy.<sup>24</sup> The complete resolution of the skin lesions between treatment with montelukast certainly argues in favor of this agent as the cause of the bruising.

To our knowledge, possible bruising caused by montelukast, although listed on the drug package insert, is not described in the existing medical literature. The underlying cause of bruising due to montelukast usage is not fully understood. However arachidonic acid metabolites may be critical in the process and montelukast may induce inhibition of platelet aggregation by interfering with platelet-leukocyte cooperation.<sup>25</sup>

This case report highlights the need for vigilance in monitoring adverse effects in drug therapy, particularly for montelukast treatment. Although leukotriene antagonists are believed to be safe drugs and are widely used for bronchial asthma and allergic rhinitis, we would like to present this unusual case in order to raise physicians’ awareness of potential adverse reactions to montelukast.

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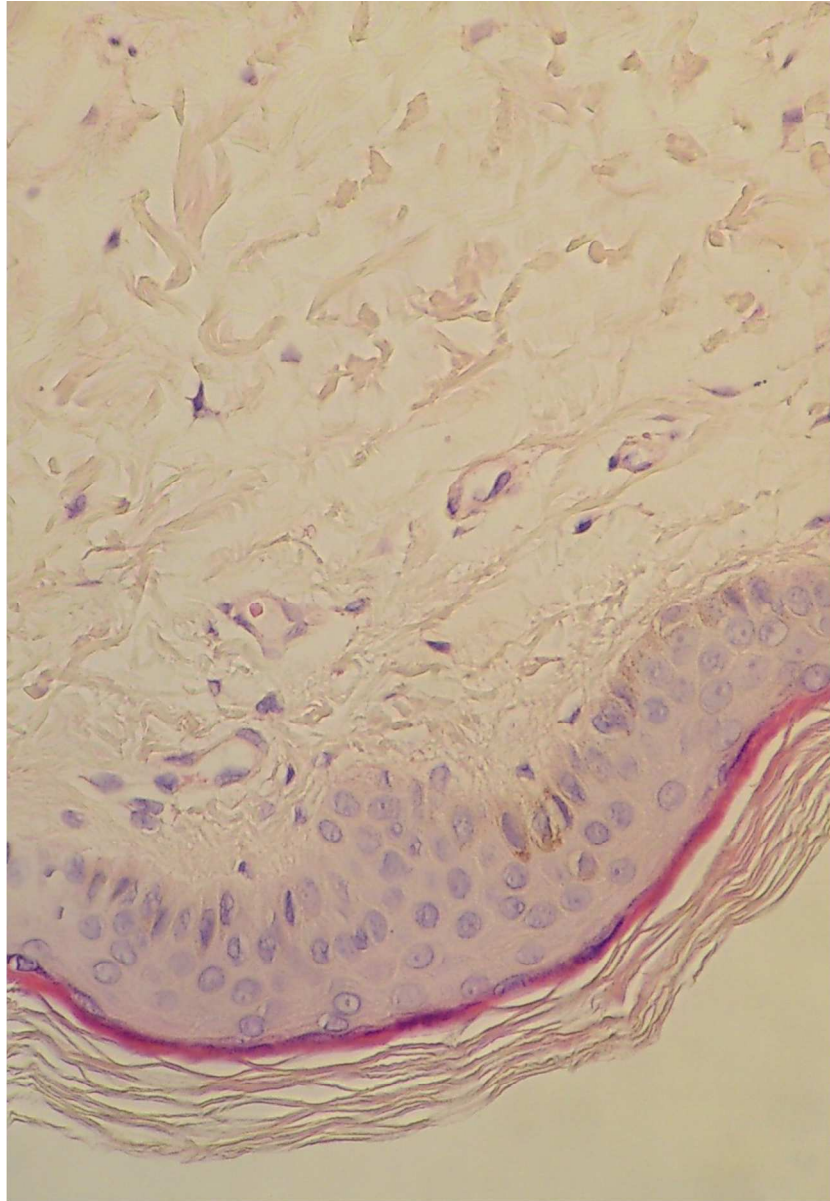
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Figure 1: Several ecchymotic lesions with 3-5 cm diameters on lower extremities.

Figure 2: Histological examination of lesions (Haemtoxylin and eosin; x40). There is no vascular inflammation and no extravasation of red blood cells around the vessel. There is slight edema in the dermis, but no eosinophils.



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