CASE REPORT

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# Churg-Strauss vasculitis in patient who received montelukast

## Churg-Strauss vaskulitis kod bolesnice lečene montelukastom

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**Abstract**

**Introduction.** Montelukast is a selective leukotriene receptor antagonist. One of side effects of this drug class is the Churg-Strauss syndrome (CSS). There is still no reliable evidence whether the expression of this syndrome could be masked by high doses of corticosteroids and become expressed by termination of corticosteroid use, or whether it could be a consequence of leukotriene receptor antagonists use. **Case report.** Female patient, aged 49 years, was hospitalized with symptoms of fever, dyspnea, cough and increased sputum production with occasional hemoptysis. She was treated for asthma during the previous year. Leukocyte differential formula registered 44% of eosinophils. IgE value was extremely elevated, with value measured to 580 kU/L and eosinophile cation protein value was 15.1 μg/L. Computed tomography of the chest described changes in the form of ground glass located in all lobes of the right lung and in the upper lobe of the left lung. Computed tomography of paranasal sinuses described changes that could resemble to polyposis, chronic sinusitis, and possible granulomatosis. Mononeuritis of peroneal nerve of the right leg was proven by electromyographic examination. Bone marrow biopsy indicated hypercellularity with domination of eosinophilic granulocytes (30%). Five out of six criteria were noted in patient's clinical presentation, after which the diagnosis of CSS was set. The patient began treatment with high doses of corticosteroids while montelukast was discontinued which resulted in disease remission. **Conclusion.** Although there is no evidence that leukotriene modifiers cause the CSS in all patients with asthma, in case of frequent exacerbations with the appearance of pulmonary infiltrates, eosinophilia and paranasal sinus abnormalities make one think of this form of vasculitis.

**Key words:**
**churg-strauss syndrome; leukotriene antagonists; diagnosis; drug therapy; treatment outcome; asthma.**

**Apstrakt**

**Uvod.** Montelukast je selektivni antagonista leukotrienskih receptora. Jedno od neželjenih dejstava ove klase lekova je Churg-Strauss sindrom (CSS). Još uvek nema pouzdanih dokaza da li ekspresija ovog sindroma može biti maskirana visokim dozama kortikosteroida i postati manifestna sa prestankom primene kortikosteroida ili bi mogla da bude neposredna posledica primene antagonista leukotrienskih receptora. **Prikaz bolesnika.** Bolesnica, stara 49 godina, hospitalizovana je sa simptomima groznice, dispneje, kašlja i povećane produkcije sputuma sa povremenim hemoptizijama. Lečila se od astme u toku prethodnih godinu dana. Leukocitnom diferencijalnom formulom registrovano je 44% eozinofila. Vrednost IgE je bila izrazito povišena, 580 kU/L, kao i vrednost eozinofilnog katjonskog proteina – 15.1 mg/L. Kompjuterizovana tomografija grudnog koša ukazala je na promene po tipu "mlečnog stakla" u svim režnjevima desnog plućnog krila i u gornjem režnju levog plućnog krila. Kompjuterizovana tomografija paranazalnih sinusa ukazala je na promene koje mogu odgovarati polipozi, hroničnom sinusitisu i mogućoj granulomatozi. Mononeuritis peronealnog nerva desne noge je potvrđen elektromiografskim pregledom. Biopsija kostne srži je ukazala na hipercelularnost sa dominacijom eozinofilnih granulocita (30%). Kod bolesnika je na osnovu pet pozitivnih od šest kriterijuma potvrđeno postojanje CSS. Terapija montelukastom je prekinuta i započet je tretman visokim dozama kortikosteroida što je rezultiralo povlačenjem znakova i simptoma bolesti. **Zaključak.** Iako ne postoje dokazi da modifikatori leukotriena izazivaju CSS kod svih bolesnika sa astmom, u slučaju čestih pogoršanja sa pojavom plućnih infiltrata, eozinofilije i abnormalnosti paranazalnih šupljina treba imati na umu i ovu formu vaskulitisa.

**Ključne reči:**
**angiitis, alergijski, granulomatozni; leukotrieni, antagonisti; dijagnoza; lečenje lekovima; lečenje, ishod; astma.**

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**Introduction**

Montelukast is a selective leukotriene receptor antagonist which became available in 1998. Specifically, it binds to and blocks cysteinyl-leukotriene type 1 receptors which are located in the airways and involved in inflammation in patients with bronchial asthma and allergic rhinitis.

One of side effects of this drug class is the Churg-Strauss syndrome (CSS). There is still no reliable evidence whether the expression of this syndrome could be masked by high doses of corticosteroids and become expressed by termination of corticosteroid use, or whether it could be a consequence of leukotriene receptor antagonists. We presented the case of a patient who was hospitalized on three occasions over 3 months due to asthma exacerbations. During these hospitalizations she was treated with systemic corticosteroids, while in regular therapy she was taking high doses of inhaled corticosteroids (ICS) and leukotriene receptor antagonist in the past year.

**Case report**

Female patient, aged 49 years, came to pulmonologist's office for examination with symptoms of fever (38°C), dyspnea, cough and increased sputum production with occasional hemoptysis. It was the third time in 3 months that she came to pulmonologist with the same symptoms, and she was hospitalized for the third time at the Clinic for Pulmonology, Clinical Center Kragujevac. The patient's first hospital stay was 3 months before, when she was diagnosed with asthma exacerbation and interstitial pneumonia. One month later, the patient was admitted to the hospital again with signs of acute respiratory failure and radiographically detected bilateral lung infiltrates. She was treated with antibiotics, corticosteroids and oxygen therapy until notable clinical and radiological improvement. Third hospitalization occurred 10 days after the second one with the identical symptoms.

She was treated for asthma during the previous year and her current therapy at that moment was: salmeterol/fluticasone propionate, 50/500 μ 2 times a day (BID), montelukast 10 mg once of day (QD), theophylline 250 mg BID, fenoterol/ipratropium bromide 0.05/0.021 mg/mL, as needed. She was former smoker with 10 pack/years.

Auscultatory findings of the lungs showed impaired breathing sound, prolonged expiratory flow, wheezing and inspiratory crackles bilaterally in basal areas. Results of laboratory analyses showed positive biohumoral inflammatory syndrome: Sedimentation rate – 30 (1st hour), White blood cell count (WBC) –10.6 x $10^9$/L, C-reactive protein (CRP) – 182.6 mg/mL. Leukocyte differential formula registered 44% of eosinophils (absolute number of 4.4 x $10^9$/L). Other hematology parameters were within normal ranges. Immunological analyses (immunoglobulines, C3, C4, antinuclear antibody – ANA, anti-neutrophil cytoplasmic antibody – ANCA) were within normal ranges, except for immunoglobulin E (IgE) value which was extremely elevated, with value measured to 580 kU/L (reference range: up to 113 kU/L) and eosinophile cation protein (ECP) value was 15.1 mcg/L (reference range: up to 11.3 mcg/L). The analysis of respiratory gases on admission to the hospital showed hypoxemia with normal $CO_2$ partial pressure (pO2–7.6 kPa; pCO2–5.9 kPa; oxygen saturation was 91%). Chest radiography showed accentuated interstitia bilaterally in basal areas with inhomogeneous opacities and infiltrates in the upper lobe of the left lung and along the right lateral wall (Figure 1). Pulmonary function tests on admission showed predominantly obstructive disorder of moderate/severe degree [FVC = 2.24 L (72.6%), $FEV_1$ = 0.90 L (34.2%), $FEV_1$/FVC = 40.17%]. Multislice computed tomography (MSCT) of the chest described changes in the form of ground glass located in all lobes of the right lung and in the upper lobe of the left lung (Figures 2 and 3).

Shortly afterwards, the patient developed a vesicular rash on nose.

Computed tomography (CT) of paranasal sinuses was also performed during the hospitalization. Changes were observed in the left maxillary and sphenoid sinuses that could resemble polyposis, chronic sinusitis, and possible granulomatosis.

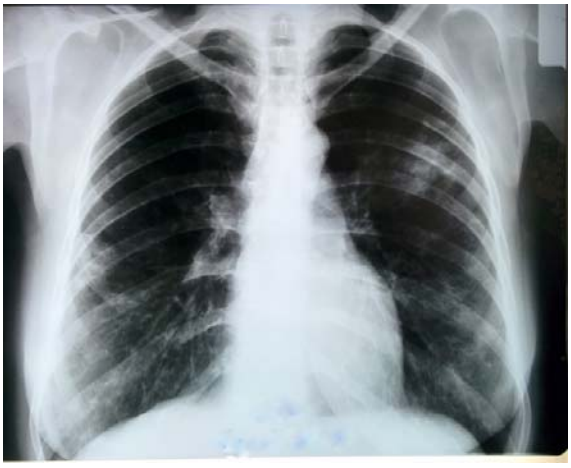

**Fig. 1 – Chest radiography showing accentuated interstitia bilaterally in basal areas, inhomogeneous opacities and infiltrates in the upper lobe of the left lung and along the right lateral wall.**

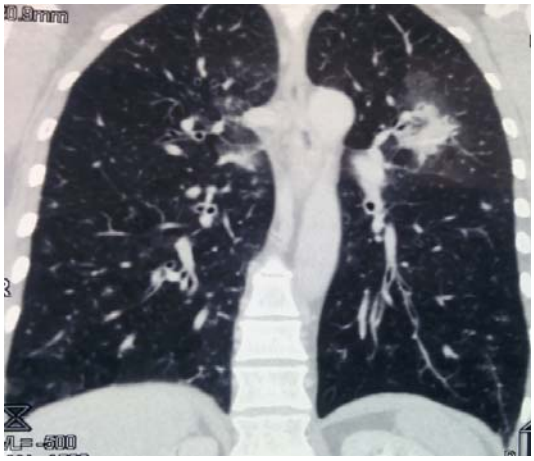

**Fig. 2 – Multislice computed tomography (MSCT) of the chest showing changes in the form of ground glass located in all lobes of the right lung and an infiltrate in the upper lobe of the left lung.**

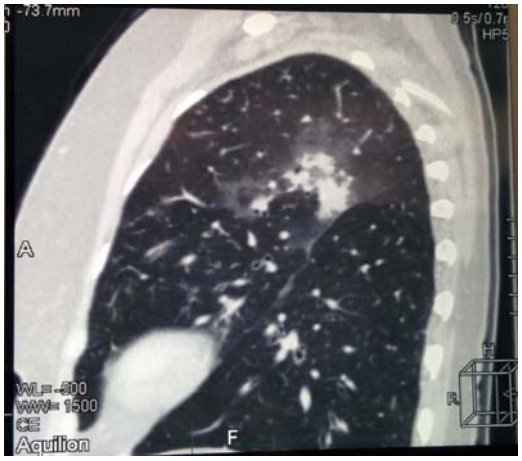


**Fig. 3 – Multislice computed tomography (MSCT) of the chest, lateral view, showing changes in the form of ground glass and an infiltrate in the upper lobe of the left lung.**

Because of the small pericardial effusion which was noted on MSCT of the chest, the patient underwent echocardiographic examination and the finding was normal. After consultation with the neurologist, the patient underwent electromyographic examination where neurogenic lesions in the tested muscles were found with findings characteristic of mononeuritis of peroneal nerve of the right leg.

Bone marrow biopsy was performed and pathohystological finding indicated hypercellularity, with domination of eosinophilic granulocytes (30%).

According to the results of all examinations which were performed, the diagnosis of the CSS was set, and the patient began treatment with high doses of corticosteroids, while montelukast was discontinued from further asthma treatment. Soon after the systemic corticosteroid therapy was introduced, regression of all signs and symptoms, and radiographic changes were notable (Figure 4). During the following year, she was weaned off oral corticosteroids and now she has intermittent asthma that is controlled by inhaled corticosteroids/long-acting beta-2-agonists ICS/LABA combination (salmeterol/fluticasone 50/500 μ) twice a day therapy.

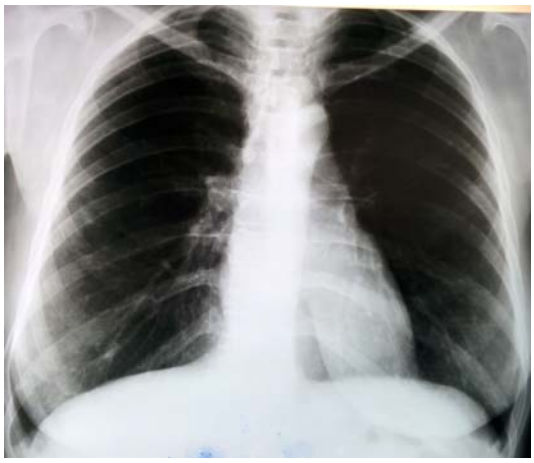

**Fig. 4 – Chest radiography on patient's discharge from hospital treatment, showing complete regression of all previously described changes.**

**Discussion**

The Churg-Strauss syndrome is a systemic form of vasculitis associated with the presence of positive ANCA antibodies. The syndrome is characterized by asthma and strictly uniform clinical presentation, whose main features are fever, eosinophilia, heart failure, renal impairment and peripheral neuropathy. The first case of CSS was described in 1951.

According to the classification made by the American College of Rheumatology, this syndrome is characterized by the following six criteria: eosinophilia, asthma, neuropathy, lung infiltration, paranasal sinus abnormalities and accumulation of eosinophiles in tissues [1].

Natural course of the disease usually evolves through three stages. Prodromal phase is also referred to as allergic phase and is characterized by asthma and rhino-sinusitis. Eosinophilic phase is manifested by the presence of peripheral eosinophilia and the involvement of internal organs (lungs, heart and/or gastrointestinal tract). Active form of the disease is characterized by peripheral eosinophilia > 10% or 1500 cells/μ. Cytotoxic proteins released by activated eosinophils could play a role in the development of the CSS. Chest X-ray is usually registering peripheral, uneven and migrating shadows or infiltrates. The third (the last) phase is the vascular phase with clinical manifestations in the form of small vessel vasculitis. In this stage pulmonary hemorrhage and glomerulonephritis usually appear.

In patients with the CSS, indicators of poor prognosis include cardiac and gastrointestinal involvement. The study of Guillevin et al. [2], showed 39% of mortality due to myocardial disease, and most of these patients died during the acute phase of their illness. Corticosteroids are the first-line treatment for the CSS, and remission rates are 80% to 90% when applying this therapy.

Five out of six criteria were noted in the described patient's clinical presentation. There were no parameters that would indicate the organ damage such as impaired kidney function, damage to the heart muscle or the gastrointestinal tract.

In recent years, new articles have been published linking the emergence of the CSS with the implementation of therapy with leukotriene modifiers such as montelukast [3–7]. The authors suggested that vascular component of the CSS was suppressed with administration of corticosteroids and the add-on therapy of montelukast usually reduced doses of corticosteroids which exposed vasculitis.

However, several patients who were not in the midst of a steroid taper developed the Churg-Strauss disease after the administration of leukotriene-receptor antagonists. Villena et al. [8] described a patient who developed rash, eosinophilia, and bilateral pulmonary infiltrates 4 months after beginning montelukast treatment while taking inhaled corticosteroids and bronchodilators only. Solans et al. [9] described an asthmatic patient who had never received oral corticosteroids and developed the CSS 4 months after initiating montelukast treatment.

It is difficult to establish the exact incidence of the CSS in patients taking leukotriene-receptor antagonists, since the available literature data are rare and variable. Keogh [10] reported that the incidence of the CSS in general population is 1 to 4 cases per million. In patients with asthma it is 20–60 cases per million patient-years, which is similar to that seen in the population receiving leukotriene receptor antagonists. A literature review from Jamaleddine et al. [11], using Medical Literature Analysis and Retrieval System Online (MEDLINE) from February 1966 to October 2000, states that 22 case reports of patients receiving leukotriene receptor antagonists who developed the CSS were identified. On the other hand, Wechsler et al. [12] reported that within 6 months of zafirlukast being made available on the market, 8 patients who received this agent for moderate to severe asthma treatment, developed the CSS. All of the patients had discontinued systemic corticosteroid use within 3 months of presentation and all developed the syndrome within 4 months of zafirlukast initiation.

Even though relationship between the CSS and montelukast treatment still remains unclear, if this case is analyzed through Naranjo algorithm[13] in order to determinate the likelihood of whether this suspected adverse drug reaction (ADR) is actually due to the drug that was administered rather than the result of other factors, the scoring result of 4 rates it as "possible ADR". Probability is assigned via score termed definite (≥ 9), probable (5-8), possible (1-4) or doubtful (0).

Regardless of this estimated probability, according to most authors [3–12], the occurrence of the CSS in the asthmatic patients receiving leukotriene receptor antagonists appears to be related to unmasking of an underlying vasculitic syndrome that is treated with corticosteroids and montelukast does not appear to directly cause the syndrome in these patients.

## Conclusion

This female patient was treated with high doses of inhaled corticosteroids and leukotriene modifiers when symptoms of the CSS appeared. After the diagnosis was set, the patient was treated with high doses of corticosteroids and montelukast was discontinued. This therapy resulted in notable regression of signs and symptoms of the CSS as well as radiographic changes. In the following year, she was weaned off oral corticosteroids and now her asthma is characterized as intermittent and controlled by ICS/LABA, with no signs or CSS symptoms relapse.

In all patients with asthma and frequent exacerbations with the appearance of pulmonary infiltrates, eosinophilia and paranasal sinus abnormalities, this form of vasculitis undoubtly should be taken into consideration.

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