CAZURI CLINICE

Churg Strauss Syndrome associated with montelukast - case report

Milena Adina Man[1], Dana Alexandrescu[2], Monica Pop[1], Antigona Trofor[3]

1. Iuliu Haţieganu University of Medicine and Pharmacy, Department of Pneumology, Cluj Napoca, Romania; 2. University of Medicine and Pharmacy, Brasov; 3. Clinic of Pulmonary Diseases Iasi, Romania

ABSTRACT

Churg-Strauss Syndrome (allergic granulomatous angiitis) is a rare systemic and pulmonary vasculitis. We report the case of a 62 years old female, non-smoker, with a 20 years history of moderate persistent asthma treated with Salmeterol/Fluticasone 50/500 µg bid for 5 years and supplemental Montelukast in the past 5 months. The patient was admitted in our hospital with fever, malaise, sensory deficits in the lower extremities, diffuse musculoskeletal and thoracic pain. Blood eosinophil was 38% of her total WBC, thoracic computed tomography evidenced ill-defined groundglass attenuation predominantly involving the lateral segment of the middle lobe. Pulmonary infiltrates with eosinophilia can be used to define eosinophilic lung diseases. We made the differential diagnosis of eosinophilic lung disease: acute or chronic eosinophilic pneumonias, allergic bronchopulmonary aspergillosis, Löffler syndrome, Churg–Strauss syndrome, bronchocentric granulomatousis, idiopathic hypereosinophilic syndromes. Bronchoalveolar lavage showed 14.6% eosinophils. Few days after hospital admission patient experienced nausea, vomiting and diarrhea. She underwent a digestive endoscopy, which showed eosinophilic enteritis according to colon biopsy. Nasal mucosa biopsy found granulomas. Anti-neutrophil cytoplasmatic antibody (ANCA) was positive at 1:20. She displayed more than four American College of Rheumatology (ACR) criteria for Churg-Strauss Syndrome (developed while she was receiving montelukast therapy). Discontinuation of Montelukast and association of oral prednisone (1mg/kgc) induced rapid improvement of symptoms and rapid decrease of peripheric eosinophils (72 hours). This case report illustrates the importance of early diagnosis of Churg-Strauss syndrome and the possible pathogenic link between leukotriene receptor antagonist use and CSS development.

Keywords: *Churg Strauss syndrome, vasculitis, hypereosinophilia, eosinophilic lung disease, montelukast*

REZUMAT

Sindrom Churg Strauss asociat terapiei cu montelukast - prezentare de caz

Sindromul Churg Strauss (angeita alergică granulomatoasă) este o vasculită pulmonară şi sistemică rară. Prezentăm cazul unei femei de 62 ani, nefumătoare, cunoscută cu astm bronşic persistent de 20 de ani, cu tratament inhalator cu salmeterol/fluticazonă 50/500µg de aproximativ 5 ani, la care s-a adaugat de 5 luni Montelukast 10 mg. Pacienta s-a internat in clinica noastră cu febră, astenie, tulburări de sensibilitate la nivelul membrelor inferioare, dureri toracice şi musculare difuze. Examinările paraclinice au arătat o eozinofilie sangvină (38% din numărul total de leucocite) iar computerul tomograf a evidenţiat prezenţa unor opacităţi imprecis delimitate cu aspect de sticlă mată, localizate la nivelul segmentului lateral al lobului mediu. Eozinofilia asociată infiltratelor pulmonare definesc plămânul eozinofilic. Am luat în discuţie diagnosticul diferenţial al eozinofiliilor cu afectare pulmonară: pneumonia acută sau cronică cu eozinofile, aspergilozele bronhopulmonare alergice, sindromul Löffler, sindromul Churg Strauss, granulomatozele bronhocentrice, sindroamele eozinofilice idiopatice. Lavajul bronho-alveolar a evidenţiat 14,6% eozinofile. La câteva zile de la internare, pacienta prezintă greţuri, vărsături şi diaree. Endoscopia digestivă cu biopsie demonstrează enterita eozinofilică. Biopsia de mucoasă nazală a arătat prezenţa granuloamelor. Anticorpii antineutrofilici citoplasmatici ANCA au fost pozitivi în titru 1:20. Conform criteriilor Colegiului American de Reumatologie (ACR), pacienta a prezentat mai mult de 4 criterii pentru susţinerea diagnosticului de sindrom Churg Strauss, apărute după iniţierea terapiei cu montelukast. Sistarea terapiei şi asocierea prednisonului oral (1mg/kgc) a dus la îmbunătăţirea rapidă a simptomelor şi descreşterea eozinofilelor sangvine în 72h. Acest caz ilustrează importanţa recunoaşterii şi diagnosticării precoce a sindromului Churg Strauss cu prezentarea principalelor etape diagnostice şi posibila asociere patogenetică cu utilizarea antileucotrienelor.

Cuvinte-cheie: *sindrom Churg Strauss, vasculită, hipereozinofilie, plămân eozinofilic, montelukast*

Introduction

Churg – Strauss Syndrome (CSS) or allergic granulomatous angiitis is a rare systemic and pulmonary vasculitis (affects small and medium vessels) defined by severe asthma associated with blood and tissue hypereosinophilia[1-4]. According to Churg and Strauss (1951) the diagnosis must include three major histologic criteria: necrotizing vasculitis, tissue inflammation with eosinophils and extravascular granulomas[5,6]**.** Lanham described in 1980 three successive phases: 1. prodromic phase with asthma and allergic manifestation; 2. tissue eosinophil infiltration (especially lung and/or myocardial, or gastrointestinal) 3. systemic and vasculitic phase[7]**.** Because these often do not coexist temporally or spatially, in 1990 the American College of Rheumatology (ACR) proposed six criteria for the definition of CSS, at least four of them being needed for diagnosis: 1. asthma; 2. peripheral eosinophilia (> 10% of total WBC count); 3. mononeuropathy or polyneuropathy ; 4. paranasal sinus abnormality; 5. pulmonary infiltrates; 6. histological proof of vasculitis and extravascular eosinophils[8,9]**.** Sensitivity of these criteria for diagnosis was 85 % and specificity was 99.7%[9,10]**.**

CSS is one of the rarest systemic vasculites of unknown etiology, but there have been several reports associating leucotriene modifier drug use and CSS development.

Contact: Man Milena Adina, 4-6, B.P. Hasdeu Street, 440463, Iuliu Hatieganu University, Cluj-Napoca, Romania, E-mail address: manmilena50@yahoo.com

Figure 1. Chest X-ray at hospital admission

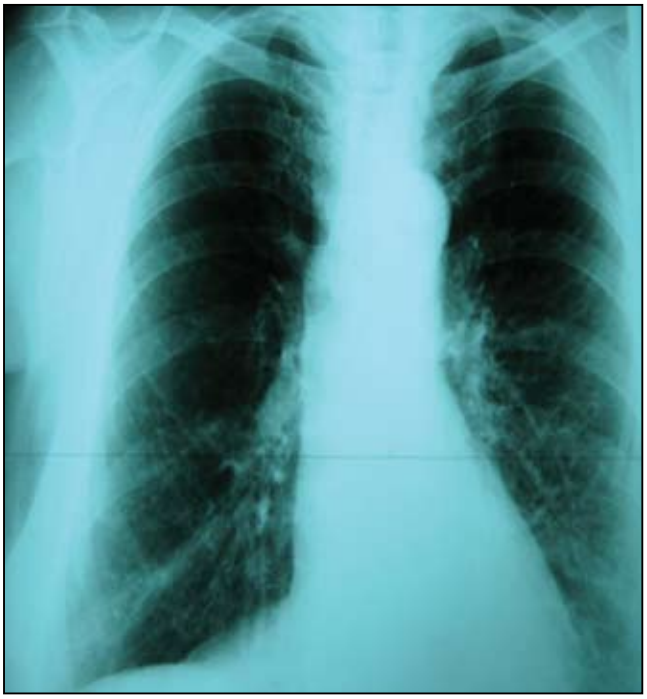
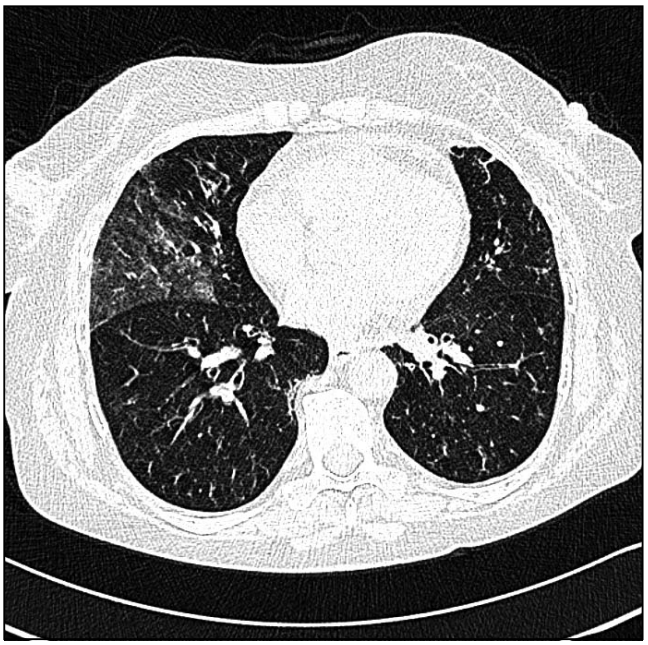


Figure 2. Chest CT scan image showing ground-glass attenuation in middle lobe



Case report

We present the case of a 62 years old female admitted in our clinic for fever, malaise, headache, general weakness, weight loss, sensory deficits in the lower extremities, diffuse musculoskeletal and thoracic pain in November 2007. The patient had a 20 years history of moderate persistent asthma treated for the past five years with Salmeterol/Fluticasone 50/500 µg b.i.d, supplemental Montelukast 10 mg/day was added in the past 5 months. Patient never received systemic steroids. She had moderate rhinitis, was a nonsmoker, without any other previous history of chronic disease, nor any noxious occupational or drug exposure.

Clinical findings. Physical examination revealed wheezing and rhonchi. Also, generalized skin rash without induration was described by patient few days before hospital admission.

Radiological findings. Chest X-ray identified only few discrete pulmonary abnormalities (fig. 1), but thoracic computed tomography evidenced ill-defined groundglass attenuation predominantly involving the lateral segment of the middle lobe associated with diffuse bronchial wall thickening consistent with the clinical history of asthma (fig. 2).

Laboratory findings. Routine and more in depth lab tests were performed to assess the possible etiology of the pulmonary infiltrates in this patient. Standard laboratory tests revealed a leukocyte count of 13.3 X 10^9/µl with 38% eosinophils, erythrocyte sedimentation rate was 72 mm/1h. The bone marrow aspirate showed increased number of cells with hypereosinophilia (40%) and no malignancy sign.

The association of pulmonary infiltrates with blood eosinophilia suggested eosinophilic lung disease. In this patient, we needed to make a differential diagnosis of eosinophilic lung disease. Possible etiologies were: acute or chronic eosinophilic pneumonias (of parasitic origin, other infectious causes, drug induced), allergic bronchopulmonary aspergillosis, Löffler syndrome (migratory, transient mild eosinophilic pneumonia), Churg–Strauss syndrome, bronchocentric granulomatousis, idiopathic hypereosinophilic syndromes. Subsequent tests aimed to define which condition did the patient have.

For differential diagnosis of hypereosinophilia syndrome we asked for additional tests such as: examination of a stool specimen for ova and parasites and allergy skin testing for *Aspergillus*. These were both negative.

Total serum IgE level was 1098 IU/ml. Assessment of rheumatoid factor in the blood was negative. We also explored the renal function for a possible systemic disease involving both the lungs and the kidney, but there was no renal involvement, as values for serum creatinine and the creatinine clearance were within normal ranges, without microscopic hematuria or proteinuria. The antibodies against neutrophil cytoplasmatic antigens –P-ANCA test (antibodies against myeloperoxidase with a perinuclear staining pattern) was positive, at a titer of 1:20.

Bronchoscopy with broncho-alveolar lavage (BAL) was performed. BAL fluid examination revealed 14.6% eosinophils, with no other findings, BAL cultures for bacteria, *Mycobacterium tuberculosis, Aspergillus,* other mycosis or other germs were negative.

Echocardiography revealed global left ventricular hypokinesia and minimal pericardial effusion, also pulmonary hypertension and diastolic dysfunction (which could be explained by a possible cardiac involvement in systemic disease).

The patient experienced sensory deficits in the lower extremity and was referred to a neurologist. The ***neurological consult*** diagnosed a peripheral neuropathy.

As few days after hospital admission the patient experienced nausea, vomiting and diarrhea, she underwent a ***digestive endoscopy*** (colonoscopy) and a colon mucosa biopsy was performed. This showed eosinophilic enteritis (Fig. 3).

Nasal mucosa biopsy was also performed and found granulomas rich in neutrophils and few eosinophils (Fig 4).

What is the diagnosis?

This patient displayed several clinical and laboratory features associating asthma, lower limb neurologic abnormalities, eosinophilic lung infiltrates, eosinophilic granulomas identi-

Figure 3. Colon mucosa biopsy slide showing eosinophilic granulomas

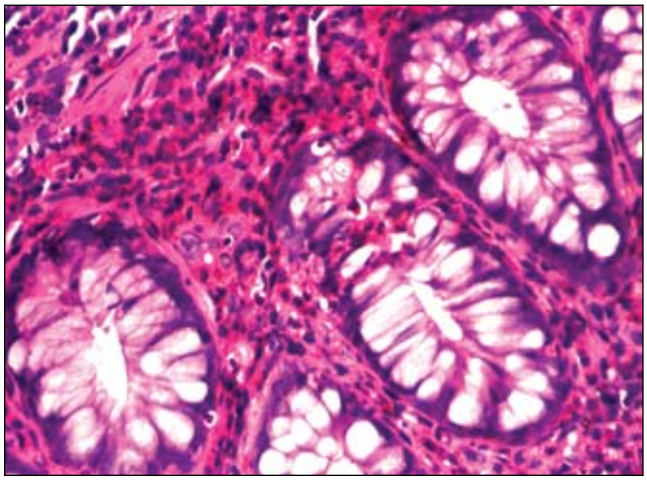
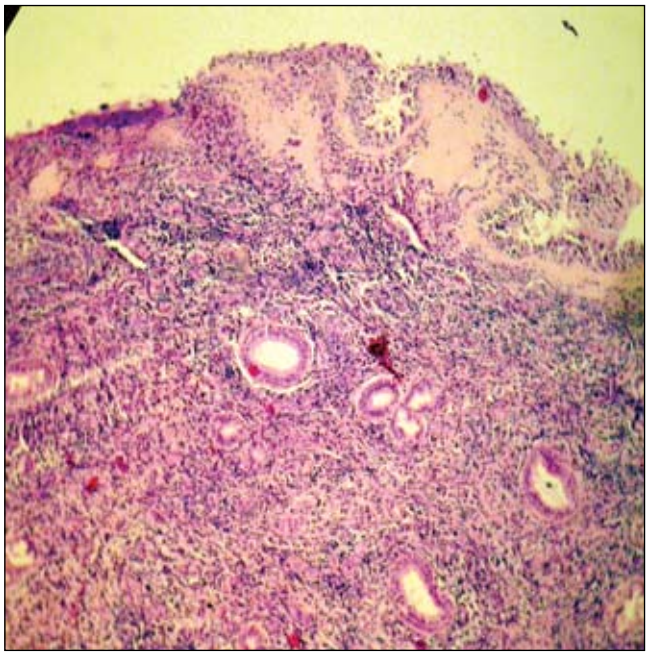


Figure 4. Nasal mucosa biopsy



fied in several sites of biopsy (nasal mucosa, intestinal mucosa). An ANCA positive test provides valuable support towards a clinically classified ANCA-related disorder. If ANCA are found in a systemic vascular syndrome developed from an initially asthmatic disease and this is accompanied by blood and tissue eosinophilia, it will definitely lead to a strong case for Churg Strauss disease involving the lungs.

In histopathology examinations, CSS consists of changes mainly affecting small vessels (arterioles, venules and capillaries) by development of an eosinophil-rich granulomatous inflammation of the respiratory tract and small vessels. There are three important fibrinoid, necrotizing, inflammatory, systemic small vessels vasculitis that are associated with high titers of antineutrophil cytoplasm antibodies to differentiate: Churg Strauss angiitis, Wegener granulomatosis and microscopic polyangiitis. Another condition clinically close to CSS is periarteritis nodosa (PAN) that distinguishes pathological findings such as predominantly affecting both medium size blood vessels and some small arteries, tending to spare capillaries, venules and arterioles.

Our patient had no new environment exposure, no new drug, and no neoplastic courses. HIV test was negative and no other infection was demonstrated. Bronchocentric granulomatosis is characterized by granulomatous and necrotising replacement of epithelium bronchial epithelium (requiring biopsy and morphological confirmation, and it is an exclusion diagnosis), but is not usually associated with other organ involvement. Idiopathic hypereosinophilic syndrome, a condition reuniting peripheral eosinophilia greater than 1500/µl for over six months and typical organ involvement (eosinophilic myocarditis also affecting endocardium tissue, pulmonary infiltrates, mono neuropathy, dermatological manifestations as angioedema or urticaria) in absence of any known cause may also resemble to Churg Strausse syndrome. In Idiopathic hypereosinophilic syndrome, asthmatic features are unlikely, yet in 40% of cases, possible dry cough or pulmonary dysfunction due to cardiac failure are encountered.

Following evidence of more than four American College of Rheumatology (ACR) Churg Strauss Syndrome (CSS) diagnostic criteria in our patient (all four developed while she was receiving montelukast therapy), we considered Churg Strauss Syndrome diagnosis in this case. This was sustained also by the fact that the patient did not report any such suggestive symptoms before initiation of Montelukast therapy. Also, she did not reduce or stop her maintenance corticosteroid therapy dose while being administered Montelukast and had no history of cortisone withdrawal, no history of systemic steroids treatment. A systemic steroid treatment could have covered a pre-existing CSS, which could have been unmasked by the stopping of steroid treatment, which is not the case in our patient. Consequently, an association between leukotrienes inhibitors treatment and CSS development could be taken into account. *Diagnosis: Churg Strauss Syndrome possible due to Montelukast therapy for asthma, in absence of reduced corticosteroid dose.*

Montelukast was discontinued and oral prednisone was associated (starting 1 mg/kgc for 1 month and than progressively tapered over another month). This generated a rapid improvement of the symptoms and rapid decrease of blood eosinophilia (in 72 hours). After 3 months, the CT scan showed no lung infiltrates. Follow-up after three years demonstrated a favorable outcome with no relapse of systemic disease, with asthma treatment with inhaled combination therapy (salmeterol/fluticasone 50/500 µg b.i.d), currently partially controlled.

Discussion

In 1994 the Chapel Hill Consensus Conference produced the definition for vasculitis and defined Churg-Strauss Syndrome as an eosinophil rich and granulomatous inflammation involving the respiratory tract in combination with necrotizing vasculitis, affecting small to medium size vessels, in association with asthma and eosinophilia[10,11,12]. CSS is a rare disease with an annual incidence ranging between 0.5 and 6.8 per million inhabitants, with mean age at onset around 50 years, with no sex predominance[7,13]. Incidence of CSS in asthma patients receiving LTRA, or other asthma therapy is 20 fold greater that in general population[14]. CSS can be difficult to diagnose because of its variable presentation. The disease can affect virtually any organ system in the body[2,10,15,16]. The patients usually have asthma and history of rhinitis/

sinusitis (preceding vasculitis by up to six years)[6]. The clinician should suspect a CSS in patients with asthma /atopy who develop significant constitutional symptoms (fever, muscle pain, malaise, joint pains), increasing cough, dyspnea, pulmonary infiltrates in the absence of infection, in patients with significant gastrointestinal disease (perforation, ischemia, bleeding) or cardiac disease (abnormalities of conduction, systolic or diastolic dysfunction), patients with skin abnormalities, peripheral eosinophilia, increased serum IgE and positive ANCA [2,14,17,18]. Patients who are on antileukotriene agents are usually ANCA negative[19]**.** The clinical suspicion and the cooperation with the pathologist for documenting the presence of eosinophilic tissue infiltration and vasculitis can lead to an early diagnosis of CSS and favors a good outcome[20]**.**

Conclusion

Even if the association between leukotriene antagonists and development of Churg-Strauss syndrome is not fully proven[22,23], in many cases being considered simply that tapering of the systemic corticosteroid treatment unmasks an underlying vasculitis, in this particular clinical case no previous systemic steroid treatment was used, and the CSS developed coincidental to the montelukast treatment.

In asthma patients for which montelukast is indicated (exercise induced asthma, asthma associated with allergic rhinitis, asthma in obese patients, in smokers, aspirin-induced asthma, viral induced wheezing episodes or asthma needing step-up in therapy in order to obtain the control of asthma)[20,21] physicians should be aware of this possible association and able to recognize the early signs and symptoms of the development of systemic vasculitis.

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