CHURG-STRAUSS SYNDROME WITH MYOPERICARDIAL INVOLVEMENT

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SUMMARY – Churg-Strauss syndrome (CSS) is a small-vessel necrotizing vasculitis typically characterized by asthma, lung infiltrates, extravascular necrotizing granulomas and hypereosinophilia. Cardiac disease is a major contributor to disease-related death in CSS. We describe a 38-year-old man with late-onset asthma, allergic rhinosinusitis, and high extravascular and peripheral blood eosinophilia, who presented with migratory pulmonary infiltrates and acute myopericarditis. Antineutrophilic cytoplasmic antibodies (ANCA) were negative. Early therapy with medium-dose methylprednisolone led to resolution of the pericardial effusion and significant clinical improvement. In the present case report, the importance of early recognition of CSS in patients with asthma and peripheral eosinophilia is discussed. Cardiac magnetic resonance imaging, besides electro- and echocardiography, may be helpful in early detection of cardiac involvement in CSS, enabling appropriate treatment aimed to prevent further disease progression and potentially fatal consequences.

Key words: *Churg-Strauss syndrome – complications; Churg-Strauss syndrome – epidemiology; Churg-Strauss syndrome – immunology; Heart diseases – diagnosis; Asthma – immunology; Case report*

Introduction

Churg-Strauss syndrome (CSS) is a small-vessel necrotizing vasculitis typically characterized by asthma, lung infiltrates, extravascular necrotizing granulomas and hypereosinophilia[1]. The cause of CSS is unknown. The presence of marked tissue and blood eosinophilia, as well as secretory products of eosinophils in blood and tissues implicate a pathogenetic role of eosinophil granulocytes. Although the mechanisms involved in eosinophil activation in CSS have not been elucidated, recent studies suggest the possible role of T lymphocytes secreting eosinophil-activating cytokines[2]. CSS is a rare disease. The estimated annual incidence of CSS is 1-3 *per* million, although epidemiological data differ among reports. Watts *et al*. report on the annual incidence of CSS in Norwich, UK, of 2.7-3.1 *per* million[3]. This was significantly higher than in two other regions. The annual incidence of CSS in Tromsø, Norway, and Lugo, Spain, is reported as 0.5 and 0.9 *per* million, respectively[4]. In a study aimed to estimate the incidence of CSS in asthmatics, Harrold *et al*. analyzed a population of 184,667 asthma drug users contributing 606,184 person-years of exposure and report on the overall incidence as high as 34.6 *per* million person-years, with no sex and age differences[5].

Clinical presentation of CSS occurs in three usually sequential stages. The initial, prodromal stage is characterized by allergic inflammation of the nose (nasal polyposis), sinuses, skin and lungs. Patients are often diagnosed with late-onset asthma during this stage. The second stage is characterized by peripheral blood eosinophilia and eosinophilic infiltration of multiple organs. In the third stage, systemic symptoms (e.g., fever, malaise, weight loss, fatigue) due to potentially life-threatening systemic vasculitis are

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common. Although the skin and the lungs are among the most often affected organs, pathological findings of necrotizing eosinophilic vasculitis could be demonstrated in nearly all major organ systems[6].

The diagnosis of CSS is based on clinical criteria, routine laboratory tests and biopsy, if possible. Classification criteria of the American College of Rheumatology include asthma, eosinophilia of >10% in peripheral blood, paranasal sinusitis, pulmonary infiltrates, sometimes transient, histologic evidence of vasculitis with extravascular eosinophils, and mononeuritis multiplex or polyneuropathy[7]. The presence of at least four of these criteria yields a sensitivity of 85% and specificity of 99.7%. Beside these criteria, in some patients the early diagnosis of CSS may be difficult, mostly due to significant differences in its severity. In addition, the stages of CSS do not necessarily follow one another consecutively, and the time interval between them may vary greatly. The histologic differential diagnosis of CSS in the lung includes disorders associated with prominent eosinophilic infiltrates or a combination of eosinophils and granulomatous inflammation (e.g., eosinophilic pneumonia, hypereosinophilic syndrome, allergic bronchopulmonary aspergillosis, Wegener granulomatosis)[8]. The prognosis of CSS is generally good. With the introduction of corticosteroid treatment, remission and survival rates have improved greatly. Refractory CSS may be responsive to cyclophosphamide, azathioprine, or high-dose intravenous immunoglobulins.

The purpose of this case report is to indicate the importance of early recognition of CSS and systemic vasculitis in patients with asthma and peripheral eosinophilia. The treatment should be targeted to prevent disease progression and its potentially fatal consequences.

Case Report

A 38-year-old man was admitted to the hospital because of an episode of syncope and an echocardiographic finding of subacute myopericarditis. Two months before, he was hospitalized for seven days because of a pulmonary infiltrate in the lower left lobe. Upon recovery, he was planned for elective nasal polypectomy. During routine preoperative testing, the patient reported malaise, generalized myalgia, occasional night sweats, increasing exertional dyspnea, and nonproductive cough. An abnormal electrocardiogram (ECG) was found: sinus tachycardia, low QRS voltage, and invert T-waves in precordial leads. Transthoracic echocardiogram (TTE) detected a moderate reduction in global contractility, distal septal hypokinesis, and pericardial effusion of 500 to 700 mL. Laboratory studies revealed peripheral blood eosinophilia ($3.6x10^9$/L), increased C-reactive protein (89.0 mg/L), and elevated gammaglobulins (29.9%; IgG 23.83 g/L), and the patient was transferred to our institution for further studies.

At admission, enquiry confirmed a history of chronic sinusitis and sinonasal polyposis for more than 10 years, and moderate persistent asthma for the last 4 years. Asthma was reasonably well controlled with regular use of a combination of salmeterol and fluticasone. On physical examination, the patient was mildly pyrexial but had no rashes or purpura. Two small bilateral painful skin nodules on the scalp were noticed. Heart sounds were muffled, otherwise normal finding. Respiratory examination revealed a mild diffuse bronchospasm.

Laboratory investigation revealed persistent peripheral eosinophilia. Immunoassays for parasitic diseases (echinococcosis, amebiasis, trichinellosis, cysticercosis, toxocariasis, strongyloidiasis, leishmaniasis, fascioliasis, and ascaridosis) were negative. Stool microscopy showed no abnormalities. In spite of negative immunoassays for parasitic infections, during initial hospitalization the patient was treated with albendazole (400 mg/day for 12 days). Current or past infection with cardiotrophic viral agents was not revealed. Antineutrophilic cytoplasmic antibodies (ANCA) and antinuclear antibody (ANA) assays yielded negative results, while rheuma factor (RF), anti-citrullinated protein (CCP), anticardiolipin antibodies (aCI-IgG, aCI-IgM), C3 and C4 components of complement were within the normal ranges. IgE was elevated (345 kIU/L). Pulmonary function tests confirmed an FEV_1/FVC ratio of 3.27/4.88 (67%), suggesting a mild obstructive defect. Bone marrow and peripheral blood investigation revealed morphologically normal hematopoiesis, and increased normal and mature eosinophils. The karyotype was normal. JAK2 V617F point mutation test and BCR-ABL p210 oncogene were negative. FIP1L1-PDGFR alfa fusion gene, a recurrent molecular lesion in idiopathic

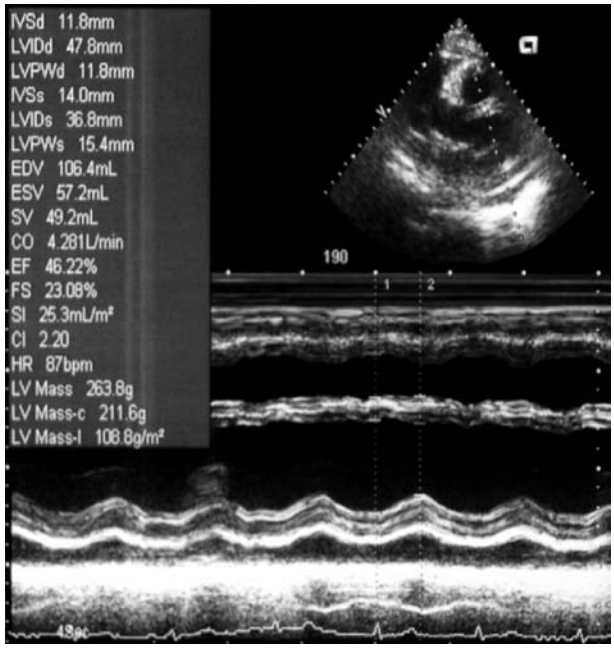

Fig. 1. M-mode echocardiogram of the left ventricle (LV) in the parasternal long-axis view: LVEF is reduced (45%-50%) due to IVS hypocontractility; slight hypertrophy of both IVS and posterior wall. Echo free space relates to the moderate effusion behind the LV through systole and diastole.

hypereosinophilic syndrome, which makes a basis for the diagnosis of chronic eosinophilic leukemia was not detected. Fiberoptic bronchoscopy visualized normal bronchial lumen, diffusely inflamed bronchial mucosa, and moderate mucopurulent bronchial secretion. Bronchoalveolar lavage (BAL) with 150 mL of warmed saline was performed. BAL cytology revealed eosinophilic alveolitis (30% of eosinophils in BAL fluid). In addition, nasal smear cytology revealed an increased number of eosinophils. Electromyography finding was normal. Smears of the skin nodule biopsy revealed eosinophils and fat cells.

TTE performed at admission detected moderate reduction in global contractility, distal septal hypokinesis, and normal morphology of the valvular apparatus. Pericardial effusion thickness, measured in diastole behind the right ventricle, was 14 mm (Fig. 1). Cardiac magnetic resonance imaging (CMRI), performed upon the resolution of pericardial effusion, demonstrated normal pericardial thickness, impaired contractility, especially of the distal septum, and paradoxical interventricular septal motion. Systolic left ventricular (LV) function was mildly impaired (LV end-diastolic volume 150 mL, LV end-systolic volume 85 mL, and LV ejection fraction 43%). Delayed post-contrast sequences

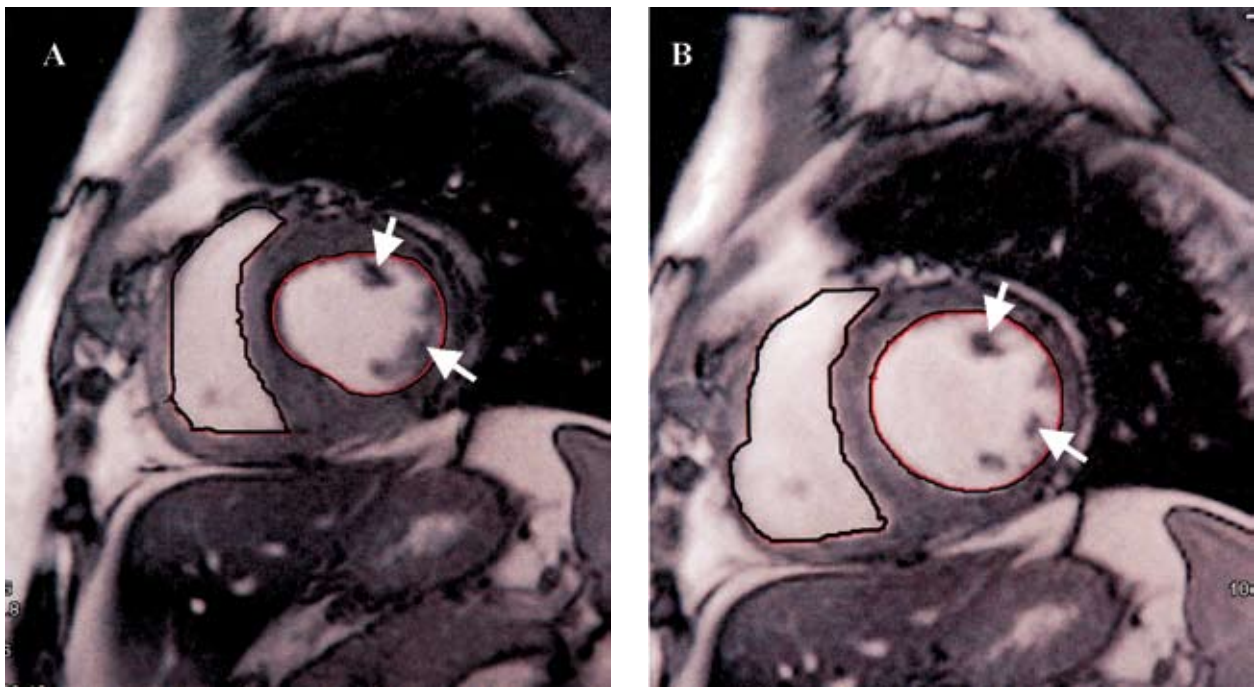

Fig. 2. Contrast CMR imaging in systole (A) and diastole (B) reveals diffuse transmural and subendocardial delayed hyperenhancement in the basal septum and both ventricles with involvement of the papillary muscles (white arrows).

(gadolinium-based paramagnetic contrast agent) demonstrated the presence of diffuse transmural contrast imbibition in the basal septum and subendocardial contrast enhancement in the septum, both ventricles, and papillary muscles. The type of diffuse contrast distribution indicated inflammation of the myocardium, while subendocardial imbibition related primarily to vasculitic lesions (Fig. 2).

The diagnosis of CSS was based on the patient's history (late-onset asthma, chronic sinusitis, sinonasal polyposis), prominent eosinophilia (peripheral blood, bone marrow, skin nodules, lungs and nasal mucosa), and recent pulmonary infiltrates. The patient fulfilled 5 out of 6 ARA classification criteria for CSS. TTE and CMRI documented myopericardial involvement. The treatment with medium-dose oral methylprednisolone led to significant clinical improvement, rapid normalization of peripheral blood eosinophilia, and resolution of the pericardial effusion.

Discussion

We present a patient with CSS with myopericardial involvement. Since the initial report describing CSS, cardiac involvement has been considered common and given a high rank among the causes of morbidity and mortality[9]. Early studies reported that cardiac failure had occurred in 47% and pericarditis in 32% of all cases, the former disorder accounting for 48% of deaths, most often due to myocardial infarction, malignant ventricular arrhythmias, heart failure, and cardiac tamponade[10].

During the last decade, cardiac complications of CSS have been studied more comprehensively, although most often in relatively small series of patients or as case reports. Using clinical evaluation, ECG, TTE, CMRI, and endomyocardial biopsy, cardiac involvement was recently documented in 22 out of 49 patients with CSS[11]. Cardiac presentations included impaired left ventricular function (50%), mild to severe valvular insufficiencies (73%), pericardial effusions (41%), and endomyocarditis (59%)[11]. Using the same diagnostic tools, a high prevalence of cardiac involvement (62%) was found even in patients with CSS in remission[12]. Clinical symptoms were present in only 26% of patients, supporting the proposal that cardiac involvement in CSS may often be silent but potentially of severe prognosis. In accordance with this, the clinical manifestations of myopericardial involvement in our patient were relatively mild and nonspecific.

Recent studies underline the important role of CMRI in the assessment of myopericardial involvement in CSS because of its potential to visualize various forms of inflammatory changes in the myocardium[11-14]. In a series of 11 patients with biopsy-proven CSS and clinical evidence of cardiac involvement, systolic left ventricular function was impaired in 6 patients, edema was present in 4 cases, 7 patients had pericardial effusion, while late enhancement lesions were detected in 9 of 11 patients[14]. It is especially important that these lesions could even be detected in patients with normal left ventricular size and function, where TTE has limited diagnostic usefulness[13,14]. In addition, CMRI could be a useful tool for direct monitoring of myocardial response to medical treatment, independent of LV ejection fraction or ECG abnormalities[15]. In our patient, CMRI also had a major clinical impact on the diagnosis of myocardial injury. Together with mild impairment of LV systolic function, CMRI visualized myocardial perfusion defects most likely secondary to vasculitis of the small myocardial vasculature and myocardial infiltration.

Churg-Strauss syndrome has previously been reported as being associated with antineutrophil cytoplasmic antibodies targeting myeloperoxidase (ANCA) in 39% to 59% of patients[16,17]. In a uniquely large cohort of 112 patients with CSS, followed for approximately 3 years and aimed to better define the clinical and biological characteristics of newly diagnosed CSS, the authors detected ANCA in 43 (38%) patients[18]. Positive ANCA was associated with renal involvement, peripheral neuropathy, and biopsy-proven vasculitis, whereas negative ANCA status was associated with heart disease and fever[18]. This could mean that ANCA are probably more involved in the vasculitic manifestations of CSS (e.g., glomerulonephritis), whereas eosinophil tissue infiltration and associated cytotoxicity would be responsible for cardiomyopathy[18,19]. Our data fit to this proposal, i.e. the CSS was ANCA-negative with high eosinophilia, eosinophilic alveolitis and cardiac involvement.

The cited findings, if confirmed, could support individual therapeutic stratification according to the clinical pattern. However, until then corticosteroids

and cyclophosphamide remain the foundation of CSS treatment[1,20,21]. The prognosis of CSS is generally good although it depends significantly on early initiation of treatment. According to the report of the European Vasculitis Study Group (EUVAS), the remission rate was 81% to 91%, the 5-year survival was 60%-97%, and the relapse frequency in the first 2 years was 15% to 35%[21].

In accordance to the proposed recommendation that mild to moderate forms of CSS could be treated with corticosteroids only[20,21], our patient was treated with medium-dose methylprednisolone. After three weeks of treatment, significant clinical improvement together with TTE-confirmed resolution of pericardial effusion was observed. Cytotoxic drugs might be necessary in less than 20% of patients, mostly in those with major life-threatening organ involvement. Other tested treatments, especially in patients with refractory and steroid-dependent CSS, include interferon-alpha[22], infliximab[23], rituximab[24], and few other approaches (plasmapheresis, anti-IL5, and anti-IgE monoclonal antibodies)[25]. When discussing treatment modalities, it should be noted that some concerns have been raised that the treatment of asthma with leukotriene receptor antagonists may be associated with an increased incidence of CSS[26]. However, the causative role of antileukotrienes in CSS has not been confirmed. The current level of evidence suggests that antileukotrienes, by reducing the need for oral corticosteroids, allow for the eosinophilic and particularly the vasculitic manifestations of CSS to be „unmasked". Therefore, monitoring for the signs and symptoms of CSS is strongly recommended in asthma patients tapered off corticosteroids.

In conclusion, CSS is a rare but potentially fatal condition, which occurs in patients with late-onset asthma. Since clinical manifestations could be subclinical in spite of significant damage of the affected organs, it is crucial to establish an accurate diagnosis and treat the patient as early as possible, thus preventing further disease progression. Increased peripheral eosinophilia and transient pulmonary infiltrates may be the initial warnings. Cardiac damage is frequent, often silent initially and undetectable with standard cardiac imaging techniques, such as cardiac ultrasound or myocardial scintigraphy. CMR imaging permits early diagnosis of different types of cardiac involvement, and therefore should be part of the diagnostic algorithm.

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Sažetak

CHURG-STRAUSSOV SINDROM SA ZAHVAĆENIM MIOPERIKARDOM

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Churg-Straussov sindrom (CSS) je nekrotizirajući vaskulitis malih krvnih žila koji je znakovito obilježen astmom, plućnim infiltracijama, ekstravaskularnim nekrotizirajućim granulomima i hipereozinofilijom. Srčana bolest je najvažniji uzrok smrti kod CSS. Opisuje se 38-godišnji muškarac s astmom kasnog nastupa, alergijskim rinosinusitisom i visokom ekstravaskularnom i perifernom eozinofilijom, koji se prezentira s migrirajućim plućnim infiltratima i akutnim mioperikarditisom. Antineutrofilna citoplazmatska antitijela (ANCA) bila su negativna. Rana terapija srednjom dozom metilprednizolona riješila je perikardijalni izljev i dovela do značajnog kliničkog poboljšanja. U ovom prikazu slučaja raspravlja se o važnosti ranog prepoznavanja CSS kod bolesnika s astmom i perifernom eozinofilijom. Uz elektro- i ehokardiografiju, magnetska rezonancija srca može pomoći u ranom otkrivanju zahvaćenosti srca kod CSS, te tako omogućiti primjereno liječenje kako bi se spriječilo napredovanje bolesti i moguće pogubne posljedice.

Ključne riječi: *Churg-Straussov sindrom – komplikacije; Churg-Straussov sindrom – epidemiologija; Churg-Straussov sindrom – imunologija; Srčane bolesti – dijagnostika; Astma – imunologija; Prikaz slučaja*