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Churg-Strauss Syndrome in a Seven-year-old Boy: A Case Report

Abdolreza Malek (MD)[1], Forough Rakhshanizadeh (MD)[2*], Sheila Kiyanifar (MD)[2]

[1]*Department of Pediatric Rheumatology, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.*
[2]*Department of pediatrics, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.*

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ABSTRACT

Churg-Strauss syndrome (CSS) is a type of vasculitis of small-to-medium sized vessels. This syndrome is known by a history of bronchial asthma with systemic necrotizing vasculitis and peripheral blood hypereosinophilia. It is currently called eosinophilic granulomatosis with polyangiitis (EGPA). This disease affects both genders and all age groups, but it is very rare among children. CSS diagnosis is based on clinical findings such as asthma, eosinophilia, rhinosinusitis, and signs of vasculitis in major organs. In cases where steroids alone or in combination with other immunosuppressive agents are used as treatment, the outcome and long-term survival are usually satisfying. In comparison with other types of systemic vasculitis, the mortality rate of this syndrome is low. In this study, we present the case of a 7-year-old boy with poorly controlled bronchial asthma since three years of age. This case had developed purpuric skin lesions, sinusitis, arthritis, and weakness of the limbs with symptoms of mononeuritis multiplex at the age of seven. After being admitted to our hospital, a series of studies, including complete blood count-diff, chest X-ray, paranasal sinus radiography, brain magnetic resonance imaging, nerve conduction study, spirometry, and serological tests for autoantibodies, were performed and he was diagnosed with CSS. Thereafter, he received regular corticosteroid therapy in combination with methotrexate, and his symptoms were generally well-controlled with the beginning of the treatment. The clinical characteristics, diagnosis, and management of CSS in children are also reviewed in this study.

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Introduction

Churg-Strauss syndrome (CSS) is a type of vasculitis that affects small-to-medium sized vessels and is described as ‘‘allergic granulomatosis and angiitis’’ (1) or ‘‘eosiniphilic granulomatosis with polyangiitis (EGPA)” (2). This syndrome is a form of vasculitis associated with anti-neutrophil cytoplasmic antibody (ANCA). The histopathologic findings of CSS are eosinophilic inflammation, extravascular granulomas, and necrotizing vasculitis affecting multiple organs (3).

The main clinical feature of the disease is asthma happening in almost 90% of patients (3). The incidence rate of CSS is up to 67 per 1000,000 cases among patients with asthma (4,5). Because vasculitis affects the central nervous system (CNS) or the epineurial vessels of peripheral nerves, neurological manifestations are common in these patients. Mononeuritis multiplex occurs in up to 76% of the patients with CSS (3). Skin involvements occurring in about 30-50% of patients include tender subcutaneous nodules, macular or popular erythematous rash, petechiae, and palpa-

***Corresponding author:** Forough Rakhshanizadeh.
Department of Pediatrics, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.
E-mail: Rakhshanizadehf@mums.ac.ir
Tel:+989155130386

ble purpura (3). ANCAs are positive in about 40% of patients (6,7).

American College of Rheumatology (ACR) has described six criteria for the diagnosis of CSS, four or more of which should be positive for the diagnosis of CSS. These criteria are: [1] asthma, [2] eosinophilia (more than 10% on differential white blood count), [3] mono- or polyneuropathy attributable to systemic vasculitis, [4] migratory or transient pulmonary infiltration, [5] paranasal sinus abnormalities, and [6] extravascular eosinophils on biopsy including arteries, arterioles, or venules (8).

CSS affects all age groups, but it is a rare syndrome among children and could have different clinical presentations. This syndrome should be considered in any patient with poorly controlled asthma that receives moderate doses of inhaled corticosteroids as treatment (3).

Case report

A seven-year-old boy presented to our hospital with complaints of fever and rash started two weeks before admission. Then, he developed weakness of the limbs and gait disturbance, as well as pain and swelling in the limb joints. On admission, the patient was febrile up to 38.5 degrees with stable vital signs, normal heart and lung auscultation findings, and normal abdominal examination. Widespread erythematous rash was observed as purpura, petechiae, and hives with priority on the side of his leg. In joint examination, we detected effusion and tenderness of the wrists, ankles, and knees. On neurological examination, mononeuritis multiplex was found to lead to gait disturbance as foot slapping gait. Distal muscle weakness of the right upper limb and left lower limb, as well as right wrist drop and left foot drop were observed. Cerebellar test and cranial nerve examination were normal. He also had a history of asthma that had been poorly controlled with inhaled corticosteroid (ICS) since three years of age.

In complete blood count with differentiation (CBC-diff) test, eosinophil count was observed to be 1012 (11%). Immunoglobulin E- levels (IgE), erythrocyte sedimentation rate (ESR), and C- reactive protein levels (CRP) were markedly elevated. Serum chemistries and urine microscopy were performed to detect any evidence of renal involvement, which was rejected. ANCA, anti-nuclear antibody (ANA), and rheumatoid factor (RF) were negative. The laboratory findings are shown in Table 1.

As shown in Figure 1, chest X-ray revealed hyperinflation of both lungs and flattening of the diaphragm. The radiography of paranasal sinus es showed a thickness of the mucosa of the right maxillary sinus (Figure 2).

Table 1. The laboratory finding of presenting patient.

CBC	**WBC (/µl)**	**Total**	9200(100%)
		Eosinophil	1012(11%)
		Neutrophil	5150(56%)
		Lymphocyte	2850(31%)
		Monocyte	185(2%)
	Hb (gr/dl)	11.9	
	Plt (/µl)	526	
IgE (IU/ml)	957		
ESR (mm/hr)	94		
P-ANCA (U/ml)	negative		
C-ANCA (U/ml)	negative		
ANA (U/ml)	negative		
RF(U/ml)	negative		

WBC: White blood cell, Hb: Hemoglobin, Plt: Platelet ANCA: anti-neutrophil cytoplasmic antibody, ANA: anti-nuclear antibody, RF: rheumatoid factor, ESR: erythrocyte sedimentation rate

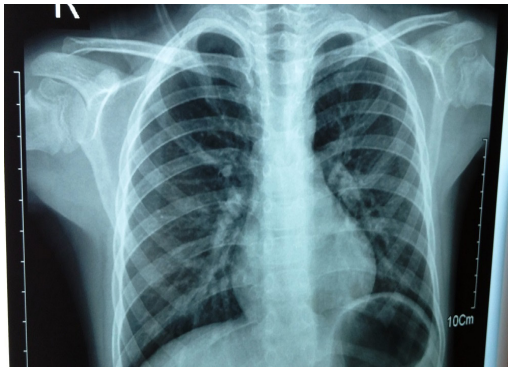

Figure 1. Hyperinflation of both lungs and flattening of the diaphragm are obvious

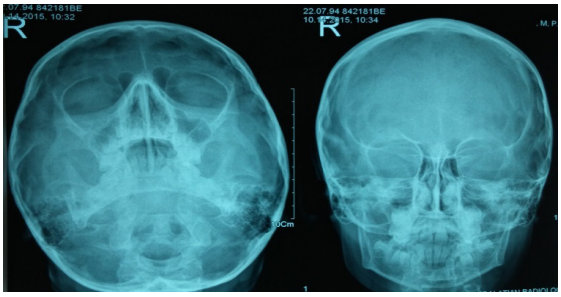

Figure 2. Paranasal sinuses radiographies: mucosal thickening in the right maxillary sinus

The patient had normal brain magnetic resonance imaging (MRI), but spirometry showed severe reversible airflow obstruction. In the nerve conduction study, the early stages of immune-me-

diated process was highly suspected, therefore, close observation was recommended.

According to the clinical presentation of a poorly controlled asthma, mononeuritis multiplex, paranasal sinusitis, and skin rash in addition to eosinophilia (more than 10% in CBC), the diagnosis of CSS was suggested. Montelukast tablets (every night half of tablets) had been prescribed for his severe cough about two weeks prior to admission. Corticosteroids pulse therapy with methylprednisolone was prescribed at a dose of 30 mg/kg daily for three days, and then prednisolone tablet was started at a dose of 2 mg/kg daily and tapered within three months. Methotrexate was initiated at a dose of 15 mg/M^2 and tapered during one year.

With the initiation of treatment, all the symptoms resolved immediately and no adverse events were noted. After one and a half years, he was asymptomatic in follow-up with normal physical examination, and his spirometry findings were significantly improved.

Discussion

CSS is a primary systemic vasculitis affecting small- and medium-sized vessels. The key features in these patients are asthma and severe eosinophilia that is presented with vasculitic organ manifestations. The pathogenesis of CSS may include damage to vascular and perivascular tissues by activated eosinophils directly secreting enzymes (10,11). The severe and sustained eosinophilia observed in the blood and organs of CSS patients is caused by chemokines such as Eotaxin 3 (CCL26) (12).

CSS usually occurs within the age range of 14 to 75 years, with the mean age of 50 years. In a recent review, Louthrenoo reported that CSS has been observed in children as young as four years old (13). Wilkinson proposed that although CSS is mostly observed in middle-aged individuals with asthma, it can develop in children, as well. (14). Also, Ozen suggested that the physician's knowledge of the clinical features of children with CSS can lead to the early diagnosis of this disease in children (15). According to Lanham et al., the disease is categorized into three phases (16). The prodromal phase consisting of allergic diseases, including allergic rhinitis, nasal polyposis, and asthma, this phase may last for years. The second phase is characterized by peripheral blood and tissue eosinophilia that cause clinical presentations resembling Loffler's syndrome, chronic eosinophilic pneumonia, or eosinophilic gastroenteritis. Finally, the third phase is a life-threatening systemic vasculitis. The vasculitis phase may present with nonspecific constitutional symptoms and signs, especially fever, weight loss, malaise, and lassitude. Usually, it takes 8-10 years for the first phase to develop into the third phase of disease (16). In our presented case, this period was four years. He had asthma and was treated with ICS since three years of age (phase 1), but despite the appropriate dose of medication, his symptoms were poorly controlled. At the age of seven, he was referred to our hospital with the manifestations of mononeuritis multiplex, arthritis, and cutaneous symptoms (phase 3).

Zwerina et al. reported interesting findings in 33 cases with CSS. At the time of clinical presentation, most children had a history of asthma (91%) and sinusitis (77%). Although pleural effusion was rarely observed (12%), pulmonary involvement presenting as nonfixed infiltration was very common (85%) (17). The key features in these patients were asthma and severe eosinophilia in combination with vasculitic organ manifestations (17). In accordance with previous studies, our presented case had asthma and sinusitis in the first phase, and eosinophilia, mononeuritis multiplex, arthritis, and skin symptoms in the second and third phases. In contrast with former studies, pulmonary involvement such as infiltration or pleural effusion were not observed.

Reports of CSS in the past primarily focused on the incidence of this disorder in the general population (1,2). However, recent studies have examined the incidence of CSS in asthmatic patients, particularly in patients with resistant asthma receiving various forms of treatments. Increase in CSS cases was observed after taking the leukotriene receptor antagonists (18,19). Wechsler and Drazen reported three patients with asthma who showed evidence of CSS after receiving Montelukast or Zafirlukast. They suggested that this vasculitis syndrome develops in patients with an underlying eosinophilic disorder that was being suppressed by corticosteroid treatment. The anti-asthmatic medications could effectively manage asthma symptoms that reduced the need of patients to oral corticosteroids (OCS), and as a result, more cases of CSS were unmasked and diagnosed (18,19). In Consistent with previous studies, our case showed presentations of the CSS vasculitis phase (e.g., mononeuritis multiplex, arthritis, and skin involvement) two weeks after the initiation of Montelukast.

CSS is a form of vasculitis that is associated with ANCA (20). Comarmond et al. performed a cohort study in a large population and found that ANCAs are present in only about 40% of cases. They suggested that CSS has two clinical subsets or phenotypes, one which is an ANCA-associated process and mainly has the features of small-vessel vascu-

litis (such as glomerulonephritis and mononeuritis multiplex) and the other is ANCA-negative and more related to eosinophilic tissue infiltration; this type predominantly leads to cardiopulmonary manifestations and fever (21). In our patient, findings confirmed that ANCAs were negative and he had features of both ANCA-negative and ANCA-positive processes. At presentation, he was febrile and had mononeuritis multiplex in association with other manifestations.

Cardiac involvement is relevant to advanced stages of the disease and terminal cardiac events have been reported in 50% of autopsy cases (22). Our patient did not have any cardiac manifestations, probably due to early stage of his disease. In future, he may develop cardiac involvement, accordingly, he should be kept under observation for the possible occurrence of this event. Zwerina et al. reported that cardiorespiratory manifestations were observed more frequently in children, while peripheral neuropathy and musculoskeletal symptoms were less common (17). On the contrary, peripheral neuropathy and musculoskeletal involvements were detected in our patient, while cardiorespiratory manifestations were not.

Mononeuritis multiplex is the most common type of neurologic manifestation. Peripheral neuropathy could also occur as a result of either vasculitis of vasa nervorum or perineural eosinophilic infiltrate (22,23). Numerous central nervous system involvements such as cerebrovascular diseases, cranial nerve palsy, convulsion, and encephalopathy have also been reported (24). In confirmation of previous studies, mononeuritis multiplex was observed as the neurologic involvement in our presented case.

Gastrointestinal (GI) manifestations associated with CSS were reported in the latest studies (22,23). Gastrointestinal tract involvements, mainly abdominal pain, usually appear in the vasculitic phase. Multiple mucousal ulcers in the colon secondary to local ischemia have been described (25). Eosinophilic gastroenteritis with the presentation of bloody diarrhea may lead to intestinal perforation. Pancreatitis and cholecystitis have also been reported in this syndrome (26). In contrast with the previous studies, GI manifestations were not observed in our case.

Conclusion

CSS is a rare disease in children, the manifestations of which depend on the patient's age. CSS should be considered in every patient with poor controlled asthma who does not respond properly to moderate doses of inhaled corticosteroid. It should be considered, especially when there are neurologic, dermatologic, GI, or other organ involvements.

Physicians should be aware of this disease because early diagnosis and appropriate treatment can lead to satisfactory improvement and reduced complications of the disease.

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None.

Conflict of Interest

The authors declare no conflict of interest.

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