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Clinicopathological Features of Churg-Strauss Syndrome With Severe Nerve Degeneration: A Case Report

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Key words: *Churg-Strauss syndrome; vasculitis; allergic granulomatosis.*

Summary. *Churg-Strauss syndrome (CSS) is a rare autoimmune vasculitis of unknown etiology that involves small- and medium-sized blood vessels. Its onset is thought to be associated with adult-onset asthma, and vasculitis typically involves vessels in the lungs. However, due to increased blood and tissue eosinophilia, vasculitis may result in the involvement multiple systems of (neurological, skin, etc.). We report a case of CSS with manifestations that included skin purpura and severe peripheral nerve degeneration in a 56-year-old woman with a recent history of asthma. After the treatment with methylprednisolone and standard immunosuppressive therapy, her rashes resolved, there were no acute asthma attacks, and the numbness in her lower limbs improved.*

Introduction

Churg-Strauss syndrome (CSS), also known as "allergic granulomatosis," is a rare disease of unknown etiology (1). CSS is an autoimmune vasculitis of small- and medium-sized vessels, which can lead to necrosis. It mainly involves vessels in the lungs, as CSS typically begins as severe asthma. However, the clinical manifestations of CSS can be complex, and organs other than the lungs can be involved.

Although the etiology of CSS remains unknown, its pathogenesis is thought to develop through 3 successive stages based on clinical observations: asthma, blood and tissue eosinophilia, and, finally, vasculitis (2). Depending on the organs affected by vasculitis, CSS patients can have presentations in the respiratory tract, intrapulmonary infiltrations, peripheral neuritis, skin injuries, and heart and gastrointestinal tract involvement (2, 3).

Asthma associated with CSS is typically adult-onset (2). We report a case of CSS with concomitant skin abnormalities and severe peripheral nerve degeneration encountered in our department in a middle-aged woman with a recent history of asthma.

Case Report

A 56-year-old woman was admitted to our hospital on December 7, 2010, due to limb numbness for more than 1 month, increased numbness for 1 week, and lower limb weakness. One month previously, she had developed hand and foot purpura and had been diagnosed with allergic purpura, which resolved after treatment with glucocorticoids. One week previously, she had developed fever as well. She had a history of bronchial asthma and allergic rhinitis for 5 years.

On physical examination, her body temperature was 38°C, the pulse rate was 78 beats per minute, the respiratory rate was 19 breaths per minute, and the blood pressure was 132/86 mm Hg. She was conscious, spoke clearly, and responded properly. The bilateral pupils were round and equal in size (3 cm in diameter), the light reflex was normal, and the bilateral nasolabial folds were normal. The tongue stretching was intermediate, and the pharyngeal reflex was normal. Meningeal irritation was not noted. She did not have symptoms typical of paranasal sinusitis, which was also ruled out by an otolaryngologist; thus, no x-ray for this condition was made.

The muscle tone of both upper limbs was normal, but that of both lower limbs was decreased. The proximal muscle strength of both upper limbs was grade 4/5. The distal muscle strength of the right upper limb was grade 3, and that of the left was grade 5. The proximal muscle strength of both lower limbs was grade 4. The distal muscle strength of the right lower limb was grade 3, and that of the left was grade 0. Glove-and-stocking hypoesthesia was noted in all the limbs. The tendon reflex of upper limbs was normal, but the patellar reflex was absent. Babinski's reflex and Kernig's sign were absent.

She had a normal cardiac rhythm and symmetrical respiration. The breath sounds were coarse, but dry or moist rales were absent. Patchy purpura was noted on the feet, hands, and hips (Figs. 1 A and B).

The laboratory test results showed a white blood cell count of 14.0×10^9/L, with 83.4% of neutrophils

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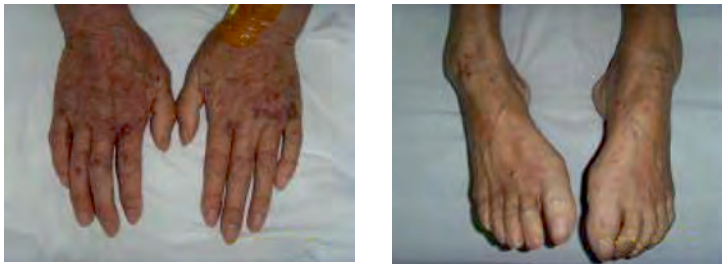

Fig. 1. Manifestation of purpura
A, patchy purpura on both hands; B, patchy purpura on both feet.

and 1.5% of eosinophils; erythrocyte sedimentation rate (ESR) was 54 mm/h, C-reactive protein (CRP) was 45.4 mg/L, serum rheumatoid factor (RF) was 170 IU/mL, antimyeloperoxidase (anti-MPO) was 125.5 IU/mL, and serum IgE was 3170 IU/mL. The serum levels of IgG, IgA, IgM, C3, C4, and CIC were within reference ranges, and the results of the human antistreptolysin O test were negative. The finding of routine cerebrospinal fluid and biochemical examinations were normal. The results of tests for antinuclear antibodies, anti-double-stranded DNA antibodies, anticardiolipin antibodies, and cytoplasmic antineutrophilic cytoplasmic antibodies (cANCAs) were negative. Before the treatment, the reaction to perinuclear antineutrophil cytoplasmic antibodies (pANCAs) was weakly positive (1:10), but it was negative (<1:10) on the patient's discharge after the treatment. The results of tests for HBsAb, HBeAb, and HbcAb were positive, but negative for *Treponema pallidum* and HIV antibodies. The findings of tests for liver and kidney functions, blood glucose, and tumor marker levels (AFP, CEA, CA199, and CA125) were normal.

A chest CT scan showed cord-like shadows in the basal segments of the lower and superior lobes of the left lung and inflammation in the anterior segment of the upper lobe and the lingular lobe of the left lung. Electromyography showed the following: sensory nerve action potential (SNAP) was present in the right median nerve; compound muscle action potential (CMAP) and SNAP were not found in the ulnar nerve; and CMAP of bilateral peroneal nerves and tibial nerves and SNAP of sural nerves were absent. No abnormalities were found on brain magnetic resonance imaging. To confirm the diagnosis, biopsies were done for the left sural nerve and gastrocnemius, and longitudinal sections were made of peripheral nerves and muscle tissues.

There was a slight loss of major basic protein (MBP)-positive myelin and a severe loss of neurofilament-positive axons accompanied by swelling and fracture of axons. Infiltration of CD3- and CD20-positive lymphocytes was noted in the neuronal interstitium and around blood vessels. The intima was hypertrophic, and the vascular lumen was stenotic. Degeneration, necrosis, and regeneration were observed in some muscle fibers, and some inflammatory cells were found in the interstitium (Figs. 2A–F).

The diagnosis was CSS. The patient was treated with methylprednisolone, and standard immunosuppressive therapy was also given (800 mg of cyclophosphamide [CTX] in 500 mL of normal saline, once monthly for 5 months). The critical laboratory variables before and after the treatment are shown in Table. After the treatment, the rashes resolved, and there were no acute asthma attacks. In addition, the numbness in the lower limbs improved, although an improvement in limb weakness was not apparent at 3-month follow-up.

Discussion

Churg and Strauss first reported CSS in 1951 (4). CSS is a rare disease with a reported annual incidence of about 0.5–6.8 per 1 million population, depending on the geographical location (3). The etiology of CSS remains unknown. It has been speculated that infiltration and degranulation of eosinophils play an important role in CSS pathogenesis. Cationic proteins and major basic proteins that are produced are cytotoxic and can destroy endothelial cells resulting in systemic vasculitis. It has also been proposed that CSS is related to type III hypersensitivity that is induced by ANCAs following stimulation by eosinophil MPO. In several cases, exposure to allergens (actinomycetes, penicillin, allopurinol, and anticonvulsants) may induce CSS.

Our patient had a history of asthma and allergic rhinitis, and purpura of the limbs had developed; the initial diagnosis was allergic purpura. Routine blood tests done before admission to our hospital showed significantly increased eosinophil counts (58.4% and 64.0% on two separate dates). She also had markedly elevated serum levels of IgE and CRP and increased ESR, which returned to reference limits following the treatment with methylprednisolone and immunosuppressive therapy.

The American College of Rheumatology initially proposed the following diagnostic criteria for CSS

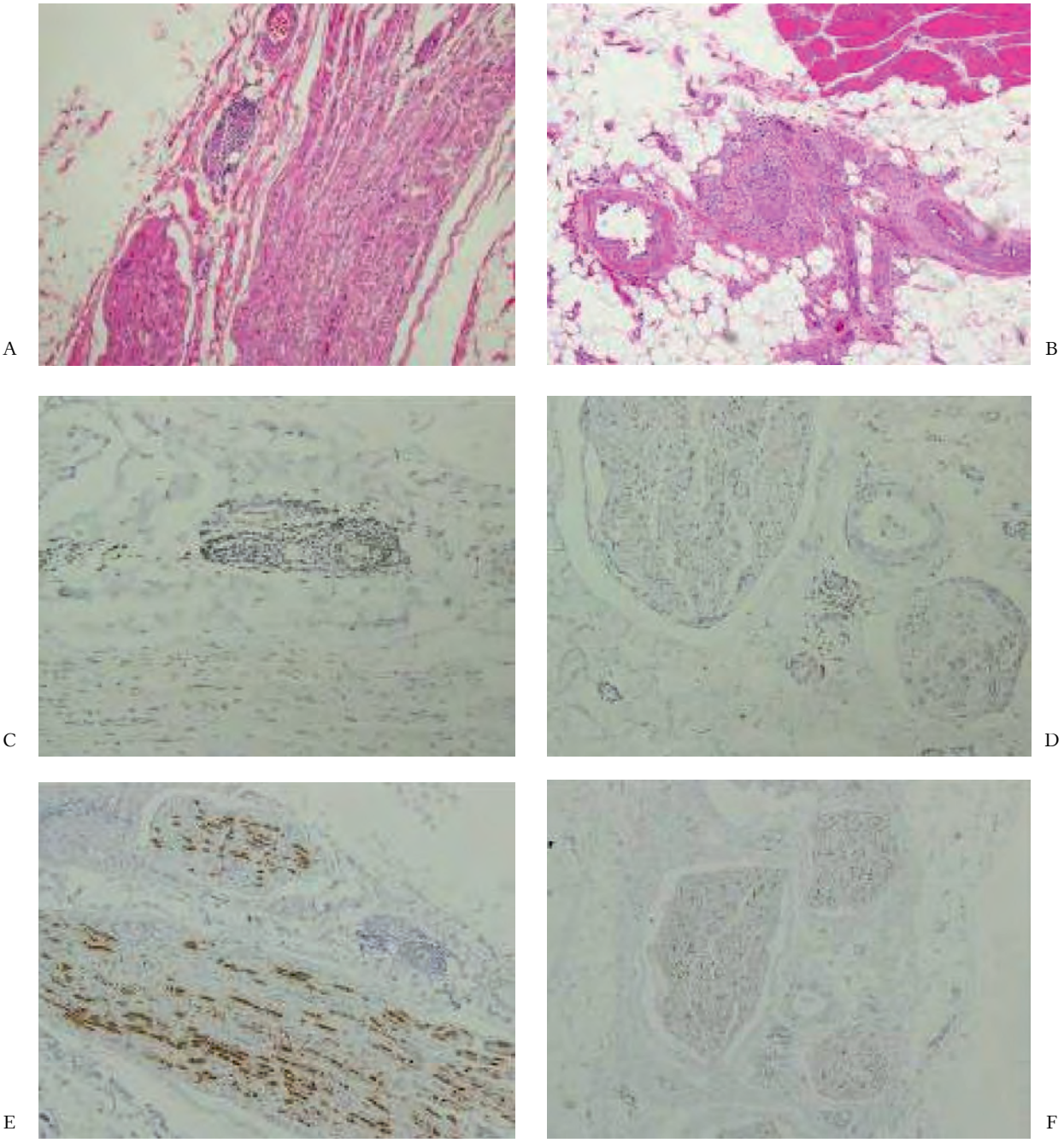

Fig. 2. Biopsy findings

A, hematoxylin-eosin staining of peripheral nerves and muscles (longitudinal sections, ×100); B, hematoxylin-eosin staining of peripheral nerves and muscles (longitudinal sections, ×100); C, CD3 staining (×200); D, CD20 staining (×200). Infiltration of CD3- and CD20-positive lymphocytes, hypertrophic intima, degeneration, necrosis and regeneration of a fraction of muscle fibers, and infiltration of inflammatory cells in the interstitium; E, MBP staining (×200). Slight loss of MBP-positive myelin; and F, neurofilament staining (×200). Severe loss of neurofilament-positive axons, accompanied by swelling and fracture of axons.

in 1990 (5): 1) asthma; 2) peripheral blood eosinophilia (>10% of leukocytes); 3) vasculitis involving one or more organs; 4) nonrheumatic pulmonary infiltration; 5) paranasal sinusitis; and 6) extracellular eosinophil infiltration. The presence of 4 or more of these criteria provided a diagnosis of CSS. However, within the same report (5), these diagnostic criteria were subsequently simplified to peripheral blood eosinophilia (>10% of leukocytes) and a documented history of either asthma or allergic diseases other than asthma and drug allergy. These latter criteria have a sensitivity of 95.0% and a specificity of 99.2%.

CSS can involve several systems. In 70% of patients with CSS, palpable purpura, erythema, subcutaneous nodules, and urticaria can be found on

Table. Critical Variables Before Treatment and During Follow-Up

Variable	Reference Range in our Hospital	Before Treatment	Before Discharge	1 Month After Discharge	2 Months After Discharge	4 Months After Discharge
RF, IU/mL	0.00–15.00	170	ND	<10.1	ND	ND
CRP, mg/L	<10	45.4	5.56	0.22	8.69	<0.17
ESR, mm/h	0–38	54	13	<38	<38	<38
IgE, IU/mL	0–100	3170	572	183	98	59
Anti-MPO, IU/mL	0.00–20.00	125.5	ND	4.53	ND	<2.0
pANCA*	–	1:10	ND	<1:10	<1:10	<1:10
cANCA*	–	<1:10	ND	<1:10	<1:10	<1:10

ND, not detected; RF, rheumatoid factor; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; MPO, myeloperoxidase; cANCA, cytoplasmic antineutrophilic cytoplasmic protein; pANCA, perinuclear antineutrophilic cytoplasmic protein.
*Indication of ANCA levels: negative, <1:10; weakly positive, 1:10; positive, >1:10; and strongly positive, 1:100.

the skin. Nearly all patients with CSS have asthma. When systemic vasculitis develops, asthma may improve or even resolve (6). The manifestations of the nervous system are also frequently documented. About 66%–75% of patients present with mononeuritis multiplex and symmetrical or asymmetrical polyneuropathy (7–9). In addition, about 27% of patients have impairments of the central nervous system that are characterized by confusion, coma, cerebral infarction, or even intracranial hemorrhage. This may be attributed to fibrinoid necrosis and inflammation of blood vessels in the nervous system, which leads to vascular occlusion and formation of microaneurysms resulting in secondary cerebral infarction and aneurysm rupture (10). Cerebral nerve involvement has been rarely reported. The incidence of cranial neuritis and ischemic optic neuritis is about 66%–93% (11).

CSS histopathology characteristically shows the infiltration of eosinophils, extravascular granuloma, and necrotizing vasculitis (8, 9, 12). Biopsy of the sural nerve followed by pathology is the main diagnostic tool for CSS peripheral neuropathy. These pathological changes can be confined to one tissue type or may be extensive. In the same tissue or organ, different pathological changes or a single change may be present. The following pathological features are also found: decreased myelinated fibers to a different extent, unmyelinated fiber loss associated with the degree of myelinated fiber loss, active axonal degeneration in 30%–70% of patients, necrotizing vasculitis in intermediate vessels (100–150 μm) and small vessels (30–50 μm) in the epineurial space of 54% of patients, hyaline degeneration or necrosis in the vessel walls, impaired internal elastic lamina in the majority of arteries, and vascular occlusion and recanalization. Vascular necrosis and granuloma formation are less frequently noted.

The clinical diagnosis should be emphasized for patients who mainly present with peripheral neuropathy. The clinical diagnosis should be based on pathological findings, and other types of vasculitis and granulomatous disease should be excluded (13). In Wegener's granulomatosis, changes in the upper respiratory tract are characterized by ulcers, necrosis, and nasal pain, and intrapulmonary lesions are prone to become cavitary. Nephropathy is usually severe, and asthma symptoms are absent. In polyarteritis nodosa, the lungs are seldom involved, and asthma symptoms are absent. Nephropathy is usually severe, and patients often die due to renal dysfunction.

With regard to laboratory tests, peripheral blood eosinophilia is typical of CSS and can be found at any CSS stage. In addition, increased serum IgE is a feature of CSS. ESR and CRP are often increased in some patients. Our patient had all of these findings either before or on admission to our hospital. The results of tests for HBV antibodies (HBsAb, HBeAb, and HbcAb) were positive, although for HBV-DNA were negative and for RF were positive. While our patient probably did not have a chronic HBV infection, this has been associated with CSS in rare cases (14). Moreover, increased RF may be found in about 86% of patients with CSS, although it is unrelated to CSS etiology (15). In about 67% of patients with CSS, the findings of tests are also positive for ANCA (16), but negative for ANCA during the remission stage (in our patient, the reaction to pANCAs before the treatment was weakly positive).

The major differential diagnosis should be made in a specific, concise way. Usually, a remarkable blood eosinophilia together with positivity for pANCA, a high MPO antibody level, and a slightly positive reaction to antiproteinase 3 antibodies suggest the diagnosis of CSS.

The remission of active CSS is usually achieved with high-dose corticosteroids (prednisone at a dosage of 1 mg/kg daily for 4 to 8 weeks) followed by tapering when inflammation is controlled (17). When disease improvement is not obvious, immunosuppressants, such as CTX, may improve the remission rate, provide for corticosteroid tapering or discontinuation, and reduce the incidence of relapse.

Leukocyte and platelet counts should be dynamically monitored. Once the leukocyte count

is $<4\times10^9$/L or platelet count is $<100\times10^9$/L, the treatment with CTX should be discontinued, and azathioprine is an alternative. If the patient responds poorly to CTX or azathioprine, corticosteroids in combination with cyclosporine A are recommended, and the treatment should be administered for at least 1 year. Those nonresponsive to this treatment can receive a plasma exchange.

For our patient, an improvement in peripheral neuropathy was not obvious, even after the treatment with methylprednisolone and standard immunosuppressive therapy. This may be attributed to her nervous system that was more severely affected when compared with other systems. In addition, the biopsy also revealed that the damage to the nerves and muscles was severe. Additional follow-up will be needed to investigate long-term therapeutic efficacy.

CSS has a good prognosis, and sequelae are rarely noted. The overall remission rate is 81%–92%. However, 26%–28% of patients may have a recurrence. Moreover, the mortality of patients with CSS who receive treatment is about 3.1% (3).

Statement of Conflicts of Interest

The authors state no conflicts of interest.

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