Churg-Strauss Syndrome with Necrosis of Toe Tips

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Churg-Strauss syndrome (CSS) is a granulomatous necrotizing vasculitis of unknown etiology associated with bronchial asthma. Despite affecting small to medium-sized vessels, necrosis of the digits due to vasculitis is extremely rare. We report a case of CSS with necrosis of the toe tips. A 37-year-old woman with asthma, who had been diagnosed with CSS 2 years ago, was admitted to our hospital with an exacerbation of CSS. The patient had a high grade fever and complained of abdominal pain and numbness of the lower extremities. Blood examination revealed marked eosinophilia. The fever pattern, abdominal pain and blood eosinophilia showed improvement by combination treatment with prednisolone and cyclophosphamide. However, the color of her right toe tips changed, and necrosis finally resulted despite antithrombotic therapy. Arteriography showed narrowing of the dorsalis pedis artery and of the more peripheral arteries of her right leg. Stump plasty with negative pressure dressing therapy for the toe tips, but not amputation, was done to preserve the leg function. While numbness of the extremities remained, no recurrence of necrosis was seen. Clinicians need to be aware that rare complications of CSS, including necrosis of the digits, can occur.

Key words: bronchial asthma, Churg-Strauss syndrome, eosinophilia, necrosis of toe tips, stump plasty

Churg-Strauss syndrome (CSS) is a rare, systemic granulomatous necrotizing vasculitis affecting small to medium-sized vessels. The clinical features include bronchial asthma, pulmonary infiltrates, allergic rhinitis, cardiac failure, and skin rash [1–7]. Systemic corticosteroids plus cyclophosphamide or immunoglobulin are still considered the cornerstone of treatment for CSS, but the effectiveness of humanized monoclonal anti-IL-5 (mepolizumab) for CSS was recently reported [8, 9]. Although the vasculitis in CSS can involve small and medium-sized muscular arteries, capillaries, veins, and venules, necrosis of the digits due to stenosis and blockage of medium-sized arteries is very rare [10–13]. We report a case of CSS with necrosis of the toe tips, which was treated by stump plasty with negative pressure dressing.

Case Report

A 37-year-old woman was admitted to our hospital because of exacerbation of Churg-Strauss syndrome (CSS). The patient had developed bronchial asthma in
her late twenties, and had been admitted once to our hospital for an asthma attack when she was 36 years old. She also had sinusitis. Two years ago, the patient became aware of numbness and eruption of her lower limbs. She was diagnosed with CSS, and started on oral corticosteroid (prednisolone 10mg/day) and an immunosuppressive drug (cyclosporin A, 100mg/day).

Her condition waxed and waned over the next 2 months, and she was finally referred to our hospital with abdominal pain and numbness of the lower extremities occurring with a high grade fever and peripheral blood eosinophilia (1,930/μL). She showed poor improvement despite a high dose of a steroid with antibiotics given by a former attending doctor. Physical examination upon admission to our hospital revealed a temperature of 38.1°C, blood pressure 140/88mmHg, pulse 136/min, and oxygen saturation 97% (during oxygen inhalation of 2L/min with nasal cannulas). On auscultation, no crackles or wheezes were heard in either lung. No systolic or diastolic murmurs were detected. A chest X-ray film and CT scan demonstrated no infiltrates in either lung. A CT scan of the abdomen showed no organic diseases. Arterial blood gases (room air) were pH7.49, P_{a}O_{2} 72.6mmHg, and PCO_{2} 33.8mmHg. Pulmonary function could not be measured due to the severity of her illness. Her blood examination revealed eosinophilia (1,116/μL) and moderate liver function abnormality, probably due to the usage of antibiotics. IgE was 836IU/ml. Anti-nuclear antibodies and rheumatoid factor were positive. β-D-glucan increased to 63.2pg/ml and Candida antigen was positive. Aspergillus antigen, cryptococcal antigen and cytomegalovirus antigen were negative. Myeloperoxidase antineutrophil cytoplasmic antibody (MPO-ANCA) was negative. The gastroscopy and colonoscopy performed at the former hospital showed some red spots, however, no typical findings of vasculitis were seen on the biopsy specimens although there were several eosinophils in the tissues.

After admission, monthly cyclophosphamide pulse therapy was started and repeated 6 times. Following this therapy, her prednisolone dosage was gradually reduced from 30mg to 15mg per day for 5 months. Her fever pattern, blood eosinophilia and abdominal pain showed improvement. However, her right toe tips changed color and necrosis finally resulted despite the combined use of antithrombotic agents (heparin, prostanoid E1) for a month. Right leg arteriography showed narrowing of the dorsalis pedis artery and of the more peripheral arteries of her right leg (Fig. 1). She was referred to the department of plastic surgery for treatment of her toe tips, and stump plasty with negative pressure dressing therapy, which was selected to save the maximum leg function, was done (Fig. 2). Afterward, numbness of the extremities remained, but no recurrence of necrosis was seen during the maintenance therapy with 15mg/day of prednisolone and 50mg/day of azathioprine. She could walk with a four-wheeled walker 40 days after the operation.

**Discussion**

Churg-Strauss syndrome was originally described by Churg as an entity apart from other vasculitides such as polyarteritis nodosa and Wegener granulomatosis (WG) [1]. The diagnostic criteria have been reported by the Research Group of Intractable

![Fig. 1](image-url) Right leg arteriography revealed stenosis and irregularity of the dorsalis pedis artery and of the more peripheral arteries.
Vasculitis, Ministry of Health, Labor, and Welfare (MHLW) of Japan [7, 10, 11]. Renal and pulmonary symptoms are characteristic in microscopic polyangiitis (MPA), and interstitial pneumonitis and pulmonary hemorrhage are common. Biopsy of the involved organs reveals necrotizing crescentic glomerulonephritis and necrotizing vasculitis of the arterioles, capillaries, and venules with few immune deposits. Granulomatous inflammation and asthma are not seen in MPA [12]. WG is differentiated from MPA by the presence of necrotizing granulomatous inflammation [12]. These lesions preferentially affect the ear, nose and throat, lung and kidney. Biopsies of the nasal mucosa, lung and kidney reveal necrotizing granulomatous vasculitis and necrotizing crescentic glomerulonephritis without immune deposits. Allergic granulomatous angiitis (AGA) can be differentiated from the other 2 diseases by the presence of asthma, eosinophilia and necrotizing granulomatous inflammation [12]. Skin biopsy reveals necrotizing vasculitis of small vessels with massive eosinophilic infiltration and extravascular granulomatosis. Those with a typical clinical course, but lacking histological findings, are classified as having Churg-Strauss syndrome. Its annual incidence is 1 to 3 cases per million, and its course often has 3 distinct phases: atopy/sinusitis/asthma, eosinophilia and vasculitis [14].

To establish a diagnosis of Churg-Strauss syndrome, these criteria by the American College of Rheumatology have been established: the presence of asthma, hypereosinophilia, mono- or polynuropathy, non-fixed pulmonary infiltrates, paranasal sinus abnormality, and extravascular eosinophilic infiltration in biopsy. Four of these 6 criteria are necessary for a diagnosis with 85% sensitivity and 99.7% specificity [11]. Our patient's symptom and history met 4 of the criteria: asthma, hypereosinophilia, mono- or polynuropathy and paranasal sinus abnormality. The biopsies of the stomach and colon did not show typical findings of extravascular eosinophilic infiltration or vasculitis. Previous treatment with prednisolone and an immunosuppressive drug might, however, have affected these histological findings. The results of right leg arteriography suggested the existence of vasculitis.

Though the vasculitis in CSS can involve small and medium-sized muscular arteries, capillaries, veins, and venules [10], necrosis of the digits due to stenosis and blockage of medium-sized arteries are rare in CSS cases. To the best of our knowledge, only 3 cases of CSS with necrosis of the digits have been reported [11-13], although there are several reports

Fig. 2  The right foot rapidly became ischemic, finally resulting in necrosis of the toe tips despite the combination therapy, including prednisolone, cyclophosphamide and antithrombotic agents (A, B). Stump plasty with negative pressure dressing therapy, which was done to preserve the leg function (C).
of thrombosis of other medium-sized arteries, including the retinal, pulmonary, and cerebral arteries [15–17]. In addition, this might be the first case in which stump plasty with negative pressure dressing therapy, but not amputation, was adopted to treat necrosis of the digits.

CSS is being increasingly recognized in asthmatic patients treated with leukotriene receptor antagonists (LTRA), though the nature of this relationship remains to be elucidated. Bibby et al. examined the association between LTRA therapy and CSS in cases registered in the FDA Adverse Event Reporting System (AERS) database and reported that LTRA was a suspect medication [18], while another paper concluded that LTRA therapy does not induce CSS, but facilitates the tapering of glucocorticoids, which unmasks the condition [19]. This woman had a history of taking leukotriene receptor antagonists, but was not taking the medicine when she developed CSS or when she had an exacerbation of it. Gastrointestinal involvement has adverse prognostic significance in CSS [20]. Although gastroscopy and colonoscopy could not demonstrate the findings of vasculitis in our case, careful follow-up is needed.

ANCA status was shown to segregate with clinical phenotype [21]. ANCA-positive patients were significantly more likely to have disease manifestations associated with small-vessel vasculitis, including necrotizing glomerulonephritis, mononeuritis and purpura, whereas ANCA-negative cases were significantly more likely to have cardiac and lung involvement. As necrosis of toe tips in CSS is rare and difficult to treat, markers useful for the prediction and prevention of necrosis remain to be investigated.

In conclusion, clinicians need to be aware that there can be uncommon clinical features of CSS, including necrosis of the digits.

References