Published in final edited form as:

J Am Acad Dermatol. 2007 April ; 56(4): 701–704. doi:10.1016/j.jaad.2006.09.028.

A Case of Churg-Strauss Syndrome Associated with Antiphospholipid Antibodies

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Abstract

BACKGROUND—Churg-Strauss syndrome (CSS) is a systemic vasculitis affecting small and medium-sized blood vessels, almost invariably affecting the lung and frequently associated with cutaneous involvement. Microvascular vaso-occlusion leading to digital gangrene is not a feature of CSS.

OBSERVATIONS—We report an unusual case of a patient with Churg Strauss Syndrome with antiphospholipid antibodies who developed severe digital gangrene in addition to cutaneous vasculitis.

CONCLUSION—The presence of antiphospholipid antibodies is not a feature usually seen in association with Churg-Strauss syndrome. While the full clinical spectrum of Churg Strauss Syndrome is still being defined, identification of additional features associated with this syndrome might help to better understand the pathogenesis of the disease and to have an impact on management and prognosis.

Introduction

Churg Strauss syndrome (CSS) or allergic granulomatous angiitis is a systemic vasculitis affecting small and medium-sized blood vessels. One hypothesis for the pathophysiology of CSS is that anti-neutrophilic cytoplasmic antibodies (ANCA) promote neutrophil sticking to vessel walls, initiating the vasculitis. Cytokine abnormalities (increased interferon alpha, interleukin 2, tumor necrosis factor alpha and interleukin 1 beta) have also been reported^{1–3}. Churg-Strauss syndrome is a multisystem disease characterized by: asthma, peripheral eosinophilia, peripheral neuropathy, pulmonary infiltrates and paranasal sinus abnormalities^{1–6}. The second most common organ involved is the skin. Cutaneous involvement, such as palpable purpura, petechiae, livedo reticularis, tender red papules or nodules most frequently on upper extremities, face and neck are commonly observed during the vasculitic phase of the disease⁷. Microvascular vaso-occlusion leading to digital gangrene

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Justification of authors' effort: manuscript written by Drs. Katalin Ferenczi and Gilliam, pathology interpretation by Drs. Gilliam, Han and Willis, clinical information by Drs. Chang, Camouse, Stern and Cooper. The authors declare no conflict of interest.

is not a feature of typical CSS and is considered an extremely rare variant of the disease. There are two reports of digital and foot gangrene in two patients with Churg Strauss Syndrome^{8, 9}. There is one case report in the literature describing a patient with Churg-Strauss disease with right retinal vein thrombosis in the presence of antiphospholipid antibodies¹⁰.

In this report we describe a patient with Churg-Strauss syndrome who developed rapidly progressive digital gangrene despite aggressive immunosuppressive treatment. Antiphospholipid antibody tests were positive for the lupus anticoagulant. The presence of antiphospholipid antibodies is not a feature usually seen in association with Churg-Strauss syndrome.

Report of a case

A 53 year old Caucasian man was admitted for work-up of bilateral lower extremity numbness and weakness, abdominal pain and Raynaud's phenomenon of the hands bilaterally. The patient also reported the development of a rash on his scalp and hands a few weeks prior to his presentation. His past medical history was significant for severe asthma requiring corticosteroids and the leukotriene antagonist montelukast (Singulair), recurrent sinusitis, diverticulitis and sigmoid colectomy for colonic perforation three months prior to his current presentation. The patient had been on montelukast from 2000 until the beginning of 2005. He was on no medications known to cause drug-induced antiphospholipid antibodies.

On examination the patient had motor and sensory deficits involving both distal lower extremities. Skin examination on admission revealed erythematous macules and purpura involving both palms and erythematous crusted papules on dorsal hands and fingers (Figure 1a). His scalp exam revealed multiple erythematous papules and plaques, some of which showed crusts and erosions.

One month later the patient developed gangrene involving the tips of his fingers on his right hand (Figure 1a). Over the next few months the dorsal hand lesions resolved but painful dry gangrene of his fingertips progressed rapidly (Figure 1b). The scalp lesions resolved in two months.

Laboratory findings showed an elevated white blood cell count of $24.0 \times 10^9/L$ (reference range: $4.4\text{--}11.3 \times 10^9/L$), an elevated absolute eosinophil count of $9.72 \times 10^9/L$ (reference range: $0.00\text{--}0.70 \times 10^9/L$), elevated rheumatoid factor of 92 IU/mL (reference range: 0–15 IU/mL), elevated IgE of 501 IU/mL (reference range: 1–150 IU/mL), ESR 111 mm/h (reference range: 1–20 mm/h), and C reactive protein of 6.48 mg/dL (reference range: 0.00–1.50 mg/dL). The patient had negative anti-neutrophil cytoplasmic antibodies (C-ANCA, P-ANCA), ANA and cryoglobulin. Antiphospholipid antibodies including both the lupus anticoagulant and beta-2 glycoprotein were moderately elevated with a DRVVT level of 56 sec (normal below 40 sec), elevated DRVVT ratio of 1.6 (normal if less than 1.3), β_2 glycoprotein AB IGA of 21 GPI unit (reference range: 0–20 GPI unit). These were interpreted by coagulation experts as consistent with, however not diagnostic of antiphospholipid antibody syndrome, since the diagnostic criteria for the latter is detection of elevated antiphospholipid antibodies on repeat labs within 12 weeks from the initial diagnosis. Serological tests for acute and chronic hepatitis B and C as well as antibodies to HIV were negative.

Chest CT revealed nonspecific ground glass opacities in the left lower lobe and a 5mm nodule at the left lung base. An MR angiogram of the abdomen revealed findings in his kidneys suggestive of multiple infarcts bilaterally.

A skin biopsy from lesions on the right thumb showed angiocentric and interstitial dermal infiltrates. These were composed of neutrophils and neutrophil fragments, and were associated

with vascular injury and prominent fibrin deposition.. Overall the findings were consistent with small vessel neutrophilic vasculitis (Figure 2 a, b). No evidence of microvascular occlusion was noted in the skin biopsy. Skin biopsy from the scalp lesions revealed an intensely inflamed dermis, with mixed neutrophilic, eosinophilic, and mononuclear cell infiltrates (not shown). The neutrophilic infiltrates were dense and involved all levels of dermis. Necrosis and leukocytoclasia with vasculitis were noted.

Review of the previous colectomy pathology specimen identified extensive vasculitis of medium sized blood vessels with prominent vasculocentric inflammation, fibrinoid necrosis, and sheets of eosinophils and neutrophils (Figure 2 c, d). Sural nerve biopsy was performed showing the presence of vasculitis (not shown). A bone marrow biopsy was unremarkable and did not show associated hematological malignancy or myelodysplastic syndrome.

The patient fulfilled all six criteria for Churg-Strauss syndrome established by the American College of Rheumatology (ACR): history of severe asthma, eosinophilia, peripheral neuropathy, paranasal sinus abnormalities, migratory or transient pulmonary opacities and biopsy showing extravascular eosinophils.

The onset of Churg-Strauss symptoms in our patient coincided with a tapering of his prednisone dose, which was given to control his severe asthma. He remained on montelukast during the onset of his CS symptoms. This scenario is typical in Churg-Strauss syndrome associated with leukotriene inhibitor treatment¹¹. It is controversial whether these drugs have a direct pathogenic role or rather unmask an already present vasculitis that is manifested when the leukotriene inhibitors permit corticosteroid doses to be reduced¹².

After diagnosis of Churg-Strauss syndrome was established oral treatment with 60 mg of prednisone and 150 mg of cyclophosphamide daily was initiated. Over the following months, despite aggressive immunosuppressive treatment, distal digit gangrene progressed (Figure 1) requiring three days of intravenous pulse dose corticosteroids with 1 gm of methylprednisone for antiphospholipid antibodies. Anticoagulation with warfarin was added to the regimen. The distal fingertip dry gangrene has very slowly stabilized. The dorsal hand skin lesions resolved and the vasculitis has not recurred. The lower extremity neuropathy and muscle strength has shown mild improvement and asthma has stabilized. The patient continues to be on lifelong anticoagulation and immunosuppressants that includes prednisone 20 mg and Imuran 150 mg daily dose. He is closely followed by pulmonology, neurology, rheumatology and ophthalmology.

Discussion

Churg-Strauss syndrome is a systemic vasculitis. We describe a patient who presented with all 6 hallmark features of Churg-Strauss syndrome: history of severe asthma, recurrent sinusitis, pulmonary infiltrate, eosinophilia, mononeuritis multiplex and colon biopsy revealing vasculitis and extravascular eosinophils. Histologic evidence of leukocytoclastic vasculitis was also seen on the skin of the dorsal hands, scalp lesions, and in the sigmoid colon. Due to the severity of vasculitis leading to colonic perforation, aggressive immunosuppressive treatment was initiated. The patient developed rapidly progressive and painful distal digital dry gangrene in spite of aggressive immunosuppressive treatment. Although he presented with classical signs and symptoms of CSS, a workup for microvascular occlusion syndrome, due to his renal infarcts and digital gangrene, revealed elevated antiphospholipid antibodies.

Development of gangrene is an exceptionally rare complication of CSS, as there are only two case reports describing digital and foot gangrene in two patients with Churg-Strauss syndrome in the absence of antiphospholipid antibodies^{8, 9}. While digital gangrene is not a typical feature of CSS, it is often seen due to vaso-occlusion in association with antiphospholipid

antibodies^{13, 14}. Lupus anticoagulant and/or anticardiolipin antibodies are typically associated with microthrombosis and vascular occlusion rather than a true leukocytoclastic vasculitis. The simultaneous presence of severe vasculitis and antiphospholipid antibodies in this patient likely led to his rapidly progressive distal digital gangrene. While the digital gangrene is probably due to the presence of antiphospholipid antibodies, no evidence of microvascular occlusion was noted on his skin biopsy, suggesting that his skin lesions were a consequence of vasculitis and not thrombosis secondary to the presence of antiphospholipid antibodies.

Our case shows that the two entities can co-exist, explaining at least in part the pathogenesis of severe microvascular occlusion in CSS. Therefore, monitoring of antiphospholipid antibodies in patients with Churg-Strauss syndrome with clinical evidence of internal organ thrombosis may be important in determining the need for prophylactic anticoagulation for prevention of thrombosis.

Leukocytoclastic vasculitis and antiphospholipid antibodies are not usually seen together. There is a report describing polyarteritis nodosa in association with anti-phospholipid antibody syndrome in two patients¹⁵. More recently Rees et al reported a 17% point prevalence of antiphospholipid antibodies in patients with primary systemic vasculitis. Antiphospholipid antibodies have been reported in association with polyarteritis nodosa, microscopic polyangiitis, Wegener's granulomatosis, giant cell arteritis, polymyalgia rheumatica, Takayasu's arteritis and Behcet's syndrome (for review see^{16, 17}). One study, however failed to find an increased prevalence of antiphospholipid antibodies in systemic vasculitis patients and their prevalence approached that in the normal population¹⁸. The case report describing a patient with Churg-Strauss disease with right retinal vein thrombosis in the presence of antiphospholipid antibodies further corroborates the potential association between these two entities¹⁰.

Identification of the CSS disease spectrum will further aid in understanding the pathogenesis of the disease and might have an impact on management and prognosis.

Acknowledgements

This work was supported by a National Institutes of Health NIAMS RO1 AR049284-03 (ACG), and the NIAMS Case Skin Disease Research Center A1-39750. We appreciate the outstanding secretarial assistance from Minjia Griesser in preparation of the manuscript.

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Figure 1.

a, b. Cutaneous lesions in a patient with Churg-Strauss syndrome. Erythematous crusted papules on dorsal hands and fingers on presentation evolving to subsequent development of cyanosis, gangrene involving the right hand fingers one month later (a). Note resolution of dorsal hand skin lesions and development of progressive distal fingertip dry gangrene six months after initial presentation (b).

Figure 2.

a,b. Histology of dorsal hand skin lesions on admission shows angiocentric and interstitial dermal infiltrates composed of neutrophils, neutrophil fragments, eosinophils and fibrin deposition in vessel walls (hematoxylin-eosin), magnification 4x (a) and 10x (b). Figure 2 c,d. Histology of sigmoid colon mesentery showing extensive vasculitis of medium sized blood vessels, prominent vasculocentric inflammation, fibrinoid necrosis, eosinophils (intravascular and extravascular) and neutrophils, magnification 20x (c) and 40x (d).