Case reports

Allergic granulomatosis and angiitis (Churg-Strauss syndrome): response to ‘pulse’ intravenous cyclophosphamide

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SUMMARY A 51 year old Chinese woman suffering from classical Churg-Strauss syndrome is presented. She deteriorated with acute pulmonary infiltrates resulting in hypoxaemic respiratory failure but responded dramatically with ‘pulse’ intravenous cyclophosphamide.

In 1951 Churg and Strauss described 13 cases of allergic angiitis and granulomatosis characterised by hypereosinophilia and systemic vasculitis occurring in patients with asthma and allergic rhinitis.1 Pulmonary infiltrates remained a hallmark of the acute vasculitic phase of the disease, occurring in 72% of patients with the Churg-Strauss syndrome in a review of published work by Lanham et al.2 Patients with fulminating pulmonary involvement can deteriorate while receiving a moderate dose of corticosteroids.3 We report a case of the Churg-Strauss syndrome occurring in a Chinese patient presenting with systemic necrotising vasculitis and acute pulmonary exacerbation. The patient rapidly developed hypoxaemic respiratory failure despite oral corticosteroid and responded dramatically after ‘pulses’ of intravenous cyclophosphamide.

Case report

A 51 year old Chinese housewife who had had allergic rhinitis for 10 years and asthmatic attacks for the past year was admitted with a two month history of increased attacks of breathlessness, showers of haemorrhagic spots over both legs, multiple small joint pain, and weakness of the extremities. She was afebrile but had malaise and weight loss of 2 kg. There was no family history of asthma or other allergic diseases. Physical examination on admission showed bilateral foot drop, small muscle wasting of both hands, and early left ulnar neuropathy with clawed hand deformity.

Laboratory investigations showed a total peripheral white blood cell count of 19-7×10⁹/l with 48% eosinophils (absolute count 9-46×10⁹/l). Her serum IgE was greater than 1000 kU/l (normal <200). Results of urine analysis, creatinine clearance, stool for parasites, and occult blood were all normal. An initial chest x ray was unremarkable. Nerve conduction velocity of upper limbs demonstrated an axonal sensory neuropathy. Lung function tests on admission suggested a significant reversible mild obstructive defect with a normal diffusion capacity (forced vital capacity (FVC) 2-16 litres, forced expiratory volume in one second (FEV₁) 1-65 litres).

Within the same week crops of new purpuric skin lesions developed over both legs, and a skin biopsy was performed. Figure 1 shows widespread destruction of blood vessel walls in the dermis associated with fibrinoid changes, infiltration of polymorphonuclear cells with leucocytosis, nuclear ‘dusts’, and extravasation of red blood cells. Dense perivascular inflammatory cell infiltrates were present, consisting predominantly of neutrophils admixed with large numbers of eosinophils and numerous mast cells. Swelling and proliferation of focal endothelial cells were also noted. Bone marrow examination indicated reactive eosinophilia with marked increase of eosinophilic precursors. Prednisone 15 mg four times a day was started.

Four days later she developed increasing dyspnoea, and a chest x ray showed rapid appearance of diffuse non-segmental confluence mottling over

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Fig. 1 (A) Dermal polymorphonuclear infiltration, more accentuated around small vessels and minor epidermal component. (Haematoxylin and eosin.) (B) Numerous eosinophil polymorphs compose the inflammatory infiltrates, and nuclear debris is more conspicuous at higher magnification, as are fibrinoid changes of the vascular wall (arrow). (Haematoxylin and eosin.)

both lung fields (Fig. 2). At that time the absolute peripheral eosinophil count reached a peak value of 11.2 x 10⁹/l. She deteriorated with respiratory distress and severe hypoxaemia despite high oxygen concentration (P⁰₂ 7.3 kPa with saturation of 0.91 while receiving 40% oxygen). Repeat lung function test showed moderate obstructive lung defect (FVC 0.76 litres, FEV₁ 0.48 litres) and a severe decrease in diffusion capacity with transfer factor of the lung for carbon monoxide (TLCO) of 15% of the predicted value. As she did not show any significant improvement over nine days after commencement of steroid, empirical treatment with pulse intravenous cyclophosphamide (750 mg/m²/dose) was given while steroid was continued. The patient showed rapid clinical and biochemical improvement soon after the initial dose of cyclophosphamide, and artificial ventilation was not required. Two weeks later her blood gases normalised with P⁰₂ 12.5 kPa and an oxygen saturation of 0.98 at room air. Chest x ray reassessment showed complete clearance of lung infiltrates. Sputum smear and culture for acid fast bacillus, other bacteria, and cytology were always negative. Repeat lung function test showed no significant obstructive lung defect (FVC 1.77 litres, FEV₁ 1.53 litres). Diffusion capacity reverted to normal with TLCO 80% of the predicted value. The vasculitic skin lesions also subsided gradually without recurrence.

Two additional pulses of intravenous cyclophosphamide were given one month apart without noticeable side effects. Both peripheral total white blood cell and eosinophil count declined dramatically after each dose of pulse cyclophosphamide (Fig. 3). Repeat serum IgE after three months was 27 kU/l. Prednisone was gradually tapered. Six months after discharge the patient remained well with residual bilateral foot drops and mild clawed hand deformity. Eosinophil count was 0.21 x 10⁹/l (2% of peripheral total white blood cell count) while
treatment was maintained with prednisone 5 mg daily and a salbutamol inhaler.

Discussion

Allergic granulomatosis and angiitis—Churg-Strauss syndrome—is a well defined disorder characterised by hypereosinophilia and systemic vasculitis occurring in individuals with asthma and allergic rhinitis. As far as we know our patient is the first Chinese patient reported in the English publications suffering from this rare condition. This patient exemplified the typical clinical course with several phases of the syndrome as highlighted by Lanham et al. There was the long prodromal phase with a 10 year history of allergic rhinitis, followed by late onset asthma for one year without any significant family history. She then presented with very marked peripheral blood eosinophilia of 11.2×10^9/l and eosinophilic tissue infiltrates together with mononeuritis multiplex involving both upper and lower extremities with cutaneous purpura. The almost fatal fulminating pulmonary involvement represented the third phase of the illness. Unlike other patients previously described our patient had no definite evidence of renal, gastrointestinal, or cardiac involvement.

Cutaneous biopsy of our patient demonstrated the typical histopathology of Churg-Strauss syndrome with prominent perivascular eosinophilic infiltration, necrotising vasculitis, and fibrinoid necrosis of vessel walls (Fig. 1). The absence of extravascular granulomas does not preclude the diagnosis of Churg-Strauss syndrome.

Radiographic chest findings in this disease have been described as transient, patchy, non-segmental parenchymal infiltrates, massive bilateral nodular infiltrates with or without cavitations, and diffuse interstitial disease. Our patient had rapid onset of reversible patchy pneumonic infiltrates coinciding with peak peripheral eosinophilia and transient severe fall in diffusion capacity in the lung function test. An open lung biopsy was not necessary to establish the diagnosis as the clinical presentation in our case was typical. Rapid fall of diffusion capacity excluded the likelihood of pulmonary haemorrhage.

Despite prednisone 60 mg a day for nine days our patient deteriorated rapidly with severe hypoxaemia and was on the verge of assisted ventilation. Under these circumstances most would advocate early aggressive immunosuppressive treatment, which now centres around the use of cyclophosphamide. The serum IgE concentration of our patient was markedly raised during the acute vasculitic phase and returned to normal during disease remission. Peripheral eosinophilia also climbed to a peak value during the fulminating pulmonary vasculitic phase. These findings are similar to reports from Hammersmith.

The immunopathogenesis of the Churg-Strauss syndrome remains unclear and this makes treatment difficult. The immunosuppressive and clinical responses to the oral preparation of cyclophosphamide occur only slowly, and the maximal effect is not seen for several weeks. We are impressed by the rapid clinical response that accompanies intra-

Fig. 2 Chest x ray showing acute onset of patchy non-segmental pulmonary infiltrates.

Fig. 3 Clinical response following 'pulses' of intravenous cyclophosphamide. I=onset of pulmonary infiltrates; 2, 3, 4=first, second, and third doses of intravenous cyclophosphamide; WBC=white blood cell count.
venous cyclophosphamide plus methylprednisolone in patients with systemic rheumatoid vasculitis. Pulse treatment with cyclophosphamide mainly disrupts humoral immunity. The experience of Bacon et al, with more than 100 cases of systemic necrotising vasculitis in patients with rheumatoid arthritis, polyarteritis nodosa, and Wegner’s disease, further confirms the efficacy of intermittent pulse intravenous cyclophosphamide in reducing both mortality and the relapsing rate. Moreover pulse intravenous cyclophosphamide is a relatively safe modality of immunosuppressive treatment. Severe side effects reported, such as haemorrhagic cystitis and infections, are significantly lower than those due to the continuous oral regimen. Our patient clearly demonstrated the extraordinary remitting effect of pulse intravenous cyclophosphamide in the phase of acute pulmonary vasculitis when oral steroid produced no rapid effect. After each dose of intravenous cyclophosphamide the total white blood cell and eosinophil count fell abruptly within days (Fig. 3) without any permanent excessive marrow suppression or other significant side effects. Prednisone could be successfully tapered to a maintenance dose of 5 mg daily after six months without relapse of the disease. A recent study of plasma pharmacokinetics of cyclophosphamide and its cytotoxic metabolites after intravenous or oral administration provides further evidence that both are equally efficacious, though the intravenous route had the additional benefit of rapid action and less overall toxicity.

We conclude that pulse intravenous cyclophosphamide is the treatment of choice for the fulminating vasculitic phase of the Churg-Strauss syndrome, particularly when rapid response is desirable, and is an alternative rapid effective treatment for pulmonary vasculitis to pulse methylprednisolone suggested by MacFadyen et al. Until further multicentre controlled studies can be undertaken these two pulse intravenous regimens or a combination of them will be the standard treatment for the acute vasculitic phase of the Churg-Strauss syndrome and other systemic necrotising vasculitis.

References
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