CASE REPORT

Systemic cytokine storm in severe eosinophilic dermatitis

Anika Singanayagam, Lucy Lamb, Julia E. Makinde, Ian Teo and Sunil Shaunak

From the Department of Medicine and Department of Infectious Diseases and Immunity, Imperial College London, Hammersmith Hospital, Du Cane Road, London W12 ONN, UK

Address correspondence to Prof S. Shaunak, Departments of Medicine, Infectious Diseases and Immunity, Imperial College London, Hammersmith Hospital, Du Cane Road, London W12 ONN, UK. email: s.shaunak@imperial.ac.uk

Learning point for clinicians
Severe eosinophilic dermatitis with systemic symptoms is rare. We report, for the first time, that the systemic clinical symptoms and high CRP (123 mg/l) were due to an IL-6 and IL-8 cytokine storm. Systemic disease control was only achieved with high dose oral prednisolone, topical triamcinolone to affected skin and dapsone.

Case report
A 27-year-old woman presented with a 12-day history of worsening fever and rash. Erythematous, indurated and pruritic lesions had been developing on her inner thighs. They went on to spread to her arms and back. She was previously fit and well with no relevant past medical or family history.

During her first week in hospital, she became intermittently confused and disorientated and was also intermittently febrile between 38.3 °C and 40 °C. Her skin lesions became ‘woody hard’ subcutaneous swelling and were associated with dark mottling of the overlying skin. During her second week in hospital, there was also florid swelling of her face, lips and neck that was typical of angioedema. As she went on to develop hypoxaemia (oxygen saturation 90% on air), hypoalbuminaemia (15 g/l) and proteinuria (0.44 g/l), but remained haemodynamically stable, she was empirically treated with C1 esterase inhibitor (for possible hereditary angioedema) and dapsone (50 mg/day) were added. A rapid recovery then followed. Return of her albumin to normal and rehabilitation was slow and led to a 26-day hospital admission. Twelve months later, she has had no disease relapse and is maintained on low-dose prednisolone and dapsone.

The plasma chemokine/cytokine profile during her systemic illness was subsequently determined for IL-1α/1β/2/4/5/6/7/8/15/16, G-CSF, GM-CSF, TNF-α, IFN-β/γ, MCP-1/2, RANTES, MIP-1/3, SDF-1, TGF-β, IP10 and MIG. Those cytokines that were increased by >5-fold over normal plasma levels at the peak of her illness are shown in Figure 1B.

Discussion
Wells syndrome was described in 1971 and was renamed eosinophilic cellulitis by Wells in 1979. The histology of the deep dermal lesion is diagnostic. Peripheral blood eosinophilia occurs in 67% of cases. IL-5 was originally reported to the major with neutrophils 9.7 × 10⁹/l, lymphocytes 2.7 × 10⁹/l, monocytes 1.4 × 10⁹/l and eosinophils 3.2 × 10⁹/l. Her CRP rose to 123 mg/l, and her d-dimers to 17 000 (normal < 560 µg/l). A bone marrow showed leuco-erythro-thrombocytoblastic features. Her mast cell typtase was raised at 27.7 µg/l (normal 2–14). An extensive screen for bacterial, viral, fungal and parasitic pathogens was negative. A skin biopsy showed diffuse infiltration of the deep dermis by eosinophils and deposition of eosinophil granular material in ‘flame figures’ (Figure 1A). The histological features were diagnostic of eosinophilic cellulitis.

In addition to systemic steroids (prednisolone), topical steroids (triamcinolone and Cutivate (face)) and dapsone (50 mg/day) were added. A rapid recovery then followed. Return of her albumin to normal and rehabilitation was slow and led to a 26-day hospital admission. Twelve months later, she has had no disease relapse and is maintained on low-dose prednisolone and dapsone.

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cytokine elevated as a consequence of clonal proliferation of abnormal CD3+CD4+ T cells. However, a study of 85 patients found elevated plasma IL-5 in only 3 patients. Antibiotics are ineffective. Steroids and dapsone have recently become the mainstay of treatment. Recurrence occurs in 56% of patients at an average of 11 months.

This is the first case report of the plasma chemokine/cytokine profile in the small sub-group of patients with eosinophilic cellulitis who develop a severe systemic illness. The plasma acute pro-inflammatory response was characterized by a large increase in IL-8 of 65-fold (that came from neutrophils) and in IL-6 of 47-fold (that came from monocytes). In everyday clinical practice, such findings, together with the raised WCC and CRP, would typically have been taken to be representative of an LPS-TLR4 mediated sepsis syndrome. This would have meant starting antibiotics. Instead, we started steroids.

Our observations serve to highlight the dramatic and systemic overstimulation of the innate immune system’s TLR4 that can be triggered and propagated by enzymatic digestion of subcutaneous high MWt hyaluronan (~2 million Da) into smaller fragments (~200,000 Da) in damaged deep dermal tissue. These hyaluronan fragments are as potent as lipopolysaccharide at binding to TLR4 and triggering a cytokine storm.

References