Diagnostic and management problems in a complex case of connective tissue disease

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Summary
A 28-year-old Nigerian woman presented with persistent pyrexia, marked pruritus, eosinophilia, myalgias, flitting arthralgias, serositis and massive splenomegaly. Intensive investigation for an infective or neoplastic aetiology proved negative. Empirical treatment for helminthic infections and tuberculosis was unhelpful. Although there were no specific clues to suggest an underlying connective tissue disease, a trial of steroids and azathioprine was introduced, with no obvious response. Her condition deteriorated to a point where it was decided that intravenous immunosuppressive therapy was needed and subsequently, her condition improved remarkably. This patient illustrates the problems in the diagnosis and management of complex disorders, particularly when classical tests for connective tissue diseases are absent. Also, we would like to report that marked pruritus can be associated with connective tissue disease.

Keywords: connective tissue disease, pyrexia, pruritus, eosinophilia, immunosuppression

Case report
A 28-year-old Nigerian woman presented in September 1992 with a 10-day history of profound malaise, fever, rigors, sore throat, productive cough, loose stools, low back pain, flitting myalgia and arthralgia, intense pruritus and an evanescent rash. She had left Nigeria seven years previously. She had had a normal vaginal delivery three months prior to admission. There was no significant other previous medical history. She was noted to have a variable pyrexia (up to 39.2°C), tender inguinal lymphadenopathy, tachycardia, dyspnoea, a soft systolic murmur at the apex, flitting synovitis affecting the knees, wrists and ankles, and an evanescent diffuse papular rash associated with marked pruritus. A Schrimer’s tear test was normal. Two months after initial presentation, the above clinical state persisted but in addition, she developed cervical lymphadenopathy, palpable splenomegaly, and splinter haemorrhages.

Investigations revealed a haemoglobin of 10.3 g/l (normochromic, normocytic), negative Coomb’s tests, eosinophilia peaking at 3.27 × 10⁹/l, erythrocyte sedimentation rate 95 mm/h, C-reactive protein maximum value 403 mg/l (normal <10 mg/l), normal liver, renal and bone biochemistry, creatine kinase normal, lactate dehydrogenase 2350 U/l (230–460), iron 8 μmol/l (11–30), total iron-binding capacity 30 μmol/l (45–72), ferritin 92 500 (17–165) and angiotensin-converting enzyme 75 U/l (8–52). An infectious disease screen revealed the following negative or normal results: numerous blood, stool and urine cultures, Mantoux test, Monospot test, anti-streptolysin O titre, serology for syphilis, coxiella, malaria, filaria, schistosomiasis, Strongyloïdiasis, brucellosis, leishmaniasis, toxoplasmosis, toxocariasis, amoebiasis, fungal precipitins, Lyme disease, hydatid disease and viral titres, including parvovirus, HIV and HTLV-I. Immunological investigations showed a negative autoantibody screen, including ENA, DNA and ANCA, polyclonal elevations in IgA 6.04 g/l (1.25–4.25), IgG 20.7 g/l (5–16), IgE 764 kU/l (1.53–114), with normal IgM and serum electrophoresis and normal C3 and C4 with a markedly elevated C3d, 20 U/ml (5–12). Radiology demonstrated an initially normal chest X-ray and computed tomography (CT) scan confirmed the enlarged spleen, thymus and heart. Repeated echocardiograms showed a small persistent posterior pericardial effusion, but no evidence of endocarditis. Biopsy of skin showed fibrinoid necrosis in superficial dermal papillae with oedema. Muscle biopsy showed no evidence of vasculitis. Bone marrow demonstrated florid reactive hyperplasia with eosinophilia, but no evidence of tuberculosis. A liver biopsy and subsequent surgical samples of spleen and lymph nodes showed non-specific inflammatory changes with no evidence of tuberculosis, lymphoma or granulomata.

On her first admission, a Trichomonas and Candida vaginal infection had been treated with no improvement to her fever. Empirical trials of amoxycillin, erythromycin and metronidazole were likewise unhelpful. In view of the eosinophilia and pruritus, a trial of thiabendazole was given, with no benefit. She was commenced on prednisolone 40 mg and azathioprine 150 mg daily for presumed connective tissue disease, again with no benefit. This was therefore stopped and followed by a long-term trial of antituberculosis therapy (isoniazid, rifampicin and ethambutol) which also resulted in no improvement.

Her intense pruritus continued throughout
her illness and remained resistant to anti-
pruritic therapy consisting of antihistamines and chlorpromazine. After five months of mala-
ise, fevers, pruritus and arthralgias, she became acutely unwell and breathless. She had been persistently anaemic, (haemoglobin 7.1 g/dl) and investigations did not support blood loss or haemolysis. The splenomegaly had increased, with an edge palpable at the umbilicus. She had a large right-sided pleural effusion and large pericardial effusion. Blood-stained fluid from the pleural effusion was negative on culture and cytology. All other investigations were un-
changed, as previously, although her rheum-
atoid factor was now positive at 1/10 240. It was decided to perform a splenectomy, because of the recurrent anaemia, and the lack of a tissue diagnosis. However, histology of the spleen showed non-specific inflammatory changes only, with no evidence of tuberculosis, lymphoma or granuloma.

Postoperatively she remained extremely unwell, being tachypnoeic with profound arthralgias. Frank synovitis of her left wrist developed which was aspiration negative on culture, and X-ray showed a small erosion on the ulnar styloid. It was decided to commence her on weekly boluses of cyclophosphamide, starting at 500 mg, increasing to 1 g, with initially 60 mg of prednisolone. After the third bolus, her condition had improved markedly. The pleural and pericardial effusions gradually resolved, and the arthralgias and synovitis abated. She is currently maintained on 7 mg of prednisolone daily, with oral boluses of 500 mg of oral cyclophosphamide every four weeks. She still has polyarthralgia with mild synovitis at the wrists, but excellent joint function.

Discussion

This patient illustrates the management diffi-
culties of complex multisystem disorders. Con-
nective tissue disease is said to account for 8–13% of all causes of a pyrexia of unknown origin.12 The initial concern was that she had an infectious disease, but multiple repeated investigations were negative and trials of empirical antimicrobial chemotherapy were unsuccessful in resolving her problems. We were concerned about an underlying neoplastic process, but the investigations tended to dimi-
nish these concerns. We considered an in-
flammatory connective tissue disease, though initial investigations, for example, ANA, were unhelpful and the introduction of prednisolone (albeit only at a modest dose) and azathioprine did not appear to improve her condition.

Because of the lingering doubt that she could have an underlying infectious disease, immunosuppression was delayed until her condition deteriorated rapidly and markedly. High-dose cyclophosphamide was then intro-
duced with rapid response, and has kept her well with no further hospital admissions for disabling symptoms or life-threatening com-
plications.

Even with the benefit of hindsight, there are still unanswered questions in this patient. It remains difficult to fit her into a diagnostic category. Eosinophilia is associated with a number of idiopathic inflammatory connective tissue diseases, including polyanerteritis nodosa/polyangitis, allergic granulomatosis with angiitis (Churg–Strauss syndrome), eosino-
philic fasciitis and severe rheumatoid arthritis with or without Feltys syndrome.3 The first three diagnoses were unlikely in view of the negative ANCA, the lack of pulmonary signs throughout the course of her disease, and negative tissue biopsies, respectively. Although she had a positive rheumatoid factor and an erosion on X-ray, she had no prolonged, sym-
metrical small joint synovitis to fulfil the 1987 revised criteria for the diagnosis of rheumatoid arthritis.4 With the arthralgia and fever, adult-
onset Still's disease was a possibility. Eosinophilia has been described in a minority of Japanese patients5 and a very high ferritin level considered diagnostically helpful when other causes have been excluded.6 However, the typical macular non-pruritic rash present in 89% of adult patients was not observed7 and the severe pruritus described by our patient is not characteristic. A further possible multisystem disease is that of idiopathic hypereosinophilic syndrome, but our patient did not have the criteria required namely, sustained hypereo-
sinophilia for more than six months.7 In fact, the hypereosinophilia resolved in our patient before the introduction of corticosteroids or immunosuppression. Finally, the intense pru-
ritus experienced by our patient has not been previously described in other patients with connective tissue disease and is not a recogn-
ised causes of pruritus in the standard medical textbooks.8

In conclusion, marked pruritus can be a feature of connective tissue disease. Our patient also illustrates the dilemmas in the manage-
ment of a severe multisystem disease, the inadequacies of our classification systems for idiopathic complex connective disease, and the power of non-specific, blind, high-dose immunosuppressives when all else had failed.

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