Case report

Still's disease associated with Coxsackie infection and haemophagocytic syndrome

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SUMMARY At the onset of Still's disease (systemic-onset juvenile arthritis) in a 12-year-old girl, serological evidence of Coxsackie B virus infection was found. Two weeks later she developed a haemophagocytic syndrome which was then treated with cytotoxic therapy. Her arthritis is still active six years later.

Key words: cytotoxic therapy, histiocytic medullary reticulosis.

In 1939 Scott and Robb-Smith described histiocytic medullary reticulosis (HMR): 'Fever, wasting, and generalised lymphadenopathy are associated with splenic and hepatic enlargement, and in the final stages jaundice, purpura, and anaemia with profound leucopenia may occur. Postmortem examination shows a systematised hyperplasia of histiocytes actively engaged in phagocytosis of erythrocytes.'¹ Until recently the disease was accepted as a malignant histiocytosis.² However, in some cases the histiocyte morphology appeared normal,³ and other patients had a self-limiting disease.^{4 5} After these reports of self-limiting haemophagocytic disorders Risdall *et al.* (1979) described 19 cases of 'virus associated haemophagocytic syndrome' (VAHS).⁶ Fourteen of these patients were immunosuppressed for renal transplantation. The disorder resembled HMR except that active virus infection was recorded in 15 patients (cytomegalovirus, herpes simplex, herpes zoster, Epstein-Barr virus, and adenovirus) and 13 patients recovered. One report of concurrent illness in father and son⁷ further emphasised that the disorder is not malignant in some cases.

An HMR-like syndrome has also been described recently in association with haematological malignancies – acute lymphoblastic leukaemia,⁸

chronic lymphatic leukaemia,⁹ Hodgkin's disease,¹⁰ Lennert's lymphoma,¹¹ and also in carcinoma of the stomach.¹² Most of the patients died from this complication of their underlying disease. In some cases a viral aetiology was considered possible.^{9 13}

This paper describes a haemophagocytic illness associated with the onset of Still's disease.

Case report

In September 1978 a girl aged 12 presented with a five-month history of joint pain and stiffness, anorexia, weight loss, and an intermittent rash on the trunk and proximal limbs. For three weeks her temperature had risen to 40°C in the evenings, and she had felt a parasternal pleuritic chest pain lasting six hours. Her illness did not respond to doxycycline over 10 days, and she was admitted to hospital. There was no family history of illness.

On examination she had a macular erythematous rash over arms and thighs. There was tenderness of shoulders, elbows, wrists, and metacarpophalangeal joints without joint swelling. Dorsiflexion of the wrists was limited and there was poor grip formation. Her temperature fluctuated from 36°C to 40°C in the afternoon over the next two weeks. Investigations revealed a haemoglobin of 12.6 g/dl, erythrocyte sedimentation rate (ESR) 60 mm/h, white blood cell count $11.1 \times 10^9/l$ with neutrophils 81%,

Accepted for publication 8 January 1985.

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lymphocytes 15%, monocytes 4%, and platelets normal. Renal and liver function tests were normal. Alkaline phosphatase of 164 IU/l was consistent with her age. Antinuclear factor and rheumatoid factor were not detected. Urine and faeces cultures were negative. Serology for leptospira, brucella, streptococcus, and yersinia were negative, and hepatitis B surface antigen was not detected. The Mantoux test was negative. Titres against Cocksackie B4 were 128 and against Cocksackie B2 were 64. These remained stable. Her tissue type was HLA-A1, B17, 27, Cw2. The electrocardiograph and x-rays of chest, elbows, wrists, and hands were normal.

Still's disease was diagnosed and she was treated with enteric coated aspirin 1300 mg three times a day. With this therapy her joint pain and rash subsided but the fever continued. The plasma salicylate level was 1.9 mmol/l.

After discharge from hospital fever, anorexia, and listlessness continued, and she was readmitted two weeks later after fainting. She was pale and slightly jaundiced with a temperature of 36°C. There was slight cervical and axillary lymphadenopathy. The liver edge was 4 cm below the costal margin, but the spleen was impalpable. Investigations showed haemoglobin 5.1 g/dl, ESR 15 mm/h, reticulocytes $3.9 \times 10^9/l$, white blood cell count $4.2 \times 10^9/l$ with neutrophils 52%, lymphocytes 45%, monocytes 3%, and platelets $55 \times 10^9/l$. A bone marrow aspirate showed normal cellularity with plentiful megakaryocytes. There was moderate dyserythropoiesis but no sideroblasts. A left shift in granulopoiesis was present with myeloblasts 8% and promyelocytes 10%. Immature monocytes were increased to 10%. A further 10% of cells were histiocytes and some of these showed phagocytosis of red cells and platelets. The bone trephine confirmed an increase in megakaryocytes and immature cells but was otherwise normal. A diagnosis of histiocytic medullary reticulosis was made.

Other investigations included prothrombin time 23.5 seconds (control 15), partial thromboplastin time with kaolin (PTTK) 60 seconds (control 39), fibrinogen 0.8 g/l, fibrin degradation products 60 mg/l, serum albumin 23 g/l, bilirubin 35 mmol/l, alkaline phosphatase 615 IU/l, serum aspartate transaminase 147 IU/l, and serum muramidase 32.5 mg/l. The Paul-Bunnell and direct Coombs' tests were negative, urea and creatinine normal, and plasma salicylate 1.6 mmol/l.

Salicylate therapy was discontinued and she was treated with vitamin K 10 mg intravenously, vincristine 2 mg, and epipodophyllotoxin (VM 26) 40 mg intravenously weekly and prednisone 60 mg daily for six weeks. In the first week she received six units of

packed cells. She remained afebrile, and her general condition improved dramatically.

The prothrombin time and PTTK became normal after one day, but after one week the fibrinogen was still reduced at 1.1 g/l and fibrin degradation products raised at 40 mg/l. Her blood count and liver function tests also rapidly improved over two weeks.

She experienced abdominal pain, possibly due to vincristine, and subsequently had three short courses of vinblastine and prednisone. After this bone marrow aspiration cytology and serum muramidase were normal. Treatment was changed to the CHOP protocol (cyclophosphamide, adriamycin, vincristine, and prednisone),¹⁴ and she received seven courses over the next seven months. During chemotherapy she had occasional joint pains and transient erythematous rash. Five months after stopping chemotherapy she developed a non-bacterial meningitis which coincided with a local epidemic of ECHO virus. Viral cultures were negative. Cocksackie antibody titres were repeated and the B4 titre had fallen to 32 and B2 to less than (Table 1).

During chemotherapy over 10 months her arthritis remained quiescent apart from occasional arthralgia. However, she developed more severe pain, morning stiffness, and evening pyrexia, with synovitis in feet, knees, and wrists and a macular rash on the trunk three months after the last CHOP course. She was treated with aspirin, indomethacin, and local steroids. Systemic steroids were required for one year. A course of gold injections was terminated when significant eosinophilia developed. At various times she has received naproxen, sulindac, and diflunisal.

In 1984, she continues to have moderately active synovitis in her hands and feet and x-rays show erosive changes in the following joints: proximal interphalangeal joints of both index and little fingers; distal interphalangeal joints of left middle, right index, middle, and ring fingers; the carpometacarpal joints of both wrists; and the tarsal and tarsometatarsal joints of both feet. She is otherwise well. Her periods began at age 14 and are normal.

The following tests are now normal: haematology apart from ESR, liver function tests and clotting

Table 1 *Cocksackie antibody titres*

	13 Sep 1978	29 Sep 1978	21 Dec 1979	6 May 1983
Cocksackie	B2 64	64	<8	<8
	B4 128	128	32	32
	B5 16	16	8	8
	B1, 3, 6 <8	<8	<8	<8

factors, immunoglobulins, luteinising hormone, follicle stimulating hormone, electrocardiograph, and chest x-ray.

Discussion

The illness at the time of our patient's second hospital admission was consistent with severe systemic Still's disease but with an unusually sudden onset of pancytopenia associated with fever, hepatomegaly, and jaundice. She had been on no drugs that one could indict in this regard. The presence of immature and mature histiocytes with phagocytosis in the bone marrow supported a diagnosis of HMR and explained the haematological findings. A leucocytosis is common in Still's disease and pancytopenia is rare in the absence of drug toxicity, though erythroid aplasia has been reported.¹⁵ The coagulation tests were consistent with an element of disseminated intravascular coagulation as previously described.⁶ No other organ biopsy was performed, so it was not known whether the histiocytic infiltration was more widespread. Although a febrile illness occurs in 20% of patients with Still's disease and is often accompanied by hepatosplenomegaly, a true hepatitis is unusual. However, Ansell has stated that the liver in children with systemic illness appears particularly vulnerable and intolerant to viral, chemical, and other insults.¹⁶ Occasionally hepatitis occurs with overenthusiastic salicylate treatment, but our patient's serum salicylate was reasonable. We felt that the liver disturbance was due to infiltration by histiocytes, though it may have been secondary to Coxsackie infection.

A diagnosis of viral infection was not made at the time of her initial febrile illness, nor at the time of her subsequent deterioration. In retrospect, however, there is evidence of a Coxsackie B2 or B4 infection. The stable raised titres to B2 and B4 in September 1978 suggest that her Coxsackie infection began some weeks or months previously. There was a small epidemic of Coxsackie infection in Christchurch which began early in 1978 and peaked late in 1978. Coxsackie virus infections have been described in association with the onset of juvenile rheumatoid arthritis by Rahal *et al.*¹⁷ and Hurst *et al.*¹⁸ Both of these patients had persisting arthritis three years later. It is tempting now to link both the onset of our patient's Still's disease and her haemophagocytic syndrome to Coxsackie B2 or B4 infection.

At the time of diagnosis of histiocytic medullary reticulosis in our patient the disease was considered to be malignant and therefore cytotoxic therapy was given. She improved rapidly with blood transfusion, vitamin K, vincristine, VM 26, and prednisone. In

retrospect it now seems more likely that this girl suffered from VAHS for which early aggressive therapy may be required to reduce the considerable reported mortality. However, prolonged cytotoxic chemotherapy (CHOP), which has been successful in HMR,³ is probably undesirable with its potential mutagenic,¹⁹ gonadotoxic,²⁰ and cardiotoxic²¹ side effects.

The activity of Still's disease was suppressed during the period of cytotoxic therapy, but three months after the last CHOP course there was a generalised flare in her joints together with pyrexia and rash. This therapy would not therefore appear to have had any long-term benefit on her Still's disease, even though it was given very early in the course of that disease.

This case illustrates both the difficulty of differentiating VAHS from HMR and the current dilemma in relation to treatment.²²

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