Case report

Still's disease and the virus-associated haemophagocytic syndrome

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SUMMARY A 15-year-old male developed features of Still's disease. He was treated, with incomplete response, with aspirin and corticosteroids. Some 10 months after the onset he contracted chickenpox and became gravely ill. A diagnosis of histiocytic medullary reticulosis was made because erythrophagocytic histiocytes were detected in marrow aspirate films. Necropsy studies showed systemic infiltration by benign-appearing histiocytes and led to the final diagnosis of the virus-associated haemophagocytic syndrome due to varicella-zoster infection in an immunocompromised patient.

The virus-associated haemophagocytic syndrome (VAHS)¹ is a rapidly progressive disorder characterised by systemic proliferation of erythrophagocytic histiocytes resulting in a clinical syndrome closely resembling that of histiocytic medullary reticulosis (HMR), now known as malignant histiocytosis (MH).² The importance of distinguishing the VAHS from HMR/MH is great, since the cytotoxic therapy appropriate for HMR/MH² would have fatal consequences if given in a case of VAHS, for which supportive measures alone are needed.³ VAHS has mostly occurred as a rare complication in patients undergoing immunosuppressive therapy, and the virus infections believed to have initiated the syndrome have usually been members of the herpes group, which includes varicella-zoster virus. In the example of VAHS we now report the patient suffered from Still's disease (juvenile chronic arthritis, JCA). The syndrome followed a varicella-zoster virus infection (chickenpox) eight months after the start of corticosteroid therapy.

Case report

A 15-year-old male developed a sore throat, diarrhoea, generalised muscular aching, pyrexia,

night sweats, stiffness of the limbs, and a macular rash over the whole of his body. He was admitted to Lancaster Royal Infirmary with a swinging temperature 37.0–40.0°C. The fauces were mildly inflamed, and small lymph nodes were palpable in both axillae, but there was neither generalised lymphadenopathy nor hepatosplenomegaly.

INVESTIGATIONS

Haemoglobin 14.1 g/dl. Leucocytes $31.9 \times 10^9/l$ (neutrophils 98%). ESR (Westergren) 113 mm in first hour. Antistreptolysin O titre 300 Todd units. Rheumatoid and antinuclear factors both negative. Infectious mononucleosis slide test negative. Viral serology: tests for Q fever, influenza, parainfluenza, psittacosis/LGV agent, adenovirus, mumps, herpes simplex, varicella-zoster, cytomegalovirus, rubella, and measles all negative.

Sternal marrow aspirate showed normal haemopoiesis. Left axillary lymph node biopsy showed a picture typical of dermatopathic lymphadenopathy. On liver biopsy and scan no abnormality was detected.

COURSE OF DISEASE

One month after admission a pericardial friction rub developed. Treatment with prednisolone, 60 mg daily, produced clinical improvement. The

haemoglobin had now fallen to 9.6 g/dl and the leucocyte count was $25.5 \times 10^9/l$ (neutrophils 90%, lymphocytes 9%, monocytes 1%). Serum albumin 31.0 g/l, globulin 58.0 g/l. Immunoglobulins: IgG, 36.5 g/l; IgA, 5.4 g/l; IgM, 2.4 g/l. Electrophoresis showed a polyclonal increase in gammaglobulins. The varicella-zoster titre was $<1/10$. HLA-B27 antigen not detected. In the synovial fluid leucocytes were $10.2 \times 10^9/l$, mainly degenerate monocytes, ragocytes numerous, suggestive of inflammatory arthritis.

Some 60 days after the onset of symptoms he developed synovitis of his wrists and knees, which persisted until his death. His condition was only partly controlled by aspirin 1200 mg qds and prednisolone 5 mg qds, and the leucocytosis persisted. He was then transferred to Manchester Royal Infirmary, where a provisional diagnosis of systemic Still's disease (JCA) was made, based on the persistent arthritis, the typical rash, the high swinging fever, the severe neutrophil leucocytosis, and the pericarditis. This diagnosis was supported by the polyclonal increase in gammaglobulins and by the negative rheumatoid factor test.

Ten months after onset his condition deteriorated a few days after his younger sister and brother had both developed chickenpox. He started to vomit, had diarrhoea, and on admission to hospital 'looked dreadful.' He had a swinging pyrexia and a leukaemoid peripheral blood picture: leucocytes $60.0 \times 10^9/l$ (neutrophils 86%, metamyelocytes 4%, lymphocytes 7%, monocytes 3%). The haemoglobin was 10.6 g/dl.

Hydrocortisone 100 mg was given four hourly by intravenous infusion. On the third day he improved, but a maculopapular rash had appeared over the trunk and limbs, and a pericardial friction rub had again become audible. Three days later the rash became vesicular and the clinical diagnosis of chickenpox was made. Fluid from a vesicle was examined (Professor M. Longson), and herpes group virus particles were identified, confirming the diagnosis of chickenpox.

In the next 10 days the leucocyte count fell rapidly to $3.1 \times 10^9/l$ and atypical monocytes were reported in the blood film. A sternal marrow aspirate showed the presence of occasional erythrophagocytic histiocytes (Figs. 1 and 2); histiocytic medullary reticulosis (HMR/MH) was diagnosed. He became jaundiced, the spleen was now palpable, thrombocytopenia ($35.0 \times 10^9/l$) was present, and death followed a cardiorespiratory arrest.

NECROPSY

Mild generalised lymphadenopathy and a moderate hepatosplenomegaly (liver 1800 g; spleen 420 g)

Fig. 1 Sternal marrow aspirate. A large histiocyte with hyperchromatic bean-shaped nucleus and abundant cytoplasm filled with ingested erythrocytes, platelets, and one nucleated haemopoietic cell. (Jenner-Giemsa stain, $\times 950$).

Fig. 2 Sternal marrow aspirate. A histiocyte with an eccentrically placed nucleus and cytoplasm stuffed with erythrocytes, showing the low nuclear-cytoplasm ratio characteristic of reactive histiocytes. (Jenner-Giemsa stain, $\times 900$).

were found. Systemic infiltration by cytologically normal histiocytes involved the liver (Fig. 3), the spleen, the lymph nodes (Fig. 4), and the bone marrow (Fig. 5). Erythrophagocytosis was marked

(Figs. 4 and 5). The final diagnosis was fatal histiocytosis which, because the cytology of the infiltrating histiocytes appeared reactive rather than neoplastic, was VAHS rather than HMR/MH.

Fig. 3 Liver. The hepatic sinusoids are massively infiltrated by histiocytes with bulky granular cytoplasm that show mostly low nuclear-cytoplasm ratio. (H and E, $\times 350$).

Fig. 4 Lymph node. A sinus in the paracortical area contains several histiocytes with eccentrically placed nuclei and cytoplasm stuffed with ingested erythrocytes. (H and E, $\times 350$).

Fig. 5 Bone marrow (necropsy). Scattered among the haemopoietic cells are several histiocytes showing low nuclear-cytoplasmic ratio and containing platelets and erythrocytes in their cytoplasm. (H and E, $\times 350$).

Discussion

It seems certain that the patient was initially suffering from JCA. The onset at under 16 years, the duration of the arthritis (10 months),⁴ together with the characteristic rash, the high swinging pyrexia, the marked neutrophil leucocytosis, and the pericarditis all support this diagnosis. The negative result for varicella-zoster viral antibody obtained early in the illness shows that he had not had chickenpox before the onset of JCA and thus supports the clinical diagnosis of varicella subsequently. Varicella-zoster virus is a member of the herpes group, and almost all the reported cases of VAHS have been due to one or other members of this group.¹⁻⁵ That a concurrent varicella infection in children receiving steroid therapy may have serious consequences is well recognised.⁶ In some cases death has ensued,⁷ but the necropsy reports have not described fatal histiocytosis.

We have to accept, with the advantage of hindsight, that the diagnosis during life of HMR/MH made in this case because of the presence of erythrophagocytic histiocytes in a marrow aspirate film was incorrect. That the distinction between reactive and neoplastic histiocytes may be difficult to achieve, especially in marrow films, has been emphasised.⁸

This case appears to be the first reported instance

of JCA complicated by VAHS. One case of rheumatoid arthritis terminated with HMR/MH,⁹ but at that date (1977) VAHS had not been separated from HMR/MH.

Our experience with this case of systemic JCA is in line with observations¹⁰ that exacerbations in this disease are often preceded by an infection, and that serious infections are likely in patients taking considerable doses of corticosteroids. The histological findings in this case are closely similar to those found in a case of VAHS following an Epstein-Barr virus infection in a youth aged 16 who died five weeks after onset⁵ and provide support for the view that a histological distinction between VAHS and HMR/MH can be achieved. But at the same time we would emphasise that such a distinction cannot safely be made on the basis of the appearance of erythrophagocytic histiocytes in a sternal marrow aspirate smear.

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