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°-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 × 10⁹/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 x 10⁹/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 x 10⁹/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 per-
sisted. 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 swing-
ing 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 x 10⁹/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 x 10⁹/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, thrombo-
cytopenia (35.0 x 10⁹/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,
×950).

Fig. 2 Sternal marrow aspirate. A histiocyte with an
eccentrically placed nucleus and cytoplasm stuffed with
erthrocytes, showing the low nuclear-cytoplasm ratio
characteristic of reactive histiocytes. (Jenner-Giemsa stain,
x900).
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, ×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, ×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), 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. That a concurrent varicella infection in children receiving steroid therapy may have serious consequences is well recognised. In some cases death has ensued, 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.

This case appears to be the first reported instance of JCA complicated by VAHS. One case of rheumatoid arthritis terminated with HMR/MH, 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 observations 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 onset 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 be made on the basis of the appearance of erythrophagocytic histiocytes in a sternal marrow aspirate smear.

References


