

Influenza A and the virus associated haemophagocytic syndrome: Cluster of three cases in children with acute leukaemia

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Abstract

At the height of the United Kingdom influenza A epidemic in December 1989, three children receiving treatment for non-T cell acute leukaemia developed pancytopenia with concomitant influenza A infection. Bone marrow histology showed prominent marrow erythrophagocytosis by morphologically mature histiocytes, consistent with the picture of virus associated haemophagocytic syndrome (VAHS). In two cases there was an initial spontaneous recovery, though recurrence of VAHS developed in one case in association with a different viral infection (cytomegalovirus) following autologous bone marrow transplantation. The third child died from cardio-respiratory failure secondary to infection with influenza A and *Klebsiella pneumoniae* sepsis.

It is suggested that influenza A should be added to the list of infective causative agents.

The virus associated haemophagocytosis syndrome (VAHS) was first described by Risdall *et al* in 1978 in a series of 19 patients with peripheral blood cytopenias associated with marrow histiocytosis and haemophagocytosis.¹ It occurs most commonly in association with the herpes group viruses, in particular cytomegalovirus (CMV)^{1,2} and the Epstein-Barr virus (EBV).^{1,3} Others, including herpes simplex,² zoster,¹ adenovirus,¹ parvovirus⁴ and the human immunodeficiency virus,⁵ have also been implicated.

Proliferative histiocytosis has also occasionally been described in association with acute leukaemias^{2,6-12} and lymphomas^{2,13-16} in the absence of documented infection. In acute lymphoblastic leukaemia (ALL) clinical features and marker studies have suggested a predominantly T cell origin, with only one previous report in common ALL.¹⁰ Most cases have occurred within six months of the initial diagnosis of the leukaemia, usually when the patient is in remission. In most cases the histiocytosis has progressed rapidly and been fatal. Some authors attribute this poor survival to evidence of a malignant histiocytic process, perhaps with a common stem cell origin as the original leukaemia.^{6,7} It has also been argued, however, that these cases may have represented a benign form of VAHS, but that continuation of chemotherapy with

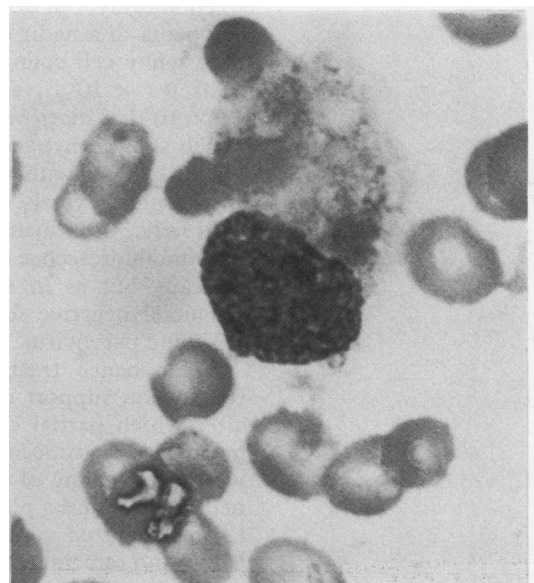
immunosuppression resulted in an unfavourable outcome.^{1,2}

Case reports

CASE 1

A 3 year old girl presented with common ALL (CD 10, CD 19, Tdt and HLA-DR all more than 95% positive, cytoplasmic μ negative). Treatment began with the United Kingdom ALL (X) protocol (arm C), but 20 months into treatment she developed an isolated central nervous system relapse. Having no donor for allogeneic bone marrow transplantation, reinduction with an intensive chemotherapy regimen was started with the intention of proceeding to autologous bone marrow transplantation.

Remission was achieved and treatment with 6-Mercaptopurine (6-MP) was begun before bone marrow transplant. Two weeks later she presented with rhinitis and a productive cough and on examination she had developed splenomegaly but had no lymphadenopathy or hepatomegaly. Serial blood counts over the next week showed a rapidly progressive pancytopenia with levels falling from normal to a nadir of haemoglobin at 7.9 g/dl, a white cell count of $1.0 \times 10^9/l$ (neutrophils $0.2 \times 10^9/l$), and a platelet count of $19 \times 10^9/l$. A bone marrow aspirate showed hypocellularity of all



Bone marrow aspirate of case 1 showing erythrophagocytosis by an activated macrophage (May-Grünwald-Giemsa stain).

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three cell lines, histiocytic hyperplasia, and pronounced haemophagocytosis (figure).

Influenza A was isolated from sputum by immunofluorescence. No other infectious agents were identified. Serology for CMV, EBV, parvovirus and influenza A was negative in both the acute and convalescent phases of infection. Treatment with 6-MP was stopped and blood and platelet transfusions were required for one week, following which a repeat marrow aspirate and trephine biopsy specimen showed an improvement in cellularity and a reduction in histiocytosis and erythrophagocytosis. Autologous bone marrow transplantation, from marrow harvested before maintenance 6-MP started, proceeded two weeks later. After a bone marrow transplantation she remained well for three months with good engraftment and no evidence of marrow histiocytosis. Subsequently, however, she developed a primary CMV infection with recurrence of VAHS and pneumonitis, which proved fatal despite active treatment with gancyclovir and immune plasma.

CASE 2

A 6 year old girl presented with common ALL (CD 10, TdT, CD 19, HLA-DR all more than 95% positive, cytoplasmic μ negative). Treatment was completed with the United Kingdom ALL (X) protocol (arm A), but with considerable haematological toxicity.

Three months after finishing treatment she relapsed with bone marrow and central nervous system disease. She was treated in an identical manner to case 1 but sustained pronounced haematological toxicity. After treatment peripheral blood counts returned to normal, but harvested marrow showed poor in vitro growth characteristics. Autologous bone marrow transplantation was not contemplated, therefore, and maintenance 6-MP was started.

Two weeks later she developed fever and malaise. There was no evidence of hepatosplenomegaly, but because of progressive pancytopenia to a nadir of haemoglobin at 8.2 g/dl, a white cell count of $0.4 \times 10^9/l$ (neutrophils $0.1 \times 10^9/l$), and to platelet count of $15 \times 10^9/l$, a marrow aspirate was performed which showed hypocellularity of all three cell lines associated with histiocytic infiltration and erythrophagocytosis.

Presence of influenza A virus was shown by immunofluorescence in a nasopharyngeal aspirate, but as in case 1, serological titres remained negative for this virus and CMV, EBV and parvovirus.

Maintenance treatment was stopped and transfusion support required for three weeks after which partial count recovery occurred: haemoglobin concentration of 11.1 g/dl, a white cell count of $1.7 \times 10^9/l$ ($1.0 \times 10^9/l$ neutrophils) and a platelet count of $47 \times 10^9/l$. She restarted continuation treatment with 6-MP and remained well eight months later.

CASE 3

A 2 year old boy presented with acute myeloid

leukaemia (AML) (FAB M2). Treatment with the Medical Research Council AML (X) protocol with initial randomisation to daunorubicin, cytosine arabinoside, and 6-thioguanine was begun. Remission was achieved after the second course of chemotherapy, though following the third course (M-amsacrine, cytosine arabinoside and etoposide), there was pronounced toxicity complicated by *Klebsiella pneumoniae* septicemia.

After recovery, and with normal bone marrow morphology, the fourth course of chemotherapy (mitozantrone and cytosine arabinoside) was started. Ten days later, and while pancytopenic (haemoglobin 6.0 g/dl, leucocyte count $0.1 \times 10^9/l$, platelet count $30 \times 10^9/l$), he became unwell again with bilateral bronchopneumonia. *Klebsiella pneumoniae* was again isolated from blood cultures, and the presence of influenza A virus was shown by immunofluorescence from a nasopharyngeal swab. Despite appropriate antibiotics, Ribavirin nebulisers, and intravenous immunoglobulins, the patient's condition deteriorated rapidly and he required artificial ventilation. Hypotension and signs of cardiac failure developed despite inotropic support and he died. Shortly after admission, an acute fall in haemoglobin concentration of 4 g/dl over 24 hours had occurred but was unexplained by haemorrhage or haemolysis.

At necropsy the lungs showed evidence of pneumonic consolidation with alveolar damage consistent with influenza A infection. Bone marrow histology showed a hypocellular marrow, and a pronounced histiocytosis with prominent erythrophagocytosis.

Discussion

Histiocytic syndromes of childhood include those of Langerhans' cell origin, previously described as "histiocytosis-X", and those of non-Langerhans' cell origin including VAHS and familial erythrophagocytic lymphohistiocytosis.¹⁷ Malignant histiocytosis, first described and named histiocytic medullary reticulosis by Scott and Robb-Smith in 1939,¹⁸ is also of non-Langerhans' cell origin.

The distinction between a malignant histiocytic condition and a benign, reactive process as in VAHS is difficult because of the lack of an identifiable clonal marker in most cases, although a 5q35 chromosome breakpoint has recently been associated with a few cases of malignant histiocytosis.^{19,20} Diagnosis of VAHS, therefore, relies on a specific clinical, haematological, and histological picture. It is characterised by a variable depression of the blood counts associated with histiocytic hyperplasia and prominent haemophagocytosis occurring in the setting of an acute infection, usually in an immunosuppressed patient.¹ Clinical findings usually include fever, lymphadenopathy, and hepatosplenomegaly. Marrow examination shows infiltration with morphologically benign histiocytes, with mature nuclear chromatin, inconspicuous nucleoli, and abundant cytoplasm. Prominent erythrophagocytosis is usually evident, though

phagocytosis of neutrophils and platelets is often also present. Hypoplasia of erythroid and myeloid lineages is usual, but megakaryocyte numbers may be increased. The release of inhibitory cytokines such as interleukin 1,²¹ tumour necrosis factor α ²² and γ -interferon²³ from activated histiocytes may account, in part, for suppression of the marrow. The syndrome is characteristically self-limiting with resolution within eight weeks. Management consists of supportive measures together with withdrawal of immunosuppression if possible.¹

In contrast, in cases of malignant histiocytosis, an underlying acute infection is not usually found, though occasional reports of case clustering have occurred and may suggest such an aetiology.²⁴⁻²⁶ Malignant histiocytes are typically immature cells with prominent nucleoli and a higher nuclear:cytoplasmic ratio.¹ Haemophagocytosis is said to be less pronounced and the distribution of histiocytes may be different from VAHS, with less marrow but more lymph node infiltration.¹

The clinical and histological findings in the three cases of histiocytosis described are most compatible with a benign reactive process, and initial recovery in two of the cases also suggests that it is not a malignant condition. Most of the reported cases of histiocytosis in association with acute leukaemia, however, are more compatible with a diagnosis of malignant histiocytosis in terms of cell morphology, distribution, and clinical outcome. Various explanations for this association have been proposed including: (i) a common stem cell origin^{6,7}; (ii) a second malignancy caused by initial leukaemia chemotherapy²⁷; (iii) malignant transformation of histiocytes after engulfing dying leukaemia cells following chemotherapy and thus exposure to common oncogenic agents.⁸

Alternatively, it is argued that these cases are in fact examples of VAHS, but that the histiocytic reaction becomes overwhelming only because of continued inappropriate immunosuppressive treatment.¹² Jaffe, however, has postulated that it is macrophage-activating lymphokines released from neoplastic T cells that account for the predominant association between the histiocytic conditions and T cell origin ALL and lymphomas.¹³ Higher concentrations of the soluble interleukin-2 receptor in cases of childhood haemophagocytic histiocytic syndromes⁴ is further evidence for T cell activation, which may in some cases have been in response to a viral infection.

In summary, two of our cases were very similar in that they followed an intensive chemotherapy protocol for relapsed common ALL. Initial recovery occurred in both cases, though recurrence of VAHS associated with CMV infection followed autologous bone marrow transplantation in case 1. Case 3 requires some caution in interpretation because the patient was pancytopenic from recent intensive chemotherapy and also had evidence of infection with *Klebsiella pneumoniae*. Prominent histiocytic hyperplasia with erythrophagocytosis, however, was pronounced in a trephine necropsy specimen and may have accounted for an acute drop in haemoglobin

concentration witnessed during his hospital stay. In all three cases viral serology for influenza A was negative because of underlying immunosuppression but the virus was isolated and identified from respiratory tract secretions by immunofluorescence.

This pathogen has not previously been associated with VAHS and should be added to the list of causative agents.

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