Haemophagocytic syndrome complicating acute lymphoblastic leukaemia

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Summary: A 41 year old female developed reactive haemophagocytic histiocytosis secondary to herpes simplex infection, during remission induction for acute lymphoblastic leukaemia. She recovered fully with acyclovir and supportive treatment. Previous publications on the association between acute lymphoblastic leukaemia and haemophagocytic syndrome are reviewed, and the nature of the haemophagocytic disorder is discussed.

Introduction

The haemophagocytic syndrome of histiocytic medullary reticulosis (HMR) is characterized by fever, weight loss, jaundice, lymphadenopathy, hepatosplenomegaly and pancytopenia, and by widespread organ infiltration by atypical histiocytes with variable haemophagocytosis.¹ More than 200 cases have now been reported, some of them under the title 'malignant histiocytosis' (MH) – a term initially considered as a synonym for HMR.^{2,3} In recent years two further types of clinical disorders with features similar to those in HMR have been recognized: (i) a potentially self-limiting disease secondary to viral and other infections;^{4,5} (ii) a terminal complication in patients with a pre-existing haematological malignancy^{6–11} or carcinoma.¹² This report describes a 41 year old female who developed a HMR-like syndrome during remission induction for acute lymphoblastic leukaemia (ALL).

Case report

A previously well 41 year old female presented in August, 1987 with a 2-week history of fever, night sweats, rhinorrhoea, malaise and fatigue. Examination revealed 1 cm lymph nodes palpable in both axillae and a tippable spleen. A blood count showed haemoglobin 9.2 g/dl, white cell count (WCC) $16.6 \times 10^9/l$, with 59% blasts, 32% lymphocytes, 2% neutrophils, 6% monocytes, 1% eosinophils and platelets $53 \times 10^9/l$. Bone marrow aspiration was hypercellular with a dense infiltration of blasts including a population of small cells with a high nuclear:cytoplasmic ratio and another of larger cells

with more cytoplasm. Cytochemistry and surface markers were as shown in Table I, the leukaemia was thus classified as CALLA +ve ALL (FAB L2). Cytogenetic studies were 46XX (normal).

Remission induction chemotherapy was commenced with oral prednisolone 100 mg/day and vincristine 2 mg intravenously/week. On day 2 the patient developed a herpes simplex lesion on the upper lip; acyclovir was commenced, with resolution over the ensuing 2 weeks. The splenomegaly and lymphadenopathy resolved and there was a prompt fall in the WCC with disappearance of all blast cells. However, despite the non-myelotoxic nature of the chemotherapy, the patient remained profoundly neutropenic and became more severely thrombocytopenic and anaemic: on day 18 the WCC was $0.8 \times 10^9/l$ with 80% lymphocytes, 16% neutrophils and 2% monocytes; platelets $16 \times 10^9/l$ and haemoglobin 8.4 g/dl. A repeat bone marrow aspiration showed markedly decreased myeloid precursors, 62% mature lymphocytes, 1% blasts and 22% abnormal mononuclear cells and macrophages, some showing erythrophagocytosis (Figure 1); a differential count of the mononuclear-macrophage cells showed predominance of mature macrophages over immature mononuclear cells by a ratio of 2.6:1;¹³ erythropoiesis was reduced (10%) and markedly dyserythropoietic. Cytochemistry of the mononuclear cells (Table I) was consistent with monocytic origin. Biochemistry, including liver function tests and coagulation studies, was normal.

The ALL treatment protocol was continued and on days 20 and 21 daunorubicin 100 mg i.v. was given. On day 30 the patient developed pneumonia; this resolved with intravenous antibiotics and leucocyte transfusions. On day 38 there was a recurrence of labial herpes simplex which settled with oral acyclovir. There was a further fall in the leucocyte and platelet counts

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Figure 1 Bone marrow aspiration (May-Grünwald-Giemsa). Day 18 showing histiocytic proliferation (× 22).

Table I Bone marrow cytochemistry and surface markers

	21.8.87	8.9.87
Sudan Black	Negative	Weak + (diffuse)
PAS	4+ block	4+ diffuse
Dual esterase	N.D.	2+
Acid esterase	Negative	N.D.
tdt	4+	3+
CD2	9%	N.D.
CD10 (CALLA)	86%	N.D.
CD19	54%	N.D.
CD22	13%	N.D.
HLA DR	21%	N.D.
IL2-R	8%	N.D.

N.D. – not done.

after daunorubicin; however, by day 47 the haemoglobin was 15 g/dl, WCC was $5.1 \times 10^9/l$ with 60% neutrophils, 32% lymphocytes, 2% monocytes, 2% band forms, 1% metamyelocytes, 3% myelocytes, and platelets $103 \times 10^9/l$. A repeat bone marrow aspiration at this time showed complete remission with no evidence of the abnormal monocytoid cells seen on the previous examination. During the period of cytopenias the patient received two red cell transfusions and several prophylactic platelet transfusions. At presentation influenza B (complement fixation) titres were raised to >512, these subsequently fell to 1:64. Herpes simplex antibody titres were raised to 1:256 at presentation and remained at this titre or at 1:128 on several occasions over the next 3 months.

Twelve months after presentation the patient is well on maintenance chemotherapy.

Discussion

A HMR-like syndrome has now been described in 19 patients with ALL (Table II). The patient described here is the first in whom the abnormal histiocytic infiltrate was demonstrated during remission induction for ALL. The majority of previously reported cases were diagnosed between 3 and 6 months from presentation with ALL, and in all but one (Patient 17, Table II) this syndrome has been fatal, possibly due to more extensive organ involvement; in our case the histiocytic infiltrate was clinically confined to the bone marrow.

The HMR-like syndrome in ALL has been thought by some authors to represent a true malignancy (malignant histiocytosis, MH),¹⁹ but others have felt it to be a reactive process.^{24,25} There have been several theories to explain the development of MH in ALL: a common stem cell could give rise to MH when the ALL clone is suppressed by chemotherapy;¹⁷ an oncogenic agent could be taken up by histiocytes from dying leukaemic cells leading to malignant transformation;²⁰ or, MH is induced by chemotherapy.²³ On the other hand, Rosner and Grünwald, reviewing 17 reported cases of this syndrome in ALL, have stressed that the majority of these patients probably had T-cell ALL, and postulated that the histiocytosis was a result of oversecretion of lymphokines by the neoplastic cells.²⁷ This was also suggested by Jaffe *et al.*⁷ who reported six cases of NHL, including two cases of T-cell lymphoma, terminating in a HMR-like syndrome.

Distinction between reactive and malignant histiocytosis on cytological criteria has been difficult due

to the heterogeneity of the abnormal cells. However, in an attempt to overcome this, abnormal mononuclear-macrophage cells (histiocytes) have been classified into five stages of maturation and a preponderance of more mature cells has been noted in reactive histiocytosis.^{13,28} In the patient described here, more mature macrophages (stages 4 and 5) outnumbered immature mononuclear cells (stages 1 and 3) by a ratio of 2.6:1, thus indicating a reactive histiocytosis. This and the short time (16 days) between the diagnosis of ALL and the demonstration of histiocytosis make a second malignancy unlikely, and she did not have a T-cell neoplasm. She did, however, have a herpes simplex infection with raised titres at presentation. Reactive histiocytosis has most commonly been secondary to the herpes group virus infections: cytomegalovirus, Epstein-Barr virus, *H. simplex*, *H. zoster*.^{4,29} An influenza-B infection immediately prior to the diagnosis of ALL was not associated with

histiocytosis on the initial bone marrow examination, thus making it a less likely cause. It is also possible that the histiocytic reaction was exacerbated by the killing of malignant cells by chemotherapy.²⁰

In summary, we present a patient who developed bone marrow histiocytosis soon after the onset of labial herpes simplex during remission induction for ALL. Acyclovir and supportive treatment resulted in complete resolution of the abnormal infiltrate despite continuation of chemotherapy. The occurrence of this HMR-like syndrome in patients with haematological malignancy should prompt the search for an underlying infection.

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Table II Histiocytic medullary reticulosis-like syndrome complicating acute lymphoblastic leukaemia

Patient no.	Sex/age (y)	Time to onset HMR	Manifestations	Diagnosis	Ref. no.
1	M/17	3 mths	Fever, splenomegaly	Autopsy	14
2	M/17	3 mths	Fever, hepatomegaly, sudden death	Autopsy	15
3	F/12	6 mths	Sepsis, bleeding	Autopsy	16
4	M/24	3 mths	Fever, hepatosplenomegaly	Scalene node biopsy Bone marrow examination	17
5	M/4	4 mths	Fever, hepatosplenomegaly, lymphadenopathy, pancytopenia	Bone marrow	18
6	M/13	6 mths	Splenomegaly, pancytopenia	Splenectomy	19
7	F/5	4 mths	Fever, hepatosplenomegaly, pancytopenia	Bone marrow Liver biopsy Splenectomy	19
8	M/1½	4 mths	Fever, recurrent infections	Bone marrow	20
9	NS	NS	ALL remission terminated by pancytopenia, jaundice, death	Autopsy in three cases; NS in other	21
10	(4 cases)	NS	ALL remission terminated by pancytopenia, jaundice, death	Autopsy in three cases; NS in other	21
11					
12					
13					
14	M/14	6 mths	Fever, hepatosplenomegaly, pancytopenia	Autopsy	22
15	F/54	7 wks	Pancytopenia	Bone marrow	23
16	M/22	3½ mths	Fever, hepatosplenomegaly, pancytopenia	Bone marrow	24
17	F/42	6 mths	NS	NS	25
18	M/6	28 mths	Fever, anaemia, leukopenia, hepatomegaly	Bone marrow	26
19	M/12	19 mths	Hepatosplenomegaly, Blasts in P.B., fever, jaundice	Autopsy	8
20	F/41	18 days	Pancytopenia	Bone marrow	This report

NS – not specified

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