References

- ¹ Gottlieb MS, Schrott R, Schauker HM, *et al.* Pneumocystis carinii pneumonia and mucosal candidiasis in previously healthy homosexual men: evidence of a new acquired cellular immune deficiency. *N Engl J Med* 1981;**305**:1425–31.
- ² Menitove JG, Aster RH, Casper JT, *et al.* T lymphocyte subpopulations in patients with classical haemophilia treated with cryo precipitate and lyophilised concentrates. *N Engl J Med* 1983;**308**:83–6.
- ³ Lederman MM, Ratnoff OD, Schillian JT, *et al.* Impaired cell-mediated immunity in patients with classic haemophilia. *N Engl J Med* 1983;**308**:79–82.
- ⁴ Saidi P, Kim HC, Raska K. T cell subsets in haemophilia. *N Engl J Med* 1983;**308**:1291–2.
- ⁵ Woodcock BA, Lilleyman JS. Portal hypertension in severe haemophilia. *Lancet* 1983;**i**:1388.
- ⁶ Walker DA, Lilleyman JS. Pseudo-aids. *Lancet* 1983;**ii**:344.
- ⁷ Communicable Disease Surveillance Centre. AIDS in the UK. *Lancet* 1983;**ii**:411.
- ⁸ Amman AJ, Cowan MJ, Wara DW, *et al.* Acquired immunodeficiency in an infant. Possible transmission by means of blood products. *Lancet* 1983;**i**:956–8.

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Familial erythrophagocytic reticulosis

Complete response to combination chemotherapy

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SUMMARY Two infants with familial erythrophagocytic reticulosis attained a durable complete remission after combination chemotherapy including intrathecal methotrexate. Though both later died, neither child had definitive evidence of tumour at necropsy.

Familial erythrophagocytic reticulosis (FER) is a rare, rapidly progressive disorder, inherited as an autosomal recessive trait,¹ and presenting between 3 and 6 months of age. There have been reports of responses to single agent chemotherapy² but, with one exception,³ remissions were short. We report two infants treated with combination ('CHOP') chemotherapy and intrathecal methotrexate (IT MTX). Both attained complete clinical remissions, for 18 months and 38 months, respectively.

Case 1

This infant, the second child of unrelated parents, presented at 2 months of age with fever and vomiting. Her brother had died at age 14 months after an illness characterised by fever, hepatosplenomegaly, and pancytopenia, and necropsy had showed histiocyte proliferation with phagocytic activity in the liver, kidneys, lymph nodes, marrow, and meninges. On examination she was pale and had hepatosplenomegaly. Her haemoglobin value was 6.6 g/dl, white blood count $4.7 \times 10^9/l$ and platelets $96 \times 10^9/l$; blood film showed a

leukoerythroblastic anaemia. Cerebrospinal fluid was normal. Her fasting serum triglycerides value was raised at 2.82 mmol/l (normal range 0.35–1 mmol/l). Bone marrow aspirate showed no obvious increase in histiocytes or erythrophagocytosis but immunological studies showed a population of cells bearing Fc (32%) and C3 (21%) receptors. Immune function including phytohaemagglutinin response, yeast opsonization, and immunoglobulins was normal. Serology for herpes simplex, cytomegalovirus, Epstein-Barr virus, toxoplasmosis, and syphilis was negative, as were bacterial and urine cultures for cytomegalovirus.

FER was diagnosed and 'CHOP' chemotherapy was begun. Intrathecal methotrexate was given with courses 2–7 (Table). Within one month the hepatosplenomegaly and pancytopenia resolved, and apart from one episode of fever and neutropenia she remained well and developed normally. Adriamycin was stopped at a cumulative dose of 450 mg/m². When chemotherapy was stopped after one year her

Table CHOP treatment regimen* (Courses repeated 3–4 weekly, depending on blood count)

Drug	Dose	Route	Timing
Adriamycin*	2.00 mg/kg	IV	Day 1
Cyclophosphamide	30.00 mg/kg	IV	Day 1
Vincristine	0.05 mg/kg	IV	Day 1
Prednisolone	4.00 mg/kg	Oral	Day 1–5

* COP=CHOP without adriamycin, which has stopped at a total dose of 450 mg/m².

bone marrow was normal, but some Fc (19%) and C3 (10%) receptor bearing cells were still present.

Seven months later progressive splenomegaly and fever recurred. Her haemoglobin value was 9.6 g/dl, and white blood count was $4.2 \times 10^9/l$ with 25% neutrophils, 57% lymphocytes, 18% monocytes, and platelets $68 \times 10^9/l$. Bone marrow was normal except for persistence of the Fc and C3 receptor bearing cells. Viral serology and bacterial cultures were negative and she was assumed to have a recurrence of FER. 'COP' (CHOP regimen without adriamycin) (Table) and intrathecal methotrexate were restarted, but clinical response was incomplete even after substitution of oral methotrexate and 6 mercaptopurine for cyclophosphamide. Three months after the disease recurrence she died suddenly and at necropsy she was found to have an *Escherichia coli* peritonitis. Histiocyte infiltration with haemophagocytosis was noted in the marrow, spleen, meninges, nodes, thymus, and liver, but was not conclusively diagnostic of FER.

Case 2

This patient was the second child of Iraqi parents who were first cousins. Their first baby had presented terminally ill at age 4 months with hepatosplenomegaly and pancytopenia. A bone marrow aspirate had shown 9% histiocytes, some showing haemophagocytosis. The child died before institution of specific treatment, but necropsy findings were strongly suggestive of FER, with haemophagocytosis in lymph nodes, spleen, marrow, and liver.

At 4 months of age our patient developed anorexia, fever, and hepatosplenomegaly. His haemoglobin value was 9.7 g/dl, his white blood count was $5.6 \times 10^9/l$, and platelets $64 \times 10^9/l$. Findings were normal or negative in the following investigations: bone marrow aspirate and biopsy, cerebrospinal fluid, liver function, cultures for bacteria and viruses, serology for toxoplasmosis, cytomegalovirus, Epstein-Barr virus and other viral pathogens, and thick smear for malaria. Serum triglycerides were 4.7 mmol/l (normal range 0.35–1 mmol/l). There was a reduced phytohaemagglutinin response, low numbers of E rosetting T lymphocytes, and a nitroblue tetrazolium test was normal. Liver biopsy showed a mild non-specific periportal infiltrate but no recognisable phagocytes.

The boy's condition deteriorated rapidly with progressive pancytopenia. Repeat bone marrow aspirate contained 13% primitive reticulum cells and monoblasts, some showing haemophagocytosis; these cells bore Fc and C3 receptors. FER, with a secondary immune deficiency, was diagnosed and 'CHOP' chemotherapy (Table) was started. Cere-

brospinal fluid contained 12 white blood cells/high power field, showing mitotic figures and phagocytosis; regular intrathecal methotrexate was given.

There was a good clinical response with resolution of hepatosplenomegaly and pancytopenia, and he started to thrive. Two months later, bone marrow aspirate was cytologically and immunologically normal. A severe episode of necrotising enterocolitis at 6 months of age was treated medically. Developmental progress was normal. Adriamycin was stopped after 7 months and 'COP' was stopped after two years. At this time, the only clinical abnormality was a small perianal lesion thought to be a haemorrhoid.

Over the next 9 months he failed to thrive. His perianal lesions enlarged. Colonoscopy showed a chronic granulomatous colitis, histologically compatible with either atypical Crohn's disease or a chronic opportunistic infection. There was a temporary response to salazopyrin and metronidazole, but four months later he developed a progressive abdominal distension and died. Necropsy showed multiple intestinal perforations, peritonitis, and empyema of the gall bladder: *Salmonella enteritidis* was cultured from bowel contents, peritoneal fluid, and bile. There was no evidence of FER.

Discussion

FER is rare and only one or two cases each year are notified to the United Kingdom Children's Cancer Study Group. It must be distinguished from virus induced and other reactive histiocytic disorders and is usually considered to be a true histiocytic malignancy.¹⁻⁶ With two exceptions,^{3,6} the disease has been lethal within 8 months of diagnosis. Treatment has usually consisted of steroids and vinca alkaloids used as single agents or in combination;^{2,4} VP 16³ and vinblastine-loaded platelets⁵ have also been used. One infant was treated with vinblastine, prednisolone, methotrexate and cyclophosphamide,⁶ but the eventual outcome has not been reported.

The clinical, haematological, and immunological findings in our two patients were compatible with the diagnosis of FER and in each instance there was a positive family history. Because of the apparent curability of malignant histiocytosis (which we regard as the sporadic equivalent of FER) by the 'CHOP' regimen,⁷ we decided to use this treatment in these two infants, stopping adriamycin after a total dose of 450 mg/m² and continuing with 'COP'. The central nervous system is frequently affected in FER^{1,4} so we also gave regular intrathecal methotrexate but, because of the children's age, no cranial irradiation. That complete clinical and haematological remission was achieved in both

patients tends to confirm (but not necessarily prove) that FER is a malignant disease. Because the first child showed evidence of disease recurrence after one year of chemotherapy, we treated the second for 24 months. Although both patients died, no definite tumour was seen in either at necropsy.

Chemotherapy may have predisposed both children to fatal infection. In the first child an opportunistic pathogen was responsible for a terminal illness mimicking Crohn's disease; chemotherapy possibly also contributed to the episode of necrotising enterocolitis.

We conclude that patients with FER may, as a result of appropriate combination systemic chemotherapy with intrathecal methotrexate, enjoy good quality, prolonged remissions of disease. Whether or not they can be cured in this way remains to be seen. Infants treated with 'CHOP', and probably other combination therapy regimens, must be observed closely for unusual complications.

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References

- 1 Farquhar JW, Claireaux AE. Familial haemophagocytic reticulosis. *Arch Dis Child* 1952;27:519-25.
- 2 Perry MC, Harrison EG, Jr, Omer Burgert E, Gilchrist GS. Familial erythrophagocytic lymphohistiocytosis. *Cancer* 1976;38:209-18.
- 3 Ambruso DR, Hays T, Zwartjes WJ, Tubergen DG, Favara BE. Successful treatment of lymphohistiocytic reticulosis with phagocytosis with epipodophyllotoxin VP 16-213. *Cancer* 1980;45:2516-20.
- 4 Lilleyman JS. The treatment of familial erythrophagocytic lymphohistiocytosis. *Cancer* 1980;46:468-70.
- 5 Woo SY, Klappenbach RS, McCullars GM, Kerwin DM, Rowden G, Sinks LF. Familial erythrophagocytic lymphohistiocytosis: treatment with vinblastine-loaded platelets. *Cancer* 1980;46:2566-70.
- 6 Fullerton P, Ekert H, Hosking C, Tauro GP. Hemophagocytic reticulosis: a case report with investigations of immune and white cell function. *Cancer* 1975;36:441-5.
- 7 Alexander M, Daniels JR. Chemotherapy of malignant histiocytosis in adults. *Cancer* 1977;39:1011-17.

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Sjögren syndrome and lupus erythematosus nephritis

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SUMMARY A 9 year old girl with symptoms of the Sjögren syndrome showed interstitial lymphocytic infiltrate on renal biopsy. Two years later she had clinical and biological evidence of systemic lupus erythematosus, as sociated with a typical glomerulonephritis.

Sjögren syndrome (keratoconjunctivitis sicca and xerostomia with or without another autoimmune disease) is uncommon in children.¹ We studied two successive renal biopsies in a child who progressed from Sjögren syndrome without autoimmune disease to systemic lupus erythematosus.

Case report

A 9 year old girl was admitted to this hospital for recurrent parotitis. The first parotid enlargement

had been noticed four years previously, when she was admitted to another hospital because of convulsions. At that time treatment with phenobarbitone had been prescribed and this had been continued for four years.

Physical examination showed bilateral conjunctivitis without corneal erosion, and cutaneous vasculitis with purpuric pattern around the nails and the mouth, associated with erythema of the palms. Laboratory investigations showed a high serum protein value (108 g/l), a raised IgG value, and circulating immune complexes detected by the Clq binding test. She had a positive antinuclear antibody test (1/1600 speckled pattern), but her anti-DNA test (on *Crithidia luciliae*) and extractable nuclear antigen test were negative. Her complement value was normal. Her blood creatinine concentration was normal and neither proteinuria nor haematuria were detected.

On sequential salivary scintigraphy, the uptake of