many large cells of histiocytic type with central nuclei and clear cytoplasm. The cells were interspersed with numerous smaller mononuclear cells. Several hours after the trephine was taken it became apparent that the patient had developed a bleeding tendency which was more severe than could be accounted for by the thrombocytopenia. There was haemorrhage from the trephine site and large bruises developed around the sites of earlier venepunctures (see Fig.).

Extensive bruising extending from venepuncture sites in antecubital fossae.

Coagulation studies demonstrated only hypofibrinogenemia. The fibrinogen level was 25 mg/100 ml (normal 200 to 400 mg/100 ml) and the fibrinogen titre was 1/16 in aminocaproic acid (EACA) and in saline (normal 1/256). No significant fibrinolysis could be detected. The euglobin clot lysis time was normal and fibrin degradation products were at the upper limit of normal at 4 µg/ml (Merskey *et al.*, 1969). It was decided that the patient had disseminated intravascular coagulation. She was given two units of fresh blood and a continuous intravenous infusion of heparin, 12,000 units in 24 hours, for seven days. Within 24 hours her plasma fibrinogen level had risen to 92 mg/100 ml, she was afebrile, and was feeling well. Seven days later the fibrinogen level was 300 mg/100 ml.

The Paul-Bunnell test was negative on three occasions during the patient's four weeks in hospital and again one month after her discharge. The Epstein-Barr virus antibody titre rose from 1/128 while in hospital to 1/2,048 six months later. It was not measured in between. There was no rise in antibody titre to cytomegalovirus. On discharge the blood picture was virtually normal with only 2%

of atypical mononuclear cells. Recovery was complicated by loss of power and sensation in the left hand owing to compression of the radial and median nerves at the elbow from haemorrhage round the joint.

Comment

The highly significant rise in EB virus antibody titre associated with the typical blood picture are enough proof that the defibrination was associated with infectious mononucleosis. The cause of the defibrination and pancytopenia is not clear. It was most probably due to low grade, diffuse intravascular coagulation, which would account for the thrombocytopenia and the low fibrinogen level. This must have begun before admission to hospital but manifested itself on the day the trephine was taken. Alternatively, bearing in mind the abnormal liver function tests, it could be speculated that the hypofibrinogenemia was a production defect. However, this is unlikely in view of the rapid response to heparin. The granulocytopenia and in part the thrombocytopenia might have been an expression of the effect of the virus on the bone marrow.

McKay and Margaretten (1967) reviewed case reports of the association between viral infections and afibrinogenemia. The arboviruses—for example, those causing the various haemorrhagic fevers which occur in the tropics, and the exanthematous viruses (varicella, variola, rubella)—are those which are most commonly implicated. Glandular fever was not included in their list, but Wintrobe (1967) mentions one patient who developed hypofibrinogenemia during the course of the disease. All authors agree that the treatment of choice is intravenous heparin.

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Complication of Methotrexate-maintained Remission in Lymphoblastic Leukaemia

R. G. RAWBONE, M. T. SHAW, J. G. JACKSON,
K. D. BAGSHAW

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As more patients with acute lymphoblastic leukaemia are being maintained in remission for longer periods methotrexate is being used in an intermittent regimen with increasing frequency. Bone marrow toxicity, oral ulceration, and diarr-

hoea are all well-known side effects of this drug, but more recently renal toxicity (Condit *et al.*, 1969) and chronic liver damage (Dahl *et al.*, 1971) have been reported during or after methotrexate therapy. Pulmonary complications in patients with acute lymphoblastic leukaemia in remission treated with intermittent methotrexate therapy have been reported by the Acute Leukaemia Group B (1969), Clarysse *et al.* (1969), and Robertson (1970). We report a case of an acute, fatal respiratory illness with the pathological features of granulomata in the lungs. This occurred in a girl with acute lymphoblastic leukaemia in remission during maintenance therapy with intermittent methotrexate.

Case Report

A 6-year-old girl was admitted to hospital on 3 April 1970 with a history of general malaise and spontaneous bruising for one week. Examination showed an ill girl with a fever of 38°C, enlarged cervical and inguinal lymph nodes, a spleen palpable 3 cm below the left costal margin, and generalized bruising and petechiae. Haemoglobin 10.8 g/100 ml, M.C.H.C. 34%, platelets 56,000/mm³ total leucocyte count 45,000/mm³ (76% blasts, 2% metamyelocytes, 17% lymphocytes, 5% neutrophils). The bone marrow was hyper-

Departments of Medical Oncology and Histopathology, Fulham Hospital, London W6 8RF

R. G. RAWBONE, M.B., B.S., Senior House Officer
M. T. SHAW, M.R.C.P., D.C.H., Senior Registrar
J. G. JACKSON, M.B., F.R.C.PATH., Consultant Pathologist
K. D. BAGSHAW, M.D., F.R.C.P., Consultant Physician

cellular and contained 54% lymphoblasts. Erythropoiesis, granulopoiesis, and megakaryocytopoiesis were greatly depressed. A diagnosis of acute lymphoblastic leukaemia was confirmed.

She was treated with an induction regimen of vincristine and prednisone followed by an intensive course of mercaptopurine, methotrexate with folinic acid rescue, and asparaginase lasting for 21 weeks. During this time she achieved haematological and clinical remission and from 14 September received oral methotrexate in a dose of 30 mg/m² twice a week as maintenance therapy.

She remained well and bone marrow aspiration on 6 November showed complete remission. When she attended the clinic on 1 January 1971 a small oral ulcer was noted. Haemoglobin 12.7 g/100 ml, M.C.H.C. 34.6% platelets 57,000/mm³, total leucocyte count 3,000/mm³ (30% neutrophils, 40% lymphocytes, 11% monocytes, 19% eosinophils). A chest radiograph was clear and nose and throat swabs grew normal flora. The methotrexate dosage was reduced to 20 mg/m² twice a week.

One week later she developed a dry cough, fever of 37.8°C, and a respiratory rate of 30/minute. Examination showed signs of a right basal pneumonia. Haemoglobin 13.1 g/100 ml, M.C.H.C. 34.6% platelets 248,000/mm³, total leucocyte count 3,300/mm³ (69% neutrophils, 31% lymphocytes). A chest radiograph showed widespread shadowing through both lung fields, most pronounced in the right lower zone, and her arterial oxygen tension was 70 mm Hg. The methotrexate therapy was stopped, 12 mg of folinic acid was administered intramuscularly, and daily treatment with ampicillin 1 g and cloxacillin 1 g by mouth was started.

Section of lung showing granulomatous formation and desquamated cells in alveoli (H. and E. $\times 48$.)

Daily nose and throat swabs grew normal flora only. Repeated laryngeal swabs showed no acid-fast bacilli on culture and repeated blood cultures were sterile after four weeks of incubation. Paul-Bunnell screening test was negative. Cold agglutinin titres were within normal limits. Serum complement fixation tests did not indicate evidence of infection with psittacosis/lymphogranuloma venereum, *Mycoplasma pneumoniae*, adenovirus, influenza A, B, or C, or herpes virus.

Sixty hours after admission her temperature rose to 39°C and her respiratory rate increased to 50/minute. Examination at this time showed widespread bronchial breathing over both sides of the chest and a radiograph showed further shadowing throughout both lung fields. Three megaunits of intravenous colistin was added to the daily antibiotic regimen. Her condition continued to deteriorate and she became cyanosed, with a respiratory rate of 140/minute. At this time her arterial oxygen tension was 56 mm Hg and she was given 100% continuous oxygen therapy on which her arterial

oxygen tension rose to 75 mm Hg. Intravenous fluids were given on account of a rising packed cell volume and blood urea with a low urinary output. Nine hours later she died.

Histological examination of tissues was restricted by the fact that only a limited necropsy was permitted. Some pieces of the right lung, liver, and kidney were obtained and no appreciable lesions were seen in the liver or kidney. The lung specimens, taken from the lower lobe, showed pronounced desquamation of lining cells of the alveoli and bronchioles. The alveoli were packed with these desquamated cells together with mixed inflammatory cells. Some areas showed granulomatous formation without caseation (see Fig.). Large mononuclear cells were present, some of which were in mitosis, and small numbers of eosinophils and multinucleated giant cells were also seen. Bacteriological and virological studies showed no evidence of infection and appropriate staining failed to show *Pneumocystis carinii*.

Comment

After prolonged induction therapy the patient had received methotrexate in a dose of 30 mg/m² twice weekly for 15 weeks before developing her terminal illness. The only abnormal finding one week before this event was a small oral ulcer and a transient mild eosinophilia.

The cause of the pneumonitis can be the subject only of speculation. The fact that no organism was found does not exclude an infective cause, especially as methotrexate is known to have an immunosuppressive action. Leukaemic infiltration of the lungs was unlikely as the bone marrow showed a picture of remission, but the presence of large mononuclear cells with frequent mitotic figures leaves the question open.

Clarysse *et al.* (1969) suggested that their cases might have been the result of an allergic reaction to methotrexate. The seven leukaemic patients in their series all recovered and a lung biopsy in one showed changes similar to those in the present case; the acute phase of the illness lasted from 10 to 14 days regardless or not of whether methotrexate therapy was continued, and no corticosteroid drugs were administered to these patients. The case described by Robertson (1970) improved during prednisone therapy. The Acute Leukaemia Group B (1969) reported three deaths from pulmonary complications of methotrexate and necropsy in one case showed infection with *Pn. carinii*. In contrast to these reports none of the 190 patients with trophoblastic tumours treated by us with much greater amounts of methotrexate for longer periods have shown such reactions.

It seems likely that the continued use of methotrexate therapy for the acute leukaemias will result in further instances of granulomatous pneumonitis. Though it is by no means certain that the process has an allergic aetiology it is important to establish whether corticosteroids have any place in its therapy.

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