ACUTE MONOCYTIC LEUKAEMIA WITH RESPONSE TO METHOTREXATE

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Acute monocytic leukaemia in childhood is much less common than the acute lymphoblastic and acute myeloblastic forms. It is also much more resistant to the conventional forms of therapy.

Among the 100 cases of acute leukaemia in childhood reviewed by Lightwood, Barrie and Butler (1960), five were diagnosed as acute monocytic: two of these received drug therapy, cortisone alone in one, and cortisone, aminopterin, mercaptopurine and nitrogen mustard in the other, and neither went into remission.

In a study of 50 consecutive cases of acute leukaemia in childhood, Thompson and Walker (1962) found only one case of acute monocytic leukaemia. The result of therapy is not mentioned separately but included with 11 cases of myeloid leukaemia. Six of this group were treated but only one showed some response.

Mahfoux and Amin (1961) reported on the beneficial effect of methotrexate in four cases of acute leukaemia. Two were said to be of acute monocytic type, but no clinical or haematological details were included.

The patient to be described had typical acute monocytic leukaemia of the Naegeli type. After failing to respond to prednisolone, mercaptopurine and repeated blood transfusions, she went into clinical and haematological remission on methotrexate (Fig. 1).

Case History

An 8-year-old girl was admitted to the Children's Hospital on January 22, 1963, with a six-week history of progressive lethargy, recurrent sore throat, swelling and bleeding of the gums, and pallor. On examination there was significant pallor of the skin and mucous membranes, gross hypertrophy of the gums (Fig. 2), and generalized slight lymphadenopathy. The liver was enlarged to one finger's breadth below the costal margin and the tip of the spleen was just palpable without inspiration.

A provisional diagnosis of acute leukaemia was made, possibly monocytic in view of the gum hypertrophy.

Haematological Investigations. Haemoglobin 5.6 g./100 ml.; white cell count 82,000 with monocytes 55%, lymphocytes 16%, polymorphs 15%, myelocytes 7%, metamyelocytes 5% (Fig. 3). Platelets 60,000.

The bone marrow contained 37% monocytes and 18% blast cells (Fig. 4). There was a significant reduction in erythroid elements (12%).

A diagnosis of acute monocytic leukaemia of the Naegeli type was made.

Course and Treatment. Therapy was commenced on the day of admission with prednisolone 15 mg. every six hours, and mercaptopurine 25 mg. twice daily. Her weight was 52 lb. (23.6 kg.). There was no sign of immediate response and her clinical condition deteriorated. By January 26 the haemoglobin was unchanged, but the white cells had risen to 150,000 per c.mm. with 60% monocytes and 3% blast cells (Fig. 1).

A transfusion of one pint of packed cells on January 27 raised the haemoglobin to 11.4 g. per 100 ml. The prednisolone dosage was reduced to 10 mg. every six hours, the mercaptopurine being continued as before.

By February 7 the haemoglobin had fallen to 5.2 g./100 ml. and the white cell count had risen to 190,000/c.mm., with 88% monocytes. After a further transfusion of one pint of packed cells on February 8, the haemoglobin rose to 10.2 g./100 ml., but by February 13 it had fallen to 7.8 g./100 ml.

Clinically there was no sign of improvement and she looked ill and was lethargic, listless and irritable. She developed extensive purpura over both legs and a small subconjunctival haemorrhage. Her face was Cushingoid from the steroid therapy, indicating adequate absorption.

Methotrexate, 4 mg. daily, was added on February 14. Two days later her haemoglobin was 5.9 g./100 ml. and the white cell count 146,000 with 74% monocytes and 2% blast cells. A further transfusion was given on February 17. Although her haemoglobin dropped from 8.7 g. on February 18 to 5.6 g. on February 25, there was a noticeable clinical improvement during this time. The white cell count fell sharply to 53,000 on February 18 and to 23,000 on February 25, with a drop in monocytes to 28%. The gum hypertrophy which was unchanged on February 14 had completely subsided by February 26.

When the white cell count dropped below 10,000

FIG. 1.—Haematological data and therapy.

FIG. 2.—Hypertrophy of the gums.

per c.mm. the methotrexate was intermittently stopped or adjusted according to the cell count. On February 28, for the first time, there were 8 nucleated red cells per 200 white cells.

The haemoglobin level remained steady at between 5 and 5.5 g./100 ml. and her clinical condition continued to improve. She was given another transfusion on March 13, after which the haemoglobin rose to 9.9 g.

Mercaptopurine was stopped on March 6. Prednisolone was gradually tapered off, under cover of a weekly injection of 40 units of corticotrophin and was discontinued on April 5.

She had an acute respiratory infection from March 12-16, which responded well to penicillin in addition to the maintenance dose of tetracycline she was already receiving. The prednisolone was temporarily increased during this period.

She was discharged on April 5 on methotrexate 2.5 mg. daily. Her haemoglobin was 8.4 g./100 ml., white cell count 4,000 with polymorphs 60%, lymphocytes 31%, monocytes 9% and 3 nucleated red cells per 100 white cells.

FIG. 3.—Peripheral blood. Numerous monocytic cells. (Leishman stain $\times 366$.)

At out-patient follow-up she continued well and was able to return to school. Her haemoglobin varied from 8 to 10 g./100 ml., and white cell count from 2,500 to 4,500.

On June 20, after a week's holiday by the sea, she was not so well. Her complexion was sallow, her haemoglobin had dropped to 7 g./100 ml. and the white cells to 2,200 with lymphocytes 52%, polymorphs 34%, monocytes 11% and blast cells 3%. There were 4 nucleated red cells per 100 white cells. The methotrexate was increased to 2.5 mg. twice daily.

By June 24 she was worse. Haemoglobin had dropped to 5.8 g./100 ml., white cell count was 3,000 with 3% blast cells. She had numerous ulcers in her mouth. By June 27 her clinical condition had deteriorated considerably, although her blood picture was unchanged. She also developed frequent loose stools.

A bone marrow biopsy showed a hypercellular marrow with a preponderance of blast cells (51%). The picture was more primitive than at the time of the first admission.

No pathogens were cultured from the stools. The diarrhoea and oral ulcers were thought to be secondary to the methotrexate. However, in view of the florid relapse in the bone marrow picture, and the presence of nucleated red cells in the peripheral blood, it was thought that the only hope lay in increasing rather than stopping the methotrexate, and the dose was raised to 2.5 mg. every six hours.

A transfusion of packed cells raised the haemoglobin to 9.0 g./100 ml. Although the white cell count remained steady, her clinical condition steadily deteriorated. In spite of the reasonable haemoglobin level she was listless and lethargic as well as irritable and uncooperative, a state frequently seen in children with relapse of leukaemia.

There was no lymphadenopathy, hepatic or splenic enlargement, or gum hypertrophy. Despite intra-

FIG. 4. Bone marrow: preponderance of monocytic cells. (Leishman stain $\times 366$.)

venous methotrexate she declined rapidly and died on July 3.

Discussion

The clinical and haematological findings in this patient are in keeping with a diagnosis of acute monocytic leukaemia. Gum hypertrophy is more common in acute monocytic leukaemia than in the other forms. Boggs, Wintrobe and Cartwright (1962) observed gum hypertrophy in 34% of their patients with monocytic leukaemia, in contrast to 8% of those with myeloblastic and 2% of those with lymphoblastic leukaemia. Watkins and Hall (1940) suggested that gum hypertrophy was limited to the Naegeli type of acute monocytic leukaemia.

The presence of myelocytes and metamyelocytes in the peripheral blood is consistent with the Naegeli type, in contrast to the Schilling type of acute monocytic leukaemia where the predominant cell resembles a histiocyte.

Boggs *et al.* (1962) define a remission as the 'return of the blood and physical abnormalities to normal in an asymptomatic patient'. They do not consider it necessary to document a bone marrow remission as an additional criterion. By these criteria methotrexate produced a remission in our patient. The abnormal clinical signs resolved and the patient was asymptomatic. The blood picture was normal apart from a low haemoglobin and platelet level. However, these showed no evidence of dropping from their steady levels.

Acute monocytic leukaemia may have a rapidly downhill course. One patient of Lightwood *et al.* (1960), with only a week's history of symptoms,

died within two days of admission. On the other hand, there are a number of cases on record who survived up to three or four months on supportive therapy. However, they did not go into clinical or haematological remission.

In view of the rapid remission produced in this patient by methotrexate, this drug may be the therapy of choice in acute monocytic leukaemia and should be administered in the first instance. There are no cases on record of remission produced in acute monocytic leukaemia in childhood by steroid or mercaptopurine therapy, so that there is no justification for an initial trial of the latter drugs.

Summary

Methotrexate produced a clinical and haematological remission of acute monocytic leukaemia

in an 8-year-old girl. The remission lasted four months and the total survival from the onset of symptoms was seven months.

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