Prolonged remission in Di Guglielmo's syndrome

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Summary

A case is reported of a 12-year-old boy with Di Guglielmo's syndrome who achieved complete remission for over three years before developing a central nervous system relapse. The poor results of treatment in this disease are reviewed and the arguments for routine central nervous system prophylaxis discussed.

KEY WORDS: erythroleukaemia, CNS prophylaxis.

Introduction

Di Guglielmo's syndrome or erythroleukaemia is an uncommon form of acute non-lymphocytic leukaemia. While the syndrome accounts for up to 10% of adult acute leukaemias, it represents only 1% of all cases of leukaemia in childhood (Pierce *et al.*, 1969). Until recently Di Guglielmo's syndrome was thought to be refractory to chemotherapy in most instances. A case is reported of a 12-year-old boy who achieved complete remission for over three years before developing central nervous system (CNS) relapse.

Case report

A previously healthy 12-year-old boy presented with a two week history of progressive pallor and tiredness. On examination there was no lymphadenopathy or hepatosplenomegaly. Peripheral blood examination showed a haemoglobin 3.9 g/dl, platelets 120×10^9 /litre, total white cell (WBC) count of 2.6×10^9 /litre (neutrophils 38%, lymphocytes 55%, blasts 7%) and five nucleated red cells per 100 WBC. The blast cells had primitive nuclei with abundant, deeply basophilic cytoplasm almost entirely occupied by large round vacuoles. The bone marrow aspirate showed 31% of cells to be erythroblasts displaying grossly megaloblastic maturation, some having bi-

zarre clover-leaf nuclei, and diffuse PAS positive cytoplasm. There were many ring sideroblasts.

Fifty-six percent of cells were blast cells, identical to those seen in the peripheral blood (Fig. 1). These were PAS negative and Sudan Black positive. Auer rods were absent. Serum B_{12} and folate were normal. These features have previously been described as characteristic of Di Guglielmo's syndrome (Damaskeshek, 1969; Scott, Ellison and Ley, 1964; Sondergaard-Petersen, 1975a). The appearance of the vacuolated blast cells is unusual but has been previously reported in erythroleukaemia (Miura, 1976).

The patient was commenced on chemotherapy with thioguanine, daunorubicin, cytosine arabinoside and prednisolone, as described by Spiers (1972). Chemotherapy was repeated at two weekly intervals for six courses; adriamycin was then substituted for daunorubicin and the treatment interval extended to 3 weeks. Complete remission with an entirely normal bone marrow was achieved at 23 weeks. After fourteen courses, chemotherapy was changed to maintenance regime of cytosine arabinoside and thioguanine for 5 days, repeated every 3 weeks. At 36 weeks lumbar puncture was performed. The cerebrospinal fluid (CSF) was clear with no cells. Six intrathecal injections of cytosine arabinoside 50 mg were given at three weekly intervals as CNS prophylaxis. All chemotherapy was discontinued 2 years after diagnosis, the patient being well and in complete remission.

Fourteen months after ceasing chemotherapy he presented with headaches, vomiting and two convulsions. His CSF now contained blast cells, identical to those in the marrow at diagnosis (Fig. 2). The CNS relapse has been successfully treated with craniospinal irradiation and further intrathecal chemotherapy using cytosine arabinoside and methotrexate. He was also given a short course of systemic chemotherapy. His CSF remains cell-free one year later. His bone marrow has remained in complete remission throughout.

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FIG. 1. Two fields from the bone marrow at presentation (Stain—May-Grunwald Giemsa) showing vacuolated leukaemic blast cells and dyserythropoietic erythroblasts. Note erythroblast with three nuclei.

Discussion

While newer chemotherapy regimes have improved survival in most categories of acute non-lymphocytic leukaemia (ANLL) over the past dec-

ade, erythroleukaemia has remained relatively refractory to treatment. In a series of 17 cases of adult erythroleukaemia reported in 1975 the longest survivor died at 20 months (Sondergaard-Petersen,

FIG. 2. Cyto-centrifuge preparation of cerebrospinal fluid showing leukaemic blast cells.

1975a). A more recent series of 6 treated with standard ANLL protocols had a median survival of only 5.6 months (Mertelsmann *et al.*, 1980). There are few reports of treatment response in children with erythroleukaemia (Choi and Simone, 1976; Ragab *et al.*, 1975). In a series of 171 children with ANLL reported by Choi and Simone (1976), three had erythroleukaemia, only one of whom achieved remission with chemotherapy. Their results show that for all categories of ANLL in children, the results of remission induction and duration were very similar to those reported for adults.

In ANLL central nervous system involvement is less common than in acute lymphoblastic leukaemia (ALL) and CNS prophylaxis during the initial treatment period is not considered mandatory. While in adults there is evidence that the type of acute leukaemia may determine the risk of CNS involvement (Law and Blom, 1977), the difference in frequency of CNS relapse between ALL and ANLL has been shown to correlate most strongly with the different durations of survival for the two diseases, regardless of the age of the patient (Wolk *et al.*, 1974; Evans, Gilbert and Zandstra, 1970). The overall frequency of CNS leukaemia in children who have not been given CNS prophylaxis is 56–83% for ALL (Evans *et al.*, 1970; Pinkel *et al.*, 1971) and 25–38% for all categories of ANLL (Evans *et al.*, 1970; Choi and Simone, 1976). However, Evans *et al.* (1970) found that over the first twelve months from diagnosis the

monthly rates of CNS leukaemia in children with ALL and ANLL were similar.

The role of CNS prophylaxis in ANLL remains controversial. Preventive cranio-spinal irradiation reduces the incidence of meningeal relapse. However, the overall survival has not been improved, possibly because irradiation reduces marrow reserve and severely limits subsequent chemotherapy dosages (Choi and Simone, 1976). In our patient the occurrence of late meningeal leukaemia in the absence of haematological relapse suggests that his initial CNS prophylaxis with intrathecal chemotherapy alone was inadequate to eradicate potentially curable cryptic meningeal leukaemia present at the time of diagnosis.

The achievement of four years of continuous haematological remission in our patient suggests that erythroleukaemia, in children at least, may be potentially curable by conventional ANLL chemotherapy, coupled with more effective CNS prophylaxis using combined cranial irradiation and intrathecal chemotherapy.

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