CHRONIC MYELOID LEUKAEMIA IN CHILDREN

By Tan Kwang Hoh, M.B., B.S., M.R.C.P.E., D.C.H.

and

Tan Sim Keng, M.B., B.S.
(Paediatric Unit (East), General Hospital, Singapore)

INTRODUCTION

Chronic leukaemia is not common in infancy and childhood. Whilst chronic myelocytic leukaemia had been reported on many occasions, chronic lymphocytic leukaemia is almost never seen in childhood. Eisenberg and Wallerstein found 30 cases in the literature up to 1934, and reports of about another 100 cases have appeared since then. Most of the authors also have reported on the relative incidence of the condition and have found it to be between 2 and 5 per cent of all cases of childhood leukaemia (*e.g.* Cooke 1953; Barret, Conrad and Crosby 1960; Lightwood, Barrie and Butler 1960; Bernard, Seligmann and Acar 1962; Reisman and Trujillo 1963).

Four cases of chronic myeloid leukaemia have been recognised in the Paediatric Unit alone within the last 2½ years, two of whom were diagnosed within the last 6 months.

Several authors have noted that the disease seen in infants and young children differs in certain respects from that of older children, in whom it usually closely resembles chronic myeloid leukaemia of adults. This concept of separating the disease into 2 distinct clinical forms of leukaemia has recently received strong support from those workers who have gone into more detailed studies of this condition.

We are presenting 4 cases of this disease condition and comparing their basic clinical haematological differences.

CASE REPORTS

One of the 4 cases is still alive at the moment. The case histories, management and clinical progress of the 4 patients are detailed below:

Case 1

S.K.C., a 10-month-old female Chinese was admitted on 30th April 1967 with the history of 2 months' ill health on and off and increasing abdominal distension. Clinical examination showed an emaciated child with pallor, marked hepatosplenomegaly, few confluent ecchymosis on the lower limbs and small discrete lymph glands palpable in the cervical, axillary and inguinal regions.

The haematological findings are illustrated in Table I and II. Serum bilirubin was 0·9 mgm % and oxyhaemoglobin and methaemalbumin were absent in the blood. Haemoglobin electrophoresis showed the presence of Hb A and F (4%).

Examination of the bone marrow revealed a hyperplasia of the myeloid series with increase of promyelocytes, myelocytes and metamyelocytes. No blast cells were seen.

Mantoux testing, chest X-rays and repeated urine examinations and cultures were carried out but did not reveal any significant findings.

The child was treated with adreno-cortical steroids, blood transfusion and 6-mercaptopurine but he rapidly deteriorated and died 15 days after admission.

Case 2

C.K.B., a 3½-month-old female Chinese was admitted on 25th May 1967 with an attack of bronchopneumonia and the leukaemic state was discovered following routine examination. The last child of a family of 9 children, she had apparently been well previously.

Clinical examination showed a pale child with hepatosplenomegaly of 3 and 2 fingers breadth below the costal margins respectively. Small discrete glands were palpable in the sub-occipital, cervical and inguinal regions. There were few ecchymosis noted suprapubically. No facial rash was seen. The haematological findings are presented in Tables I and II.

The haemoglobin electrophoresis showed presence of Hb A and F (9·4%).

The bone marrow showed hyperplasia of white cell series with predominance of myelocytes. There was no increase in the blast cells. The erythropoiesis was normoblastic but reduced. There were few megakaryocytes. The leucocyte alkaline phosphatase score was 26 (normal 92).

The infant was treated with Inj. Penicillin and Inj. Streptomycin for her bronchopneumonia. The temperature subsided and she recovered. Two weeks after admission, the blood picture was almost similar to that taken on admission and the repeated bone marrow aspiration again showed hyperplasia of myelocyte and metamyelocyte series.

The patient was treated as a case of chronic myeloid leukaemia with Prednisolone, Myeleran, blood transfusion and later switched to 6-mercaptopurine but the course was one of gradual downhill and expired 6 weeks after admission.

Case 3

W.M., a 6-year-old female Chinese was admitted with history of swellings in the neck, axillary and inguinal regions with loss of appetite and associated weight loss over the last 2 months. The lumps in the neck were noted to have increase in size over the last 2 months.

Clinical examination revealed a pale, toxic looking child with marked generalised lymphadenopathy in the cervical, axillary and groin regions (see Figs. 1, 2, 3, 4.). She was thought to be suffering from Hodgkin's disease. The blood picture was more suggestive of chronic myeloid leukaemia (see Tables I and II).

Bone marrow examination showed predominance of promyelocytes, myelocytes and metamyelocytes with very few megakaryocytes.

The child's condition deteriorated very rapidly and died 4 days after admission before any specific therapy could be instituted.

An autopsy carried out confirmed diagnosis of chronic myeloid leukaemia with evidence of hepatosplenomegaly and histology showing gross infiltration of myeloid cells series with predominance of myelocytes and metamylocytes into lymph nodes, the liver especially in the portal tracts and into the splenic pulp.

Case 4

A.H. bin O., a 9½-year-old male Malay who presented with 3 months' history of weight loss, pallor and increasing abdominal mass over the last month. Clinical examination revealed a pale looking child with hepatosplenomegaly. The spleen was palpable 4 finger breadths below the costal margin. Small lymph glands were also palpable in the neck, axillae and groin and there was sternal tenderness.

The haematological findings were shown in Tables I and II.

TABLE I

Case	Name	Hb	Ret.	Platelet	B.S.R.	Hb Electrophoresis
1.	S.K.C.	6·8 Gm%	5%	30,000/c.mm.	46 mm	Hb A & F (4%)
2.	C.K.B.	10·0 Gm%	-	50,000/c.mm.	52 mm	Hb A & F (9·4%)
3.	W.M.	30 Gm%	< 1%	15,000/c.mm.	110 mm	-
4.	A.H.	48 Gm%	< 1%	580,000/c.mm.	80 mm	-

TABLE II

Case	Name	W.B.C.	Myelocyte	Metamyelocyte
1.	S.K.C.	20,000/c.mm.	20 %	18 %
2.	C.K.B.	100,000/c.mm.	15 %	20 %
3.	W.M.	181,000/c.mm.	24 %	22 %
4.	A.H.	100,000/c.mm.	-	-

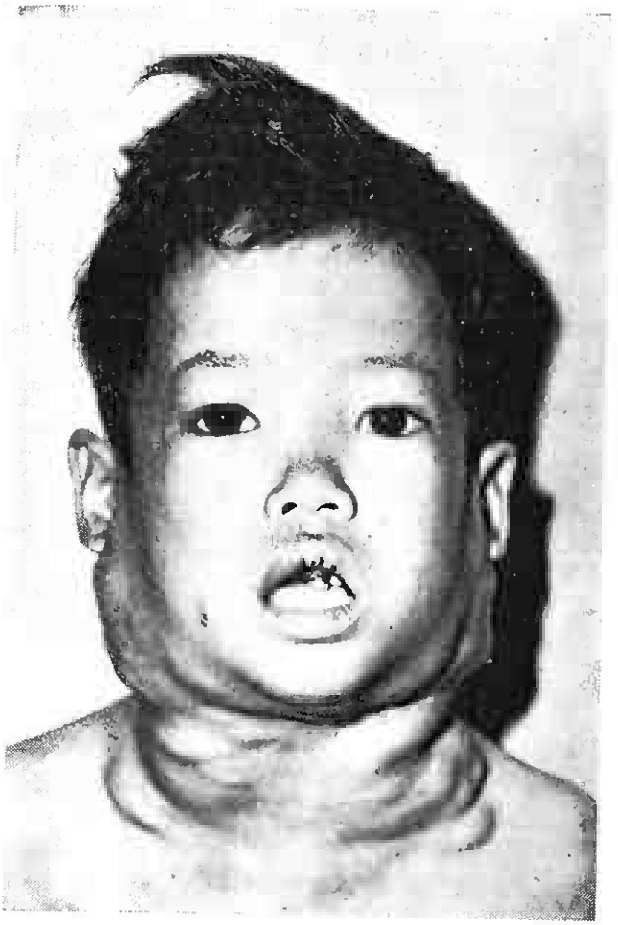

Fig. 1.

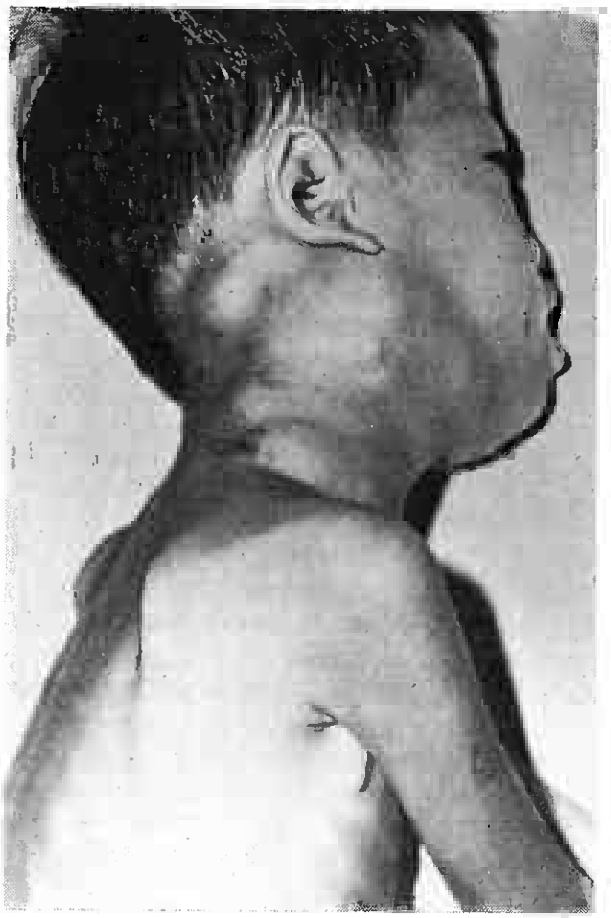

Fig. 3.

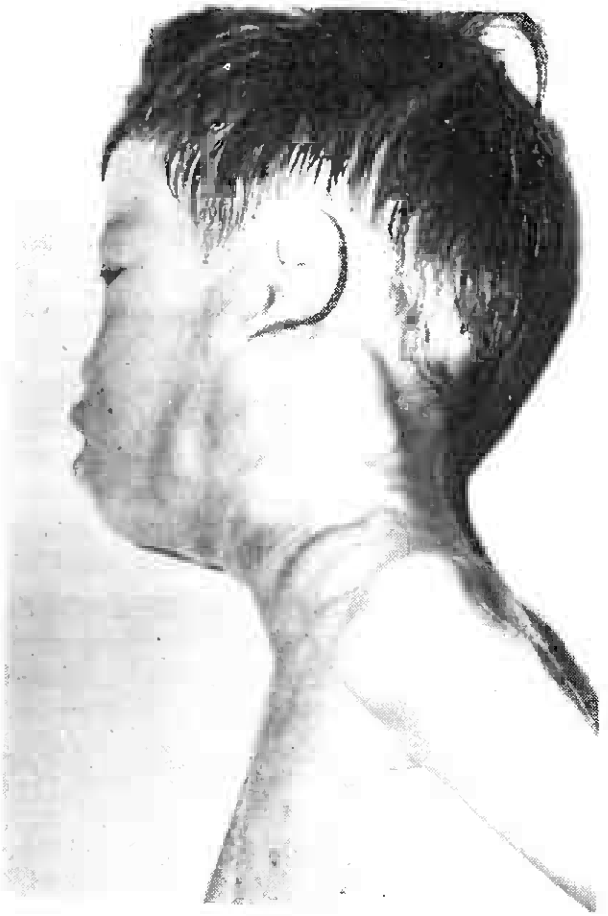

Fig. 2.

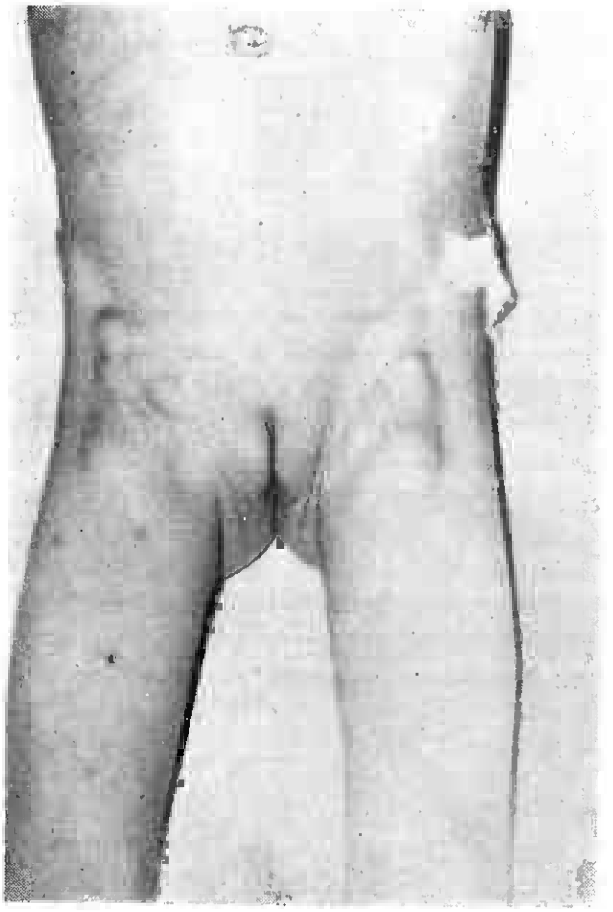

Fig. 4.

The peripheral blood film revealed a hyperleucocytosis with predominance of myelocytes and metamyelocytes. Bone marrow examination showed myeloid hyperplasia with predominance of myelocytes. No blast cells or megakaryocytes were seen and erythropoiesis was depressed, being normoblastic in type. The patient was started on Busulphan in October 1965 and had a good response to the treatment. He is still alive progressing satisfactorily with barely any hepatosplenomegaly and normal blood counts.

DISCUSSION

Chronic myeloid leukaemia with its characteristic blood picture and a similar pattern in the bone marrow is seldom difficult to diagnose. The onset of the disease however is often difficult to designate because of its vague symptomology. Attention is usually drawn to the underlying haematologic disorder following a routine blood count for low grade fever, weight loss, anorexia or hepatosplenomegaly noted in an ordinary clinical examination. The high white cell count with shift to the left and the presence of few metamyelocytes and myelocytes suggest a leukaemoid reaction at first. In chronic myeloid leukaemia the leucocyte alkaline phosphatase is low.

The chronic myeloid leukaemia in adults is more familiar. It bears certain specific features for it to be defined: the chronic course of the disease, the extremely high white cell count, the big spleen and liver, the hyperleucocytosis of mainly myelocytic and metamyelocytic type and a similar pattern in the bone marrow with blast cells comprising no more than 3%, the normal or raised platelet counts in the early stage of the disease and the presence of the Ph' chromosome —consensusly opined to a small member of chromosome pair 21 with deleted portions of its long arms.

Several authors have noted that chronic myeloid leukaemia in infants differs in certain aspects from that in older children in whom it usually resembles chronic myelocytic leukaemia in adults. It is our purpose here to present 4 such cases and review the basic clinical, haematological, cytogenetic differences and the therapeutic response of these 2 types of chronic myeloid leukaemia. With our small number of cases we have to rely predominantly on studies by overseas group for reviewing the main features.

The infantile type with its onset mainly in the infantile age group has less marked splenomegaly than the adult type but is characterised by greater lymph nodes enlargement which may go on to suppuration. Hardisty et al (1964) noted a facial rash as one of the presenting symptoms in all of their 4 cases of juvenile type studied but this was never seen in the adult type. No rashes were noted in our 4 cases. The rash described ranged from a simple erythematous rash on the cheeks, to atypical eczematous rash resembling xanthomata, eczematous rash with weeping to a papillar rash with butterfly distribution on the face.

It is characterised by thrombocytopenia early in course of disease with associated bleeding tendency. The total leucocyte count is usually not as high as in adult type, measuring in terms of tens of thousands rather than hundreds of thousands. The bone marrow patterns are essentially the same except that there may be higher proportion of lymphocytes and relatively few megakaryocytes in the juvenile type.

The red cell precursors were found in the blood at some stage of the disease but this feature was somewhat more pronounced in the infantile type and that large numbers of normoblasts appeared in the peripheral blood towards the end of the disease quite uncorrelated to the anaemia or steroid therapy.

The clinical course tends to have an acute and toxic onset with a much shorter course in spite of the chronic leukaemic cell type.

The therapeutic response of the juvenile type tends to be resistant to the usual agents as Busulphan and 6-mercaptopurine which are known to give impressive remissions in the adult type. If a remission is likely, it is more probable with 6-mercaptopurine than with Myeleran. Reisman and Trujillo (1963) claimed impressive remission in 3 of their 4 cases of juvenile type with 6-mercaptopurine.

The most striking difference between the 2 types concerned the presence or absence of Ph' chromosome and the persistence of Hb-F production. The Ph' chromosome had been found to be present in the adult type.

Hardisty et al (1964) in Chromosomal Studies found that in the infantile type there was structural anomaly in one of the small actocentric chromosomes which appears to consist of a condensation of chromatin on the long arms rather than loss of material as in the Ph' chromosomes. This was isolated in only 2 cases and may well be significant.

In both forms of chronic myeloid leukaemia there is over-production of neutrophils with low alkaline phosphatase activity and it might well

be that this was determined by loss of genetic material from autosome 21 in the adult type and by inactivation of the same genes associated with structural alternation of the chromosome in the infantile type.

The relation of chromosome 21 to leukocyte formation or function is evident by the leukocyte alkaline phosphatase activity which is always low in chronic myeloid leukaemia but high in Mongolism with Trisomy 21 (Ross et al 1963, Bloom, Gerald, Diamond 1966).

The foetal Hb averages 40-50% in the infantile form while it averages 2-7% in the adult type (Hardisty, Speed, Till 1964). Beaver, Ellis and White (1960) found Hb-F levels between 15 and about 50 per cent throughout the course of the disease in each of 2 children with this type of leukaemia in whom the diagnosis was made during the fourth year of life. Acute leukaemia in childhood is commonly associated with a moderate increase of Hb-F but it has not been observed above 10% (Smith, C.H. 1966).

The continued formation of large amounts of Hb-F has two possibilities: It can be an acquired imbalance in globin-chain synthesis secondary to the leukaemic process with defective Beta chain synthesis and compensatory reactivation of Gamma chains. (Beaven, Stevens, Dance and White 1963) described a case of Hb-H formation in leukaemia. The other possibility that remains is that this type of leukaemia may well be a congenital disorder characterised by continued Hb-F production after birth and leading to full expression in the leukaemic state months or years later. This is supported by fact that majority of cases of congenital leukaemia are granulocytic in type in contrast to the predominance of acute lymphoblastic leukaemia in childhood. One may go so far as to postulate that this type of granulocytic leukaemia is essentially a congenital disorder perhaps due to a structural and functional abnormality in autosome 21 of an embryonic haemopoietic cell and requiring a variable time for development of its full effect including the Ph' chromosomes.

Among the 4 cases described in this paper, 3 of them Cases 1, 2, and 3, seemed to fall into the infantile type and Case 4 conforms more to the adult type. Clinical evidence of ecchymosis and petechae were seen in Cases 1 and 2 and thrombocytopenia was seen in all the first 3 cases. Although lymph glands were palpable in all the 4 cases, the lymph gland enlargement in Case 3 was outstanding as it was even larger than some of the lymphadenopathy of acute leukaemia that we had seen. The only significant clinical finding in Case 4 was pallor and a very large spleen.

Haemoglobin electrophoresis was done in Cases 1 and 2 and unlike those reported by other workers (Hardisty et al 1964), the result was not high.

The clinical course of the 3 infantile type, *viz.* Cases 1, 2 and 3 was short and fatal although steroid, Busulphan and 6-mercaptopurine had been tried on 2 of them. Whereas Case 4 which resembles the adult type responded to therapy and is still alive and well 2 years after treatment was first started.

SUMMARY

Four cases of chronic myeloid leukaemia in children were presented, 3 of them were of the infantile type and one of the adult type. The 3 cases of the infantile type occurred in the younger age group and had clinical manifestation such as purpura and enlarged lymph glands which were different from the case that resembled the adult type. The clinical course of the infantile type of chronic myeloid leukaemia was also short and fatal.

The clinical, haematological, cytogenetic differences and the therapeutic response of these 2 types of chronic myeloid leukaemia were briefly discussed.

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