A Case of Prolonged Thrombocytopenia in Childhood Terminating in Leukemic Reticuloendotheliosis

By COLIN A. S. GALLOWAY AND ELIZABETH M. INNES

THE ONSET of acute leukemia is usually considered to have occurred over a fairly short period preceding the development of the diagnostic clinical and hematologic findings. It is rare to elicit a history of any previous blood disorder which could be considered to be a possible related etiologic factor. In recent years, attention has been drawn to what has been termed a preleukemic state in occasional cases in which evidence of disordered hematopoiesis has been recorded for considerable periods before the final diagnosis of acute leukemia was established, but nearly all such reports have related to adults. It would, therefore, seem worthwhile to record in some detail the unique case of a boy who, at the age of 2 years, had severe and persistent thrombocytopenia, unaccompanied by any other obvious hematologic abnormality, until at the age of 7½ years the blood picture became that of a leukoerythroblastic anemia merging after 18 months into a terminal acute leukemia of the reticuloendotheliosis variety. The outstanding features of interest would appear to be the duration of the preleukemic phase manifested by thrombocytopenia alone and the extreme rarity of reticuloendotheliosis in childhood.

CASE HISTORY

The patient, B. Q., was born 6 weeks prematurely on 10/5/54, the only child of healthy unrelated parents. The birth weight was 4½ lbs. but early progress was entirely normal. His mother developed acute lymphatic leukaemia 6 months after the birth, and died 2 months later. No other family history of leukemia was elicited.

The patient was first admitted to the Royal Hospital for Sick Children in Edinburgh on 19/5/56 with a 2-week history of pyrexia, sore throat and skin rash which had not responded to penicillin. Examination revealed an inflamed throat, a temperature of 103.2 F., a macular rash on the thighs, forearms and dorsum of the hands, and a petechial rash on the abdomen, neck and buttocks. There was no hepatosplenomegaly or abnormal lymphadenopathy. Blood examination showed: Hb. 82 per cent (11.9 Gm. per cent); white count 23,000 per cu. mm. (normal differential); platelets 26,000 per cu. mm.; bleeding time (Ivy) 13½ minutes; Hess test positive. Marrow specimens consisted largely of marrow blood but appeared normal, apart from an absence of megakaryocytes. No platelet agglutinins could be demonstrated.

The pyrexial illness subsided rapidly, but the thrombocytopenia persisted and was unaffected by corticosteroid therapy (fig. 1). Over the next 7 years the patient remained well, apart from a tendency to easy bruising, occasional epistaxes and purpuric eruptions. The thrombocytopenia continued (table 1,A), but still there was no lymphadenopathy or splenomegaly and the peripheral blood picture remained otherwise normal. In December 1961, normoblasts and occasional myelocytes appeared in the peripheral blood.
and thereafter remained a constant finding. In March 1963, the spleen was first noted to be enlarged. By this time, the epistaxes had tended to become more severe, so that in May 1963 admission to the hospital was necessitated, and the blood picture was noted to be frankly leukoerythroblastic (table 1, B). A normochromic anemia was present and the red cells showed marked aniso- and poikilocytosis with many tear drop forms. Two attempts to aspirate marrow failed, and in view of this difficulty in conjunction with the blood picture and the splenomegaly a tentative diagnosis of myelofibrosis was made. A surgical biopsy of the right iliac crest showed no increase in bony trabeculation or fibrosis, though there was marked infiltration of the marrow with large primitive cells, thought to be reticulum cells, together with an increase in reticulin material (fig. 2). No megakaryocytes were seen. Chromosome studies at this time revealed no abnormality and the leukocyte alkaline phosphatase was within normal limits. The anemia was corrected by blood transfusion and antibiotics were given in view of local infection in relation to the bone biopsy site.

Considerable weight loss occurred and marked hepatosplenomegaly developed in association with a persistent anemia requiring repeated blood transfusions (fig. 1). No lymphadenopathy was detected. Small numbers of reticulum cells first appeared in the peripheral blood in July 1963 and from August onward the leukocyte count rose to 30,000–120,000 per cu. mm., the majority of the cells being large and primitive, some being typical reticulum cells and some resembling early forms of monocyte or histiocyte (table 1, C; fig. 3).

The progress of this leukemic phase was unchecked by a course of prednisilone in a dose of 40 mg. daily for 2 months, and by two courses of splenic irradiation of 60 and 1,000 rads, respectively, given at an interval of 2 months (fig. 1). Death occurred on 8/12/63.

The salient features at autopsy were marked hepatosplenomegaly and the absence of enlarged lymph nodes. Microscopically diffuse infiltration by large primitive cells was found throughout the spleen, liver, bone marrow and lymph nodes, and to a lesser extent in other organs. The liver was otherwise normal and there was no evidence of extraduillary hematopoiesis; the spleen on the other hand showed a considerable degree of fibrosis probably due to the radiotherapy.

**Discussion**

This case presents three features which are of particular interest and which may or may not be interrelated. These are: the mother's leukemia,
The prolonged period of thrombocytopenia and the terminal leukemic reticuloendotheliosis.

The Question of Familial Leukemia

The role of familial influences in the etiology of leukemia is a debatable subject. Videbaek in a study of pedigrees of 209 patients with leukemia concluded that the familial incidence of the disease is at least 8.1 per cent.
Table 1.—Representative Peripheral Blood Pictures

<table>
<thead>
<tr>
<th>Date</th>
<th>Stage</th>
<th>Hb%</th>
<th>Platelets per cu. mm.</th>
<th>White cells per cu. mm.</th>
<th>N%</th>
<th>L%</th>
<th>M%</th>
<th>E%</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>A 7/12/57</td>
<td>Thrombocytopenic</td>
<td>89</td>
<td>53,000</td>
<td></td>
<td>89</td>
<td>53</td>
<td>2</td>
<td>6</td>
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<td></td>
<td></td>
<td>(12.9 Gm.)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>B 16/5/63</td>
<td>Leukoerythroblastic</td>
<td>45</td>
<td>27,000</td>
<td></td>
<td>45</td>
<td>32</td>
<td>1</td>
<td></td>
<td>Normoblasts 46/100 WBC</td>
</tr>
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<td></td>
<td></td>
<td>(6.6 Gm.)</td>
<td></td>
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<td></td>
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<td></td>
<td>Reticulocyte 13%</td>
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<td></td>
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<td></td>
<td></td>
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<td>Metamyelocytes 15%</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Myelocytes 7%</td>
</tr>
<tr>
<td>C 2/12/63</td>
<td>Leukemic</td>
<td>21</td>
<td>50,000</td>
<td></td>
<td>15</td>
<td></td>
<td></td>
<td></td>
<td>Reticulum 10%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(4.5 Gm.)</td>
<td></td>
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<td></td>
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<td></td>
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<td>Primitive mononuclear cells 75%</td>
</tr>
</tbody>
</table>

and there are a number of reports in the literature of leukemia occurring in several members of a family. However, although many instances have been recorded in which a leukemic mother has given birth to a normal baby, in only 1 reported case has such a mother given birth to a baby who developed leukemia. It is interesting to note that this baby was apparently normal at birth, and acute lymphatic leukemia later became manifest at the age of 9 months. In the present case the patient’s mother did not develop overt leukemia until 6 months after his birth, and it is a matter for speculation as to whether some hereditary influence may have been involved in the subsequent development of hematologic abnormalities in the child. In Videbaek’s series there were many instances in which, as in the present case, the nature of the leukemia varied within the same family.

The Prolonged Thrombocytopenia

Thrombocytopenia in childhood is most commonly of the idiopathic variety, and the majority of cases run a short acute course with spontaneous recovery within a matter of weeks. However, chronic idiopathic thrombocytopenia may occur in which remarkably low platelet counts persist over a period of years associated with few clinical signs. The marrow in such cases contains normal or increased numbers of megakaryocytes, whereas in the present case megakaryocytes were absent from the marrow. It seems possible, therefore, that this child may have had a congenital hypoplastic type of thrombocytopenia which was not discovered until his admission to hospital with an acute infection at the age of 2 years. The relationship of this hematologic abnormality to the subsequent development of leukemia is by no means clear, but it may be that it represents simply an early phase of the same condition. Occasionally, in cases of leukemia there is a clinically apparent preleukemic phase characterized by depression of one or more elements in the peripheral blood associated with hyperplasia and maturation arrest in the bone marrow. This stage may last for a matter of months, or more rarely years, before frank leukemia supervenes. Meacham and Weisberger have reported 10 such cases, 6 of whom developed acute myeloid or...
monocytic leukemia after a preleukemic phase averaging 16 months. This series appears to include the only other report of a preleukemic state occurring in a child. Another series of 12 cases, all adult, was reported by Block et al.\textsuperscript{10} and 11 of these subsequently developed either acute myeloid or stem cell leukemia. No definite diagnosis had been reached in the remaining case which, nevertheless, appears to be the only example in the literature of a preleukemic phase being initiated by an isolated thrombocytopenia. The longest preleukemic state in this series is 27 months. These two reports suggest that the average duration of the preleukemic phase is somewhat less than 2 years, so that the $5\frac{1}{2}$ years in the present case is unusually long. Williams,\textsuperscript{11} however, reported on an adult male who showed the features of aplastic anemia intermittently over a period of $8\frac{1}{2}$ years before developing acute myeloid leukemia, and Firkin et al.\textsuperscript{12} and Collins et al.\textsuperscript{13} have reported cases demonstrating preleukemic disorders of 10 and 12 years, respectively.

\textit{The Phase of Leukemic Reticuloendotheliosis}

Leukemic reticuloendotheliosis is now recognized by most hematologists as a separate entity, but it constitutes a rare variety of leukemia and is particularly uncommon in childhood. The condition may occur in either an acute form (when it pursues a course clinically indistinguishable from other types of acute leukemia) or in a chronic form when, as in the present case, it may closely resemble myelofibrosis. It is characterized by an insidious onset, associated with progressive anemia and gradual enlargement of the spleen which may ultimately become very large. A hemorrhagic diathesis associated with marked thrombocytopenia is common, and hepatic enlargement is also usually present although lymphadenopathy is less commonly encountered.\textsuperscript{14} Reticulum cells appear in the peripheral blood eventually in virtually all cases and it is upon the presence of these cells in blood and marrow that the diagnosis depends. It is of interest to note that Bouroncle et al.\textsuperscript{14} reported failure to obtain marrow fragments on aspiration in 77 per cent of their cases, and similar difficulty was encountered in the present case. Leukemic reticuloendotheliosis is a uniformly fatal condition and treatment is palliative only. Some patients may respond well initially to radiotherapy or to splenectomy where there is definite evidence of hypersplenism.\textsuperscript{15} Isaéis\textsuperscript{16} reports a case in whom mustine therapy produced temporary benefit, but Bouroncle\textsuperscript{14} found no response to nitrogen mustard therapy in 10 cases. Corticosteroids may be helpful, particularly if there is a definite hemolytic anemia. The present case appeared to respond neither to splenic irradiation nor to corticosteroids. It was not considered justifiable to attempt splenectomy in view of the marked bleeding tendency associated with severe thrombocytopenia, and cytotoxic drugs were not employed for the same reason. It should be emphasized that leukemic reticuloendotheliosis has rarely been reported as occurring during childhood. The largest series to date has been 26 cases reported by Bouroncle\textsuperscript{14} and all of these were in adults. The occasional papers which have appeared concerning individual cases in childhood have all reported an acute type of the disease and it appears that
the present case is the first to be recorded of a child in whom the clinical course and hematologic findings correspond at all closely to the chronic form of the disease as seen in adults.\textsuperscript{14} Vaithianatha\textsuperscript{7} recently described the case of a mongol child aged 2½ years who developed an acute leukemia characterized by the presence of large numbers of reticulohistiocytes in the peripheral blood and marrow in association with tumor formation and destruction of the mandible and facial bones. The total duration of the illness in this child was 5 months. At least 1 and possibly 2 other cases of leukemic reticuloendotheliosis were included in the remarkable series of 5 cases of acute leukemia reported by Anderson\textsuperscript{2} as occurring in a sibship of 8 children, but here again the course was acute and the total survival time short.

In view of the possibility that a congenital factor may have been of etiologic significance in the present case, it is interesting to note that a similar factor may also have been operative in the other children referred to above. Thus, Vaithianatha's case was a mongol, and it seems probable that some familial or hereditary factor must have been at work in a family in which 5 children developed leukemia. It is suggested, on a purely speculative level, that in the case described in this paper the child was born with a congenital defect in the primitive mesenchymal cells of the reticuloendothelial system. This may have been inherited from his mother, either as a genetic abnormality or by the vertical transmission of virus, as described by Gross.\textsuperscript{18} The defect manifested itself in early life as a failure to differentiate towards megakaryocytes, and later as a more widespread failure of differentiation with proliferation at the primitive reticulum cell level.

**Summary**

The case history is reported of a 2-year-old boy who presented with persistent thrombocytopenia, developed a leucoerythroblastic blood picture at 7½ years and died at 9 years of leukemic reticuloendotheliosis. His mother died of acute lymphatic leukemia shortly after the birth, and some of the hereditary aspects of leukemia are discussed. It is suggested that the thrombocytopenia represented a preleukemic state, of unusually long duration, and that this and the leukemic reticuloendotheliosis were different phases of the same basic disorder. The surmise is made that heredity may play a part in the etiology of leukemic reticuloendotheliosis in childhood, a period of life when this disorder is very rare.

**Summario in Interlingua**

Es reportate le caso de un puero de 2 annos de etate qui se presentava con persistente thrombocytopenia, disveloppava un leucoerythroblastic imagine sanguinee al etate de 7 annos e medie, e moriva al etate de 9 annos de reticuloendotheliosis leucemic. Su matre moriva de acute leucemia lymphatic brevemente post su nascentia, e certes del aspectos hereditari de leucemia es discutite. Es postulate que le thrombocytopenia representava un stato preleucemic de inusualmente longe duration e que isto e le reticuloendotheliosis leucemic esseva diferente phases del mesme disordine fundamental. Es notate como hypothese que le hereditate ha possibilemente un rolo in le etiologia
de reticuloendotheliosis leucemic del pueritia, i.e., de un periodo del vita in le qual iste disordine es extrememente rar.

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REFERENCES
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