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thalassaemia, adds validity to the above suggestion. As shown in the follow-up data this very rapid fall in Hb was essentially limited to the first 2 months of life. Alternatively, the early onset of the disease may have been caused by the exchange transfusion performed at birth for hyperbilirubinaemia of unknown aetiology.

Blood regeneration after exchange transfusion occurs at a time when the synthesis of γ-chain has declined and the synthesis of β-chain predominates. For this reason the genetic defect of β-chain synthesis would be expressed clinically earlier than usual. This hypothesis would be correct only if the exchange transfusion had lowered the infant's Hb. However, the low Hb level observed after the exchange transfusion was quickly corrected by transfusion of 400 ml whole blood, which should have raised her Hb to at least 17 g/dl.

From a practical point of view this paper demonstrates the use of globin-chain synthesis measurements in the identification of homozygous β-thalassaemia when haematological data are inconclusive. This should also be considered in the differential diagnosis of hypochromic anaemia developing in the first 2 months of life after exchange transfusion at birth.

Summary

An infant with homozygous β°-thalassaemia developed neonatal jaundice and severe anaemia during the first few weeks of life. It is suggested that thalassaemia itself with excessive red cell destruction from birth could be the cause of neonatal jaundice and early presentation of the disease. Alternatively, this early onset may depend on exchange transfusion performed at birth for jaundice of unknown aetiology. Globin-chain synthesis measurement is useful in the identification of homozygous β°-thalassaemia when the haematological data are inconclusive.

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Chronic myeloid leukaemia in a child

A closely observed case

Chronic myeloid leukaemia (CML) is occasionally manifest in adults by the finding of a persistent neutrophil leucocytosis with no apparent cause. Signs of CML then develop and the disease pursues its usual fatal course. Philadelphia chromosome (Ph1) positive 'adult type' CML is rare in childhood: the Manchester Children's Tumour Register notes only 9 cases in 23 years. We here report the case of a 12-year-old boy who was found to have a persistent leucocytosis after an operation. The Ph1 chromosome was found in the marrow and 2½ years later the disease transformed into an acute leukaemia, apparently lymphoblastic and with central nervous system (CNS) leukaemia.

Case report

A Pakistani boy was found to have an undescended left testis and was admitted for orchiopexy. Pre-operative Hb level was 12:3 g/dl and physical examination unremarkable; the spleen was not palpable. After a routine, uncomplicated operation he became very ill with a toxic confusional state. White cell count was 76 × 10⁹/l, with 99% neutrophils showing marked 'toxic' granulation. Platelet count was also high (410 × 10⁹/l). His temperature rose to 40°C on the second postoperative day and a clinical diagnosis of sepsicaemia was made although no organism was grown from the blood. There was
considerable haematoma formation in the wound which had to be re-explored twice; it healed very slowly. Despite clinical improvement, the white cell count remained high and the marrow was therefore examined. An aspirate showed it to be active and hypercellular but without morphological abnormality.

The Ph1 chromosome was demonstrated in every metaphase examined and it became clear this was indeed a case of CML. Other findings at this time included a normal serum B12 level (187 pg/ml) with B12 binding proteins raised to twice normal (3510 pg/ml) and a relative increase of transcobalamin I (36%). The neutrophil alkaline phosphatase score was high (280) on one occasion, but low (10-20) thereafter (normal range 30-100). HbF was not increased.

The patient was observed without specific treatment but his parents requested that a more aggressive approach be taken and so he was treated with the COAP regimen, i.e. a single injection of vincristine and cyclophosphamide followed by 5 days of cytosine arabinoside and prednisolone. Initially this was given in reduced dosage but then continued with full doses. This produced little change in the blood or bone marrow. He was next treated with busulphan, then underwent splenectomy, and subsequently given busulphan maintenance. The Fig. shows some haematological parameters of his progress.

More than 2 years after presentation and while on busulphan, the white cell count rose dramatically and examination of the marrow clearly showed blastic transformation. The blast cells resembled lymphoblasts; all special stains, namely PAS, Sudan black, and peroxidase, were negative. The great majority of cells bore neither T nor B cell markers and in vitro culture of the marrow persistently showed very low numbers of colony-forming cells and clusters and a deficient production of colony-stimulating factor. However, terminal deoxynucleotidyl transferase activity was shown in the blood on several occasions with raised levels of 2 U/10⁶ cells. (Dr R. Saffhill).

He was given vincristine and prednisolone and continued on the Memphis VIII protocol for acute lymphoblastic leukaemia (ALL) with weekly methotrexate, daily 6-mercaptopurine, and 3-monthly vincristine and prednisolone. After this he was troubled by recurrent epistaxes, febrile episodes, and the side effects of the corticosteroids, but remained well enough to attend school at least intermittently. The bone marrow showed a partial response to therapy, in that it became hypoplastic with less than 10% of blasts, but this was not maintained.

Nine months after transformation, he was re-admitted with a feverish illness, headache, and lassitude, and although there were no focal neurological signs, a lumbar puncture showed white cells (825 × 10⁹/l) almost all of which were leukaemic blasts. A diagnosis of CNS leukaemia was made and he was given intrathecal methotrexate. The blasts appeared more undifferentiated than previously, but terminal deoxynucleotidyl transferase levels were still raised.

Fig. Levels of Hb, platelets, and white blood cells during treatment of the patient.
Discussion

There are two points of interest in this case. Firstly, as far as we know, this form of presentation of CML has not been reported in a child; and secondly, the transformation into an acute disease resembling ALL has been observed closely throughout.

Adults have occasionally been described who developed a neutrophil leucocytosis and were found to have a Ph1 chromosome in their marrows. Such patients often remain well for long periods (e.g. Canellos and Whang-Peng, 1972) until acute transformation occurs. This is generally thought to be the fortuitous discovery of the disease during its long presymptomatic period. This boy almost certainly had a leucocytosis before his operation and, postoperative problems apart, was without symptoms for a further 2 years. Recently there have been reports of cases of apparent ALL in which the Ph1 chromosome has been demonstrated (Beard et al., 1976). It is thought that these may be cases of CML in which the chronic phase has escaped detection, either because it was entirely asymptomatic or very brief. Had this boy not had an operation, he almost certainly would have presented 2½ years later in the guise of childhood ALL.

The blast cells, whether inspected in the blood, marrow, or CSF appeared primitive and undifferentiated using Romanovsky stains, and were negative by common cytochemical techniques. The majority of cells in the marrow and CSF had neither T nor B cell markers, but terminal deoxynucleotidyl transferase activity was detectable in the blood on several occasions after transformation, in concentration of the same order as is found in ALL. This enzyme is present in normal thymic cells and in normal bone marrow in low concentration, but high concentrations are thought to be a specific marker for lymphoblasts (McCaffrey et al., 1975; Hoffbrand et al., 1977), and a similar case to ours was described by Oken et al. (1976) in which the enzyme was a marker for the blast cells in transformed CML.

The identity of the blast cells in transformed CML often presents a puzzle. In some cases, the resemblance to myeloblasts is marked and cytochemical studies are consistent with this appearance. In other cases the resemblance to lymphoblasts is considerable and various lymphoblast markers may be shown. Shaw et al. (1975) stressed the heterogeneity of the appearance of the cells in their series of transformed cases of CML.

Modest success has been reported in cases showing features of ALL by the use of treatments designed for that disease (e.g. Oken et al., 1976), and as the outlook is so black in transformed CML, this approach has much to recommend it. More fundamental questions are raised by the phenomenon of apparent translation of CML into ALL. These are discussed by Boggs (1975).

Summary

A 12-year-old boy with persistent leucocytosis was found to have chronic myeloid leukaemia. 2 years later the disease transformed into an acute lymphoblastic leukaemia-like syndrome, with central nervous system leukaemia and terminal deoxynucleotidyl transferase activity in the blood.

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