Transient erythroblastopenia of childhood with CD10, TdT, and cytoplasmic μ lymphocyte positivity in bone marrow

A B M Foot, M N Potter, J E Ropner, T B Wallington, A Oakhill

Abstract
Over three years, three children presented with anaemia, reticulocytopenia, and marrow erythroblastopenia. A pronounced lymphocytosis was also evident in two of the marrow aspirates, with increased numbers of cells bearing the immunophenotype TdT+, CD10+ HLA DR+, and cytoplasmic μ+, and reported to be compatible with acute lymphoblastic leukaemia (ALL). The clinical course of the illness was fully compatible with transient erythroblastopenia of childhood (TEC), and all three children remained well one to four years after initial presentation. It is concluded that increased numbers of lymphoid cells with a common or pre-B ALL phenotype may be found in bone marrow aspirates of children with TEC, and should not be misdiagnosed as acute leukaemia.

Transient erythroblastopenia of childhood (TEC) is a self-limiting disorder of unknown aetiology, characterised by an anaemia lasting a few weeks. Since it was first described in 1970, this condition has been recognised increasingly in children in the United States, although a review of the literature suggests that it is less common in Europe, with few reported cases in the United Kingdom. Although typically described as a pure red cell hypoplasia, the finding of clinically important neutropenia is not uncommon, and bone marrow aspiration is advisable to rule out the possibility of malignancy.

Methods
Over three years (1985-1988), three children, previously in good health, presented with anaemia; preliminary investigation showed that one was also neutropenic. Bone marrow aspiration was performed in each case. Cell surface marker studies were performed on sterile samples of bone marrow. In brief, after separation on a Ficoll-Hypaque gradient the washed mononuclear cells were labelled with mouse monoclonal antibodies or conventional anti-sera to CD3, CD7, CD21, CD10, HLA DR and κ or λ. After a further wash cells were treated with fluorescein conjugated with anti-mouse or appropriate species immunoglobulin, washed, and mounted on microscope slides. The percentage of cells reacting with each reagent was assessed by fluorescence microscopy, counting at least 100 cells for each specificity. For detection of TdT and cytoplasmic μ, cytocentrifuge preparations of separated mononuclear cells were fixed before reacting with appropriate polyclonal antibodies, again using an indirect immunofluorescence method.

Case reports
Details of the relevant laboratory data are described in tables 1 and 2.

Table 1 Patient details and presenting data

<table>
<thead>
<tr>
<th>Case No</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Presentation</th>
<th>Haemoglobin (g/dl)</th>
<th>White cell count/ neutrophils (×10³/l)</th>
<th>Platelets (×10³/l)</th>
<th>Mean corpuscular volume (fl)</th>
<th>Reticulocytes (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2-2</td>
<td>F</td>
<td>Hemiparesis Pallor</td>
<td>2-7</td>
<td>10-6/5-2</td>
<td>445</td>
<td>77</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>4-1</td>
<td>M</td>
<td>Hemiparesis Pallor</td>
<td>6-0</td>
<td>5·4/1·6</td>
<td>478</td>
<td>77</td>
<td>0·2</td>
</tr>
<tr>
<td>3</td>
<td>2-9</td>
<td>F</td>
<td>Pallor</td>
<td>4·5</td>
<td>6·5/0·7</td>
<td>575</td>
<td>83</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 2 Details of bone marrow lymphocyte counts and subsets

<table>
<thead>
<tr>
<th>Case</th>
<th>Lymphocyte count as percentage of total nucleated cells</th>
<th>CD10</th>
<th>DR</th>
<th>TdT</th>
<th>Cytoplasmic μ</th>
<th>T cell: CD3</th>
<th>CD7</th>
<th>B cell: CD1g</th>
<th>CD21</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>17</td>
<td>53</td>
<td>64</td>
<td>70</td>
<td>10</td>
<td>61</td>
<td>20</td>
<td>17</td>
<td>Not done</td>
</tr>
<tr>
<td>2</td>
<td>51</td>
<td>65</td>
<td>80</td>
<td>70</td>
<td>20</td>
<td>Not done</td>
<td>20</td>
<td>Not done</td>
<td>Not done</td>
</tr>
<tr>
<td>3</td>
<td>48</td>
<td>10</td>
<td>71</td>
<td>20</td>
<td>75</td>
<td>Not done</td>
<td>69</td>
<td>60</td>
<td>Not done</td>
</tr>
</tbody>
</table>

Department of Paediatric Oncology, Royal Hospital for Sick Children, Bristol
A B M Foot
M N Potter
A Oakhill

Department of Haematology, Gloucestershire Royal Hospital
J E Ropner

Department of Immunology, Southmead Hospital, Bristol
T B Wallington

Correspondence to: Dr A B M Foot
Accepted for publication 2 July 1990
null
the suspicion of leukaemia.6,7 Gerrits et al. studied one such case in greater detail, using immunofluorescence markers, and found a subpopulation of 7% showing cALLa positivity. We, too, found an accompanying lymphocytosis in two of our cases, and although morphology showed most to be small and mature, marker studies identified a large immature population in all three. The normal marrow in children may contain a population of up to 5% of mononuclear cells at an early stage of B lymphocyte differentiation, expressing TdT, HLA DR, and CD10, but the finding of proportions much in excess of this is characteristically associated with common ALL. In some other non-malignant blood disorders increased numbers of cells bearing the same immature phenotype have been described. This is particularly so in stressed or regenerating marrows following cytotoxic treatment, bone marrow transplantation, and aplastic anaemia, and the distinction from leukaemic blasts has proved difficult using this characteristic alone.8 It has been suggested that they represent a population of regenerating lymphoid cells, most probably of early B lineage. The finding of CD10 positivity, together with TdT and cytoplasmic μ positivity in all of our cases, gives the picture of an immature population of cells, predominantly at the pre-B stage. This could mistakenly be interpreted as ALL, out of context with the clinical and morphological findings. Transient pancytopenia with documented recovery before the development of ALL (the syndrome of “pre-leukaemic aplasia”) can occur in common ALL.9 All patients described in that series, however, had proceeded to overt leukaemia within a year of primary presentation of their transient hypoplasia.

The finding of bone marrow lymphocytosis in TEC, as seen in two of our cases, remains unexplained. Clinically important lymphocytosis has also been noted in cases of congenital hypoplastic anaemia, and in one case has even led to treatment with cytotoxic agents on the erroneous assumption that this represented acute leukaemia.10 Miale et al. argued that these young lymphoid cells could be erythroid precursors,11 and Inoue et al have documented B lymphocyte antigens on erythroid colony and burst forming cells.12 In our cases, however, it is clear that the lymphocytosis is a consequence of an outpouring of immature lymphocytes, and is consistent with other examples of a stressed marrow.

Although the aetiology remains obscure, reports of clustering implicate an infectious agent.13,14 It is of particular interest to note that in case 3 most of the lymphocyte population consists of mature reactive T cells, as shown by CD3 and HLA DR positivity. Unlike the documented link between human parvovirus B19 infection and aplastic crises in patients with chronic haemolytic anaemia, however,15 no particular agent has as yet been identified. This is confirmed in our series, with negative virological screening, including IgG and IgM specific parvovirus antibodies. The presence of reactive lymphocytosis is also suggestive of an immunological response. The mechanism of the anaemia in TEC has previously been explored, and in many cases seems to have an autoimmune element.16,17 The mode of suppression of erythropoiesis, however, does not seem to be uniform, with IgG, IgM, and cell mediated immunosuppression all being described. Thus both aetiology and the mechanism of TEC seem to be heterogeneous, but yet result in a similar final common pathway.

Finally, it is interesting to note that two of these children presented with transient hemiparesis. The association of transient neurological disorder at presentation of TEC has been reported.18-20 In one report Young et al. proposed that the transient hemipareses in an anaemic child (haemoglobin concentration 4 g/dl) might have been caused by anaemic hypoxia, and they support this with hypothetical calculations.19 The range of anaemia at onset of neurological disturbance (4.2-9.1 g/dl) and the varied symptomatology described in the small series by Michelson and Marshall, however, would suggest a more complex, as yet unknown aetiology.20

In conclusion, a marrow lymphocytosis with CD10, TdT, and cytoplasmic μ positivity can occur in TEC. Although clinical features and bone marrow morphology should suggest the diagnosis of the benign condition of TEC, the occurrence of immature lymphocytes should be recognised to prevent a false diagnosis of leukaemia.

Dr A B M Foot is supported by the Alex Wolton Trust.