Distinction between aleukaemic prodrome of childhood acute lymphoblastic leukaemia and aplastic anaemia

M M Reid, G P Summerfield

Abstract

Aims: To document the features of the so-called aplastic presentation of childhood acute lymphoblastic leukaemia (ALL) and to determine whether this prodrome can be distinguished from aplasia.

Methods: The peripheral blood and bone marrow appearances of all cases of childhood ALL presenting in one health region of England in 13 years and eight months were reviewed. All cases presenting with cytopenia without circulating blasts and marrow aspirates with no infiltrate of blasts were studied in detail.

Results: Four of 305 (1.3%) children presented in this way. All four had reticulin fibrosis and increased cellularity in all or part of the marrow biopsy specimen. All were girls. Three had common and one surface membrane immunoglobulin positive ALL. Reassessment of this prodrome, by combining the features of four previously reported series of similar cases with the present one, highlighted the female preponderance (19 of 22 cases), bone marrow fibrosis (10 of 11 evaluable cases), prominent bone marrow lymphocytes (14 of 22 cases) and temporary recovery (all 12 evaluable cases). Six of 14 evaluable cases had bone marrow biopsy specimen appearances of apparently uniform hypocellularity, but only one of these did not have fibrosis.

Conclusions: If, in addition to an aspirate, a bone marrow trephine biopsy is carried out the prodrome can be distinguished from aplasia in most cases. The similarity of this prodrome to aplastic anaemia is merely superficial. Clinicians and morphologists may fail to appreciate the implications of this mode of presentation if the term “aplastic” continues to be used to describe this aleukaemic prodrome of ALL.

The correct diagnosis may not always be immediately apparent in children with acute lymphoblastic leukaemia (ALL) who present without detectable blasts in the blood, even after bone marrow examination. Following an early suggestion that aplastic anaemia might in some children be preleukaemic, Melhorn et al. showed that “aplastic anaemia” in childhood which responded to steroids was in fact a precursor to ALL. Since then several series of similar cases and a number of individual case reports have been described. We present four more cases with a similar illness.

Methods

All cases of childhood ALL presenting in the northern health region of England since one of the authors (MMR) became involved in their diagnosis were studied. Between January 1978 and August 1991 four of 305 (1.3%) cases first presented without peripheral blood or bone marrow evidence of leukaemia. Romanovsky stained bone marrow smears and bone marrow biopsy specimens stained with haematoxylin and eosin and with silver for reticulin were examined. Appropriate cytochemical stains confirmed the eventual diagnosis. Immunophenotyping was carried out by standard fluorescence techniques. Cytogenetic analysis of bone marrow cells was performed using standard G banding techniques.

Case reports

CASE 1

A 9 year old girl had a 12 month history of flitting joint pains diagnosed as seronegative polyarthritis. She was treated with salicylates but not with steroids. Six months before presentation she had a cellulitic-like lesion on her forehead, which resolved after treatment with co-trimoxazole, and erythema nodosum on her legs. Her initially normal haemoglobin concentration fell to 10 g/dl and neutrophil count to <2.0 × 10^9/l. Platelet numbers remained normal. The liver and spleen were not enlarged. Bone marrow aspirate was hypocellular, with lymphocyte predominance and no blasts. A bone marrow biopsy specimen showed both hypo- and hypercellular areas with disorganised architecture, an infiltrate of lymphocytes, and a diffuse moderate increase in reticulin. Aplastic anaemia was excluded. Toxic damage, collagen vascular disease, and preleukaemia were considered. One month later the haemoglobin concentration was 9.9 g/dl, platelets 127 × 10^9/l, and white cells 12 × 10^9/l with 50% blasts. A marrow aspirate showed 90% blasts, which were periodic acid Schiff (PAS) block positive and Sudan black negative. ALL (L1) was diagnosed. Immunophenotyping showed: Tdt 81%, CD10 95%, CD20 20%, CD2 <1%, surface membrane immunoglobulin (SMIg) 61%, μ 51%, α, γ,
Immunophenotyping nised.

neutrophils was 2 g/dl, platelets
189 x 10^9/l, and white cells 1.7 x 10^9/l, with
no neutrophils or blasts. A bone marrow aspirate
was hypocellular with lymphocyte predominance
and less than 5% blasts. A bone marrow biopsy
specimen showed hypo- and hypercellular areas and
an infiltrate of lymphocytes and other unidentifiable
mononuclear cells. Reticulin was massively increased.
Cyto-
genetic analysis of bone marrow failed. Aplastic
anaemia was excluded. Toxic damage, non-
haemoopoietic malignancy, and preleukaemia
were considered. Raised urinary catechola-
mine metabolites led to a diagnosis of neuro-
blastic tumour. She was transfused with further
investigations, including computed tomogra-
phy (not available on site at that time) and
repeat catecholamine estimation, showed no
abnormality. Initial treatment for neuroblas-
toma was stopped and she was observed. The
blood count returned to normal. Six months
later haemoglobin was 9 g/dl, platelets
44 x 10^9/l, and white cells 64 x 10^9/l, all of
which were blasts. A bone marrow aspirate
showed complete replacement with blasts,
10% with PAS block positivity, none positive
with Sudan black. ALL (L1) was diagnosed.
Immunophenotyping showed Tdt 95%, CD10
92%, CD19 88%, CD2 <1%, CD7 9%,
SMIg <1%. Cyto genetic analysis showed an
apparently normal 46 XX karyotype.

CASE 3
A 12 year old girl presented with malaise, pallor,
and swellings at the angles of her jaw. Her
haemoglobin was 5 g/dl, platelets
91 x 10^9/l, and white cells 0.9 x 10^9/l, with
no neutrophils or blasts. A bone marrow
aspirate was hypocellular. Most cells were
lymphocytes. A bone marrow biopsy specimen
showed hypo- and hypercellular areas with an
infiltrate of lymphocytes. Reticulin was greatly
increased in the cellular areas. Cytospin pre-
parations of a collagenase digested biopsy core
contained normal myeloid cells, megakaryo-
cytes, a lymphocytic infiltrate (80% of cells)
and 10% blasts. Immunophenotyping showed
<5% Tdt and CD10 positive cells. Cytogen-
etic analysis showed an apparently normal
46 XX karyotype. Aplastic anaemia was exclu-
ded. Toxic damage, collagen vascular disorder,
and preleukaemia were considered. A biopsy
specimen of the facial swelling showed pus, no
granulomata, and no sign of malignancy. She
was transfused and observed. Two weeks later
she had 5 x 10^9/l neutrophils and 300 x 10^9/l
platelets. Four weeks after presentation blasts
appeared in her blood. A bone marrow aspirate
showed 90% blasts, which were negative on
cytochemical staining. ALL (L1) was diag-
nosed. Immunophenotyping showed Tdt 80%,
CD10 97%, CD19 96%, CD7 2%, SMIg
<1%. Cytogenetic analysis showed four sim-
ilar clones with 44 or 45 chromosomes, com-
mon features being a ring X and i(9q).

CASE 4
A 5 year old girl presented with fever, malaise,
vomiting, pallor and drowsiness and later had a
grand mal fit. Bilateral papilloedema with
focal neurological signs was noted. Haemoglobin
was 4.2 g/dl, platelets 41 x 10^9/l, and white
cells 42 x 10^9/l, with neutrophils < 2 x 10^9/l
and no blasts. She had renal failure with a
serum creatinine concentration of 426 µmol/l.
Klebsiella and a coagulase negative Staphylo-
coccus were isolated from blood culture. A
computed tomography scan showed mild
hydrocephalus but no intracranial mass lesion.
A bone marrow aspirate contained a few
hypercellular particles and showed dysery-
thropoiesis, prominent lymphocytes, occasional
aggregates of small mononuclear cells and
<5% blasts. A bone marrow biopsy specimen
showed no evidence of aplastic anaemia, but
contained an infiltrate of small cells and
considerable fibrosis. Non-haemoopoietic
tumour and leukaemia were considered.
Immunophenotyping of marrow cells showed
Tdt <1%, CD10 <1%, CD19 <1%, CD2
86%. No cells expressed N-CAM (neural cell
adhesion molecule). Cytogenetic analysis
showed an apparently normal 46 XX kar-
yotype. No diagnosis was made and the cause
of the lymphocytic infiltrate was unknown. She
responded to intravenous fluids and anti-
biotics, received red cell and platelet transfu-
sions, and, because of the raised intracranial
pressure, was given a reducing course of
dexamethasone. She made a complete clinical
and haematological recovery. Eighteen months
later haemoglobin was 9.6 g/dl, platelets
52 x 10^9/l, and white cells 16 x 10^9/l with
blasts 4 x 10^9/l. A bone marrow aspirate
contained 95% Sudan black negative blasts.
ALL (L1) was diagnosed. Immunopheno-
typing showed Tdt 24%, CD10 >90%, CD7
<1%, CD33 <1%, SMIg <1%. Cytogenetic
analysis was unsuccessful.

All were treated according to Medical
Research Council protocols, case 1 according
to UKALL VIII, and cases 2–4 according to
UKALL X. Remission was achieved in cases 1,
2, and 4. Cases 1 and 2 remained in first
complete remission eight and five years after
starting treatment. Case 3 responded but died of
an Enterobacter septicaemia before remission
was achieved. Case 4 had isolated central
nervous system (CNS) relapse 15 months after
diagnosis and remained alive but with persisting
CNS disease five years after diagnosis.

Discussion
The four cases described here represent 1-3% of
cases of ALL diagnosed over a
period of 13 years and eight months in one
health region of England. All presented with
anaemia (three severe) and varying degrees of
neutropenia. Three had well preserved platelet
counts. The time interval between first pre-
sentation to hospital and diagnosis of leuk-
aemia ranged between four weeks and 18
months. All had an infiltrate of lymphocytes,
Summary of clinical features of aleukaemic prodrome of childhood ALL

<table>
<thead>
<tr>
<th>Study</th>
<th>No of cases</th>
<th>No of girls</th>
<th>Anaemia</th>
<th>Neutropenia</th>
<th>Platelets &gt; 10^9/l</th>
<th>Platelets &lt; 40 x 10^9/l</th>
<th>Marrow lymphocytes</th>
<th>Marrow fibrosis</th>
<th>Uniformly hypocellular biopsy specimen</th>
<th>Temporary recovery</th>
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<tr>
<td>Mellhorn et al 3-5</td>
<td>6</td>
<td>5</td>
<td>6</td>
<td>6</td>
<td>3</td>
<td>2</td>
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<td>2</td>
<td>2</td>
<td>1</td>
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<td>ND</td>
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<td>8</td>
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<td>2</td>
<td>4</td>
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<td>9</td>
<td>7</td>
<td>14</td>
<td>10 (11)</td>
<td>6 (14)</td>
<td>12 (12)</td>
</tr>
</tbody>
</table>

(*) Number of evaluable cases. ND not done or not reported. * One girl, given steroids before bone marrow examination, is not included.

not blasts, in the first marrow aspirate examined. Two had temporary recovery of blood counts before the diagnosis of leukaemia was made. Their prodrome is similar to that described in the previous series 2-4 in several respects. We are reluctant to suggest that our four cases comprise yet another rare prodrome of ALL and suspect that they and the previously reported series are all examples of the same phenomenon.

Three of the present cases developed common ALL, as did all of those tested in one of the earlier series, 5 but case 1, some of whose details have been reported already, 6 is unusual in that her blasts expressed surface µ chain without any of the other features of B-ALL. Too few cases have been described to exclude the possibility that null (as opposed to non-B, non-T) or T-ALL might present in this way. There is no evidence that these patients do any worse than average, provided they are not treated with steroids at the first presentation, but the numbers are small. The perceived benefit of response to steroids 6 reflected an approach to diagnosis which existed before the widespread use of effective treatment for ALL, and is clearly outweighed by the risk of subsequent emergence of resistant leukaemia.

Both children in this and the most recent series 7 who were treated with steroids had central nervous system relapses.

Some differences in interpretation of the presenting features between the present four children and those previously described prompted a reappraisal of this prodrome. The distribution of the major clinical features within the published series is shown in the table, together with those of the present one. Important features of the marrow in our cases are the increased cellularity in some areas in each child, and the increased reticulin. In two of the series 5-7 bone marrow trephine biopsies were either not done or not reported in most patients, but few centres would now make a diagnosis of aplastic anaemia without biopsy confirmation. In the group reported by Bresnach et al 7 uniform hypocellularity was not confirmed in two of the seven with evaluable marrow biopsy specimens. If our cases are included only six of 14 evaluable patients had truly hypocellular bone marrow despite the meagre cellularity of the aspirated material. Fibrosis, present in 10 of the 11 evaluable cases, might have contributed to the poor cellularity of the aspirated marrow. Severe thrombocytopenia is not common and nine had platelet counts of >100 x 10⁹/l at presentation. In most cases, therefore, the similarity with aplastic anaemia was superficial once full investigation, including bone marrow biopsy, had been carried out.

Nineteen of the 22 cases (86%; 95% confidence intervals 65–95%) described in these five series have been girls. It seems unlikely that this disproportionate sex ratio is merely due to chance. Of equal interest is the temporary recovery of haemopoiesis without specific treatment observed in all 12 evaluable children. This behaviour may induce a false sense of security which may be transmitted to their families.

The pathogenesis of this prodrome is obscure. The rate of fibrosis is similar to that expected in childhood ALL of B lineage 7 and may reflect reaction of bone marrow fibroblasts to occult lymphoblasts. This hypothesis could be examined in future cases by molecular techniques to detect minimal presenting (as opposed to residual) disease if bone marrow samples from the presenting illness and their subsequent ALL are stored. But what of the peripheral cytopenia documented in most cases? The recovery after blood transfusion resembles the behaviour of transient erythroid hypoplasia in childhood (TEC). Although TEC is not usually accompanied by severe neutropenia, and almost never by thrombocytopenia, parvovirus B19 infection oftens. 8 Prolonged B19 infection with chronic failure of erythropoiesis does occur in some immune suppressed children, notably those already being treated for ALL, and one such case showed some response to treatment with infusions of immune plasma. 8 Perhaps these children have an unusual complication of a common virus infection due to immune dysfunction before leukaemia is diagnosed. It remains possible that the rate of putative viral infection is similar in boys and girls but that development of frank leukaemia is delayed in girls by some other immunological mechanism. There are no data in this or the previous reports to advance hypotheses about pathogenesis beyond speculation. Virological, immunological, and bone marrow culture studies may offer clues in future cases if the importance of the presentation symptoms are appreciated.

In summary, the striking and most common features of this prodrome, other than its rarity
(1–2% of cases of childhood ALL), peripheral blood cytopenia, and the diagnostic problems it poses, are female preponderance, fibrotic bone marrow with lymphocytic, not blastic, infiltration, hypercellularity of some areas of the bone marrow of many cases and temporary recovery of the blood count. It should not be confused with the familiar picture of ALL presenting with few circulating blasts, because in such cases the diagnosis is usually obvious on first examination of the bone marrow, nor with aplastic anaemia. Perhaps the prodrome could more usefully be described as “aleukaemic” than as “aplastic”. The difference is more than semantic. Prominence given to the term “aplastic” in earlier reports of this mode of presentation may mislead haematologists and clinicians and result in failure to appreciate the importance of a syndrome which few would now describe as “aplastic”. It is a potentially recognisable preleukaemic prodrome in its own right.

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