Letters to the Editor

Neutropenia preceding acute lymphoblastic leukaemia

Preleukaemic syndromes for acute non-lymphoblastic leukaemia have been well defined but haematological abnormalities preceding acute lymphoblastic leukaemia are rare. These include aplastic anaemia and erythroid hypoplasia with neutropenia, usually with evolution to acute leukaemia in less than six months. One case of isolated neutropenia was reported eight months before the development of acute lymphoblastic anaemia (ALL). Inoshita described myelodysplasia progressing to ALL and reviewed 17 cases with haematological abnormalities prior to its diagnosis. We have recently seen a patient who presented with neutropenia and thrombocytopenia 34 months before the development of ALL, with resolution of the neutropenia after remission induced by chemotherapy.

Case report

A 19 year old white man presented in August 1982 with malaise. His haemoglobin concentration was 13.6 g/dl, white cell count 1.8 × 10^9/l, platelet count 220 × 10^9/l, and mean corpuscular volume 103.5 fl. White cell differential comprised 42.6% neutrophils, 57% lymphocytes, 0.2% monocytes, and 0.2% eosinophils. The blood film showed no unusual morphological features. A bone marrow aspirate was normocellular with normoblastic erythropoiesis, plentiful megakaryocytes, depressed myeloid precursors with a slight left shift, but less than 2% blasts. Lymphocytes were prominent (fig 1) and morphologically normal. Immunological analysis of the marrow was not performed. A trephine biopsy specimen showed no evidence of infiltration by abnormal cells. Peripheral blood lymphocyte subtypes showed a high OKT3 positive population (81%) but normal T4:T8 ratio and high Ia positive population (55%), suggesting an activated T cell population. Erythrocyte sedimentation rate, auto, antibody screen, B12 and folate concentrations, and viral studies yielded normal results. Tests for neutrophil autoantibodies were not performed, and karyotype analysis was 46 XY. Neutropenia persisted and a repeat bone marrow aspirate in May 1984 was unchanged. Repeat blood lymphocyte analysis showed no abnormal T cell population. In June 1985 he developed circulating blast cells, and bone marrow aspirate showed infiltration by lymphoblasts (fig 2). Immunological studies suggested common ALL of B cell origin, with 95% blast cells TdT positive. Karyotype analysis was difficult but suggested two pseudodiploid clones, 46 XY, -8, 9q+, +mar (?7p+) and 46 "Bq++". He was entered into the UKALL XA trial and achieved complete remission with resolution of neutropenia.

Initially the cause of this patient's neutropenia was unexplained. Morphologically the peripheral blood and marrow lymphocytes were normal with no evidence of large granular lymphocytes or of marrow infiltration, and there was no obvious immunological disorder or drug regimen which could be associated with neutropenia. The abnormalities described could be explained in several ways. Firstly, leukaemia was already present with an abnormal clone capable of suppressing myelopoiesis but undetected morphologically. Secondly, the neutropenia was the initial manifestation of a stepwise progression to the development of ALL, or the neutropenia was unrelated to the subsequent development of ALL. Although morphological evidence of ALL was absent, the resolution of neutropenia after treatment suggests that the two were related. Neutropenia is often present when ALL is diagnosed although the reasons for this are not clear—marrow infiltration does not seem to explain it entirely, and culture studies have suggested inhibition of colony primary units—granulocyte, macrophage colonies in both ALL and normal marrow by sera and cells from patients with ALL. Kinetic studies in ALL have suggested that the doubling time is about 18 days, and it has been computed that growth of a single cell to 10^9 cells would require 3-5 years. The findings in our case would not be inconsistent with this, with an initially undetectable clone slowly developing over the period of observation.

An alternative postulate assumes that two different disease processes were present and unconnected—we have no evidence for an alternative aetiology for the neutropenia such as drugs, systemic lupus erythematosus, rheumatoid arthritis or T suppressor lymphocytosis, although we cannot exclude an idiopathic immune-mediated neutropenia. Resolution of the neutropenia under these circumstances could be attributable to immunosuppression associated with treatment for the acute leukaemia.

We believe it more likely, however, in view of the marrow lymphocytosis, absence of other associated underlying disease, and the response to treatment that this patient's...
neutropenia was related to an initially undetected clone of cells capable of suppressing myelopoiesis, which overtly presented 34 months later as ALL. Neutropenia should be regarded as a cytopenia which may rarely precede the onset of ALL.

Table  Organisms isolated from each blood culture system

<table>
<thead>
<tr>
<th>Positive in Bactec</th>
<th>Positive in Oxoid</th>
<th>Positive in both</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 α-haemolytic streptococcus</td>
<td>1 α-haemolytic streptococcus</td>
<td>1 Candida</td>
</tr>
<tr>
<td>13 Coagulase-negative staphylococcus</td>
<td>16 Coagulase-negative staphylococcus</td>
<td>25 Coagulase-negative staphylococcus</td>
</tr>
<tr>
<td>E coli</td>
<td>2 E coli</td>
<td></td>
</tr>
<tr>
<td>Klebsiella oxytoca</td>
<td>1 Group B streptococcus</td>
<td></td>
</tr>
<tr>
<td>Ps paucimobilis</td>
<td>1 Streptococcus faecalis</td>
<td></td>
</tr>
<tr>
<td>2 mixed cultures of Strep- tococcus faecalis with Proteus sp</td>
<td>1 Lactobacillus</td>
<td></td>
</tr>
<tr>
<td>Proteus sp and Strep- tococcus anginosus with Coagulase-negative Staphylococcus</td>
<td></td>
<td>2 Propionibacterium</td>
</tr>
</tbody>
</table>

References

Comparison between Bactec and Oxoid blood culture systems in a neonatal intensive care unit

For several years our laboratory has used the Bactec system for routine blood cultures from neonates. The predominant isolates are coagulase negative staphylococci, and the rest of the isolates are group B streptococci, Staphylococcus aureus, coliforms, α-haemolytic streptococci, Pseudomonas spp. lactobacilli, and Candida spp. As clinically important anaerobes are only rarely isolated from neonatal blood cultures from the Southmead special care baby unit, we felt justified in substituting an Oxoid Signal bottle for the Bactec 7D (anaerobic) bottle.

The Oxoid Signal is capable of detecting the range of blood culture isolates from the unit' but has not been assessed using the small volumes of blood usually cultured from neonates, and concern has been expressed about its reliability in clinical use.1 The table shows the organisms isolated during the period when blood culture sets of one Bactec 6B (aerobiotic) and one Oxoid Signal bottle were used. Coagulase negative staphylococci and Candida were grown in both systems. Bactec failed to grow a group B streptococcus and two E coli, while Oxoid Signal failed to grow three coliforms (Klebsiella oxytoca, Escherichia coli, Proteus mirabilis).

The clinical importance of the other isolates positive in only one system is more difficult to assess. False positive results were rare, being 3-9% with Oxoid and nil with Bactec. When the same organism was isolated in both bottles, 85% (23 of 27) were positive on the same day, and the other four were positive in Bactec first. When organisms were isolated from only one bottle 17 of 25 Oxoid Signal cultures and 16 of 20 Bactec cultures were positive at 24 hours, but both failed to grow isolates likely to be clinically important.

Reasons for the failure of both bottles to isolate likely pathogens may be related to contamination or the small volume of blood inoculated into each bottle. The preponderance of coagulase negative staphylococci in neonatal cultures makes contamination rates difficult to assess, but it seems likely that the volume of blood cultures is important and the question arises as to whether the inoculum should be split between several cultures or committed to one. It may be that in the absence of blood volumes to fulfill adequately the manufacturer's protocol for a double bottle system (such as Bactec) it may be better to place all the blood available into a single bottle culture system. A further potential advantage of the use of single culture bottle regimen (Oxoid) would be an approximate 25% saving in cost compared with a double Bactec system; unlike Roberts and Kaczmarski,2 we did not have many false positive signals with the Oxoid system.

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References

Improved blood free selective medium for isolating Campylobacter jejuni from fecal specimens

We confirm some of the observations made by workers in Preston on the efficacy of modified charcoal cefoperazone deoxycholate agar (modified CCDA) in isolating "thermophilic" campylobacters from lumen faecal specimens.1,2 We compared modified CCDA with Skirrow's medium7 which had been our standard selective medium. The Skirrow's medium was prepared from Columbia agar base (Oxoid CM 331), lysozome horse blood, and Skirrow's selective supplement (Oxoid SR69) and modified CCDA prepared from Campylobacter blood free selective agar base (Oxoid CM 739) and a cefoperazone selective supplement (Oxoid SR125). Equal quantities of faeces were spread on each medium using a cotton tipped swab and the plates kept incubated microaerobically in anaerobic jars, evacuated to 550 mm Hg, before adding 10% carbon dioxide in nitrogen without a catalyst, and plates were examined after