Bone marrow fibrosis in acute lymphoblastic leukaemia of childhood

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SUMMARY A prospective study of bone marrow fibrosis was made in a group of 40 children with acute lymphoblastic leukaemia to see whether it affected the prognosis or course of the disease. Secondary myelofibrosis (SMF) was present at diagnosis in 57% of the cases. It was not statistically significantly related to the prognosis or course of the disease. Thus, although trephine biopsy occasionally provided useful information in differential diagnosis and when aspiration was difficult, it provided little information of use for management.

Bone marrow fibrosis may be primary or secondary. Idiopathic primary myelofibrosis is usually considered to be one of the myeloproliferative syndromes (Dameshek, 1951). Secondary myelofibrosis (SMF) may be associated with a variety of bone marrow disorders such as malignant disease, tuberculosis, and haemolytic anaemia. It is not uncommon in acute leukaemia and occurs in both lymphoblastic and granulocytic types (Kundel et al., 1964). SMF often makes bone marrow aspiration difficult in leukaemia.

There have been few extensive studies of SMF in acute leukaemia. Kundel et al. (1964) investigated 40 cases of acute lymphoblastic leukaemia and 20 cases of acute myelogenous leukaemia. They suggested that it indicated a ‘definitely poorer’ prognosis. Devred and Diebold (1974) studied 402 patients with blood diseases but included only two cases of acute lymphoblastic leukaemia. Burston and Pinniger (1963) included 15 cases of acute leukaemia in their study but did not classify them any further. Other authors have reported only small series.

Methods

All patients presenting with acute lymphoblastic leukaemia (ALL) between 1 April 1974 and 1 October 1975 had a trephine needle biopsy performed at diagnosis and at variable intervals thereafter. The tissue was taken from the posterior iliac crest with a Gardner or Jamshidi needle. Our practice is to do initial investigations under general anaesthesia (Evans et al., 1971) and the period of anaesthesia was not thereby prolonged.

The sample was fixed in formol-saline, decalcified in Gooding and Stewart’s solution for 24 hours, and stained by methods described by Drury and Wallington (1967) using haematoxylin and eosin, the methenamine silver method for reticulin, and Masson’s trichrome.

Myelofibrosis was assessed independently by two observers as normal (0), slightly (+), moderately (++), and considerably (+++) increased on the basis of the reaction with the reticulin stain (Kundel et al., 1964). Only a ++ or +++ reaction was considered to be pathologically increased. Independent reports on whether pathological SMF was present varied in only two cases. These two reports were excluded from our analysis.

The periodic acid-Schiff (PAS) reaction was scored by counting the percentage of positive PAS cells out of 200 counted from the marrow smears. Acute lymphoblastic leukaemia was diagnosed by the criteria of Hayhoe et al. (1964)—cells show a high nucleocytoplasmic ratio, nuclei not indented or twisted, erythroblasts absent from blood, and less than 50% of marrow cells.

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Results

The distribution of reticulin fibres was variable, some marrows showing a uniform increase and others a patchy distribution. Three cases showed no increase in reticulin and 13 showed a slight increase (+) that was not considered pathological. In 17 cases the increase was moderate (+++) and in four considerable (+++). The initial trephine aspiration was unsuccessful in three cases. Thus out of the 37 successful trephines at diagnosis 21 (57%) showed an abnormal increase in reticulin. In all these cases SMF was of the type described by Devred and Diebold (1974) as a diffuse reticulin fibrosis. For convenience we have analysed the cases in two groups—firstly, the 21 cases with increased reticulin ('reticulin positive') and, secondly, the remaining 16 cases ('reticulin negative').

The differences between the presenting features of these two groups in age distribution, organ enlargement, PAS score, and white blood cell count were not statistically significant (Table). The reticulin-negative group contained more boys but the difference did not reach the 5% level of statistical significance ($\chi^2 = 3.16$, df = 1, $P = 0.08$). One patient in each group was identified as a case of T-cell leukaemia. One child was Asian, the remainder were white. One child in the reticulin-negative group had Down's syndrome. All patients received a standard induction protocol for ALL and were treated by cranial irradiation with intrathecal methotrexate. No statistically significant difference was found between the mean white cell counts for each group during remission.

Table  Comparison of presenting features in patients with and without a pathological increase in reticulin

<table>
<thead>
<tr>
<th>Reticulin increase*</th>
<th>Median age (years)</th>
<th>Sex</th>
<th>Median WBC ($\times 10^9$/l)</th>
<th>Marked organ enlargement</th>
<th>Median PAS score</th>
</tr>
</thead>
<tbody>
<tr>
<td>0, +</td>
<td>5-8</td>
<td>M</td>
<td>3-20-4</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>++, +++</td>
<td>6-0</td>
<td>F</td>
<td>10-11</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>P value</td>
<td>0.8</td>
<td>0.08</td>
<td>0.26</td>
<td>-</td>
<td>0.88</td>
</tr>
</tbody>
</table>

*+ = Slight; ++ = moderate; +++ = considerable.

SMF when present at diagnosis cleared completely within three months of attaining remission in the group with ++ reticulin. All patients with +++ reticulin showed some delay in clearing but had all done so by the ninth month of remission. SMF progressively increased in five cases during remission, on two occasions concomitant with disseminated bacterial illness. No cause was found for the increase in the other three cases. In all cases the reticulin cleared within six months. Details of SMF before, during, and after relapse of their leukaemia is available for analysis in 11 of the reticulin-negative group and eight who were reticulin positive. In no case was there an increase in reticulin predating a marrow relapse. Only one patient in the reticulin-negative group developed SMF in relapse, and this cleared in second remission and did not recur in second relapse. In the reticulin-positive group SMF recurred in relapse in four patients, in each case with a considerable increase (+++). This degree of SMF only partially recovered in the one patient who achieved a second remission.

The cellularity of bone marrow smears was assessed as increased, normal, or reduced and there was no significant difference in cellularity between the SMF-positive and -negative cases ($P > 0.06$). In many of the SMF-positive cases there was difficulty in aspiration. Fibrous clots were present in the smear and cellularity was assessed on slides when this had not occurred. There was no correlation between collagen fibrosis, found in 24% of cases, and the amount of reticulin. No cases of severe collagen fibrosis occurred.

Survival and length of first remission for the reticulin-positive and -negative groups were calculated by the life table method and compared by the logrank method (Peto et al., 1977) (Figs 1, 2). Although the curves for both survival and first remission show what appear to be considerable differences, analysis shows that the levels of statistical significance fail to reach the 5% level for first remission ($P = 0.052$) or survival ($P = 0.072$). If the $P$ value for reticulin as a prognostic factor is adjusted for the influence of white cell count the result is a value of 0.171, which confirms that some of the correlation of reticulin with remission time is a consequence of the association of reticulin with a higher white cell count. A further adjustment of the $P$ value for the influence of white cell count and PAS score gives a result of 0.157, further emphasising that the presence of reticulin is not a prognostic factor independent of white cell count or PAS score.

Discussion

Our survey does not confirm the conclusion of Kundel et al. (1964) that SMF indicates a poorer prognosis. Statistical analysis showed that it is either not a prognostic factor independent of white cell count and PAS positivity or it is too weak a factor to be statistically significant.

Serial trephine biopsies on 19 patients who relapsed showed that those who were reticulin-negative at diagnosis were unlikely to develop SMF in relapse. In the relapsed reticulin-positive cases there was a
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Fig. 1 Length of first remission and reticulin content of marrow at diagnosis. Difference just fails to reach the 5% level of statistical significance (P = 0.052).

Fig. 2 Survival time and reticulin content. Better survival of patients with raised reticulin is not statistically significant (P = 0.072).

50% chance that SMF would recur. In no case was it possible to predict relapse by an increase in SMF. Indeed, three patients had a transient rise during remission for no apparent cause and these patients have not relapsed on long-term follow-up.

Classical myelofibrosis is usually assumed to accompany abnormal proliferation of the myeloid/erythroid/megakaryocytic elements of the bone marrow such as occurs in the myeloproliferative syndromes. Secondary myelofibrosis is not usually considered to be a complication of lymphoid disease of the bone marrow. However, our results and those of Kundel et al. show clearly that it is found in a number of patients with lymphoid disease and also that children may be affected as well as adults. This suggests that myelofibrosis may accompany leukaemic myeloproliferative disorders within the bone marrow of any cell type, possibly caused by the products of cell death (Policard, 1962).

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References


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