Autopsy Findings in Leukaemia

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Out of 38 leukaemic cases only 16 had extensive leukaemic infiltration at death. 15 patients had slight or moderate and 7 no infiltration at all. 12 of the 15, and 5 of the 7 died with septicaemia. The latter patients must have died of complications rather than of the leukaemia itself.

Although it has been possible to reduce the incidence of septicaemia during life, terminal septicaemia does not yet seem to be preventable. Septicaemia was revealed at autopsy in 27 of 38 patients; 25 of these also had clinical signs of septicaemia before death. Necrotizing gastrointestinal lesions may cause endogenous infection.

In the present material, almost every second patient had fungal septicaemia. Out of 7 patients having oral candidiasis in vivo 5 had systemic candidiasis at autopsy, but only half of the patients with systemic candidiasis had visible oral growth.

Modern treatment of leukaemia seems to be able to prevent intracranial haemorrhage in 90% of the cases.

On the other hand, vacuolization of muscle and liver tissue was a frequent finding in leukaemia. It is suggested as being caused by fatty degeneration. Vacuolization of myocardial cells was found in 7 out of 13 cases. Among these 7, 4 had had intermittent hypokalaemia.

Key words: autopsy findings – acute leukaemia – candida – septicaemia

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Modern haematology tries to achieve as many complete remissions as possible in acute leukaemia in relapse, as well as in the acute, so-called blastic phases of chronic leukaemia. This is done by vigorous cytostatic therapy, and by efforts to prevent complications which may become fatal before a renewed remission is achieved. The most important of these complications are septicaemia and haemorrhage (Silver et al. 1958, Frei et al 1965, Hersh et al 1965, Viola 1967, Armstrong et al 1971, Hughes 1973, Atkinson et al 1974).

One of the purposes of the present work

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was to study which of these complications is more common. A second purpose was to examine whether bacterial infection is more or less common than fungal infection at death.

It is well known that infection in acute leukaemia is secondary to severe granulocytopenia. However, it is not known at present how often the final granulocytopenia is caused by remaining leukaemic marrow infiltration and how often marrow aplasia is the cause. To investigate this was the third purpose of our study.

MATERIAL AND METHODS

Material

The material used in this study is from the years 1965–1975 but mainly from the past 5 years. Charts, autopsy specimens, in vivo bone marrows, and autopsy protocols of 25 patients with acute myeloblastic leukaemia, 8 patients with acute lymphoblastic leukaemia, 1 patient with chronic lymphocytic leukaemia, and 4 patients with chronic myeloid leukaemia were examined retrospectively. Several patients with chronic leukaemia, where no autopsy was performed, were excluded.

Methods

Autopsies performed during the course of this study include microscopy of all organs, but autopsy records collected from the files usually include only bone marrow, spleen, lymph nodes and liver. The sections were stained with haematoxylin-eosin and van Gieson. Sections from all cases were stained according to gram, periodic acid Schiff, and the methenamin silver methods in order to search for bacteria and fungi. Sections were scrutinized for leukaemic infiltration which was graded none, slight or moderate, and extensive; special efforts were made to reveal even very slight infiltration. In all tissues, a careful search was made for the presence of bacteria or mycelia. Single or few bacteria or mycelia were disregarded, but foci or larger clumps in organs other than lungs or intestine were considered as histological evidence of septicaemia. Fever over 39°C for 2 or more consecutive days was considered as a clinical sign of septicaemia. In 17 cases, cultures from lungs, liver, spleen and heart blood were also obtained. Positive cultures at autopsy were considered as microbiological evidence of septicaemia.

Bone marrow smears taken in vivo were stained according to May-Grünwald-Giemsa. Bone marrow sections were stained with haematoxylin-eosin.

RESULTS

Leukaemia

In many cases there was no evidence of leukaemia at the macroscopical autopsy examinations; only the microscopical evaluation established the diagnosis. In some cases (as discussed below) not even the microscopical examination revealed evidence of leukaemia. In these cases, the diagnosis of leukaemia was based on the bone marrow material collected in vivo.

Bone marrow sections were available in 38 patients. Only 16 of these had extensive leukaemia. They had hypercellular marrows with extensive leukaemic infiltration, little or no fat and, in 13 of the cases, extra-medullary leukaemic infiltration.

The remaining 22 cases did not have fullblown leukaemia; 9 of these had aplastic or hypoplastic bone marrow, and most of the remaining 13 had little or no leukaemic infiltration, but active myeloid and erythropoietic haemopoiesis. Thus, 7 of the patients died without demonstrable leukaemia and 12 with slight or moderate leukaemic infiltration.

Septicaemia

Histopathological or bacteriological signs of septicaemia could be found in 27 of the 38 patients. 20 of these patients had bacterial
clumps in the various organs (Figure 1), although no inflammatory response could be noted. Most of the septicaemia patients had both clinical and postmortal signs of septicaemia (Table 1). 12 had fungal septicaemia, extrapulmonary by definition in all 12, and in addition pulmonary in 10 patients (Figure 2). Of 7 patients with oral candidiasis in vivo before death, 5 had systemic candidiasis at autopsy and 2 had extensive pulmonary candidiasis. In contrast, 5 patients without oral candidiasis also had systemic fungal infection.

Most patients with septicaemia had granulocytopenia, and vice versa, but 6 patients developed septicaemia although they had more than 500 granulocytes/μl, and 3 escaped septicaemia with fewer granulocytes (Table 2).

**Gastrointestinal lesions**

Only in 5 patients were satisfactory microscopical sections of the small or large intestine available. In 3 of these, only normal postmortal changes and scanty bacteria in the mucosa were present. In 2 others lesions were found; one had submucosal bacterial clumps, surprisingly mostly gram positive, and one showed mucosal sloughing.

**Haemorrhage**

10 out of the 38 patients had appreciable haemorrhage, which in 4 could conceivably

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Figure 1. Large foci of bacilli in liver tissue. A large number of the liver cells are necrotic but there is no cellular inflammatory response. H & E, x 400.

Figure 2. Focus of candida spores in kidney. Note absence of inflammatory response. H & E, x 400.
TABLE 1
Correlation between clinical and postmortem signs of septicaemia

<table>
<thead>
<tr>
<th>Clinical and autopsy evidence</th>
<th>Clinical sign; no unequivocal histological evidence</th>
<th>Only autopsy evidence</th>
<th>Neither</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>6*</td>
<td>3**</td>
<td>4***</td>
</tr>
</tbody>
</table>

Probable cause of death: * Mainly severe leukaemic infiltration in various organs, cardiac failure, and pneumonia. 2 cases had positive blood cultures; 4 had single mycelia in some organs.
** 2 out of 3 had fungal septicaemia. 1 patient had bacterial septicaemia.
*** 1 patient had a localized abscess and 2 had cardiac failure.

TABLE 2
Clinical evidence of septicaemia, degree of leukaemia and the terminal granulocyte count in 38 leukaemics with septicaemia at autopsy

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Clinical septicaemia</th>
<th>No clinical septicaemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone marrow inf.</td>
<td>None</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Extensive</td>
<td>14</td>
</tr>
<tr>
<td>Septicaemia at autopsy</td>
<td>Bacterial</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Fungal + Bacterial</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Fungal</td>
<td>7</td>
</tr>
<tr>
<td>Granulocyte count/μl</td>
<td>0–50</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>50–500</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>500–1500</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>over 1500</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4</td>
</tr>
</tbody>
</table>

have been a contributory cause of death. 2 cases of subarachnoidal haemorrhage (1 very small), 3 cases of intracerebral haemorrhage and 5 cases of gastrointestinal bleeding were found.

Pathologic changes in other organs
Liver cells showed fatty change in 23 out of 38 cases which included all the cases without leukaemic infiltration in the bone marrow (Figure 3). No recorded abuse of alcohol was found in these patients.
Vacuolization of myocardial cells was found in 7 out of 13 cases (Figure 4).

Among these 7, 4 had had hypokalaemia intermittently.

DISCUSSION

Leukaemia
Of the patients in the study, only 4 had active chemotherapy given during the 10 days before death, but 19 had massive leukaemic infiltration at autopsy. It is a debatable question whether more active or different chemotherapy could have induced remission in these patients.

However, not all patients died with a picture of extensive leukaemia. In 7 out of 38
patients no leukaemia at all could be found in the autopsy material and in 12 cases the leukaemia was slight or moderate. Many of these patients died with septicaemia secondary to granulocytopenia. These patients could perhaps have been saved by more rigorous preventive and therapeutic measures against septicaemia (Powles & Russell 1975, Scarffe 1975). The cause of the granulocytopenia in these patients could have been the cytostatic treatment or a hypothetical leukaemic stem cell damage.

Septicaemia

Systemic attempts including numerous blood cultures were made to discover bacterial septicaemia during life, and most patients had both autopsy and clinical evidence of septicaemia. However, negative blood cultures cannot absolutely exclude septicaemia, probably because bacteraemia lasts only a short time. This suggestion is supported by the many negative cultures of heart blood at autopsy in the present study, in spite of positive cultures in other organs.

During the past few years, increasing measures have been taken, in our department as well as elsewhere, to prevent septicaemia. These measures include patient isolation (Siegel et al 1971, Jensen 1973) and granulocyte transfusions (Borberg et al 1975, Medenica et al 1975, Powles & Russell 1975, Scarffe 1975). Moreover, increas-

Figure 3. Marked fatty change in liver without leukaemic infiltration. H & E, x 250.

Figure 4. Myocardial cells showing marked vacuolization. H & E, x 400.
ing knowledge of the nature of the septicaemia in leukaemia has facilitated its treatment with antibiotics (Silver et al. 1958, Frei et al. 1965, Hersh et al. 1965, Viola 1967, Armstrong et al. 1971, Hughes 1973, Atkinson et al. 1974). As a result, a decreasing incidence and frequency of severe infection in the early stages of leukaemia has been achieved (Lantz et al. 1976). Later, however, the majority of the leukaemic patients still die of terminal, intractable septicaemia.

In previous in vivo studies, infections with *Candida albicans* were found only in a few per cent of all patients (Atkinson et al. 1974). The present autopsy evidence suggests that almost every second septicaemic patient may have fungal infections. Fungal infections are more difficult to diagnose in vivo than bacterial infections, and are therefore sometimes overlooked. It is our impression that long-lasting, low, refractory continuous fever without signs of bacterial infection, often signifies systemic candidiasis. Even slight oral candidiasis almost always signifies systemic candida infection.

**Gastrointestinal lesions**

It has been suggested previously that endogenous, gram negative infection in leukaemia may be caused by penetration of intestinal bacteria into the circulation via necrotizing ulcers in the ileum and colon (Steinberg et al. 1973). In some present cases similar observations were made. This is not unexpected since ulceration and abscess formation at the oral and anal end of the gastrointestinal canal are often observed in acute leukaemia.

**Haemorrhage**

Modern prevention of haemorrhage in thrombocytopenic patients with platelet transfusions (Höcker & Reizenstein 1975) appears to be relatively effective; in only 4 out of the 38 present patients did bleeding seem to be an appreciable contributory cause of death.

**Other organs**

Separate studies have demonstrated a decrease in the serum potassium and total body potassium value (Lantz 1975, Höcker & Reizenstein 1974). Further studies of the degenerative changes of muscle and liver cells which may contribute to the decrease found in total body potassium are now in progress.

**REFERENCES**


