Surgery for the acute abdomen in adults with leukaemia

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Summary: In a retrospective analysis five of 104 patients with acute leukaemia undergoing cytotoxic chemotherapy developed abdominal signs requiring emergency surgical exploration. Two common features in these patients were the inclusion of cytosine arabinoside in their treatment regimen and a necrotizing lesion involving the terminal ileum, appendix, and right colon. Appendicectomy was performed in two and hemicolecctomy in three. Of the patients receiving high-dose cytosine arabinoside one died in the immediate post-operative period and two after recovery from surgery but before marrow regeneration; the remaining two patients received conventional dose cytosine arabinoside, and both recovered. The inclusion of this agent is standard in modern treatment programmes, resulting in significant improvement in long-term disease-free survival, so that a greater awareness of this complication is necessary. Early surgery, utilizing modern support techniques, is recommended as feasible and appears to offer the only realistic chance of survival.

Introduction

The development of an acute surgical abdomen during the pancytopenic period following the administration of cytotoxic chemotherapy for leukaemia is well recognized (Seligman et al., 1972; Steinberg et al., 1973; Sherman & Woolley, 1973; Rasmussen & Freeman, 1975; Exelby et al., 1975; Varki et al., 1979; Kies et al., 1979; Lehman & Armitage, 1980; Yates et al., 1982; Mackinnon et al., 1982; Jones & Abramson, 1983). In addition to coincidental causes such as acute appendicitis, a specific syndrome of necrotizing enterocolitis has been recognized (Steinberg et al., 1973; Sherman & Woolley, 1973). In view of the steadily improving results for long-term disease-free survival and possible cure in acute leukaemia (Jacobs & Gale, 1984; Lister & Rohatine, 1982), it is important to be aware of this complication, with management centred on early surgical exploration and intensive support which includes an appropriate antibiotic regimen and effective granulocyte and platelet transfusions. Considering the extremely poor prognosis of this syndrome (Steinberg et al., 1973; Sherman & Woolley, 1973; Yates et al., 1982) and evidence that surgical management offers an alternative option (Rasmussen & Freeman, 1975; Exelby et al., 1975; Lehman & Armitage, 1980), we present our experience with five such consecutive patients.

Materials and methods

A retrospective analysis of the case records from 104 consecutive patients with acute leukaemia admitted to the Groote Schuur Hospital, Cape Town, between July 1982 and March 1984 was undertaken. Five patients developed an acute abdomen requiring surgical exploration. These case records were analysed to correlate haematological diagnosis, chemotherapy, and clinical presentation with laparotomy findings and post-operative course.

Results

The incidence of patients requiring major abdominal surgery in this group was 5%. The clinical and laboratory features are summarized in Table 1. There were four males and one female, with a mean age of 33.8 years (range 14–62 years). Three had a diagnosis of acute myeloblastic and two of acute lymphoblastic leukaemia. All were severely neutropenic and thrombocytopenic at the time of presentation with their abdominal symptoms. All had received extensive prior chemotherapy. Patients 1 to 4 had leukaemia refractory to standard induction regimens, while patient 5

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Table I  Pertinent features of 5 patients who developed abdominal catastrophes

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>White cell count $\times 10^3/\ell$</th>
<th>Blood culture</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>62</td>
<td>F</td>
<td>Refractory AML*</td>
<td>0.4</td>
<td>Bacillus species</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(contaminant)</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
<td>M</td>
<td>Refractory ALL†</td>
<td>0.1</td>
<td><em>Staphylococcus epidermidis</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td><em>Streptococcus bovis</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(?contaminant)</td>
</tr>
<tr>
<td>3</td>
<td>23</td>
<td>M</td>
<td>Refractory AML</td>
<td>0.4</td>
<td>Negative</td>
</tr>
<tr>
<td>4</td>
<td>14</td>
<td>M</td>
<td>Refractory ALL</td>
<td>0.7</td>
<td>Negative</td>
</tr>
<tr>
<td>5</td>
<td>20</td>
<td>M</td>
<td>AML in second remission</td>
<td>0.3</td>
<td>Negative</td>
</tr>
</tbody>
</table>

*AML: acute myelocytic leukaemia; ALL: acute lymphoblastic leukaemia.

was in a second remission and receiving consolidation chemotherapy. Blood cultures yielded either negative results or growth of contaminant organisms and were consequently not helpful in guiding the choice of antibiotics.

The details of the acute abdominal presentation are summarized in Table II. All patients had the onset of symptoms within an average of 8 days (range 3–13 days) of commencing chemotherapy. A variety of chemotherapeutic agents were given, but cytosine arabinoside was common to all the programmes. Two patients (Nos. 1 and 5) received conventional doses, while patients 2, 3 and 4 received high-dose cytosine arabinoside defined as 3 g/m$^2$ every 12 hours for 6 days in patient 2 and 2 g/m$^2$ every 12 hours for 5 days in patients 3 and 4. The clinical presentation in all patients was that of a surgical abdomen, characterized by acute onset of colicky pain associated with fever and frequently with diarrhoea, which was blood stained in one patient (No. 4). Three patients had nausea with vomiting. Abdominal examination revealed signs of peritoneal irritation, generalized in three, but more localized to the right lower quadrant in two. Radiographic findings in two patients were consistent with the presence of a paralytic ileus. Findings at laparotomy (Table II) included non-specific haemorrhagic or gangrenous bowel in four, with acute appendicitis in one. In three patients the

Table II  Features at the time of presentation with signs and symptoms of acute abdomen

<table>
<thead>
<tr>
<th>Patient</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days from chemotherapy to symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>Cytosine arabinoside VP16-213 Adriamycin</td>
<td>High-dose cytosine arabinoside m-AMSA</td>
<td>High-dose cytosine arabinoside</td>
<td>High-dose cytosine arabinoside</td>
<td>Cytosine-arabinoside VP16-213 Adriamycin</td>
</tr>
<tr>
<td>Clinical presentation</td>
<td>Nausea</td>
<td>Vomiting</td>
<td>Diarrhoea</td>
<td>Right lower quadrant peritonitis</td>
<td>Peritonitis</td>
</tr>
<tr>
<td>Laparotomy</td>
<td>Oedematous right colon and caecum</td>
<td>Gangrenous right colon and caecum</td>
<td>Right hemicolec-tomy</td>
<td>Gangrenous right colon and caecum</td>
<td>Right hemicolec-tomy</td>
</tr>
<tr>
<td>Surgical procedure</td>
<td>Right hemicolec-tomy</td>
<td>Died 10 days post-operative</td>
<td></td>
<td>Died 3 days post-operative</td>
<td>Died 14 days post-operative</td>
</tr>
<tr>
<td>Outcome</td>
<td>Recovered</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
surgeon performed right hemicolectomy, and in two
the appendix was removed. Two patients who received
conventional doses of cytosine arabinoside recovered
fully simultaneously with marrow regeneration. The
three patients who received high-dose cytosine arabi-
oside died within 2 weeks. Although patients 2 and 4
had recovered from surgery, their deaths were
associated with the complications of prolonged
marrow aplasia, while patient 3 died shortly after
surgery.

Discussion

The incidence of patients requiring major abdominal
surgery in this series is 5%, which approximates
closely to that reported by others (Wagner et al., 1970;
Steinberg et al., 1973; Exelby et al., 1975; Yates et al.,
1982), although the development of an acute abdomen
has been reported to occur in as many as 28% of
patients with acute leukaemia (Jones & Abramson,
1983). The clinical presentation of these five patients
was characteristic and included, within several days of
receiving chemotherapy, the appearance of fever,
vomiting, diarrhoea, gastrointestinal bleeding, abdomi-
al peritonitis, with localization in the right lower
quadrant of the abdomen. Radiographic changes are
usually not specific (Wagner et al., 1970; Exelby et al.,
1975). This syndrome, which has been variously labelled as typhilitis (Wagner et al., 1970; Varki et al.,
1979), neutropenic enterocolitis (Kies et al., 1979), the
ileocaecal syndrome (Sherman & Woolley, 1973), and necrotizing enterocolitis (Stein-
berg et al., 1973; Yates et al., 1982) should now be
sufficiently well characterized, occurring frequently in
patients with acute leukaemia who are receiving
intensive induction or consolidation chemotherapy
during the phase of temporary marrow aplasia with
peripheral blood granulocytopenia and thrombo-
cytopenia.

The pathogenesis is not clear, although primary gut
necrosis with secondary infection appears to be the
likeliest explanation (Leach et al., 1969; Slavin et al.,
1978). The reason for the frequent involvement of the
caecum and ascending colon is obscure. The syndrome
seems to be most frequently associated with the use of
cytosine arabinoside and an anthracycline (Yates et al.,
1982; Jones & Abramson, 1983), although it has
been reported following a variety of other chemother-
apeutic regimens. The present series is remarkable
for the association of the syndrome with the prior or
concomitant administration of high-dose cytosine
arabinoside (Johnson et al., 1985). Prolonged marrow
aplasia is a feature of this chemotherapy programme
and although two of the patients recovered from the
surgery, survival ultimately depends also on the return
of peripheral circulating granulocytes and platelets.

The management of this catastrophic complication
has been controversial (Johnson et al., 1985), and
although recovery without surgical intervention is
exceptional (Table III), survival appears to depend on
a combination of well planned surgery with recovery
of bone marrow function. The role of broad spectrum
antibiotics, with platelet and granulocyte transfusions,
has contributed significantly to the support of the
patient during the post-operative period until marrow

<table>
<thead>
<tr>
<th>Author</th>
<th>Patients treated surgically</th>
<th>Outcome (recovered)</th>
<th>Patients treated conservatively</th>
<th>Outcome (recovered)</th>
</tr>
</thead>
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<tr>
<td>Seligman (1972)</td>
<td>2</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steinberg (1973)</td>
<td>2</td>
<td>0</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Sherman (1973)</td>
<td>3</td>
<td>1</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Rasmussen (1975)</td>
<td>5</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exelby (1975)</td>
<td>9</td>
<td>5</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Slavin (1978)</td>
<td></td>
<td></td>
<td>28</td>
<td>0</td>
</tr>
<tr>
<td>Varki (1979)</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kies (1979)</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lehman (1980)</td>
<td>3</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yates (1982)</td>
<td>2</td>
<td>2</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>Mackinnon (1982)</td>
<td>5</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jones (1983)</td>
<td></td>
<td></td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>34</td>
<td>24</td>
<td>73</td>
<td>2</td>
</tr>
</tbody>
</table>

(71%) (3%)
recovery occurs, and is probably the reason for the increasing proportion of patients who survive and recover from surgery (Table III).

Conclusions

Five patients who developed an acute surgical abdomen while receiving chemotherapy for acute leukaemia are reported. The syndrome of necrotizing colitis is characterized, and its association with the use of high-dose cytosine arabinoside has been noted.

An approach to management utilizing modern supportive facilities together with surgical interven-
tion appears to offer the only chance of survival. This attitude is considered worthwhile in view of the improved long-term outlook in patients with acute leukaemia, many of whom may now be cured.

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