Serious complications following treatment of chronic idiopathic thrombocytopenic purpura

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Summary: Six patients had serious complications as consequences of treatment of idiopathic thrombocytopenic purpura. Five had splenectomy-related complications, one of them developed fatal intra-abdominal bleeding. Three patients acquired operation-related serious infection, two of them died. Serious neutropenia after vinblastine-loaded platelets occurred in one patient leading to pseudomonas septicaemia and panophthalmitis with permanent vision loss of left eye. Recurrence thrombocytopenia occurred in every case during serious complications. Early detection by awareness of the possibility of serious complications can reduce morbidity and mortality occurring after therapy of idiopathic thrombocytopenic purpura.

Introduction

Chronic idiopathic thrombocytopenic purpura (chronic ITP) is an autoimmune disorder characterized by destruction of autoantibody-bound platelets by the reticuloendothelial system. In most cases, the responsible autoantibody is IgG with or without fixed complement C3. Various methods have been used for the treatment of chronic ITP. Splenectomy and administration of corticosteroids are the mainstays but approximately 25% of patients have disease refractory to these conventional measures. The patients in whom refractory ITP develops undergo therapy with vincristine, azathioprine, cyclophosphamide, vinblastine-loaded platelets, danazol, colchicine and high-dose intravenous gammaglobulin. Each measure can lead to undesirable side effects, and since many patients receive more than one therapeutic regimen, serious consequences may occur. These complications, mostly infection related, can lead to serious, and sometimes fatal, damage especially if they are not recognized.

We report here serious complications following treatment of 6 chronic ITP patients.

Case reports

During January 1962 to December 1985, 698 ITP patients were seen at our haematology unit.

Diagnosis was made according to published criteria. All cases received corticosteroids as initial therapy. Therapeutic splenectomies were performed in 146 patients (20%), 43 of whom had significant and prolonged episodes of thrombocytopenia after splenectomy and were considered to have refractory ITP. Some refractory cases received immunosuppressive agents alone or combined with corticosteroids as long-term or intermittent therapy. Six patients (detailed below) were found to have serious consequences of treatments. The relevant clinical data are summarized in Table I.

Case 1

A 21 year old woman was referred from another hospital after failure of conventional corticosteroid administration for ITP. When she was first seen in our haematology clinic, a severe cushingoid appearance was observed. Splenectomy was performed and resulted in the platelet count rising from 0 to 100 x 10^9/l in 5 days. On the seventh day postoperatively, she complained of back pain which was followed by confusion and a hypotensive episode. In spite of whole blood transfusion her condition deteriorated and sudden cardiac arrest developed before an exploratory laparotomy could be done. Autopsy revealed haemoperitoneum of 3 litres and also haemorrhage with necrosis of the tail of the pancreas.

Case 2

A 43 year old woman attended the Gynaecology
### Table 1  Summary of clinical data

<table>
<thead>
<tr>
<th>Case (sex)</th>
<th>Age (years)</th>
<th>Duration of ITP before serious complication</th>
<th>Treatment received</th>
<th>Minor side-effect of treatment</th>
<th>Treatment leading to serious complication</th>
<th>Serious complication</th>
<th>Platelet count at time of serious complication ($\times 10^9/l$)</th>
<th>Prednisolone received during complications (mg/day)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (F)</td>
<td>21</td>
<td>3 y</td>
<td>Steroids, splenectomy (elective)</td>
<td>Severe Cushing's effect</td>
<td>Splenectomy</td>
<td>Intraperitoneal haemorrhage</td>
<td>5</td>
<td>40–60</td>
<td>Dead</td>
</tr>
<tr>
<td>2 (F)</td>
<td>43</td>
<td>5 mo</td>
<td>Steroids, splenectomy (elective)</td>
<td>Cushing's effect, steroid myopathy</td>
<td>Splenectomy</td>
<td>Subdiaphragmatic abscess, septicaemia</td>
<td>10–50</td>
<td>40–60</td>
<td>Dead</td>
</tr>
<tr>
<td>3 (F)</td>
<td>40</td>
<td>5 y</td>
<td>Steroids, splenectomy (elective)</td>
<td></td>
<td>Splenectomy</td>
<td>Lung abscess, septicaemia</td>
<td>0–20</td>
<td>20–40</td>
<td>Dead</td>
</tr>
<tr>
<td>4 (F)</td>
<td>20</td>
<td>3 mo</td>
<td>Steroids, splenectomy (elective)</td>
<td>Severe Cushing's effect</td>
<td>Splenectomy</td>
<td>Subdiaphragmatic abscess</td>
<td>5–10</td>
<td>20–40</td>
<td>Survives with persistent thrombocytopenia</td>
</tr>
<tr>
<td>5 (F)</td>
<td>40</td>
<td>23 y</td>
<td>Steroids, splenectomy (emergency)</td>
<td>Cushing's effect</td>
<td>Splenectomy</td>
<td>Ischaemic gangrene of jejunum</td>
<td>5–20</td>
<td>40</td>
<td>Survives with persistent thrombocytopenia</td>
</tr>
<tr>
<td>6 (F)</td>
<td>19</td>
<td>3 y</td>
<td>Steroids, splenectomy (elective) vincristine cyclophosphamide vinblastine-loaded platelet</td>
<td>Cushing's effect</td>
<td>Vinblastine-loaded platelet</td>
<td>Pseudomonas septicaemia and panophthalmitis</td>
<td>0</td>
<td>30–60</td>
<td>Permanent loss of vision in left eye</td>
</tr>
</tbody>
</table>
Department because of hypermenorrhoea for 3-4 months. Dilatation and curettage showed endometrial hyperplasia with squamous metaplasia of the endometrium. Bleeding per vaginam continued after curettage and the complete blood count showed moderate thrombocytopenia. The bone marrow examination was consistent with ITP. Prednisolone 40 to 60 mg per day resulted in a platelet count of $100 \times 10^9/\text{l}$ within 4 weeks of medication. Bleeding per vaginam decreased but was not entirely stopped. After abdominal hysterectomy and splenectomy at the same time the platelet count rose to $130 \times 10^9 - 450 \times 10^9/\text{l}$. Prednisolone was tapered off in 6 weeks, after which low grade fever occurred. She was readmitted to the hospital 4 weeks later. A provisional diagnosis of systemic lupus erythematosus was made on the basis of fever, alopecia, and polyarthralgia but the immunological profiles did not confirm this diagnosis. She was discharged 3 weeks later on prednisolone 60 mg/day but was admitted again 2 weeks later because of high grade fever. At this time, clinical examination led to a diagnosis of subdiaphragmatic abscess, confirmed by exploratory laparotomy. Her postoperative condition was complicated by enterocutaneous fistula and septicaemia which did not respond to systemic antibiotics. She expired 3 weeks after the last operation.

Case 3

A 40 year old woman was first seen 5 years previously because of anaemia and thrombocytopenia. Evaluation at that time pointed to the diagnosis of autoimmune haemolytic anaemia and thrombocytopenia (Evans’ syndrome). Repeated studies of LE cells and antinuclear factors were negative. Prednisolone and cyclophosphamide were used with partial response and occasional relapse of anaemia and thrombocytopenia. One serious episode of thrombocytopenia required therapeutic splenectomy which brought the platelet count to normal level within one week postoperatively. Pneumonia of the left lower lobe and transient thrombocytopenia developed 4 weeks later. Conventional antibiotic therapy improved the infectious process and corticosteroids reversed thrombocytopenia to normal. However, 4 weeks later both episodes relapsed with progression of pneumonia to lung abscess. The responsible organism was identified as Proteus species and appropriate antibiotics were used. Mucosal bleeding required high dose corticosteroids which retarded clearance of infection. Uncontrollable sepsis was the leading cause of death 10 weeks after last admission.

Case 4

A 20 year old woman was diagnosed as having ITP and referred from a rural hospital because of poor response to corticosteroids. Elective splenectomy was considered. The operation was uneventful but the postoperative condition was complicated by fever and recurrent thrombocytopenia on the ninth day postoperatively. Exploratory laparotomy revealed a left subdiaphragmatic collection from which bacteriological culture showed the same microorganism as on blood culture, i.e., Salmonella group B. It took at least 5 weeks after the last operation before she could be discharged from the hospital with continued thrombocytopenia.

Case 5

A 40 year old woman was first diagnosed as having ITP in 1963 when she was 17 years old. The major problems were generalized ecchymoses and hypermenorrhoea. Prednisolone was given intermittently during bleeding episodes with partial response. She refused therapeutic splenectomy. In January 1985, she experienced sudden onset of severe headache. Computed tomography showed an intracerebral haematoma at the left angular gyrus. The platelet count at that time was zero. Emergency splenectomy was performed and the platelet count rose to $20 \times 10^9/\text{l}$ with improvement of the neurological deficits. She was maintained on prednisolone 40 mg/day. Three weeks after splenectomy she experienced sudden onset of generalized abdominal pain. Physical examination revealed signs of peritoneal irritation. The platelet count remained below $20 \times 10^9/\text{l}$. Exploratory laparotomy was decided on after 4 units of platelet concentrate were transfused. Serosanguinous ascites and a six-inch gangrenous segment of jejunum was found, 6 inches away from the duodeno-jejunal junction. Resection with end-to-end anastomosis was performed without postoperative complication. Surgical section revealed thrombotic occlusion of corresponding mesenteric veins.

Case 6

A 19 year old woman had petechiae and ecchymoses 3 months before ITP was diagnosed. Her thrombocytopenia was partially reversed by high dose prednisolone (more than 40 mg/day). The Cushing effect was, however, intense and splenectomy was decided on. Complete recovery was achieved for only 3 months postoperatively and thrombocytopenia with occasional mucosal bleeding recurred. Prednisolone and cyclophosphamide were
used without any promising result. Three daily
doses of vinblastine-loaded platelets were tried. High fever, diarrhoea, and abdominal distension
developed at the same time when marked leuko-
penia (1.3 x 10^9/l) occurred, 2 days after the last
dose of vinblastine-loaded platelets. A panop-
thalmitis rapidly followed which proved to be due
to Ps. aeruginosa septicaemia. She subsequently
recovered from the serious episode but with
permanant loss of vision in her left eye.

A summary of clinical data is shown in Table I. All patients received corticosteroids as an initial
treatment and were either steroid-nonresponsive or
steroid-dependent. Cushing’s effect developed in 5
patients, and was severe in two. Serious compli-
cations occurred as a consequence of splenectomy
in 5 patients (Cases 1–5). One patient (Case 6) had
pseudomonas septicaemia following vinblastine-
induced leuokpenia. Three who had splenectomy-
related complications died, one from massive
intra-abdominal bleeding, two from uncontrollable
infection. Thrombocytopenic episodes usually oc-
curred during serious complications.

Discussion

Corticosteroids are accepted as conventional treatment of ITP. However, long-term cortico-
steroid administration can lead to many undesirable
effects. Among them are hypertension, hyper-
glycaemia, Cushing’s appearance, myopathy and
increased susceptibility to infection. These side
effects, especially the last one, may have some
considerable influence on the outcome of splen-
ectomy. Our first case demonstrated an effect of
long-term corticosteroid administration on tissue
healing. Rupture of a ligated vessel was a possible
cause of the fatal intra-abdominal bleeding. Corticosteroids might have delayed clearance of
bacterial infections in Cases 2–4.

Splenectomy has been accepted as an effective
treatment of ITP after failure of corticosteroids.
Serious complication following splenectomy is un-
common. Block et al. reported three post-
operative deaths (4.4%) among 67 ITP patients
undergoing splenectomy. In their series two patients
died within 10 days after operation from the effects
of haemorrhage. It is possible that corticosteroids
might have retarded clearance of microorganisms
leading to uncontrollable infections. Corticosteroids
may also hamper inflammatory reaction and delay
early recognition of infectious process, as occurred
in patients 2 and 3.

One patient had ischaemic gangrene of the
jejunum 3 weeks after splenectomy. This com-
plication was not the result of rebound thrombo-
cytosis since the platelet count was low at that time.
Although detection of lupus circulating anti-
coagulant was not done, the negative immune
profiles and the occurrence of such complications at
short duration after splenectomy made lupus
circulating anticoagulant an unlikely cause of
intestinal ischaemia. The relationship between
splenectomy and intestinal gangrene is unknown
although one can speculate about disturbance of
the mesenteric circulation during the operation.

A variety of non-steroidal immunosuppressive
agents have been used in the treatment of ITP
refractory to splenectomy and use of cortico-
steroids. In order to reduce both short and long-
term hazards from such agents, a variety of therapeu-
tic options including dosage modification have been tried. Vinblastine-loaded platelets
were claimed to be effective in refractory ITP. Unless
removal of free drug is inadequate, serious side
effects including neutropenia are unusual. Our
patient 6 was an exceptional case, having severe
granulocytopenia following vinblastine-loaded
platelets. Permanent loss of vision in her left eye
was a serious consequence of complicating pseudo-
monas septicaemia and panopthlmitis.

Clinicians need to be aware that serious
complications may occur in ITP patients during
treatment. Early recognition of such complications
is the only way to save the patients. Among
predisposing factors are combination therapy
especially with corticosteroids and splenectomy.
Elective splenectomy should be avoided in any
patients with Cushing’s effect. Recurrent thombo-
cytopenia was a constant finding and may be used,
combined with other manifestations, as a warning
sign of serious consequences.

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