Cerebral involvement with disseminated intravascular coagulation in intestinal disease

F. P. Ryan, W. R. Timperley, F. E. Preston, and C. D. Holdsworth

From the Departments of Medicine, Neuropathology, and Haematology at the Royal Infirmary, Sheffield

SUMMARY Over a two-and-a-half-year period at the Sheffield Royal Infirmary, six patients developed disseminated intravascular coagulation as a serious complication of intestinal disease. There was clinical evidence of cerebral involvement in all six patients, and small vessel thrombi were demonstrated in the brains of all three cases examined post mortem. Where the true significance of the cerebral disorder was not recognised, this led to delay in the diagnosis with serious risk to the patient. In the single case in which the diagnosis was made early, the intravascular coagulation was completely reversed with heparin therapy.

Previous authors have demonstrated an increased incidence of large vessel thrombosis in inflammatory bowel disease (Bargen and Barker, 1936; Graef et al., 1966). Cerebral venous thrombosis has been reported as a complication of ulcerative colitis and Crohn's disease (Harrison and Truelove, 1967; Borda et al., 1973; Silverstein and Present, 1971). Coagulation studies in patients suffering from inflammatory bowel disease have shown increased levels of factors V and VIII and fibrinogen, in addition to the well recognised thrombocytosis (Lam et al., 1975). The syndrome of disseminated intravascular coagulation has not, to our knowledge, been reported in intestinal disease. This study was prompted by the unusual presentation of the first case to be described, in whom the florid neurological disorder was found to be misleading.

Patients and methods

The six cases described were collected from admissions to the Sheffield Royal Infirmary over a two-and-a-half-year period. Four patients suffered from Crohn's disease, one patient suffered from ulcerative colitis, and one from coeliac disease. The average age of these patients was 35 years. Summaries of the clinical details are shown in Table 1.

In all six cases, neurological disorder was a prominent feature of the intravascular coagulation syndrome. This always took the form of a diffuse encephalopathy, in five cases beginning with clouding of consciousness and progressing over a period of days to delirium, sometimes with agitation, and finally a deep coma. The sixth patient remained in coma after a general anaesthetic. There was evidence of focal cerebral involvement in two patients, in case 1 with cerebellar signs such as ataxia and dysarthria, and in case 3 in whom Jacksonian convulsions corresponded to focal abnormalities on the electroencephalogram. Well recognised manifestations of disseminated intravascular coagulation, such as petechiae, excessive bruising and a bleeding tendency, were shown by all six patients. However, the relative timing of these manifestations in relation to the onset of cerebral disorder was inconstant, and in cases 1, 4, and 6 the cerebral disorder was the most prominent initial feature so that early diagnosis was dependent on recognition of this type of presentation.

In cases 2, 3, and 4, Gram-negative sepsis was present before the onset of the disseminated intravascular coagulation and, although the intravascular coagulation was a very significant factor in the mortality of these patients, failure to control the sepsis was equally important. In cases 1, 5, and 6 in whom there was no evidence of Gram-negative sepsis, the intravascular coagulation occurred unexpectedly and constituted the main cause of mortality in the two fatal cases.

Plasma fibrinogen was measured using the method of Ellis and Stransky (1961). Serum fibrinogen degradation products (FDPs) were measured using the Burroughs Wellcome haemagglutination-inhibition kit. As soon as disseminated intravascular coagulation was suspected all patients were subjected to serial
Table 1  Summary of clinical details of six cases

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Intestinal condition</th>
<th>Clinical details</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20</td>
<td>Crohn's disease of ileum and colon</td>
<td>Acute onset of confusional state with restlessness and vomiting. Increasingly confused, disorientated, and weak with dysarthria and ataxia. Later coma with purpura, melena, and shock. Died 6 days after onset</td>
</tr>
<tr>
<td>2</td>
<td>23</td>
<td>Crohn's disease of jejunum, ileum, and colon</td>
<td>Admitted in shock with purpura and pyrexia. Confused, disorientated, weak, sluggish pupillary reactions. Later delirium and coma. Blood culture grew coliform. Treated with heparin and antibiotics. Died on third day</td>
</tr>
<tr>
<td>4</td>
<td>26</td>
<td>Crohn's disease of ileum and colon</td>
<td>Recurrent intra-abdominal abscesses after small bowel resection. Confused and irrational. Later purpura and bleeding per rectum. Went on to delirium, coma, and death. Heparin given late</td>
</tr>
<tr>
<td>5</td>
<td>42</td>
<td>Ulcerative colitis, hyposplenism</td>
<td>Immediate shock after pan-protocolectomy. Coma, bleeding from the perineum, and extensive bruising of flanks. Intravascular coagulation diagnosed early and treated with heparin. Intravascular coagulation cured and patient survived</td>
</tr>
<tr>
<td>6</td>
<td>49</td>
<td>Coeliac disease</td>
<td>Untreated coeliac with pancytopenia. Treated with gluten-free diet and oxymethalone. Hb and WBC returned to normal with clinical remission. After 3 months sudden deterioration with abdominal pain and haematuria. IVP normal. Confusion, delirium, and later coma. Heparin given late and patient died</td>
</tr>
</tbody>
</table>

Table 2  Haematological evidence of disseminated intravascular coagulation

<table>
<thead>
<tr>
<th>Case</th>
<th>PT (seconds)</th>
<th>TT (seconds)</th>
<th>Platelets x10^9/l</th>
<th>FDP (mg/l)</th>
<th>Plasma fibrinogen (g/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>17 (12)</td>
<td>N</td>
<td>24</td>
<td>80</td>
<td>N</td>
</tr>
<tr>
<td>2</td>
<td>18 (12)</td>
<td>18 (11)</td>
<td>10</td>
<td>20</td>
<td>N</td>
</tr>
<tr>
<td>3</td>
<td>15 (11)</td>
<td>N</td>
<td>20</td>
<td>40</td>
<td>N</td>
</tr>
<tr>
<td>4</td>
<td>14 (11)</td>
<td>N</td>
<td>&lt;10</td>
<td>640</td>
<td>N</td>
</tr>
<tr>
<td>5</td>
<td>14 (10-5)</td>
<td>14 (10-5)</td>
<td>46</td>
<td>40</td>
<td>N</td>
</tr>
<tr>
<td>6</td>
<td>23 (11)</td>
<td>N</td>
<td>27</td>
<td>80</td>
<td>N</td>
</tr>
<tr>
<td>Normal</td>
<td>150-350</td>
<td>0-20</td>
<td>1-5-3-0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

measurements of the platelet count, prothrombin time, thrombin time, serum FDPs, and plasma fibrinogen. The brain was examined in three of these cases. In four of the five fatal cases a necropsy was performed.

Results

There was haematological evidence of disseminated intravascular coagulation in each case (Table 2). The prothrombin time was significantly prolonged and the platelet count was considerably reduced in each case. The serum FDPs were increased in five cases and were borderline in one. In the latter case, the prolonged thrombin time in the presence of a normal plasma fibrinogen was not corrected by the addition of 1 normal plasma. This, in a patient who was not on heparin therapy, was thought possibly to be due to the antithrombin activity of high molecular weight FDPs.

The strikingly successful response to heparin therapy in case 5 is shown in Figure 1. In spite of intensive care, steroids, and antibiotics, the intravascular coagulation syndrome progressed until heparin was administered.

Necropsy was carried out in cases 1, 2, 4, and 6. Unfortunately, the brain was not examined in case 4.

In case 1 Crohn's disease was found to affect the colon and terminal ileum, and bleeding had occurred from the involved areas of colon and from multiple acute superficial gastric erosions. There was extensive intravascular coagulation with occlusion of the inferior vena cava up to the origin of the renal veins; of medium-sized pulmonary arteries; and of small vessels in the ileum, prostate, pancreas, and heart. The brain was the most severely affected organ. Macroscopically the brain showed multiple petechial haemorrhages, dusky areas of discoloration in the cortical grey matter, particularly in the depths of the sulci, and small areas of early softening in the territory of small penetrating vessels (Fig. 2). These lesions were found in the territory of all three major cerebral arteries on both sides. No major vessel infarcts were present in the brain.

Histologically, numerous medium-sized and small vessels were totally or partially occluded by fibrin-rich thrombus with surrounding ischaemic lesions such as early necrosis, severe vacuolation of cells and neuropil, and small haemorrhages (Fig. 3). The cerebellum was particularly severely affected. Vessels plugged with thrombus were also found in the myocardium, lungs, pancreas, prostate, ileum, and kidneys but none was present in the liver or spleen.

Macroscopical examination of the brain in case 2 showed areas of softening and petechial haemorrhages, and histological examination showed similar features to those described in case 1. In addition
Cerebral involvement with disseminated intravascular coagulation in intestinal disease

ETNAMIL SELLAN
TEST 40- so = 20-10.

Fig. 1 Case 5. Successful response to heparin therapy

Fig. 2 Case 1. Macroscopic section of the brain showing dusky areas on grey matter (areas of ischaemia) and petechial haemorrhages (arrows)
there were some small pyaemic abscesses. Occlusion of small blood vessels with fresh thrombus was also seen in the pulmonary and renal vessels but these organs were less severely involved than the brain.

Necropsy in case 4 showed petechial haemorrhages in the larynx, trachea, and bronchi, and the adrenal glands were haemorrhagic. He had suffered a terminal perforation of the sigmoid colon. Historically, vessels occluded by fresh thrombus were present in the kidneys.

Case 6 showed widespread involvement of many organs by disseminated intravascular coagulation; the brain was the most severely affected. Histological lesions were similar to those described in case 1 but in this case there were several infarcts in the brainstem.

Discussion

In this study haematological evidence of disseminated intravascular coagulation was obtained in every case. The normal plasma fibrinogen levels may be explained by the fact that patients with inflammatory bowel disease tend to have raised plasma fibrinogen levels to start with (Lam et al., 1975).

Postmortem examination confirmed the clinical diagnosis of disseminated intravascular coagulation in all three cases examined.

The trigger mechanisms for the induction of the intravascular coagulation in these patients are undoubtedly complex. While in case 1 the trigger may have been the inflammatory process in the bowel itself, there can be little doubt that, in the other three patients with Crohn's disease, Gram-negative sepsis was the deciding factor. In the one patient with ulcerative colitis and the patient with coeliac disease, hyposplenism may have been an important factor. Since first describing hyposplenism in ulcerative colitis (Ryan et al., 1975) we have come to recognise it as a common complication of this disease. The development of shock and disseminated intravascular coagulation in the early postcolectomy period appears to follow a recurring pattern in such patients. Possibly the impaired clearance of thrombogenic materials by a damaged reticuloendothelial system in these patients may permit the development of a Schwartzman-like reaction (Hjort and Rapaport, 1965).

The fact that neurological disorders, implying...
Cerebral involvement, were a common and prominent feature in these patients was surprising. The pathological findings in the brains were very similar to those reported in diabetic ketoacidosis (Timperley et al., 1974), where such features as confusion, delirium, and coma were also common clinical features.

The prominence of neurological abnormalities in these patients tended to delay the diagnosis. Delay in the institution of therapy with heparin led to further worsening of the intravascular coagulation, often followed by the onset of gastrointestinal bleeding, making therapy with heparin more hazardous. In the patients in whom heparin was withheld or given late, the disseminated intravascular coagulation worsened and the patients died. In the patient suffering from ulcerative colitis, previous experience with the complications of hyposplenism resulted in the diagnosis being made early; in this patient the intravascular coagulation was readily reversed with heparin therapy.

Inflammatory bowel disease is an uncommon cause of death at the Sheffield Royal Infirmary; these cases include the majority of fatalities during the two-and-a-half year period of study. It appears, therefore, that disseminated intravascular coagulation is a common and serious complication in patients dying from inflammatory bowel disease. It is vital to consider the diagnosis of disseminated intravascular coagulation in any patient with intestinal disease who develops an unexplained neurological disorder, particularly of the 'encephalopathic' type described above.

We should like to thank Professor H. L. Duthie and Mr W. Morris Jones for help in the surgical management of these cases; also Dr J. Jarratt who reported the EEG in case 3.

References


