SEVERE INTESTINAL INVOLVEMENT IN WEGENER’S GRANULOMATOSIS: REPORT OF TWO CASES AND REVIEW OF THE LITERATURE

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SUMMARY
The clinical and pathological manifestations of severe intestinal involvement in Wegener’s granulomatosis were studied by a review of the literature and reports of two patients. Altogether, six cases, two females and four males, were studied. One patient developed two episodes of bowel manifestations necessitating immediate surgical interventions. The average age at onset of intestinal symptoms was 43.3 yr (26–55 yr) and, in all cases, the first signs of such manifestations developed within the first 2 yr of disease. Prior to the onset of intestinal symptoms, immunosuppressive therapy was administered in six of seven instances. Acute abdominal pain with signs of peritonitis or distention only constituted the main clinical picture in six of the seven events. The last episode was manifested clinically with profuse diarrhoea with blood and mucus. Of the seven instances of severe intestinal manifestations, the small bowel was involved in two, the large bowel in three, and both the small and large bowel were affected in two episodes. Histological evidence of vasculitis in the bowel was demonstrated in three of the seven biopsy specimens, while in four, ischaemia, inflammation and ulceration were the pathological findings. Intestinal perforation was seen four times and surgery was performed in six of seven episodes. Severe intestinal involvement is rare in Wegener’s granulomatosis. The initial bowel manifestations occur within the first 2 yr of disease, and affect both the large and small bowel. Histologically, vasculitis, ischaemia, inflammation and ulceration are the prevailing findings. Death due to intestinal catastrophe occurred in one of the six patients reported. Most likely, the manifestations are associated with the disease process rather than related to the use of immunosuppressive agents.

KEY WORDS: Wegener’s granulomatosis, Intestinal manifestations.

WEGENER’s granulomatosis is a multisystemic disease of unknown aetiology characterized by necrotizing vasculitis and granulomatous inflammation [1]. Antibodies against cytoplasmic neutrophilic granules (cANCA) are present in ~80% of patients [2]. The disease typically involves the upper airways, the lungs and kidneys, but the inflammatory destructive lesions may develop in almost any organ [3].

Although affection of the gut may be detected at autopsy in a significant number of patients [4], clinical manifestations of severe intestinal disease are infrequently reported [5–8]. The intestinal involvement in Wegener’s granulomatosis is addressed by the reports of two patients from our department and four similar cases described in previous publications.

CASE 1
The patient was a male who in August 1986, at the age of 24 yr, developed fatigue, polyarticular joint pain and sustained low-grade fever. In January 1987, he was troubled by recurrent upper respiratory tract infections, sinusitis, uveitis, weight loss and mouth ulcerations. Radiographs showed pulmonary infiltrates bilaterally and histological examination of a biopsy from the maxillary sinus showed ulcerations and necrotizing vasculitis. A renal biopsy revealed mesangio-proliferative glomerulonephritis. cANCA were positive (titre 320). Later in the disease course (1990), the patient developed recurrent episcleritis, intraorbital granulomas resulting in unilateral blindness and cardiac infarction (1993).

Cyclophosphamide and corticosteroids were administered and, at the end of January 1988, i.v. cyclophosphamide 300 mg every second week and prednisolone 50 mg/day were given. At the beginning of February 1988, he was admitted to hospital because of abdominal pain, constipation, nausea and vomiting. On 19 February, the patient suddenly experienced increasing abdominal pain with signs of peritonitis. Hb was 7.8 g/l, C-reactive protein (CRP) 358 mg/l, serum albumin 19 g/l, and moderate fever developed.

A laparotomy revealed a single large perforation in the distal part of the sigmoid colon, a gangrenous gall bladder, an obliterated cystic artery, and ischaemic changes in the outer parts of the right kidney, and the ascending and transverse colon. The colon and gall bladder were excised. Owing to multiple intra-abdominal abscesses, a second operation was performed 9 days later, and the patient was given antibiotics (gentamycin, penicillin and tinidazole). Treatment with cyclophosphamide was continued. The patient then recovered slowly and was discharged from hospital 3 months later without any abdominal complaints.

Histological examination of the resected colon showed ulceration and vasculitis in medium-sized arteries. Biopsy of the right renal cortex revealed focal segmental proliferative glomerulonephritis with crescents. Histology of the gall bladder showed necrosis of the wall and necrotizing vasculitis of the cystic artery. Granulomas were not found.

CASE 2
The patient was a female who in December 1984, at the age of 44 yr, developed polyarthralgia and recurrent
upper respiratory tract infections. Radiographs revealed pulmonary infiltrations bilaterally. Microscopic examinations of biopsy specimens obtained from the lungs showed necrotizing granulomatous vasculitis. The urine contained a few cellular casts and tests for cANCA were positive. She was treated with oral corticosteroids and cyclophosphamide, but the development of haemorrhagic cystitis necessitated cessation of the latter. During 1987–1994, corticosteroids, trimethoprim and chlorambucil were administered with some beneficial effect.

In October 1986, she was treated with oral corticosteroids, chlorambucil, naproxen and paracetamol. On the 13th of this month, the patient suddenly developed abdominal pain and distention. A laparotomy, performed the next day, revealed free air in the abdomen and severe inflammation of the sigmoid colon. Perforations were not observed. Histological examination of the resected sigmoideum showed serosal and subserosal inflammation. Vasculitis with predominantly mononuclear cells and some eosinophils and giant cells was found in three medium-sized subserosal arteries. Perforations were not detected microscopically. The administration of oral corticosteroids was ceased, but treatment with chlorambucil was continued.

Nine years later, the patient had a serious exacerbation of pulmonary symptoms. Monthly i.v. cyclophosphamide (750 mg) was given in October, November and December 1995, and every second week from mid-December to late January 1996. Prednisolone was administered at a daily dose of 20 mg orally.

The patient was admitted to hospital on 29 January 1996 with a 4 h history of progressive abdominal pain and distention. A tumour-like process was felt in the central part of the abdomen, and some bluish colour was seen at the same location. Signs of peritonitis were present and her general condition deteriorated rapidly. A laparotomy was performed. The entire colon was gangrenous and the small intestine appeared ischaemic. Microscopic examination of the resected colon showed ischaemic changes without signs of vasculitis or granulomatous inflammation. Cyclophosphamide was continued, and later on the patient was given two pulses of i.v. methylprednisolone in order to enhance wound healing. She then recovered slowly and was discharged from hospital on 12 March 1996.

**DISCUSSION**

We have presented two patients with biopsy-verified Wegener’s granulomatosis who altogether developed three episodes of severe intestinal manifestations necessitating acute surgical intervention. Both patients met the ACR 1990 classification criteria for Wegener’s granulomatosis [9] and had positive tests for cANCA. Neither of the patients experienced clinical signs or symptoms of inflammatory bowel disease, and eosinophilia and hepatitis B antigenaemia were not recorded.

In both patients, the therapeutic regime consisting of either i.v. cyclophosphamide or oral chlorambucil was continued throughout the intestinal episode, and after 2 and 3 months, respectively, they were discharged from hospital without abdominal complaints. In all three events, oral corticosteroids had been employed prior to the development of intestinal complications.

Involvement of the gastrointestinal tract does occur in Wegener’s granulomatosis. In one series of 45 patients [7], 10% had gut symptoms at presentation or during a relapse of the disease. In a review of 56 cases studied at necropsy, Walton [4] found focal necrotizing arteriolitis in the intestine in 24% of the cases, but clinical data were not provided in that report. On the other hand, severe intestinal involvement in Wegener’s granulomatosis appears infrequently, and standard textbooks of rheumatology very rarely mention such manifestations when addressing the disorder. Moreover, in the study of 158 patients seen at the National Institutes of Health [3], intestinal manifestations were not reported. Reviewing the available medical literature, we have in addition to the present two cases found four cases of Wegener’s granulomatosis who presented severe bowel involvement (Table I).

The patients were four males and two females, and the age at onset of intestinal manifestations varied from 26 to 55 yr (Table I). All patients had classical Wegener’s granulomatosis, involving both the lungs and kidneys. cANCA were determined in two patients only, and were positive in both. In all patients, the first signs of intestinal involvement occurred within the first 2 yr of disease (1–24 months). One patient (no. 6) developed a second episode (no. 6b) of gut affection after a disease duration of 11 yr, post-dating the initial intestinal event by ~9 yr. Consequently, intestinal manifestations unambiguously appear in the early stages of Wegener’s granulomatosis and have been reported exclusively in cases exhibiting classical involvement of lungs and kidneys.

Acute abdominal pain with signs of peritonitis constituted the main clinical picture in five of six cases. One patient presented with profuse diarrhoea with blood and mucus [7], and the remaining case (no. 6b) developed abdominal pain and distention only. As shown in Table I, intestinal manifestations of Wegener’s granulomatosis may be localized to any part of the gastrointestinal tract, and perforations appear as the most common cause of immediate abdominal emergency.

Interestingly, vasculitis was detected in only three specimens out of the seven histological examinations (Table I). Granulomas were not observed microscopically, but one case (no. 6a) demonstrated both vasculitis and giant cells. Similarly, among the 56 patients with Wegener’s granulomatosis studied at necropsy by Walton [4], granulomas were not observed in the intestine. In four of the seven cases of the present report, histological examinations revealed ischaemic changes, ulceration and inflammation only. The variety of histological markers in the organs affected and the inconsistency of demonstrable vasculitis and granulomatous inflammation raise the question of the aetio-pathogenesis of the intestinal manifestations seen in Wegener’s granulomatosis.
### TABLE I

Ischaemic intestinal disease in Wegener's granulomatosis

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<td>Age (yr)</td>
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<td>46</td>
<td>43</td>
<td>50</td>
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<tr>
<td>cANCA</td>
<td>nd</td>
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<td>nd</td>
<td>nd</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Kidney</td>
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<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Disease duration</td>
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<td>1 month</td>
<td>11 months</td>
<td>9 months</td>
<td>18 months</td>
<td>10 months</td>
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<td>P + O</td>
<td>P + Ch</td>
</tr>
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<td>Small bowel</td>
<td>Rectum</td>
<td>Distal ileum</td>
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<td>Sigmoid</td>
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<tr>
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<td>–</td>
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<tr>
<td>Necrosis</td>
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<tr>
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<td>–</td>
<td>+</td>
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<tr>
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<td>Death</td>
<td>Survival</td>
<td>Survival</td>
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</tr>
</tbody>
</table>

P. prednisolone; C. cyclophosphamide; A, azathioprine; Ch, chlorambucil.

*Patient 6: the a denotes the first episode of bowel involvement and the b the second event.
†Denotes the start of therapy prior to the intestinal event.

The use of immunosuppressive therapy has been incriminated as an aetiologcal factor in intestinal necrosis and perforation [10]. Among 100 patients receiving either long-term immunosuppression to prevent homograft rejection or on chemotherapy for leukaemia, Matalo and co-workers [10] encountered eight instances of intestinal perforation and necrosis. In none of the cases had cyclophosphamide been administered. The authors [10] discussed corticosteroids as a possible causative agent, the putative mechanism being a breakdown of intestinal mucosal resistance to bacteria. Among the six patients with Wegener’s granulomatosis and severe intestinal involvement in this report, immunosuppressive therapy was administered in six of the seven events. All patients used corticosteroids and, in addition, immunosuppressives were prescribed in six of seven episodes. In five of these, immunosuppression was continued throughout the event and, in two events, such therapy was initiated because of bowel manifestations. Consequently, the high frequency of immunosuppressive treatment among such cases clearly suggests an aetiopathogenic association. The case reported by Haworth and Pusey [7], however, shows that severe intestinal involvement in Wegener’s granulomatosis may occur in the absence of immunosuppressive therapy.

It is also likely that intestinal disease in Wegener’s granulomatosis occurs during active phases of the disease, which may explain the frequent use of immunosuppressive therapy in cases with intestinal disease. In three of the reviewed episodes, there was a close temporal relationship between the administration of such therapy and the development of intestinal lesions (Table I). Evidently, such a relationship may suggest a drug-induced reaction, but it is also likely that the intestinal manifestations, as a feature of active disease, necessitated the initiation of immunosuppressive therapy. The continuation of the therapeutic regimen throughout the intestinal event in the majority of cases, and the rather favourable outcome, may be interpreted in favour of the latter proposal. Such a view is further supported by the histological findings of vasculitis in three of the resected bowels. Finally, neither cyclophosphamide nor corticosteroids have so far been incriminated as responsible agents for the development of such pathological features. We therefore tentatively suggest that intestinal perforation and necrosis should be regarded as complications of Wegener’s disease itself rather than as complications induced by its coherent medical therapy. At present, continuation of such treatment in the event of intestinal catastrophe may be recommended.

In conclusion, intestinal perforation and necrosis are rare events in Wegener’s granulomatosis, being reported in six patients only. More than one episode of severe gut involvement in the same patient is reported for the first time. Both the small and the large bowel may be involved, and the clinical picture develops rather acutely and most often early in the disease course. Histological examination of resected intestinal material may reveal slight inflammation, ulceration and ischaemia only, or typical vasculitis changes. Evidence suggests that the intestinal manifestations may be regarded as part of the Wegener’s disease complex rather than a complication of immunosuppressive therapy.

**References**

4. Walton EW. Giant cell granuloma of the respiratory