Frequency, Diagnosis, Treatment, and Outcome of Gastrointestinal Disease in Granulomatosis with Polyangiitis and Microscopic Polyangiitis

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Frequency, diagnosis, treatment, and outcome of gastrointestinal disease in granulomatosis with polyangiitis and microscopic polyangiitis

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Abstract

Objectives

Involvement of the gastrointestinal (GI) tract is a rare complication of granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA). The aim was to describe frequency, diagnosis, treatment and outcome of GI disease in a large series of patients in a single center.

Methods

A database, which includes all patients with GPA and MPA diagnosed since 1997 in a defined area of Southeastern Sweden as well as prevalent older cases and tertiary referral patients, was screened for patients with GI disease. Data were retrieved from the patient's medical records, and GI manifestations of vasculitis were defined as proposed by Pagnoux in 2005.

Results

Fourteen (6%) of 216 consecutive patients with GPA/MPA had GI manifestations.

Abdominal pain and GI bleeding were the most common symptoms. Radiology was important for detection of GI disease, while endoscopy failed to support the diagnosis in many patients.

Due to perforation, 5 patients underwent hemicolectomy or small intestine resection. Primary anastomosis was created in 2/5 and enterostomy in 3/5 patients. One patient had a hemicolectomy because of lower GI bleeding. One sigmoid abscess was treated with drainage, and one intra-abdominal bleeding with arterial coiling.

Two patients died due to GI disease. GPA and MPA patients with and without GI disease exhibited a similar overall survival.

Conclusions

GI disease was found in 6% among 216 patients with GPA or MPA. Surgery was judged necessary only in cases with GI perforation or severe bleeding. Multidisciplinary engagement is strongly recommended.

Key indexing terms: Surgery, gastrointestinal tract, vasculitis, ANCA

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running footline: gastrointestinal in ANCA vasculitis

Introduction

Granulomatosis with polyangiitis (GPA) (formerly Wegener's granulomatosis) and microscopic polyangiitis (MPA) are vasculitic diseases characterized by necrotizing vessel wall inflammation and anti-neutrophil cytoplasmic antibodies (ANCA) directed to proteinase-3 (PR3) or myeloperoxidase (MPO). Similar organ manifestations can be found in the kidneys, peripheral nerves, skin and joints in both diseases, whereas granulomatous lesions in lungs and nose are restricted to GPA. Although considered uncommon, many case reports have been published concerning gastrointestinal (GI) involvement in MPA (1,2) and GPA (3-15). In older literature the occurrence of GI involvement was reported to be 5-11% in GPA (7,15) and 6-56% in MPA (16). In a more recent paper, GI disease was found in 7% of 673 subjects with MPA or GPA included in EUVAS or French clinical trials (17). Previously, MPA was not delineated from polyarteritis nodosa (PAN) in the American College of Rheumatology (ACR) criteria from 1990, so there is confusion concerning the classification of these diseases when older and more recent reports are compared. In 1999 it was reported that 14-40% of PAN patients had GI disease (16). High incidence rates of GI involvement have also been reported for adult IgA vasculitis (formerly known as Henoch Schönlein purpura) (48%) (18) and eosinophilic granulomatosis with polyangiitis (8-62%) (16), which is another pauci-immune small vessel vasculitis sometimes associated with ANCA.

The diagnostic procedure of GI symptoms in GPA or MPA patients has been included in previous case reports and to some extent also in larger case series (19). The aim of the present study was to evaluate GI disease in a large consecutive series of MPA and GPA patients seen at a tertiary referral center in Sweden.

We wanted to study the diagnostic procedure more in detail, and also prognosis as reflected by patient survival. In previous studies patient survival has been worse in GPA and MPA patients with GI disease (17,20). We also wanted to focus on the surgical procedures to see if

these patients should be handled differently from other patients with GI perforation or bleeding.

Methods

Patient retrieval. The county of Östergötland is located in south-east Sweden and has a population of 440000. In 1997 we initiated a prospective register to include all newly diagnosed patients with GPA and MPA living in this area. All of these patients are treated at the departments of Rheumatology or Nephrology at Linköping University Hospital. Tertiary referred patients from other regions, as well as patients diagnosed before 1997, were also included in this regional vasculitis registry. Data from patients with gastrointestinal disease were retrospectively extracted from patient charts. Birmingham vasculitis activity score (BVAS v.3) was used for definition of organ manifestations and clinical disease activity (21). BVAS scores were recorded at the time of visit in patients diagnosed after 1997, and estimated by retrospective chart review in patients diagnosed before 1997. Date of diagnosis was defined by start of induction therapy.

Classification. Vasculitis was diagnosed as described by Watts et al, and classified as GPA and MPA using the European Medicines Agency (EMA) algorithm (22).

Patients were categorized into serotypes based on PR3-ANCA or MPO-ANCA judged by enzyme linked immunosorbent assays (conventional ELISA, capture ELISA, or high-

sensitivity ELISA). Before 1997 only results regarding immunofluorescent ANCA-staining patterns ('cytoplasmic' and 'peripheral' staining-patterns, *i.e.* "C-ANCA" and "P-ANCA", based on ethanol-fixed polymorphonuclear neutrophilic granulocytes) were available for some GPA and MPA patients, but only from one suffering from GI disease. Patients with C-ANCA were grouped together with anti-PR3-positive and P-ANCA with anti-MPO-positive patients. GI involvement was defined as proposed by Pagnoux: 1) GI symptoms, such as diffuse abdominal pain with acute onset or GI bleeding, that were present at the time of GPA or MPA diagnosis (or within the next 3 months) and responded to specific therapy for vasculitis; 2) GI symptoms that occurred during a relapse, diagnosed on the basis of extraintestinal features of GPA or MPA and/or responded to specific therapy for vasculitis; and/or 3) GI tract vasculitis that was histologically proven on biopsy or at autopsy (19). In order to qualify for inclusion in the present study, symptoms should not have been caused by GI infection (*i.e.* *Candida albicans*, Cytomegalo-virus, *Clostridium difficile*) or nausea caused by drugs such as cyclophosphamide.

Ethics. The study was performed according to the declaration of Helsinki and approved by the local ethical committee in Linköping, Sweden (M157-05).

Statistics. Patient characteristics are shown as median values and inter-quartile ranges. GPA and MPA patients with gastrointestinal manifestations were compared to those without. Median values were compared using Mann Whitney U-test for continuous data, and Chi-square test for comparison of proportions. Patient survival plots were calculated according to Kaplan-Meier, and log-rank test was used to examine differences between groups. Statistica v 13 was used for statistical work.

Results

Clinical characteristics of patients with GI disease in GPA and MPA. GI disease was diagnosed in 14 patients during the period 1987-2015, representing 6.5 % of all consecutive subjects in the registry (6.7% if tertiary patients and patients diagnosed before 1997 were excluded). Table 1 shows the general characteristics of patients with GI compared to those without GI disease, and Table 2 shows more clinical details about each of the 14 subjects with GI disease. The patients with GI disease were followed for a median follow up time of 6.8 (quartiles 3.2-15.2) years, and patients without GI disease for 7.5 (3.3-14.5) years.

Age, gender, GPA vs MPA, PR3-ANCA vs. MPO-ANCA, organ involvement, plasma creatinine, and CRP levels did not differ between the groups. However, disease activity assessed with BVAS at diagnosis was higher in patients with GI symptoms ($p=0.001$), and 11/14 patients with GI disease had renal involvement manifested by hematuria (and often albuminuria) but plasma creatinine levels was not increased in all cases.

As shown in Table 3, GI symptoms were never the first symptom of GPA or MPA, GI symptoms and other GPA or MPA symptoms started concomitantly in only one patient, and only 6 patients had GI symptoms at the time of diagnosis of GPA or MPA. The median duration of GI symptoms was 28 days (range 1-102) (Table 3).

Table 4 shows GI symptoms, as well as results of radiologic, endoscopic, and histologic examinations. Abdominal pain was the most common symptom, followed by nausea and bleeding. As shown in table 4 and 5, no patient had upper GI bleeding, whereas 7 of 14 patients had rectal bleeding (and further one case had an intraabdominal bleeding). However, bleeding was the main reason for more intensive care in only 5 cases (Table 5). Three out of

seven patients with bleeding did not report abdominal pain. In patients with GI bleeding the severity differed between cases. Anemia was seen in all patients, and Table 5 shows the number of blood units given (2, 7, 9, 12, 12 units of blood transfusion and one case where data could not be extracted from the patient record). Three patients (No 6, 12, 13) experienced acute drop in blood pressure together with rapidly decreasing blood hemoglobin indicative of more extensive bleeding.

Radiologic findings. Radiology proved to be of great importance to indicate GI disease in GPA and MPA (Table 4). During the period of 1987-1997, plain abdominal X-ray (first line examination in 4 patients without contrast and in 2 patients with oral/rectal contrast) was the standard radiologic method. With this method pneumoperitoneum can be identified, and by the use of oral contrast medium increased wall thickness could be visualized. In the later part of the study period computed tomography (CT) was utilized in most cases (first line examination in 7 patients and after plain X-ray in further 2 patients), and in addition to pneumoperitoneum and increased wall thickness CT also detected abscesses, hematoma, and ascites (Table 4).

Ultrasonography (US) (primarily in 2 patients) and magnetic resonance imaging (MRI) (1 patient) were less commonly used in this case series. US showed swollen intestinal walls in one patient, and in another subject an abscess was diagnosed and treated by US guided drainage. MRI detected wall thickening of the ileum in one patient. Bleeding scintigraphy was performed in one patient but was not conclusive.

Endoscopy and histology findings. As shown in Table 4, gastroscopy showed red and swollen esophageal, gastric, or duodenal mucosa indicative of inflammation in 3 of 5 patients. None of

patients had ulcers. Vasculitis was confirmed by histology in 2 of these 3 patients with macroscopic signs (esophagus and duodenum, respectively).

Colonoscopy was normal in 3 patients, and in a fourth subject (case No 8) a colon polyp was removed. In that patient a new colonoscopy was performed later because of continuing bleeding. In spite of uncharacteristic macroscopic findings histologic examination revealed vasculitis in the colonic wall. In a fifth patient (case No 11) colonoscopy revealed sigmoid diverticulosis and a swollen intestinal wall. Further one case underwent rectoscopy showing blood but normal mucosa (case No 3).

Intestinal capsule endoscopy was performed in one patient and showed a swollen jejunal mucosa and focal inflammation of the duodenal bulb. Gastrosocopy had shown inflammatory appearance in the esophagus in the same patient (No 13).

Four surgically removed specimens were subjected to histological examination. Two specimens showed small vessel vasculitis, one with granuloma (No 4) and one without granuloma (No 8), while the others (No 7 and 9) did not show vasculitis although the clinical picture spoke in favor of GI vasculitis. The key messages are that these GPA and MPA patients may have severe bleeding in the whole GI tract without obvious endoscopic ulcers, and that more or less unspecific redness and “inflammatory signs” of the mucosa may reveal areas where biopsy shows vasculitis. Furthermore, vasculitic lesions bleeding into the small intestine may be difficult to localize with endoscopic or radiological methods. Pancreatitis or gall bladder lesions were not detected in any patient.

Surgical treatment of GI disease in patients with GPA or MPA. Five patients underwent surgery due to colon perforation (Table 5). No 2 and 3 went through left-sided colectomy while No 4 and 9 had right-sided hemicolectomy performed. Small intestine resection was done in No 7. One patient had a right-sided hemicolectomy done because of lower GI

bleeding (No 8). Among patients with intestinal perforation, resection and primary anastomosis of the intestine was performed in patients No 4 and No 7 who had received only small amounts of immunosuppressive therapy preoperatively. In the other cases intestinal resection was followed by creation of an enterostomy, the type depending on the level of perforation.

One patient with a sigmoid abscess was, as mentioned above, treated with ultrasound-guided drainage and antibiotics (No 11).

Three patients presented with signs of left-sided colon disease, in two of these diverticula were later found to be present (No 11 at colonoscopy, and No 3 at operation). The symptoms in these two patients may have been due to diverticula representing “locus minoris” sensitive to immunosuppressive therapy or vasculitis. In patient No 2, no diverticula were found during operation, ruling out diverticulitis in that case. At presentation of GI symptoms, case No 2 also had nose symptoms and increasing serum creatinine from 200 to 782 $\mu\text{mol/L}$ indicating active GPA.

In Case 3, ENT, joints, and kidneys were involved at first diagnosis of GPA, and at relapse new pulmonary infiltrates, nose symptoms with crusting, increasing serum creatinine, and CRP 186 $\mu\text{g/L}$ were present. Ten days later the pulmonary infiltrates decreased but rectal bleeding and GI perforation presented 59 days after relapse of vasculitis. Serum creatinine (156 $\mu\text{mol/L}$ before relapse) varied between 278-165-217 $\mu\text{mol/L}$ during the time span between relapse and start of GI symptoms making date of renal remission difficult to define.

Case No 11 had migrating joint pain, biopsy confirmed renal vasculitis, and CRP 98 mg/L at diagnosis of MPA. Serum creatinine decreased from 175 to 139 $\mu\text{mol/L}$, but 35 days later it increased to 377 $\mu\text{mol/L}$ interpreted as active disease prompting addition of plasma exchange. GI symptoms presented 71 days after diagnosis of MPA and at that time the weight had decreased 10 kg since diagnosis and CRP was 142 mg/L .

One patient was treated with arterial coiling due to bleeding into the abdominal cavity (No 6).

Conservative therapy was sufficient in 6 patients with GI disease. This included bowel rest, antimicrobial therapy, parenteral nutrition, and blood transfusions in those with GI bleeding. Immunosuppressive therapy, consisting of various combinations of high dose prednisolone, intravenous pulses of methylprednisolone, rituximab, cyclophosphamide, and plasma exchange, was continued, restarted or increased when GI involvement was diagnosed (Table 3).

Patient survival and outcome. During the 1990:s two patients died because of GI disease 24 and 30 days after presentation of GI symptoms (Patient No 2 and 3). Further 3 patients died 10 months to 13 years after GI disease, but without relation to GPA or MPA. As shown in Figure 1, patient survival assessed with Kaplan-Meier analysis did not reveal any differences comparing GPA or MPA patients with or without GI disease ($p=0.89$, log-rank test). No patient suffered from short bowel syndrome postoperatively.

Discussion

In this single center study of consecutive patients with GPA or MPA we found GI disease in 6% out of 216 patients. Previously most patients have been reported as case reports or small case series. Out of 45 subjects with GPA, Haworth reported four patients with GI disease in 1984 (7), and Pagnoux reported 6 GPA and 4 MPA from a register of 344 mixed vasculitides also including polyarteritis nodosa and eosinophil granulomatosis with polyangiitis (19). Contrary to this, GI manifestations were not mentioned in a case series of 158 GPA patients from 1998 (23), whereas Walton as early as 1958 found GI vasculitis in 22% of 56 autopsy cases with GPA (24). When discussing frequency, selection bias is important to consider. For example, the patients in Walton's series were all dead and probably represented cases with severe GPA. Since 1997 we treat and monitor all patients with GPA and MPA in our capture area, and the frequency of GI disease among the tertiary referred patients did not differ, so we believe 6 % is a representative figure for unselected patients with GPA and MPA. This figure is very similar to the 7% GI disease found in 673 subjects with MPA or GPA included in EUVAS or French clinical trials probably excluding less severe disease like patients with isolated ENT involvement (17). The diagnosis of GI disease in GPA and MPA is not always straight forward. Therefore it is important to define GI disease in these patients in a standardized manner. We adopted the definitions proposed by Pagnoux in 2005. The symptoms should not be explained by GI infections (25,26), or simply be nausea caused by cyclophosphamide. In patients with left-sided colon perforation it can be difficult to distinguish between diverticulitis precipitated by vasculitis or as a complication to immunosuppressive therapy in a locus minoris, or a combination of both. Therefore, such cases were included in our study. Others have considered the GI manifestations in GPA and

MPA as probably associated with the disease process rather than related to the use of immunosuppressive agents (4).

The most common symptoms were abdominal pain and rectal bleeding occurring in 79% and 50%, respectively. Similar rates have been reported by others (pain/bleeding in 97% in ref 19). Diarrhea occurred in some of our patients and has also been reported previously (4). ANCA is associated with vasculitis preferentially in small and medium-sized vessels and usually not detectable with angiographic techniques. However, one patient with intraabdominal bleeding had angiographic micro-aneurysms in the inferior mesenteric artery which is consistent with vasculitis. GPA and MPA affecting also larger vessels have been described by others (27-32).

All patients had GPA or MPA symptoms from other organs, for example 11 of 14 patients had concomitant renal vasculitis manifested by urine abnormalities (hematuria and often albuminuria), but not always by increased plasma creatinine levels. The GI symptoms presented *after* the onset of other GPA or MPA symptoms in all but one patient, and after diagnosis of GPA or MPA in 8/14 patients. Thus, being aware of the patient's medical history and symptoms outside the gut are key issues for a surgeon confronted with a patient with GI symptoms, in order to make a timely diagnosis of GI involvement.

The diagnosis of GI disease relies on a combination of associated clinical symptoms and biopsies from other organs, and on ANCA analyses, as well as on imaging and endoscopy with biopsies from the GI tract. Abdominal CT was helpful in suggesting GI disease in many patients, but it cannot provide definite evidence. CT may show diffuse or multifocal bowel wall thickening with or without bowel distension or an abnormal enhancement pattern of the intestinal wall, but it may also be normal. Ascites and signs of perforation may also be seen (10).

The role of endoscopy in the diagnosis of GI disease related to GPA or MPA is controversial (19). It is common with normal macroscopic findings even in cases with severe involvement, and endoscopic biopsies are often inconclusive. However, uncharacteristic ulcers or an inflammatory picture may be found not only in the gastroduodenal and colonic tracts but also in the esophagus. The most typical endoscopic picture has been described as multiple, small, round and clear ulcers associated with obstructed blood flow (3). Furthermore, endoscopy can be of differential diagnostic importance. In this study, gastroscopy detected unspecific signs of inflammation in three of five patients, and colonoscopy showed unspecific macroscopic findings in one patient. Double balloon enteroscopy has been recommended as GI disease is often localized in the small bowel (3,33), and in one of our patients capsule endoscopy of the GI tract showed a swollen jejunal mucosa and focal inflammation of the duodenal bulb. GI involvement was confirmed in specimens taken endoscopically or during surgery in some but far from all of our patients. In one report of GI involvement associated with different vasculitides, vasculitis could only be detected histologically in 3 of 36 biopsies during endoscopy, whereas surgical removed specimens showed signs of ischemic and/or thrombotic necrosis due to vasculitis in 8 of 9 cases (19). In our study the diagnostic yield from endoscopic biopsies was somewhat better, while the yield from surgically removed specimens was 2 in 4. Supplementary Table summarizes GI findings in patients with GPA or MPA reported previously.

Due to corticosteroids and often frail patients in a bad general condition, the healing process is often hampered. This must be considered when surgery is necessary. One question is if primary anastomosis or temporary enterostomy should be performed in cases with intestinal perforation. Two of our patients with intestinal perforation went through successful resection and primary anastomosis of the intestine. These patients were previously healthy and had only

received small amounts of immunosuppressive therapy preoperatively. In our other cases with GI perforation, intestinal resection was followed by creation of a temporary stoma, which may be a safer procedure especially if widespread inflammation or abscesses are present.

However, one of our patients did well after US-guided drainage and antibiotics of an abscess surrounding sigmoid diverticulitis.

If optimal immunosuppressive therapy is used the GI wall may heal after a couple of weeks. However, during this period the GI wall is injured and surgery must therefore be considered in cases with perforation or continuing severe GI bleeding. In this study medical treatment alone was sufficient in nearly half of the patients. Eager surveillance with repeated CT scans is recommended as patients with high doses of corticosteroids may develop peritonitis without clinical signs.

Two of our 14 patients died because of the GI disease. However, compared to patients with GPA or MPA without GI disease, the patient survival was similar contrasting to previous studies where patients with GI disease had a worse prognosis (17,20). Although our case series reporting GI disease among patients with GPA or MPA is larger than many other series, the power to detect a real difference of survival is too limited. However, the survival curves are almost identical (Figure 1), and one may speculate that an alternative explanation might be that the good outcome observed in this study has not occurred by chance, possibly due to early diagnosis and treatment, as well as more efficient and less toxic therapy during recent years. We also believe that a close co-operation between surgeons and rheumatologists is of benefit for the patient. Further studies are needed to answer if patient survival is as bad as previously thought and if survival has become better during recent years.

There is a general lack of evidence for how GI disease in GPA or MPA should be treated, and most recommendations are based on expert opinion. For example rituximab was in a recent

European consensus document graded as equally effective as cyclophosphamide (34), but there are only a few case reports concerning the use of rituximab in patients with MPA or GPA and GI involvement (35).

In conclusion, we found that GI disease was a rare but significant complication in this large population based series of patients with GPA and MPA.

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Figure 1. Patient survival in GPA and MPA for patients with (dotted line) or without (straight line) gastrointestinal disease.

Table 1. Clinical characteristics of patients with GPA and MPA with and without gastrointestinal disease. Mann-Whitney U-test was used for continuous variables and Chi-square test for frequencies.

	Without GI disease n=202	With GI disease n=14	p-value
Men/women (%)	108/94 (53/47)	9/5 (64/36)	0.43
Age*, median (quartiles)	63.4 (53.3-73.0)	65.7 (50.3-77.5)	0.55
Tertiary referral patients (%)	39 (19)	3 (21)	0.86
GPA/MPA (%)	120/82 (59/41)	10/4 (71/29)	0.37
PR3-/MPO-/no or missing ANCA /both (%)	120/70/7/5 (59/35/3.5/2.5)	10/4/0/0 (71/29/0/0)	0.86
Organ involvement*:			
kidney (%)	137 (68)	11 (79)	0.40
lung (%)	73 (36)	8 (57)	0.12
ENT (%)	84 (42)	5 (36)	0.67
peripheral nerves(%)	51 (25)	4 (29)	0.78
skin (%)	22 (11)	3 (21)	0.23
joints (%)	78 (39)	6 (43)	0.75
eyes (%)	19 (9)	1 (7)	0.78
Isolated ENT disease (%)	16 (8)	-	0.27
Plasma creatinine*, µmol/l median (quartiles)	123 (80-272)	125 (88-216)	0.89
Plasma CRP*, mg/L median (quartiles)	81 (18-142)	98 (82-170)	0.16
BVAS* median (quartiles)	15 (12-20)	22 (15-28)	0.001

*at time of diagnosis

GI=gastrointestinal, GPA=granulomatosis with polyangiitis, MPA=microscopic polyangiitis.
PR3=proteinase 3, MPO=myeloperoxidase, ENT=ear, nose, throat, BVAS=Birmingham
vasculitis activity score

Table 2. Clinical characteristics of GPA and MPA patients with gastrointestinal disease.

Patient No	Year of GI disease	Age/sex/tertiary referred	phenotype/serotype	Organ involvement	CRP at diagnosis of GPA or MPA (mg/L)	BVAS at first diagnosis of GPA or MPA
No 1	1987	43/M/yes	GPA/anti-PR3	J,ENT,L,K	ESR 71	9
No 2	1992	58/M/no	GPA/anti-PR3	J,ENT,K	ESR 55	28
No 3	1994 (relapse)	84/F/no	GPA/anti-MPO	ENT,L,K	35	23
No 4	1997	50/M/yes	GPA/P-ANCA	Testis	105	12
No 5	1998	48/F/no	MPA/anti-MPO	K	91	22
No 6	2000	55/M/no	GPA/anti-MPO	S,J,ENT,L,K,eye,prostate	177	37
No 7	2000	52/M/no	GPA/anti-PR3	PNS,L	82	23
No 8	2001	74/M/no	GPA/anti-PR3	PNS,L,K	258	30
No 9	2005	84/F/no	GPA/anti-PR3	J,PNS,L	81	20
No 10	2007	77/M/no	GPA/anti-PR3	S,ENT,L,K,penis	100	23
No 11	2008	75/F/no	MPA/anti-MPO	J,K	85	15
No 12	2011	79/F/yes	GPA/anti-PR3	L,K	180	24
No 13	2012	73/M/no	MPA/anti-PR3	J,PNS,K	163	30
No 14	2013 (relapse)	49/M/no	MPA/anti-MPO	S,K	10	14

M=male, F=female, GPA= granulomatous with polyangiitis, MPA=microscopic polyangiitis, PR3=proteinase 3, MPO=myeloperoxidase, S=skin, J=joints, PNS=peripheral nerve system, ENT=ear nose throat, L=Lung, K=Kidney, BVAS=Birmingham vasculitis activity score, CRP=C-reactive protein, ESR=erythrocyte sedimentation rate (mm) (shown when CRP was not available)

Table 3. Time course of GI symptoms related to diagnosis, as well as immunosuppressive therapy before and after gastrointestinal symptoms, are shown in the table. A negative value indicate onset before diagnosis of MPA or GPA. Date of diagnosis was defined by start of immunosuppressive therapy (mostly corticosteroids).

Patient No	First GPA or MPA symptoms (days from diagnosis)	First GI symptoms (days from diagnosis)	Approximate duration of GI symptoms (days)*	Dose Prednisolone/ other therapy at onset of GI symptoms	Additional immune therapy after GI symptoms
1	-49	+81	79	30 mg/Cyc oral	CYC iv, PE
2	-105	+14	31	60 mg/MP iv, Cyc iv, PE	-
3	-200 (diagnosis of relapse)	+59	24	20 mg/Cyc iv	-
4	-201	-12	9	0 mg/none	MP iv, Pred, CyC iv
5	-59	-52	57	0 mg/none	MP iv, Pred, Cyc iv, PE
6	-49	+7	1	40 mg/Cyc iv, PE	-
7	-48	0	43	0 mg/MP iv, Cyc oral	PE
8	-8	-2	38	0 mg/none	Pred, Cyc oral
9	-56	+26	15	20 mg/MP iv, Cyc iv	Rtx
10	-8	-8	14	0 mg/none	MP iv, Pred, CyC iv, Rtx, PE
11	-249	+71	4	20 mg/Cyc iv, PE, Rtx	-
12	-17	+3	102	0 mg/MP iv	Pred, Cyc iv, Rtx, PE
13	-32	-2	53	0 mg/none	MP iv, Rtx, PE
14	-10 (diagnosis of relapse)	+19	12	40 mg/Rtx	-

Cyc=cyclophosphamide, Pred=prednisolone, MP=methyl prednisolone pulse, iv=intravenous, Rtx=rituximab, GI=gastrointestinal, PE=plasma exchange

*Duration of GI symptoms is approximated as some, but far from all, patients were operated

Table 4. Gastrointestinal manifestations and diagnostic findings in 14 patients with GI disease associated with GPA or MPA.

Pat No	GI symptom	X-ray/CT/MR/US findings	Endoscopy	Biopsy (endoscopy/op)
No 1	rectal bleeding	abd. X-ray with oral and rectal contrast: OK	G: OK, C: not done	-
No 2	abd. pain	abd. X-ray: free gas, US postop 1: inconclusive CT post op 1: ascites, colonic X-ray post op 1: sigmoid. leakage, US post op 2: drainage abscess	-	colon op 2: sigmoiditis with rupture autopsy: inconclusive
No 3	abd. pain, rectal bleeding, vomiting	abd. X-ray without contrast: free gas	R: blood, normal mucosa	-
No 4	abd. pain	abd. X-ray without contrast: free gas	-	granulomatous vasculitis
No 5	abd. pain rectal bleeding	abd. X-ray with oral contrast: irregular and swollen bowel wall, CT: ascites, US: swollen bowel walls	-	-
No 6	abd. pain + intraabd. bleeding	arterial angiography: microaneurysms (vasculitis) in inferior mesenteric artery, CT: abdominal hematoma	-	-
No 7	abd. pain, vomiting	CT: free gas, swollen bowel walls	-	perforat. ulcers, submuc. inflam. no vasculitis or granuloma
No 8	rectal bleeding	arterial abdominal angiography: OK	G: OK, C: polypectomy but bleeding did not stop	vasculitis in colon
No 9	abd. pain	CT: free gas	-	colon: no vasculitis/granuloma
No 10	abd. pain, vomiting	abd. X-ray without contrast: subileus, CT: wall thickening + dilatation of prox. small bowel, mesenteric edema	-	-
No 11	abd. pain	CT: wall thickening + 2 abscesses around sigmoid colon US: abscesses, US-drainage	C: sigmoid diverticulosis + swollen intestinal wall	-
No 12	dysphagia, diarrhea, edema, rectal bleed.	CT: mesenteric and subcutaneous edema, later ascites	G: inflammation in pylorus + bulb, no ulcers, C: OK	-
No 13	abd. pain, vomiting, rectal bleeding	CT: wall thickening + dilatation of small bowel MR: wall thickening of ileum wall	G: esophag. unspec. red areas C: OK, Capsula endoscopy: swollen jejun. mucosa, focal inflam. duod. bulb	esophagitis + vasculitis
Nr 14	abd. pain, rectal bleeding, vomiting	CT: OK	G: duod. mucosa contact bleeding, edema, fibrin (heavy inflamm.) C: OK	gangrenous ulceration, vasculitis

G=gastro, C=colon, R=rectum, CT=computed tomography, US=ultra sound, MR=Magnetic resonance, Abd.= adominal

Table 5. Surgical and/or conservative therapy in 14 patients with gastrointestinal disease associated with GPA or MPA.

Patient No	GI event leading to emergency intervention	Type of intervention	Outcome
No 1	rectal bleeding, anemia	9 blood /4 weeks	died 13 years later (renal failure)
No 2	1. lower left abdom. pain, X-ray: free air 2. two weeks later increasing SIRS, sigmoid perforation	1. laparotomy: sigmoiditis + localized purulent peritonitis, perforation not found. Ileostomy, drainage, no resection, abdomen closed. 2. re-laparotomy: sigmoid perfor. but no diverticula. Sigmoid resection ad modum Hartmann + colostomy, bowel rest, antibiotics, assisted ventilation, hemodialysis.	died 30 days later (multiorgan failure)
No 3	lower left abdom. pain, peritonitis	laparotomy: perforated sigmoid diverticulitis. Sigmoid resection ad modum Hartmann + colostomy.	died 24 days later (multiorgan failure)
No 4	1. abdominal pain, peritonitis 2. abdominal pain	laparotomy: Two perforations in ascending colon. Right hemi-colectomy + ileo-colic resection, primary anastomosis.	healthy 2016
No 5	lower right abdom. pain	bowel rest, antibiotics, no blood transfusion	healthy 2016
No 6	abdom. pain, CT: hematoma	arterial coiling, bowel rest, assisted ventilation, blood (number /1day unknown)	healthy 2016
No 7	1. abdom. pain, peritonitis 2. distended bowels, fever	1. laparotomy: multiple small bowel perforations. Small bowel resection, prim. anastomosis, delayed closure of abdomen, bowel rest, antibiotics, assist. ventilation. 2. re-lapartomy: no perforation, diffuse peritonitis, abdomen closed.	healthy 2016
No 8	rectal bleeding	right hemi-colectomy, ileostomy, delayed abdom. closure, bowel rest, 12 blood/8 d	died 10 months (heart infarction)
No 9	abdom. pain, CT: free air	laparotomy: several ileo-cecal ulcers + perforations. Right hemicolectomia +dual-barrel ileo-/colo-stomy (not temporary), antibiotics, omeprazole, bowel rest.	healthy 2016
No 10	abdom. pain, CT: partial small bowel obstruction	bowel rest	died 5 years later (malignancy)
No 11	low abdom. pain, CT: abdom. abscess	US-guided drainage of sigmoid abscess, antibiotics, bowel rest	healthy 2016
No 12	rectal bleeding, abdom. pain	antibiotics, omeprazole, nasogastric draining, bowel rest, 12 blood/7 weeks	healthy 2016
No 13	rectal bleeding	7 blood/ 8 weeks, omeprazole, bowel rest	healthy 2016
No 14	rectal bleeding, abdom. pain	2 blood/2 days, antibiotics, omeprazole, nasogastric draining, bowel rest	healthy 2016

US: ultra sound, GI: gastrointestinal, CT: computed tomography, SIRS: systemic inflammatory response syndrome. Time to death relates to months or years after start of GI symptoms. Blood refers to units of blood transfusion.

Supplementary Table 1. Reported cases or case series with GPA or MPA and GI disease cited in the reference list.

Ref/ Year	No of pat./ GPA / MPA	Mainly GI pain/ GI bleeding	GI region	GI macroscopic appearance	GI micro appearance or angiography	Surgery	Dead related to GI disease
1/ 2009	1 MPO	rectal bleeding	E: sigmoid	multiple small deep ulcers	-	unknown	yes
2/ 2011	1 MPA	rectal bleeding	E: sigmoid	diffuse reddening + erosion	vasculitis	no	no
3/ 2011	1 GPA	abd. pain	E: whole colon + small bowel	round ulcers	inflam. + fibrosis*	no	no
4/ 1998	2 GPA	abd. pain	Pat. 1- S: sigmoid Pat. 2- S: sigmoid	1: perforation 2: severe inflammat.	1+2: medium - sized arterial vasculitis	1. colon and 2. sigmoid resection	no, no
6/ 1986	1 GPA	abd. pain	S: entire small bowel	inflam. + ulcers + perforation	no vasculitis	perforations oversewn	yes
7/ 1984	1 GPA	bloody diarrhea	E: rectum R: ileum, caecum	ulcerated mucosa	normal	no	no
8/ 1982	1 GPA	abd. pain	S: ileum	several ulcers, perfor.	non-specific ulcers	55 cm ileum resection	no
9/ 2003	1 GPA	rectal bleeding	E: small bow. S1: entire small bowel S2: prox. jejun S: ileum	patchy ulcers S1: inflammation S2: ulcers, nodular, bleeding ulcers, perforation	S2: ulcers, inflammation, fibrosis *	60 cm jejunal resection	no
10/ 2007	1 GPA	abd. pain	S: ileum	ulcers, perforation	small + medium-sized vasculitis	1.1 m ileum resection	no
11/ 2004	1 GPA	abd. pain + rect. bleed.	E: ileum + ascending colon	bleeding ulcers, nodular lesions	?	no	no
12/ 2010	1 GPA	abd. pain + rect.+upper bleeding	E: stomach S: entire small bowel, caecum	E: gastritis, blood S: inflam., necrosis, perforation	small + medium-sized vasculitis	right hemi- colectomy	yes
13/ 2009	1 GPA	rectal + upper bleeding	E: duodenum	ulcer	-	endoscopic sclero- therapy	yes
14/ 1999	1 GPA	abd. pain	S: small bowel	perforation, thick + granulated serosa	-	local small bow. resect.	no
15/ 1991	1 GPA	rectal bleeding	E: normal colon S: terminal ileum	serosal + mucosal ulcers, erythema	-	local excision + oversewing	yes
19/ 2005	6 GPA	abd. pain 6/6, rectal bleeding 2/6	-	ulcers (gastroduod. 2/6, colorectal 2/6, esop. 1), gastritis 1/6	-	-	unknown
19/ 2005	4 MPA	abd. pain 4/4, rectal bleeding 1/4	S: 1 small bowel + colon S: 1 small bowel	bowel perforation 1/4 bowel occlusion 1/4 GI infarction 1/4	-	-	no (2 cases), unknown (2 cases)
35/ 2013	1 GPA	rectal bleeding	E+S: ileum, caecum, ascend. colon	E: multiple ulcers S: perforation	E: ulcers, inflammation, S: vasculitis	intestinal resection, rituximab	no
Our cases		6 abd. pain 3 bleeding 5 both	See Table 5	See Table 5	See Table 4	See Table 5	2/14 cases died

E=endoscopy, S=surgery, R=radiology

*angiography in reference 3: vasculitis lesions in ant. + inf. mesenterial arteries, normal angiography in reference 9