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

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ABSTRACT. ***Objective.*** 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 that 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, *et al* in 2005.

Results. Fourteen (6.5%) 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. Because of 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 1 intraabdominal bleeding condition with arterial coiling. Two patients died from GI disease. GPA and MPA patients with and without GI disease exhibited a similar overall survival.

Conclusion. GI disease was found in 6.5% 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. (First Release February 1 2018; J Rheumatol 2018;45:529–37; doi:10.3899/jrheum.170249)

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Granulomatosis with polyangiitis (GPA; formerly Wegener's granulomatosis) and microscopic polyangiitis (MPA) are vasculitic diseases characterized by necrotizing vessel wall inflammation and antineutrophil 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 European Vasculitis Society (EUVAS) or French clinical trials[17]. Previously, MPA was not delineated from polyarteritis nodosa (PAN) in the American College of Rheumatology 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 patients with PAN 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], another pauciimmune small-vessel vasculitis sometimes associated with ANCA.

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

We wanted to study the diagnostic procedure in more

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

MATERIALS AND METHODS

Patient retrieval. The county of Östergötland is located in southeast Sweden and has a population of 440,000. 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 GI 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 algorithm[22].

Patients were categorized into serotypes based on PR3-ANCA or MPO-ANCA judged by ELISA (conventional, capture, 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 patients with GPA and MPA, and only for 1 of those with 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, *et al*: (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 mos) 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]. To qualify for inclusion in the present study, symptoms should not have been caused by GI infection (i.e., *Candida albicans*, cytomegalovirus, *Clostridium difficile*) or nausea caused by drugs such as cyclophosphamide (CYC).

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

Statistics. Patient characteristics are shown as median values and interquartile ranges. GPA and MPA patients with GI 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 followup time of 6.8 years (quartiles 3.2–15.2), and patients without GI disease for 7.5 years (3.3-14.5).

Age, sex, GPA versus MPA, PR3-ANCA versus MPO-ANCA, organ involvement, plasma creatinine, and C-reactive protein (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 were 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 1 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 vomiting and bleeding. As shown in Table 4 and Table 5, no patient had upper GI bleeding, whereas 7 of 14 patients had rectal bleeding (and another 1 case had intraabdominal bleeding). However, bleeding was the main reason for more intensive care in only 5 cases (Table 5). Three out of 7 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, and 12 units of blood transfusion and 1 case in which data could not be extracted from the patient record). Three patients (No. 6, 12, and 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 1987–1997, plain abdominal radiograph (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 used in most cases (first-line examination in 7 patients and after plain radiograph 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 1 patient, and in another subject an abscess was

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

Characteristics	Without GI Disease, n = 202	With GI Disease, n = 14	p
Men/women (%)	108/94 (53/47)	9/5 (64/36)	0.43
Age*, yrs, median (quartiles)	63.4 (53.3–73.0)	65.7 (50.3–77.5)	0.55
Tertiary referral patients, n (%)	39 (19)	3 (21)	0.86
GPA/MPA, n (%)	120/82 (59/41)	10/4 (71/29)	0.37
PR3–/MPO–/no or missing ANCA/ both, n (%)	120/70/7/5 (59/35/3.5/2.5)	10/4/0/0 (71/29/0/0)	0.86
Organ involvement*, n (%)			
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, eyes	78 (39), 19 (9)	6 (43), 1 (7)	0.75, 0.78
Isolated ENT disease, n (%)	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; CRP: C-reactive protein; BVAS: Birmingham Vasculitis Activity Score.

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

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

* ESR, mm/h (CRP was not available). GPA: granulomatosis with polyangiitis; MPA: microscopic polyangiitis; GI: gastrointestinal; PR3: proteinase 3; MPO: myeloperoxidase; S: skin; J: joints; PNS: peripheral nerve system; L: lung; K: kidney; BVAS: Birmingham Vasculitis Activity Score; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate.

diagnosed and treated by US-guided drainage. MRI detected wall thickening of the ileum in 1 patient. Bleeding scintigraphy was performed in 1 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 the 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, 1 case underwent rectoscopy, showing blood but normal mucosa (case No. 3).

Intestinal capsule endoscopy was performed in 1 patient and showed a swollen jejunal mucosa and focal inflammation

Table 3. Time course of gastrointestinal (GI) symptoms related to diagnosis, as well as immunosuppressive therapy before and after GI symptoms. A negative value indicates 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 Pred/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	—

*Duration of GI symptoms is approximated because some, but far from all, patients were operated on. CYC: cyclophosphamide; Pred: prednisolone; MP: methylprednisolone pulse; IV: intravenous; RTX: rituximab; PE: plasma exchange; GPA: granulomatosis with polyangiitis; MPA: microscopic polyangiitis.

of the duodenal bulb. Gastroscopy 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, 1 with granuloma (No. 4) and 1 without granuloma (No. 8), while the others (No. 7 and 9) did not show vasculitis, although the clinical picture suggested GI vasculitis. The key messages are that these patients with GPA and MPA 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. Further, 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 for colon perforation (Table 5). Nos. 2 and 3 went through left-sided colectomy while Nos. 4 and 9 had right-sided hemicolectomy. 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, treated with US-guided drainage and antibiotics (No. 11).

Three patients presented with signs of left-sided colon disease; in 2 of these diverticula were later found (No. 11 at coloscopy, and No. 3 at operation). The symptoms in these 2 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 surgery, 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 μmol/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 μg/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 μmol/l before relapse) varied between 278–165–217 μmol/l during the time 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 μmol/l, but 35 days later it increased to 377 μmol/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 for 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 was continued, restarted, or increased when GI involvement was diagnosed;

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

Patient No.	GI Symptom	Radiograph/CT/MR/US Findings	Endoscopy	Biopsy (endoscopy/surgery)
1	Rectal bleeding	Abd. radiograph with oral and rectal contrast: OK	G: OK, C: not done	—
2	Abd. pain	Abd. radiograph: free gas; US post-op 1: inconclusive; CT post-op 1: ascites; colonic radiograph post-op 1: sigmoid. leakage; US post-op 2: drainage abscess	—	Colon surgery 2: sigmoiditis with rupture. Autopsy: inconclusive
3	Abd. pain, rectal bleeding, vomiting	Abd. radiograph without contrast: free gas	R: blood, normal mucosa	—
4	Abd. pain	Abd. radiograph without contrast: free gas	—	Granulomatous vasculitis
5	Abd. pain, rectal bleeding	Abd. radiograph with oral contrast: irregular and swollen bowel wall; CT: ascites; US: swollen bowel walls	—	—
6	Abd. pain + intraabd. bleeding	Arterial angiography: microaneurysms (vasculitis) in inferior mesenteric artery; CT: abdominal hematoma	—	—
7	Abd. pain, vomiting	CT: free gas, swollen bowel walls	—	Perforated ulcers, submucosal inflam., no vasculitis or granuloma
8	Rectal bleeding	Arterial abdominal angiography: OK	G: OK; C: polypectomy but bleeding did not stop	Vasculitis in colon
9	Abd. pain	CT: free gas	—	Colon: no vasculitis/granuloma
10	Abd. pain, vomiting	Abd. radiograph without contrast: subileus; CT: wall thickening + dilatation of prox. small bowel, mesenteric edema	—	—
11	Abd. pain	CT: wall thickening + 2 abscesses around sigmoid colon; US: abscesses, US drainage	C: sigmoid diverticulosis + swollen intestinal wall	—
12	Dysphagia, diarrhea, edema, rectal bleeding	CT: mesenteric and subcutaneous edema, later ascites	G: inflammation in pylorus + bulb, no ulcers; C: OK	—
13	Abd. pain, vomiting, rectal bleeding	CT: wall thickening + dilatation of small bowel; MR: thickening of ileum wall	G: esophageal unspecified red areas; C: OK; capsula endoscopy: swollen jejunal mucosa, focal inflam. duodenal bulb	Esophagitis + vasculitis
14	Abd. pain, rectal bleeding, vomiting	CT: OK	G: duodenal mucosa contact bleeding, edema, fibrin (heavy inflam.); C: OK	Gangrenous ulceration, vasculitis

G: gastro; C: colon; R: rectum; CT: computed tomography; US: ultrasound; MR: magnetic resonance; Abd.: abdominal; GPA: granulomatosis with polyangiitis; MPA: microscopic polyangiitis.

it consisted of various combinations of high-dose prednisolone, intravenous pulses of methylprednisolone, rituximab (RTX), CYC, and plasma exchange (Table 3).

Patient survival and outcome. During the 1990s, 2 patients died of GI disease 24 and 30 days after presentation of GI symptoms (patients 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 had short bowel syndrome postoperatively.

DISCUSSION

In this single-center study of consecutive patients with GPA or MPA, we found GI disease in 6% of 216 patients. Previously, most patients have been reported as case reports or small case series. Out of 45 subjects with GPA, Haworth and Pusey reported 4 with GI disease in 1984[7], and Pagnoux, *et al* reported 6 GPA and 4 MPA from a register of 344 mixed vasculitides also including polyarteritis nodosa and eosinophilic GPA[19]. In contrast, GI manifestations were not mentioned in a case series of 158 patients with GPA from 1992[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 treated and monitored all patients with GPA and MPA in our 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 such as patients with isolated ENT involvement[17].

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

PatientNo.	GI Event Leading to Emergency Intervention	Type of Intervention	Outcome
1	Rectal bleeding, anemia	9 blood/4 weeks	Died 13 yrs later (renal failure)
2	1. Lower left abdom. pain, radiograph: 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. Hartmann sigmoid resection + colostomy, bowel rest, antibiotics, assisted ventilation, hemodialysis.	Died 30 days later (multiorgan failure)
3	Lower left abdom. pain, peritonitis	Laparotomy: perforated sigmoid diverticulitis. Hartmann sigmoid resection + colostomy	Died 24 days later (multiorgan failure)
4	1. Abdominal pain, peritonitis. 2. Abdominal pain	Laparotomy: Two perforations in ascending colon. Right hemicolectomy + ileocolic resection, primary anastomosis	Healthy 2016
5	Lower right abdom. pain	Bowel rest, antibiotics, no blood transfusion	Healthy 2016
6	Abdom. pain; CT: hematoma	Arterial coiling, bowel rest, assisted ventilation, blood (no./1 day unknown)	Healthy 2016
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-laparotomy: no perforation, diffuse peritonitis, abdomen closed.	Healthy 2016
8	Rectal bleeding	Right hemicolectomy, ileostomy, delayed abdom. closure, bowel rest, 12 blood/8 d	Died 10 mos later (heart infarction)
9	Abdom. pain, CT: free air	Laparotomy: several ileocecal ulcers + perforations. Right hemicolectomia + dual-barrel ileo-/colostomy (not temporary), antibiotics, omeprazole, bowel rest.	Healthy 2016
10	Abdom. pain, CT: partial small bowel obstruction	Bowel rest	Died 5 yrs later (malignancy)
11	Low abdom. pain, CT: abdom. abscess	US-guided drainage of sigmoid abscess, antibiotics, bowel rest	Healthy 2016
12	Rectal bleeding, abdom. pain	Antibiotics, omeprazole, nasogastric draining, bowel rest, 12 blood/7 weeks	Healthy 2016
13	Rectal bleeding	7 blood/8 weeks, omeprazole, bowel rest	Healthy 2016
14	Rectal bleeding, abdom. pain	2 blood/2 days, antibiotics, omeprazole, nasogastric draining, bowel rest	Healthy 2016

Time to death relates to months or years after start of GI symptoms. *Blood* refers to units of blood transfusion. US: ultrasound; GPA: granulomatosis with polyangiitis; MPA: microscopic polyangiitis; CT: computed tomography, SIRS: systemic inflammatory response syndrome.

The diagnosis of GI disease in GPA and MPA is not always straightforward. Therefore, it is important to define GI disease in these patients in a standardized manner. We adopted the definitions proposed by Pagnoux, *et al* in 2005[19]. The symptoms should not be explained by GI infections[25,26], or simple nausea caused by CYC. In patients with left-sided colon perforation, it can be difficult to distinguish between diverticulitis precipitated by vasculitis or as a complication of 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%[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, 1 patient with intra-abdominal bleeding had angiographic microaneurysms in the inferior mesenteric artery, which is consistent with vasculitis. GPA and MPA affecting larger vessels have been described by others[27,28,29,30,31,32].

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 1 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 is important for a surgeon confronted with a patient with GI symptoms, allowing 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

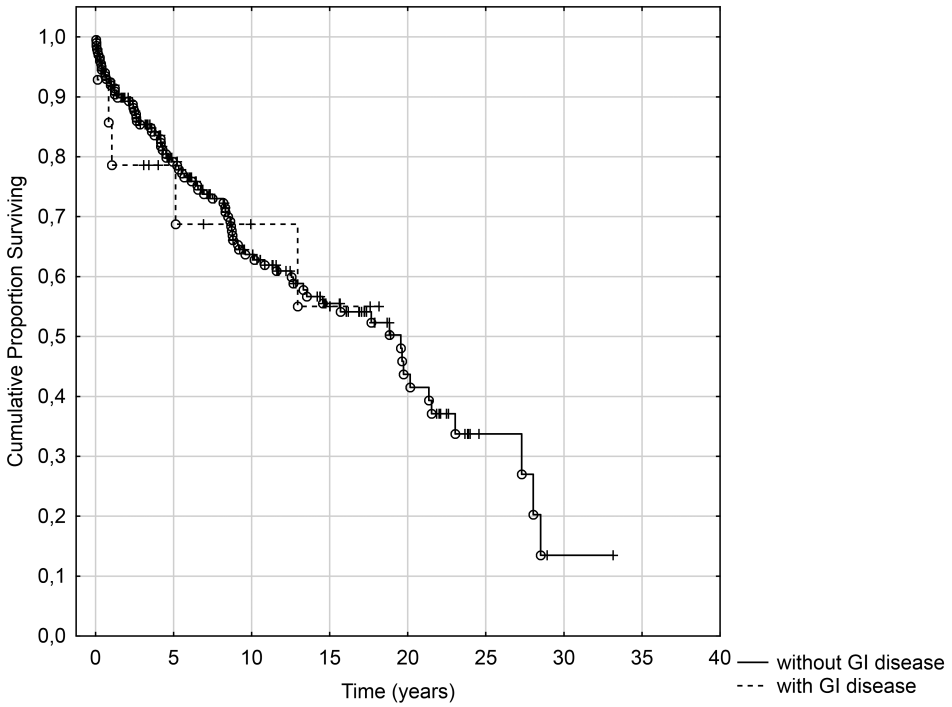

Figure 1. Patient survival in GPA and MPA for patients with (dotted line) or without (straight line) GI disease. GPA: granulomatosis with polyangiitis; MPA: microscopic polyangiitis; GI: gastrointestinal.

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 being debated[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]. Further, endoscopy can be of differential diagnostic importance. In our study, gastroscopy detected unspecific signs of inflammation in 3 of 5 patients, and colonoscopy showed unspecific macroscopic findings in 1 patient. Double balloon enteroscopy has been recommended because GI disease is often localized in the small bowel[3,33], and in 1 of our patients, capsule endoscopy of the GI tract showed swollen jejunal mucosa and focal inflammation of the duodenal bulb.

GI involvement was confirmed in specimens taken endoscopically or during surgery in some, but not all of our patients. In 1 report of GI involvement associated with different vasculitides, vasculitis could be detected histologically in only 3 of 36 biopsies during endoscopy, whereas surgically 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 1 summarizes GI findings in patients with GPA or MPA reported previously (available with the online version of this article).

Because of corticosteroids and patients who are often frail and in a bad general condition, the healing process is often hampered. This must be considered when surgery is necessary. One question is whether 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, 1 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 continued severe GI bleeding. In our study, medical treatment alone was sufficient in nearly half of the patients. Close surveillance with repeated CT scans is recommended because patients with high doses of corticosteroids may develop peritonitis without clinical signs.

Two of our 14 patients died of GI disease. However, compared to patients with GPA or MPA without GI disease, the patient survival rate was similar, contrasting to previous studies in which 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 an alternative explanation might be that the good outcome observed in our study has not occurred by chance and is possibly due to early diagnosis and treatment, as well as more efficient and less toxic therapy during recent years. We also believe that close cooperation between surgeons and rheumatologists is of benefit to the patient. Further studies are needed to answer whether patient survival is as bad as previously thought and whether survival has increased 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, in a recent European consensus document, RTX was graded as equally effective as CYC[34], but there are only a few case reports concerning the use of RTX in patients with MPA or GPA and GI involvement[35].

We found that GI disease was a rare but significant complication in this large population-based series of patients with GPA and MPA.

ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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