CASE REPORTS

A case of fatal gastrointestinal hemorrhage in granulomatosis with polyangiitis

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Received: February 20, 2017 **Accepted:** March 20, 2017 **Online Published:** March 31, 2017
DOI: 10.5430/crim.v4n2p34 **URL:** https://doi.org/10.5430/crim.v4n2p34

ABSTRACT

Although granulomatosis with polyangiitis (GPA) can affect any organ, gastrointestinal (GI) involvement is uncommon. Moreover, death from massive GI hemorrhage is a rare entity, with few cases described in the literature. In our report, we present a case of a patient with GPA who developed massive ulcerative bleeding, which ultimately proved fatal. Given the paucity of reports available, the significant potential for morbidity, and the fact that concurrent immunosuppressive therapy may themselves exacerbate the risk of bleeding, we reviewed 49 case reports of patients with GPA and GI involvement from 1982 to June 2016 in an attempt to shed light on a little seen sequelae that warrants a high index of suspicion.

Key Words: Granulomatosis with polyangiitis, Gastrointestinal hemorrhage, Immunosuppressive therapy

1. INTRODUCTION

Granulomatosis with polyangiitis (GPA) is a systemic vasculitis of small- and medium-sized vessels characterized by granulomatous and necrotizing inflammation with the potential for multi-organ involvement, most commonly affecting the respiratory tract and kidneys.[1] Gastronintestinal (GI) manifestations in GPA are uncommon, but the morbidity from GI involvement can be severe.[2]

In our case report, we describe an unusual case of GPA that presented with catastrophic upper GI ulcers that proved fatal. Our report also reviews the relevant literature, including 49 case reports of GPA involving the GI tract, published from 1982 to June 2016, in an attempt to amalgamate the most common clinical manifestations and management approaches of this little-seen entity.

2. CASE PRESENTATION

In January of 2015, a 61-year-old gentleman, Mr. X, presented to our hospital with a five-day history of persistent abdominal pain, with associated anorexia and weight loss. Despite an unremarkable abdominal examination, there were concerns for malignancy, and thus an abdominal and pelvic computed tomography (CT) was performed. Imaging failed to reveal any intra-abdominal or intra-pelvic abnormalities, but did note an irregular mass in the lower lobe of the right lung. A subsequent CT thorax confirmed the presence of a mass in the right lung, measuring 5.4 cm $\times$ 4.6 cm, in addition to another irregular mass in the upper lobe of the left lung, measuring 6.0 cm $\times$ 5.4 cm encasing the origin of the left subclavian artery.

Histology obtained via a transthoracic lung needle biopsy demonstrated extensive necrosis with suppuration, fibrinous

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exudate, and focal areas of regenerative stromal tissue with no evidence of malignant cells, vasculitis, or well-formed granulomas.

After defaulting on follow-up, Mr. X re-presented one month later following a bout of hemoptysis. On this occasion, a repeat CT thorax showed interval progression of the initial lung with an increase in size and mediastinal extension. He would undergo a bronchoscopy and a transtracheal needle biopsy of the right lung lesion, which again demonstrated necrotic tissue with scattered multinucleate giant cells and fibrosis. Of note, all fungal and bacterial respiratory cultures had returned negative at this point.

Two weeks following his second lung biopsy, Mr. X began to develop purpuric skin lesions and gingivitis associated with an acute kidney injury and normocytic normochromic anemia. An autoimmune screen was positive for c-ANCA. He would eventually undergo skin and gum biopsies showing medium-sized vasculitis with granuloma (see Figure 1 and Figure 2), and a kidney biopsy revealing ANCA-associated segmental necrotizing glomerulonephritis with crescents (see Figure 3). Mr. X was ultimately diagnosed with GPA.

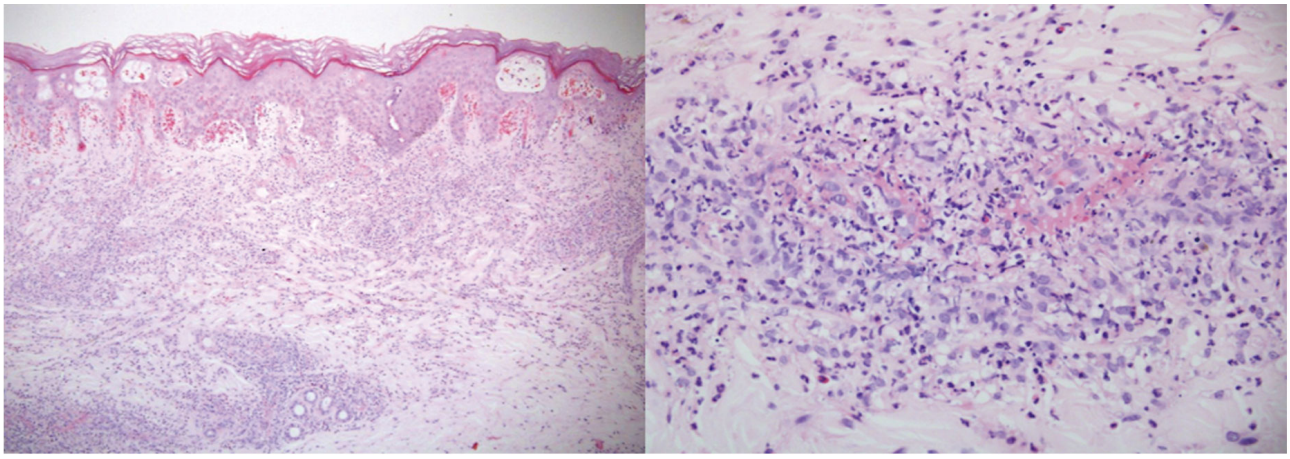

Figure 1. Skin biopsy. Hematoxylin & eosin (H&E) stain (40× [left] and 400× [right] magnification): Leukocytoclastic vasculitis with fibrinoid necrosis, neutrophilic infiltrate and karryorhectic debris.

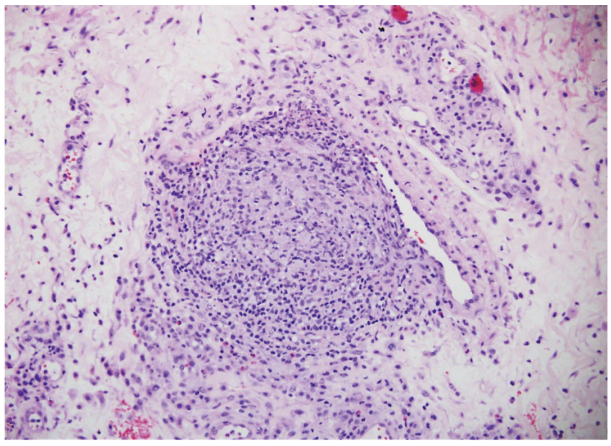

Figure 2. Oral mucosa biopsy. Hematoxylin & eosin (H&E) stain (200× magnification): Granulomatous vasculitis.

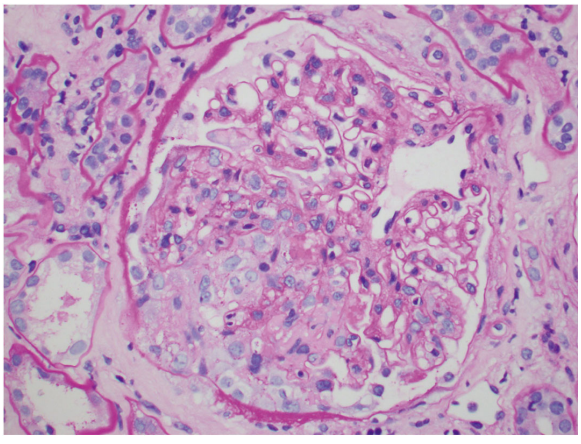

Figure 3. Kidney Biopsy. Periodic acid-Schiff (PAS) stain (400× magnification): Glomeruli with cellular crescent.

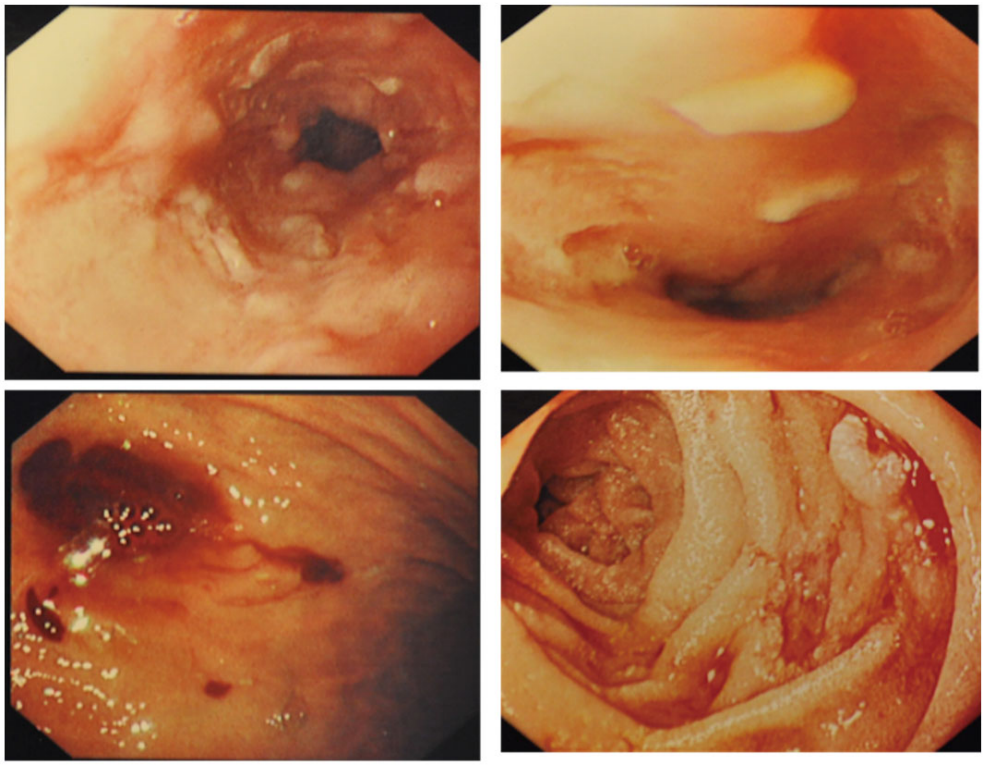

Figure 4. Esophagogastroduodenoscopy (EGD) showing multiple large ulcers from mid-esophagus to gastro-esophageal junction and distal duodenum

Mr. X was first started on oral prednisolone 1 mg/kg/day and pulsed intravenous cyclophosphamide. Two days later, he complained of acute epigastric pain associated with tenderness and a significant drop in his hemoglobin. He initially declined an esophageal gastro-duodenoscopy (EGD) but agreed to it when he developed further epigastric pain and a 2 g/dl drop in his hemoglobin level to 6.6 g/dl. Intravenous esomeprazole bolus was given followed by infusion. An emergent EGD showed multiple large ulcers from the mid-esophagus to the gastro-esophageal junction. A large amount of fresh blood was seen in the distal duodenum, obscuring the view of distal structures (see Figure 4).

Despite an initial injection of adrenaline, complete hemostasis was unable to be achieved. The procedure was then put on hold, and a repeat same-day EGD was resumed with a smaller-sized pediatric colonscope under monitored anesthesia care. The repeat EGD again showed multiple ulcers in the esophagus and stomach with no actively bleeding lesions. However, on advancement of the scope into the proximal jejunum, exposed vessel at the base of an ulcer was noted, and hemostasis was finally achieved by local injection of adrenaline and hemoclip application.

Mr. X was then transferred to the high-dependency unit and treated with continuous intravenous esomeprazole infusion. His immunosuppressive therapy was withheld in view of the risk of exacerbating his GI bleeding. Unfortunately, despite initial seemingly promising progress, Mr. X would ultimately go on to develop acute massive melena two days after his scope, and succumbed to refractory hypovolemic shock.

3. Discussion

GPA, formerly known as Wegener's granulomatosis, is a systemic vasculitis of small-and medium-sized vessels characterized by necrotizing granulomatous inflammation that typically affects the respiratory tract and commonly involves the kidneys. GPA has an incidence of 5-10 cases per million population with males and females equally affected.[1]

According to American College of Rheumatology (ACR, 1990), GPA is defined by the presence of at least two of the four criteria: 1) nasal or oral inflammation, 2) abnormal chest radiograph with either the presence of nodules, fixed infiltrates or cavities, 3) urine sediment with hematuria or red cell cast, and 4) granulomatous inflammation on biopsy within an artery or in the perivascular area of an artery or arteriole.[3] Our patient fulfilled the ACR criteria by having the evidence of pulmonary lesions and granulomatous inflammation seen in the skin, gum and kidney biopsies. The positive serum c-anti-neutrophilic cytoplasmic antibodies (ANCA) further support the diagnosis of GPA.

 ISSN 2332-7243 E-ISSN 2332-7251

GPA is a systemic disease that can affect any organs. Among the clinical manifestations, organs commonly affected include ear, nose and throat (70%-100%), lungs (50%-90%), kidneys (40%-100%), peripheral nervous system (6%-13%), skin (10%-50%) and eyes (14%-60%).[4] Gastrointestinal involvement is notably rare, ranging from 0%-26% of cases in adults.[4–8]

The symptoms, onset and the severity of gastrointestinal involvement in patients with GPA vary. Symptoms that are previously reported in the literature include gingivitis, esophageal and gastric ulcers, small bowel perforation, colonic ulceration, non healing perianal ulcers, cholecystitis, pancreatitis, pancreatic mass and splenic necrosis.[9–15]

To date, gastrointestinal involvement in GPA is still poorly understood with only scattered case reports available. The most recent larger study to our knowledge is the study done by Masiak , the authors studied the clinical manifestations of gastrointestinal tract involvement in 9 out of 34 patients with GPA treated in their department.[16] In order to further explore the clinical significance of this rare manifestation, we perform a literature review on cases reported on this subject from 1982 to June 2016.

The PubMed database from 1982 to June 2016 on GPA with gastrointestinal tract involvement in English literature was reviewed. A total of 49 case reports were explored. In addition to our case, the summary of the demographics and the clinicopathologic characteristics of these cases (a total of 50 cases) are shown in Table 1.

Table 1. Summary of cases of gastrointestinal involvement in patients with GPA in English literature from year 1982-June 2016

Cases	Age (Yr)	Sex	GI site	Pathology	Biopsy	Respi*/renal involvement	Onset of GI symptoms#	cANCA	Therapy prior$	Surgery	Outcome
Spiera et al., 1994 [17]	54	F	Esophagus	Erosions	Necrotizing granulomatous inflammation	Y/Y	4 weeks	NS	N	N	Death
Fallows et al., 2000 [18]	34	F	Esophagus	Ulcerations	Inflammation, fibrinoid necrosis	N/Y	At onset	+ve	N	N	Survival
Matsumoto et al., 2007 [19]	72	M	Esophagus	Erosions, ulcerations	Inflammation	Y/Y	At onset	+ve	N	N	Survival
Yamaguchi et al., 2007 [20]	52	F	Esophagus	Stenosis	NS	N/N	2 months	+ve	N	N	Survival
Arista et al., 2005 [9]	55	M	Esophagus, stomach	Ulcerations	Ulcerations	Y/Y	At onset	+ve	N	N	Survival
Deger et al., 2008 [21]	34	M	Esophagus, stomach, duodenum, jejunum	Ulceration, bleeding	Inflammation, fibrinoid necrosis, vasculitis	Y/Y	3 months	-ve	N	Y	Survival
Alexander et al., 2015 [22]	56	F	Esophagus, ileum	Ulcerations, perforation	Inflammation, necrotic debris	Y/Y	At onset	+ve	N	N	Death
Steele et al., 2001 [10]	34	F	Esophagus, stomach, colon	Ulcerations, bleeding	Inflammation	Y/Y	3 weeks	+ve	N	N	Survival
Koçak et al., 2012 [23]	39	M	Esophagus, duodenum, colon	Ulcerations, bleeding	Inflammation, necrotizing granulomas, vasculitis	Y/Y	2 months	+ve	Y	Y	Survival
Reddy et al., 2006 [11]	34	F	Esophagus, stomach, duodenum, colon, rectum	Ulcerations, strictures	Inflammation	Y/Y	10 weeks	+ve	Y	N	Survival
Our case	61	M	Esophagus, stomach, duodenum	Ulcerations, bleeding	No biopsy taken	Y/Y	8 weeks	+ve	Y	N	Death
Yamauchi et al., 1995 [24]	55	M	Stomach	Ulcerations, bleeding	Mononuclear cell infiltration	Y/Y	1 month	+ve	Y	N	Survival
Zheng et al., 2015 [7]	31	F	Stomach	Ulcerations	Chronic inflammation, granulomas	N/Y	At onset	+ve	N	N	Survival
Shahedi et al., 2013 [25]	57	M	Stomach, duodenum, jejunum	Inflammation	Inflammation	Y/Y	At onset	+ve	N	N	Survival
Malik et al., 2015 [26]	48	M	Stomach	Ulcerations	Chronic inflammation, non-necrotizing granulomatous	Y/N	At onset	+ve	N	N	Survival
Arhan et al., 2009 [27]	40	M	Duodenum	Ulcerations	NS	Y/Y	4 months	+ve	Y	N	Death
Marie et al., 2010 [28]	31	M	Duodenum, sigmoid, rectum	Erosions, ulcerations	Inflammation surrounding blood vessel	N/N	At onset	+ve	N	N	Survival
Samim et al., 2010 [6]	35	M	Proximal jejunum	Perforation, bleeding	Inflammation, ulcerations	Y/Y	4 months	+ve	Y	Y	Survival
Skaife et al., 2000 [12]	69	M	Distal jejunum	Perforation	Vasculitis	Y/Y	At onset	+ve	N	Y	Death

(Table 1 continued on page 38)

Table 1. (continued.)

Cases	Age (Yr)	Sex	GI site	Pathology	Biopsy	Respi*/renal involvement	Onset of GI symptoms#	cANCA	Therapy prior$	Surgery	Outcome
Veinot et al., 2003 [29]	71	F	Jejunum, ileum	Ischemia, necrosis	Ulcerations, necrosis, vasculitis	Y/Y	2 years	+ve	Y	Y	Survival
Shaikh et al., 2006 [13]	44	F	Distal jejunum, ileum, colon	Perforation	Vasculitis, necrosis	N/N	8 weeks	+ve	Y	Y (> 1)	Survival
Bulus et al., 2013 [30]	47	F	Jejunum, ileum	Necrosis, perforation	Necrotizing granulomatous vasculitis	Y/Y	At onset	+ve	N	Y	Death
Mcnabb et al., 1982 [31]	50	M	Distal ileum	Ulcerations, perforation	Nonspecific inflammation	Y /Y	9 months	NS	Y	Y	Survival
Coward et al., 1985 [32]	46	M	Distal ileum	Ulcerations, bleeding	Vasculitis	Y/Y	6 months	NS	Y	Y (> 1)	Survival
Geraghty et al., 1986 [33]	46	M	Distal ileum, colon	Ulcerations, perforation	NS	Y/Y	4 weeks	NS	Y	Y	Death
Tokuda et al., 1989 [34]	37	M	Distal ileum	Perforation	Vasculitis	Y/Y	2 years	NS	Y	Y	Survival
Tupler et al., 1991 [35]	55	F	Distal ileum, cecum	Necrosis, perforation	Necrotizing granulomas, vasculitis	Y/Y	1 year	NS	NS	Y	Death
Izzedine et al., 2001 [36]	45	M	Distal ileum	Ulcerations	Inflammation	Y/Y	9 years	+ve	N	N	Survival
Kitamura et al., 2004 [37]	32	M	Distal ileum, asc. colon	Ulcerations, bleeding	Nonspecific inflammation, vasculitis	Y/Y	9 months	+ve	N	N	Survival
Akça et al., 2005 [38]	56	M	Distal ileum	Necrosis, perforation	Ulcerations, inflammation, fistula, fibrosis	Y/N	6 months	+ve	Y	Y	Survival
Macías et al., 2005 [39]	28	NS	Distal ileum, colon	Bowel wall thickening	Vasculitis, granulomas	Y/N	NS	-ve	NS	Y	Death
Strivens et al., 2005 [40]	54	F	Distal ileum, colon	Perforation	Vasculitis	Y/Y	6 weeks	+ve	NS	Y	Survival
Kuwahara et al., 2006 [41]	30	M	Distal ileum to rectum	Ulcerations	Inflammation, granulomas	Y/Y	2 months	+ve	N	N	Survival
Beppu et al., 2011 [42]	33	M	Distal ileum, trans. colon, cecum	Ulcerations	Inflammation, fibrosis	Y/Y	1 year	+ve	Y	N	Survival
Dag et al., 2013 [43]	29	M	Distal ileum, cecum, asc. colon, hepatic flexure	Ulcerations, bleeding	Nonspecific inflammation	Y/Y	6 months	+ve	N	Y	Survival
Deniz et al., 2007 [44]	44	M	Ileum	Perforation	Ulcerations, necrotizing granulomas, vasculitis	Y/N	1 month	+ve	NS	Y	Survival
Yildirim et al., 2010 [45]	32	M	Ileum	Perforation	Inflammation, necrotizing granulomatous vasculitis	Y/N	2 weeks	+ve	Y	Y	Death
Akbulut et al., 2012 [5]	47	M	Ileum	Perforation, fistula	NS	Y/Y	1.5 year	NS	Y	Y	Death
Srinivasan et al., 1999 [46]	56	F	Small bowel	Perforation	Granulomatous reaction	N/N	10 weeks	+ve	Y	Y	Survival
Chow et al., 2003 [47]	46	M	Small bowel	Ulcerations, bleeding	Vasculitis	Y /Y	5 weeks	+ve	Y	Y (> 1)	Survival
Dinić et al., 2013 [48]	52	F	Small bowel	Perforation	NS	Y/Y	10 months	+ve	N	Y	Death
Schneider et al., 1997 [14]	41	M	Colon	Ulcerations	Ulcerating colitis	Y/Y	3 years	+ve	N	N	Survival
Qian et al., 2010 [49]	79	F	Colon	Ulcerations, bleeding	Inflammation, ulcerations	Y/Y	At onset	+ve	N	N	Survival
Morchón Simón et al., 2011 [50]	43	M	Colon	Inflammation	Inflammation	Y/Y	At onset	+ve	N	N	Survival
Yoshikawa et al., 2015 [51]	30	M	Colon	Inflammation , bleeding	Inflammation	N/N	At onset	+ve	N	N	Survival
Srivastava et al., 2014 [52]	45	F	Colon	Inflammation	Vasculitis	Y/Y	1 week	+ve	Y	Y	Survival
Storesund et al., 1998 [53] Case1	26	M	Sigmoid	Perforation	Vasculitis	Y/Y	18 months	+ve	Y	Y	Survival
Storesund et al., 1998 [53]	46	F	Sigmoid	Inflammation	Vasculitis	Y /Y	10 months	+ve	Y	Y	Survival
Case 2&	55	F	Small bowel, colon	Necrosis	Ischemia		11 years		Y	Y	Survival
Haworth et al., 1984 [54]	43	F	Rectum	Ulcerations	Neutrophils	Y/Y	11 months	NS	N	N	Survival
Sinnott et al., 2013 [55]	29	M	Rectum	Inflammation	Inflammation	Y/Y	At onset	+ve	N	N	Survival

Note. * (respiratory): including symptoms of either upper or lower respiratory tract; #: interval between onset of other GPA symptoms to gastrointestinal manifestation, $: immunosuppressive therapy prior to GI manifestation.Y: yes, N: no, NS: not sure, +ve: positive; &: same patient, developed 2 distinct episodes of GI complications 9 years apart.

In contrast to the equal frequency of GPA in males and females in larger clinical studies, our literature review shows more males (31 patients) to females (18 patients) presented with gastrointestinal manifestations in GPA.[56, 57] This is, however similar to a smaller study where GPA was about 1.5 times commoner in males.[8] The age of onset of the cases reported in our review ranges from 26 to 79 year.

Out of the total 50 case reports, 38 patients had classical GPA involving both the lungs and kidneys while only 5

patients presented unusually without either. Out of the 42 case reports with c-ANCA status documented, 40 cases were positive. This is consistent with the previous study which suggested most patients (approximately 90%) with active, generalized GPA had positive serum ANCA.[58]

Overall, GPA can affect any part of the gastrointestinal tract. In fact, most of the cases reported involved multiple locations. Of note, small bowel had the highest frequency with 33 cases while rectum involvement was only reported in 2 cases. Esophageal and gastric manifestations were reported in 9 and 11 cases respectively.

Inflammation and ulcerations were the most frequently seen pathology in endoscopy or laparotomy and among all the cases reported, 17 patients suffered from gastrointestinal perforation. Microscopically, most cases showed non-specific inflammation and ulceration. These frequent non-specific inflammation found in biopsies is not uncommon and was previously suggested by Camilleri *et al.* that it might be a result of biopsy taken too superficially.[59] The difficulty in demonstrating the presence of granulomatous inflammation/vasculitis from gastrointestinal tract mucosa places a challenge to differentiate GPA from inflammatory bowel disease.[14,25]

In all patients, only 15 cases had gastrointestinal symptoms appeared at the onset of the disease. The gastrointestinal involvement in GPA occurred from 1 week to 11 years. This is in contrast to Masiak *et al.*'s study where all their patients (9 out of 34) manifested gastrointestinal symptoms within the first year with the most common symptoms being abdominal pain and gastrointestinal bleeding.[16]

As gastrointestinal involvement in GPA is rare, the use of immunosuppressive therapy especially corticosteroid has been speculated to be the possible cause to the development of gastrointestinal manifestations in GPA.[16,53] In our literature review, a total of 21 patients developed gastrointestinal symptoms after immunosuppressive therapy. Of the cases with known duration of therapy prior to the gastrointestinal manifestations, the period of time ranges from 1 day to 12 months. 11 cases detected vasculitis/granulomatous inflammation histopathologically. Most of these cases (16 patients) improved and survived. Furthermore, Izzedine *et al.*'s patient presented with gastrointestinal manifestation as a relapsing symptom of GPA.[36] These results suggest that the gastrointestinal tract involvement is likely a result from the disease process of GPA itself rather than due to the immunosuppressive agents.

Interestingly, out of the 25 cases that required surgery, 3 patients had more than 1 operation. In fact, some of the patients described in the case reports required multiple endoscopies to localize and control the source of bleeding. This may suggest that gastrointestinal manifestations in GPA can be progressive and/or recurrent.

GPA is the most common form of life-threatening small-vessel vasculitis, however, death from gastrointestinal complication is extremely rare. Luqmani *et al.* identified 255 patients with GPA and long-term mortality in patients with GPA was compared with matched population-based controls, there was only 1 patient died from bowel perforation in within a year. Most of the causes of death were due to infection, disease activity and renal failure.[2]

In our literature, a total of 12 patients passed away despite treatment. As most of the cases reported involved multiple organs, the higher mortality rate in our review (24%) may likely be that the gastrointestinal manifestations occur during the acute phase of the disease and death occurs due to multi-systemic involvement. It is unsure whether gastrointestinal involvement could indicate a poor prognostic factor given its rare occurrence in GPA. However, given the high mortality rate and the possible catastrophic gastrointestinal hemorrhagic and perforation incidents in such manifestation, a high clinical suspicion, early treatment and close surveillance upon initiation of immunosuppressive agents are warranted.

4. Conclusions

Although uncommon, massive GI ulcerative bleeding can occur in GPA as a result of the underlying disease and/or aggravated by concurrent immunosuppressive therapy. This can be potentially catastrophic and warrants a high index of suspicion and close monitoring.

Ethics

Written informed consent was obtained from the patient's next of kin for publication of this case report and accompanying images.

Conflicts of Interest Disclosure

The authors have no competing interests to declare.

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