A case of fatal gastrointestinal hemorrhage in granulomatosis with polyangiitis

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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] Gastrointestinal (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 right lung, measuring 5.4 cm × 4.6 cm, in addition to another irregular mass in the upper lobe of the left lung, measuring 6.0 cm × 5.4 cm encasing the origin of the left subclavian artery.

Histology obtained via a transthoracic lung needle biopsy demonstrated extensive necrosis with suppuration, fibrinuous
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 karyorhectic 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.
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 the 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.\[2\]

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.
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, esophageal and gastric ulcers, small bowel perforation, kidneys (40%-100%), peripheral nervous system (6%-13%), skin (10%-50%) and eyes (14%-60%).[4] 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 | eANCA | Therapy | Surgery | Outcome |
|-------|----------|-----|---------|-----------|--------|---------------------------|---------------------|-------|---------|---------|---------|
| Spera et al., 1994[1][3] | 54 | F | Esophagus | Erosions | Necrotizing granulomatous inflammation | Y/Y | 4 weeks | NS | N | N | Death |
| Fallows et al., 2000[10] | 34 | F | Esophagus | Ulcerations | Inflammation, fibrinoid necrosis | N/N | 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 |
| Araba et al., 2005[5] | 55 | M | Esophagus, stomach | 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, bleeding | Inflammation, necrotic debris | Y/Y | At onset | +ve | N | N | Death |
| Steele et al., 2001[14] | 34 | F | Esophagus, stomach, colon | Ulcerations, bleeding | Inflammation | Y/Y | 3 weeks | +ve | N | N | Survival |
| Kocak 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, bleeding | No biopsy taken | Y/Y | 8 weeks | +ve | Y | N | Death |
| Yamashita et al., 1995[24] | 55 | M | Stomach | Ulcerations, bleeding | Mononuclear cell infiltration | Y/Y | 1 month | +ve | Y | N | Survival |
| Zheng et al., 2015[17] | 31 | F | Stomach | Ulcerations | Chronic inflammation, granulomas | N/Y | At onset | +ve | N | N | Survival |
| Shafee 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 |
| Ahan et al., 2009[27] | 40 | M | Duodenum | Ulcerations | NS | Y/Y | 4 months | +ve | Y | N | Death |
| Marat 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[29] | 35 | M | Proximal jejunum | Perforation, bleeding | Inflammation, ulcerations | Y/Y | 4 months | +ve | Y | Y | Survival |
| Skalife et al., 2000[30] | 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}\^3 | Surgery | Outcome |
|-------|----------|-----|---------|-----------|--------|--------------------------|----------------------|-------|-----------------|---------|---------|
| Veine et al., 2003 \[59\] | 71 | F | Jejunum, ileum | Ischemia, necrosis | Ulcerations, necrosis, vasculitis | Y/Y | 2 years | +ve | Y | Y | Survival |
| Shahin et al., 2006 \[11\] | 44 | F | Distal jejunum, ileum, colon | Perforation | Vasculitis, necrosis | N/N | 8 weeks | +ve | Y | Y (> 1) | Survival |
| Buls et al., 2013 \[57\] | 47 | F | Jejunum, ileum | Necrosis, perforation | Necrotizing granulomatous vasculitis | Y/Y | At onset | +ve | N | Y | Death |
| McNabb et al., 1982 \[51\] | 50 | M | Distal ileum | Ulcerations, perforation | Nonspecific inflammation | Y/Y | 9 months | NS | Y | Y | Survival |
| Coward et al., 1985 \[52\] | 46 | M | Distal ileum | Ulcerations, bleeding | Vasculitis | Y/Y | 6 months | NS | Y | Y (> 1) | Survival |
| Gengenb et al., 1986 \[53\] | 46 | M | Distal ileum, colon | Ulcerations, perforation | NS | Y/Y | 4 weeks | NS | Y | Y | Death |
| Tokuda et al., 1999 \[54\] | 37 | M | Distal ileum | Perforation | Vasculitis | Y/Y | 2 years | NS | Y | Y | Survival |
| Tagger et al., 1991 \[55\] | 55 | F | Distal ileum, cecum | Necrosis, perforation | Necrotizing granulomas, vasculitis | Y/Y | 1 year | NS | NS | Y | Death |
| Izedzine et al., 2001 \[56\] | 45 | M | Distal ileum | Ulcerations | Inflammation | Y/Y | 9 years | +ve | N | N | Survival |
| Kitamura et al., 2004 \[57\] | 32 | M | Distal ileum, ascending colon | Ulcerations, bleeding | Nonspecific inflammation, vasculitis | Y/Y | 9 months | +ve | N | N | Survival |
| Akça et al., 2005 \[58\] | 56 | M | Distal ileum | Necrosis, perforation | Ulcerations, inflammation, fistula, fibrosis | Y/N | 6 months | +ve | Y | Y | Survival |
| Macias et al., 2005 \[59\] | 28 | NS | Distal ileum, colon | Bowel wall thickening | Vasculitis, granulomas | Y/N | NS | -ve | NS | Y | Death |
| Strivens et al., 2005 \[60\] | 54 | F | Distal ileum, colon | Perforation | Vasculitis | Y/Y | 6 weeks | +ve | NS | Y | Survival |
| Kuwahara et al., 2006 \[61\] | 30 | M | Distal ileum to rectum | Ulcerations | Inflammation, granulomas | Y/Y | 2 months | +ve | N | N | Survival |
| Beppu et al., 2011 \[62\] | 33 | M | Distal ileum, trans. colon, cecum | Ulcerations | Inflammation, fibrosis | Y/Y | 1 year | +ve | Y | N | Survival |
| Dug et al., 2013 \[63\] | 29 | M | Distal ileum, cecum, ascending colon, hepatic flexure | Ulcerations, bleeding | Nonspecific inflammation | Y/Y | 6 months | +ve | N | Y | Survival |
| Deniz et al., 2007 \[64\] | 44 | M | Ileum | Perforation | Ulcerations, necrotizing granulomas, vasculitis | Y/N | 1 month | +ve | NS | Y | Survival |
| Yildirim et al., 2010 \[65\] | 32 | M | Ileum | Perforation | Inflammation, necrotizing granulomatous vasculitis | Y/N | 2 weeks | +ve | Y | Y | Death |
| Akbulut et al., 2012 \[66\] | 47 | M | Ileum | Perforation, fistula | Vasculitis | Y/Y | 1.5 year | NS | Y | Y | Death |
| Srinivasan et al., 1999 \[67\] | 56 | F | Small bowel | Perforation | Granulomatous reaction | N/N | 10 weeks | +ve | Y | Y | Survival |
| Chow et al., 2003 \[68\] | 46 | M | Small bowel | Ulcerations, bleeding | Vasculitis | Y/Y | 5 weeks | +ve | Y | Y (> 1) | Survival |
| Dnác et al., 2013 \[69\] | 52 | F | Small bowel | Perforation | NS | Y/Y | 10 months | +ve | N | Y | Death |
| Schneider et al., 1997 \[70\] | 41 | M | Colon | Ulcerations | Ulcerating colitis | Y/Y | 3 years | +ve | N | N | Survival |
| Qun et al., 2010 \[71\] | 79 | F | Colon | Ulcerations, bleeding | Inflammation, ulcerations | Y/Y | At onset | +ve | N | N | Survival |
| Morchon Simon et al., 2011 \[72\] | 43 | M | Colon | Inflammation | Inflammation | Y/Y | At onset | +ve | N | N | Survival |
| Yoshikawa et al., 2015 \[73\] | 30 | M | Colon | Inflammation, bleeding | Inflammation | N/N | At onset | +ve | N | N | Survival |
| Srivastava et al., 2014 \[74\] | 45 | F | Colon | Inflammation | Vasculitis | Y/Y | 1 week | +ve | Y | Y | Survival |
| Storesund et al., 1998 \[75\] | 26 | M | Sigmoid | Perforation | Vasculitis | Y/Y | 18 months | +ve | Y | Y | Survival |
| Storesund et al., 1998 \[76\] | 46 | F | Sigmoid | Small bowel, colon | Necrosis | Y/Y | 10 months | +ve | Y | Y | Survival |
| Case 2 \[77\] | 55 | F | Sigmoid | Small bowel, colon | Necrosis | Y/Y | 11 years | +ve | Y | Y | Survival |
| Hare et al., 1984 \[78\] | 43 | F | Rectum | Ulcerations | Neutrophils | Y/Y | 11 months | NS | N | N | Survival |
| Sinnott et al., 2013 \[79\] | 29 | M | Rectum | Inflammation | Inflammation | Y/Y | At onset | +ve | N | N | Survival |

*Note: $: interval between onset of other GPA symptoms to gastrointestinal manifestation. $: 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. This is, however similar to a smaller study where GPA was about 1.5 times commoner in males. 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.\textsuperscript{[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.\textsuperscript{[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.\textsuperscript{[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.\textsuperscript{[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.\textsuperscript{[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.\textsuperscript{[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 within a year. Most of the causes of death were due to infection, disease activity and renal failure.\textsuperscript{[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 manifestations, 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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