Case Report
Successful Antimicrobial Treatment of Phlegmonous Gastritis: A Case Report and Literature Review

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Accepted 22 August 2018; Published 16 September 2018

Academic Editor: Massimo Breccia

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Phlegmonous gastritis is an uncommon acute bacterial infection of the stomach that carries a fatal prognosis in spite of the advent of antibiotics. A high index of suspicion is required in patients with risk factors. An immunocompromised state is identified as one of the most important risk factors. We hereby report a case of successful antimicrobial treatment of phlegmonous gastritis in a patient who was receiving intensive chemotherapy for acute myelogenous leukemia. We have also carried out a review of literature over the past ten years. Streptococcus pyogenes is identified as the most common causative organism, and patient presentation is usually nonspecific. Conservative treatment with prompt institution of antibiotics can lead to rapid resolution in the majority of patients.

1. Introduction
Phlegmonous gastritis (PG) is a rare acute bacterial infection, which primarily involves the submucosal layer of the stomach wall, but can also involve the muscularis layer and rarely the mucosa [1–3]. It is rapidly fatal if untreated and thus requires prompt diagnosis and management. Even with the correct diagnosis and antimicrobial therapy, the mortality rate remains high at 27–40% [2, 3]. PG primarily affects the middle-aged population of 45–74 years, with a 65% male predominance [4]. The underlying etiology is largely unknown, although an immunocompromised state associated with malignancy, chemotherapy-induced neutropenia, acquired immunodeficiency syndrome (AIDS), alcoholism, and immunosuppressive drugs is considered an important risk factor [5]. We herein report a patient who developed PG in the setting of prolonged neutropenia related to relapsed acute myeloid leukemia (AML) and intensive chemotherapy and was successfully treated with systemic antimicrobial therapy.

2. Case Presentation
The patient reported is a 56-year-old woman who was diagnosed with acute myeloid leukemia (AML) with cytogenetic abnormality of inversion 16 in 2013. She achieved a complete remission (CR) after standard induction chemotherapy with 7+3 regimen consisting of ara-C and daunorubicin followed by consolidation with high-dose ara-C (HiDAC). She relapsed a year later and was re-induced with a salvage chemotherapy regimen MEC (mitoxantrone, etoposide, and cytarabine) achieving a second CR, which was followed by a matched unrelated allogeneic stem cell transplant (allo-SCT). Her posttransplant course was uneventful without significant graft versus host disease and prolonged requirement for immunosuppression. Two years after allo-SCT, she had a central nervous system (CNS) relapse of her original leukemia and presented with an infiltrating lesion in the lumbar-sacral spine; her CSF cytology was positive for myeloblasts. She was admitted to the hospital to receive reinduction chemotherapy; her vitals
Upon admission were as follows: temperature 37.7 °C, blood pressure (BP) 129/65 mmHg, heart rate (HR) 72/min, and respiratory rate (RR) 14/min. She was started on intrathecal chemotherapy with ara-C and systemic chemotherapy with the salvage chemotherapy regimen FLAG-IDA (fludarabine, ara-C, and idarubicin). The day chemotherapy started for the patient was noted as day 1. On day 10, the patient developed neutropenic fever, and the white blood count (WBC) noted to be <0.1 × 10^9/L with absolute neutrophil count (ANC) of 0. She was started on intravenous (IV) cefepime 2 g every 8 h after evaluation for underlying infectious etiology was done. The work up did not isolate any organism and included blood culture, urine culture, and chest X-ray. On day 16, the patient developed left upper quadrant abdominal pain. Vital signs then were as follows: maximum temperature (T_max) 37.5 °C, along with HR of 80–94/min, RR 16–18/min, and BP SBP 105–126/DBP 55–71 mmHg. Her blood tests then were as follows: WBC <0.1 × 10^9/L, ANC 0, hemoglobin 8.0 g/dl, platelet 12 × 10^9/L, and serum blood chemistry and liver function tests were noted to be without significant derangements. A CT scan of the abdomen was performed that showed diffuse thickening of stomach wall (Figure 1(a)), concerning for infectious or infiltrative malignant process. Her absolute neutrophil count had been at the nadir for 10 days prior to this development. Her antimicrobial coverage was increased to include anaerobic coverage by changing her antibiotic regimen from IV cefepime 2 g every 8 h to IV piperacillin/tazobactam 3.375 g every 6 h, leading to short-lived symptomatic improvement for roughly two weeks. Upon symptom recurrence, the patient was noted to be febrile with T_max of 39.5°C, along with HR of 109–139/min, RR 18–20/min, and BP SBP 94–124/DBP 55–71. Two sets of peripheral blood cultures were drawn which did not show growth of any organism after 5 days of incubation. The patient continued to remain hemodynamically stable.

An upper gastrointestinal (GI) endoscopy was performed which showed a large ulcerative lesion with purulent discharge and inflammatory changes (Figure 2). *Citrobacter freundii*, *Enterococcus faecalis*, and *Bacillus cereus* were isolated from culture on gastric biopsies. Imaging, endoscopic, and microbiological findings were consistent with phlegmonous gastritis.

Infectious disease service was consulted, IV piperacillin/tazobactam 3.375 g every 6 h was stopped, and the antibiotic regimen was changed to IV vancomycin (managed per pharmacy protocol based on weight and renal function) and IV meropenem 1 g IV every 8 h. The recommendation for broad coverage of microorganisms was made by infectious disease service, given the high risk of mortality associated with phlegmonous gastritis. Prophylactic antifungal and antiviral for neutropenia were continued. Organism susceptibilities were carried out for *Citrobacter freundii* and *Enterococcus faecalis*, which revealed *Citrobacter freundii* to be resistant to ampicillin, cefazolin, and cefuroxime, while *Enterococcus faecalis* was noted to be pansensitive. Per organism susceptibility and with the help of infectious disease service, her antibiotic regimen was changed to IV cefepime 2 g every 8 h, IV metronidazole 500 mg IV every 8 h, and IV vancomycin per pharmacy protocol. This antibiotic regimen was continued for a total of two weeks. The patient’s gastrointestinal symptoms resolved quickly, and she was able to resume normal diet. Follow-up CT scan a month later showed marked improvement in gastric thickening (Figure 1(b)). She is currently doing well with her AML in remission and no recurrence of her GI symptoms.
| Author/Year          | Sex | Age | Cause/risk factor                                      | Symptoms                                      | Pathogen/s                                      | Diagnosis | Intervention/management                      | Complications                                      | Result         |
|---------------------|-----|-----|-------------------------------------------------------|-----------------------------------------------|------------------------------------------------|-----------|-----------------------------------------------|---------------------------------------------------|----------------|
| Ajibe H, 2008       | M   | 74  | Endoscopic submucosal dissection for gastric adenocarcinoma | Epigastric pain, fever                        | Citrobacter freundii, Enterobacter cloacae, and Streptococcus | CT, EGD, EUS | Antibiotics, total gastrectomy               | Nil                                               | Discharge      |
| Alonso et al., 2013 | F   | 55  | None                                                  | Chest pain                                    | Streptococcus pyogenes                          | CT        | Antibiotics, endoscopic abscess drainage     | Nil                                               | Discharge      |
| Fan JQ, 2013        | M   | 65  | Esophagectomy for esophageal adenocarcinoma           | Fever, dyspnea                                | Nil                                             | CT, EGD   | Antibiotics                                  | Nil                                               | Discharge      |
| Flor-de-Lima F, 2015| M   | 7   | Acute tonsillitis                                     | Epigastric pain, nausea, vomiting             | Streptococcus pneumonia, EBV                    | CT, EGD with biopsy | Antibiotics                                  | Nil                                               | Discharge      |
| Guo et al., 2009    | M   | 57  | CML, myeloid sarcoma                                  | Fever, fatigue, chest pain                    | Pseudomonas, Klebsiella                         | CT, EGD   | Antibiotics, surgery (not gastrectomy)      | Upper GI bleed                                   | Death          |
| Huang et al., 2017  | F   | 60  | Uncontrolled DM                                       | Fever, fatigue, chest pain                    | MDR Streptococcus                              | EGD       | Antibiotics                                  | Nil                                               | Discharge      |
| Ishigami T, 2008    | M   | 70  | None                                                  | Fever, abdominal pain                         | EGD                                             | Antibiotics | Nil                                           | Discharge      |
| Itonaga M, 2012     | F   | 70  | EUS-FNA for pancreatic tumor                          | Fever, abdominal pain                         | Alpha-hemolytic Streptococcus                  | Ct, EGD, EUS | Antibiotics                                  | Nil                                               | Discharge      |
| Kato et al., 2015   | M   | 64  | DM, chronic pancreatitis                              | Epigastric pain, nausea                       | Peptostreptococcus                             | CT, EGD with biopsy | Antibiotics, EUS-guided pseudocyst drainage | Antibiotics | Nil                                               | Discharge      |
| Kim BY, 2017        | M   | 51  | Ankylosing spondylitis                                | Nausea, vomiting                              | Nil                                             | CT, EGD   | Antibiotics, surgery (not gastrectomy)      | Bilateral pleural effusions                       | Discharge      |
| Kim et al., 2010    | M   | 48  | Alcoholism, uncontrolled DM                           | Abdominal pain, vomiting                      | Klebsiella spp.                                | EGD       | Antibiotics, surgery (not gastrectomy)      | Nil                                               | Discharge      |
| Kim et al., 2016    | M   | 74  | Alcoholic cirrhosis, DM, recent EGD, gastric adenocarcinoma | Epigastric pain, nausea, vomiting             | Klebsiella, Acinetobacter                      | CT, EGD with biopsy | Antibiotics                                  | Nil                                               | Discharge      |
| Kim NY, 2011        | M   | 66  | None                                                  | Fever, nausea, vomiting                       | Polymicrobial (gram positive and gram negative organisms) | CT, EGD with biopsy | Antibiotics                                  | Nil                                               | Discharge      |
| Liu YJ, 2013        | M   | 84  | Colon cancer, prostate cancer                         | Epigastric pain, nausea, vomiting             | Bacillus spp.                                  | CT, EGD   | Antibiotics                                  | Sepsis, disseminated intravascular coagulation    | Death          |
| Matsumoto H, 2015   | M   | 74  | Myelofibrosis, multiple myeloma, neutropenia         | Epigastric pain, nausea                       | Streptococcus pyogenes                         | CT, EGD with biopsy | Antibiotics, total gastrectomy              | Gastric submucosal dissection                     | Death          |
| Min et al., 2014    | F   | 51  | Gastric ulcer                                         | Abdominal pain, vomiting                      | Streptococcus pyogenes                         | CT, exploratory laparotomy                      | Antibiotics, total gastrectomy                   | Gastric submucosal dissection                     | Discharge      |
| Morimoto et al., 2014| M | 77  | DM, gastric ulcers                                    | Epigastric pain, nausea, vomiting             | Group A Streptococcus                          | CT        | Antibiotics                                  | Death                                              |               |
| Nomura K, 2015      | F   | 80  | None                                                  | Epigastric pain, vomiting                      | Enterobacter cloacae and E. faecium            | CT, EGD with biopsy | Antibiotics, total gastrectomy (worsening gastric strictures) | Nil | Discharge |
Table 1: Continued.

| Author/Year       | Sex | Age | Cause/risk factor       | Symptoms                              | Pathogen/s                  | Diagnosis                      | Intervention/management      | Complications                                 | Result                      |
|-------------------|-----|-----|-------------------------|---------------------------------------|-----------------------------|--------------------------------|--------------------------------|----------------------------------------------|-----------------------------|
| Paik DC, 2010     | M   | 45  | Recent paranasal sinus surgery | Abdominal pain, nausea, vomiting      | *Streptococcus pyogenes*    | CT, exploratory laparotomy EGD | Antibiotics                   | Respiratory failure, renal failure, coagulopathy | Discharge                   |
| Park CW, 2010     | F   | 73  | Gastric outlet narrowing | Epigastric pain, abdominal distension | *E. coli, Acinetobacter*    | CT, EGD with biopsy             | Antibiotics, pyloric stent    | Nil                                           | Discharge                   |
| Rada-Palomino et al., 2014 [8] | M   | 62  | HIV                     | Epigastric pain, hematemesis, diarrhea | *Streptococcus pyogenes*    | CT, EGD with biopsy             | Antibiotics                   | Nil                                           | Discharge                   |
| Saito M, 2012     | F   | 55  | ALL                     | Neutropenia                           | *Bacillus spp.*             | CT, EGD with biopsy             | Antibiotics                   | Nil                                           | Discharge                   |
| Sakata T, 2011    | F   | 63  | None                    | Fever                                 | None reported               | CT, EGD with biopsy             | Antibiotics, drainage         | Nil                                           | Discharge                   |
| Shiozawa K, 2009  | M   | 62  | Uncontrolled DM         | Epigastric pain                       | None reported               | CT                             | Antibiotics, drainage         | Nil                                           | Discharge                   |
| Munroe CA, 2010   | M   | 58  | Chronic hepatitis B     | Epigastric pain, nausea, fever        | *Alpha-hemolytic Streptococcus* | CT, EGD, EUS with biopsy      | Antibiotics, aspiration       | Nil                                           | Discharge                   |

CML: chronic myeloid leukemia; DM: diabetes mellitus; HIV: human immunodeficiency virus; ALL: acute lymphoblastic leukemia; EBV: Epstein-Barr virus; VRE: vancomycin-resistant Enterococcus; MDR: multidrug resistance; Strep: *Streptococcus*; EUS: endoscopic ultrasound; CT: computed tomography; EGD: esophagogastroduodenoscopy; FNA: fine needle aspiration.
3. Discussion and Literature Review

Phlegmonous gastritis is a rare infection with less than 500 cases reported in literature [3]. We have carried out a bibliographic search using PubMed from 2007 to 2017 using the keyword “Phlegmonous Gastritis” and found 36 articles, in English, Spanish, and Japanese, of which we reviewed 25.

Our limited data review showed that there have been only 4 cases reported in the USA and 3 in Europe in the last 10 years, whereas the bulk was reported in Southeast Asia, namely Japan (13) and Korea (8). In addition to an immunocompromised state, the other reported risk factors are increased age, gastric mucosal injury from chronic gastritis, peptic ulcer, endoscopic procedures, gastric cancer, achlorhydria, infection, and malnutrition [6, 7]. Our review found malignancy to be a risk factor in 32% of the cases (8/25). The mortality rate has been reported to be higher in groups with an identified risk factor as compared to those without one [8]. PG has been further classified into primary and secondary types [1]. The primary type is usually idiopathic or occurs after direct damage to the gastric mucosa due to trauma, cancer, and endoscopic interventions, thereby leading to direct microbial invasion. The secondary type is either associated with infection of neighboring organs, such as infection due to pancreatitis, hepatic abscess, and cholecystitis, or hematogenous/lymphogenous spread from other organs.

PG is a rare infection that usually presents with nonspecific gastrointestinal symptoms. A high index of suspicion is necessary, especially in immunocompromised individuals. Epigastric/abdominal pain is the most common symptom, with other symptoms including but not limited to being fever, nausea, vomiting, and, less often, diarrhea and hematemesis [6]. PG should be highly suspected if a CT scan shows diffuse thickening of the stomach wall. The upper GI endoscopy should be performed as visual and microbiologic findings help establish the diagnosis and guide antimicrobial therapy. Although, *Streptococcus pyogenes* is the most frequently reported isolated organism in about 70% of cases, polymicrobial infection as seen in our patient is also quite common [2, 8, 9]. Our review of cases followed a similar pattern, wherein *Streptococcus* spp. was the most common pathogen identified in 44% of cases, but there were also other uncommon pathogens isolated such as *Citrobacter, Acinetobacter, Enterobacter* spp., and *Bacillus* spp., and even resistant pathogens like MDR (multidrug-resistant) *Streptococcus* and VRE (vancomycin-resistant enterococcus) (Table 1).

It is imperative to initiate empiric broad-spectrum antimicrobial coverage as soon as there is the clinical suspicion of possible phlegmonous gastritis, followed by adjustments as per microbiological culture results and clinical course. Early diagnosis and prompt institution of antibiotics has been shown to prevent patient mortality and defer the need of a surgical intervention [7]. All of the patients in our review received antibiotics, with resolution seen in 22/25 (88%) of the cases and death in 3/25 of the cases (12% mortality). This illustrates that prompt recognition and awareness of phlegmonous gastritis as possible complication of prolonged neutropenia in patients with hematological malignancies can clearly impact outcomes.

Invasive modality for management includes surgical gastrectomy and is mainly reserved for those with impending local complications such as perforation or sepsis [6, 7]. As mentioned above if promptly recognized, majority of the patients can be treated via conservative measures. Patients with hematologic malignancies are a unique population that is extremely susceptible to this complication due to prolonged neutropenia, secondary to intensive chemotherapy regimens. Prompt intervention and assistance from multiple medical specialties is needed to prevent fatality from this aggressive infection. Our case highlights the need for awareness of this rare infectious complication amongst health care professionals who take care of immunocompromised patients especially those suffering from hematological malignancies as knowledge of this rare complication can clearly impact patient mortality. Table 1 shows the major clinical characteristics, imaging findings, microbiology results, treatment, and survival outcomes from our literature review.

Conflicts of Interest

The authors declare that that there are no conflicts of interest regarding the publication of this paper.

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