

Hemorrhagic Bullae Caused by *Bacteroides fragilis* in a Patient with Intra-abdominal Infection

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Skin manifestations due to intra-abdominal infection are uncommon but could be a warning sign of severe infection. We report a 58-year-old uremic female who had acute cholecystitis and pneumatosis intestinalis. She developed periumbilical hemorrhagic bullae and finally had a fatal outcome with medical therapy. Severe intra-abdominal infection such as pneumatosis intestinalis should be suspected when periumbilical bullae increase in size. [*J Formos Med Assoc* 2008;107(8):659–662]

Key Words: *Bacteroides fragilis*, hemorrhagic bullae, intra-abdominal infection, skin manifestations

There are various skin manifestations caused by systemic infections. Most skin infections are due to different cutaneous pathogens like cellulites, necrotizing fasciitis, and staphylococcal scaled-skin syndrome.¹ But systemic infection may manifest with skin lesions such as Cullen's sign.² Here, we describe the case of a 58-year-old woman with acute cholecystitis, ileus, and pneumatosis intestinalis who developed two hemorrhagic bullae located at the periumbilical area that mimicked Cullen's sign, but *Bacteroides fragilis* was isolated from the bullae aspirate. Although medication was given, she died. To our knowledge, a pathogen isolated from such a skin manifestation related to intra-abdominal infection has never been reported. We analyze this case and review the literature on skin manifestations associated with intra-abdominal infections.

Case Report

The patient was a 58-year-old woman with chronic pancreatitis and chronic kidney disease who had had continuous ambulatory peritoneal dialysis for 8 years and had also recently been undergoing regular hemodialysis. She was hospitalized due to abdominal pain and fever of 4 days' duration. The characteristics of the abdominal pain were a dull feeling, radiating to the back, aggravated by food intake and relieved when she rested. Her body temperature was 38.3°C. On examination, there was epigastric tenderness without rebounding pain. Baseline investigation on admission on June 6, 2006 revealed elevated C-reactive protein (CRP) of 228.18 µg/mL (normal, < 5 µg/mL), and leukocytosis (white blood cell count of 17,600/µL with differential count of neutrophil 79.0%).

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The platelet level on admission was 215,000/ μ L. The amylase level was 131 U/L (normal, <123 U/L) and lipase level was 29 IU/L (normal, <58 IU/L). Pancreatitis was diagnosed with a computed tomography (CT) examination finding of pancreas swelling without hemorrhage and ascites formation.

Ampicillin/sulbactam 2 g/1 g QD was given because of suspicion of acute exacerbation of pancreatitis with bacterial infection. The fever subsided 3 days after admission but the abdominal pain persisted around the right upper quadrant (RUQ) area, and she had had no stool passage. The physical examination revealed no rebounding pain in the RUQ and a hypoactive bowel sound. Plain abdominal X-ray revealed ileus. At the same time, a 2 \times 1.5 cm bluish patch and a 2 \times 2.2 cm brownish bulla appeared at the right side of her periumbilical area (Figure 1). Laboratory data revealed the following: leukocytes, 19,160/ μ L; CRP, 378.25 μ g/mL; prothrombin time, 13.6 seconds/10.6 seconds (control); international normalized ratio, 1.30; partial prothrombin time, 33.6 seconds/39.6 seconds (control). The two skin lesions became confluent to a 4 \times 3 cm grayish bulla. The antibiotics were changed to ceftazidime 2 g QOD and vancomycin 1 g Q4D for ongoing peritoneal sepsis.

Gallium-67 citrate whole body inflammation scan revealed a heterogeneous active gallium-avid radiotracer accumulation in the abdomen.



Figure 1. A 2 \times 1.5 cm bluish patch with well-defined margin and a 2 \times 2.2 cm brownish papule with well-defined margin located at the right periumbilical area.

Abdominal CT revealed cholelithiasis with acute cholecystitis and mechanical obstruction of the small bowel. She underwent percutaneous transhepatic gallbladder drainage, which seemed to relieve the RUQ pain. The antibiotics were changed to piperacillin/tazobactam due to persistent leukocytosis, fever, and abdominal distension. Physical examination revealed a silent bowel, and the subsequent CT revealed pneumatosis intestinalis. She was thought to have ischemic bowel disease (Figure 2), and surgical intervention was suggested, but the patient's family refused and the patient died the next day.

Bacteroides fragilis was cultured from the bullae aspirate after inoculum on CDC anaerobe blood agar (BD, BBL) and *Bacteroides* bile esculin/CDC anaerobe laked sheep blood agar with KV (kanamycin/vancomycin) bi-plate (BD, BBL) for 48 hours at 37°C under anaerobic conditions (Forma 3940 Series Environmental Chambers, Thermo Fisher Scientific, Inc.). No pathogen was found on Gram stain of the bullae aspirate. All other cultures including blood and bile yielded no pathogens. There was no increased number of isolation of *B. fragilis* on the day this patient's bacteria were inoculated, suggesting that the isolation was not related to laboratory contamination. The *B. fragilis* was susceptible to chloramphenicol, clindamycin and cefmetazole; it had intermediate

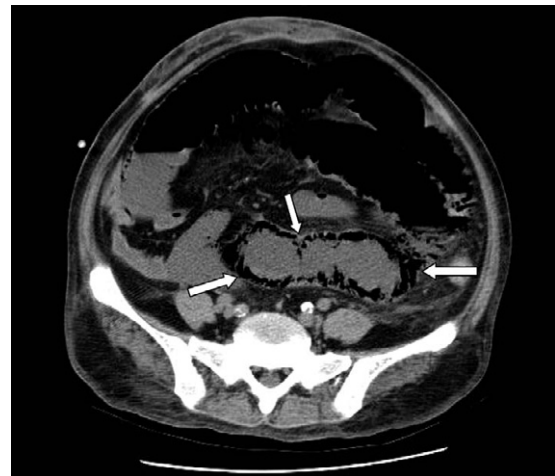


Figure 2. Abdominal computed tomography 4 days later revealed intramural gas collections in the small intestine (arrows). The stomach and small bowel loops were distended and pneumatosis intestinalis was diagnosed.

susceptibility to meropenem; and it was resistant to penicillin, ampicillin/sulbactam, metronidazole and piperacillin/tazobactam by the agar dilution method using brucella agar supplemented with 5% sheep blood, hemin and vitamin K₁ as recommended by CLSI/NCCLS (M11-A4).³

Discussion

The 58-year-old patient with chronic pancreatitis had an intra-abdominal infection that manifested as cholecystitis, pancreatitis and ileus. The skin lesions may be related to the episode of acute pancreatitis on the periumbilical area which appeared as a bluish discoloration like Cullen's sign,² or intra-abdominal infection, like cholecystitis. The presence of pneumatosis intestinalis on the following CT suggested that the hemorrhagic bullae represented disease progression.

Skin lesions related to intra-abdominal infections may begin with a small painless maculopapular eruption, then rapidly progress to hemorrhagic bullous, ulcerative, or nodular lesions.⁴ The well known periumbilical skin lesion known as Cullen's sign was first recognized to be relevant to ruptured ectopic pregnancy by Cullen in 1918.⁵ The sign is classically associated with severe acute pancreatitis,² but it has also been described in retroperitoneal necrotizing fasciitis⁶ and other intra-abdominal infections like sclerosing peritonitis.⁷ The proposed mechanism of Cullen's sign is the accumulation of blood in subcutaneous tissue diffused along the fascial plane or via the falciform ligament secondary to intraperitoneal or retroperitoneal bleeding.⁸ Cases without hemorrhage were proposed to relate to inflammation.⁹ The other reported periumbilical skin lesions related to infection include staphylococcal scalded-skin syndrome,¹⁰ ectopic cutaneous schistosomiasis,¹¹ and *Mycobacterium* infection.¹² Other well-recognized skin manifestations that originate from intra-abdominal infection include ecthyma gangrenosum¹³ and Grey-Turner's sign.⁷ The infected cutaneous lesion associated with pneumatosis intestinalis that possibly originated

through a break in the bowel mucosa has not been documented. Although pneumatosis intestinalis is benign in children older than 1 month,¹⁴ it is lethal in adults.¹⁵ It is believed that multiple factors cause pneumatosis intestinalis, the most prominent and ominous of which is the ischemic insult to the gastrointestinal tract.¹⁶ The pneumatosis intestinalis associated with infections are common,¹⁷ and Gram-negative bacteria comprise a large proportion.¹⁸ Other pathogens including cytomegalovirus,¹⁹ HIV,²⁰ and cryptosporidiosis²¹ have been reported. However, the isolation of *B. fragilis* has never been reported.

B. fragilis is a Gram-negative anaerobic rod and many intra-abdominal infections are associated with this pathogen.²² *B. fragilis* is not invasive, but can participate in intra-abdominal infections in the event of a disrupted mucosal wall of the intestine.²³ *Bacteroides* infections may be noted in gastrointestinal surgery, perforated or gangrenous appendicitis, perforated ulcer, diverticulitis, trauma, and inflammatory bowel disease.²⁴ *B. fragilis* has been shown to induce abscess formation as the sole infecting organism.²⁵ The *Bacteroides* are among the most aerotolerant of anaerobes, able to tolerate atmospheric concentrations of oxygen for up to 3 days.²⁶ To our knowledge, isolation of the pathogen from cutaneous bullae associated with intra-abdominal infection has not previously been reported. Our reported isolate harboring multiple drug resistance was alarming and emphasized the necessity of antimicrobial susceptibility testing to choose appropriate therapy.

In conclusion, the initial skin manifestation like Cullen's sign with subsequent development of hemorrhagic bullae may indicate progression of intra-abdominal infection and *B. fragilis* should be considered as the pathogen when choosing antimicrobial therapy.

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