Bacteroides fragilis: A Case Study of Bacteremia and Septic Arthritis

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ABSTRACT

A 67-year-old African-American male presented with nausea, vomiting, diarrhea, fever, and knee pain. Four sets of blood cultures were collected and resulted in the growth of *Bacteroides fragilis* in all anaerobic bottles. Later, a fluid and tissue sample from the patient's knee grew the same species of bacteria. The patient was placed on intravenous antibiotics to fight the infection.

ABBREVIATIONS: CT = computerized tomography; NIDDK = National Institute of Diabetes and Digestive and Kidney Diseases; PMNs = polymorphonuclear neutrophils; BUN = blood urea nitrogen; CBC = complete blood count; BAP = blood agar plate; BBE = *Bacteroides* bile esculin; Ref = Reference; Adm = Admission; C = critical result; NA = not applicable; BCC = blood cultures collected

INDEX TERMS: *Bacteroides fragilis*; bacteremia; septic arthritis; anaerobic infection; gout

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CASE HISTORY

A 67-year-old African-American male was admitted to a local hospital two days after seeing his primary physician with the chief complaint of pain in his knee. Since this patient had a history of severe tophaceous gout, his primary physician administered a shot of Depo-Medrol to relieve some of the pain caused by the gout flare. The patient had a history of hypertension and chronic renal insufficiency as well. Besides pain in his left knee, he also was experiencing symptoms of nausea, vomiting, diarrhea, fever and some chills for about a week. After a few more days of not feeling well, the patient was advised to go to the hospital. After his initial blood work came back abnormal, he was admitted to the hospital. On admission, he was diagnosed with anion gap metabolic acidosis which correlates with the laboratory results in Table 1. The severe anion gap quickly improved after admission, as depicted by the laboratory results from Day 1 in Table 2. Also striking were laboratory results correlating with acute renal failure.

As evident in Table 2, an elevated white blood cell count, as well as a shift in the white cell differential and a high sedimentation rate, most likely encouraged the collection of blood cultures on this patient. Four sets of blood cultures were drawn over two consecutive days. As a result, the laboratory isolated *Bacteroides fragilis* from the anaerobic bottles of all four sets. The patient's symptoms and laboratory results were consistent with bacteremia as well. Moreover, the patient's knee was still very painful and swollen, so a physician aspirated synovial fluid. The fluid from his left knee was thick and opaque with a green tint and a foul odor. The purulence

Table 1. Arterial Blood Gases on Admission

Analyte	Result	*Ref Range
pH blood	7.29	7.35-7.45
PCO2	28	35-45 mmHg
PO2	101	80-100 mmHg
HCO3	13	22-26 mmol/L

* Ref = Reference

and odor gave the doctor the impression that the patient had an infection superimposed over the gout. The synovial fluid and a tissue sample, collected during surgery on the knee the next morning, went to the laboratory for culture. The fluid and tissue also grew *B. fragilis*; therefore the patient was diagnosed with septic arthritis as well.

CHARACTERISTICS OF *Bacteroides fragilis*

Bacteroides fragilis is an obligate anaerobe which will appear as a gram negative bacillus on a gram stain. It is part of the normal flora of the human gastrointestinal tract. *Bacteroides* species comprise about 30% of the bacterial population in the lower intestine (1). Moreover, *B. fragilis* predominantly colonizes the lower left colon (2). *Bacteroides* species are considered commensal organisms because they benefit their hosts in numerous ways, such as assisting in the digestion of complex carbohydrates and development of the immune system, as well as contributing to the biotransformation of bile salts and vitamin synthesis. However, like many indigenous microflora, *Bacteroides* species can become an opportunistic pathogen once released into sterile areas. In fact, *B. fragilis* is the most commonly isolated organism in anaerobic infections (1).

Although this organism is an anaerobe, it can tolerate oxygen and even grow in the presence of nanomolar concentrations of oxygen. Studies have attributed the aerotolerance and oxidative stress response of *B. fragilis* to enzymes which detoxify and protect the bacterium from oxygen radicals. These detoxification enzymes include catalase and superoxide dismutase (3). Interestingly, there are also reports of certain genes for metabolic enzymes on *B. fragilis* that are actually stimulated by oxygen exposure. One such gene is involved in starch utilization (1). One thing is certain: its aerotolerance allows its survival in a spreading infection and contributes to its virulence (3).

Other potent virulence factors include its complex polysaccharide capsule, fimbriae, adhesions, enterotoxin, and proteolytic enzymes. The capsule of *B. fragilis* mediates resistance to death by both complement and phagocytosis, and it initiates the host immune response known as abscess formation. Although abscess formation is an attempt to isolate an infectious organism, it can ultimately lead to further spread of the infection if left untreated. Also, *B. fragilis* may possess peritrichous fimbriae and lectin-like adhesions. These cell surface structures are involved in the adherence of the organism to tissues, hence initiating its destruction. *B. fragilis* enterotoxin in some strains may destroy tight junctions in intestinal epithelium, resulting in diarrhea (3).

PATHOGENESIS

Anaerobic infections are usually polymicrobial, and *Bacteroides fragilis* is commonly isolated in such infections. The most common cause is of a gastrointestinal nature because that is where *B. fragilis* is naturally found in humans. Infections by *B. fragilis* are often initiated when the mucosa of the intestinal wall is disrupted, such as in gastrointestinal surgery, perforated or gangrenous appendicitis, diverticulitis, or inflammatory bowel disease. Therefore, the most common infection caused by *Bacteroides* species is intra-abdominal sepsis of the peritoneal cavity surrounding the intestines. If the infection progresses, it can cause further complications such as bacteremia and rarely septic arthritis like the patient described in this case study. If an abscess were to form in the large intestine initiated by the *B. fragilis* capsule, it could expand and cause an intestinal obstruction, erosion of blood vessels, and a fistula to form between organs. If the abscess were to rupture first, it could also result in bacteremia and possibly a disseminated infection (3).

The cause of the bacteremia and septic arthritis by *B. fragilis* in this case study was unclear to the physicians at the hospital. Upon admission, the 67-year-old male received a computerized tomography (CT) scan of his abdomen and pelvis. The CT scan showed an anomaly of both kidneys believed to be a congenital defect, but there was no evidence of hydronephrosis. It also showed a non-obstructive bowel and diverticulosis without evidence of acute diverticulitis or an abscess. During his hospital stay, he also received a colonoscopy. Although some areas of the ascending and descending colon were not looked at thoroughly, the examiner noted significant diverticulosis of the left colon and a few diverticula on the right. Furthermore, no lesions were seen.

According to the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), diverticulosis increases with age and about 50% of people over the age of 60 have diverticulosis. Diverticula are pouches that bulge outward where the lining of the colon has weakened. A majority of people with diverticulosis do not show symptoms or any discomfort. It is when diverticula become inflamed that symptoms arise corresponding to diverticulitis. Symptoms include abdominal pain, nausea, vomiting, fever, chills, and a change in bowel habits (4). The patient in this case study was experiencing almost all of these symptoms even though there was no CT or colonoscopy evidence of diverticulitis or an abscess.

The significant diverticulosis in the left colon, where *B. fragilis* is prominent, appears to be the most likely source of this infection. A peritoneal fluid culture may have aided in this investigation. Whether directly or through the peritoneal cavity, *B. fragilis* spread to this patient's blood and caused bacteremia. On average, anaerobic organisms cause about 4% of bacteremias (range of 0.5% to 9%). One study shows that incidence of positive anaerobic blood cultures has decreased. However, within those positive cultures, the percentage caused by *B. fragilis* has increased. This is most likely due to the virulence and increased resistance of *B. fragilis* to antibiotics compared to other anaerobes (5).

Ultimately, *B. fragilis* was also cultured from the patient's left knee. Although septic arthritis is rare, it is more common among patients with a chronic joint condition (3). It becomes clear that this patient is at high risk for septic arthritis because of his history of tophaceous gout. Although it is fairly easy to differentiate between septic arthritis and gout, it becomes more difficult when they coexist. Patients can present with fever, joint pain and swelling in both conditions; therefore, it is important to promptly culture synovial fluid when a joint is acutely inflamed during a gout flare. In general, synovial fluid in septic arthritis has a white cell count greater than 50 x 10^9/L with polymorphonuclear neutrophils (PMNs) exceeding 90% (6).

CORRELATION OF LABORATORY RESULTS

At admission, the patient's chemistry laboratory results correlated with the diagnosis of anion gap metabolic acidosis. He presented to the hospital with a severe anion gap of 32.0 mmol/L, but this was quickly resolved after admission. The arterial blood gas results at admission in Table 1 are consistent with metabolic acidosis because the blood pH was less than 7.35, and bicarbonate was significantly decreased (7). Bicarbonate accounts for a majority of the total carbon dioxide found in blood. Therefore, the decrease in bicarbonate explains the decreased carbon dioxide level present at admission (8). Causes of metabolic acidosis include diarrhea increasing the loss of bicarbonate and renal failure compromising the excretion of acids (7).

More striking in Table 2 was the increase in blood urea nitrogen (BUN) and creatinine after admission, indicating a renal or postrenal condition. In this case, the patient was diagnosed with acute renal failure. Therefore, decreased glomerular filtration due to kidney failure compromised the excretion of urea and creatinine causing elevated levels in the blood (9). Although BUN and creatinine levels remained elevated, they began to slowly decrease over the days to follow. Potassium and carbon dioxide levels also significantly increased from admission to Day 1. Electrolytes such as potassium and carbon dioxide are regulated by the kidneys, so acute renal failure also contributed to their elevation. Moreover, in metabolic acidosis, hydrogen ions replace intracellular potassium ions causing an increase of potassium in the plasma (8).

Hematology results were also significant in this case. The presence of uric acid crystals in two synovial fluids from the patient's left knee confirmed the presence of gout. The patient's symptoms, an elevated white cell count with a majority of neutrophils, and an increased sedimentation rate most likely encouraged the collection of blood cultures. Although generalized, the patient's symptoms of fever, nausea, vomiting, and diarrhea are consistent with sepsis. Complete blood count (CBC) results at admission and over several days are available in Table 2. Neutrophilia is often present in a bacterial infection. This is supported by laboratory evidence in Table 2, which shows a significant increase in neutrophils from admission to Day 1. Deposits of uric acid crystals, which collect in the joints of a patient suffering from gout, attract neutrophils to the site. The release of toxic substances during the process of phagocytosis and death helps mediate an inflammatory process (10). The inflammation in the patient's knee at the time explains the increased sedimentation rate of 100 mm/hr (11).

A nucleated cell count and differential was also performed on two synovial fluids, one before and one after treatment for the *Bacteroides fragilis* infection was started. The first synovial fluid had a nucleated cell count of 256 x 10^9/L with 92% neutophils, which is consistent with septic arthritis (6). The second synovial fluid collected after treatment had a significantly decreased nucleated cell count of 30.4 x 10^9/L with 99% neutrophils. The patient's white blood cell count remained elevated throughout the progression of the infection. In addition, the red blood cell count, hemoglobin and hematocrit results in Table 2 are consistent with anemia.

A total of four anaerobic bottles in blood culture sets, as well as, synovial fluid and tissue from the patient's left knee, grew the organism *Bacteroides fragilis*. Once received in the laboratory, blood culture bottles were placed in an automated machine. The blood culture machine at this hospital detects bacterial growth via a colorimetric reaction initiated by pH changes caused by the production of carbon dioxide by bacteria. The synovial fluid was directly inoculated onto

the appropriate media, including blood agar, chocolate agar, MacConkey agar, and thioglycollate broth. The tissue was ground up first and then inoculated. Plate media was streaked for isolation of bacteria. Then, the inoculated media was placed in the appropriate incubator set at 35 to 37 degrees Celsius, with or without carbon dioxide. Before going into the incubator, anaerobic plates were placed in either an anaerobic pouch or jar in order to maintain the appropriate environment for the growth of anaerobes (12). Gram stains of the positive blood culture bottles and the synovial fluid revealed a gram negative bacillus. No organisms were seen on the tissue gram stain.

Bacteroides fragilis can be cultured with a variety of media. *B. fragilis* grows towards the bottom of the thioglycollate broth because it is an anaerobe, and it only grows on the anaerobic blood agar plate (BAP). Also, this bacterium usually grows on anaerobic BAP supplemented with the antibiotics, kanamycin and vancomycin, indicating resistance. The colonies on anaerobic BAP are white to gray, circular, convex, and nonhemolytic. On *Bacteroides* bile esculin (BBE) agar, *B. fragilis* colonies appear to be light to dark gray and are surrounded by a dark gray zone, indicating esculin hydrolysis. Another characteristic of *B. fragilis*, which aids in its identification, is that it is resistant and therefore grows in 20% bile (12). In addition, rapid identification system kits can be used to identify anaerobic bacteria. The system is based on microbial degradation of various substrates, and a number is calculated based on the reaction results. The number is then entered into a computer program which identifies the organism. The *B. fragilis* isolates in this case were determined to be beta-lactamase positive; no other susceptibility testing was performed.

TREATMENT

There are currently no automated methods for determining

Table 2. Chemistry, Hematology and Microbiology Laboratory Results

Analyte	[1]Adm	Day 1	Day 2	Day 3	Day 4	[2]Ref Range
Chemistry:						
BUN	6.8	33.2	24.3	19.3	21.4	2.9-9.3 mmol/L
Creatinine	150	292	203	221	239	44-106 mmol/L
Sodium	139	134	133	136	140	135-145 mmol/L
Potassium	3.9	5.9	5.6	5.7	[3]C6.1	3.6-5.0 mmol/L
Chloride	101	110	105	103	107	98-111 mmol/L
CO2	6	16	21	24	25	21-31 mmol/L
Anion Gap	32.0	8.0	7.0	9.0	8.0	2.0-19.0 mmol/L
Hematology:						
RBC count	4.33	3.69	3.5	3.41	3.18	4.2-5.5 x 10^12/L
Hemoglobin	132	96	95	92	85	130-170 g/L
Hematocrit	0.41	0.30	0.29	0.28	0.27	0.38-0.50 L/L
Platelet count	489	454	505	517	533	150-400 x 10^9/L
WBC count	17.3	12.7	13.1	20.8	21.7	4-10.5 x 10^9/L
Neutophils	50.0	87.6	87.9	88.8	94.3	42-75 %
Lymphocytes	43.0	7.3	5.7	4.6	3.0	16-46 %
Monocytes	7.0	4.9	6.3	6.6	2.7	1-13 %
Eosinophils	0.0	0.2	0.0	0.0	0.0	0-8 %
Basophils	0.0	0.0	0.1	0.0	0.0	0-2%
Microbiology:	[4]NA	NA	2 [5]BCC	2 BCC	NA	NA

[1] Adm = Admission
[2] Ref = Reference
[3] C = critical result
[4] NA = not applicable
[5] BCC = blood cultures collected

the susceptibility of anaerobes; however, three techniques are presently practiced and give reproducible results. These susceptibility methods are agar dilution, broth microdilution panels, and the Etest (AB Biodisk). For treatment of anaerobic bacterial infections, clindamycin is considered to be the gold standard. However, *Bacteroides fragilis*' antibiotic resistance to clindamycin has increased over the years. It was reported that 26% of *B. fragilis* strains were resistant to clindamycin in 2000. Moreover, *B. fragilis* have the highest occurrence of resistance to beta-lactams among all anaerobes because of the production of beta-lactamase. For example, greater than 97% of *B. fragilis* strains are resistant to penicillin G. Therefore, beta-lactam/beta-lactamase inhibitor combination treatments are usually most effective. In fact, it was reported that nationally less than 2% of *B. fragilis* strains were resistant in 2000. These combination treatments include ampicillin/sulbactam, ticarcillin/clavulanate, and piperacillin/tazobactam. The most potent of all the beta-lactam agents are three carbapenems including imipenem, meropenem, and ertapenem. Worldwide, less than 0.2% of *B. fragilis* strains are resistant (13).

The 67-year-old patient with *B. fragilis* bacteremia and septic arthritis was treated with Zosyn (piperacillin/tazobactam) at first. However, after continuing to spike fevers while on the treatment, physicians placed him on clindamycin instead. Ultimately, the patient was placed on meropenem (1g IV every 8 hours), as recommended by the infectious disease specialist at the hospital. As discussed above, meropenum displays the least resistance among *B. fragilis* organisms and most likely ensures a successful elimination of the bacterial infection. Four more sets of blood cultures and another synovial fluid culture resulted in no growth and therefore confirmed the antimicrobial treatment worked.

CONCLUSION

When the patient was discharged, he was successfully treated for the *Bacteroides fragilis* infection in both his blood and left knee. He also had a successful surgery to remove gouty deposits and drain his left knee, relieving the pain and swelling. However, physicians at the hospital could not exactly pinpoint the source of the *B. fragilis* infection because there was no evidence of diverticulitis, an abscess, or lesion during the CT scan or colonoscopy. Therefore, there is a possibility that this patient could have a recurrent infection.

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