

[CASE REPORT]

Successful Empiric Therapy for Postsplenectomy Sepsis with *Campylobacter fetus* in an Abattoir Worker with Follicular Lymphoma

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Abstract:

Asplenia may yield an increased risk of fulminant sepsis with various pathogens. Human infection with *Campylobacter fetus* is rare, but it often presents with non-gastrointestinal tract infection among immunocompromised individuals. A 55-year-old abattoir worker presented with a fever. He had had splenectomy for follicular lymphoma and rituximab maintenance therapy by four months before the presentation. Blood cultures yielded *C. fetus*, and the administration of meropenem dissolved the bacteremia. Further maintenance therapy was withheld, and no recurrence of infection has been observed for seven years. Asplenia, occupational exposure, and/or rituximab maintenance therapy might have been precipitating factors of this rare infection.

Key words: *Campylobacter fetus*, sepsis, splenectomy, rituximab, follicular lymphoma, abattoir

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Introduction

The asplenic population is heterogeneous and includes patients with splenectomy after trauma, hematologic diseases such as malignant lymphoma or sickle cell disease, chronic idiopathic thrombocytopenic purpura or chronic graft-versus-host disease after allogeneic hematopoietic stem cell transplantation, untreated human immunodeficiency virus infection, or severe celiac disease (1, 2). While the risk of postsplenectomy sepsis is highly variable according to the underlying causes of asplenia as well as the patient's age or the interval since splenectomy, its mortality and morbidity are generally high (1). Overwhelming postsplenectomy infection (OPSI), an extremely severe case, is defined as septicemia and/or meningitis occurring at any time after splenectomy and carries a very high mortality of 50% (3). The most common pathogens of postsplenectomy sepsis are encapsulated organisms, represented by *Streptococcus pneumoniae* and *Haemophilus influenzae* type b. Guidelines recommend vaccinations to reduce the risk of invasive pneumo-

coccal disease substantially (4). An increased risk of infection in those with asplenia has also been reported with *Neisseria meningitidis*, *Capnocytophaga canimorsus*, *C. cynodegmi*, *Babesia microti*, *Plasmodium* species, *Bordetella holmesii*, *Escherichia coli*, *Staphylococcus suis* and *S. aureus* (1, 5, 6).

Campylobacter are Gram-negative zoonotic bacterial pathogens causing human and animal diseases. *C. jejuni* and *C. coli* account for 95% of human *Campylobacter* isolates, and their infections predominantly cause diarrheal disease. *C. fetus*, on the other hand, is frequently responsible for non-gastrointestinal tract infection, such as sepsis, endocarditis, infectious aneurysms, osteomyelitis, and meningitis (7). Human infection of *C. fetus* is rather rare, and it is more likely to be developed among immunocompromised hosts (7). Anecdotes and small case series have clarified that hematological diseases may also pose an increased risk of infection with *C. fetus* (8, 9).

We herein report a case of successful empiric antimicrobial therapy for postsplenectomy sepsis with *C. fetus*. Since postsplenectomy sepsis with this organism has been scarcely

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Table. Laboratory Data at Admission.

WBC	14.6 ×10 ³ /μL	total protein	5.8 g/dL	uric nitrogen	33 mg/dL
myelocyte	2.0 %	albumin	2.8 g/dL	creatinine	1.48 mg/dL
metamyelocyte	2.0 %	total bilirubin	1.0 mg/dL	Na	132 mmol/L
stab	7.0 %	ALP	636 U/L	K	4.1 mmol/L
segmented	87.0 %	γGTP	69 U/L	Cl	93 mmol/L
lymphocyte	2.0 %	AST	37 U/L	CRP	37.83 mg/dL
hemoglobin	12.7 g/dL	ALT	44 U/L	IgG	946 mg/dL
MCV	90.3 fL	LDH	175 U/L	IgA	111 mg/dL
platelet	15.2 ×10 ⁴ /μL	amylase	22 U/L	IgM	66 mg/dL

**Figure.** Enhanced computed tomography showed that the ascending colon (arrow heads) was edematous.

described, we discuss the risk factors and likely causes that may have contributed to this rare infection. We obtained written informed consent from the presented patient according to the Declaration of Helsinki for the current report.

Case Report

A 55-year-old male veterinarian was admitted to our hospital because of a 2-month history of an intermittent fever. About two years before the admission, he had first come to a medical attention because of an 8-cm submucosal mass in the stomach detected at a medical checkup. Because a definitive diagnosis could not be made pre-operatively, he had undergone total gastrectomy, cholecystectomy and splenectomy for the suspected advanced malignancy at a local hospital. The surgical pathology revealed gastric follicular lymphoma, grade 2, with stage IIE disease. Two weeks after the surgery, a 23-valent pneumococcal polysaccharide vaccine was administered. Computed tomography (CT), fluorodeoxyglucose-positron emission tomography (FDG-PET), and a bone marrow biopsy showed no signs of residual lymphoma.

About a year after the surgery, he requested rituximab maintenance therapy for follicular lymphoma and received 375 mg/m²/week rituximab for four weeks at our hospital. Three months after the rituximab administration (approximately 1.5 years after splenectomy), he started to complain of a loss of appetite and an intermittent fever. Oral levoflox-

acin was prescribed and started soon after each febrile episode. The fever was ameliorated temporarily, but another febrile episode recurred several days after the cessation of the previous prescription. With the recurrent febrile episodes for two months, he became debilitated and was admitted to our hospital. He reported no history of diarrhea. He was a veterinarian working at an abattoir and he had no other medical history beside the follicular lymphoma. His colleagues at the abattoir had not experienced any infectious episodes, as he had explained.

At admission, the patient was weary and feverish, but a physical examination did not show any local signs of infection. Given the possibility of OPSI, the empiric administration of meropenem was initiated soon after three sets of blood culture. His blood counts and chemistries revealed a significant inflammatory response (Table). His serum level of immunoglobulins was within the reference range of normal. An interferon-gamma release assay for mycobacterium was negative. A pharyngeal swab tested negative for influenza virus antigen with rapid paper chromatography. X-ray and CT showed that he did not have relapse of lymphoma nor any documented infection, such as pneumonia. The ascending colon was partially edematous (Figure), but a total colonoscopy failed to confirm any pathologic changes in the mucosal membrane. There were no peripheral lymphadenopathies. Echocardiography did not reveal any signs of endocarditis.

The blood cultures yielded Gram-negative rods, but subsequent passaged cultures were not initially successful, so the pathogens could not be identified. Feces culture isolated non-pathologic *E. coli* and *Bacillus* spp., which were considered part of his normal intestinal flora. The one-week administration of meropenem ameliorated the fever, but a week after its discontinuation, fever ensued. The same antibiotics were restarted after another three sets of blood culture, which produced identical Gram-negative spiral-shaped organisms. With the successful passage of cultures under 25 °C microaerobic conditions, *C. fetus* was identified based on its biochemical profiles as evaluated with the API-campy test kit (SYSMEX bioMérieux, Tokyo, Japan). The four-week administration of meropenem resolved the bacteremia. Additional rituximab maintenance therapy was withheld, and he also changed his workplace from the abattoir to an office. The patient has been free from further episodes of bacteremia.

mia, and there has been no recurrence of lymphoma for seven years.

Discussion

The present case exhibited a persistent infection of *C. fetus* for about two months despite intermittent antibiotic therapies. The Gram-negative organisms repeatedly detected in multiple blood cultures were retrospectively considered to have been the same bacteria. *C. fetus* is known to harbor surface-layer proteins (SLPs), which account for its resistance to complement-mediated killing and phagocytosis (10). Tu et al. observed high-frequency DNA rearrangement within the coding regions for the SLPs in as short as a 20-day interval, implying that a persistent infection of *C. fetus* could be facilitated by the organism's ability to adjust its antigenicity of SLPs to the environmental challenges (10). The SLPs might therefore have been associated with the refractory nature of the infection in the present case, although a study to examine the SLP expression of the present strain could not be performed.

The spleen is a major site of immune response to blood-borne antigens, and it harbors macrophages responsible for clearing the blood of unwanted substances even in the absence of specific immunity (11). Asplenia may lead to impairment of phagocytic functions and dysfunction in both adaptive and innate immunity (5). As a result, asplenic patients may have an impaired clearance capacity of not only IgG-coated bacteria but also non-opsonized pathogens and may carry a life-long risk of infection (1, 6). Rituximab reduces the population of antibody-producing precursor plasma cells, leading to a decreased antigenic response. The serum complement may also be excessively consumed by the ADCC activity of rituximab in a setting of a high tumor burden (12). A meta-analysis of rituximab maintenance therapy for follicular lymphoma showed an elevated rate of infection-related adverse events, although the infections did not reduce the overall survival (13). Though the total serum gamma globulin level was not decreased after rituximab administration (data not shown), both splenectomy and adjuvant rituximab administration might have contributed to the functional impairment of the humoral responses. However, which factor contributed most to the bacteremia in the present case remains unclear.

Human infection of *C. fetus* is more likely to be observed among at-risk individuals with underlying medical conditions than in the general population. Sakran et al. described a patient with *C. fetus* infection after splenectomy for thalassemia (14). According to anecdotes or small case series, other predisposing conditions may include diabetes mellitus, HIV infection, hematological malignancy, hypogammaglobulinemia, liver cirrhosis, corticosteroid and other immunosuppressive treatments, cardiovascular disease with valve abnormalities, and medical device implants (7-9, 15-18). Aging and pregnancy may also increase the risk of its infection (7, 19). Wagenaar et al. suggested that the general

population might be repeatedly exposed to undetected levels of *C. fetus* through contaminated foods or other routes (7), implying the importance of a high level of caution among high-risk individuals.

In the present case of asplenia, environmental exposure to the pathogen may have been an additional risk factor. Outbreaks of *C. fetus* infection as an occupational hazard among abattoir workers and farmers without known underlying medical conditions have been previously described (20, 21). The abnormal ascending colon detected on CT might have been a route of infection after the oral exposure to *C. fetus* at the abattoir. However, similar infectious episodes among our patient's coworkers at his work place were not noted. His underlying medical conditions, including asplenia and rituximab exposure, might therefore have been more strongly associated with the increased risk of *C. fetus* infection than excessive exposure through his working environment, although occupational surveillance was not conducted for this pathogen.

Prophylactic antimicrobial therapy after splenectomy is recommended to prevent fulminant sepsis for only select patients, such as children under 5 years of age (1). However, for adult patients, there is no standard antimicrobial prophylaxis, and empiric antibiotics and patient education may be more important. Since the initial symptoms of asplenic sepsis may be nonspecific and mild (22), a high level of caution and empiric intervention may be warranted to decrease its severity (6). Antimicrobial resistance among *Campylobacter* spp. is a worldwide phenomenon. Fernandez-Cruz et al. mention that quinolones should be discouraged for empirical therapy for the bacteremia (23), while Liao et al. assert that carbapenems should be considered (24). Susceptibility test results of the strain for CFPM, MEPM, and MINO in the present case were 'resistant', 'susceptible', and 'susceptible', respectively. Although the antibiotic selection should be guided by the susceptibility of the individual strain, the optimum choice and duration of empiric therapy for at-risk individuals remain controversial.

The present case may therefore be a representative case of an at-risk asplenic individual, as this patient might have harbored an immunocompromised medical condition and been subject to an at-risk work environment. The present findings should encourage medical staff to discuss the risks of less-common infections with asplenic patients.

The authors state that they have no Conflict of Interest (COI).

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