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Case Report

Gastrointestinal variant of Lemierre's syndrome complicating ruptured appendicitis

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A B S T R A C T

Fusobacterium necrophorum is a non-spore-forming, obligate anaerobic, filamentous, gramnegative bacillus that frequently colonizes the human oral cavity, respiratory tract, and gastrointestinal tract. Fusobacterium species have rarely been implicated in cases of gastrointestinal variant of Lemierre's syndrome. We describe a case of F. necrophorum bacteremia associated with suppurative porto-mesenteric vein thrombosis (PVT) following acute ruptured appendicitis. In addition, we list the documented twelve cases of Fusobacterium pylephlebitis. Recanalization of the porto-mesenteric veins and relief of the extrahepatic portal hypertension were achieved with early empiric antibiotic and local thrombolytic therapy. Our patient's case underscores the importance of recognizing Fusobacterium bacteremia as a possible cause of suppurative PVT after disruption of the gastrointestinal mucosa following an acute intraabdominal infectious process. Early treatment of this condition using anticoagulation and endovascular thrombolysis as adjunctive therapies may prevent PVT complications.

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Introduction

Fusobacteria are non-sporulating, obligate anaerobic, filamentous, gram-negative bacilli belonging to the Bacteroidaceae family. They are constituents of the normal flora of the oropharynx, the female genitourinary tract and the gastrointestinal tract [1,2]. Fusobacterium species have traditionally been associated with Lemierre's syndrome (LS), a potentially fatal complication of head and neck infections, which is characterized by septic thrombophlebitis of the internal jugular vein (IJV) and/or its tributaries (e.g. facial vein) [1,2]. Thrombus formation and rapid bacterial growth can cause septic embolization to distant sites including the lungs, joints, bones, skin and soft tissues, muscles, liver, spleen, kidneys, heart, and brain [3]. Moreover, variants of Lemierre's syndrome have been described in multiple anatomic locations such as the cavernous sinus, ovarian veins, suprahepatic veins, and the porto-mesenteric venous system [2]. Fusobacterium species have been linked to porto-mesenteric vein thrombosis (PVT) in at least twelve reports (Table 1), with two-third of the cases possibly propagating from the lower gastrointestinal tract (GIT). We report a rare case of

portal, splenic and mesenteric vein thrombosis associated with Fusobacterium necrophorum following acute ruptured appendicitis. No oropharyngeal involvement was identified to suggest the classic form of LS. To our knowledge, this is the first reported case linking Fusobacteria to PVT with a simultaneous documented intra-abdominal source. This case also illustrates the potential benefits of anticoagulation and endovascular thrombolysis as adjunctive therapies in prevention of PVT complications.

Case presentation

A previously healthy 32-year-old Caucasian male initially presented with a two day-history of worsening epigastric pain. He was diagnosed with a ruptured appendicitis and required emergent laparoscopic appendectomy. Following the procedure he was discharged home but continued to have fevers and abdominal pain. One week later, he returned to the emergency department with severe, worsening right upper quadrant epigastric pain radiating to the back without guarding, rebound tenderness or abdominal ecchymosis. He denied alcohol or recreational drug use and could provide no preceding history suggestive of oropharyngeal or respiratory tract infection. Upon examination the patient was found to be in septic shock (temperature 103 °F, pulse 108 beats/minute and mean arterial pressure of 47 mmHg). Oral, neck, respiratory, cardiovascular and neurological examinations were unremarkable. He was transferred to the medical intensive

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Table 1
Porto-mesenteric vein thrombosis associated with *Fusobacterium* species.

References	Patient age (y), sex	Past medical history	Infection source	Anticoagulation	Antibiotic therapy	Outcome	Workup for Lemierre's syndrome	Underlying coagulation disorder
Reported cases of pylephlebitis caused Fusobacterium necrophorum								
Current case (2014)	34, M	Previously healthy	Acute perforated appendicitis	Local thrombolysis and IV heparin	Pip/taz followed by clindamycin	Survived and clinically improved. Portal cavernous sinus formation	Negative	Negative
Hamidi K, et al. (2008)	23, M	Previously healthy	No abdominal infectious focus	LMWH followed by fluindione	AM/CL	Survived and clinically improved. Portal cavernous sinus formation	Not performed	Negative
	41, M	Alcoholism	No abdominal infectious focus	No	No	Loss of follow up. Left the hospital against medical advice	Not performed	Not done
Soo R, et al. (1999)	31, M	Previously healthy	No identified abdominal infectious focus	IV heparin followed by warfarin	IV metronidazole and Penicillin G followed by AM/CL and metronidazole	LFTs normalized over 6 months	Not performed	Negative
Shahani L, et al. (2011)	34, M	Chronic pancreatitis and alcoholism	Hepatic, pancreatic and splenic abscesses	No	Tigecycline	Clinically improved. Resolution of liver abscesses with portal cavernous transformation	Negative	Was not considered
Clarke MG, et al. (2003)	19, F	Previously healthy	Hepatic abscesses	IV heparin followed by long term warfarin	Benzyl Penicillin, metronidazole and ciprofloxacin	Clinically improved. Resolution of liver abscesses and portal cavernous sinus transformation	Not performed	Was not considered
Redford MR, et al. (2005)	53, M	Previously healthy	No abdominal infectious focus	LMWH followed by warfarin	Benzyl PCN and metronidazole followed by clindamycin	The patient made a complete clinical recovery	Not performed	Was not considered
Reported cases of pylephlebitis caused Fusobacterium nucleatum								
Bultink IE, et al. (1999)	23, M	Previously healthy	Possible pharyngitis. No abdominal focus	IV heparin	Imipenem followed by 6 weeks of IV PCN	Patient had clinical recovery but portal vein thrombosis persisted	Not performed	Negative
Zheng L, et al. (2014)	73, M	HTN, DM, CAD	No oropharyngeal or abdominal focus	LMWH followed by warfarin	Cefepime followed by clindamycin	The patient made a complete clinical recovery	Negative	Negative
Verna EC, et al. (2004)	56, M	Ulcerative colitis	No oropharyngeal or abdominal focus	No	Clindamycin for 2 weeks	Patient had clinical recovery but portal vein thrombosis persisted	Negative	Elevated serum factor VIII
El Braks R, et al. (2004)	71, F	Urinary continence	Pharyngitis. No abdominal focus	IV heparin	Pip/taz for 2 weeks followed by ofloxacin for additional 3 weeks	Patient had clinical recovery but left branch portal vein thrombosis persisted	Not performed	Negative
Etienne M, et al. (2001)	68, M	Lung and GU TB, thrombocytopenia, recurrent PE, and IVC filter	Possible oropharyngeal source. No abdominal focus	LMWH for 24 days	Cefotaxime and metronidazole for 24 days followed by 2 weeks of oral metronidazole	Patient had clinical and radiological recovery	Not performed	Negative
Schweigart JH, et al. (2005)	67, M	TB, stroke, DM, Afib, CKD and IgG paraproteinemia	Possible oropharyngeal source. No abdominal focus	Long-term warfarin	Clindamycin	Clinically improved	Not performed	Negative

Abbreviations: Afib; atrial fibrillation, AM/CL; amoxicillin/clavulanate, CAD; coronary artery disease, CKD; chronic kidney disease, DM; diabetes mellitus, F; female, GU; genitourinary, HTN; hypertension, IV; intravenous, IVC; inferior vena cava, LFTs; liver function tests, LMWH; low-molecular weight heparin, M; male, PCN; penicillin, PE; pulmonary embolism, Pip/taz; piperacillin/tazobactam, TB; tuberculosis.
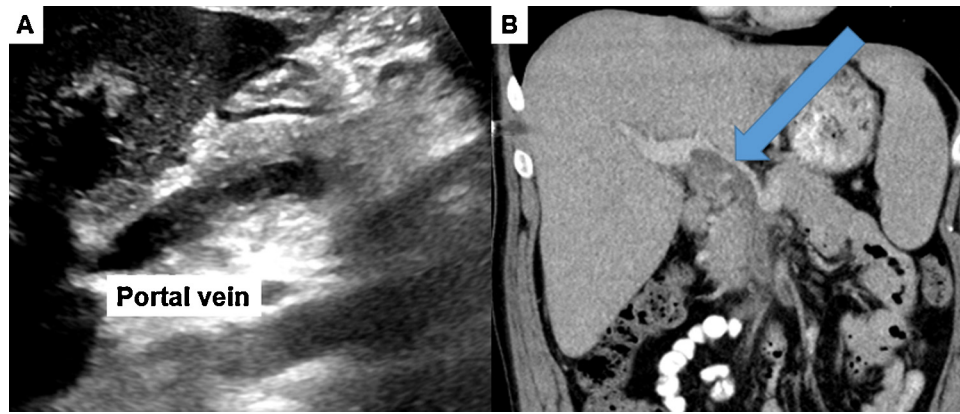
Fig. 1. A computerized axial tomography (CAT scan) of the abdomen and pelvis with intravenous contrast and ultrasound Doppler studies showed splenomegaly with acute thrombosis of the proximal main portal vein at the confluence of the superior mesenteric vein (SMV) and splenic vein. No hepatic abnormalities were identified to suggest cirrhosis, infarct, abscess or cavernous transformation.

care unit and received aggressive fluid resuscitation, vasopressors and initiation of broad coverage antibiotics with vancomycin and piperacillin/tazobactam. Laboratory investigations showed an elevated white blood cell count of 15,100 cells/mm [3], with an absolute neutrophil count of 12,400 cells/mm [3]. Platelet count, hemoglobin, electrolytes, renal function, pancreatic enzymes and liver function tests were all within the normal range. Urine drug screen, blood alcohol test, HIV ELISA and viral hepatitis profile were also negative. A computerized axial tomography (CAT scan) of the abdomen and pelvis with intravenous contrast and ultrasound Doppler studies showed splenomegaly with acute thrombosis of the proximal main portal vein at the confluence of the superior mesenteric vein (SMV) and splenic vein (Fig. 1). No hepatic abnormalities were identified to suggest cirrhosis, infarct, abscess or cavernous transformation. Comprehensive hypercoagulability workup was negative. Interestingly, the anaerobic bottles

of two sets of blood cultures taken on admission yielded thin filamentous gram negative bacilli, eventually identified as *F. necrophorum* on day six of the admission. CAT-scans of the head, neck and chest showed no evidence of any brain, pulmonary or cervical (including the IJV) involvement. The gastrointestinal variant of Lemierre's syndrome was thus diagnosed. Following the identification of *F. necrophorum*, vancomycin was discontinued and metronidazole was added to the regimen. The patient was anticoagulated with intravenous heparin, but the patient's abdominal pain persisted and the thrombus continued to progress on subsequent imaging. At this point, venography revealed the presence of cavernous transformation of the portal vein (Fig. 2). Transhepatic endovascular thrombolysis was attempted to mitigate the thrombotic disease, and was successful in recanalizing the porto-mesenteric veins (Fig. 3). The patient was discharged home on warfarin and oral clindamycin for six more weeks leading to complete symptom relief.

Discussion

Pylephlebitis, defined as septic thrombophlebitis of the portal vein and/or its tributaries, has rarely been reported in the modern era of antibiotics [4]. Its diagnosis hinges on positive culture data in

Fig. 2. Venography revealed the presence of cavernous transformation of the portal vein.

Fig. 3. Transhepatic endovascular thrombolysis was attempted to mitigate the thrombotic disease, and was successful in recanalizing the porto-mesenteric veins.

conjunction with radiological evidence of acute thrombosis of the portal vein. This complication can occur secondary to any abdominal or pelvic suppuration either in the regions drained by the portal system or in structures contiguous to the portal vein, typically appendicitis or diverticulitis [4]. Early diagnosis with prompt medical and surgical treatment may reduce the incidence of ascending portal septic thrombophlebitis to 0.05% in acute appendicitis and 3% in ruptured appendix [5]. Liver abscesses and bowel ischemia are known acute complications of pylephlebitis, and portal hypertension is a possible chronic sequela [2]. Enteric gram-negative bacilli and anaerobes, most notably *Bacteroides fragilis*, are common organisms associated with pylephlebitis, with concomitant bacteremia seen in up to 80% of cases [6]. Isolated cases of pylephlebitis associated with *Fusobacterium* species have been described but none of these patients had an identifiable infectious GIT source (Table 1). Four cases of pylephlebitis have been linked to *Fusobacterium nucleatum* LS. One theory is that following oropharyngeal infection, septic emboli to the mesentery can cause contiguous microabscesses to the GIT (e.g. lymphadenitis) with subsequent spread to the porto-mesenteric venous system. Another hypothesis is bacterial seeding of preexisting portal thrombosis. Other cases of reported fusobacterial pylephlebitis had no discernible site of entry, and appear to be due to subclinical primary infection affecting the lower GIT. In the patient we describe, the source of the pathogen was most likely the appendix, where *F. necrophorum* is a known part of the commensal anaerobic colonic flora and is further known to play an important role in the pathogenesis of appendicitis [7]. The exact pathogenesis of pylephlebitis related to *F. necrophorum* is unknown, but several mechanisms have been proposed. Following disruption of the mucosal appendiceal architecture, the organism can enter the venous system via the appendicular vein, eventually draining to the ileocolic vasculature, the superior mesenteric vein and then to the portal vein [8]. Alternatively, the organism could invade the periappendicular tissues, causing perivenous inflammation (periphlebitis) and luminal thrombosis (endophlebitis). The thrombogenic ability of virulent *Fusobacterium* strains has also been attributed to the lipid A component of the lipopolysaccharide (LPS) endotoxin, which activates the human Hageman factor (factor XII) and thereby the intrinsic pathway of coagulation [9]. Furthermore, these strains can also increase leucotoxin production resulting in activation and aggregation of human platelets [10]. The fusobacterial thrombogenic activity and locally generated proteolysis allow tissue damage, penetration through host barriers, and invasion of regional veins, thereby causing serious infections. These bacterial characteristics appear to favor direct porto-mesenteric invasion as the mode of pathogenesis of pylephlebitis, rather than seeding pre-existing thrombus.

Imaging techniques such as ultrasound and contrast-enhanced CT scan are the diagnostic tools of choice for PVT. Ultrasound is especially helpful because of its accuracy, non-invasiveness, and low cost. There is also evidence that this modality has an acceptable sensitivity and specificity for the diagnosis of appendicitis or appendiceal masses with adequate training [11]. Nonetheless, contrast-enhanced CT scan has the advantage of better sensitivity and specificity over ultrasound, particularly when establishing extent of thrombus and for evaluation of solid organ abnormalities, such as liver abscesses [12].

A multidisciplinary approach is needed to treat patients with pylephlebitis to achieve the best therapeutic outcome. Treatment involves the use of appropriate antibiotics and surgical drainage of the primary suppurative focus. Despite prompt and appropriate antimicrobial treatment, clinical response and defervescence in patients with the gastrointestinal variant of LS might be delayed. This could be related to the difficulty in adequate antimicrobial penetration into the infected thrombus. Additionally, antibiotics are slow to sterilize the original infected, necrotic source, which may allow persistent fevers. For these reasons, prolonged antibiotic therapy is often required (usually 4–6 weeks) but ideal duration of therapy remains unclear [13]. Antibiotics should be tailored according to the culture and susceptibility data when available. Usually, *F. necrophorum* is sensitive in vitro to penicillin/beta-lactamase inhibitor combinations, metronidazole, cephalosporins, chloramphenicol, carbapenems, and clindamycin [14]. Antimicrobial resistance among *F. necrophorum* is rare. A review of 100 *F. necrophorum* isolates from 1990 to 2000 revealed that only 2% of strains were resistant to penicillin, and 15% were resistant to erythromycin [14]. Metronidazole has excellent penetration into most tissue including the central nervous system, and can be given orally without sacrificing bioavailability [15]. The benefit of adjunctive anti-coagulation to achieve recanalization of occluded porto-mesenteric venous system has yet to be clearly demonstrated. Nevertheless, its use has been advocated on the presumption that pylephlebitis might lead to bowel compromise and ischemia [6]. Furthermore, anti-coagulation may reduce septic embolization to the liver from infected portal thrombi and prevents liver abscesses. Indications for anti-coagulation include documented progression of thrombus while on antibiotics, fever unresponsive to treatment and the presence of a hypercoagulable state [16]. Radiological or operative interventions in the form of thrombectomy and thrombolysis with direct intra-vascular infusion of thrombolytics have been advocated for pylephlebitis with peritoneal signs or enteric compromise [17,18]. Three main routes of endovascular therapy for mesenteric thrombus have been described: trans-arterial, trans-jugular and trans-hepatic. All three techniques involve the slow infusion of tissue plasminogen activator (tPA). Other endovascular techniques such as thrombectomy, angioplasty and stenting can be performed adjunctively. Regardless of the endovascular method selected, available data from small studies seem to support the use of thrombolysis in the setting of acute symptomatic porto-mesenteric vein thrombus [19,20].

Conclusion

Fusobacterium species are classically associated with LS but have infrequently been implicated in clinical cases of pylephlebitis [2]. Our review of the medical literature revealed only twelve previously documented cases (Table 1). We believe that fusobacterial pylephlebitis has been historically underdiagnosed, as culprit anaerobic gram-negative organisms could not previously be reliably identified. The comparatively unsophisticated anaerobic culture methods of the past may have led to misattributed causation by other organisms and, as *F. necrophorum* has historically been known by more than 50 names, confusion with nomenclature may have confounded identification [2]. The results of our patient's history, physical examination, blood cultures and imaging studies were consistent with the gastrointestinal variant of LS. Furthermore, based on the pathophysiology of the organism and the patient's recent acute appendicitis, it appears reasonable to implicate the appendix as the source of the pylephlebitis. Because of possible resistance to several antibiotic classes, *Fusobacterium* bacteremia is best treated empirically by means of combination therapy until final susceptibility results are available. This case underscores the importance of recognizing *Fusobacterium* species as a possible cause of pylephlebitis. As the consequences of untreated PVT could be debilitating, we additionally suggest the use of anticoagulation and consideration of endovascular thrombolysis, in the setting of acute symptomatic porto-mesenteric vein thrombus.

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Conflicts of interest

All authors declare that they have no conflicts of interest.

Authorship statement

All work in this manuscript is original. All authors had access to the data and played a role in writing the manuscript. Each accepts responsibility for the content.

Consent

Written informed consent was obtained from the patient for publication of this case report. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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