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A case report of mesenteric and portal vein thrombosis in a patient with *Fusobacterium nucleatum* bacteremia

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ABSTRACT

Background: *Fusobacterium* bacteria are fastidious commensals in the human oropharyngeal microbiome. As pathogens, *Fusobacterium* are associated with diverse infectious and inflammatory conditions, including Lemierre's syndrome, colorectal cancer, and inflammatory bowel disease. Portal and mesenteric thromboses associated with *Fusobacterium* are case-reportable; due to the rarity of these reports, the full spectrum of presentations and outcomes remains unknown.

Case presentation: A 71-year-old man presented with two weeks of abdominal pain and night sweats. He was found to have extensive portal and mesenteric venous thromboses and pancolitis. Initial workup for hypercoagulable risk factors was negative; after discharge, blood cultures became positive for *Fusobacterium nucleatum*. The patient was treated with antibiotics and anticoagulation with complete resolution of symptoms, thromboses, and colitis.

Conclusions: This report demonstrates the protean nature of *Fusobacterium*-associated disease, which in this patient was portal and mesenteric venous thromboses without oropharyngeal disease. We discuss the modes of transmission, mechanisms of infection, and what remains unknown about the causes and consequences of *Fusobacterium*-associated disease. This report also demonstrates that cases with atypical abdominal thromboses, despite a negative comprehensive workup, deserve a high suspicion for other causal factors that are not part of standard diagnostic evaluation.

1. Background

Fusobacterium species are fastidious gram-negative anaerobes generally found as commensal flora in the human oropharyngeal microbiome. As a pathogen, *Fusobacterium* typically causes oropharyngeal infections and can lead to Lemierre's syndrome: septic thrombophlebitis of the internal jugular vein. While most thrombotic events due to *Fusobacterium* are related to vasculature of the head and neck, abdominal infections and portal venous thromboses have also been reported [1–3]. These reports suggest that much is still unknown about the spectrum and mechanisms of *Fusobacterium*-associated disease. Despite the association of *Fusobacterium* with thrombosis, fastidious bacteremia is an uncommon enough cause of venous thrombosis that even when a thrombophilia workup is indicated (e.g., for recurrent clot, clot at a young age, or clot in multiple or unusual locations), blood cultures are not consistently included as part of a standard evaluation. Here we describe a case of a 71-year-old man who presented with two weeks of abdominal pain and night sweats and was found to have extensive portal and mesenteric vein thromboses. Ultimately, blood cultures grew *Fusobacterium nucleatum*.

2. Case presentation

A 71-year-old male with coronary artery disease, stable pulmonary nodules, and obesity was admitted to our hospital after presenting with severe abdominal pain for two weeks. The pain was worst on the left side, waxing and waning, and exacerbated by eating. Ten days before this evaluation, he had presented to primary care clinic and was

Abbreviations: IBD, inflammatory bowel disease; CT, computed tomography.

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diagnosed with *Klebsiella aerogenes* urinary tract infection; however, ciprofloxacin for five days did not improve his symptoms.

Review of systems was notable for night sweats, poor appetite, and mild weight loss. There was no vomiting, diarrhea, melena, hematochezia, rash, or recent trauma, surgery, or hospitalizations. There was a minimal remote smoking history and no use of alcohol or recreational drugs. There was no family history of malignancy, coagulation disorders, or inflammatory bowel disease (IBD). Colon cancer screening had not been performed.

In the emergency department of our hospital, vital signs were normal. Bowel sounds were normal, and there was mild abdominal tenderness in the left lower quadrant; otherwise, the abdomen was nontender and soft. Rectal examination showed no significant stool burden, and fecal occult blood testing was negative. Oropharyngeal exam was normal. The white blood cell count was 20.6 K/μL with 90.5 % neutrophils, the platelet count 504 K/μL, and the hemoglobin level 13.6 g/dL. The level of alanine transaminase was 116 U/L, aspartate aminotransferase 66 U/L, and alkaline phosphatase 207 U/L. The levels of lactate, lipase, creatinine, and troponin were normal. The level of D-dimer was 5384 ng/mL. Partial thromboplastin time was normal, and INR was 1.2. C-reactive protein level was 232 mg/L and erythrocyte sedimentation rate was 64 mm/h. Urinalysis showed resolution of the prior urinary tract infection. Testing for SARS-CoV-2 RNA by nasopharyngeal swab was negative. Fecal calprotectin was negative. Computed tomography (CT) of the abdomen and pelvis with contrast showed pancolitis with dilated thrombosis at the portosplenic confluence extending into the superior mesenteric vein and inferior mesenteric vein (Fig. 1). Additional imaging showed no pulmonary emboli and no lower extremity deep venous thrombosis. Blood cultures were collected. Given the presence of portal and mesenteric thromboses and pancolitis, therapeutic enoxaparin and empirical ceftriaxone and metronidazole were started. The patient received serial abdominal exams, bowel rest, and fluids.

Because of the mesenteric location of the clot, a hypercoagulability workup was performed. Inherited thrombophilia testing was negative for Protein C deficiency, Protein S deficiency, Antithrombin III deficiency, Prothrombin G20210A mutation, and Factor V Leiden. Antiphospholipid testing (after heparinase treatment) was negative. These studies were collected 3.5 hours after the first dose of therapeutic enoxaparin was administered, and none of these studies would have been false-negative due to acute thrombosis or enoxaparin. Examination and laboratory tests were not consistent with nephrotic syndrome, severe liver disease, heart failure, paroxysmal nocturnal hemoglobinuria, or thrombotic microangiopathy. CT of the chest with contrast showed stable pulmonary nodules without evidence of malignancy. Further review of the CT of the abdomen and pelvis was negative for evidence of abdominal malignancy, pancreatitis, splenomegaly, or cirrhosis.

During the next five days, the abdominal pain resolved, and the liver enzymes improved. The patient was discharged on rivaroxaban and a seven-day course of cefpodoxime and metronidazole with a plan for a follow-up CT venogram. Subsequent to discharge, the blood cultures collected at the time of admission became positive after eight days, with one of the anaerobic bottles of two sets growing *Fusobacterium nucleatum*. Although the antibiotics used inpatient and at discharge (particularly metronidazole) are active against *Fusobacterium*, antibiotics were transitioned to amoxicillin-clavulanate because of better institutional experience with amoxicillin-clavulanate. Although the long time to growth and single positive bottle suggested low bacterial burden, the antibiotic course was lengthened to three weeks because of the potential septic clot burden. Evaluation in the hematology clinic was recommended.

At early follow-up, the patient continued to do well without abdominal pain and with normal oral intake. He declined outpatient colonoscopy. Peripheral blood next-generation sequencing and bone marrow biopsy were conducted, demonstrating a DNMT3A R882H clonal hematopoiesis (11 % variant allele frequency) but no evidence of myelodysplastic or myeloproliferative neoplasms. Overall, this patient's history and workup placed him only at mildly increased risk for venous thrombosis: the only risk factors uncovered were older age (4X), obesity (2.2X) and CHIP (2.1X) [4,5]. A follow-up CT venogram was performed three months after hospital discharge which showed complete resolution of the thromboses and colitis (Fig. 2). Anticoagulation was discontinued at that time.

3. Discussion and conclusions

Fusobacterium species cause diverse local and disseminated infections. Although *F. necrophorum* is the species associated with Lemierre's syndrome, the closely related *F. nucleatum* has emerged as an

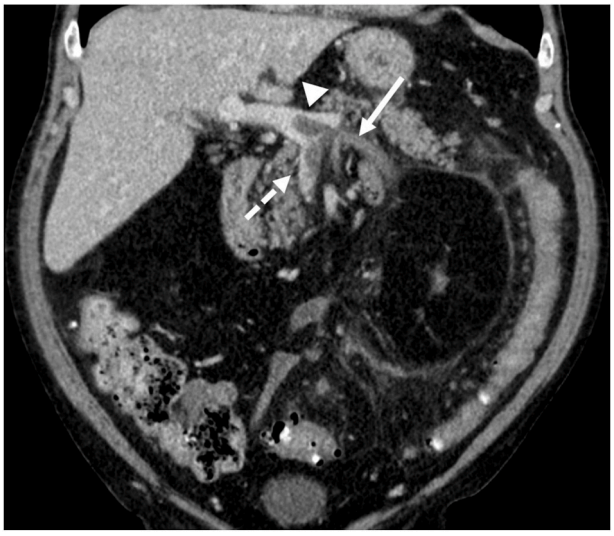

Fig. 1. Mesenteric and portal venous thrombosis and pancolitis.
A coronal CT image obtained on presentation demonstrates occlusive thrombus in the expansile inferior mesenteric vein (solid arrow) and non-occlusive thrombus in the superior mesenteric vein (dashed arrow), extending into the main portal vein (arrowhead), which remains non-occlusive. Additional findings include mesenteric vascular congestion in the left hemiabdomen and pericolonic stranding suggestive of ischemic colitis involving the transverse and descending colon.

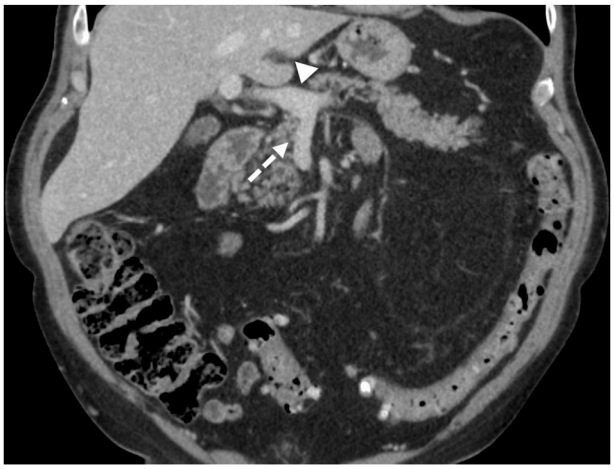

Fig. 2. Resolution of thrombosis and colitis after antibiotics and anticoagulation.
A coronal CT image obtained three months after antibiotics and anticoagulation demonstrates a widely patent main portal vein (arrowhead) and superior mesenteric vein (dashed arrow) as well as resolution of colitis.

important pathogen associated with colon cancer, IBD, and adverse pregnancy outcomes [6]. The association between *F. nucleatum* and thrombosis, although less established, has been reported in several cases, including those of the iliac, portal, and mesenteric veins [1–3,7,8]. This association has not yet been explained mechanistically, but previous studies provide several clues. At the molecular level, *Fusobacterium* species bind and invade diverse cell types and stimulate inflammatory responses [9]. Adhesins have been implicated as key virulence factors that allow these microbes to anchor polymicrobial communities in the oral cavity, adhere to epithelial surfaces, and invade the vasculature through cell-cell junctions [6]. The adhesin protein, FadA, binds cadherins of colonic epithelial cells and vascular endothelial cells, facilitating adherence and invasion. *F. nucleatum* has also been demonstrated to elicit inflammatory host cytokines, including IL-6, IL-8, and TNFα [10,11]. Through these combined effects, *F. nucleatum* infection may promote thrombus formation by providing a platform of endothelial cell dysfunction and a local inflammatory milieu.

How does *F. nucleatum* invade extraoral sites to contribute to thrombosis? This question has been more thoroughly examined with preclinical models in pregnancy complications, where several studies have pointed to the importance of hematogenous spread of *F. nucleatum* from the maternal oral cavity to the intrauterine cavity [9,12,13]. There are at least two possibilities for spread to the large intestines and associated vasculature: (1) via hematogenous spread, as is the case for pregnancy, and (2) via translocation from the oral cavity to the intestine. In either scenario, why thrombosis would occur in the gastrointestinal vasculature is unclear but may reflect pathogen-specific virulence factors or areas of impaired defense due to existing gastrointestinal disease.

F. nucleatum has also been implicated as a driver of colon cancer and IBD, conditions that themselves can promote thrombosis. *F. nucleatum* has been shown to promote colorectal carcinogenesis through direct effects on the expression of oncogenic and inflammatory genes, as well as through the suppression of host immunity [14,15]. In IBD, *F. nucleatum* has been proposed to impair the integrity of intestinal epithelium, stimulate pro-inflammatory factors, and exacerbate disease [16,17]. Ample evidence demonstrates an elevated risk of thromboembolic events in individuals with colorectal cancer or IBD [18,19]. Thus, the literature demonstrates a potential causal link between *Fusobacterium* infection and thrombosis through exacerbation of underlying colonic pathology. Furthermore, this literature suggests that *Fusobacterium*-associated thrombosis in the abdominopelvic vasculature is not just "Lemierre's of the gut" but rather may be quite mechanistically distinct from necrobacillosis of the jugular vasculature in terms of chronic versus acute inflammatory mechanisms.

Taken together, our report supports the growing recognition of *F. nucleatum* as a clinically important yet under-recognized contributor to venous thrombosis at many anatomic sites. Nevertheless, the aforementioned literature presents numerous possible explanations for the pathogenesis of our case. The order of events among bacteremia, thrombosis, and other possible inciting factors is difficult to dissect. Although *F. nucleatum* has been shown to promote a hypercoagulable environment directly, consideration of an underlying hypercoagulable state (for instance, malignancy or rheumatologic condition) is warranted. Furthermore, ischemic colitis secondary to thrombosis may breed a favorable environment for gut translocation or hematologic colonization; it is possible that *F. nucleatum* bacteremia is an end result rather than upstream in the causal chain of events. Given the diversity of plausible explanations for thrombosis in the setting of *F. nucleatum* bacteremia, we propose that patients with this syndrome warrant a broad workup including a full hypercoagulability evaluation and colonoscopy to evaluate for IBD and colon cancer. Future studies should address methods for earlier detection, whether detection may herald underlying gastrointestinal disease, and the relationship between oral and colonic bacterial burden and thrombosis.

4. Limitations

This case report has potential limitations. As an individual case, associations can only be drawn between *Fusobacterium* and mesenteric and portal venous thrombosis based on the temporal coincidence in this patient, on the sparse existing literature reporting other cases, and on theoretical biological mechanisms. It therefore will be important for future work to consider a more systematic examination such as an observational trial or retrospective cohort analysis for the occurrence of fastidious infection among patients with otherwise unexplained thrombosis in unusual locations or demographics. In addition, the patient in this case declined colonoscopy, and thus we cannot rule out an underlying malignancy as a risk factor for thrombosis, especially in association with *Fusobacterium* infection. Finally, it is possible that the fame of Lemierre's syndrome has contributed to *Fusobacterium* being overreported in association with thrombosis and that other altered microbe-host interactions are not given sufficient attention as risk factors and consequences of thrombosis.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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