Identification and Management Implications of *Fusobacterium Nucleatum* Pylephlebitis

Shoja Rahimian, Maria Labra, Ian Garrahy, Rebecca Brown, Navdeep Sangha, Urvi Patel and Andrew Rettew

**Abstract:** Suppurative thrombophlebitis of the portal vein, or pylephlebitis, is a rare infectious manifestation. Only few cases resulting from *Fusobacterium* species have been reported, demonstrating the disease that is in some ways analogous to Lemierre’s syndrome, or suppurative thrombophlebitis of the internal jugular vein. Of these, *Fusobacterium nucleatum* represents an important subtype with unique colon cancer risk. With high mortality rates up to 32% being described in the past, prompt identification and treatment of pylephlebitis is necessary to avoid poor outcomes with this condition, including complications such as intestinal ischemia and portal hypertension. This condition typically presents alongside bacteremia, for which antibiotic therapy typically targets anaerobic organisms of oral and intestinal mucosa, as well as *Streptococcus* species. The use of anticoagulation therapy for pylephlebitis is supported by limited data, which shows potential benefit for preventing worsening thrombosis and liver atrophy. Here we present a case of *F. nucleatum* pylephlebitis who presented with related bacteremia and liver abscess after a dental infection, and treated with anaerobic coverage antibiotics including amoxicillin clavulanate until resolution of his hepatic abscess and with anticoagulation with apixaban for a total of 6 months.

**Keywords:** *Fusobacterium Nucleatum*, Pylephlebitis, Suppurative Thrombophlebitis

**Introduction**

Pylephlebitis is a vascular extension of infection which has been described as suppurrative or septic thrombophlebitis of the portal vein. Appendicitis and diverticulitis have been the leading precipitators to this rare complication found in case reports, while often involving bacteria such as the *Bacteroides fragilis*, *Escherichia coli*, and *Streptococcus* species. More rarely (nearly 5% in a review of 100 cases), *Fusobacterium* species have been identified as the pathogen and called a gut variant of Lemierre’s syndrome, drawing similarity to the clinical situation with *Fusobacterium* infection of the internal jugular vein (Kanellopoulou et al., 2010). The diagnosis of pylephlebitis is often made by visualization of portal vein thrombosis accompanied by bacteremia.

Bacteremia is present in most cases, which can be polymicrobial. The source for these infections is variable, which can include oral abscesses, inflammatory bowel conditions such as appendicitis and diverticulitis, as well as colon cancer in the case *Fusobacterium* species. Hematogenous spread of the bacteria can lead to intravascular extension and inflammation of the portal vein and thrombus formation.

Several complications can arise without appropriate treatment. In the absence of antibiotic therapy, pylephlebitis can be complicated by hepatic abscess, bowel infarction, and death (Dean et al., 1995). The associated mortality rates with pylephlebitis have been historically as high as 32%, necessitating rapid recognition and appropriate management for better outcomes (Plemmons et al., 1995). Anticoagulation has been associated with improved outcomes compared to...
antibiotics alone, particularly in regards to the complication of portal hypertensive (Kanellopoulou et al., 2010). Herein, a case of fusobacterium pylephlebitis with some of the aforementioned findings is described, accompanied with discussion of specific management considerations of this rare condition.

Case Description

A 47-year-old man with history of poor dentition presented with severe acute abdominal pain and one week of progressive fatigue, myalgias, upper abdominal discomfort, and fevers. He reported what he had perceived to be an upper tooth abscess with spontaneous purulent drainage two weeks prior that had gone untreated. On presentation, he had a fever with temperature of 38.7°C, heart rate of 90 beats per minute, respiratory rate of 22 breaths per minute, and blood pressure of 130/70 mm Hg. He was ill-appearing on physical exam, along with finding of several broken teeth without obvious abscesses. Laboratory studies were mostly within or close to normal limits with most significant exceptions of leukocytosis with white blood cell count of 25 × 10^3/µL, predominantly neutrophilic at 85%, and thrombocytosis with 667 × 10^3 platelets/µL (Table 1).

Imaging with maxillo-facial Computed Tomography (CT) with contrast found bilateral maxillary periapical molar abscesses. Abdominal CT imaging in evaluation of sepsis also found several hypodense foci in the liver potentially representing early abscesses, as well as diffuse portal vein thrombosis (Fig. 1). The CT also demonstrated inflammatory changes of the proximal sigmoid colon with associated adenopathy, which was noted for future evaluation. Magnetic Resonance Imaging (MRI) of the abdomen further described the venous thrombosis and the liver lesions were again visualized as suspicious for abscess, although not highly specific which led to a biopsy. The liver biopsy was consistent with findings of abscess wall with acute and chronic inflammation with granulation tissue.

Following concerns for sepsis and the imaging, patient was started on broad spectrum antibiotics with intravenous vancomycin and piperacillin-tazobactam and unfractionated heparin infusion for the portal vein pylephlebitis. Blood cultures obtained prior to initiation of antibiotics returned Fusobacterium nucleatum in one of two blood specimens. Patient’s fever subsided and patient’s subsequent blood cultures were negative for bacterial growth. Transthoracic echocardiogram was negative for valvular vegetation. Based on antibiotic sensitivity of the F. nucleatum, intravenous piperacillin tazobactam was continued for 6 weeks with transition to oral amoxicillin clavulanate which was continued for additional 8 weeks given findings of improved, yet residual liver abscess on repeat MRI. Regarding the portal vein thrombosis, he had hypercoagulable testing which was negative for JAK2 mutation as well as cardiolipin and beta-2 glycoprotein IgG and IgM antibodies further supporting the representation of portal vein suppurative thrombophlebitis. He was transitioned to apixaban 5 mg twice daily on discharge, with plan to continue for three months with repeat MRI at that time. Given persistent portal vein thrombosis on the repeat 3-month MRI, which now described thrombosis as chronic (Fig. 2), decision was made to continue anticoagulation to complete a total of six months of therapy. The proximal sigmoid colon abnormality which was noted on patient’s CT was investigated using colonoscopy and biopsy after 3 months from his initial presentation, which identified three benign hyperplastic polyps.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Value</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>133.00 mmol/L</td>
<td>136-145 mmol/L</td>
</tr>
<tr>
<td>Potassium</td>
<td>3.80 mmol/L</td>
<td>3.5-5.1 mmol/L</td>
</tr>
<tr>
<td>Calcium</td>
<td>9.20 mg/dL</td>
<td>8.6-10.3 mg/dL</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.77 mg/dL</td>
<td>0.6-1.3 mg/dL</td>
</tr>
<tr>
<td>Estimated glomerular filtration rate</td>
<td>108.00 mL/min</td>
<td>&gt;100 mL/min</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>140.00 IU/L</td>
<td>34-104 IU/L</td>
</tr>
<tr>
<td>Aspartate aminotransferase</td>
<td>21.00 IU/L</td>
<td>13-39 IU/L</td>
</tr>
<tr>
<td>Alanine aminotransferase</td>
<td>30.00 IU/L</td>
<td>7-52 IU/L</td>
</tr>
<tr>
<td>Lactic acid</td>
<td>2.00 mmol/L</td>
<td>0.6-1.4 mmol/L</td>
</tr>
<tr>
<td>Total bilirubin of</td>
<td>0.50 mg/dL</td>
<td>0.3-1.0 mg/dL</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>13.80 g/dL</td>
<td>14.0-17.5 g/dL</td>
</tr>
<tr>
<td>White blood cell</td>
<td>$25 \times 10^3/\mu$L</td>
<td>4.8-10.8 × 10^3/µL</td>
</tr>
<tr>
<td>Platelet</td>
<td>$667 \times 10^3/\mu$L</td>
<td>130-400 × 10^3/µL</td>
</tr>
<tr>
<td>JAK2 PCR, blood not detected</td>
<td>Not detected</td>
<td>Not detected</td>
</tr>
<tr>
<td>Cardiolipin IgM, IgG</td>
<td>Not detected</td>
<td>Not detected</td>
</tr>
<tr>
<td>Beta-2 glycoprotein IgM, IgG</td>
<td>Not detected</td>
<td>Not detected</td>
</tr>
</tbody>
</table>
The sigmoid colon finding prompted colonoscopy in this patient, highlighting the importance of having a higher suspicion for colon cancer in patients with \(F. \text{nucleatum}\) infections, particularly those with suggestive of colon source. This is because \(F. \text{nucleatum}\) does not typically present in normal gastrointestinal microbiota but conversely has been found to be enriched in the gastrointestinal tract and more specifically tumor samples of patients with colon cancer (13%, 76 out of 598 tissue samples in one study) (Mima et al., 2015). Multiple mechanisms for \(F. \text{nucleatum}\) tumorigenesis have been described including binding of \(F. \text{nucleatum}\) to the overexpressed colon cancer cell marker of D-galactose-\(\beta(1-3)\)-N-acetyl-D-galactosamine during either transit or overt bacteremia, followed by proinflammatory effects and colon epithelial hyperproliferation (Datorre et al., 2021).

The antibiotic treatment should ideally be broad to cover the typical organisms behind pylephlebitis at first, then be directed at the sensitivities of the identified organism. Antibiotic choices among cases of pylephlebitis with liver abscess have consisted of beta-lactams, metronidazole, clindamycin, or carbapenems. There has been variable treatment duration, however most often 6-8 weeks in other reports, as well as guided based on resolution with repeat imaging (Rahmati et al., 2017).

The role of anticoagulation in the management of pylephlebitis is controversial as data regarding its impact on outcomes is limited. In the absence of anticoagulation, worsening of the thrombosis has been reported in some cases and even liver atrophy in one particular \(F. \text{nucleatum}\) case (Verna et al., 2004). The main reason to use systemic anticoagulation is to increase chances of thrombus resolution and venous recanalization, as demonstrated in one study of 67 patients. In that retrospective analysis, median time to portal vein thrombus resolution on anticoagulation was 3 months with maximum 18 months (Naymagon et al., 2020). Imaging was utilized starting at 3 months to document resolution, which can be a valuable method to guide anticoagulation duration as well as length of antibiotic therapy. One could also extrapolate available data from Lemierre syndrome to help guide the role of anticoagulation in this case. In one observational study of 82 patients, there was an association of thrombus presence with more severe disease, without a noted difference in outcomes with anticoagulation (Nygren et al., 2021). In contrast, a case series did show an overall trend towards expedited thrombus resolution with the addition anticoagulation with the recommendation to consider blood thinners in extensive thrombi cases (Phua et al., 2013).

A definitive role for anticoagulation remains to be elucidated. As such our clinical decisions were limited to available data which lacks robust randomized clinical data, and ultimately made using informed decision making with the patient. Future directions will likely continue to be derived from review of rare cases of this

**Discussion**

Pylephlebitis, or suppurrative thrombophlebitis of the portal vein, typically occurs in the context of an intraabdominal infection or abdominal sepsis. As also seen in the case described herein, fever and abdominal pain are the most prevalent symptoms of Pylephlebitis (Baril et al., 1996). Oral infection is a risk factor that has been shown to precede \(Fusobacterium\) liver abscess and pylephlebitis, and in this case was an important clue to pursuing the diagnosis, particularly with CT of abdomen and pelvis (Jayasimhan et al., 2017). CT is the preferred imaging to not only effectively identify portal vein thrombosis, but also to find other areas of concomitant abdominopelvic infections (Balthazar and Gollapudi, 2000). Diverticulitis is a main infectious source for phlebitis which can also be diagnosed with CT. In this case, CT identified hepatic abscess and the sigmoid colon inflammation.

\(Fusobacterium\) species are anaerobic, gram-negative species that are part of the human oral microbiota. As a pathogen, \(Fusobacterium\) necrophorum is classically associated with Lemierre’s syndrome, or suppurrative thrombophlebitis of the internal jugular vein, but has been implicated in similar infectious process with the portal vein (Mellor et al., 2017; Bolstad et al., 1996). In such instances, \(Fusobacterium\) pylephlebitis have been called a unique variant of Lemierre’s syndrome. \(Fusobacterium\) nucleatum, named such given its nucleated appearance on microscopy, has also been reported in a few of such cases of gastrointestinal Lemierre’s syndrome (Mellor et al., 2017; Etienne et al., 2001; Rahmati et al., 2017; Tariq et al., 2020; Tharu et al., 2020).

The sigmoid colon finding prompted colonoscopy in this patient, highlighting the importance of having a higher suspicion for colon cancer in patients with \(F. \text{nucleatum}\) infections, particularly those with suggestive of colon source. This is because \(F. \text{nucleatum}\) does not typically present in normal gastrointestinal microbiota but conversely has been found to be enriched in the gastrointestinal tract and more specifically tumor samples of patients with colon cancer (13%, 76 out of 598 tissue samples in one study) (Mima et al., 2015). Multiple mechanisms for \(F. \text{nucleatum}\) tumorigenesis have been described including binding of \(F. \text{nucleatum}\) to the overexpressed colon cancer cell marker of D-galactose-\(\beta(1-3)\)-N-acetyl-D-galactosamine during either transit or overt bacteremia, followed by proinflammatory effects and colon epithelial hyperproliferation (Datorre et al., 2021).

The antibiotic treatment should ideally be broad to cover the typical organisms behind pylephlebitis at first, then be directed at the sensitivities of the identified organism. Antibiotic choices among cases of pylephlebitis with liver abscess have consisted of beta-lactams, metronidazole, clindamycin, or carbapenems. There has been variable treatment duration, however most often 6-8 weeks in other reports, as well as guided based on resolution with repeat imaging (Rahmati et al., 2017).

The role of anticoagulation in the management of pylephlebitis is controversial as data regarding its impact on outcomes is limited. In the absence of anticoagulation, worsening of the thrombosis has been reported in some cases and even liver atrophy in one particular \(F. \text{nucleatum}\) case (Verna et al., 2004). The main reason to use systemic anticoagulation is to increase chances of thrombus resolution and venous recanalization, as demonstrated in one study of 67 patients. In that retrospective analysis, median time to portal vein thrombus resolution on anticoagulation was 3 months with maximum 18 months (Naymagon et al., 2020). Imaging was utilized starting at 3 months to document resolution, which can be a valuable method to guide anticoagulation duration as well as length of antibiotic therapy. One could also extrapolate available data from Lemierre syndrome to help guide the role of anticoagulation in this case. In one observational study of 82 patients, there was an association of thrombus presence with more severe disease, without a noted difference in outcomes with anticoagulation (Nygren et al., 2021). In contrast, a case series did show an overall trend towards expedited thrombus resolution with the addition anticoagulation with the recommendation to consider blood thinners in extensive thrombi cases (Phua et al., 2013).

A definitive role for anticoagulation remains to be elucidated. As such our clinical decisions were limited to available data which lacks robust randomized clinical data, and ultimately made using informed decision making with the patient. Future directions will likely continue to be derived from review of rare cases of this
condition, to which we hope to have contributed to by the description of our case and its management.

**Conclusion**

Pylephlebitis demonstrates a rare pattern of infectious spread from typically gastrointestinal sources. However, bacteria from oral microbiota such as *F. nucleatum* should also be considered along with careful consideration towards ruling out colonic sources and the association with colon cancer. With better recognition and initiation of antibiotics, the previously poor survival rates can be diminished. Nevertheless, there is a need for further studies to elucidate the role of systemic anticoagulation in the treatment of pylephlebitis.

**Author’s Contributions**

Shoja Rahimian and Rebecca Brown: Conceptualization and initial drafting of the manuscript and editing, research with literature search, data curation and analysis. Subsequent revisions and editing, including figures.

Ian Garrabhy and Navdeep Sangha: Conceptualization and initial drafting of the manuscript and editing, research with literature search, data curation and analysis.

Maria Labra and Urvi Patel: Initial drafting of the manuscript and editing, research with literature search, data curation and analysis.

Andrew Retew: Conceptualization and initial drafting of the manuscript and editing, research with literature search, data curation and analysis. Provided supervision of the project as a topic expert.

**Ethics**

This article is original and contains unpublished material. The corresponding author confirms that all of the other authors have read and approved the manuscript and no ethical issues involved.

**References**


