Fusobacterium Liver Abscess

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Abstract
Fusobacterium is well characterized as an oropharyngeal pathogen that may induce a septic thrombophlebitis by direct extension of abscess into an adjacent neck vessel (Lemierre’s syndrome); its potential for visceral abscess formation, however, remains under-recognized. A 65-year-old man with a recent history of multiple rim-enhancing liver lesions presented to the emergency room with fever and abdominal pain. Based on interval increase in the size of the lesions, abscess was suspected. A liver biopsy was performed, and although no organism could be identified on routine microscopy, Warthin-Starry stain revealed Gram-negative bacilli consistent with an anaerobic Fusobacterium species as the underlying etiology of liver abscess formation. Subsequent anaerobic culture results confirmed the diagnosis. This case highlights the importance of consideration for Fusobacterium infection in the setting of liver abscess if anaerobic organisms have not yet been excluded on initial culture evaluation.

Introduction
Situated at the confluence of the portal and systemic circulations, the liver represents both a common site of metastatic disease and the most common site of visceral abscess, accounting for up to 48% of such infections in one case series [1]. Thus – particularly because metastases to the liver may show necrosis and/or bleeding – the presence of a rim-enhancing fluid collection within the liver often raises the differential diagnosis of tumor versus infection. Fine needle aspiration or core biopsy with histologic examination and culture are the preferred methods for resolving this question, but a definitive diagnosis may be confounded by a necrotic background and false-negative culture results. In particular, a negative culture result of aspirated fluid – the gold standard for diagnosis of most infec-
tions – raises concern for an occult malignancy. However, standard culture methods do not effectively exclude infection by unusual organisms such as mycobacteria or ameba, or by obligate anaerobic bacteria such as *Fusobacterium* sp.

*Fusobacterium* are filamentous Gram-negative anaerobic bacteria commensally inhabiting the oropharynx and gastrointestinal and female genital tracts [2, 3], initially characterized because of the frequent isolation of *Fusobacterium necrophorum* in cases of Lemierre’s syndrome [4]. Lemierre’s syndrome – a septic thrombophlebitis of the internal jugular vein secondary to pharyngeal infection – was initially associated with high mortality [3], but improvements in antibiotic therapy have reduced this to less than 10% [5]. As the incidence of Lemierre’s syndrome as well as the mortality from this condition have decreased, *Fusobacterium* sp. are less frequently included in the differential diagnosis of deep abscess. Nevertheless, given the classic constellation of findings in Lemierre’s syndrome, oropharyngeal infection by *Fusobacterium* may be identified even in the setting of negative culture results (which may occur in up to 10–15% of cases, possibly secondary to the stringent need for anaerobic culture conditions for isolation of this organism [5]). In the case of visceral infection, on the other hand, these organisms may be easily missed due to a low index of suspicion and the aforementioned difficulties in isolation via culture. We report a case of *Fusobacterium* liver abscess that illustrates these diagnostic challenges and the utility of biopsy in diagnosis of this rare liver infection.

**Case Report**

A 65-year-old man presented to the emergency department with fever, chills, nausea and abdominal pain. A week prior to this admission the patient had been worked up for hematuria, a computed tomography (CT) scan of the abdomen showing multiple rim-enhancing liver lesions. The differential diagnosis at that time included metastatic colon carcinoma, amebic abscess and bacterial abscess seeded from sigmoid diverticulitis. Five days prior to admission, the patient underwent colonoscopy with biopsies, which showed acute inflammation but no evidence of malignancy. On the day of admission, repeat CT scan showed interval increase in size of his rim-enhancing liver lesions (fig. 1) as well as acute cecal diverticulitis, chronic pancreatitis and a large thrombus in the portal vein. Based on the interval increase in size of the liver lesions and the colonoscopy findings, an infectious etiology was favored and four drains were placed for presumed abscesses (confirmed with drainage of purulent fluid) and empiric treatment with ciprofloxacin and metronidazole was initiated. The patient was also started on heparin for his portal vein thrombosis 3 days after admission (transitioned to Lovenox twice daily 6 days after admission). On day four, the causative organism for the patient’s abscesses remained unidentified and a liver biopsy was performed to re-evaluate for the possibility of neoplasia or an unusual organism.

The liver biopsy showed neutrophil-rich debris (fig. 2a), consistent with abscess, and liver parenchyma embedded in fibrous tissue and scattered mixed inflammation consistent with abscess wall; no peliosis or viropathic changes were appreciated. Immunohistochemical staining for CD34 and CD31 showed no evidence of a vascular neoplasm, and S100 was negative, arguing against a neural crest-derived tumor (not shown). No bacteria were identified on Gram stain (fig. 2b), and no fungal organisms were seen on periodic acid-Schiff diastase or Gomori methenamine-silver stains. Also, there were no mycobacterial organisms on an acid-fast bacilli-stained slide (not shown). Warthin-Starry (WS) stain, however, showed filamentous bacteria within the necrotic debris (fig. 2c, d) consistent with *Fusobac-
Fusobacterium infection [6]. A week after admission, detection of Fusobacterium sp. in cultures of the patient’s hepatic abscess fluid confirmed the diagnosis of Fusobacterium liver abscess.

In the interval between the biopsy and identification of the causative organism, ciprofloxacin was empirically changed to ceftriaxone because of concern for Streptococcus milleri infection; the patient improved on the combination of ceftriaxone 1 g daily and metronidazole 500 mg three times daily, his drains were removed, and he was discharged 8 days after admission on antibiotics as described above.

Discussion

At the time of histologic examination, diagnostic considerations for this patient included metastatic malignancy (especially colonic adenocarcinoma), hepatocellular carcinoma, vascular malformation/tumor and infection. In this case, the absence of a primary tumor meant that despite negative initial culture results suspicion for an infectious process remained high, but occult malignancy could not be excluded, and this resulted in liver biopsy.

In the setting of radiologic evidence of a concerning liver lesion, the primary purpose of biopsy is to exclude malignancy. Additionally, it is possible that tissue biopsy will provide evidence of an unusual organism or a diagnostic yield of the more common Gram-positive and -negative bacteria and/or fungi (including staphylococcal or streptococcal species, Klebsiella sp. and Candida sp.). In this case, routine sections stained with hematoxylin and eosin (H&E) provided strong evidence against a neoplastic etiology and indicated an infectious/inflammatory process. In addition to removing malignancy from the differential diagnosis, the biopsy findings in such a case can thus highlight potentially spurious or incomplete culture results and encourage the search for atypical organisms.

When typical bacterial or fungal pathogens are not recovered from culture of a liver abscess, infection by obligate anaerobes, mycobacteria [6], Burkholderia pseudomallei or ameba [7] should be considered. Since culture methods are either time-consuming (mycobacteria) or ineffective (classically with amoeba, but also in a subset of anaerobic infections), microscopic examination can be crucial for timely diagnosis. Amebic abscess was considered unlikely in this patient based on imaging and the quality of the aspirated fluid. In the absence of a travel history, the patient was not at risk for B. pseudomallei infection, which is endemic to Southeast Asia and Northern Australia. Nevertheless, a broad panel of stains was performed to evaluate for these – and other even less common – organisms. As illustrated in figure 2, this workup revealed WS-positive bacilli within the necrotic debris, consistent with Fusobacterium sp.

Fusobacterium are Gram-negative, WS-positive anaerobes first recognized for their causative role in Lemierre’s syndrome [7], as described above. Additionally, rare cases of F. necrophorum hepatic abscess have been described (13 case reports to date, summarized in [8]). The pathogenesis of liver infection remains unknown, although the proposed mechanisms include hematogenous spread from dental caries/peritonsillar abscess [9] or spread through the portal circulation in the setting of diverticular disease [10]. Most of the cases reported to date are not associated with immune deficiency (and this patient did not have any reported immune deficiency). Given the rarity of this infection and difficulties in isolating it from culture (both in this case and others, see [8]), it may be missed, especially in the acute or subacute setting. Thus, biopsy may represent the first opportunity for diagnosis of Fusobacterium infection. Unfortunately, Fusobacterium bacilli can be easily overlooked amongst necrotic debris on routine H&E-stained tissue sections (fig. 2a). WS staining, however, readily highlights Fusobacterium and allows for a presumptive diagnosis (fig. 2c, d), as in this...
case. As described above, *Fusobacterium* sp. were eventually isolated from culture of the patient's drain fluid, confirming the diagnosis. It should be noted that full speciation of the causative organism was not performed in this case; although all reported cases of *Fusobacterium* liver abscesses have been due to *F. necrophorum*, it is theoretically possible — although unlikely — that another *Fusobacterium* species was the causative organism in this case. Furthermore, it can be hypothesized that the patient's portal vein thrombosis represented a Lemierre's-like syndrome directly initiated by *Fusobacterium* thrombus.

Most *Fusobacterium* isolates are sensitive to ampicillin, although 2% of isolates are resistant (with 15% resistance to erythromycin also noted). Most isolates are sensitive to metronidazole [9]. Antibiotic therapy should be continued for 4–6 weeks after discharge; patients with good drainage of their abscess should receive 2–4 weeks of parenteral antibiotics, while incomplete drainage necessitates 4–6 weeks of parenteral therapy. The remainder of the course may be finished with oral medication selected based on sensitivity results [8].

In summary, *Fusobacterium* should be considered in the differential diagnosis of a culture-negative liver abscess, particularly in the setting of thrombosis. Furthermore, consulting pathologists must maintain a high degree of vigilance for *F. necrophorum* when evaluating biopsies from such cases.

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**Disclosure Statement**

The authors affirm that they have no conflicts of interest to disclose.

**References**

Fig. 1. Admission CT scan showing multiple intrahepatic abscesses (arrowhead). Axial (a) and coronal (b) views are shown.

Fig. 2. Microscopic examination showed fragments of neutrophil-rich debris (consistent with abscess) and liver parenchyma embedded in fibrous tissue (consistent with abscess wall). Immunohistochemical stains for tumor were negative (not shown) and no definite organisms were detected on H&E- (a) or Gram-stained sections (b) (1,000×). WS silver stain (c, d), however, revealed long rod-shaped bacteria, consistent with Fusobacterium sp. (arrowheads) (1,000×).