

Actinomycosis of the Common Bile Duct Diagnosed by Endoscopic Ultrasound Fine-Needle Aspiration

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Endoscopic ultrasound (EUS) is a useful modality for examining the pancreaticobiliary system, as it provides high-resolution images without interference from bowel gas and fat. EUS fine-needle aspiration (FNA) has contributed greatly to the diagnosis of hepatobiliary and pancreatic diseases. In this case report, we present a patient with hepatobiliary actinomycosis diagnosed by EUS. *Actinomyces* are gram-positive, beaded, filamentous, anaerobic bacteria that form chronic granulomatous lesions and suppurative abscesses. These bacteria frequently colonize the upper respiratory, gastrointestinal, and female genital tracts but rarely invade the hepatobiliary system in the absence of gastrointestinal surgery or trauma to the bowel.

Case Report

A 64-year-old Jamaican woman with no significant medical history presented to another institution with a 2-month history of jaundice, weight loss, itching, and right upper quadrant discomfort. An abdominal computed tomography (CT) scan revealed an enhancing soft tissue mass that involved the gallbladder fossa and extended from the pancreatic head to the porta hepatis (Figure 1). An intrauterine device (IUD) was also identified. The patient underwent an endoscopic retrograde cholangiopancreatography, which revealed a stented mid-bile duct stricture. Suspicious cells were found from the common bile duct (CBD) brushing. The patient presented to our institution 1 month later with

persistent right upper quadrant abdominal pain. Laboratory examination revealed a white blood cell count of 6.0×10^3 cells/mm³, aspartate aminotransferase level of 28 U/L, alanine aminotransferase level of 34 U/L, alkaline phosphatase level of 265 U/L, total bilirubin level of 0.9 mg/dL, and direct bilirubin level of 0.4 mg/dL. The patient's CA 19-9 level was unremarkable. EUS revealed a 4.5-cm \times 4.3-cm heterogeneous isoechoic mass abutting the portal vein and CBD, extending from the proximal pancreas to the porta hepatis (Figure 2). EUS-FNA revealed reactive ductal hyperplasia with actinomycotic organisms and atypical ductal cells.

The patient underwent removal of her IUD and began treatment with ceftriaxone sodium (Rocephin,



Figure 1. Computed tomography scan showing a soft tissue mass (arrows) in the gallbladder fossa.

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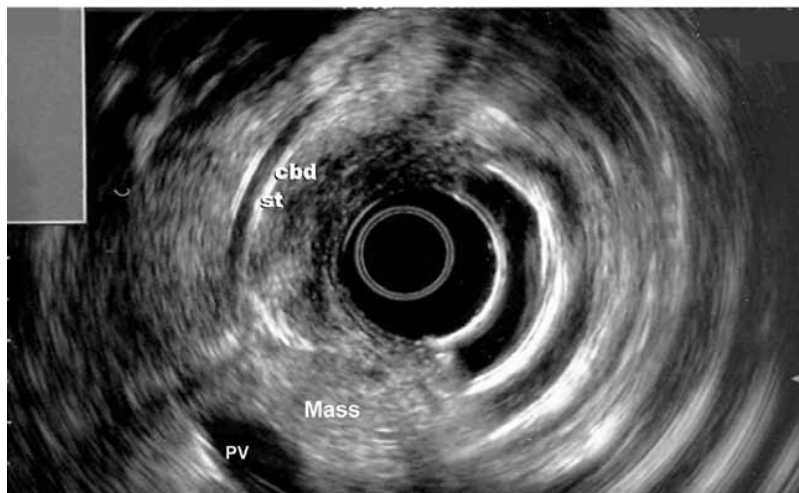


Figure 2. Endoscopic ultrasound showing a heterogeneous isoechoic mass abutting the portal vein (PV) and common bile duct (CBD). A stent (st) is also present.

Hoffman-La Roche), which was changed to doxycycline upon development of toxic epidermal necrolysis. Despite the use of antibiotics, the mass increased in size, and a laboratory examination revealed worsening biliary obstruction (evidenced by increases in alkaline phosphatase level to 693 U/L, total bilirubin level to 8.0 mg/dL, and direct bilirubin level to 5.3 mg/dL). The patient subsequently underwent a cholecystectomy and hepaticojejunostomy. Surgical pathology revealed acute inflammation, with a foci of papillary carcinoma in the CBD.

Discussion

Actinomycosis is a rare disease characterized by a chronic, progressive, granulomatous infection caused by the *Actinomyces* species, of which *Actinomyces israelii* is the most frequently isolated.¹ *Actinomyces* are gram-positive, micro-aerophilic or obligatorily anaerobic filamentous bacteria endogenous to the oral cavity and the genitourinary and gastrointestinal tracts.²⁻⁴ These bacteria are opportunistic and lack virulence; therefore, disease typically follows an indolent course that may last several years.⁴ Penetration and propagation occur through contiguous spread in immunocompromised states or upon breaching the normal barrier.^{2,4-6} Due to the large filaments of the cells, lymphatic spread is rare. Hematogenous spread to the liver is a rare but serious complication.¹ The characteristic granulomatous inflammatory response is followed by necrosis and extensive fibrosis, with fistulization as a common late outcome.⁶

Long-term IUD use is a known risk factor for developing pelvic actinomycosis.^{7,8} On rare occasions, local endometritis can progress to an ascending infection with intra-abdominal abscesses.⁸ In one study, the colonization rate of vaginal flora with *Actinomyces* was 11.4% in

patients with an IUD.⁹ Approximately 0.5–1.0% of patients with an IUD develop actinomycosis, particularly after the device has been in place for at least 3 years.⁸ This diagnosis should be considered in any woman with an IUD who presents with abdominal pain and an abdominopelvic mass on imaging.

Actinomycosis occurs most frequently in the cervicofacial (50%), abdominal (20%), and thoracic (15%) regions.^{2,5} The incidence of abdominal disease is 0–3 cases per year in the United States.¹⁰ Abdominal actinomycosis may present as a mass lesion mimicking malignancy, diverticular abscess, tuberculosis, or Crohn's disease. Diagnosis is often made only during surgical exploration.^{4,7,8,11} Abdominal actinomycosis typically occurs after gallbladder, appendiceal, or colonic surgery, with the appendix and ileocecal valve comprising the most common sites of infection.^{4,12}

Hepatobiliary actinomycosis is extremely rare and may present as acute or chronic cholecystitis, biliary colic, or pancreatitis.^{2,13} Liver involvement is reported in only 5% of patients.¹⁴ Involvement of the gallbladder is rare; to our knowledge, only 18 cases have been reported in the literature.¹ Isolated actinomycosis of the CBD without liver or gallbladder involvement has been reported in 1 case.¹⁵ The proposed pathogenesis of hepatobiliary actinomycosis is retrograde spread from the duodenum into the CBD.^{1,12,15}

There is no pathognomonic radiographic sign of actinomycosis. However, CT frequently reveals infiltrative, enhancing areas of decreased attenuation, with contrast invading surrounding tissues.^{1,4,11} Ultimately, tissue biopsy is necessary for diagnosis.

Once actinomycosis is diagnosed, prolonged antibiotics are required due to reactive fibrosis formed by the bacteria.² Recommended first-line treatment consists of a penicillin-derivative drug administered over 6–12 months.

Alternative treatments include tetracycline, erythromycin, clindamycin, or doxycycline.^{4,12} Surgery is indicated for debridement, removal of sinus tracts, and fistula repair.^{2,4} To our knowledge, carcinoma of the gallbladder has only once been reported in association with actinomycosis of the gallbladder.¹³

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Review

If Cancer Is Not the Answer: Endoscopic Ultrasound–Guided Biopsies in the Diagnosis of Infections

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The use of endoscopic ultrasound (EUS) with fine-needle aspiration (FNA) was first reported in the 1990s.¹ Since then, this minimally invasive method has gained widespread acceptance due to its ability to acquire tissue in difficult-to-access structures. EUS-guided FNA can target a wide range of lesions, including those within the diges-

tive tract wall (subepithelial tumors) and those in proximity to the gastrointestinal lumen in the chest, abdomen, and pelvis. EUS-FNA can obtain samples for cytologic assessment as well as core biopsies via a Trucut needle for histologic analysis. These biopsies may increase the diagnostic yield or enable more detailed analysis in select cases^{2,3}; however, technical limitations of the EUS-guided Trucut needle hinder its widespread use.

Although an EUS-guided biopsy can serve many functions, the most common reason to obtain such a biopsy is to distinguish malignant conditions from benign ones, hence the saying: tumor is the rumor, tissue is the issue, and cancer is the answer. However, benign conditions have their own diagnostic challenges for the clinician and pathologist. First, a “negative” biopsy may not be sufficient to exclude cancer. Furthermore, certain clinical circumstances require a specific diagnosis—beyond the exclusion of malignancy—in order to guide appropriate patient management.

The case report by Thadani and associates exemplifies how EUS-guided biopsy can help to identify an infectious disease.⁴ The authors report a rare case of actinomycosis with a mass lesion in the extrahepatic bile duct. They were able to definitively diagnose the infectious organism through direct microscopic identification with EUS-guided FNA. Although this presentation of actinomycosis is extremely rare, endemic fungal infections are frequently diagnosed in a similar fashion. An example is histoplas-

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mosis, which is highly prevalent in the Mississippi and Ohio River Valleys in the United States.⁵ Clinical manifestations of histoplasmosis range from asymptomatic or transient nonspecific respiratory symptoms to life-threatening sepsis in rare cases. Mediastinal lymphadenopathy is frequently found and may mimic malignancy on computed tomography and positron emission tomography scans. Biopsy with EUS or endobronchial ultrasound guidance is usually safe and easy in this setting. The pathologist may note the following findings (from least specific to most specific): the absence of malignant cells with benign lymph node tissue, granulomatous inflammation with or without necrosis, and identification of the infectious agent. The differential diagnosis for granulomas in these cases includes sarcoidosis, other fungal infections, and tuberculosis. Other causes of granulomas in lymph nodes include sarcoid-like reactions to tumors, drug reactions (from anti-tumor necrosis factor therapy), environmental exposures (eg, beryllium, talc), and malignancies that induce a granulomatous response (eg, lymphoma, carcinoma). These causes are less common but should still be considered in the clinical context.

Necrotizing granulomatous inflammation caused by infection with *Histoplasma capsulatum* can typically be distinguished from non-necrotizing granulomas of sarcoidosis, particularly if abundant necrosis is present.^{6,7} However, the classical appearance is not always seen, and pathologic overlap exists between the 2 conditions (such as focal necrosis in sarcoidosis and non-necrotizing granulomas in histoplasmosis).^{8,9} Sampling error and poor specimen quality may cause further difficulties. In my clinical practice, I experienced a case in which FNA cytology of an abnormal lymph node suggested non-necrotizing granulomas but histology of an EUS-guided Trucut biopsy of the same lymph node showed necrotizing granulomas.

Granulomatous infections can also present with hilar lymphadenopathy and joint pain, mimicking clinical features of acute sarcoidosis and emphasizing that sarcoidosis remains a diagnosis of exclusion.¹⁰ Cytopathologic and histopathologic granuloma findings should be interpreted in the context of pretest probability. EUS-FNA is reportedly highly accurate for diagnosing sarcoidosis when infectious causes of granulomatous inflammation are rare.^{11,12} However, these results cannot be translated to areas that are endemic for fungal infections.

As in the case report by Thadani and colleagues, direct visualization of the infectious organism provides a highly specific diagnosis.⁴ The budding yeasts of *H. capsulatum* usually require special silver stains (Gomori methenamine) to be seen in necrotizing granulomas. An exception to this rule is disseminated histoplasmosis, in which organisms may be readily identified within mac-

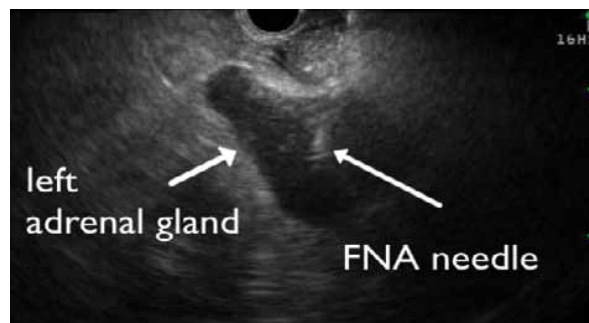


Figure 1. Transgastric endoscopic ultrasound–fine-needle aspiration (FNA) of the left adrenal gland.

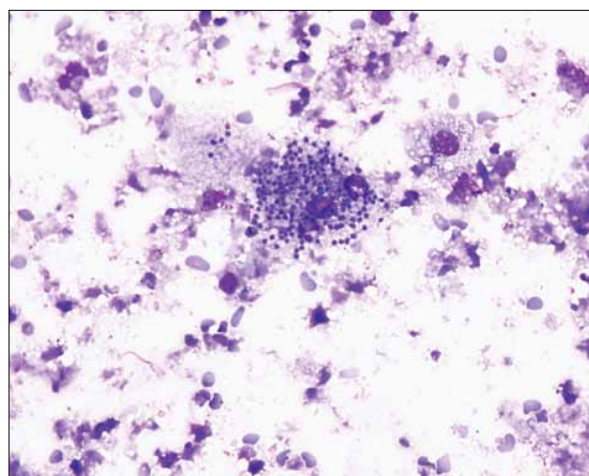


Figure 2. Histiocytes with histoplasma (left adrenal gland fine-needle aspiration, Diff-Quik stain, 600 \times). Image courtesy of Dr. Robert A. Robinson, Department of Pathology, University of Iowa Hospitals and Clinics, Iowa City, Iowa.

rophages via hematoxylin and eosin stains in histologic preparations or Romanowsky-based stains in cytologic preparations.⁷ Although other organisms may appear similar, the clinical setting typically facilitates a definitive diagnosis.⁵

EUS can also help diagnose disseminated histoplasmosis with adrenal gland involvement,¹³ as in the case of an 86-year-old man who presented to my practice with weight loss, fatigue, night sweats, chills, dry cough, and hypotension. Bilateral adrenal gland masses raised suspicion for malignancy. Transgastric EUS-guided FNA of the left adrenal gland was performed (Figure 1), and cytology showed necrosis and an organism with the typical appearance of *H. capsulatum* (Figure 2). The patient slowly improved with itraconazole therapy.

Similarly, tuberculosis is an important differential diagnosis in the setting of granulomatous lymphadenopathy. As with histoplasmosis, EUS can provide a minimally invasive method for obtaining a tissue diagnosis if mediastinal lymph nodes are involved.^{14,15} Caseating or necrotizing granulomas are typical findings and may be histomorphologically identical to findings associated with histoplasmosis.⁷ However, it is also possible that FNA merely reveals non-necrotizing granulomas, which may make distinction from sarcoidosis and other granulomatous reactions difficult unless stains or cultures for acid fast bacilli (AFB) are positive. In a recent series evaluating EUS-guided FNA for suspected tuberculosis of mediastinal lymph nodes, 25 of 46 patients with a final diagnosis of tuberculosis had granulomas with necrosis, 4 patients had necrosis only, and 17 patients had granulomas without necrosis.¹⁴ Of the 17 patients with non-necrotizing granulomas, 6 patients had positive AFB stains. AFB cultures, in addition to smears, increase the diagnostic yield and are more likely to be positive if necrosis is present.¹⁶

Although EUS-guided FNA is not performed under sterile conditions, bacterial cultures of the aspirates appear to be accurate for diagnosing purulent infections. Fritscher-Ravens and associates performed EUS-guided FNA in 16 patients with suspected mediastinal abscesses.¹⁷ Purulent inflammation or positive gram stains were found on smears in 13 patients and 6 patients, respectively. Culture and sensitivity testing identified the organisms and aided drug therapy in all 16 patients. The control group consisted of 9 patients who underwent EUS-guided FNA for suspicion of infected lesions, though infection was ultimately not found. EUS aspirate cultures were either sterile or had a low bacterial count.

In conclusion, both neoplasms and non-neoplastic infectious conditions can be diagnosed with minimal invasion via EUS-guided biopsies. Although diagnosis can be complex in infections due to overlapping cytopathology and histopathology and varying sensitivities and specificities for identifying organisms, EUS often obviates the need for highly invasive surgical procedures and should be considered in the diagnostic algorithm.

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