Primary Hepatic Actinomycosis: Case Report and Literature Review

by Duane E. Deivert, Chad E. Potteiger, Michael Komar, Srinivasan Dubagunta and Steven Meschter

Actinomycosis is a rare cause of liver abscess and most commonly occurs as a consequence of prior infection or abdominal surgery. Primary hepatic actinomycosis accounts for less than 5% of all cases.

We present a case of primary hepatic actinomycosis occurring several years after endoscopic and surgical treatment of a hepatic artery pseudoaneurysm. The clinical picture was suggestive of metastatic cholangiocarcinoma; however, histologic evaluation of a fine-needle aspirate demonstrated organisms consistent with *Actinomyces*. Exploratory laparotomy did not identify any nidus of infection. We presume that the previous interventions provided a portal of entry for the bacteria, leading to indolent abscess formation. After a prolonged course of antibiotic therapy, the symptoms resolved and subsequent imaging demonstrated resolution of the hepatic abscesses.

The case is presented to illustrate the rarity of primary hepatic actinomycosis, the challenges in establishing an accurate diagnosis, and appropriate medical and surgical treatment of hepatic actinomycosis.

INTRODUCTION

Actinomycosis is a spectrum of chronic, suppurative infections caused by anaerobic or microaerophilic, fungus-like bacteria. The bacterium was first described in 1877 as filaments radiating from a central mass—the name *Actinomyces* literally means "fungus with rays (1)." It is a commensal inhabitant of the oral cavity and aero-digestive tracts, and results in invasive disease only when the integrity of the mucosal barrier is compromised. Cervicofacial, thoracic, abdominal and pelvic infections have been described, with cervicofacial abscesses being far more common. Primary hepatic actinomycosis is rare and actinomycotic liver abscesses usually arise as a result of infection, such as appendicitis or diverticulitis, or prior surgery. Months or years often pass from the time of infection until it becomes clinically apparent. Local infection can lead to fistula and sinus formation, as well as contiguous extension without regards to tissue planes, explaining why it is often mistaken for a malignant process. Actinomycosis has been referred to as one of the great imitators and "the most misdiagnosed disease often missed by experienced clinicians (2)."

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Actinomycosis is often diagnosed at the time of surgical exploration either by the surgeon who identifies the characteristic sulfur granules, or by the pathologist reviewing the histologic specimen. The organism is very fastidious and proper specimen handling and culturing techniques are important to improve the diagnostic yield. Often a single dose of antibiotics will preclude bacteriologic identification.

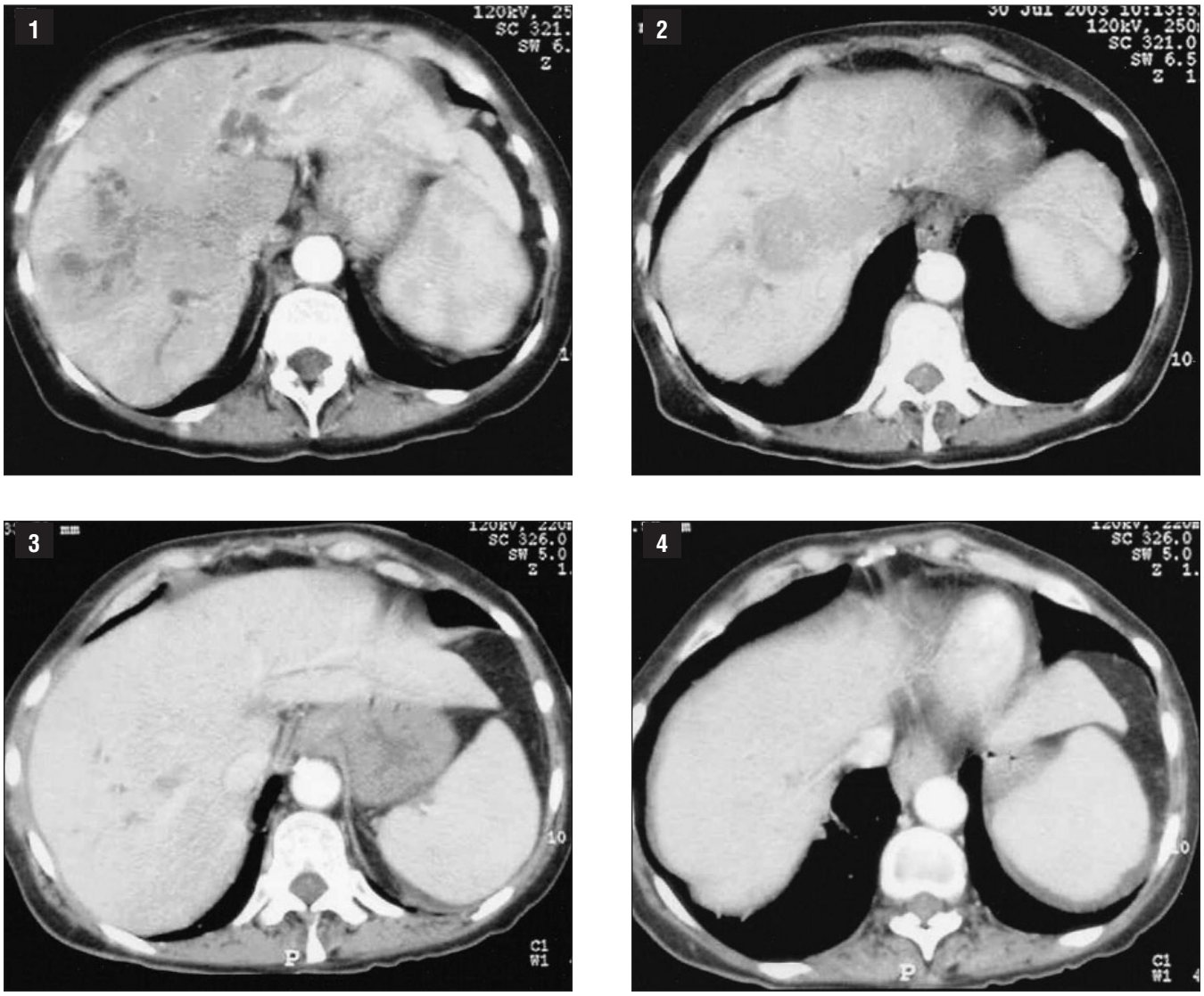
CASE REPORT

We present the case of a 61-year-old female who initially presented to her primary care physician with a four-month history of right upper quadrant abdominal pain, nausea, vomiting, occasional diarrhea, low-grade fevers, chills, and night sweats. She had lost approximately 25 pounds in the same interval. Her past medical history was significant for extensive tobacco abuse, hypertension which was well-controlled, and hyperlipidemia which was treated with Atorvastatin. She had a total hysterectomy in 1977 for a uterine leiomyoma and had a appendectomy at that time. She also reported having a cholecystectomy in 1999 after presenting with gastrointestinal hemorrhage, but could not provide further details.

Laboratory evaluation at that time was significant for a mild anemia. A colonoscopy was performed to evaluate her anemia and diarrhea, which revealed moderate sigmoid diverticulosis but was otherwise unremarkable; an upper endoscopy revealed chronic gastritis and antral biopsies were negative for *H pylori.* Several weeks later she developed jaundice and ascites. Further diagnostic studies were delayed due to a lack of insurance coverage. A contrast enhanced computed tomography (CT) scan of the abdomen and pelvis was eventually obtained four months later which demonstrated marked intrahepatic ductal dilatation, multiple low-density lesions were identified in the right lobe of the liver (Figures 1, 2), as well as moderate ascites, and a 5 cm soft-tissue density adjacent to the liver and pancreas which was concerning for a pancreatic mass. A liver panel at that time was markedly abnormal with an alkaline phosphatase of 1340 U/L (normal 25–125), AST of 91 U/L (normal 8-46), ALT of 88 U/L (normal 8–50), and a total bilirubin of 5.4 mg/dL (normal 0.3–1.3). She was subsequently referred to our institution for further diagnostic evaluation (Figure 1–4).

Initial evaluation included an endoscopic ultrasound (EUS) and endoscopic retrograde cholangiopancreato-graphy (ERCP) to further evaluate the possible pancreatic mass and biliary dilatation. The EUS identified intrahepatic ductal dilatation and a malignant appearing 11 × 10 mm celiac lymph node, but no focal pancreatic lesions. Fine needle aspiration (FNA) of the lymph node was consistent with a reactive lymph node and flow cytometry demonstrated benign lymphocytes without evidence of lymphoma. Diffuse dilatation of the left intrahepatic ducts with a focal 15 mm stenosis at the bifurcation of the hepatic duct was noted on ERCP, which was suspicious for a Klatskin tumor; however, multiple brushings did not identify any malignant cells and a 10 Fr stent was placed. Ascitic fluid obtained via paracentesis demonstrated a high albumin gradient consistent with portal hypertension and cytology was negative for malignant cells. She was noted on endoscopic examination to have retained food products in the duodenal bulb and possible extrinsic compression causing intraluminal narrowing in the second portion of the duodenum. These findings, along with her nausea and vomiting, prompted an upper GI series which revealed focal stenosis with mild duodenal obstruction, as well as a large diverticulum.

She was later admitted with increasing right upper quadrant abdominal pain, nausea, vomiting, and worsening ascites. Her jaundice had improved, but she continued to have intermittent low-grade fevers, chills, and drenching night sweats. On physical examination, she was a cachectic, ill-appearing white female, in mild distress. Her temperature was 37.6 degrees Celsius, blood pressure 95/60, pulse 106. Her skin was not jaundiced and her sclera were clear. There were no stigmata of chronic liver disease. Heart and lung examinations were normal. The abdomen was mildly distended and there was a moderate amount of ascites present. She was tender in the right hypochondrium; there was no guarding or rebound tenderness. There were no palpable masses, and the liver and spleen were not enlarged. The remainder of the examination was normal. Her laboratory studies were significant for an elevated white blood cell count of 11, 700 per µL with 80 percent neutrophils, normocytic anemia with a hemoglobin of 9.0 g/dL, hematocrit was 27.7%, and platelet count was 306,000 per µL. Serum electrolytes



Figures 1–4. Contrast enhanced CT scan of the abdomen. Top (1,2): Images obtained in July 2003, soon after the patients symptoms initially developed, demonstrating multiple hypodense lesions in the right lobe of the liver and intrahepatic ductal dilatation. Bottom (3,4): Repeat CT scan performed in October 2003 after approximately 8 weeks of antibiotic therapy, shows complete resolution of these lesions.

were normal, as was her renal function. Alkaline phosphatase was significantly improved at 295 U/L, and the AST, ALT, and bilirubin had normalized.

At the time of admission, it was felt that she likely had an occult malignancy with liver metastasis, or possibly a hepatic abscess given her persistent constitutional symptoms. A Ceretec tagged WBC scan showed multiple cold foci within the liver but no evidence of abscess, and repeat paracentesis was non-diagnostic. CT guided FNA biopsy of the liver lesions was ultimately performed. Cytology was negative for malignant cells and was suggestive of a hepatic abscess with acute inflammation and foci of necrotic debris. Aggregates of gram-positive, filamentous, branching organisms which were non-acid-fast were demonstrated on histologic examination of the biopsy specimen, consis-

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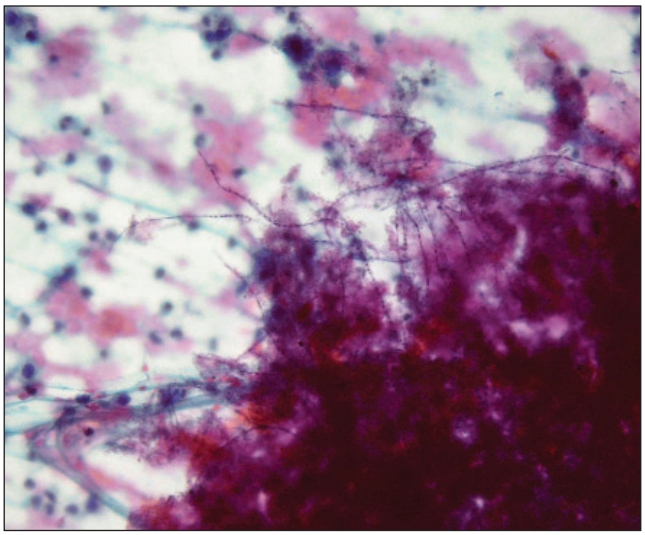

Figure 5. Papinaucola smear of biopsy specimen obtained from hepatic lesion by fine-needle aspiration. Histologic evaluation demonstrated granules containing aggregates of branching, filamentous, gram-positive organisms which were non-acid fast, consistent with Actinomycosis.

tent with *Actinomyces* (Figure 5), but there was inadequate specimen to send for culture. She was started on empiric broad-spectrum antibiotics due to persistent fevers and an increasing white blood cell count. Multiple cultures of urine, blood, and ascitic fluid were negative, and there was no evidence of pneumonia on chest radiograph. Due to concerns for an actinomycotic abscess, a repeat CT guided aspiration was performed to obtain specimen for culture. Anaerobic cultures, obtained after she received several days of antibiotics, failed to isolate a bacteriologic organism.

She denied any history of appendicitis, diverticulitis, pelvic infection, or use of a contraceptive intrauterine device. Upon reviewing her records from another institution in regards to her gallbladder surgery, it was discovered that she had a complicated biliary fistula in January 1999. She presented with abdominal pain, jaundice, and melena. Further evaluation revealed cholelithiasis and mild intra-hepatic ductal dilatation. She later developed hematemesis and was treated at another tertiary care center for an upper gastrointestinal bleed. The source of bleeding could not be identified on endoscopy and a celiac angiogram was performed which revealed a hepatic artery pseudoaneurysm with biliary fistula. She had multiple coil embolizations but developed recurrent hematemesis and hemobilia several weeks later. She ultimately underwent an open cholecystectomy and repair of the fistula. An intra-operative cholangiogram at that time demonstrated narrowing of the proximal common bile duct. The surgical pathology was consistent with chronic cholecystitis and adenomyoma.

She underwent repeat colonoscopy and upper endoscopy which failed to demonstrate a source for her hepatic abscess or primary focus of actinomycosis, and an exploratory laparotomy was subsequently performed. A large, fluctuant area was noted in the right lobe of the liver which was opened and thick, purulent material was drained. Firm, fibrotic tissue at the base of the abscess was biopsied. The peri-hepatic mass, located retroperitoneally and not emanating from the pancreas, contained multiple vascular coils. There were no sulfur granules identified grossly and permanent sections of the surgical specimens revealed fibrous connective tissue with acute and chronic inflammation, as well as fibrosis, consistent with the findings of a hepatic abscess. Smears and special stains were negative for bacteria, fungus, acid-fast organisms, and amoeba; aerobic and anaerobic cultures obtained from both the liver abscess and retroperitoneal mass were negative.

She was eventually discharged from our institution following a prolonged hospitalization with several post-operative complications including a pulmonary embolism and line-related sepsis. No extra-hepatic focus of infection could be identified despite extensive diagnostic procedures. We presume that her previous endoscopic interventions and biliary surgery were the inciting event that led to hepatic seeding and actinomycotic abscess formation. She was initially treated with Ceftriaxone and Flagyl for treatment of her hepatic abscess, and was discharged on Gatifloxacin and Flagyl. A follow-up CT scan (Figure 3, 4) after completing eight weeks of antibiotics showed complete resolution of the hepatic abscesses. Her antibiotics were discontinued after several months of therapy and she has done well since that time without any recurrent symptoms.

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DISCUSSION

Actinomyces are filamentous, anaerobic, gram-positive organisms which are part of the normal microflora of human and animal oral cavities, as well as the respiratory tract, appendix and cecum (3). *A israelii*, the most prevalent human pathogen, was first described in 1878 when Israel discovered granules obtained from a human autopsy that were similar to those seen in bovine "lumpy jaw" caused by *A bovis*. *A bovis* is not known to cause human disease, but other species including *A naeslundii, A odontolyticus, A viscosis, A meyeri,* and *A proprionica* have been identified in humans (3).

Host defenses typically prevent infection by *Actinomyces*, but disruption in mucosal barriers can lead to local invasion of organisms. Abdominal abscesses usually arise as a complication of infection or surgery, with appendicitis being present in 72% of cases of abdominal actinomycosis (4,5). Antecedent surgery including tooth extraction, appendectomy, cholecystectomy, or surgery for diverticulosis, trauma, or neoplasm predispose to infection in up to 45% of cases (6,7). Hepatic actinomycosis has also been diagnosed several years after surgical drainage of a pancreatic pseudocyst in a patient with chronic pancreatitis (8). Other predisposing factors include gastrointestinal perforation, presence of foreign bodies, or neoplasia (3).

Following the initial inoculation, a purulent focus is formed with surrounding inflammation. The involved tissue becomes hard and indurated, often forming draining fistulas that discharge characteristic sulfur granules (7,9). Infection spreads via direct extension without regards to tissue planes, or less commonly by hematogenous or lymphatic dissemination (7). In cases of hepatic actinomycosis, bacteria are presumably conveyed from a primary focus to the liver via the portal vein. The higher incidence of right lobe involvement may be secondary to the distribution of portal venous and hepatic blood flow (10). Sinus tracts can allow liver abscesses to extend to adjacent structures including the abdominal wall, diaphragm, retroperitoneum (6), or even the pleural space (4).

Cervico-facial disease is most common, followed by pulmonary, and abdominal or pelvic actinomycosis (6). In a large series of 181, there were only 51 cases of abdominal or pelvic actinomycosis, and only 9 patients had hepatic involvement (6). "Primary" hepatic actinomycosis, in which no other focus of infection can be identified, accounts for only 5% of all cases (1,4). Pelvic actinomycosis is increasing in prevalence and the theory behind its pathogenesis is evolving. Although previously thought to occur as a result of extension from the gastrointestinal tract, there is a clear association between pelvic actinomycosis and use of intrauterine devices (IUDs) in women. IUDs likely facilitate extension of *Actinomyces* from the vaginal mucosa to the adnexal structures, resulting in a spectrum of disease ranging from asymptomatic cervical colonization to tubo-ovarian actinomycotic abscesses (7). The presence of *Actinomyces* in cervicovaginal preparations correlates with the use of IUDs in 90% of patients (9).

Abdominal actinomycosis has been described following endoscopic therapy for pancreatico-biliary disorders, including two cases complicating pancreatic and biliary stent placement in patients with chronic pancreatitis (11). Pancreatic head masses and liver lesions suspicious for metastatic pancreatic carcinoma were identified radiographicly, which resolved with appropriate antibiotic therapy after identification of colonies of *Actinomyces*. They too proposed that endoscopic therapy may have permitted invasion by *Actinomyces* with subsequent extension to the liver via contiguous, biliary, or hematogenous dissemination (11). Brewer reported a case of actinomycosis of the gallbladder and liver that was analogous to ours, in that partial duodenal obstruction demonstrated on upper GI series was discovered at the time of surgery to be secondary to peri-hepatic inflammation (12).

Several reviews have identified epidemiologic data, as well as symptoms and physical findings relating to hepatic actinomycosis. As in other causes of hepatic abscesses, there is a male predominance (>70%), with most cases of actinomycosis occurring in the fourth or fifth decade, similar to the age distribution seen in other causes of pyogenic abscesses (10,13). The clinical course, however, is more indolent and the infection was primarily felt to be cryptogenic. The most common symptoms were fever, abdominal pain, anorexia and weight loss present in the majority of patients, and were present, on average, for one to six months prior to presentation (10). On physical examination, patients were universally febrile, 57% had

abdominal tenderness, while 40% had hepatomegaly (10). Laboratory findings of anemia, elevated ESR, leukocytosis, and an elevated alkaline phosphatase were present in >90% of cases, while fewer than one-third had elevated transaminases (10). Similar data has been reported elsewhere (13), including a review of 11 cases of hepatic actinomycosis in Japan (14).

The diagnosis of actinomycosis is based on the microscopic identification of characteristic sulfur granules or typical organisms, or recovery of *Actinomyces* in anaerobic culture. Sulfur granules, which are discrete aggregates of mycelial elements surrounded by distinct clubs of the gram-positive branching organisms (6), are not pathognomonic and are also seen in *Nocardia*, *Streptomyces*, and botryomycosis (*Staphylococcus*) (3). Inflammation and fibrosis in chronic abscesses may hinder the identification of such granules and multiple biopsy sections must be examined (6). Brown reports that 181 of 365 suspected cases at the Armed Forces Institute of Pathology were confirmed microscopically based on the presence of granules containing gram-positive branching bacilli; *Actinomyces* was isolated via culture in only 16 patients and sulfur granules were rarely identified grossly (6). Others also report that the diagnosis is usually accomplished microscopically and cultures were negative in more than one-third of patients (10,13).

In cases where bacteria where isolated, abscesses were often found to be polymicrobial. *A israelii* was the most common isolate (60%) (13), and mixed infections with other anaerobes, as well as aerobic gram positive cocci, gram negative rods, and yeast have been identified (6,10,13,15). Negative cultures were attributed to prior antibiotic use, improper specimen collection or handling, failure to culture specifically for anaerobes, or failure to culture for a sufficient amount of time (10). Culturing of multiple samples of purulent material in enriched media under strict anaerobic conditions with carbon dioxide, and an extended incubation period of five to 10 days is suggested to improve the diagnostic yield and successful isolation of *Actinomyces* (6). Direct inoculation of both aerobic and anaerobic culture bottles with aspirated pus or biopsy material at the bedside may also improve the sensitivity of cultures (14). Alternatively, immunofluorescence staining for common species of *Actinomyces* is available from the Center for Disease Control, and may prove to be a useful diagnostic tool (2). In tropical regions where amoebiasis is endemic, hepatic abscess are presumed to be amoebic and are treated empirically (16). Due to the similarity in presentation and appearance, hepatic actinomycosis can be extremely difficult to diagnosis. However, serologic tests for amoebiasis are highly specific; negative serologies or failure to respond to Metronidazole should raise concern for actinomycotic abscess and culture may be essential in establishing a diagnosis (10).

Historically, actinomycosis is frequently misdiagnosed due to the vague symptoms and its tendency to imitate other infectious or malignant processes. Hepatic actinomycosis is rarely suspected on clinical grounds and surgery can be beneficial in establishing a definitive diagnosis, especially when malignancy cannot be excluded (3). The advent of improved radiographic imaging modalities and advanced diagnostic techniques, however, has obviated the need for surgical exploration. Sulfur-colloid scans (17,18) and gallium scans (10) are useful in establishing an early clinical diagnosis. The most frequent radiographic finding using CT or ultrasound imaging is a single hypodense abscess or mass, which is often mistaken for a primary tumor or metastasis (13). Although the findings are nonspecific, imaging is very useful in the localization of abscesses for percutaneous needle aspiration (10). In cases of hepatic actinomycosis, percutaneous aspiration and drainage should be considered as both a diagnostic and therapeutic modality to possibly avoid exploratory surgery. Tissue can be examined histologically for the presence of characteristic organisms or sulfur granules and specimens can be obtained for staining and culture (19). In one report, percutaneous sampling was effective in establishing a diagnosis in 24 of 33 cases (72.7%), and was not inferior to surgery (13). Currently, the role of surgery in management of actinomycosis is not clear, but is probably beneficial as an adjunct to medical therapy for incision and drainage of abscesses, debridement of necrotic material, treatment of empyema, or removal of persistent sinus tracts (3,7).

Actinomyces are extremely sensitive to Penicillin and medical therapy is generally highly effective in eradicating the disease. Initial therapy should be given parenterally in high doses, followed by a prolonged course

of oral therapy to prevent recurrence (10). Penicillin G is recommended at a dose of 10 to 20 million units per day for four to six weeks, followed by oral Penicillin for up to 12 months (3). Tetracycline, Erythromycin, and Clindamycin are acceptable alternatives in patients with allergy to Penicillin (2). In cases of polymicrobial abscesses, antibiotic therapy should be tailored to ensure adequate coverage of any associated pathogens (13). The total duration of therapy is determined by the clinical, laboratory, and radiographic improvement.

The overall mortality has been reported between 8.8% (13) and 11% (10), and there is no significant survival advantage when comparing surgical treatment to medical therapy (13). Poor outcomes are most often attributed to delayed diagnosis or inadequate therapy.

CONCLUSION

Our case demonstrates a unique diagnostic dilemma, which is not atypical for primary hepatic actinomycosis. Given the clinical picture, the patient was initially presumed to have a malignant process with hepatic metastases, likely from a cholangiocarcinoma given the findings of focal hepatic duct stenosis, left intrahepatic ductal dilatation, jaundice and ascites. Only after multiple biopsies were negative for malignancy, and an aspirated specimen demonstrated micro-organisms consistent with *Actinomyces*, was the diagnosis of hepatic abscess considered. The clinical signs and symptoms are nonspecific and could also occur with malignancy. Surgery was probably not necessary in this case, but exploratory laparotomy was performed due to our concerns for an occult malignancy. Aside from the liver abscess, no other focus of *Actinomyces* could be identified, and is therefore considered a rare case of primary hepatic actinomycosis. Failure to isolate the organism on multiple cultures was likely due to a delay in obtaining a specimen for culture, and also the concurrent administration of empiric antibiotics due to signs of infection and systemic inflammatory response. We presume that her previous surgery, endoscopic therapy, and embolization procedures allowed a portal of entry for the bacteria leading to indolent abscess formation. Following a prolonged course of antibiotic therapy, subsequent imaging, including a recent CT scan, demonstrated no recurrent abscess formation. ■

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