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CASE REPORT

Primary hepatic actinomycosis mimicking a tumor (inflammatory pseudotumor): Case report and literature review

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ABSTRACT

Actinomycosis often manifests with abscesses in the cervicofacial region. Hepatic involvement occurs usually secondary to an intraabdominal infection. "Isolated or primary hepatic actinomycosis (PHA) defines actinomycosis in which the source of infection cannot be demonstrated elsewhere. Herein, we aimed to highlight hepatic actinomycosis in the differential diagnosis of hepatic mass lesions, and also its occurrence even in patients without underlying risk factors. A 24-year-old man, who presented with epigastric and right-upper-quadrant abdominal pain, fever, weight loss, and had a tumor-like mass in the liver was admitted to our hospital. He had no predisposing risk factors or comorbidities. We reviewed all the cases with PHA, who had no predisposing risk factors, in English medical literature from 1993 to 2014. Actinomycotic hepatic pseudotumors should be considered in the differential diagnosis of solitary liver lesions even in patients without any predisposing factors. Multi-disciplinary approach is important in the diagnosis and management. *J Microbiol Infect Dis 2015;5(2): 79-84*

Key words: Actinomycosis, *Actinomyces spp*, inflammatory pseudotumor, liver

Tümörü taklit eden primer hepatik aktinomikoz (Inflamatuar Psödotümör): Olgu sunumu ve literatür derlemesi

ÖZET

Aktinomikoz genellikle servikofasiyal bölgede abseler şeklinde ortaya çıkar. Karaciğer tutulumu çoğunlukla batın içi enfeksiyonlara ikincil olarak gelişir. "İzole veya Primer Hepatik Aktinomikoz (PHA)" başka bir enfeksiyon odağının gösterilemediği karaciğer yerleşimli aktinomikozu tanımlar. Burada, hepatik aktinomikozun karaciğerde saptanan kitle lezyonlarının ayırıcı tanısında yer alması gerektiğini ve risk faktörü olmayan hastalarda da gelişebileceğini vurgulamayı amaçladık. Epigastrik hassasiyet, sağ üst kadran ağrısı, ateş, kilo kaybı yakınmalarıyla başvuran 24 yaşında erkek hasta, görüntülemede karaciğerde tümör-benzeri kitle saptanması nedeniyle hastanemize yatırıldı. Hastanın, Aktinomikoz için herhangi bir risk faktörü veya eşlik eden hastalığı yoktu. İngilizce tıp literatüründeki 1993-2014 yılları arasındaki tüm benzer PHA olgularını derledik. Aktinomikotik karaciğer psödotümörleri, hiçbir risk faktörü veya ek hastalığı olmayan hastalarda bile soliter karaciğer lezyonlarının ayırıcı tanısında hatırlanmalıdır. Tanı ve tedavide multidisipliner yaklaşım çok önemlidir.

Anahtar kelimeler: Actinomycosis, *Actinomyces spp*, inflamatuvar psödotümör, karaciğer

INTRODUCTION

Actinomyces spp are Gram positive, anaerobic and filamentous bacilli, and are commensals of the oral cavity, gastrointestinal and genital tract. Actinomycosis is a chronic, slowly progressive, suppurative and granulomatous disease caused by Actinomyces israelii.[1,2] It has been called "the most misdiagnosed disease" and the diagnosis may be missed even by

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experienced clinicians. Although its incidence has been diminishing, it is so often confused with a tumor.[3] Infection occurs through mucosal disruption and invasion. Although most patients manifest with abscesses in the cervicofacial region, cases of thoracic, abdominal, pelvic and central nervous system actinomycosis have also been reported. The ileocecal region is the most frequently involved region in the abdomen.[4,5] Hepatic actinomycosis is a rare disease with an overall mortality rate of 7.6%.[6] The symptoms and signs are similar to other pyogenic liver abscesses, but the course is more indolent in actinomycosis.[7] Hepatic involvement which occurs usually secondary to intraabdominal infection has been reported in 15% of abdominal disease and in 5% of all cases of actinomycosis.[8] If the source of the infection cannot be demonstrated, these cases are classified as isolated or primary hepatic actinomycosis (PHA).[7,9] Sometimes hepatic lesions may mimic malignant lesions both clinically and radiologically and those lesions are referred as "inflammatory pseudo-tumor".[7,8,10] In majority of the previously reported cases with actinomycosis, there is at least one predisposing condition or comorbidity. However, our patient was a young immunocompetent adult with no underlying risk factors or diseases. Therefore, by describing this case and reviewing similar cases, we aimed to highlight hepatic actinomycosis in the differential diagnosis of hepatic mass lesions, and also its occurrence even in patients without underlying risk factors or predisposition, in addition, to point out the importance of a multi-disciplinary approach in the differential diagnosis and management. Written informed consent for presentation of this case has been obtained from our patient.

CASE REPORT

A 25-year-old previously healthy man presented to our hospital because of anorexia, weight loss, abdominal distension, right upper quadrant abdominal pain and fever of a year's duration. Medical history was unremarkable. On examination, tenderness on the right upper quadrant of the abdomen of the patient and hepatomegaly (8 cm under the costal margin) were noted on palpation. He had no dental carries or signs of periodontitis. Laboratory tests revealed elevated erythrocyte sedimentation rate (84 mm/h, normal 0-12 mm/h), C-reactive protein level (CRP) (122 mg/L, normal 0-3 mg/L), and anemia (hemoglobin 8.9 mg/dl, hematocrit 29%, normal 12-16 mg/dl, 42-52%, respectively). Liver transaminases were within normal limits. Abdominal ultrasound (US) revealed a hypoechoic mass 91x71mm in diameter with irregular borders in the left lobe of liver. On computed tomography (CT) scan, an isodense [denoting a tissue having a radiopacity (radiodensity) similar to that of another or adjacent tissue] lesion 85x75 mm in diameter with a thick and irregular capsule, and invasion of the overlying ribs which had no contrast enhancement (Figure 1) was visualized. Tumor markers [Carcinoembryonic antigen (CEA), carbohydrate antigen (CA)19-9, CA 12-5, CA 15-3, alpha fetoprotein] were normal. Serologic tests for Hepatitis B and C viruses, Human immunodeficiency virus (HIV), Cytomegalovirus, Herpes Simplex Virus, *Echinococcus granulosus* and *Entamoeba histolytica* were all negative. Indirect hemagglutination test for hydatid cyst was also negative.

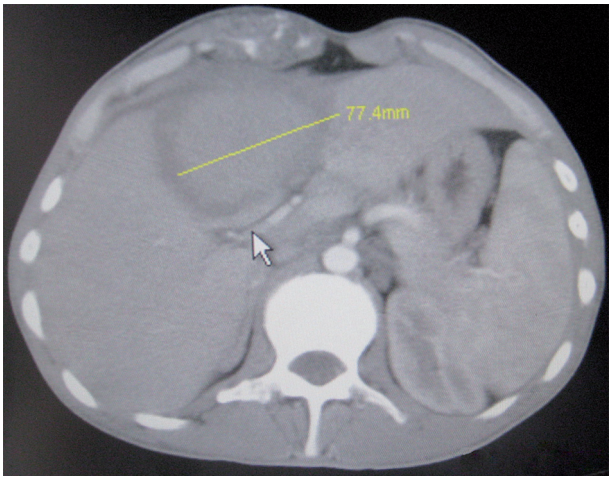

Figure 1. Computerized tomography image of the abdomen: An isodense lesion 85x75 mm in diameter with a thick and irregular capsule, and invasion of the overlying ribs which had no contrast enhancement

Intravenous ceftriaxone 2x1 g (1 gram every 12 h) and metronidazole 4x500 mg (500 milligrams every 6 h) were initiated empirically. Blood and urine cultures were negative, however fever continued for 10 days after the initiation of antibiotic treatment. The patient underwent exploratory laparotomy which revealed a tumor-like mass (10x10 cm in diameter in liver segment 4, 5 and 6) infiltrating the duodenum, colon and the abdominal wall. Histopathologic examination of the core biopsy frozen section demonstrated degeneration in parenchymal cells, mild to moderate inflammatory cell infiltration in portal areas (Figure 2a, 2b, 2c).

Bacterial cultures remained sterile, possibly because of fastidious nature of growth and prior antibiotic therapy. Microscopic examination of PAS,

Giemsa and Grocott's methenamine silver stained specimens revealed aggregates of branching filamentous microorganisms termed "sulfur granules" forming a granular structure in focal microabscesses (Figure 2a, 2b, 2c). These findings were compatible with actinomycosis which caused an inflammatory pseudotumor. Examination of the oral cavity, panoramic dental X-ray, upper and lower gastrointestinal endoscopy, colonoscopy, abdominal US, thoracic and abdominal CT scans failed to demonstrate any other likely focus of infection or site of origin. Therefore, it was considered as a PHA. Ampicillin-sulbactam 4x1.5 g (1,5 grams every 6 h) iv for 2 weeks and then amoxicillin-clavulonate 2x1 g po for the next 10 weeks were administered. A control abdominal USG of the patient after 12 weeks showed complete resolution of the previous hepatic lesion.

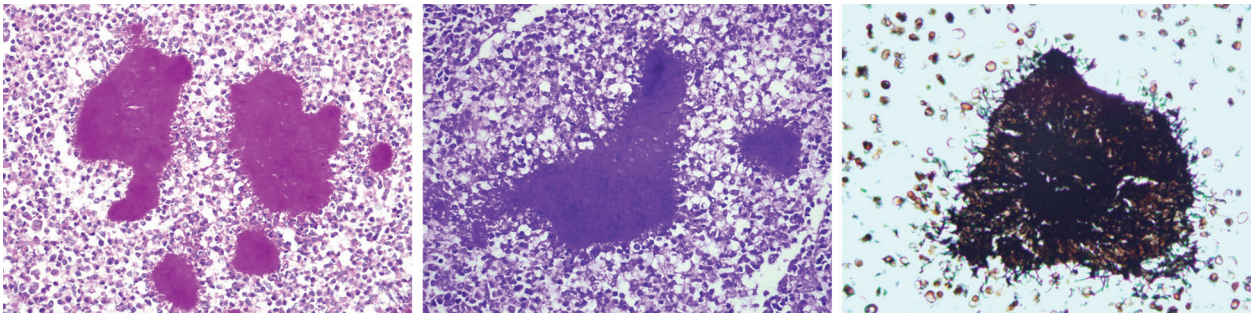

Figure 2a, 2b, 2c. Microscopic examination of PAS (2a), Giemsa (2b) and GROCOTT (2c) stained specimens revealed aggregates of branching filamentous microorganisms termed "sulfur granules" forming a granular structure in focal microabscesses. Inflammatory reaction and fibrosis with polymorphonuclear cells, lymphoplasmocytes, and histiocytes were visualized.

DISCUSSION

Actinomyces spp cause opportunistic infections more commonly. The anatomical distribution is 60% cervicofacial, 15% thoracic, 20% abdominal, and 5% other sites.[11] *Actinomyces spp* produces proteolytic enzymes and can spread by direct invasion and extension without regard to tissue planes.[12,13] Spread to the liver occurs via direct extension from a contiguous abdominal focus or hematogenously from a distant lesion via portal vein or hepatic artery. Hepatic lesions occasionally infiltrate the diaphragm and are complicated by pleural and lung lesions, can form cutaneous fistula and sinus tracts, and extend to the abdominal and pelvic organs.[11] The tumor-like lesion in our case infiltrated to the abdominal wall and was attached to the colon and duodenum.

Hepatic actinomycosis usually occurs in males (70-97% of cases) in the fourth and fifth decades.[6,9,14] Risk factors include poor oral hygiene, previous dental procedures, perforated peptic ulcer, colonic diverticulitis, abdominal or pelvic surgery, abdominal wall trauma, gastrointestinal foreign body or lesions, gallstones, immunosupression, diabetes mellitus, inflamatory bowel disease such as ulcerative colitis, alcoholism, intravenous drug abuse, long-standing intra-uterine device in females.[6,9,11,15,16] The most common predisposing event has been reported to be appendicitis.[17] Our patient had no underlying risk factors. He had no history of blunt abdominal trauma or surgery. Also, no underlying cause of immunosuppression was detected. CD4, CD8 counts, serum IgG, IgA, IgM levels were normal. We reviewed the English language literature (pubmed, google scholar) for similar PHA cases with no underling risk factors or predisposition from 1993 to September 2014. We excluded the cases with comorbidity or predisposing risk factors for actinomycosis. We summarized the demographic, clinical, diagnostic and therapeutic features of the reviewed similar cases in Table 1.[1,2,6,9-17]

In patients with hepatic actinomycosis, the presenting symptoms are often nonspecific. Fever, abdominal pain, and weight loss are common presenting complaints, with a subacute onset and a prolonged course.[8,9,18] Symptoms are usually present for 1-6 months prior to the patient's presentation.[9] Although most reported cases of hepatic actinomycosis had abnormal liver function tests, transaminases may be within normal limits and therefore misleading.[8] Laboratory examination often demonstrates a leukocytosis (75%) with a shift to the left and elevation of alkaline phosphatase (83,3%).[15] The CRP level also could be above normal.[6,16]

Table 1. The demographic, clinical, diagnostic and therapeutic features of the reviewed cases with primary hepatic actinomycosis

Refe-rence No.	Age/gender	Risk factors/ Predisposition/ Comorbidity	Symptoms, (duration)	Radiological features- Localization	Microbiologic Findings	Means of Diagnosis	Treatment	Treatment duration and Prognosis / Outcome	Coexistent infection/ ekstrahepatic complication
Ref. 2	75% M, (40-60 yrs old)	23/36 cases cryptogenic	Fever, pain, anorexia, weight loss, (1-6 mo)	Right lobe involved > 4 times more frequently	Actinomycosis recovered in 17/36 (47%) cases	Laparotomy in 25/36 (69%)	Open surgical drainage/hepatic lobectomy in 13, percutaneous drainage in 6	1/23 (0,04%) mortality	none
Ref. 9	4-year-old boy	US, small Intestine X-ray, colonoscopy normal	3 mo	Right lung, diaphragm, and right hepatic lobe.	Branching filaments with pseudohyphae *A.israeli, B.fragilis, Fusobacterium spirilli*	US, CT	Hepatic mass partially resected, Penicillin G, chloramphenicol, metronidazole for 2 mo, Penicillin V for 6 mo	well	none
Ref. 10	41, M		right back pain and cough	CT and MRI: 5x10 cm tumor in the anterior superior segment of liver, extending to diaphragm and right lung.	sulfur granules, Gram stain and Grocott stain positive and Ziehl-Neelsen stain negative		hepatectomy with partial resections of diaphragm and right pulmonary lobe	no recurrence at 1 yr postoperatively	Right lung
Ref. 11	86, M	3 d, no Predisposing factors in most cases		Partial hepatectomy in 6/11 (hepatic tumor suspected). Liver abscess in 5/11.	*Actinomyces spp* cultured from aspirated pus		Percutaneous drainage, long-term intravenous high-dose minocycline and piperacillin	satisfactory	Complicated by DIC
Ref. 12	34, M and 56 Additional cases (4-86 y), (70.2% male)	36/57 (80.7%) cryptogenic		single hypodense mass/abscess (68.4%)	(35.2%) mixed usually with anaerobic bacteria	culture negative (33%) surgical 29/35 (83%) or percutaneous 24/33 (73%) diagnosis		Mortality 9%, with medical therapy alone and 4% with medical and surgical therapy	none
Ref. 13	53, M	Immune-competent		hepatic tumour mass on abdominal sonography and computerized tomography		exploratory laparotomy, right posterior segmentectomy			none
Ref. 14	11, F	none	pain, distension, anorexia, weight loss, firm-painful mass in liver (4 wk)	US and CT: a 4.5x7.5 cm mass in liver	percutaneous liver biopsy unrevealing. Sulfur granules in drained fistula material between liver and skin, Actinomyces spp. isolated	US-guided aspirati, US-guided Percutaneous liver biopsy	Intravenous penicillin G for 1 mo, then po amoxicillin		Fistulization through abdominal wall and spontaneous draining from skin (Cutaneous fistula)

Refe-rence No.	Age/gender	Risk factors/ Predisposition/ Comorbidity	Symptoms, (duration)	Radiological features- Localization	Microbiologic Findings	Means of Diagnosis	Treatment	Treatment duration and Prognosis / Outcome	Coexistent infection/ ekstrahepatic complication
Ref. 6	40, F	none	8 mo	US: 2 subcapsular hypoechoic heterogeneous lesions in right liver lobe. CT: 2 hypodense subcapsular lesions with thick walls enhanced in postcontrast series in right liver lobe	chronic inflammation, abscess formation containing actinomyces colonies	Laparotomy and biopsy	6-wk parenteral penicillin G and, following 6-mo oral amoxicillin.	good	Massive pleural effusion, atelectasia. Right pulmonary empyema
Ref. 15	50, F	Immune-competent	dyspnea, significant weight loss and intermittent fever (2 mo)	Abdominal US and CT: metastatic liver disease? Pleural and pericardial effusion		histological examination	Prolonged treatment with high dose penicillin	Complete resolution, control US normal	none
Ref. 1	67 cases, Predominantly M	(50/67) 75% cryptogenic		right lobe in half, mimicked a liver tumor in 45%, single in 2/3	coexisted with infections by common bacteria in 32%	examination of surgical (84%) or percutaneous (79%) specimens	Antibiotic therapy alone in 50% combined antibiotic treatment with surgical or percutaneous drainage in 50%	Mortality rate: 7.6%.	none
Ref. 16	40, M	none	abdominal pain, weight loss (1 mo)	CT: hypodense cystic lesions in right and left lobe. US and CT: cystic lesions with necrotic debris in right and left lobe	actinomycotic colonies with a surrounding suppurative granulomatous reaction	Laparotomy and biopsy	Surgical debridement and drainage surgery iv penicillin G, po penicillin V	4 wk iv + 2 mo po	None
Ref. 17	37, M	Immune-competent	intermittent fever and upper left abdominal pain (2 mo)	US: heterogeneous abscess with a hypoechoic center and honeycomb enlarged spleen. CT: ill-defined hypodense lesion in spleen. MRI: multiloculated splenic lesion, laparotomy showed multiple liver nodular lesions and a splenic abscess.	filamentous branching bacilli, sulfur granules within H&E stained necrotic foci. Grocott methenamine silver nitrate staining splenic and hepatic actinomycosis	Explaratory laparotomy, histopatholo-gically	splenectomy and ceftriaxone for 6 days + penicillin for 1 mo iv and oral for 3 mo	Control Abdominal MRI after 4 mo: complete resolution, patient asymptomatic for 2 years	Splenic involvement

M: male, F: female, CT: computerized tomography, MRI: magnetic resonance imaging, US: ultrasound, DIC: disseminated intravascular coagulation, mo: month/-s, wk: week/-s, H&E: hematoxylin and eosin, iv: intravenously, po: per oral.

A single hypodense mass, as in our case, is the most common radiological finding (observed in 2/3 of the cases), but it may also cause multiple lesions.[16,18] Lesions were most often described as single or multiple abscesses and soft central loculations containing white or yellow pus. As the differential diagnosis from malignant lesions could not be made with radiologic studies[7], actinomycosis is often misdiagnosed as primary or metastatic liver tumor.[6,15] Hepatic lesions mimicking malignant lesions both radiologically and clinically are called "inflammatory pseudo-tumor". Right liver lobe is four times more frequently affected then the left lobe.[13] Infectious diseases in the differential diagnosis include pyogenic liver abscesses, amebiasis and echinococcosis.

Because of its fastidious nature, it is difficult to cultivate the microorganism and it may take up to two weeks to grow in culture media. Blood cultures grew the bacteria in 15.4% of the cases. In 82.9% of the patients, diagnostic specimen was obtained by surgical intervention.[18] Gram staining and microscopy can reveal yellow clusters of filaments surrounded by neutrophils, known as "sulfur granules". Definitive diagnosis is based upon microscopic visualization of typical 'sulfur granules' (microcolonies of the organism) or recovery of Actinomyces organisms in anaerobic culture. The diagnosis also may be suggested by visualization of organisms with the characteristic branched, gram-positive, filamentous, and often beaded morphology.[9,13] Nocardia species are indistinguishable from Actinomyces organisms by Gram stain but can be excluded by staining specimens with a modified acid-fast protocol.[9] Besides histopathological appearance, positive Gram staining and presence of sulfur granules were other findings in diagnosis of actinomycosis.

The treatment of isolated hepatic actinomycosis is managed by antibiotic treatment only in one half of the cases, surgical excision or percutaneous drainage in addition to antibiotic therapy may be necessary in the other half.[6,9] Actinomycosis species are generally susceptible to penicillin G and amoxicillin but resistant to ciprofloxacin.[11] Tetracycline, erythromycin, doxycycline, clindamycin, rifampicin, chloramphenicol, ceftriaxone and imipenem are alternative agents for antimicrobial therapy.[6,18] Combined surgical excision /drainage and 12 weeks of antimicrobial therapy resulted in the recovery of the patient.

CONCLUSION

PHA is a rare disease among solitary liver masses and can mimick malignant tumors clinically and radiologically. Therefore, it should be considered in the differential diagnosis of space-occupying solitary liver lesions even in patients with no predisposing risk factor. Multi-disciplinary collaboration is important in the diagnosis and management.

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