A 60-Year Literature Review on Hepatic Actinomycosis

Sofia Maraki^a Viktoria Eirini Mavromanolaki^b Dimitra Stafylaki^a
Eliza Anagnostopoulou^c Panagiotis Moraitis^a Anna Kasimati^a Boris Treptow^c

^aDepartment of Clinical Microbiology and Microbial Pathogenesis, University Hospital of Heraklion, Heraklion, Greece; ^bUniversity of Crete Medical School, Heraklion, Greece; ^cDepartment of Surgical Oncology, University Hospital of Heraklion, Heraklion, Greece

Highlights of the Study

- Hepatic actinomycosis (HA) is a rare intra-abdominal infection accounting for 15% of cases of actinomycoses.
- HA is usually cryptogenic and is more common among males and in immunocompetent individuals.
- Diagnosis of HA is often difficult because of its indolent course and nonspecific clinical presentation and imaging findings.
- Treatment options include antimicrobial agents, drainage of the abscess, and surgical resection of the necrotic tissue.

Keywords

Hepatic actinomycosis · Liver abscess

Abstract

Hepatic actinomycosis (HA) is a rare infection with an indolent course, atypical clinical manifestations, nonspecific laboratory and imaging findings, and challenging diagnosis. We describe a case of a 35-year-old female who developed HA 2 weeks after gastrectomy. In addition, we analyzed clinical characteristics and outcome of 157 additional cases of HA identified in a 60-year literature review. Patients with HA were predominantly male (57%) and more than one-half were between 40 and 70 years of age. The infection was cryptogenic in 80.8% of cases. Risk factors for HA were identified in 63.1% of the patients. Clinical presentation included fever (57.7%), abdominal pain (52.1%), weight loss (45.1%), anorexia (27.5%), fatigue and chills (12.7% each), and malaise (12%) over a 2.35

± 3.5 months period. Leukocytosis, elevated alkaline phosphatase, erythrocyte sedimentation rate, and C-reactive protein were the most frequent laboratory findings. Radiologic imaging revealed that the right lobe was more frequently affected (62.5%) with a single lesion found in two-thirds of cases. Diagnosis was achieved by histopathologic examination in 70.6% of cases. Cultures yielded *Actinomyces* in 45 instances, with *A. israelii* being the most frequent species. Less than one-half of the patients were treated only with antibiotics, while the others received combined medical and surgical treatment. The median duration of antibiotic therapy was 135 days. The presence of multiple lesions or solid tumor-like lesions (without liquefaction) was significantly associated with medical therapy alone. The outcome was favorable in most cases (94%). Although rarely encountered, HA should be considered in patients with a chronic or subacute inflammatory process of the liver to promptly diagnose and treat.

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Introduction

Actinomycosis is a chronic suppurative, granulomatous infection caused by non spore-forming, filamentous, anaerobic Gram-positive bacteria of the genus *Actinomyces*. These microorganisms are part of the commensal flora of the oropharynx and the gastrointestinal and the female genital tract. Disruption of the mucosa may lead to infection. Among pathogenic species, *Actinomyces israelii* predominates in human infections [1]. Cervicofacial, thoracic, and abdominal actinomycoses are the most frequent clinical forms of the infection in humans. Liver involvement is rare accounting for 15% of the cases of abdominal actinomycosis. The diagnosis of hepatic actinomycosis (HA) is difficult and is often delayed because of its indolent course and the nonspecific clinical and radiological findings [1, 2]. The preoperative rate of diagnosis is less than 10% [3]. Regarding actinomycosis, Cope [4] states that there is “no disease which is so often missed by expert clinicians.” A case of HA in a patient who had undergone gastrectomy is presented here, with a review of all reported cases over the last 60 years.

Case Report

A 35-year-old woman was admitted to the General Hospital of Rethymno, Greece, with a 5-day history of fever up to 38.3°C, chills, and diarrhea. She had a history of a laparoscopic sleeve gastrectomy 2 weeks earlier.

CT scan of the chest and abdomen revealed a hypodense cystic lesion of 10 × 5.5 cm on the right lobe of the liver suggestive of pyogenic abscess and a small amount of right pleural effusion. The patient was started on piperacillin-tazobactam (4.5 g every 8 h i.v.) and metronidazole (500 mg every 8 h i.v.) and was transferred to the University Hospital of Heraklion. On admission, laboratory tests showed a leukocytosis of $16.1 \times 10^9/L$ (neutrophils 83%), mild anemia (hemoglobin 10.0 g/dL), elevated gamma-glutamyltransferase level (66 IU/L; normal: <38 IU/L), and elevated C-reactive protein level of 13.29 mg/dL (normal: <0.5 mg/dL). The rest of the tests were normal. On the same day, the patient underwent ultrasound-guided therapeutic and diagnostic aspiration of the liver abscess (Fig. 1). Pus from the abscess cavity was drained through a pigtail catheter, and the pus was sent for microbiological analysis. Gram stain revealed Gram-positive branching filamentous rods consistent with *Actinomyces* species. Anaerobic cultures yielded pure growth of *Actinomyces odontolyticus* that was identified using Vitek 2. Identification was further confirmed by matrix-assisted laser desorption/ionization time of flight mass spectrometry (MALDI-TOF MS), as well as by 16S rRNA gene sequencing analysis. Antimicrobial susceptibility testing was performed by the Etest method, and the results were interpreted according to the Clinical and Laboratory Standards Institute (CLSI) guidelines. The organism was susceptible to penicillin, ampicillin, amoxicillin/clavulanate, piperacillin/tazobactam, cefoxitin, imipenem, meropen-

Fig. 1. Coronal contrast-enhanced CT image demonstrating the hepatic lesion in the right lobe with a drainage catheter in place (arrow).

nem, moxifloxacin, tigecycline, tetracycline, chloramphenicol, and vancomycin and resistant to metronidazole and clindamycin. Once antimicrobial susceptibilities were available, the antibiotics were switched to cefoxitin (1 g every 6 h). The amount of drainage from the pigtail decreased over the following days, and the catheter was removed after 31 days of use. Follow-up abdominal sonography on days 6 and 11 after pus drainage showed progressive shrinkage of the abscess with sizes of 5.7 × 4.9 cm and 4.7 × 2.4 cm. After discharge, amoxicillin-clavulanic acid (1 g every 12 h) was prescribed. A follow-up abdominal CT performed 8 months after discharge showed the complete resolution of the infection.

Review of the Literature

We conducted a search (using the PubMed/MEDLINE, Scopus, and ScienceDirect databases) of the medical literature from January 1960 to July 2021, using the following keywords “Hepatic actinomycosis,” OR “liver actinomycosis.” We also included additional cases identified in the references of the cited papers. Articles written in English, Spanish, French, and German were included. We found 157 additional cases, and the following variables were recorded: patients’ demographics, comorbidities, clinical symptoms, radiological characteristics, laboratory findings, causative agent and co-pathogens, method of diagnosis, treatment, and outcome. Percentages were calculated based on the actual number of patients with available data.

Three-quarters of the cases of HA have been reported in the last 30 years. Table 1 summarizes the patients’ demographics and their comorbidities. Ninety patients

Table 1. Characteristics of the 158 patients with hepatic actinomycosis

Age (mean $\pm$ SD)	49.3 $\pm$ 18.1	Range, 4–88
Gender (M/F)	90/68	57%/43%
Comorbidities	99 ^a	63.1%
Remote abdominal/pelvic surgery	32	32.3%
Diabetes mellitus	20	20.2%
Alcohol abuse	14	14.1%
Dental caries/abscesses	13	13.1%
IUCD	11	11.1%
Viral hepatitis	5	5.1%
Chololithiasis/cholangitis	4	4.0%
Illicit drugs	3	3.0%
End-stage renal disease-in hemodialysis	2	2.0%
Miscellaneous [#]	12	12.1%

^a Most of the patients had more than one comorbidities. [#] Miscellaneous: chronic pancreatitis ($n = 2$), hepatic insufficiency ($n = 1$), squamous cell carcinoma of the throat ($n = 1$), rectal adenocarcinoma ($n = 1$), sigmoid colon neoplasm ($n = 1$), corticosteroid treatment ($n = 4$), and immunosuppressive medication ($n = 2$).

(57%) were males and 68 (43%) were females. The mean age of patients with HA was 49 ± 18.6 years (range, 4–88 years). Among the 158 HA patients, only 8 were pediatric cases [5–12]. The disease had a worldwide distribution with most cases being reported in Asian countries (36.7%). European and North American countries ranked second and third with 28.5% and 27.8% of cases, respectively.

Predisposing factors for HA were identified in 99 patients (63.1%). Most patients had more than one comorbidity. In particular, remote surgical abdominal or pelvic procedures were described in 32.3% of patients [3, 13–41]. Recent abdominal or pelvic surgery (≤ 1 year) was reported in 25 cases including intrauterine contraceptive device (IUCD) removal ($n = 12$) [42–53], appendectomy ($n = 3$) [54–56], gastrectomy ($n = 2$) [57, present case], cholecystectomy ($n = 3$) [34, 37, 58], total pancreatectomy [59], stenting bile and pancreas ($n = 2$) [29, 60], perforated peptic ulcer ($n = 1$) [61], and drainage of a rectal abscess ($n = 1$) [62]. Other predisposing conditions included diabetes mellitus, alcohol abuse, dental caries or abscesses, the use of IUCD, viral hepatitis, chololithiasis and cholangitis, the use of illicit drugs, and end-stage renal disease-in hemodialysis. Most patients (94.9%) were immunocompetent. Only 8 patients had underlying immunosuppressive conditions, including hemodialysis ($n = 2$) [21, 63], on corticosteroids ($n = 4$) [17, 64–66], or other immunosuppressive drugs ($n = 2$) (tacrolimus, hydroxychloroquine) [3, 40]. The infection was cryptogenic and considered as primary in 80.8% of the patients, while in 19 (12.2%), 10 (6.4%), and 1 (0.6%) was secondary to pelvic, abdominal, and pulmonary actinomycosis, respectively.

Table 2. Radiological and anatomic characteristics of hepatic actinomycosis

Characteristic (patients, n)	N (%)
Type of lesion (139)	
Cystic/abscess-like	78 (56.1)
Solid/tumor-like	61 (43.9)
Lesions, n (152)	
Single	102 (67.1)
Multiple	50 (32.9)
Location (152)	
Right lobe	95 (62.5)
Left lobe	32 (21.1)
Both	25 (16.4)

Fever was the most frequent presenting symptom in 82/142 cases (57.7%). The mean $\pm$ SD temperature was $38.6^\circ\text{C} \pm 1.03^\circ\text{C}$ (range; 36.5°C – 41°C). Other symptoms were abdominal pain in 52.1% of the patients, weight loss in 45.1%, anorexia in 27.5%, chills in 12.7%, fatigue in 12.7%, malaise in 12%, night sweats in 10.6%, vomiting in 7.7%, nausea in 4.9%, diarrhea in 4.2%, headache in 2.8%, and myalgias in 1.4% of them. The onset of symptoms was mainly subacute, with a mean $\pm$ SD duration of symptoms of 2.35 ± 3.5 months (range, 4 days–2 years). Acute presentation of symptoms (≤ 2 weeks duration) was observed in only 31 cases (24.6%) [6, 11, 22, 23, 27, 28, 31, 41, 47, 65, 67–85, and the present case].

Findings on physical examination included right upper quadrant tenderness in 49/100 cases (49%), fever in 36/100 cases (36%), hepatomegaly in 30/100 cases (30%),

Table 3. Diagnosis of hepatic actinomycosis

Technique-diagnostic method	Cases, n (%)
Surgical drainage	13 (8.4)
Histopathology	11 (7.1)
Culture	2 (1.3)
Percutaneous drainage	41 (26.5)
Histopathology	12 (7.8)
Culture	25 (16.8)
Culture + blood culture	3 (1.9)
Surgical biopsy	34 (21.9)
Histopathology	26 (16.8)
Culture	7 (4.5)
PCR	1 (0.6)
Surgical resection	26 (16.8)
Histopathology	23 (14.9)
Culture	3 (1.9)
Percutaneous biopsy	34 (21.9)
Histopathology	33 (21.3)
Culture	1 (0.6)
Blood culture	3 (1.9)
Autopsy	4 (2.6)

an abdominal mass in 22/100 cases (22%), cachexia in 7/100 (7%), dental caries/periodontal disease in 7/100 cases (7%), and jaundice in 6/100 (6%). Laboratory tests revealed leukocytosis with a left shift in 85.3% of cases. The mean $\pm$ SD leukocyte count was $16.9 \pm 7.5 \times 10^9/L$ (range $5.0\text{--}47.0 \times 10^9/L$). Elevated erythrocyte sedimentation rate and C-reactive protein levels were found in all reported cases (31 and 42 cases, respectively). Elevated alkaline phosphatase was found in 79.4% of cases. Aspartate aminotransferase was reported in 61 cases and was found elevated in 15 cases and slightly elevated in 4. Alanine aminotransferase was reported in 63 cases and was found elevated in 12 cases and slightly elevated in 7. Elevated bilirubin or jaundice was found in 11 cases of the 37 reported [11, 28, 38, 43, 62, 69–73, 86].

Diagnostic radiologic imaging was performed by abdominal ultrasound and CT scan, while magnetic resonance imaging was performed in a small number of cases. The type of lesions included cystic/abscess-like appearance in almost two-thirds of cases, and in the rest, imaging demonstrated a mass, frequently misdiagnosed as primary or metastatic liver cancer. A single lesion was found in 67.1% of patients, and the right lobe was the most commonly affected (62.5%) (Table 2). The infection extended to the surrounding tissues in 78 cases: diaphragm ($n = 20$), abdominal wall ($n = 19$), lung ($n = 17$), pleura ($n = 8$), colon ($n = 5$), stomach ($n = 3$), gallbladder ($n = 2$), pancreas ($n = 2$), and kidney ($n = 2$).

Table 4. *Actinomyces* species isolated and co-isolates in mixed infections

Microorganisms	n (%)
<i>Actinomyces</i> species ($n = 32$)	
<i>A. israelii</i>	17 (53.2)
<i>A. meyeri</i>	4 (12.5)
<i>A. odontolyticus</i>	4 (12.5)
<i>A. naeslundii</i>	4 (12.5)
<i>A. turicensis</i>	1 (3.1)
<i>A. cardiffensis</i>	1 (3.1)
<i>A. bovis</i>	1 (3.1)
Anaerobes ($n = 21$)	
<i>Fusobacterium</i> spp.	7 (33.3)
<i>Bacteroides</i> spp.	4 (19)
<i>Prevotella oris</i>	1 (4.8)
<i>Peptostreptococcus</i> spp.	3 (14.3)
<i>Eubacterium lentum</i>	1 (4.8)
<i>Propionibacterium acnes</i>	1 (4.8)
Mixed anaerobic flora	4 (19)
Aerobic Gram-negative bacilli ($n = 9$)	
<i>Pseudomonas aeruginosa</i>	2 (22.2)
<i>Proteus mirabilis</i>	1 (11.1)
<i>E. coli</i>	1 (11.1)
<i>Klebsiella pneumoniae</i>	1 (11.1)
<i>Haemophilus parainfluenzae</i>	1 (11.1)
<i>Capnocytophaga</i> spp.	2 (22.2)
<i>Eikenella corrodens</i>	1 (11.1)
Gram-positive aerobic bacteria ($n = 13$)	
<i>Streptococcus</i> spp.	6 (46.2)
<i>Enterococcus</i> spp.	3 (23.1)
<i>S. aureus</i>	1 (7.7)
<i>S. epidermidis</i>	1 (7.7)
<i>Abiotrophia</i> spp.	1 (7.7)
<i>Corynebacterium</i> spp.	1 (7.7)
Yeasts ($n = 3$)	
<i>Candida</i> spp.	3 (100)

Fistulas to the skin (through the abdominal wall), the bronchial tree, the lung, and the pericardial space were described in a limited number of cases [9, 13, 39, 62, 87]. Rare complications included thrombosis or obstruction of the portal vein ($n = 8$) [29, 43, 45, 88–91], hepatic vein thrombosis ($n = 3$) [23, 49, 80] and inferior vena cava thrombosis or obstruction ($n = 2$) [23, 81], cardiac tamponade ($n = 3$) [28, 92, 93], and gastrointestinal bleed ($n = 1$) [94].

Diagnosis was confirmed by histopathologic examination of surgical samples in 60 cases: biopsy ($n = 26$), drainage ($n = 11$), and resection ($n = 23$) or percutaneous samples ($n = 45$): biopsy ($n = 33$) and drainage ($n = 12$). Diagnosis was confirmed by postmortem examination of the liver tissue in 4 cases [69, 89, 93, 95]. Cultures of surgical and percutaneous specimens yielded *Actinomyces*

Table 5. Univariate analysis of clinical and radiological characteristics associated with management of patients with hepatic actinomycosis

Variable	Surgical or percutaneous drainage	Medical therapy alone	<i>p</i> value	Odds ratio
Age in years (mean, range)	48 (4–82)	50 (6–82)	0.69	
Male sex, <i>n/n</i> (%)	32/69 (46)	37/69 (53)	0.49	
Comorbidities, <i>n/n</i> (%)	36/83 (43)	47/83 (57)	0.1	
Cystic lesions, <i>n/n</i> (%)	37/65 (57)	28/65 (43)	0.1	
Solid tumor-like lesions, <i>n/n</i> (%)	9/35 (25)	26/35 (75)	<0.0001	0.1 (0.04–0.3)
Single lesion, <i>n/n</i> (%)	36/70 (48)	34/70 (51)	0.8	
Multiple lesions, <i>n/n</i> (%)	13/39 (33)	26/39 (66)	0.0062	0.10–0.66

Continuous variables were analyzed by two-sided *t* test. *p* < 0.05 was considered statistically significant. All other analyses were performed with Fisher's exact test.

species in 12 and 27 instances, respectively. Diagnosis was confirmed by blood cultures in 3 cases [70, 96, 97] and by culture of both blood and percutaneous drainage sample in 3 other cases [71, 74, 77] (Table 3). Identification to the species level was performed in 32 cases, using either conventional methods, or the API system, the automated VITEK 2 system, MALDI-TOF MS, and 16S rRNA sequencing analysis. Genomic polymerase chain reaction (PCR) analysis was performed in 7 instances [28, 63, 71, 75, 80, 97, and the present case]. *A. israelii* was the most frequently isolated species (Table 4). The infection was mixed in 32 cases, and the isolated co-pathogens are shown in Table 4.

Therapy involved antibiotic administration alone (*n* = 62), combined antibiotic treatment and surgical drainage (*n* = 21), combined antibiotic treatment and percutaneous drainage (*n* = 31), combined antibiotic treatment and liver lobe resection (*n* = 31), and surgery alone (*n* = 4). The median duration of antibiotic therapy was 135 days (range: 7–730 days). The most frequently administered antibiotics were intravenous penicillin G (60.8%), followed by long-term oral penicillin (26.9%), amoxicillin (19.2%), doxycycline (6.2%), amoxicillin-clavulanic acid (4.6%), or clindamycin (3.8%). Importantly, univariate analysis demonstrated that the presence of multiple lesions or solid tumor-like lesions was significantly associated with medical therapy alone without the need for surgical intervention (Table 5). The majority of patients (94%) responded well to treatment. The mortality rate in relation to types of treatment is presented in Table 6. Mortality was not significantly different (*p* = 1.0) between those who received combined antibiotic treatment and surgical drainage and those treated with antibiotics alone.

Table 6. Type of therapy and mortality rate

Type of therapy	Patients, <i>n</i>	Mortality rate, <i>n</i> (%)
Antibiotics alone	62	4 (6.5)
Antibiotics + hepatectomy	31	0 (0)
Antibiotics + surgical drainage	21	1 (4.8)
Antibiotics + percutaneous drainage	31	0 (0)
Resection	4	0 (0)
All cases	150	9 (6)

Data on the type of treatment of 8 patients are missing.

Discussion

Human actinomycosis was first recognized in 1878 by Israel, who also later identified the microorganism's cultural characteristics and its anaerobic nature. Actinomycosis has been a common infection in the pre-antibiotic era, but its incidence has decreased with the advent of antibiotics. However, actinomycosis continues to be a problem in developing countries due to the low socioeconomic status and the limited access to medical therapy. Liver involvement is rare, accounting for only 5% of all cases of actinomycosis [1, 2]. Only sporadic cases and case series of HA have been reported. The present review revealed the global distribution of the disease with its burden being higher in Asia, as recently reported [98]. A male predominance (3:2.3) was observed, and most patients were immunocompetent. The peak incidence of the disease is reported to be in the fourth decade of life, with cases being less frequent in children and elderly aged 80 years and above.

Liver involvement may occur via extension from a contiguous abdominal focus or by hematogenous spread via the portal vein following mucosal injury induced by surgical or endoscopic manipulations, ulcer, foreign bodies, intra-abdominal infection, or immunosuppression [1, 2]. One or more comorbidities were observed in more than half of the cases reviewed, with remote abdominal and pelvic surgery and diabetes mellitus being the most common. Nevertheless, most of the cases (80.8%) were cryptogenic.

Symptoms of HA are variable, nonspecific, and indolent with most common manifestations being fever, abdominal pain, weight loss, and anorexia. Laboratory findings include leukocytosis with a left shift, erythrocyte sedimentation rate, C-reactive protein, and alkaline phosphatase elevations. Imaging features are also nonspecific and often mimic primary or metastatic neoplasms [19, 25, 27, 33, 35, 39, 40, 60, 80, 84, 85].

Demonstration of aggregates of filamentous Gram-positive organisms in “sulfur granules” of biopsy specimens or aspirated pus is suggestive of actinomycosis. The isolation in culture of *Actinomyces* species confirms the diagnosis. However, in a notable percentage of cases, cultures did not yield the causative microorganism. This is due either to previous antimicrobial treatment or to inhibition of growth by other microorganisms, and to inadequate culture conditions and short incubation period of culture specimens. Suitable and adequate sampling, handling, and processing of the samples is necessary for diagnosis. MALDI-TOF provides quick and accurate identification to the genus level, while 16S rRNA sequencing is the reference method for definitive identification. PCR can also be used for direct detection of the microorganism in clinical specimens [2]. *A. israelii* was the predominant species, while *A. odontolyticus*, the species isolated from the aspirated pus of our patient, is relatively rare [51, 74, 75]. Other bacterial species were concomitantly isolated in many studies; these “companion microbes” serve as co-pathogens contributing to the inhibition of host immune responses and reducing the oxygen tension [1, 2].

Therapeutic options include antibiotics, drainage of the abscess, and resection of the necrotic tissue. Treatment of the infection with prolonged courses of antibiotics is recommended, to avoid recurrence [2]. *Actinomyces* are susceptible in vitro to many antibiotics. Penicillin G is the drug of choice and must be given intravenously for 4–6 weeks, followed by oral penicillin V for 6–12 months. Tetracyclines, doxycycline, erythromycin, and cephalosporins are effective alternatives [2]. In case of the pres-

ence of co-pathogens, antimicrobial treatment should include coverage of these organisms. In our case, treatment included drainage of the abscess combined with intravenous therapy, followed by a maintenance oral therapy. Of interest, the presence of multiple lesions and solid lesions (without evidence of liquefaction) was significantly associated with conservative management without the need for surgical intervention. The more advanced cases require combined medical therapy and drainage of the abscess or surgical resection of the necrotic tissue for optimal outcome. However, despite the delayed diagnosis, the outcome of HA was excellent in most cases, with a mortality rate of 6%.

HA, although rarely encountered, should be considered in the differential diagnosis of patients with chronic constitutional symptoms and evidence of solitary or multiple hypodense liver lesions and laboratory findings of chronic inflammation. Diagnosis is established by histological examination and cultures or PCR of the exudate and the biopsy or the surgical specimen. Medical therapy alone or combined with surgery has proven to be highly effective for management of this infection.

Statement of Ethics

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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