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AIM AND SCOPE

World Journal of Hepatology (*World J Hepatol*, *WJH*, online ISSN 1948-5182, DOI: 10.4254), is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJH covers topics concerning liver biology/pathology, cirrhosis and its complications, liver fibrosis, liver failure, portal hypertension, hepatitis B and C and inflammatory disorders, steatohepatitis and metabolic liver disease, hepatocellular carcinoma, biliary tract disease, autoimmune disease, cholestatic and biliary disease, transplantation, genetics, epidemiology, microbiology, molecular and cell biology, nutrition, geriatric and pediatric hepatology, diagnosis and screening, endoscopy, imaging, and advanced technology. Priority publication will be given to articles concerning diagnosis and treatment of hepatology diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

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CASE REPORT

Clostridium paraputrificum septicemia and liver abscess

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Abstract

We report the first case of a healthy 23-year-old female who underwent an interventional radiology-guided embolization of a hepatic adenoma, which resulted in a gas forming hepatic liver abscess and septicemia by *Clostridium paraputrificum*. A retrospective review of Clostridial liver abscesses was performed using a PubMed literature search, and we found 57 clostridial hepatic abscess cases. The two most commonly reported clostridial species are *C. perfringens* and *C. septicum* (64.9% and 17.5% respectively). *C. perfringens* cases carried a mortality of 67.6% with median survival of 11 h, and 70.2% of the *C. perfringens* cases experienced hemolysis. All *C. septicum* cases were found to have underlying liver malignancy at the time of the presentation with a mortality of only 30%. The remaining cases were caused by various *Clostridium* species, and this cohort's clinical course was significantly milder when compared to the above *C. perfringens* and *C. septicum* cohorts.

Key words: *Clostridium*; Hemolysis; Liver cell adenoma; Morbidity; Mortality; Pyogenic liver abscess

Core tip: To our best knowledge, this is the first case where a liver abscess grew *C. paraputrificum*. Although pyogenic liver abscesses caused by *Clostridium* species are extremely rare, early and accurate diagnosis of clostridial hepatic abscess and timely interventions are paramount, as it carries an extremely high morbidity and mortality. However, depending on the exact causative *Clostridium* species, the clinical course can vary unexpectedly.

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INTRODUCTION

Pyogenic liver abscesses caused by *Clostridium* species are extremely rare[1], and only 57 cases have been reported in the English medical literature (Table 1). *C. perfringens* was responsible for more than a half of these reported cases. This species carries an extremely high mortality rate, especially when associated with hemolysis[2-4]. The previously reported 20 *C. perfringens* cases showed a median age of 65 years at the time of presentation[5]. Advanced age, underlying malignancy, liver cirrhosis, and immunocompromised conditions including dialysis, transplant and diabetes mellitus were identified as risk factors[2,5-8]. Here we present a very unusual case of a healthy 23-year-old female who underwent interventional radiology (IR) embolization for a hepatic adenoma and presented within 24 h with a gas forming hepatic liver abscess and septicemia. Due to the extremely rapid clinical presentation where the embolized tumor was completely replaced by a gas forming abscess within a day, *C. perfringens* was suspected as the causative organism. Unlike many other fatal *C. perfringens* hepatic abscess cases, our patient did not have any signs of hemolysis nor experienced any end-organ failure. Future speciation work-up revealed *C. paraputrificum*. There have been five case reports of septicemia caused by *C. paraputrificum*[9-13]. However, this is the first case of a gas forming hepatic abscess.

CASE REPORT

A 23-year-old healthy female with obesity (body mass index of 37 kg/m^2) and Polycystic Ovarian Syndrome on oral contraceptive pills was evaluated for intermittent, right upper quadrant abdominal pain. She was found to have a hepatic adenoma measuring 5.2 cm × 3.3 cm × 6.6 cm abutting the liver capsule in segment 7 (Figure 1) on imaging. The patient's oral contraceptive pill was discontinued for the more than three months, since the adenoma was diagnosed. A repeat computerized tomography (CT) scan did not show regression of the mass (Figure 2). Due to ongoing intractable abdominal right upper quadrant pain and risk of potential rupture, a surgical resection was presented as an option *vs* IR-guided embolization as an alternative option given her body habitus and fatty liver on magnetic resonance imaging study. The patient elected to proceed with IR embolization.

Angiogram showed conventional hepatic artery anatomy, and the adenoma was exclusively fed by a single branch coming off of the posterior right hepatic artery (Figure 3). The tumor was completely embolized with 100-300 μm trisacryl gelatin microspheres (Embosphere®, Merit Medical Systems, Inc., South Jordan, United States). The patient was discharged home the same day.

The next day, the patient began to experience a rapid onset of right upper abdominal pain, nausea, vomiting and fever of 101.5 °F. In the emergency room, the patient was tachycardic with a heart rate in the 120 s. She experienced right upper abdominal tenderness on physical exam. Blood tests showed a white blood cell (WBC) count of 16.4 Thou/μL, a lactic acid of 2.4 nmol/L, a serum aspartate transaminase (AST) of 671 U/L, a serum alanine transaminase (ALT) of 310 U/L, and a total bilirubin (T. bili) of 1.4 mg/dL. A CT scan showed the embolized tumor in segment 7 completely replaced with multiple gas pockets (Figure 4). A set of blood cultures was sent, and the patient was started on vancomycin, levofloxacin and metronidazole (patient has a penicillin allergy). The next day, the set of blood cultures grew gram positive rods. The patient's serum WBC was elevated to 25 Thou/μL. Later that day, the preliminary blood culture revealed *clostridium* species. With ongoing fever and the newly diagnosed *clostridium* species infection, a repeat CT scan was performed to rule out potential life threatening gas gangrene. The repeat CT scan showed no changes.

The patient remained persistently febrile, despite antibiotic therapy and subsequent blood cultures showing no growth. The culture speciation showed *Clostridium paraputrificum* and no other organisms were isolated. Despite improving leukocytosis, an IR-guided drain was placed on hospital day 10 due to the persistent fevers. One hundred and twenty cc of dark turbid sterile fluid was aspirated, and the gram stain showed many neutrophils. No bacteria were isolated. Aspirin was started because the patient's platelet count rose above 500 Thou/μL. Over the next a few days since the drain placement, the fluid character became less turbid. However, the color became frankly bilious. The daily drain output persistently remained less than 200 cc, indicating a low output bile leak. Thus an ERCP was not performed. On Hospital day 16, the patient was afebrile for the first time. The patient was discharged home on hospital day 17 since the patient was afebrile for 48 hours. At the time of discharge, the drain output was less than 100 cc per day and the patient was discharged on oral metronidazole only.

The patient presented two weeks after discharge with a follow-up CT, which revealed a significantly reduced gas filled abscess cavity (Figure 5). The IR drain was taken out as the daily output remained minimum, less than 5 cc per day. Oral metronidazole was continued for two more weeks post drain removal. Upon completion of the antibiotic course, blood tests showed a WBC of 9.5 Thou/μL, a platelet count of 379 Thou/μL, an AST of 27 U/L, an ALT of 30 U/L, and a T. bili of 0.6 mg/dL.

Table 1 Fifty-seven reported clostridial hepatic abscess cases in the English medical literature

Case	Author	Year	Age	Sex	Species	Underlying disease	HML	SSE	TTD	PLM	PMI
1	Fiese[35]	1950	67	M	*C. perfringens*	Cholecystitis	No	Yes	-	No	Yes
2	Kivel *et al*[36]	1958	68	F	*C. perfringens*	DM	Yes	No	5 d	No	No
3	Kahn *et al*[37]	1972	44	F	*C. septicum*	Colon cancer	No	Yes	-	Yes	Yes
4	D'Orsi *et al*[38]	1979	52	F	*C. septicum*	Colon cancer	No	Yes	-	Yes	No
5	D'Orsi *et al*[38]	1979	51	F	*C. ramosum*	Melanoma	Yes	No	2 d	Yes	No
6	D'Orsi *et al*[38]	1979	29	M	*C. ramosum*, *C. sporogenes*	Peri-ampullaryCa	No	Yes	-	Yes	Yes
7	Mera *et al*[39]	1984	6	F	*C. perfringens*	Fanconi's anemia	Yes	No	14 h	No	No
8	Nachman *et al*[40]	1989	6	M	*C. bifermentans*	Blunt trauma	No	Yes	-	No	No
9	Yood *et al*[41]	1989	64	F	*C. perfringens*	Systemic vasculitis	No	Yes	-	No	No
10	Batge *et al*[42]	1992	61	M	*C. perfringens*	Pancreatic cancer, DM	Yes	Yes	-	No	No
11	Rogstad *et al*[43]	1993	61	M	*C. perfringens*	None	Yes	No	3 h	No	No
12	Thel *et al*[32]	1994	39	F	*C. septicum*	Breast Ca, Bone M. txp	No	Yes	-	Yes	No
13	Gutierrez *et al*[44]	1995	74	M	*C. perfringens*	None	Yes	No	6 h	No	No
14	Jones *et al*[45]	1996	66	F	*C. perfringens*	OLT, DM	Yes	No	10 h	No	No
15	Lee *et al*[34]	1999	33	F	*C. septicum*	Uterine cancer	No	Yes	-	Yes	No
16	Eckel *et al*[46]	2000	65	F	*C. perfringens*	Cholangiocarcinoma	Yes	Yes	-	Yes	Yes
17	Urban *et al*[47]	2000	68	M	*C. septicum*	Colon cancer	No	Yes	-	Yes	No
18	Sakurai *et al*[48]	2001	75	F	*C. difficile*	Hepatic cyst	No	Yes	-	Yes	No
19	Kreidl *et al*[8]	2002	80	M	*C. perfringens*	DM, dialysis	Yes	No	11 h	No	No
20	Sarmiento *et al*[49]	2002	57	M	*C. septicum*	Colon cancer	No	Yes	-	Yes	No
21	Hsieh *et al*[50]	2003	23	M	*Unusual C. spp.*	Blunt trauma	No	Yes	-	No	No
22	Quigley *et al*[51]	2003	73	M	*C. perfringens*	Hepatic cyst	-	No	0 h	Yes	Yes
23	Elsayed *et al*[52]	2004	27	M	*C. hathewayi*	Cholecystitis	No	Yes	-	No	No
24	Fondran *et al*[53]	2005	63	M	*C. perfringens*	Pancreatic cancer	No	Yes	-	Yes	Yes
25	Au *et al*[7]	2005	65	M	*C. perfringens*	DM, dialysis	Yes	No	3 h	No	No
26	Kurtz *et al*[54]	2005	50	F	*C. septicum*	Colon cancer	No	Yes	-	Yes	No
27	Ohtani *et al*[55]	2006	78	M	*C. perfringens*	DM	Yes	No	3 h	No	No
28	Daly *et al*[56]	2006	80	M	*C. perfringens*	DM	Yes	No	3 h	No	No
29	Loran *et al*[57]	2006	69	F	*C. perfringens*	None	Yes	No	6 h	No	No
30	Chiang *et al*[58]	2007	46	F	*C. perfringens*	Cholecystitis	No	No	7 d	No	No
31	Abdel-Haq *et al*[59]	2007	11	M	*C. novyi type B*	Blunt trauma	No	Yes	-	No	No
32	Umgelter *et al*[60]	2007	87	F	*C. perfringens*	Colon cancer	No	Yes	-	Yes	No
33	Tabarelli *et al*[61]	2009	65	F	*C. perfringens*	Pancr. Ca s/p whipple	No	No	27 d	No	Yes
34	Merino *et al*[62]	2009	83	F	*C. perfringens*	None	Yes	No	3 d	No	No
35	Saleh *et al*[63]	2009	53	M	*C. septicum*	Colon cancer	No	Yes	-	Yes	No
36	Meyns *et al*[64]	2009	64	M	*C. perfringens*	DM	Yes	No	2 d	No	No
37	Ng *et al*[4]	2010	61	F	*C. perfringens*	DM	Yes	Yes	-	No	Yes
38	Rajendran *et al*[65]	2010	58	M	*C. perfringens*	None	Yes	Yes	-	No	No
39	Bradly *et al*[66]	2010	52	M	*C. perfringens*	OLT	Yes	No	6 h	No	No
40	Ogah *et al*[67]	2012	6	F	*C. clostridioforme*	None	No	Yes	-	No	No
41	Qandeel *et al*[68]	2012	59	M	*C. perfringens*	DM, s/p elective chole	Yes	Yes	-	No	No
42	Kim *et al*[69]	2012	80	F	*C. perfringens*	Hilar cholangiocarcinoma	No	No	3 d	No	Yes
43	Huang *et al*[70]	2012	54	M	*C. baratii*	Cholecystitis	No	Yes	-	No	No
44	Sucandy *et al*[71]	2012	65	M	*C. septicum*	Colon cancer	No	No	2 d	Yes	No
45	Law *et al*[5]	2012	50	F	*C. perfringens*	Rectal cancer	Yes	No	7 d	Yes	No
46	Raghavendra *et al*[72]	2013	63	M	*C. septicum*	Colon cancer	No	Yes	-	Yes	No
47	Kitterer *et al*[73]	2014	71	M	*C. perfringens*	OLT, Gastroenteritis	Yes	No	13 h	No	No
48	Imai *et al*[74]	2014	76	M	*C. perfringens*	None	Yes	No	6.5 h	No	No
49	Kurasawa *et al*[2]	2014	65	M	*C. perfringens*	DM	Yes	No	6 h	No	No
50	Eltawansy *et al*[75]	2015	81	F	*C. perfringens*	DM, Gastroenteritis	No	No	N/A[1]	No	Yes
51	Li *et al*[76]	2015	71	M	*C. perfringens*	HCC, Hepatitis B	Yes	Yes	-	Yes	No
52	Rives *et al*[77]	2015	63	M	*C. perfringens*	Colon cancer	No	Yes	-	Yes	No
53	Lim *et al*[6]	2016	58	M	*C. perfringens*	None	Yes	No	7.5 h	No	No
54	Hashiba *et al*[78]	2016	82	M	*C. perfringens*	DM	Yes	No	2 h	No	No
55	Kyang *et al*[79]	2016	84	M	*C. perfringens*	Gastric adenoCA	No	Yes	-	Yes	Yes
56	Ulger *et al*[80]	2016	80	F	*C. difficile*	DM	No	No	18 d	No	No
57	García *et al*[81]	2016	65	M	*C. perfringens*	DM	Yes	Yes	-	No	Yes

[1]Exact time of TTD was not discussed, but terminal vent weaning was initiated and subsequently expired. HML: Hemolysis; SSE: Survival of septic episode; TTD: Time to death; PLM: Presence of liver mass; PMI: Polymicrobial infection.

DISCUSSION

Pyogenic liver abscess (PLA) is an uncommon disease. Various incidences have been reported throughout the world: 1.1 in Denmark[14], 2.3 in Canada[15] and 17.6 per 100000 population in Taiwan[16]. In the United States, the incidence is 3.6 per 100000 population with a reported in-hospital mortality rate of 5.6%[17].

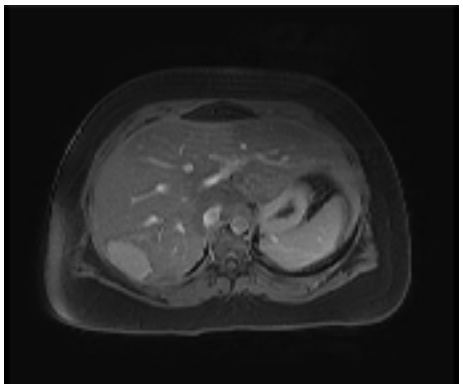

Figure 1 Magnetic resonance imaging of the segment 7 hepatic adenoma measuring 5.2 cm × 3.3 cm × 6.6 cm.

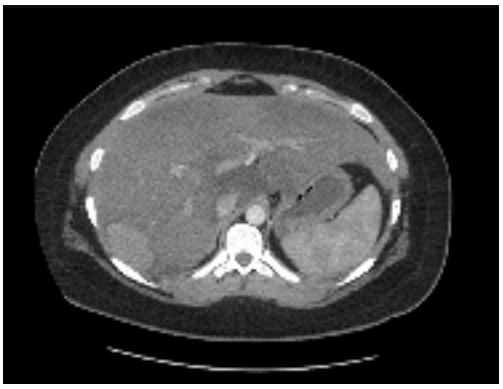

Figure 2 Computed tomography after stopping oral contraceptive pills for 3 mo. No change in size.

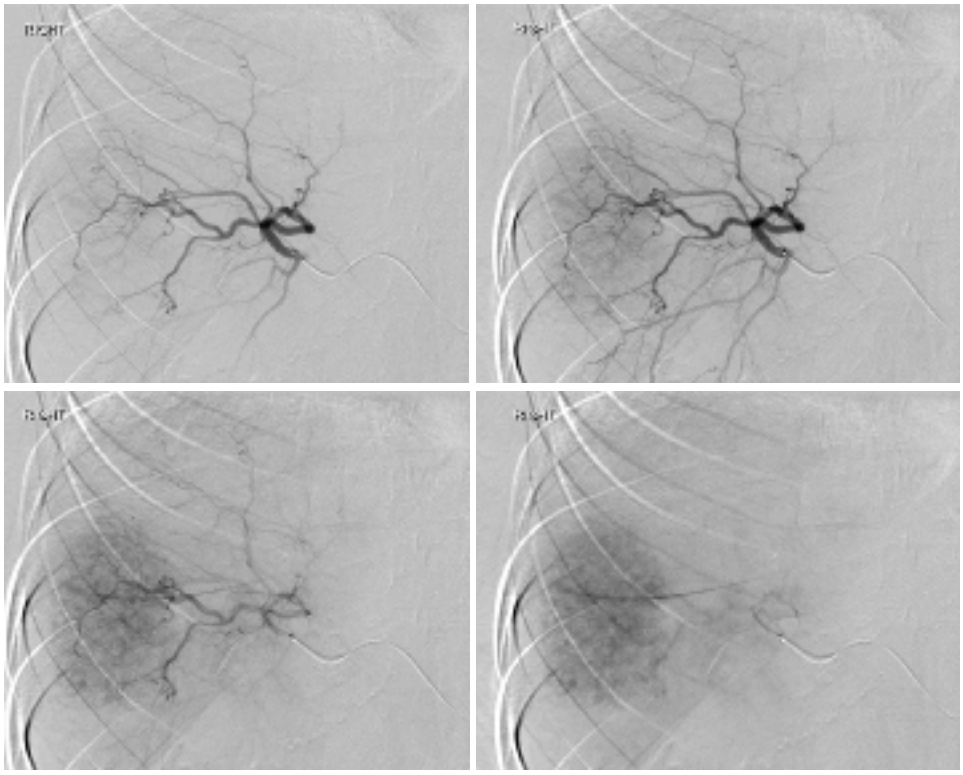

Figure 3 Interventional radiology angiogram of the hepatic adenoma.

The incidences of gas forming pyogenic liver abscess (GFPLA), also known as emphysematous liver abscess, are even rarer, contributing 6.6% to 32% of PLA[16,18-21]. It carries a significantly higher mortality rate, 27.7% to 37.1%[22-25]. For those who presented with GFPLA, their incidence of septic shock was higher (32.5% *vs* 11.7%) and they presented with a shorter duration of symptoms (5.2 d *vs* 7.6 d) when compared to those who presented with non-gas forming pyogenic liver abscess (NGFPLA)[22].

The single strongest risk factor for GFPLA appears to be the presence of diabetes and poorly controlled blood glucose[15,18,22]. According to a case report series done in Taiwan which compared 83 patients with GFPLA against 341 NGFPLA patients, 85.5% of those with GFPLA had diabetes mellitus with an initial glucose level of 383.0 ± 167.7 (mg/dL) *vs* 33.1% with an initial glucose level of 262.6 ± 158.0 (mg/dL)[22]. Similar findings were reported from another single center series from South Korea, where 76% (19 out of 25) were found to have diabetes when comparing 25 patients with GFPLA against 354 NGFPLA patients[18]. The most common causative organism for GFPLA was *Klebsiella pneumoniae* contributing 77% to 88%[18,22,25]. *Escherichia*, *Streptococcus*, *Enterococcus*, *Pseudomonas*, *Morganella*, *Enterobacter*, *Serratia*, *Bacteroides* and *Clostridium* species were responsible for the remaining[22].

An extremely small portion of GFPLA is caused by clostridial species. The two most commonly reported

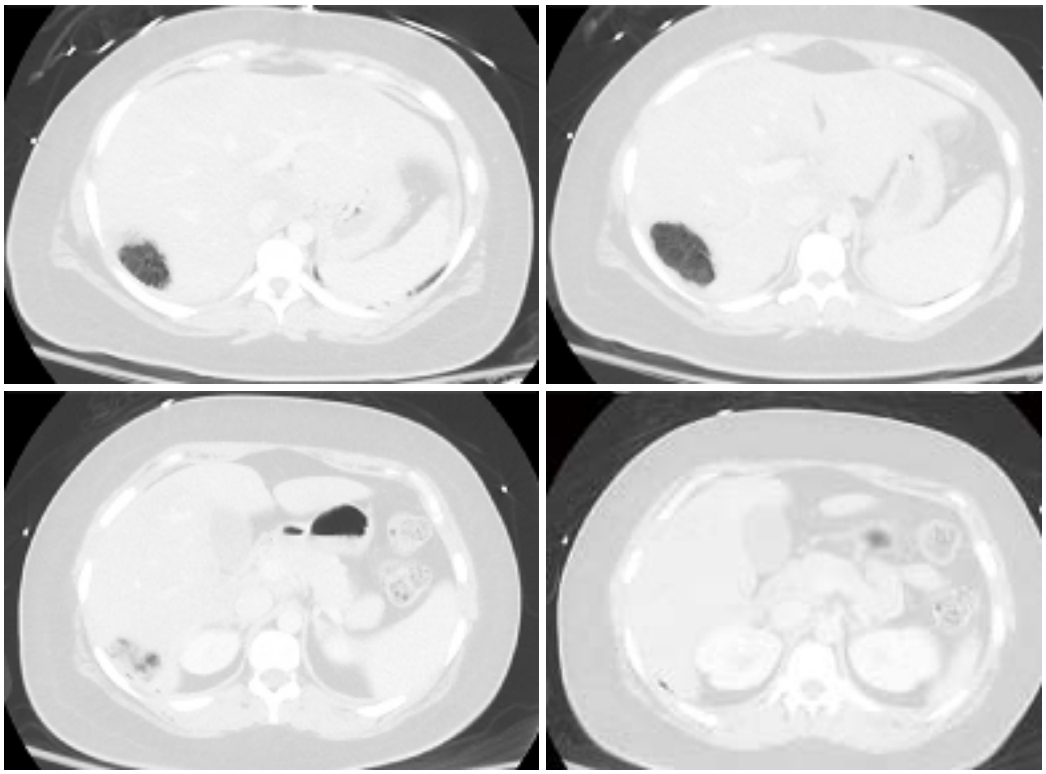

Figure 4 The tumor completely replaced by gas pockets.

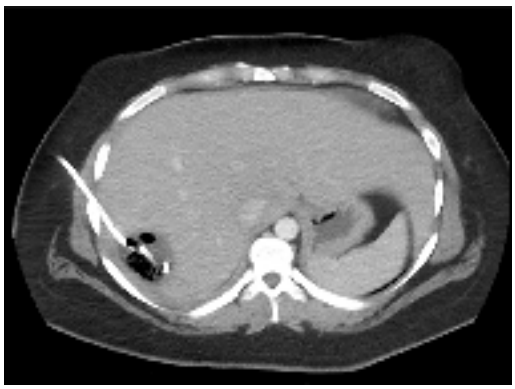

Figure 5 Follow-up computed tomography. The gas pocket reduced.

clostridium species are *C. perfringens and C. septicum*. We performed a PubMed literature search and identified 57 *clostridium* hepatic abscess cases reported in the English medical literature (Table 1). Our search showed that *C. perfringens* was responsible for 37 cases (64.9%) and *C. septicum* was responsible for 10 cases (17.5%). Nine cases were caused by *C. difficile, C. ramosum, C. sporogenes, C. baratii, C. bifermentans, C. clostridioforme, C. hathewayi,* and *C. novyi type B*. In one case, the exact speciation was not provided due to the institution's microbiology limitation for identifying rare clostridial species.

C. perfringens septicemia has been reported to carry a mortality rate ranging from 70%-100%[4]. Massive intravascular hemolysis is a well-known complication, occurring in 7%-15% of *C. perfringens* bacteremia cases[26-28]. *C. perfringens*'s alpha-toxin has been shown be the key virulent factor for this clinical course, by inducing gas gangrene and causing massive hemolysis by destroying red cell membrane integrity[3]. In our 37 cases of *C. perfringens* hepatic abscess, the mortality rate was 67.6% (25/37). 70.2% (26/37) experienced hemolysis (Table 1). Among the 25 patients who died, one patient died prior to arriving to the hospital. The mean time of survival for these 24 patients was 11 h. Among the 25 patients who died, only 4 patients (16%) were found to have poly-microbial infection, whereas among those who survived, 6 patients (50%) were found to have poly-microbial infection. The most common underlying disease was diabetes (11/37) followed by underlying malignancy (10/37). Interestingly, 7 patients were found to have no clear underlying medical disease.

Among the 10 cases of *C. septicum* species (Table 1), the patient survival was greater, 70% (7/10). Furthermore, no hemolysis was reported in contrast to the *C. perfringens* cases. Of note, *C. septicum also* produces alpha toxin, but it was shown to be unrelated to the alpha toxin of *C. perfringens*[29]. *C. septicum* infection has been well known to be associated with underlying occult malignancy[30-33]. It has been hypothesized that a rapidly growing tumor with anaerobic glycolysis provides a relatively hypoxic and acidic environment for germination of the clostridial spores[34]. In fact, all of the ten patients had infected liver tumors at the time of the presentation, and only one patient (10%) was found to have a poly-microbial infection.

The remaining 10 cases where the infection was

caused by various clostridial species, including the one with no provided speciation, appeared to have a milder clinical course when compared to the above *C. perfringens* and *C. septicum* cohorts (Table 1). The mortality rate was lower, only 20%, and median age at the time of presentation was significantly younger, 27 years. Interestingly, trauma was the underlying disease for the three cases.

Here, we report a young, healthy 23-year-old female who was diagnosed with a hepatic abscess caused by *Clostridium paraputrificum*. Due to the extremely rapid clinical presentation and from the initial imaging study where the mass was completely replaced with multiple gas pockets, a *C. perfringens* infection was highly suspected. Unlike many typical *C. perfringens* hepatic abscess cases, our patient did not experience hemolysis nor had any end organ failure requiring ICU care. In addition, our patient did not have the typical risk factors for *C. perfringens* nor *C. septicum* infections, except for having a tumor in the liver. At the end, the causative organism was identified as *Clostridium paraputrificum*, which has not been reported before in the literature. A *Clostridium* hepatic abscess is an extremely rare case and *C. perfringens* is the most common causative organism. Early accurate diagnosis and timely interventions are paramount, as it carries an extremely high mortality. However, depending on the exact causative clostridial species, the clinical course can vary significantly.

ARTICLE HIGHLIGHTS

Case characteristics

A healthy 23-year-old female developed a *Clostridium paraputrificum* gas forming liver abscess within 24 h after interventional radiology hepatic adenoma embolization.

Clinical diagnosis

The patient's source of sepsis was unequivocally identified once an imaging study showed a gas forming liver abscess.

Differential diagnosis

Klebsiella pneumonia was suspected to be the causative organism initially as it is known to contributing 77% to 88% of all gas forming pyogenic liver abscesses.

Laboratory diagnosis

In addition to severe leukocytosis and lactic acidosis, elevated lactate dehydrogenase, deceased haptoglobin and elevated bilirubin, signs of massive hemolysis, can be also seen in certain patients.

Imaging diagnosis

A gas forming liver abscess can be diagnosed with an abdominal X-ray or ultrasound, but typically a computed tomography scan is commonly used for the diagnosis.

Pathological diagnosis

A needle aspiration of the hepatic abscess and/or blood culture often will yield the causative organism.

Treatment

An early recognition and treatment with antibiotics is paramount as *Clostridium* hepatic abscess infections are often extremely aggressive and lethal.

Related reports

There have been five case reports of septicemia caused by *C. paraputrificum*, however, none of them caused hepatic abscess.

Term explanation

Pyogenic liver abscess (PLA) is an uncommon disease. The incidences of gas forming pyogenic liver abscess (GFPLA) also known as emphysematous liver abscess, are even rarer, contributing 6.6% to 32% of PLA.

Experiences and lessons

A *Clostridium* hepatic abscess requires early accurate diagnosis and timely interventions, as it carries an extremely high mortality. However, depending on the exact causative clostridial species, the clinical course can vary significantly.

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