【 ORIGINAL ARTICLE 】

Infectious Hepatic Cyst: An Underestimated Complication

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Abstract:
Objective　An infectious hepatic cyst (IHC) is a hepatic cyst complicated with secondary infection and is generally assumed to be rare. However, we have experienced no small number of patients with IHC in recent clinical practice. We therefore examined the incidence and clinical characteristics of IHC.
Methods　The medical records of patients with IHC who were hospitalized at our institution between January 2012 and December 2016 were retrospectively reviewed. Their demographic factors, biochemical, bacteriological, imaging, and treatment results were explored and compared with those of patients with pyogenic liver abscess (PLA).
Patients　Twelve patients with IHC and 39 with PLA were identified.
Results　The IHCs were significantly larger in diameters than the PLAs, and patients with IHCs tended to be older and more often women than those with PLAs. IHCs showed characteristic imaging features, including heterogeneous contents with occasional fluid-debris levels, a thickened cystic wall with rim enhancement, perilesional edema and hyperaemia. Patients with IHCs had a significantly shorter hospital stay than those with PLAs.
Conclusion　Physicians should note that IHCs are not rare. A careful imaging evaluation can suggest an IHC, and the timely aspiration of the content can lead to an accurate diagnosis. The cystic wall may keep the infectious material confined within the IHC, resulting in the observed good treatment outcome with catheter drainage.

Key words: infectious hepatic cyst, hepatic cyst, pyogenic liver abscess, percutaneous catheter drainage, *Klebsiella pneumoniae*, multiloculation

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Introduction

Simple hepatic cysts (SHCs) are frequently encountered as incidental findings during imaging studies, with a reported prevalence of 18% using computed tomography (CT) (1). SHCs are well-circumscribed, nonenhancing, anechoic or water-density lesions with a thin, imperceptible, smooth wall on ultrasonography (US) and CT (Fig. 1A) (2). SHCs have no evidence of complex internal features, such as septations, mural irregularity or nodularity, and are homogeneously hypo- and hyperintense on T1- and T2-weighted images, respectively, in magnetic resonance imaging (MRI) (2).

SHCs are more often found in women than in men, with an estimated women-to-men ratio of 1.5:1 (3). SHCs are be-lieved to be congenital and may slowly increase in size (4). Therefore, they are more often found in patients older than 40 years of age. Although SHCs are not usually associated with troublesome symptoms, they occasionally become symptomatic as a result of complications, such as obstructive jaundice, rupture, intracystic hemorrhaging and infection (3-6).

Infectious hepatic cysts (IHCs) that result from secondary infection in SHCs are generally assumed to be rare (7-9). However, we have experienced no small number of IHCs in our recent clinical practice. Therefore, we investigated the incidence, clinical and imaging findings and microbiological and therapeutic characteristics of IHCs. We reviewed the institutional medical records over the preceding five-year period and performed multifaceted comparisons between patients with IHC and those with pyogenic liver abscess
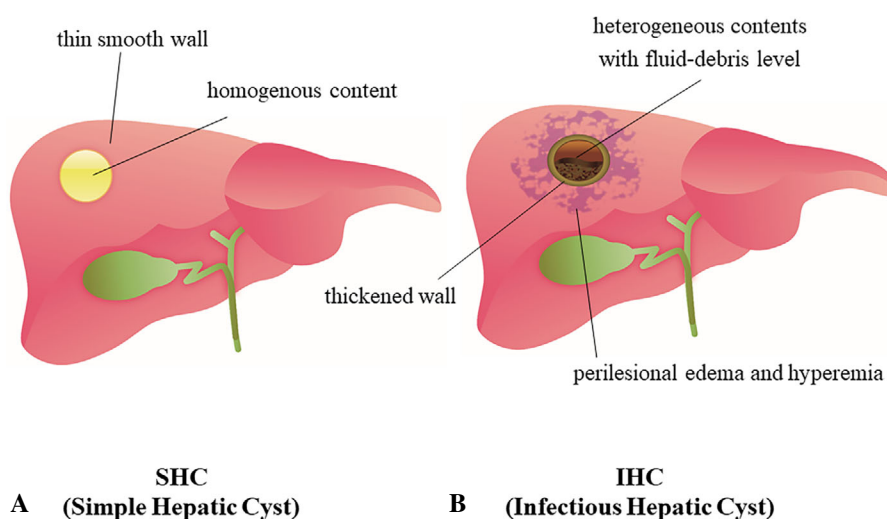
Figure 1. Schematic representation of a simple hepatic cyst and an infectious hepatic cyst. (A) A simple hepatic cyst is a well-circumscribed lesion with a homogenous content and a thin imperceptible smooth wall. It has no complex internal features, such as septations, mural irregularity or nodularity. (B) An infectious hepatic cyst shows characteristic imaging features including a thickened wall, heterogeneous content with a fluid-debris level, and edema of the perilesional hepatic parenchyma. If a previous image could be obtained, steep increase in the diameter would be apparent.

(PLA).

In addition, the mechanisms involved in the susceptibility of the cysts to infection was also discussed. Recent studies on polycystic liver disease have made intriguing suggestions regarding the increased vascular structure surrounding hepatic cysts (10-12). The present article provides a useful summary of the latest information on IHCs.

Materials and Methods

Study design

The present study is a retrospective cohort analysis of patients with IHC. Electronic medical records were reviewed to identify patients with a discharge diagnosis of IHC. We also examined all patients with a discharge diagnosis of PLA and found several patients with a true diagnosis of IHC. Clinical presentation, demographic features, biochemical and serological markers, imaging findings, microbiology of pathogenic organisms and the therapeutic course of the illness were evaluated. The ethics committees of our institutional review board approved this study in accordance with the Declaration of Helsinki (number CTM16-011). Written informed consent was obtained from all patients. Data collection and analyses were conducted on anonymized samples.

Patient inclusion and exclusion criteria

The patient inclusion criteria were (a) patients who were hospitalized at our institutional department between January 2012 and December 2016, and (b) patients whose primary reason for hospitalization was IHC. The only exclusion criterion was the coexistence of presumable primary infectious foci other than IHC.

Diagnostic criteria for IHC

The diagnosis for IHC was based on clinical and microbiological signs of infection, such as a fever with leukocytosis, characteristic imaging features (13), samples consistent with abscess obtained by aspirations, bacterial cultures of blood or pus, microscopic observation of ameba trophozoites in stools or pus on a wet-mount examination, positive results on fluorescent antibody tests against *Entamoeba histolytica* or enzyme-linked immunosorbent assays against *Echinococcus multilocularis* and the resolution of the lesions with antibiotic therapy with/without drainages (14).

The characteristic imaging features of IHC were as follows: (a) thickened walls of the cysts, increased and heterogeneous internal echogenicity or densities (Fig. 1B, 2A, 3), complex internal features, such as fluid-debris levels (Fig. 2B, 4B), and occasional gas bubbles (4); (b) peripheral rim enhancement in the thickened wall with perilesional edema and hyperaemia on contrast-enhanced CT (Fig. 3); (c) hyperintensity of the cysts on both T1-weighted images (Fig. 4A) with hyperintense perilesional edema on T2-weighted images of MRI and (d) a steep increase in the cystic diameter compared with previous studies, if available (13).

Patients with PLAs were selected using the same criteria for IHC patients. The characteristic imaging features of PLA were based on those of previous reports (14, 15).

Treatment strategies

After blood culture sampling, empirical treatments with broad-spectrum antibiotics were commenced immediately. Both patients with IHCs and PLAs larger than 3 cm in di-
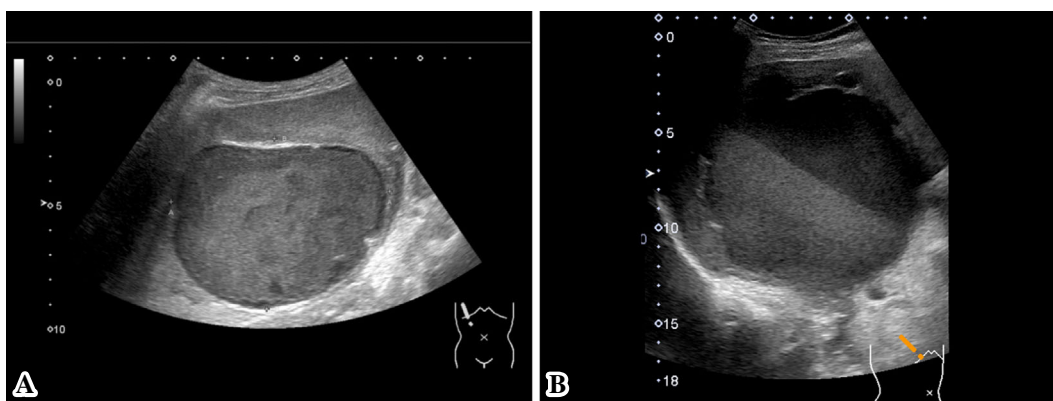
Figure 2. Ultrasonographic images showing large IHCs. (A) Ultrasonographic image of a patient shows a large IHC with a thickened wall and increased heterogeneous echogenicity of its content, which is extremely different from that of the homogeneously anechoic content of a simple cyst. (B) Ultrasonographic image of a patient shows a large IHC with fluid-debris level. IHC: infectious hepatic cyst
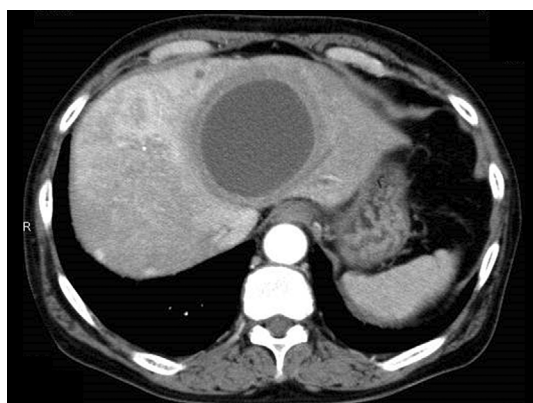
Figure 3. CT image showing a large IHC. Contrast-enhanced CT image demonstrates the enhancing thickened wall of a IHC with perilesional edema and inflammatory enhancement of the surrounding liver parenchyma. IHC: infectious hepatic cyst

ameter predominantly underwent source control by percutaneous catheter drainage (PCD) (14, 16-18).

Statistical analyses

The primary statistical objective was to identify meaningful differences in clinical characteristics or laboratory data between patients with IHCs and PLAs. Standard statistical methods were used to analyze the results. Continuous variables were compared using the Mann-Whitney rank-sum or Student's *t*-test and categorical variables by chi-squared tests. Continuous variables were presented as the mean± standard deviation or median, and categorical variables were presented as the absolute values or percentages. p values below 0.05 (two-tailed) were considered statistically significant. All analyses were performed using the EZR v1.26 software program (Division of Hematology, Saitama Medical Center, Jichi Medical University, Saitama, Japan) (19).

Results

After the application of the inclusion and exclusion criteria, 12 patients with IHC and 39 patients with PLAs were included in this study. During the study period, a total of 2,117 patients were hospitalized at our institutional department. All patients with IHC developed the lesion as a result of a bacterial infection, and none had amebic or parasitic infection. No IHCs were complicated with intracystic hemorrhaging. The baseline demographic and clinical characteristics of the patients with IHCs and PLAs are shown in Tables 1 and 2. Male predominance was inconspicuous in patients with IHCs (58%) compared to those with PLAs (72%). The chief complaint of abdominal pain tended to be more common in patients with IHCs than in those with PLAs. IHCs were significantly larger in diameters and significantly more frequently found in the hepatic left lobe than PLAs. IHCs tended to present as solitary lesions compared with PLAs. The laboratory data were not markedly different between the two groups.

All IHCs showed heterogeneous contents with thickened cystic walls but no multiloculation or septation (Fig. 2, 3). In contrast, 66.7% of PLAs exhibited multiloculation. In patients who could not undergo contrast-enhanced CT because of concomitant renal impairment, MRI demonstrated a well-defined hyperintense lesion on T1- and T2- weighted images (Fig. 4A and B).

Patients with IHC underwent PCD significantly more often than those with PLAs. In patients with lesions <3 cm in diameter, PCD was performed when the diagnosis of infection was equivocal. The demonstration of purulent contents then confirmed the diagnosis of IHC. Cystography during PCD revealed that there was no direct communication between the IHCs and the biliary duct system (Fig. 4C).

The overall positive rates for bacterial culture were 42% and 54% in patients with IHCs and PLAs, respectively;
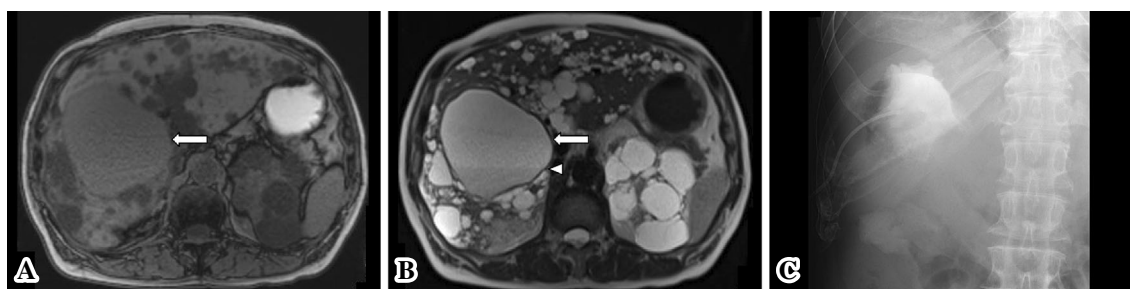
Figure 4. **Magnetic resonance and cystography images of a patient with ADPKD showing a large IHC. (A) T1-weighted image of MRI shows a IHC (arrow) hyperintense compared to the other numerous uncomplicated hepatic cysts. (B) T2-weighted image of MRI also shows a IHC (arrow) that has a fluid-debris level (arrow head). Its intensity is slightly different from that of the other uncomplicated cysts. (C) Cystography during percutaneous catheter drainage demonstrates no direct communications between the hepatic cyst and the biliary duct system. ADPKD: autosomal dominant polycystic kidney disease, IHC: infectious hepatic cyst**

Klebsiella pneumoniae was the most commonly isolated pathogen in both groups.

All patients with IHC were discharged alive with resolution of the infection. Patients with IHCs had a significantly shorter hospital stay than those with PLAs.

Discussion

This study aimed to evaluate the clinical and therapeutic characteristics of IHCs and to compare these findings with those of PLAs. We identified 12 patients with IHCs, a relatively large population. IHCs were significantly larger in diameters than PLAs. The IHC group included more women and older patients, and these patients more frequently complained of abdominal pain than the PLA group. Abdominal pain might be induced by the rapid expansion of IHCs. These results were consistent with the findings reported in previous publications, in which IHCs were large, not rare in the hepatic left lobe, and frequently found in older women compared with PLAs (3-6, 9).

Most previous studies on IHC were anecdotal case reports, small case series or reports associated with autosomal-dominant polycystic liver disease coupled with autosomal-dominant polycystic kidney disease (ADPKD) (5, 7-9, 20-25). To our knowledge, the present study includes the largest number of patients with IHC. Patients with SHCs seldom undergo periodic inspections, thus limiting our understanding of the accurate incidence of IHCs. Sallee et al. reported 4 patients with IHCs (6 episodes, 2 definite and 4 likely) during the 11-year follow-up of 389 patients with ADPKD (26). The incidence of IHCs in patients with ADPKD was calculated to be 0.001 episodes per patient per year. Compared with the Sallee's report, our study included an impressively large number (n=12) of patients with IHC. Improvements in imaging technologies, the aging of our society and sociogeographical differences (food, climates, environment, economic situation and prevailing pathogens) may affect the incidence of IHC. For example, as people

grow older, existent hepatic cysts tend to increase in size, and the host immunity may deteriorate, thereby increasing the probability of developing an IHC (4, 27). Physicians should be aware that the IHCs may be more frequent than previously regarded (28).

All IHCs in the present study resulted from bacterial infection. Secondary amebic or parasitic infections in SHCs were not found. However, blood with/without pus specimen culture was sterile in 49% of cases. This relatively low yield of bacterial cultures is consistent with the result of recent meta-analyses (9). Thirty-nine (76%) patients in the present cohort had already received antibiotics from their primary care physicians prior to their arrival. The culture positivity rate was 67% for patients who had not received antibiotics before arrivals and 46% for those who had already received antibiotics. Because of the wide acceptance of sepsis guidelines, many physicians administer antibiotics promptly to patients with suspected sepsis or infection (29). However, a negative blood culture is preferable if it is truly negative, as bacteremia implies an infection beyond the liver and a significantly increased risk of fatality (18, 30).

Multiple factors seem to be implicated in the susceptibility of the cysts to infection. Imaging studies, including cystography, revealed no direct communications between the IHCs and the biliary duct system in our cases (Fig. 4C), raising the possibility of hematogenous infection of the cysts (2, 3, 6, 31). Recent accumulating evidence of the pathogenesis of polycystic liver disease has prompted intriguing suggestions regarding the vasculatures surrounding the hepatic cysts (10-12). Cystic cholangiocytes have an immature, fetal-like phenotype and aberrantly produce VEGF, which can promote the expansion of the portal vascular bed surrounding the abnormal biliary structures. The growth of an aberrant vascularization in close proximity to hepatic cysts accelerates the proliferation of the cystic cholangiocytes. These enlarged cysts and expanded vasculatures subsequently result in an increased probability of the hematogenous spread of bacteria to cysts.

Table 1. Demographic and Clinical Characteristics of Patients with IHCs and PLAs.

		IHC	PLA	p value
Patients, n (male:female)		12 (7:5)	39 (28:11)	0.4
Age, year		73.7±9.0	70.5±13.4	0.7
Symptomatic onset to diagnosis, days		9.3±8.2	5.7±6.0	0.1
Clinical presentation, n (%)				
	Fever and chills	6 (50)	25 (64.1)	0.3
	Abdominal pain	5 (41.7)	6 (15.4)	0.05
	Anorexia	1 (8.3)	1 (2.6)	0.3
	General malaise	0	7 (17.9)	0.05
Number of the lesions, n		1.3±0.7	2.5±2.1	0.2
range, n (%)	1	9 (75)	24 (61.5)	
	2-4	3 (25)	5 (12.8)	
	≥5	0	10 (25.6)	
Location of the lesion, n (%)				
	Right lobe	5 (41.7)	30 (76.9)	0.02
	Left lobe	7 (58.3)	4 (10.3)	0.0004
	Bilateral lobes	0	5 (12.8)	0.1
Diameter of the lesion, cm		8.3±2.9	5.2±2.7	0.005
range, n (%)	≤3 cm	0	13 (33.3)	
	3.1-5.0 cm	1 (8.3)	8 (20.5)	
	5.1-7.4 cm	5 (41.7)	10 (25.6)	
	7.5-9.9 cm	3 (25.0)	4 (10.3)	
	≥10 cm	3 (25.0)	4 (10.3)	
Multiloculation (sepation), n (%)		0	26 (66.7)	0.0001
Route of infection, n (%)				
	Cryptogenic	5 (41.7)	13 (33.3)	0.6
	Biliary	5 (41.7)	14 (35.9)	0.7
	Portal pyemia	0	8 (20.5)	0.08
	Hematogenous	1 (8.3)	2 (5.1)	0.7
	Urinary tract infection	1 (8.3)	2 (5.1)	0.7

p values were calculated to identify statistically significant differences between patients with IHCs and PLAs. IHC: infectious hepatic cyst, PLA: pyogenic liver abscess

Table 2. Laboratory and Bacteriological Test Results in Patients with IHCs and PLAs.

	Reference range	IHC	PLA	p value
Peripheral white-cell count, /mm^3	3,300-8,600	9,800±4,160	10,560±4,680	0.3
Total bilirubin, mg/dL	0.4-1.5	1.2±0.7	1.7±2.0	0.8
Albumin, g/dL	4.1-5.1	3.1±0.4	3.0±0.6	0.7
Prothrombin-time INR		1.2±0.2	1.3±0.3	0.7
Alanine aminotransferase, U/L	7-23	79±113	82±105	0.2
Alkaline phosphatase, U/L	106-322	580±305	566±359	0.7
Creatinine, mg/dL	0.46-0.79	1.0±0.5	0.9±0.3	0.7
C-reactive protein, mg/L	0-1.4	157±92	146±92	0.7
Procalcitonin, ng/mL	≤0.05	2.1±3.8	8.1±13	0.2
Isolated bacterial pathogens, %				
Klebsiella pneumoniae		25.0	28.2	0.6
Streptococcus anginosus group		0	10.3	0.001
Enterococcus spp.		16.7	2.3	0.002
Escherichia coli		0	5.1	0.02
others		0.0	7.7	0.003
negative culture		58.3	46.1	0.9
Percutaneous catheter drainage, n (%)		10 (83.3)	16 (41.0)	0.01
Surgical drainage, n (%)		0	1 (2.6)	0.6
Length of hospital stay, days		16.6±14.5	22.9±15.1	0.04
Fatality, n (%)		0	2 (5.1)	0.4

IHC: infectious hepatic cyst, PLA: pyogenic liver abscess, INR: International normalized ratio

During cystography, the tight injection of the contrast medium was avoided to prevent engorgement of the cyst, due to the risk of bacterial spreading. However, given the relatively high proportion of a presumed biliary route of infection (42%, Table 1), thin or temporary connections between the IHCs and the biliary systems could not completely be ruled out.

One IHC patient with hepatic polycystic disease and ADPKD was observed in the present cohort (Fig. 4). Hepatic polycystic disease is seen in up to 40% of patients with ADPKD (10, 20). Liver cyst complications, such as infection and internal hemorrhaging, may be more common in patients with ADPKD than in those with SHCs because of the increased number of hepatic cysts (2). However, IHC is far less common than infectious renal cysts in patients with ADPKD, as infectious renal cysts occur via the ascending urinary tract infections, in contrast to the hematogenous route of IHC infections (21, 22).

The preferred treatment of IHCs is the combination of antibiotic administration and PCD for both effective source control and a definite infection diagnosis. Despite the significantly larger diameters of lesions, patients with IHCs required significantly shorter hospital stays than those with PLAs (Table 2). The cystic wall might mitigate the spread of infectious materials and confine them within the cavity, thereby resulting in their efficient elimination by PCD.

Infection in a hepatic cyst is a clinical diagnosis that depends on the signs and symptoms suggestive of infection, and its confirmation remains difficult despite recent advances in imaging technologies (9, 32). It is sometimes challenging to differentiate IHC from other broad differential diagnoses, such as hemorrhagic cysts, biloma and cystic neoplasm (31). A careful evaluation of certain imaging features, such as the cyst complexity, including heterogeneous internal features (Fig. 2, 3) and fluid-debris levels (Fig. 2B, 4B), thickened walls and rim enhancement with perilesional edema (Fig. 3), is useful for achieving an accurate diagnosis (2, 4). The hyperintensity of the cysts on T1-weighted MR images (Fig. 4A) may help diagnose IHCs or hemorrhagic hepatic cysts (HHCs) (13). High-signal-intensity edema around the lesions on T2-weighted images may indicate IHCs rather than HHCs (2, 21). In contrast, discordance between US and CT findings regarding cyst features may suggest a diagnosis of HHCs (33). In HHCs, US usually characterizes the intracystic blood clot as papillary, nodular tumorous or irregular septal projections, making the lesion indistinguishable from a cystadenocarcinoma, whereas, CT cannot clearly visualize intracystic blood clot or hemorrhaging as well as US does. A finding of septations on both US and CT scan strongly supports the diagnosis of malignancy. Notably, IHCs are rarely multilocular (13).

However, imaging studies may not always show a positive result in the early phase of the infection. Indeed, changes to the infected cystic content can occur as late as one month after infection (23). Repeated imaging studies should be performed, even if no typical findings are obtained initially (24). ¹⁸F-Fluorodeoxyglucose positron-emission tomography coupled with CT can be used to support the diagnosis of an infectious cyst, although such an approach has drawbacks of high costs and limited availability (10, 25). If the diagnosis of IHC is equivocal, the demonstration of purulent fluid by aspiration should be employed to confirm the diagnosis.

Several limitations associated with the present study warrant mention. First, the sample size was small, which can lead to statistical errors that cannot be fully excluded. Second, this was a retrospective study based on medical records from routine clinical practice. Third, limitations in providing exhaustive information and the lack of a control group were inherent to this study design. Fourth, our patients might have had region-specific characteristics and might not have reflected the general population. For example, parasitic hepatic cysts are seldom encountered in our region. Given these limitations, our findings should be validated in a larger population.

In conclusion, 12 patients with IHCs were found in this retrospective analysis of the past 5 years, reminding us that IHC is not rare. *Klebsiella pneumoniae* accounted for the majority of identified pathogens in these patients. IHCs were managed predominantly with a combination of PCD and antibiotics. Despite the significantly larger size of the lesions, the length of the hospital stay of the patients with IHCs was significantly shorter than that of those with PLAs. The cystic wall keeps the infectious material confined within the IHC, resulting in good treatment outcomes. Nevertheless, infection of a hepatic cyst is a clinical diagnosis, and detecting such an infection can be challenging in some instances. Careful clinical and imaging evaluations can suggest an IHC, and the timely aspiration of the content can lead to an accurate diagnosis.

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