

Intrahepatic pancreatic pseudocyst: A review of the world literature

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Author contributions: Demeusy A and Cunningham SC designed and performed the research; Sill AM contributed analytic tools; Demeusy A, Sill AM and Cunningham SC analyzed the data; Demeusy A, Hosseini M and Cunningham SC wrote the paper; all authors drafted the article or revised it critically for important intellectual content, and approved the current version.

Conflict-of-interest statement: The authors declare no conflicts of interest regarding this study.

Data sharing statement: There are no additional data available for this study.

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Manuscript source: Invited manuscript

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Received: June 25, 2016
 Peer-review started: June 28, 2016
 First decision: September 7, 2016
 Revised: September 26, 2016
 Accepted: November 1, 2016
 Article in press: November 2, 2016
 Published online: December 18, 2016

Abstract

AIM

To investigate and summarize the literature regarding the diagnosis and management of intrahepatic pancreatic pseudocysts (IHPP).

METHODS

A literature search was performed using PubMed (MEDLINE) and Google Scholar databases, followed by a manual review of reference lists to ensure that no articles were missed. All articles, case reports, systematic reviews, letters to editors, and abstracts were analyzed and tabulated. Bivariate analyses were performed, with significance accepted at $P < 0.05$. Articles included were primarily in the English language, and articles in other languages were reviewed with native speakers or, if none available, were translated with electronic software when possible.

RESULTS

We found 41 published articles describing 54 cases since the 1970s, with a fairly steady rate of publication. Patients were predominantly male, with a mean age of 49 years. In 42% of published cases, the IHPP was the only reported pseudocyst, but 58% also had concurrent pseudocysts in other extrapancreatic locations. Average IHPP size was 9.5 cm and they occurred most commonly (48%) in the left hemiliver. Nearly every reported case was managed with an intervention, most with a single intervention, but some required up to three interventions. Percutaneous treatment with either simple aspiration or with an indwelling drain were the most common interventions, frequently performed along with stenting of the pancreatic duct. The size of the IHPP correlated significantly with both the duration of treatment ($P = 0.006$) and with the number of interventions required ($P = 0.031$). The duration of therapy also correlated with the initial white blood cell (WBC) count ($P = 0.048$).

CONCLUSION

Diagnosis of IHPP is difficult and often missed. Initial size and WBC are predictive of the treatment required. With appropriate intervention, most patients achieve resolution.

Key words: Pseudocyst; Intrahepatic; Percutaneous; Pancreatic; Drainage

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Core tip: Intrahepatic pancreatic pseudocysts (IHPPs) are rare and the pathophysiology is not entirely clear, but they likely result from proteolytic pancreatic fluid tracking from the pancreas into the surrounding tissue. This fluid may then migrate along planes such as the hepatogastric or hepatoduodenal ligaments, to penetrate the hepatic parenchyma. The initial size of the IHPP and the initial white blood cell are predictive of the number of treatments required and the overall duration of treatment required. Percutaneous approaches have been successful and result in good clinical outcomes.

Demeusy A, Hosseini M, Sill AM, Cunningham SC. Intrahepatic pancreatic pseudocyst: A review of the world literature. *World J Hepatol* 2016; 8(35): 1576-1583 Available from: URL: <http://www.wjgnet.com/1948-5182/full/v8/i35/1576.htm> DOI: <http://dx.doi.org/10.4254/wjh.v8.i35.1576>

INTRODUCTION

A pancreatic pseudocyst is an abnormal collection of pancreatic fluid generally due to pancreatitis, exists for at least 4 wk, have a well-defined wall, and contain essentially no solid material^[1,2]. They are more commonly seen in patients with alcohol-associated pancreatitis (20%) than with gallstone pancreatitis (6.6%)^[3]. Although most commonly immediately peripancreatic or intrapancreatic, they can occur in truly extrapancreatic locations throughout the peritoneal cavity as well as the mediastinum^[4,5].

Extrapancreatic pseudocysts are relatively uncommon, estimated to occur in up to 22% of patients with pancreatic pseudocysts^[5]. The location depends on where the pancreatic enzymes are released and the path they travel. One of the least common locations for truly extrapancreatic pseudocysts is within the liver^[4,5]. Here we describe such a case of an intrahepatic pancreatic pseudocyst (IHPP), and exhaustively review, and analyze, the world literature on IHPP.

A 56-year-old male with a history of acute alcoholic pancreatitis presented with intermittent chronic abdominal pain. Magnetic resonance imaging revealed a 1.3-cm lesion in the body of the pancreas consistent with a small pancreatic pseudocyst. Computed tomography (CT) 4 mo later revealed a new, 18-cm-long, bilobed fluid collection, wrapped about the hepatoduodenal ligament,

not only communicating with the original fluid collection but also insinuating itself deeply into the hepatic parenchyma (Figures 1A), with evidence of communication to the erstwhile intrapancreatic pseudocyst (Figure 1B). Given worsening right upper quadrant abdominal pain, fever, chills, anorexia and significant weight loss, and an unknown age of the new IHPP, percutaneous transhepatic drainage was performed of the more superficial, inferior lobe (Figure 2, fluid was high-amylase and culture-negative), as well as endoscopic pancreatic sphincterotomy, and pancreatic-duct stenting. Follow-up CT one week later revealed a significant reduction in the size of both lobes of the pseudocyst. Three weeks later, however, he developed worsening abdominal fullness, pain and fevers. Repeat CT showed the superficial, inferior lobe to be well drained with the pigtail in place (Figure 3A), but the deeper superior collection was found to be larger containing a small bubble of gas (Figure 3B), with the connecting bridge collapsed. The drain was therefore repositioned into this deeper lobe (Figure 4, culture-positive). Following this procedure, the patient improved clinically and was discharged on 4 more weeks of IV antibiotics. Two weeks later he required aspiration of a small liver abscess (low-amylase, culture-positive), although his pseudocysts remained collapsed. At this point the drain was removed. Interval imaging one month and three months (Figure 5) later revealed no residual fluid collections and he remains drain-free, off antibiotics, gaining weight, and productive at work.

MATERIALS AND METHODS

A PubMed and Google Scholar search using key words "pseudocyst", "pancreatic", and "intrahepatic" followed by extensive cross-reference review revealed 41 published articles on patients with IHPP. All articles, case reports, systematic reviews which also added a case, letters to editors, and abstracts were analyzed and the data tabulated for comprehensive review and statistical analysis. Bivariate analyses were performed in Statistical Package for the Social Sciences (IBM Corporation, New York, NY, United States). Statistical review of the study was performed by a biomedical statistician.

Articles included were primarily in the English language, but also included French, German, Portuguese, Czech, Korean, and Japanese. Foreign-language articles were reviewed with native speakers or, if native speakers were not available, then the articles were translated with electronic software when possible.

RESULTS**Prevalence and patient characteristics**

We identified 41 articles containing 54 cases of IHPP in the literature, the earliest identified case being published in 1974 (Table 1). These are primarily single case reports and mini case series but included two relatively thorough review articles which reviewed 26 cases^[6] and 23 cases^[7]. Two of the cases were notable in that the IHPP formation

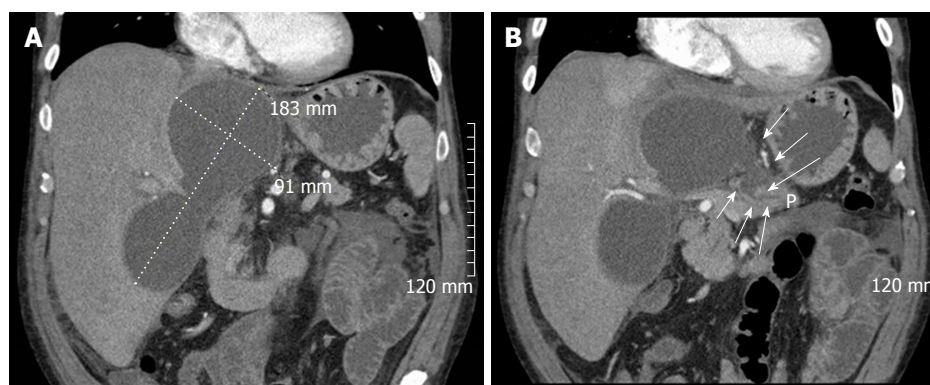


Figure 1 Abdominal computed tomography images showing bilobed intrahepatic pancreatic pseudocysts (A), including connection to main pancreatic duct (B, arrows).



Figure 2 Abdominal computed tomography image showing percutaneous transhepatic drainage of the more superficial, inferior lobe.

was thought to be secondary to ectopic pancreatic tissue and not an inflammatory pancreatic process^[8,9]. In many of the cases (42%), the IHPP was the only reported pseudocyst, but a significant number also had other concurrent pseudocysts, the most common of which were intra- or peripancreatic pseudocysts (71%).

Diagnosis

Diagnosis of an IHPP can be difficult as it is uncommon and it is not often part of the initial differential of a patient presenting with abdominal pain. Furthermore, if the presentation is delayed, imaging may reveal the IHPP but without inflammatory changes of the pancreas. Abdominal pain was the primary complaint in 91% of cases, but physical exam was generally nonspecific. Only 17% ($n = 9$) of patients were noted to have a palpable abdominal mass or hepatomegaly, and 15% ($n = 8$) had peritoneal signs. Initial diagnosis was often *via* CT (53%) or ultrasound (US) (33%) but nearly every patient in our database (91% of cases where imaging is mentioned) did get a CT scan at some point in the diagnostic or therapeutic process, and CT is generally considered to be the imaging modality of choice for these patients currently. Prior to the widespread availability of the CT scan, however, a significant workup was often done to identify the etiology of a patient's presentation

and in some cases would include a gastrointestinal transit studies, endoscopy, venogram, arteriogram, or exploratory laparotomy where the lesions were finally identified^[10-12]. Endoscopy has been used effectively in several cases, not only including initial diagnosis^[13], but also with therapeutic intervention^[14,15], as discussed further below.

The diagnosis of an IHPP was often delayed with the lesions often initially being mistaken for intrahepatic biliary dilatation, hemangioma, hepatic cyst, pyogenic liver abscess, amebic abscess, biloma, malignancy, echinococcal cyst, or even peritoneal tuberculosis^[10,13,16-19]. Although IHPP lesions may be clinically suspected in a patient based on the presentation and radiological imaging, definitive diagnosis was rarely made until analysis of the cystic fluid was performed demonstrating a high amylase content^[6,7,17,20,21].

Management

Despite advancements in, and the increasing availability of, imaging modalities, especially the CT scan, the number of reported cases and the type of management techniques have not evolved significantly. There are no widely accepted management guidelines for IHPPs and therefore clinicians have tailored the treatment to the individual patient based on judgment, taking into account many factors, such as underlying etiology, location of the pseudocyst, concomitant lesions, and other patient comorbidities.

Most patients reviewed were symptomatic (91% of reported cases) and required either transcutaneous or surgical intervention. Prior to the development of advanced radiological imaging, more patients underwent a laparotomy and open drainage^[10,12,22].

In recent years, however, several less invasive methods have been used to manage IHPPs. Unlike the more commonplace peripancreatic or intrapancreatic pseudocysts, for IHPPs the most common method was percutaneous aspiration or drainage (Table 2) which provided a definitive diagnosis, and was usually well tolerated with minimal complications in these patients^[6,7,23]. Simple needle aspiration alone with either US or CT

Table 1 Published cases

Ref.	Year	Language	Clinical features
Gautier-Benoit <i>et al</i> ^[12]	1974	French	Abdominal pain, weight loss
Cécile <i>et al</i> ^[10]	1974	French	Same patient as published by Gautier
Quevedo <i>et al</i> ^[16]	1975	Portuguese	Unknown location, died prior to intervention
Siegelman <i>et al</i> ^[4]	1980	English	Edematous pancreas, IHPP aspirated
Epstein <i>et al</i> ^[21]	1982	English	2 patients. Abdominal pain, distension, vomiting, diarrhea, chest pain, ascites
Hospitel <i>et al</i> ^[18]	1983	French	
Atienza <i>et al</i> ^[38]	1987	French	Abdominal pain, jaundice, palpable liver
Roche <i>et al</i> ^[11]	1987	French	Weight loss, hepatomegaly, splenomegaly
Shimayama <i>et al</i> ^[39]	1988	Japanese	Abdominal pain, febrile
Lantink <i>et al</i> ^[22]	1989	English	Abdominal pain
Schaefer <i>et al</i> ^[8]	1989	German	Abdominal pain, anorexia, DVT/PE
Okuda <i>et al</i> ^[34]	1991	English	2 patients, abdominal pain, anorexia, guarding; 1 resolved spontaneously
Slim <i>et al</i> ^[40]	1992	French	
Aiza <i>et al</i> ^[37]	1993	English	Right epigastric pain
Hamm <i>et al</i> ^[5]	1993	German	Abd pain, fever, weight loss
Králík <i>et al</i> ^[9]	1993	Czech	8 patients
Wang <i>et al</i> ^[27]	1993	English	Abdominal pain, pruritis, dark urine, light stools
Scappaticci <i>et al</i> ^[35]	1995	English	Abdominal pain, weight loss
Bayo Poleo <i>et al</i> ^[41]	1997	Spanish	Abdominal pain, blood per rectum
Lederman <i>et al</i> ^[23]	1997	French	Epigstric pain and tenderness, peritonitis
Mehler <i>et al</i> ^[30]	1998	French	Abdominal pain, palpable liver
Mofredj <i>et al</i> ^[6]	2000	English	3 patients, abdominal pain, vomiting, diarrhea, jaundice, guarding
Sugiyama <i>et al</i> ^[42]	2000	Japanese	
Shibaski <i>et al</i> ^[33]	2002	English	Abdominal pain, tenderness, guarding, diarrhea
Bong <i>et al</i> ^[43]	2003	Korean	Abdominal pain
Ancel <i>et al</i> ^[44]	2005	French	Abdominal pain
Balzan <i>et al</i> ^[29]	2005	English	Abdominal pain, cystic dystrophy of duodenal wall
Bhasin <i>et al</i> ^[25]	2005	English	Abdominal pain
Gamanagatti <i>et al</i> ^[20]	2006	English	Abdominal pain, rigid abdomen
Les <i>et al</i> ^[17]	2006	English	Vomiting, melena, tachycardia
Casado <i>et al</i> ^[26]	2007	English	Abdominal pain, nausea
Yi <i>et al</i> ^[45]	2008	Korean	Abdominal pain
Al-Ani <i>et al</i> ^[19]	2009	English	Epigastric pain, fever, diaphoresis, guarding, palpable abdominal mass
Atia <i>et al</i> ^[36]	2009	English	
Chahal <i>et al</i> ^[13]	2009	English	Abdominal pain, nausea, vomiting, hepatomegaly
Guesmi <i>et al</i> ^[7]	2009	English	Abdominal pain
Bhasin <i>et al</i> ^[24]	2010	English	Abdominal pain, vomiting, weight loss
Kibria <i>et al</i> ^[14]	2010	English	2 patients, abdominal pain
Baydar <i>et al</i> ^[15]	2013	English	Abdominal pain
Devangan <i>et al</i> ^[28]	2015	English	Abdominal pain, nausea, vomiting, jaundice
Martínez-Sanz <i>et al</i> ^[46]	2015	English	Abdominal pain, weight loss, anorexia, palpable epigastric mass
Current case	2016	English	Abdominal pain

DVT: Deep-vein thrombosis; PE: Pulmonary embolism; IHPP: Intrahepatic pancreatic pseudocysts.

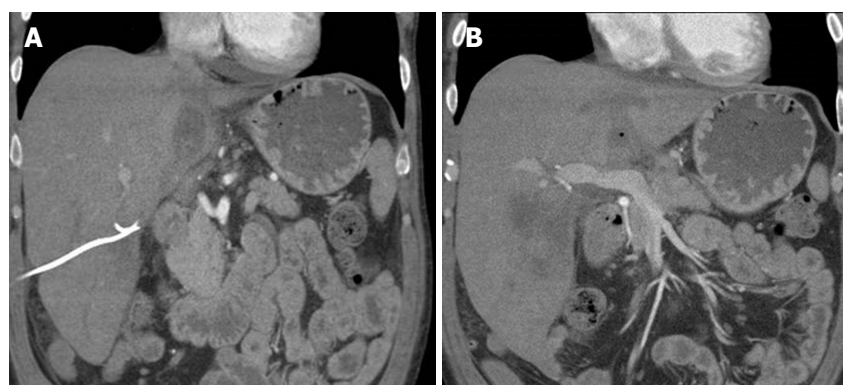


Figure 3 Abdominal computed tomography images showing the superficial, inferior lobe to be well drained with the pigtail in place (A), but the deeper superior collection containing a small bubble of gas (B).

guidance was performed as often as drainage (Table 2). While it aided in the definitive diagnosis by providing an

amylase value of the fluid, it was often not completely therapeutic, with 38% of the aspiration-only cases in

Table 2 Summary of cases (*n* = 54)

Mean age (range)	Gender (%)	No. of IHPP (% of cases)	Size (range)	Location (% , <i>n</i>)	No. of interventions (% , <i>n</i>) ¹	Intervention (% , <i>n</i>) ²	Infection (% , <i>n</i>) ³
49 (15-76) yr	Male (80%)	1 (67)	9.5 (3-18) cm	Right lobe (11%, 6)	0 (9%, 4)	Operative (25%, 15)	Culture positive
		2 (15)		Left lobe (48%, 26)	1 (60%, 27)	Simple aspiration (28%, 17)	(16%, 5)
	Female (20%)	3 (13)		Right and left lobes (17%, 9)	2 (24%, 11)	Percutaneous drainage (28%, 17)	Culture negative
		4 (4)		Unavailable (24%, 13)	3 (7%, 3)	Endoscopic (8%, 5)	(84%, 27)

¹Excludes three cases lacking mention of an intervention, and two cases with non-IHPP interventions; ²Accounts for total number of interventions performed on patient population; some patients underwent several interventions. Does not include those patients who underwent nasopancreatic drainage (5%, 3) or medical intervention (5%, 3); ³Excludes 15 reports which did not make mention of culture status. IHPP: Intrahepatic pancreatic pseudocysts.



Figure 4 Abdominal computed tomography image showing drain was repositioned into the deeper lobe seen in Figure 3B.



Figure 5 Abdominal computed tomography image showing resolution of the intrahepatic pancreatic pseudocysts at 3 mo following the initial intervention.

the literature requiring additional interventions.

In addition to either percutaneous drainage or aspiration, there were several other approaches or adjunctive procedures which have been utilized to manage an IHPP. Although most cases are managed percutaneously or operatively, there is an increasing experience with endoscopic approaches. These have included endoscopic retrograde pancreatography (ERCP) with pancreatic duct stenting, endoscopic transpapillary nasopancreatic drainage, pancreatic duct balloon dilatation, and ERCP-guided aspiration (Table 2)^[13-15,24,25]. Bhasin *et al.*^[24,25] for example, reviewed 11 patients with atypically located pseudocysts, treated with ERCP and transpapillary nasopancreatic drainage. Placement of a nasopancreatic drain across the disruption was successful in 10 of the 11 patients (90.9%), with resolution of the extrapancreatic pseudocysts in 4-8 wk, with a follow-up period of 3-70 mo.

Operative interventions on patients with IHPPs have been generally reserved for those refractory to, or inappropriate for, nonoperative treatment, such as cases of diagnostic uncertainty^[26], rupture^[22], or severe infection^[27]. All 15 operative interventions (Table 2) to manage these IHPPs were open operations and included partial resection with drainage of the cavity into a Roux limb^[8,9,22] and complete resection/excision of the lesion^[26,28]. In 10 reports the operation was the first intervention, in 4 reports it was the second intervention, and in one report it was the third intervention (likely,

see below). The four second-intervention operations followed percutaneous aspiration in two cases^[8,22] and percutaneous drainage in two cases^[12,29]. The one third-intervention report^[5], however, included 19 extrapancreatic pseudocysts, eight of which were intrahepatic, but it is not clearly reported which if any of those eight IHPP patients underwent which operation. We found no report of postoperative pancreatic fistula development complicating operation.

Outcomes/complications

Although spontaneous resolution of pseudocysts with conservative (noninterventional) management has been reported, complications in these cases included persistent nausea and vomiting, rupture, fistula tract formation, abscess formation if not sterile, or obstruction of the venous or biliary system due to mass effect.

Outcomes were generally very good for patients presenting with these IHPP, with 45% of patients achieved complete resolution of both the cyst and symptoms. In addition, 21% of patients experienced partial resolution of the cyst but total resolution of their symptoms by the time of the follow-up. In our analysis, we noted a statistically significant correlation between the size of the IHPP and both the duration of treatment ($P = 0.006$) and the number of interventions required ($P = 0.031$).

Infection of these pseudocysts was reported in

16% of the cases (Table 2), but an organism is not always reported and it is usually unknown whether organisms were part of the original process, or later infected the pseudocyst. Many cases were associated with leukocytosis [mean reported white blood cell (WBC) count of 15000] but without correlation to positive cultures on pseudocyst aspiration. Although there is no correlation between infection and final outcome, we did note a statistically significant positive correlation between the initial WBC count and the duration of treatment ($P = 0.048$).

There are four reported deaths in the IHPP literature, three of which had undergone a percutaneous drainage procedure^[7,16,20,30]. Of note, two of these cases had an infectious component either of the intrahepatic pseudocyst or another concomitant pseudocyst^[20,30].

DISCUSSION

IHPPs frequently present with abdominal pain and are diagnosed with either US or CT imaging. Although the mechanism by which IHPPs develop is not entirely clear, the time to presentation varies tremendously with reports ranging from 6 d to 2 mo^[26,29]. It is understood, however, that although a collection of pancreatic fluid is not called a "pseudocyst" until it has been present for at least 4 wk, according to the 2012 revision of the Atlanta classification and definitions by international consensus^[1], many of the IHPP reports reviewed here predate that nomenclature. Therefore, we have retained the term "pseudocyst" in these cases.

The process of IHPP formation begins of course with an inflammatory or traumatic episode during which pancreatic duct disruption occurs, resulting in the leakage of pancreatic fluid into the surrounding tissue. Then, once the pancreatic proteolytic enzymes are found outside the pancreatic parenchyma, they may migrate along planes (e.g., hepatogastric, hepatoduodenal) or, by digesting tissue, across planes into the hepatic parenchyma. The end result of this is often observable by imaging and on anatomical-pathological findings, evidencing rupture of the main pancreatic duct and active communication with the intrahepatic collection, as shown in several reported cases^[5,21,31-34], and in our case (Figure 1). However, communication does not always persist and in these select cases, may actually be more amenable to conservative management or observation.

The most common extrapancreatic location for pancreatic pseudocyst development is within the lesser sac and may be seen alone or along with an IHPP^[4]. An IHPP may be either subcapsular or intraparenchymal with CT imaging of the former characterized by peripheral location and a biconvex appearance^[20,29]. They are further characterized by their spatial location in either the right lobe, left lobe, or involving both lobes. It has been hypothesized that the location of the pancreatic inflammation (e.g., head vs tail) is correlated with the tract the fluid takes and eventual location in

the liver of the IHPP with several different paths described^[4,5,13,15,16,19,33-37]. However, we did not find this to be a statistically significant correlation. The left lobe was by far the most common location for an IHPP (Table 2) with fluid that likely traveled through the hepatogastric ligament.

Although IHPPs may resolve spontaneously, this is uncommon. As in our case, symptoms, or occasionally diagnostic uncertainty, generally require intervention to prevent complications such as infection, fistula, rupture, and mass-effect obstruction of the biliary or portal systems. Our experience certainly echoes that in the literature, *viz.*, that percutaneous or surgical drainage is usually well tolerated and results in resolution of the pseudocyst and improvement in associated symptoms. Treatment of course depends on the location, size, and effects of the pseudocyst, patient stability, and whether or not the lesion remains in persistent communication with the pancreas. In addition to the primary drainage methods to address the IHPP, several adjunctive procedures have been done, some of which were reportedly novel for this indication. Examples include placement of pancreatic duct stent, endoscopic placement of a nasopancreatic drain, or FNA during endoscopy^[13,24,25]. Recurrence of these pseudocysts has not been described in the literature although is certainly possible, and indeed likely, that there were recurrences, the absence of which may be due to lack of longitudinal follow-up, lack of publication, or the rarity of the condition.

Our case was particularly interesting in that the pseudocyst was very large and bilobed, originating around the hepatoduodenal ligament and extending into the liver. The interval presentation between his pancreatitis flare and initial presentation allowed the pancreas to return to fairly normal appearance. This supports the idea that the hepatoduodenal ligament may be a critical structure in the formation of IHPPs.

In conclusion, although IHPPs are often not included in the differential diagnosis of a patient presenting with an intrahepatic lesion, in the right setting and population of patients, it should be considered as an important differential diagnosis. Analysis of this sparse literature has been instructive in revealing a significant correlation between the size of the IHPP and both the duration of treatment and the number of interventions required. The duration of therapy was also correlated with the initial WBC count. These observations may help with prediction of the clinical course in future cases.

COMMENTS

Background

The authors have summarized and analyzed the literature on intrahepatic pancreatic pseudocysts (IHPP), to facilitate an appreciation for this study's relevance and to help understand its significance for the field as a whole.

Research frontiers

Current important areas in the research field as related this study include the establishment of a registry.

Innovations and breakthroughs

The key advances in the current study is the recognition that size of the IHPP correlates with both the duration of treatment and the number of interventions required. The duration of therapy was also correlated with the initial white blood cell count.

Applications

These observations may help with prediction of the clinical course in future cases.

Peer-review

This is an interesting paper on intrahepatic pseudocyst. Conclusions are interesting. Please elaborate if possible more on the role of endoscopic treatment in such cases.

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P- Reviewer: Furihata M, Somani P **S- Editor:** Gong ZM

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