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RESEARCH ARTICLE

Inflammatory pseudotumors of the liver: experience of 114 cases

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Abstract Hepatic inflammatory pseudotumors (HIPT) are rare benign neoplasms with unknown etiology and a great potential for mimicry, challenging diagnostics, and treatment features. The aim of the study was to retrospectively analyze the imaging, pathological, and clinical features of HIPT in our large cohort of patients in order to increase the understanding and suggest a scoring system for treatment approaches. Retrospective study analyzed 114 HIPT cases recorded from July 2006 to July 2012, when surgery was performed. Data were compared with chi-square test. In our study population, the mean age was 53.14±10.98 years, with 69 male and 45 female patients. Most presented symptoms were abdominal pain (59/144, 41.0 %), fever (48/114, 42.1 %), abdominal distension (35/144, 24.3 %), and weight loss (12/144, 8.3 %). Laboratory examinations were normal. Sixteen cases were HBsAg positive and 8 had liver cirrhosis. Most of the tumors were located in the right lobe (79/114, 69.3 %), 33 in the left lobe, and 2 in the caudal lobe. Three imaging modalities, such as ultrasonography (US), computed tomography (CT), and magnetic resonance imaging (MRI), were compared and showed significant differences in sensitivity and sensibility. HIPT diagnostics are challenging, and conservative treatment should be prioritized as soon as the diagnosis is made. CT and MRI seem to have comparable diagnostic sensitivity. We propose a guideline for consideration of operative approach.

Keywords Hepatic inflammatory · Pseudotumors · Diagnosis · Imaging characters · Treatment

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Introduction

Inflammatory pseudotumors (IPT) are uncommon benign neoplasms. Their origin is believed to be inflammatory or infectious in most of the cases since they presumably develop from a condition, which provokes a xanthogranulomatous inflammatory response that heals with scarring. Therefore, IPTs' histological profile is variable but with a predominance of inflammatory and myofibroblastic spindle cells. IPTs have been described in various tissues including heart, liver, and pancreas [1].

They might mimic a malignant tumor, particularly, metastatic disease.

The first report of hepatic IPT was described by Pack and Bakerin in 1953 [2] and until 2011, only about 300 cases had been reported in medical literature [3]. Because of its rareness,

there are no conclusive data on incidence, anatomic distribution, etiology, mortality, or malignant potential of IPTs. Furthermore, as a result, there is a lack of profound knowledge of their nature, resulting in a lack of clear clinical diagnostic and therapeutic guideline, as well as evidence for prognostic predictions. Due to the absence of standardized diagnostic approaches, most of IPT patients undergo surgical interventions a priori.

In our study, we conducted a retrospective analysis of 114 cases with hepatic IPT. All of the patients have been diagnosed and treated in our hospital. We describe the diagnostic imaging, pathological and clinical features were used to diagnose the IPTs, as well as the treatment alternatives that could have been applied. Our study aims to increase the understanding of hepatic IPT (HIPT), to compare medical imaging methods used for the diagnostics, and to propose potential diagnostic guidelines in order to facilitate diagnosis making and treatment approach to avoid redundant surgeries.

Materials and methods

We conducted a retrospective unicentric study on patients diagnosed with hepatic IPT and who underwent therapeutic surgery from July 2006 to July 2012, at the Eastern Hepatobiliary Surgery Hospital in Shanghai, China. A study population of 114 patients has been selected. The diagnosis of HIPT was always confirmed in pathology analysis. The clinical records were reviewed for (1) preoperative blood tests including tests for viral hepatitis, liver function (total bilirubin (TBIL), alanine aminotransferase (ALT), aspartate transaminase (AST)), and tumor markers (serum alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA), and carbohydrate antigen determinant (CA19-9)); (2) medical imaging modalities including ultrasonography (US), computer tomography (CT), and magnetic resonance imaging (MRI), from which at least one was used for diagnostics before the surgical intervention. We investigated the population characteristics, the sensibility and sensitivity of the imaging, as well as the predictive and diagnostic value of the laboratory parameters. Statistically, the data were compared by chi-square test. Differences with a P value<0.05 were considered significant.

Results

Patients and clinical data

The mean age of the patients in our study population was 53.14±10.98 years with 69 male and 45 female patients. The patients presented unspecific symptoms including abdominal pain (59/144, 41.0 %), fever (48/114, 42.1 %), abdominal distension (35/144, 24.3 %), weight loss (12/144, 8.3 %), hypodynamia (10/144, 7.0 %), nausea (15/144, 10.4 %), emesis (14/144, 9.7 %), and radiating pain (11/144, 8.0 %). One hundred ten cases presented with solitary tumor and 4 cases with multiple tumors. Tumor markers were mostly in normal range: AFP (mean±SD: 21.83±138.30 ug/l), CEA (mean±SD: 4.64±12.35 ug/l), and CA19-9 (mean±SD: 99.94±237.03 ug/l). Several patients had an abnormal hepatic function showing hyper TBIL (mean±SD: 21.82±6.56 umol/L), ALT (mean±SD: 36.15±39.12 u/L), and AST (mean±SD: 55.09±294.47 u/L). Sixteen cases were positive of HBsAg, and 8 had liver cirrhosis. Anatomically, tumors were mostly (in 79 cases) located in the right lobe, 33 in the left lobe, and 2 in the caudal lobe. None of the patients had a history of liver trauma or inflammatory bowel diseases. Thirty patients had a history of biliary tract disease, and 18 suffered from diabetes mellitus. All the patients underwent operations in our hospital; correspondently, 79 had right-liver tumor resection, 33 had left-liver tumor resection, and 2 had caudal-lobe tumor resection. There were very few postoperative complications including pleural effusion (22/114, 19.3 %), diaphragmatic fluid collection (21/114, 18.4 %), ascites (15/114, 13.2 %), intra-abdominal abscess (3/114, 2.6 %), bile leak (1/114, 0.8 %), wound infection (1/114, 0.8 %), hemorrhage (1/114, 0.8 %), and pneumonia (1/114, 0.8 %). All the patients recovered well and were discharged (Table 1).

Imaging features

All of the patients have had at least one medical imaging method used for the diagnostics. One hundred seven cases underwent US examination. Among them, there were 101 mixed echoes, 3 hyperechoic, and 3 hypoechoic foci. No patient showed isoechoic foci. Twenty lesions appeared with well-defined margins. Only 1 patient was diagnosed with HIPT.

Forty patients received a diagnostic preoperative CT scan. All the lesions demonstrated low density in the plain phase. In arterial phase, enhancement was rapid in 1, inhomogeneous in 29, peripheral in 4 lesions and no marked enhancement in 6 lesions. There were 31 lesions with well-defined margins. In 4 out of 40 patients, HIPT was diagnosed correctly.

Forty-six patients received MRI examination. In T1-weighted images, 44 cases were hypointense and 2 were isointense. In T2-weighted images, 8 cases were hypointense, 27 were isointense, 6 were hyperintense, and 5 presented a heterogeneous intensity. In the artery phase, enhancement was inhomogeneous in 35 lesions and peripheral in 2. The lesion margins were clearly identifiable in 5 cases and not clear in 41 cases. Five cases were correctly diagnosed with HIPT (Fig. 1a–c, Tables 2 and 3).

Statistically, the preoperative diagnostic performance (sensitivity, sensibility) of the three imaging modalities (US, CT, and MRI) shows considerable differences ($\chi^2=8.85$, $P=$

Table 1 Clinical characteristics

Clinical features	Data
Age (mean±SD) (y)	53.14±10.98
Gender (male/female)	69/45
Symptoms	
Abdominal pain	59
Fever	48
Abdominal distension	35
Weight loss	12
Hypodynamia	10
Nausea	15
Radiating pain	11
Vomit	14
Number of tumor	
1	110
≥2	4
AFP (mean±SD) (ug/l)	21.83±138.30
CEA (mean±SD) (ug/l)	4.64±12.35
CA19-9 (mean±SD) (u/ml)	99.94±237.03
TBIL (mean±SD) (umol/l)	21.82±56.56
ALT (mean±SD) (u/l)	36.15±39.12
AST (mean±SD) (u/l)	55.09±294.47
PT (mean±SD) (s)	11.80±1.01
HBsAg	
Positive	16/114
Negative	98/114
Cirrhosis	
No	106/114
Yes	8/114
Tumor location	
Right lobe	79/114
Left lobe	33/114
Caudate lobe	2/114
Past history of biliary tract disease	30
Past history of liver trauma	0
Associated diabetes mellitus	18
Associated Crohn's disease	0
Right liver tumor resection	79
Left liver tumor resection	33
Caudal lobe tumor resection	2
Postoperative complications, (n)	
Hemorrhage	1
Liver failure	0
Diaphragmatic fluid	21
Abscess	3
Bile leak	1
Pleural effusion	22
Wound infection	1
Ascites	15
Pneumonia	1

0.003). CT and MRI are more conclusive than US (US versus CT: χ^2=7.28, P=0.007; US versus MRI: χ^2=8.43, P=0.004). But there is no significant difference between CT and MRI (χ^2 =0.017, P=0.895). While CT and MRI appeared more efficient in diagnostic approaches, there were no statistical differences in the detection of tumor expansion between the three radiological methods (US, CT, and MRI: χ2=2.19, P=0.14; US versus CT: χ2=0.27, P=0.61; US versus MRI: χ2=1.44, P=0.23; CT versus MRI: χ2=2.12, P=0.15) (Tables 3 and 4).

Histopathological and immunohistochemical characteristics

Macroscopically, most of the tumors presented a grayish-white surface and hard tumor texture. Only 9 cases showed signs of liver cirrhosis. The mean tumor size was 3.8±2.4 cm in diameter (range 0.2 to 11.0 cm). Twenty-two lesions had evidence of hemorrhage.

Microscopically, most cases showed a typical pathological profile of a lymphoplasmacytic type with inflammatory cell infiltration including lymphocytes, plasma cells, and oxyphil cells. No atypical cells were seen in any of the patients (Fig. 2). Immunohistochemistry revealed 19.8 % (18/91) of HBsAg-positive patients. Some tumors expressed PCNA (6/14, 42.9 %), CK-18 (13/89, 14.6 %), CK-19 (9/95, 9.5 %), PCEA (42/85, 49.4 %), CD-34 (9/97, 9.2 %), MUC-1 (4/81, 4.9 %), and Hep-1 (3/95, 3.3 %) (Table 5).

Discussion

HIPTs are benign, hyperplastic, and mostly solitary tumor nodules. These non-parenchymal inflammatory lesions are often located in the right-liver lobe [4, 5]. To date, the exact etiology of HIPT still remains unknown. Some hypotheses of possible etiologies include autoimmune disorders, vascular diseases, and infections [6, 7]. In our study population, there were 30 cases with past history of biliary tract disease and 18 cases with diabetes mellitus. These cases have experienced infectious events before HIPT symptoms occurred. All of the symptoms that the patients presented with were unspecific. The most common clinical symptoms were abdominal pain (59/144, 41.0 %), fever (48/114, 42.1 %), and abdominal distension (35/144, 24.3 %). Other symptoms included were mostly weight loss, hypodynamia, nausea, vomit, and radiating pain. Most laboratory investigations, including liver functions and tumor markers, were normal. This underlines the benign nature of HIPT. However, we observed in our study what has been previously reported: HIPT associated slight elevations of liver enzymes and CA19-9 [8, 9]. Although liver enzymes, transaminases, and tumor markers as CEA and CA19-9 might be slightly increased in HIPT, one has to consider the limitation of their diagnostic impact. Most of the intra-abdominal inflammatory processes are associated with

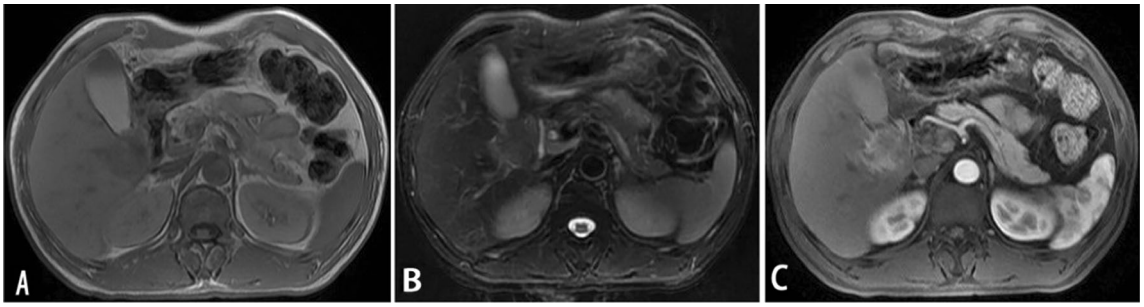

Fig. 1 MRI examination. **a** T1-weighted image with hypointense hepatic lesion. **b** T2-weighted images with isointense lesion. **c** Inhomogeneous enhancement in the artery phase, and the lesion margins were not clearly identifiable

Table 2 Imaging features of HIPT

Examination	Data
US examination	
Hyperecho	3
Hypoecho	3
Isoecho	0
Mixed echoes	101
CT examination	
Plain phase	
Low density	40
High density	0
Heterogeneous density	0
Arterial phase	
Rapidly enhanced	1
Inhomogeneously enhanced	29
No marked enhanced	6
Peripherally enhanced	4
Slightly enhanced	0
Partly enhanced	0
Gradually enhanced	0
MRI examination	
T1-weighed phase	
Low intensity	44
Isointensity	2
High intensity	0
Heterogeneous intensity	0
T2-weighed phase	
Low intensity	8
Isointensity	27
High intensity	6
Heterogeneous intensity	5
Arterial phase	
Rapidly enhanced	0
Inhomogeneously enhanced	35
No marked enhanced	8
Peripherally enhanced	2
Slightly enhanced	1
Partly enhanced	0
Gradually enhanced	0

transaminases and an unspecific increase of CEA. Only significant elevations of these values might considerably assist to differentiate hepatic carcinoma from HIPT.

Microscopically, HIPT is characterized by fibroblastic proliferation and chronic inflammatory cell infiltration [10]. Different proportions or distributions of histological compositions might reflect in different areas within one lesion. This results in a variety of imaging appearance and diagnostic hardness. Adequate sampling in multiple sections is crucial in order to establish the correct diagnosis.

In our study, 107 cases received a US diagnostic, 40 cases underwent a CT scan, and 44 cases underwent MRI. Most of the patients presented with mixed echoes in the US examination, the tumor margins were well defined in 20 cases and diffused (pathologic) in 87. Only one patient was correctly diagnosed with HIPT with the help of US exam. On the CT scans, all the tumors showed low density during the plain phase, and most were inhomogeneously enhanced during the arterial phase (29/40, 72.5 %). Tumor margins were well defined in 9 and pathological in 31 cases. In 4 out of 36 patients, HIPT was correctly diagnosed with a CT scan. Five cases were diagnosed correctly with the help of MRI. MRI examinations revealed 44 lesions with low intensity in T1-weighted phase and 27 lesions with isointensity in T2-weighted phase. Likewise, most cases were inhomogeneously enhanced during arterial phase (35/46, 76.1 %). The tumor margins were well defined in 5 cases and diffused in 41 cases. Yan etc. [10] suggested that the reason for these phenomena was the absence of a direct hepatic arterial blood supply, and the capillary vessels that were being surrounded by the tumors.

Table 3 Preoperative diagnostic performance of the three imaging

Imaging modalities	Correct	Incorrect/inconclusive
US	1	106
CT	4	36
MRI	5	41

US, CT, and MRI: $\chi 2=8.85$, $P=0.003$; US versus CT: $\chi 2=7.28$, $P=0.007$; US versus MRI: $\chi 2=8.43$, $P=0.004$; CT versus MRI: $\chi 2=0.017$, $P=0.895$

Table 4 Boundary of tumors in the three imaging

Imaging modalities	Well defined	Ill defined
US	20	87
CT	9	31
MRI	5	41

US, CT, and MRI: $\chi 2=2.19$, $P=0.14$; US versus CT: $\chi 2=0.27$, $P=0.61$; US versus MRI: $\chi 2=1.44$, $P=0.23$; CT versus MRI: $\chi 2=2.12$, $P=0.15$

Statistically, our results show an obvious superiority of CT and MRI over US in terms of diagnostic conclusiveness (US, CT, and MRI: $\chi 2=8.85$, $P=0.003$). However, CT and MRI showed no statistically significant difference in their diagnostic accuracy for HIPT (CT versus MRI: $\chi 2=0.017$, $P=0.895$). This allows the conclusion that both examination techniques are comparable, and when HIPT is being suspected, there is no advantage of combining CT and MRI techniques or use one or the other in order to obtain a more conclusive diagnostic. When we analyzed the visibility of tumor margins, surprisingly, the three imaging modalities showed no statistical difference (US, CT, and MRI: $\chi^2=2.19$, $P=0.14$; US versus CT: $\chi^2=0.27$, $P=0.61$; US versus MRI: $\chi 2=1.44$, $P=0.23$; CT versus MRI: $\chi^2=2.12$, $P=0.15$).

Facing the fact that clinical symptoms are mostly unspecific, the laboratory values are often not abnormal, and the medical imaging are not always conclusive, the definite diagnosis of HIPT mainly manifests in the histopathologic report. Koea et al. claimed that the diagnosis of HIPT was relatively straightforward when a pathology statement is present. He described the lesions consisting mainly of densely hyalinized collagenous tissue with inflammatory infiltrate of predominantly plasma cells [11]. Further research, however, revealed more details about a very complex and variable cellular composition of HIPT. Based on the cell composition, some authors

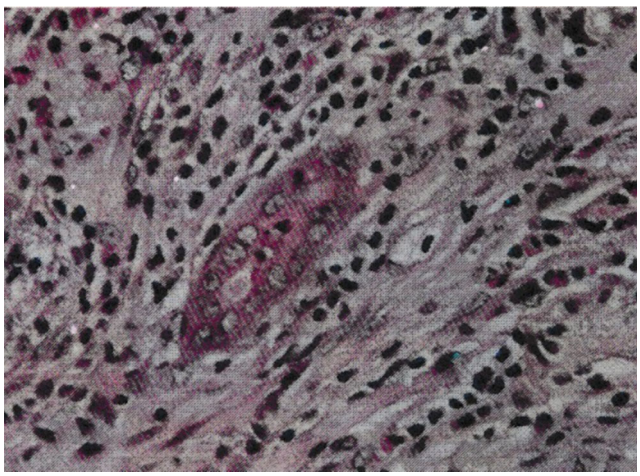

Fig. 2 Representative pathology report: lesions of densely hyalinized collagenous tissue with inflammatory infiltrate with predominantly plasma cells and eosinophils; no atypical cells or atypical mitoses, no central necrosis, periportal inflammatory reaction

Table 5 Immunohistochemical analysis

Antibody	Percentage of positively
Hep-1	3/95 (3.3 %)
HBsAg	18/91 (19.8 %)
CK18	13/89 (14.6 %)
CK19	9/95 (9.5 %)
CD34	9/97 (9.2 %)
PCNA	6/14 (42.9 %)
PCEA	42/85 (49.4 %)
MUC-1	4/81 (4.9 %)
SMA	42/84 (50 %)
VI	2/7 (28.6 %)

divided HIPT into three histopathologic subtypes: xanthogranuloma-type pseudotumors, plasma cell granuloma-type pseudotumors, and sclerosing pseudotumors [12]. These types differ not only in pathological, but also in clinical features such as clinical presentation, locations, and shapes. Still, there is no uniformly accepted classification system. It was previously reported that the presence of myofibroblastic spindle cells, infiltrated plasma cells, and chronic inflammatory cells without cellular anaplasias or atypical mitoses was the histopathologic characteristics of HIPT [13, 14]. In our study, these features were compatible with our findings, PCEA and SMA were positive in most cases. Other studies classified hepatic inflammatory pseudotumors into two categories based on their major histologies: fibrohistiocytic (with histiocytic infiltration, such as xanthogranulomatous inflammation and multinucleated giant cells) and lymphoplasmacytic types (with inflammatory processes, mainly infiltration by lymphocytes and plasma cells). Their clinicopathological features, including immunohistochemistry, clinical presentation, and the location of the tumors, were diverse.

Despite the benign nature of HIPT, some authors reported their recurrence and potential of malignant transformation [15, 16]. Thus, the treatment still remains a controversial point in the literature. Some authors recommended radical resection of the lesions, if the anatomic location allows it or there are no contra indications to the surgical intervention [5, 17]. Others assertively opine that conservative approaches including antibiotics, nonsteroidal anti-inflammatory drugs, steroids, and biliary drainage should be prioritized [18, 19]. In our study, all the patients underwent a surgery because of the diagnostic uncertainty, even if the imaging was very suggestive in some cases.

In conclusion, the most important pace toward a correct HIPT treatment is the accurate diagnosis. Our results allow to list a constellation of clinicopathological features, which are suggestive for HIPT and could be used as a basis for clinical diagnostic guidelines: (1) HIPT mostly presents with

atypical symptoms, however, predominantly with abdominal pain, fever, and abdominal distension; (2) patients with past medical history of intra-abdominal inflammatory disease, especially biliary tract diseases, as well as diabetes mellitus, are more likely to develop HIPT; (3) blood tests are frequently normal, slightly elevated liver enzymes and CA19-9, as well as patients with associated hepatitis virus infection and liver cirrhosis are favorable factors to the diagnosis making; (4) lesions located in the right lobe are more likely to be HIPT than those in the left (rare) or caudate lobe (very rare); (5) through US examination, the majority showed mixed echoes; (6) during the CT plain phase, the majority showed low density, and most demonstrated inhomogeneously enhanced in arterial phase; (7) during the T1-weighed phase, the majority showed low intensity. During the T2-weighed phase, most appeared in isointensity. And doing arterial phase, most also demonstrates inhomogeneously enhanced. When our clinicians meet similar cases, we should remain alert for the diagnosis of HIPT. And then, US and CT or MRI should be recommended. Indeed, we could reach to the right diagnosis on the basis of imaging findings, clinical, and test characteristics.

Sometimes, fine-needle biopsy could be helpful. The conservative treatment should be prioritized as soon as the diagnosis is determined. If the conservative treatment is not efficient, operation should be considered.

Conflicts of interest None.

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