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Review paper

Intrahepatic splenosis: a world review

Weh Shien Toh[1], Kai Siang Chan[1,2], Cristine Szu Lyn Ding[3], Cher Heng Tan[4], Vishal G. Shelat[2]

[1]MOH Holdings, Singapore
[2]Department of General Surgery, Tan Tock Seng Hospital, Singapore
[3]Department of Pathology, Tan Tock Seng Hospital, Singapore
[4]Department of Diagnostic Radiology, Tan Tock Seng Hospital, Singapore

Abstract

Splenosis is defined as the autotransplantation of viable splenic tissue throughout various anatomic compartments. Intrahepatic splenosis (IHS) is rare and diagnosis is often challenging. This study aims to provide a comprehensive review on IHS. A literature review was performed on PubMed database. Fifty-six articles with 59 reported cases were included. The majority of the patients were male (*n* = 49, 83.1%). Median age was 51 years. Risk factors for hepatocellular carcinoma (HCC) included hepatitis B (*n* = 8, 13.6%) and cirrhosis (*n* = 12, 20.3%). The majority of the patients were asymptomatic (62.7%) and did not have risk factors for HCC (55.9%). We report a diagnostic triad for IHS: 1) previous history of abdominal trauma or splenectomy, 2) absence of risk factors for liver malignancy and 3) typical imaging features. Non-invasive diagnostic tests such as technetium-99m-tagged heat-damaged red blood cell scintigraphy are useful in diagnosis. Malignancy should be ruled out in the presence of risk factors for HCC.

Key words: intrahepatic splenosis, hepatocellular carcinoma, splenectomy, liver tumour, liver mass.

Address for correspondence:

Dr. Kai Siang Chan, Department of General Surgery, Tan Tock Seng Hospital, 11 Jalan Tan Tock Seng, Singapore 308433, e-mail: kchan023@e.ntu.edu.sg

Introduction

Splenosis was first described by Albrecht in 1896 and subsequently named by Buchbinder and Lipkoff in 1939 [1]. Splenosis is defined as the autotransplantation of viable splenic tissue throughout various anatomic compartments of the body. Previous splenectomy, abdominal trauma or splenic rupture predisposes to splenosis [2]. Intra-abdominal splenosis involving the serosal surface of the small or large bowel, parietal peritoneum and mesentery is relatively common [3]. However, intrahepatic splenosis (IHS) is rare, with many authors quoting fewer than 50 cases published to date [4-6]. Diagnosis of IHS is often challenging as patients are often asymptomatic or present with non-specific abdominal pain, and radiological imaging findings may resemble other hepatic lesions, particularly hepatocellular carcinoma (HCC), adenoma and focal nodular hyperplasia (FNH). With the increase in abdominal imaging for patients with vague abdominal symptoms and better quality of imaging technology, incidental liver lesions are common. Once a liver lesion is detected, a clinician is faced with a challenge to diagnose the lesion with certainty with the primary goal of ruling out a malignancy. IHS is a benign condition and does not warrant surveillance or intervention unless the patient is severely symptomatic. Definitive diagnosis of IHS is possible with percutaneous needle biopsy, intra-operative frozen section or post-operative histopathological analysis or technetium-99m-tagged (Tc-99m) heat-damaged red blood cell (RBC) scintigraphy. However, patients undergoing additional diagnostic tests may bear unnecessary costs and morbidity. This is compounded by anxiety associated with the waiting interval or knowledge of false negative reports. Hence it is important to understand this pathological condition and its clinical features. To date, there are two literature reviews on IHS which summarize reported cases [4, 7]. However, these reviews do not include the clinical presentation, presence of risk factors

for malignancy, laboratory investigations and imaging characteristics. This study aims to provide a comprehensive overview on IHS.

Material and methods

A literature review was performed on PubMed database for the keywords "intrahepatic splenosis" OR "hepatic splenosis" from the period of 1939 to 2019. The last search was performed on 18 January 2020. The search yielded 81 articles: 11 articles were not in English, 6 articles were not case reports or series, 5 articles included isolated extrahepatic splenosis, 1 article was on splenosis in animals, 1 article included an incidental finding of splenosis on autopsy, and the full text was not available for 1 article. The remaining 56 articles were included in the analyses, with a total of 59 reported cases (Table 1) [4-59]. Year of study, age, sex, reason for splenectomy, time from splenectomy to presentation, presence of risk factors for HCC, clinical presentation, laboratory investigation results, imaging features, initial differential diagnoses and method of confirming diagnosis were extracted from the articles. Figure 1 is a graphical representation of the trend of reporting of cases of IHS, which shows an increasing trend in reporting.

Results

Fifty-nine patients with IHS are reported with male predominance (n = 49, 83.1%) and a median age of 51 years (range 21-73 years). The majority of the patients had a prior history of splenectomy (n = 57, 95.0%). Two patients did not have any history of abdominal trauma or splenectomy. The median time from splenectomy to diagnosis of splenosis was 21 years (range 1.5-47 years). Reported risk factors for HCC were as follows: 1) hepatitis B (n = 8, 13.6%), 2) hepatitis C (n = 12, 20.3%), 3) heavy alcohol use (n = 2, 3.4%), 4) fatty liver (n = 3, 5.1%) and 5) cirrhosis (n = 12, 20.3%). 33 (55.9%) patients did not have any of the abovementioned risk factors for HCC. The majority of the patients were asymptomatic (n = 37, 62.7%). 19 patients (32.2%) presented with abdominal pain and/or discomfort and 3 patients (5.1%) had atypical presentations: 1 patient had flu-like symptoms, loss of weight and loss of appetite and 2 patients had chronic lower back pain.

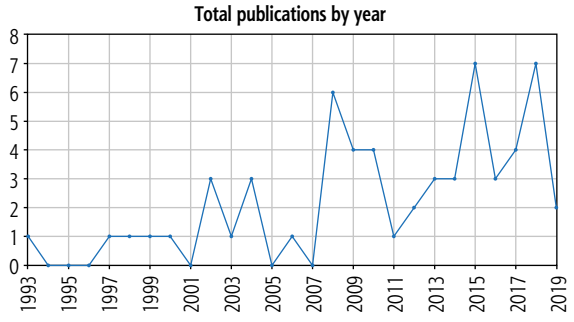

Fig. 1. Pictorial representation showing the increasing trend of reporting of cases of intrahepatic splenosis

Many of the reported cases do not include the essential laboratory investigations such as alanine aminotransferase (ALT), aspartate aminotransferase (AST) and α-fetoprotein (AFP). Of those cases which included these investigations, 12 out of 36 patients (33.3%) had transaminitis, and 6 out of 34 patients (17.6%) had raised AFP. The majority of the reported cases were isolated IHS; 4 (6.8%) of the cases included both intrahepatic and extrahepatic splenosis. The specific imaging features and patterns of enhancement can be found in the appendix (Table 2).

HCC was considered the initial diagnosis in 29 patients (49.2%). IHS was considered as the primary diagnosis in 9 patients (15.3%). There were several reported modalities for confirmatory diagnoses: open liver resection (n = 21, 35.6%), laparoscopic liver resection (n = 2, 3.4%), explorative laparotomy (n = 7, 18.9%), explorative laparoscopy (n = 3, 5.1%), percutaneous needle biopsy (n = 15, 25.4%), and Tc-99m denucleated RBC scintigraphy (n = 10, 16.9%). One patient (1.7%) only had the contrasted CT scan resembling splenic enhancement and was diagnosed with IHS based on the clinical history of splenectomy and absence of risk factors for HCC [56].

Discussion

Splenosis is an acquired condition and is defined as the autotransplantation of splenic tissue following abdominal or splenic trauma or splenectomy, displacing fragmented splenic tissues which may subsequently regrow at implanted sites by acquiring a vascular supply. It has been suggested that local hypoxia induced by hepatic diseases and/or aging may induce splenic erythropoiesis of previously seeded tissues [60]. This is in contrast to an accessory spleen, which is a congenital condition due to the failure of embryological fusion of the splenic primordium and arises from the left side of the dorsal mesogastrium [2, 38].

The major dilemma in the diagnosis of IHS is the need for exclusion of malignancy such as HCC or liver metastases. Radiological findings for IHS mimic the hallmarks of HCC: hyperenhancement in the arterial phase with delayed washout in the portal venous phase and low signal intensity in the hepatobiliary phase [61]. In the presence of risk factors such as hepatitis B, hepatitis C, heavy alcohol use and/or cirrhosis, pri-

Table 1. Summary of 59 reported cases of intrahepatic splenosis from 1939 to 2019

No.	Year	First author	Age/ Sex	Reason for splenectomy	Time* (years)	Risk factor for HCC	Clinical presentation	Laboratory investigations#	No. of lesions	Location	Size (cm)	Initial diagnosis	Confirmatory diagnosis
1	1993	Yoshimitsu [8]	51/F	Banti syndrome	23	Cirrhosis	Asymptomatic	ALP elevated	1	S3	2.5	HCC	Surgery (liver resection)
2	1997	Gruen [9]	38/F	Trauma	20	Fatty liver	Asymptomatic	ALT, AST, ALP, bilirubin elevated	1	S3, S4	3.9	HCC/FNH	Surgery (liver resection)
3	1998	D'Angelica [10]	38/F	Trauma	20	Alcohol	Asymptomatic	ALT, AST, ALP, GGT, bilirubin elevated	1	S3, S4	2.5	Adenoma/FNH	Surgery (liver resection)
4	1999	Foroudi [11]	59/F	NM	47	Nil	Upper abdominal pain and back pain	Normal	Multiple	Right lobe	NM	Liver metastasis	Tc-99m DRBC
5	2000	De Vuysere [12]	50/M	Trauma	34	Nil	Epigastric pain	Normal	Multiple	S2	6	Hepatic splenosis	Surgery (biopsy)
6	2002	Gamulin [13]	49/M	Trauma	37	Nil	Asymptomatic	Normal	1	Left lobe	6.6 × 4.2	B-cell lymphoma	Surgery (explorative laparotomy)
7	2002	Lee [14]	43/M	Trauma	20	HBV Cirrhosis	Asymptomatic	Normal, except for INR	1	S6	3.5	HCC	Surgery (liver resection)
8	2002	Pekkafali [15]	21/M	Trauma	15	Nil	Epigastric pain	Normal	1	Left lobe	3.4 × 2.3	Hepatic splenosis	Tc-99m DRBC
9	2003	Kim [16]	43/M	Trauma	21	HBV Cirrhosis	Asymptomatic	Normal	1	S6	3	HCC	Surgery (liver resection)
10	2004	Di Costanzo [17]	58/M	Trauma	46	HBV Cirrhosis	Abdominal pain	AFP elevated	1	S2	4.8	HCC	Needle biopsy, Tc-99m DRBC
11			48/F	Trauma	41	HCV Cirrhosis	Asymptomatic	ALT, AST and AFP elevated	1	S3	3.1	HCC	US-guided biopsy
12	2004	Kondo [18]	55/M	Trauma	31	HCV	Asymptomatic	NM	1	S7	3.5	HCC/FNH/ haemangioma	US-guided percutaneous biopsy
13	2006	Ferraioli [19]	40/M	Trauma	28	HCV	Asymptomatic	Normal	1	S7	6 × 3.1	Hepatic splenosis	US-guided biopsy
14	2008	Choi [20]	32/M	Trauma	26	HBV carrier	Asymptomatic	AST elevated	Multiple	S4a, S6	1.0-3.0	HCC	Surgery (explorative laparotomy)
15	2008	Grande [21]	41/M	Trauma	35	Nil	Asymptomatic	Normal	Multiple	S7	0.5-4.5	Hepatic splenosis	Tc-99m DRBC
16	2008	Imbriaco [22]	39/M	Trauma	24	Nil	Abdominal pain	NM	Multiple	Left and right lobes, pancreatic tail, adjacent to upper pole of left and right kidneys	3.0	Neoplasm	Surgery (explorative laparotomy)

Table 1. Cont.

No.	Year	First author	Age/ Sex	Reason for splenectomy	Time* (years)	Risk factor for HCC	Clinical presentation	Laboratory investigations#	No. of lesions	Location	Size (cm)	Initial diagnosis	Confirmatory diagnosis
17	2008	Lu [23]	59/M	Trauma	NM	HBV	Asymptomatic	Normal	Multiple	S7, left lobe	1.2-2.2	Hepatic splenosis	Tc-99m DRBC
18	2008	Nakajima [24]	41/M	Trauma	21	Nil	Incidental finding on work-up for acute enteritis	NM	1	S6	NM	Hepatic splenosis	US-guided biopsy
19	2008	Yeh [25]	64/M	Trauma	8	HCV	Asymptomatic	ALT, AST elevated	1	S6	2.5	HCC	Surgery (liver resection)
20	2009	Hilal [26]	60/M	Trauma	46	Cirrhosis	Flu-like symptoms, loss of weight, loss of appetite	LFT deranged, AFP elevated	Multiple	S7	2 × 2.5 and 4.5	HCC	Explorative laparoscopy
21	2009	Kashgari [27]	52/M	Trauma	30	HCV Cirrhosis	Asymptomatic	ALT, AST elevated	1	S7	2.1 × 1.5	HCC	US-guided biopsy
22	2009	Menth [28]	43/M	Trauma	25	HCV Cirrhosis	Asymptomatic	ALT, AST elevated	Multiple	S2	0.4-3.6	HCC	Tc-99m DRBC
23	2009	Yu [29]	54/M	Trauma	20	Nil	Asymptomatic	Normal	1	S2	4	Uncertain	Surgery (liver resection)
24	2010	Mescoli [30]	68/F	No splenectomy	NA	Cirrhosis	Abdominal pain	NM	Multiple	S3, S5, S7	6.2-11	FNH/ haemangioma	Percutaneous biopsy
25			54/M	Iatrogenic	12	Nil	Asymptomatic	NM	1	Left lobe	3	Liver metastasis	Surgery (explorative laparotomy)
26	2010	Tsitouridis [31]	63/M	Trauma	20	Nil	RUQ pain	NM	1	Left lobe	8	Splenosis	CT-guided biopsy
27			64/M	Gastric leiomyo-sarcoma	1.5	Nil	Asymptomatic	NM	1	NM	5	Peritoneal implantation	CT-guided biopsy
28	2011	Kang [32]	54/M	Trauma	15	Nil	Asymptomatic	Normal	2	S2	0.7 × 0.6, 2.3 × 1.9	Liver metastasis	Surgery (liver resection)
29	2012	Li [33]	61/M	Trauma	NM	Nil	Asymptomatic	NM	Multiple	NM	NM	Hepatic splenosis	Needle biopsy
30	2012	Liu [7]	38/M	Trauma	14	HBV	Asymptomatic	Normal	1	S2	3.3 × 2.7	Liver tumour	Surgery (laparoscopic resection)
31	2013	Inchingolo [34]	53/M	Trauma	33	NASH	Asymptomatic	GGT elevated	1	S3	3.5	HCC/adenoma	Surgery (laparoscopic converted to open liver resection)
32	2013	Krawczyk [35]	39/F	Trauma	NM	Nil	Abdominal pain	NM	2	S2, adjacent to major curvature of stomach	3.2 × 2.0	Adenoma	Tc-99m DRBC

Table 1. Cont.

No.	Year	First author	Age/ Sex	Reason for splenectomy	Time* (years)	Risk factor for HCC	Clinical presentation	Laboratory investigations#	No. of lesions	Location	Size (cm)	Initial diagnosis	Confirmatory diagnosis
33	2013	Leong [36]	56/M	Trauma	NM	Nil	Chronic epigastric pain	NM	1	S3	3.7 × 4.6 × 3.1	Carcinoid neuroendocrine tumour	Surgery (liver resection)
34	2014	Kandil [37]	45/F	Haemolytic anaemia	20	HCV	Chronic abdominal pain	Normal	1	Left lobe	5 × 4	HCC	Surgery (explorative laparotomy)
35	2014	Sato [38]	58/M	No splenectomy	NA	HCV Cirrhosis	Asymptomatic	ALT, AST, AFP elevated	1	Right lobe	3.9 × 3	HCC	Surgery (liver resection)
36	2014	Tinoco Gonzalez [39]	60/M	Trauma	NM	HCV	Asymptomatic	NM	1	S3	4.8	HCC/ Adenoma	Surgery (liver resection)
37	2015	Grambow [40]	53/M	Trauma	9	Alcohol Cirrhosis	Incidental finding due to refractory ascites secondary to decompensated cirrhosis	Normal	1	S3, S4b	3.5	HCC	Surgery (laparotomy)
38	2015	Li [41]	67/F	Trauma	5	HCV Cirrhosis	Asymptomatic	LFT deranged, AFP elevated	1	Left lobe	NM	HCC	Surgery (explorative laparotomy)
39	2015	Liu [6]	33/M	Trauma	30	Nil	Asymptomatic	Normal	Multiple	Left and right lobes	4.2 × 3.0	HCC	FNA biopsy
40	2015	Tamm [42]	43/M	Trauma	NM	Nil	RUQ pain	NM	1	S3	2.8	Nil	Tc-99m DRBC
41	2015	Toktas [43]	40/F	Idiopathic thrombocytopenic purpura	7	Nil	Asymptomatic, persistent low platelets	NM	1	S2/S3	7.0 × 3.0	Nil	Surgery (liver resection)
42	2015	Wu [44]	33/M	Trauma	12	Nil	Asymptomatic	Bilirubin elevated	1	S2	3.5 × 2.0	HCC	Surgery (explorative laparotomy)
43	2016	Fung [45]	55/M	Trauma	37	Nil	Asymptomatic	Normal	2	S6, S7	2.27 × 3.04 and 1.15 × 1.21	Nil	Surgery (liver resection)
44	2016	Chen [46]	51/M	Trauma	20	Nil	Asymptomatic	NM	2	Left and right lobes	2.1; 3.3 × 2.6	HCC	US-guided biopsy
45	2016	Jereb [47]	22/M	Trauma	18	Nil	Asymptomatic	Normal	Multiple	S2, S6, S7	2.6	Liver metastases	Surgery (explorative laparoscopy)
46	2017	Keck [48]	66/M	NM	NM	Chronic HCV	Asymptomatic	Normal	Multiple	S7, S8	5.3	Nil	Needle biopsy
47	2017	Somsap [49]	51/M	Thalassemia	20	Nil	Abdominal pain	ALT, AST, bilirubin elevated	1	Left lobe	NM	HCC	Surgery (liver resection)
48	2017	Wang [5]	54/M	Trauma	23	Chronic HBV	RUQ pain	Normal	1	Right lobe	3.9 × 3.6	HCC	Surgery (liver resection)

Table 1. Cont.

No.	Year	First author	Age/ Sex	Reason for splenectomy	Time* (years)	Risk factor for HCC	Clinical presentation	Laboratory investigations#	No. of lesions	Location	Size (cm)	Initial diagnosis	Confirmatory diagnosis
49	2017	Wang [50]	42/M	Trauma	16	HBV, HCV, fatty liver	Chronic low back pain	Normal	1	S4	2.3 × 1.8	HCC	Surgery (liver resection)
50	2018	Aramoana [51]	58/M	Trauma	37	Nil	RUQ pain	Normal	1	S6	4.6 × 3.4	HCC	Surgery (liver resection)
51	2018	Budak [52]	46/M	Trauma	30	Nil	NM	NM	2	S6, S7	3.6	HCC/hepatic splenosis	Tc-99m DRBC
52	2018	Guzman [53]	43/M	Trauma	16	Nil	Acute RUQ pain	ALT, AST elevated	1	S2	2.5	Adenoma	Percutaneous needle biopsy
53	2018	Smolen [54]	35/M	Trauma	12	Nil	Chronic abdominal pain	Normal	Multiple	Left and right lobes	4.3	Adenoma/FNH	Tc-99m DRBC
54	2018	Teles [55]	73/M	NM	NM	Nil	Low back pain	CEA elevated	Multiple	Left and right lobes, lumbar spine	4.9	Primary or secondary neoplasia	Surgery (open liver resection)
55	2018	Varghese [56]	50/M	Trauma	40	Nil	Asymptomatic	NM	1	Right lobe, multiple extrahepatic nodules	3.0	Nil	Contrasted CT scan resembling splenic enhancement and clinical judgement
56	2018	Vergara [57]	69/M	Trauma	NM	Nil	RUQ pain, dyspnoea, lower limb oedema	Normal	Multiple	S6, near falciform ligament, left para-vesical space	6.5 × 4.6	Nil	Needle biopsy
57	2018	Xuan [58]	54/M	Trauma	5	Nil	Asymptomatic	Normal	1	S4	4.5 × 3.3	HCC	Surgery (liver resection)
58	2019	Guedes [59]	68/M	Trauma	44	Nil	Chronic epigastric and right hypochondrium pain	Normal	1	S6	3.0	HCC/Adenoma	Surgery (laparoscopic liver resection)
59	2019	Luo [4]	41/M	Trauma	21	Nil	Asymptomatic		1	Right lobe	NM	HCC	Surgery (explorative laparoscopy)

AFP – α-fetoprotein, ALP – alkaline phosphatase, ALT – alanine aminotransferase, AST – aspartate aminotransferase, CT – computed tomography, F – female; FNA – fine needle aspiration, FNH – focal nodular hyperplasia, GGT – γ-glutamyltransferase, HCC – hepatocellular carcinoma, INR – international normalized ratio, LFT – liver function test, M – male, NA – not applicable, NM – not mentioned, RUQ – right upper quadrant, S1-S7 – segments I to VII of the liver, Tc-99m DRBC – technetium-99m-tagged heat-damaged red blood cell scan, US – ultrasound

**Time (years) refers to the interval after splenectomy to discovery of intrahepatic splenosis*

#Laboratory investigations refer to basic liver function test and tumour marker (AFP). Hepatitis B and C serology is not included

Table 2. Patterns of enhancement on imaging of all cases (n = 59) of intrahepatic splenosis from 1939 to 2019

No.	Year	Author	CT findings	MRI findings	Angiography
1	1993	Yoshimitsu [8]	Non-contrast: homogeneous low attenuation mass Contrast: enhanced from the periphery in the early phase, low attenuation in the delayed phase	T1-W: homogeneously low intensity T2-W: not obtained PDI: high intensity	Mass supplied by the left hepatic artery No definite neovascularity
2	1997	Gruen [9]	Contrast: high-attenuation mass	NA	NA
3	1998	D'Angelica [10]	Contrast: high-density mass	NA	NA
4	1999	Foroudi [11]	Contrast: multiple foci of enhancing soft tissue densities	NA	NA
5	2000	De Vuysere [12]	Non-contrast: slightly hypodense Contrast: homogeneously hyperdense in the arterial phase, isodense in the portal venous phase, and slightly hypodense in the late phase	Pre-contrast T1-W: hypointense Pre-contrast T2-W: hyperintense Post-contrast (small iron oxide particles (SPIO-Endorem): remained slightly hyperintense relative to the hypointense liver	NA
6	2002	Gamulin [13]	Contrast: heterogeneous enhancement	NA	NA
7	2002	Lee [14]	Contrast: early contrast enhancement and washout on delayed phase	NA	Tumour stained in segment 6 through the inferior phrenic artery No feeding vessel from hepatic or superior mesenteric artery
8	2002	Pekkafali [15]	Non-contrast: slightly hypodense with prominent hypodense rim around the lesion Contrast: hyperdense in the arterial phase, isodense in the portal venous phase and hypodense in the equilibrium phase	Pre-contrast T1-W: homogenously hypointense with hypointense rim Pre-contrast T2-W: isointense to liver with thin hypointense rim Post-contrast: hyperintense to liver	NA
9	2003	Kim [16]	Contrast: homogeneously well enhanced in the arterial phase and isodense in the equilibrium phase	NA	Mass supplied by inferior phrenic artery
10	2004	Di Costanzo [17]	Contrast: arterial hypervascularization and rapid "washout" of the contrast medium on portal venous phase	NA	NA
11			Contrast: early enhancement on the arterial phase and complete "washout" of the lesion on portal venous phase	NA	NA
12	2004	Kondo [18]	Contrast: low-density tumour in arterial phase, with vessels penetrating inside the tumour. Nearly homogeneous enhancement in portal venous phase	T1-W: low signal intensity T2-W: high signal intensity	Hypervascular tumour supplied by the right hepatic artery

Table 2. Cont.

No.	Year	Author	CT findings	MRI findings	Angiography
13	2006	Ferraioli [19]	NA	Contrast material-enhanced T1-W: liver tumour and accessory spleen were hypointense T2-W: liver tumour and accessory spleen were hyperintense	NA
14	2008	Choi [20]	Contrast: Lesion in segment IVa: slight enhancement during both the arterial and portal phase Lesion in segment VI: slight enhancement only in the portal phase	Contrast: enhancement during arterial phase and slightly hyperintense signal in the liver parenchyma during portal phase	Subtle tumour staining in segment IVa and no tumour staining in segment VI
15	2008	Grande [21]	Non-contrast: slightly hypodense compared to the liver Contrast: hyperdense in the arterial phase and isodense in the portal phase	NA	NA
16	2008	Imbriaco [22]	Non-contrast: hypodense Contrast: heterogeneous enhancement in the arterial phase, hypodense compared with the surrounding parenchyma during the portal and equilibrium phases	Pre-contrast T1-W: hypointense Pre-contrast T2-W: slightly hyperintense Post-contrast: nonhomogeneous enhancement during the arterial phase, hypointensity during the portal and equilibrium phases	
17	2008	Lu [23]	Non-contrast: two hypodense nodules Contrast: homogeneously hyperdense in the arterial phase, isodense in the portal venous phase, and slightly hypodense in the equilibrium phase.	Pre-contrast T1-W: homogeneously hypointense Pre-contrast T2-W: hyperintense contrast (Gd-DTPA): global enhancement in arterial phase, isointense in portal phase	
18	2008	Nakajima [24]	Non-contrast: hypodense mass Contrast: strong enhancement at the early phase and pooling enhancement at the late phase	T1-W: hypointense mass T2-W: hypointense mass	
19	2008	Yeh [25]	Non-contrast: isodense Contrast: persistent homogeneous enhancement in the arterial and portal venous phases	Pre-contrast T2-W: intermediate to high signal Plain phase: iso-signal in the plain phase Post-contrast: heterogeneous enhancement in the arterial phase and persistent homogeneous enhancement in the portal venous phase	Tumour stain with blood supply via perirenal vessel
21	2009	Kashgari [27]	NA	Pre-contrast T1-W: mildly hypointense Pre-contrast T2-W: homogenously hyperintense Contrast (gadopentetate dimeglumine): heterogenous early arterial enhancement, isointense in porto-venous and equilibrium phase	NA
20	2009	Hilal [26]	Contrast: hypervascular nodule with increased enhancement in the venous phase	Contrast (gadolinium): hypervascular nodule in arterial and portal venous phase	NA
22	2009	Menth [28]	NA	Contrast (Gd-DTPA): marked enhancement in early arterial phase Contrast (SPIO) T2-W: lacks iron uptake	Regular branches of hepatic artery No pathologic vessels or parenchymal foci of hypervascularity
23	2009	Yu [29]	Contrast: strong and slightly inhomogeneous enhancement in the arterial phase, diminished enhancement in the portal venous phase	T1-W: hypointense T2-W: slightly hyperintense	

Table 2. Cont.

No.	Year	Author	CT findings	MRI findings	Angiography
24	2010	Mescoli [30]	Contrast: hyper-enhancement in arterial and portal phases The largest nodule showed a hypodense central (necrotic) area	NA	NA
25			Contrast: hypervascular nodule	NA	NA
26	2010	Tsitouridis [31]	Non-contrast: slightly hypodense Contrast: increased enhancement during arterial phase with hypodense rim surrounding lesion. Lesion is isodense during portal phase	Pre-contrast T2-HASTE: intermediate-to-high signal intensity Post-contrast T2-HASTE: homogeneous enhancement with imaging characteristics of an extrahepatic-intraperitoneal lesion	NA
27			Contrast: hypodense with peripheral enhancement in both arterial and portal phases	Pre-contrast T2-HASTE: intermediate-to-high signal Post-contrast T2-HASTE: delayed peripheral enhancement Coronal plane: imaging characteristics of an extrahepatic lesion mimicking peritoneal implantation	NA
28	2011	Kang [32]	No parenchymal abnormality in liver	T1-W: low signal intensity T2-W: slightly high signal intensity slightly high signal intensity on the SPIO-enhanced T2-W: high signal intensity	NA
29	2012	Li [33]	Non-contrast: isodense masses mirroring residual spleen Contrast: enhancement in both hepatic mass and residual spleen	Pre-contrast T1-W: hypointense Pre-contrast T2-W: hyperintense Contrast: heterogeneous enhancement in arterial phase	NA
30	2012	Liu [7]	Non-contrast: homogeneous soft tissue mass with surrounding low-density aureole Contrast: slightly lower density than the liver especially in arterial phase	NA	NA
31	2013	Inchingolo [34]	Contrast: marked enhancement in arterial phase, remained hyperdense in portal venous phase	Post-contrast (gadolinium): increased arterialization after gadolinium injection with some loss of signal in the in-phase, indicating hemosiderin accumulation in the tissue DWI: restricted diffusion within the lesion	NA
32	2013	Krawczyk [35]	NI	Pre-contrast T2-W: hyperintense lesion in liver, with additional lesions dorsal to stomach that looks typical for regenerate spleen tissue Post-contrast T1-W: homogeneous enhancement	
33	2013	Leong [36]	Hypervascular lesion	Non-cystic irregular lesion with features suggestive of neuroendocrine tumour	
34	2014	Kandil [37]	Contrast: enhancement in arterial phase	NA	NA
35	2014	Sato [38]	Contrast: slightly inhomogeneous enhancement in arterial phase, with diminished enhancement in the equilibrium phase	Pre-contrast T2-W: hyperintense Post-contrast (Gd-EOB): hypointense compared to surrounding liver parenchyma	NA

Table 2. Cont.

No.	Year	Author	CT findings	MRI findings	Angiography
36	2014	Tinoco [39]	NA	Hypervascular lesion Contrast: homogeneous enhancement in arterial phase, with lavage in the portal phase and equilibrium	NA
37	2015	Grambow [40]	Contrast: hypervascular mass with enhancement typical for HCC	NA	NA
38	2015	Li [41]	Contrast: strong homogeneous enhancement in arterial phase and hypodense during portal phase	Pre-contrast T1-W: slightly hyperintense Pre-contrast T2-W: slightly hyperintense Post-contrast T2-W: hyperintense during arterial phase and hypointense during the portal phase	Hypervascular tumour supplied by the branches of the hepatic artery
39	2015	Liu [6]	NI	T2-W: intermediate-to-high signal intensity	NA
40	2015	Tamm [42]	Non-contrast: slightly hypodense Contrast: hypodense during arterial phase and hyperdense during portal venous phase	Pre-contrast T1-W: hypointense Pre-contrast T2-W: mildly hyperintense Post-contrast: no brisk arterial enhancement was present after contrast administration. Presence of homogeneous enhancement at 1 minute, with central washout and a residual rim of peripheral enhancement at 5 minutes	
41	2015	Toktas [43]	Isodense with spleen	NA	NA
42	2015	Wu [44]	Non-contrast: homogeneous hypodense mass	T1-W: low signal intensity T2-W: high signal intensity	NA
43	2016	Fung [45]	Contrast: early arterial enhancement with contrast washout in delayed phase	Pre-contrast T1-W: hypointense Pre-contrast T2-W: hyperintense Post-contrast T2-W: enhancement in arterial phase followed by washout in delayed phase	NA
44	2016	Chen [46]	Contrast: marked enhancement at arterial phase and delayed phase	Pre-contrast T1-W: low signal intensity Post-contrast T1-W: lower enhancement after contrast administration	NA
45	2016	Jereb [47]	Contrast: hypodense lesions in portal phase	Post-contrast T1-W: hypointense in both arterial and late phase Post-contrast T2-W: hyperintense during arterial phase, hypointense in late phase	NA
46	2017	Keck [48]	NA	Arterial enhancement with washout	NA
47	2017	Somsap [49]	NA	Pre-contrast T1-W: hypointense Post-contrast T1-W: heterogenous enhancement during arterial phase, more homogeneous in portal and delayed phase	NA
48	2017	Wang [5]	Non-contrast: hypodense Contrast: strong homogeneous enhancement in arterial phase and hypodense during portal phase	Pre-contrast T1-W: slightly hypointense Pre-contrast T2-W and DWI: high signal intensity Post-contrast T2-W: uneven enhancement with decreased signal during the delayed phase	NA

Table 2. Cont.

No.	Year	Author	CT findings	MRI findings	Angiography
49	2017	Wang [50]	Contrast: marked homogeneous enhancement in arterial and portal venous phase, with diminished enhancement in the equilibrium phase	Pre-contrast T1-W: hypointense Pre-contrast T2-W: hyperintense Post-contrast: moderate homogeneous enhancement with marked delayed ring enhancement mimicking a pseudocapsule similar to hepatocellular carcinoma (HCC) in equilibrium phase	NA
50	2018	Aramoana [51]	Contrast: enhancement in arterial phase	Post-contrast T2-W: peak enhancement at 60 s and washout at 10 min	NA
51	2018	Budak [52]	NA	T2-HASTE: hyperintense Post-contrast T1-W: hepatic lesion showed marked enhancement in arterial phase. Multiple nodule formations in peritoneal cavity similarly showed similar contrast uptake pattern	NA
52	2018	Guzman [53]	NI	NI	NA
53	2018	Smolen [54]	Non-contrast: multiple isodense lesions Contrast: hyperenhancement in arterial phase, iso- to hypoenhancement in portal and delayed phase) Carcinoma could not be ruled out	NA	NA
54	2018	Teles [55]	NI	NI	NA
55	2018	Varghese [56]	Contrast: heterogeneous "arciform" enhancement in arterial phase, with continued homogeneous enhancement in delayed phase with slow washout	NA	NA
56	2018	Vergara [57]	Contrast: mild enhancement in arterial phase	Pre-contrast T1-W: low signal intensity Pre-contrast T2-W: slightly hyperintense Post-contrast T1-W: lower enhancement compared surrounding liver parenchyma	NA
57	2018	Xuan [58]	Non-contrast: slightly hypodense Contrast: inhomogeneous enhancement during arterial phase and diminished enhancement during the portal and equilibrium phase	Pre-contrast T1-W and T2-W: slightly hypointense DWI: slightly hyperintense Post-contrast: strongly heterogeneous and hyperintense during the arterial phase and relatively hypointense during the portal	NA
58	2019	Guedes [59]	NA	Pre-contrast T1-W: hypointense Pre-contrast T2-W: hyperintense Post-contrast: increased vascularity and washed out during late venous phase	NA
59	2019	Luo [4]	Non-contrast: multiple hypodense lesions Contrast: enhancement during arterial phase with hypodense rim surrounding lesion. Lesions washed out in portal venous phase	NA	NA

CT – computed tomography, DWI – diffusion-weighted imaging, Gd-DTPA – gadolinium-diethylenetriaminepentaacetic acid, Gd-EOB – gadoxetic acid, HCC – hepatocellular carcinoma, MRI – magnetic resonance imaging, PDI – proton density image, SPIO – superparamagnetic iron oxide, T1-W – T1-weighted, T2-W – T2-weighted

NA – not applicable, NI – no information on enhancement pattern

mary liver malignancy such as HCC should always be excluded. Our study shows that the majority of the patients present with incidental liver lesions and do not have risk factors for HCC. In this group of patients, IHS should be considered and non-invasive or minimally invasive methods of confirmatory diagnosis should be explored. A non-invasive method to confirm the diagnosis of splenosis is the use of Tc-99m heat-damaged RBC scintigraphy [9]. This involves *in vitro* labelling of the patient's RBC with Tc-99m, heating the RBC at 49°C for 20 minutes, and subsequently injecting the patient with the Tc-99m labelled heat-damaged RBC and imaging with planar and single-photon emission computed tomography (SPECT) 30 minutes later [62]. Splenic tissues will phagocytose the heat-damaged RBCs, enabling radioisotope uptake of Tc-99m labelled RBCs. This is a specific and relatively sensitive method of diagnosis of splenosis as compared to the use of sulfur colloid, as the spleen takes up more than 90% of heat-damaged RBC as compared to 10% of sulfur colloid [42, 63]. However, improper preparation of heat-damaged RBCs such as overheating or underheating may result in false negatives [64]. In addition, scintigraphy has poor anatomic localization, which warrants the need to correlate the lesions with higher definition scans such as magnetic resonance imaging (MRI). Our study shows that Tc-99m labelled heat-damaged RBC is not widely used to diagnose IHS. This could be due to its limited availability or cost. Another clue suggestive for IHS is the absence or decreased number of Howell-Jolly bodies seen in peripheral blood smears, which would be normally seen in patients with asplenia [65].

In addition, though radiological findings for splenosis may mimic other hepatic lesions, Tsitouridis *et al.* described the characteristic imaging of IHS on CT and MRI imaging: hypodense lesion on non-contrast CT. Following contrast administration, the lesion is hyperdense in the arterial phase, isodense in the portal venous phase and hypodense in the delayed phase [31]. MRI findings include homogeneous hypointensity and hyperintensity prior to contrast administration on T1-weighted and T2-weighted images respectively, with a characteristic hypointense rim surrounding the lesion on T1-weighted imaging [31]. In addition, demonstration of classic heterogenous or arciform enhancement in the arterial phase with homogeneous enhancement in the delayed phase is classic for splenic enhancement and may suggest HIS [56]. Based on available data, the diagnosis of IHS can be made based on the 'triad' of 1) history of splenectomy or abdominal trauma, 2) absence of risk factors for liver malignancy and 3) typical imaging pattern on contrast enhanced imaging. Considering this 'triad' as a diagnostic hallmark of IHS, sensitivity of this triad in all the 59 reported cases was: 96.6% (n = 57/59) for one or more features, 52.5% (n = 31/59) for two or more features and 5.1% (n = 3/59) for all three features. Undoubtedly, the presence of all three cardinal features is rare, but is likely able to confirm the diagnosis of IHS without the need for surgical resection. We were unable to analyse the specificity of this triad as all the cases reported are diagnosed to be IHS.

Other imaging modalities such as the use of contrast-enhanced ultrasound can exclude HCC. On contrast-enhanced ultrasound, HCC appears as homogeneous and hyperechoic compared with the surrounding liver tissue after contrast administration, with a rapid washout and becoming a hypoechoic lesion in the portal and sinusoidal phases [19]. Superparamagnetic iron oxide (SPIO) administration in MRI scans can aid in tissue characterization. SPIO is taken up by the reticuloendothelial cells of the liver and spleen and has been shown to improve the detection rate of benign hepatocellular tumours [66]. IHS will demonstrate hypointensity on T2-weighted MRI due to phagocytosis of iron particles by splenic reticuloendothelial cells. Abdominal imaging does have its limitations and may not provide a definite diagnosis. Absolute diagnosis as with any malignant lesion is possible by sampling the tissue. Percutaneous image-guided needle biopsy can establish a definite diagnosis by demonstrating normal splenic tissue with red pulp and white pulp, lymphocyte B cells and CD3-positive lymphocyte T cells [27]. The use of fine needle aspiration cytology has been previously reported to avoid unnecessary surgery [67]. However, results may be inconclusive, and patients may have to bear additional costs of further diagnostic tests.

Surgical resection should be reserved for patients with inconclusive imaging scans or biopsy findings, abdominal symptoms not attributed to any other pathology, those in whom malignancy cannot be ruled out with certainty, or those with presence of risk factors for HCC. Explorative laparoscopy with intraoperative frozen section could be considered to reduce morbidity following liver resection [7, 26]. Should patients be diagnosed with IHS using non-invasive or minimally invasive methods, surgery can be avoided if patients are asymptomatic [57]. It has been reported that the average interval from trauma and abdominal splenosis is 10 years (range from 5 months to 32 years) [68, 69]. This is in contrast to our review, which demonstrated a median time of 21 years (range 1.5-47 years) from splenectomy to diagnosis of splenosis. Nevertheless, splenosis should still be considered

in patients with a history of splenectomy regardless of the time from splenectomy. There have been two reported cases of IHS without any history of abdominal trauma or splenectomy: a 68-year-old woman presenting with recurrent abdominal pain [30]; and an asymptomatic 58-year-old man presenting with work-up for transaminitis [38]. There is no explanation for this phenomenon, but these occurrences are rare and IHS should only be a diagnosis of exclusion in the absence of prior history of abdominal trauma or splenectomy.

In conclusion, this review summarizes the available body of evidence for IHS. We also report a diagnostic triad: 1) history of splenectomy or abdominal trauma, 2) absence of risk factors for liver malignancy and 3) typical imaging features on contrast-enhanced imaging. In the presence of risk factors for HCC, malignancy should be ruled out. Non-invasive diagnostic tests such as Tc-99m heat-damaged RBC scintigraphy are useful in diagnosis. Surgery is reserved for patients with (1) abdominal pain or other symptoms which cannot be attributed to pathology or (2) inability to rule out malignancy. Clinicians should be aware of this rare pathology and all cases should be reported to enhance the knowledge and understanding of this disease.

Disclosure

The authors declare no conflict of interest.

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