Intrahepatic splenosis: a world review

Weh Shien Toh¹, Kai Siang Chan¹,², Cristine Szu Lyn Ding³, Cher Heng Tan⁴, Vishal G. Shelat²

¹MOH Holdings, Singapore
²Department of General Surgery, Tan Tock Seng Hospital, Singapore
³Department of Pathology, Tan Tock Seng Hospital, Singapore
⁴Department 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 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.

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  | 2006 | Foroudi [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/FN/Haemangioma | US-guided percutaneous biopsy |
| 13  | 2006 | Ferraioli [19] | 40/M | Trauma | 28 | HCV | Asymptomatic | Normal | 1 | S7 | 6 × 3.1 | HCC | 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 | HCC | Surgery (liver resection) |
| 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) |
| No. | Year | First author | Age/ Sex | Reason for splenectomy | Timea (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                 | 5              | NM                  | 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  | Normal                  | 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,  | LFT deranged, AFP elevated | Multiple       | S7        | 2 x 2.5  | 4.5            | HCC                |
| 21  | 2009 | Kashgari [27]| 52/M     | Trauma                 | 30             | HCV Cirrhosis       | Asymptomatic         | ALT, AST elevated       | 1             | S7        | 2.1 x 1.5 | HCC              | US-guided biopsy       |
| 22  | 2009 | Menth [28]   | 43/M     | Trauma                 | 25             | 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/ haemangiomata | Percutaneous biopsy |
| 25  | 2010 | Tsitouridis [31]| 63/M | Trauma                 | 20             | Nil                 | RUQ pain             | NM                      | 1             | Left lobe | 3         | Liver metastasis | Surgery (explorative laparotomy) |
| 26  | 2010 | Inchingolo [34]| 53/M | Trauma                 | 33             | NASH                | Asymptomatic         | GGT elevated            | 1             | S3        | 3.5       | HCC/adenoma       | Surgery (laparoscopic resection) |
| 27  | 2013 | Kruczyk [35] | 39/F     | Trauma                 | 14             | Nil                 | Abdominal pain       | Normal                  | 1             | S2        | 3.2 x 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 | 4.2 × 3.0 | HCC               | Surgery (explorative laparotomy) |
| 39  | 2015 | Liu [6]      | 33/M     | Trauma                  | 30            | Nil                 | Asymptomatic           | Normal                  | Multiple       | S3        | 2.8      | Nil               | Tc-99m DRBC |
| 40  | 2015 | Tamm [42]    | 43/M     | Trauma                  | 7             | Idiopathic thrombocytopenic purpura | Asymptomatic, persistent low platelets | NM                      | 1             | S2/S3    | 7.0 × 3.0 | Nil               | Surgery (liver resection) |
| 41  | 2015 | Toktas [43]  | 40/F     | Trauma                  | 12            | Nil                 | Asymptomatic           | Bilirubin elevated      | 1             | S2        | 3.5 × 2.0 | HCC               | Surgery (explorative laparotomy) |
| 42  | 2015 | Wu [44]      | 33/M     | Trauma                  | 37            | Nil                 | Asymptomatic           | Normal                  | 2             | S6, S7    | 2.27 × 3.04 and 1.15 × 1.21 | Nil | Surgery (liver resection) |
| 43  | 2016 | Fung [45]    | 55/M     | Trauma                  | Nil           | Asymptomatic        | Normal                 | 2 Left and right lobes | 2             | S2/S6/S7  | 2.6      | Liver metastases | Surgery (explorative laparoscopy) |
| 44  | 2016 | Chen [46]    | 51/M     | Trauma                  | Nil           | Asymptomatic        | Normal                 | 2 Left and right lobes | 2.1: 3.3 × 2.6 | HCC | US-guided biopsy |
| 45  | 2016 | Jeeb [47]    | 22/M     | Trauma                  | 18            | Nil                 | Asymptomatic           | Multiple                | S2, S6, S7    | 2.6      | Liver metastases | Surgery (explorative laparoscopy) |
| 46  | 2017 | Keck [48]    | 66/M     | NM                       | Nil           | 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 | 3.9 × 3.6 | 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) |
| 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 x 1.8 | HCC             | Surgery (liver resection) |
| 50  | 2018 | Aramoana [51] | 58/M     | Trauma                  | 37            | RUQ pain             | Normal                | 1                        | S6            | 4.6 x 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, lumbar spine | 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 extrhepatic nodules | 3.0       | Nil       | Contrast CT scan resembling splenic enhancement and clinical judgement |
| 56  | 2018 | Vergara [57]  | 69/M     | Trauma                  | NM            | RUQ pain, dyspnoea, lower limb oedema | Normal | Multiple | S6, near falciform ligament, left para-vesical space | 6.5 x 4.6 | Nil | Needle biopsy |
| 57  | 2018 | Xuan [58]     | 54/M     | Trauma                  | 5             | Nil                  | Asymptomatic          | Normal                   | 1              | S4        | 4.5 x 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 (exploratory laparoscopy) |

*AFP – α-fetoprotein, ALP – alkaline phosphatase, ALT – aspartate aminotransferase, AST – asparagine 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 1 to 7 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.
| No. | Year | Author                  | CT findings                                           | MRI findings                                      | Angiography                                                                 |
|-----|------|-------------------------|-------------------------------------------------------|--------------------------------------------------|-----------------------------------------------------------------------------|
| 1   | 1993 | Yoshimitsu [8]          | Non-contrast: homogenous low attenuation mass         | T1-W: homogeneously low intensity                 | Mass supplied by the left hepatic artery                                    |
|     |      |                         | Contrast: enhanced from the periphery in the early phase, low attenuation in the delayed phase | T2-W: not obtained                                | No definite neovascularity                                                  |
| 2   | 1997 | Gruen [9]               | Contrast: high-attenuation mass                       | NA                                               |                              |
| 3   | 1998 | D'Angelica [10]         | Contrast: high-density mass                          | NA                                               |                              |
| 4   | 1999 | Foroudi [11]            | Contrast: multiple foci of enhancing soft tissue densities | NA                                               |                              |
| 5   | 2000 | De Vysere [12]          | Non-contrast: slightly hypodense                      | Pre-contrast T1-W: hypointense                    | NA                                                                          |
|     |      |                         | Contrast: homogeneously hyperdense in the arterial phase, isodense in the portal venous phase, and slightly hypodense in the late phase | Pre-contrast T2-W: hypointense                    |                              |
|     |      |                         |                                                      | Post-contrast [small iron oxide particles (SPIO-Endorem): remained slightly hyperintense relative to the hypointense liver |                              |
| 6   | 2002 | Gamulin [13]            | Contrast: heterogeneous enhancement                   | 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 | Pekkafalli [15]         | Non-contrast: slightly hypodense with prominent hypodense rim around the lesion | Pre-contrast T1-W: homogeneously hypointense with hypointense rim | NA                                                                          |
|     |      |                         | Contrast: hyperdense in the arterial phase, isodense in the portal venous phase and hypodense in the equilibrium phase | Pre-contrast T2-W: isointense to liver with thin hypointense rim |                              |
|     |      |                         |                                                      | Post-contrast: hyperintense to liver              |                              |
| 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                                               |                              |
| 11  |      |                         | Contrast: early enhancement on the arterial phase and complete “washout” of the lesion on portal venous phase | 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                        | Hypervascular tumour supplied by the right hepatic artery                  |
|     |      |                         |                                                      | T2-W: high signal intensity                       |                              |
| No. | Year | Author       | CT findings                  | MRI findings                                                                 | Angiography                          |
|-----|------|--------------|------------------------------|------------------------------------------------------------------------------|---------------------------------------|
| 13  | 2006 | Ferraioli    | 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         | 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       | 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     | Non-contrast: hypodense      | Pre-contrast T1-W: hypointense  
Pre-contrast T2-W: isodense  
Post-contrast: nonhomogeneous enhancement during the arterial phase, hypointensity during the portal and equilibrium phases | Pre-contrast T1-W: homogeneously hyperintense  
Pre-contrast T2-W: slightly hyperintense  
Post-contrast: enhancement in arterial phase, isointense in portal phase |
| 17  | 2008 | Lu           | Non-contrast: two hypodense nodules  
Contrast: homogeneous enhancement in the arterial phase, hypodense compared with the surrounding parenchyma during the portal and equilibrium phases | Pre-contrast T1-W: hypointense mass  
Pre-contrast T2-W: isointense in portal venous phase, and slightly hypodense in the equilibrium phase | Tumour stain with blood supply via perirenal vessel |
| 18  | 2008 | Nakajima     | 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 | Tumour stain with blood supply via perirenal vessel |
| 19  | 2008 | Yeh          | Non-contrast: isodense  
Contrast: persistent homogeneous enhancement in the arterial phase 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 |
| 20  | 2009 | Kashgari     | NA                           | Pre-contrast T1-W: mildly hypointense  
Pre-contrast T2-W: homogeneously hyperintense  
Contrast (gadopentetate dimeglumine): heterogeneous early arterial enhancement, isointense in portal venous and equilibrium phase | Pre-contrast T1-W: homogeneously hyperintense  
Pre-contrast T2-W: slightly hyperintense  
Contrast (SPIO): T2-W: lacks iron uptake  
Regular branches of hepatic artery  
No pathologic vessels or parenchymal foci of hypervascularity | NA                                    |
| 21  | 2009 | Hilal        | Contrast: hypervascular nodule with increased enhancement in the venous phase | Contrast (gadolinium): hypervascular nodule in arterial and portal venous phase | NA                                    |
| 22  | 2009 | Menth        | 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           | Contrast: strong and slightly inhomogeneous enhancement in the arterial phase, diminished enhancement in the portal venous phase | T1-W: hypointense  
T2-W: slightly hyperintense | NA                                    |
| No. | Year | Author | CT findings | MRI findings | Angiography |
|-----|------|--------|-------------|--------------|-------------|
| 24  | 2010 | Mescoli | Contrast: hyper-enhancement in arterial and portal phases. The largest nodule showed a hypodense central (necrotic) area. | NA | NA |
| 25  | 2010 | Tsitouridis | Contrast: hypervascular nodule | NA | NA |
| 26  | 2010 | Tsitouridis | 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  | 2011 | Kang | 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 | 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 | 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. | NA |
| 30  | 2012 | Liu | 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 | Contrast: marked enhancement in arterial phase, remained hypodense 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 | 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. | NA |
| 33  | 2013 | Leong | Hypervascular lesion | Non-cystic irregular lesion with features suggestive of neuroendocrine tumour. | NA |
| 34  | 2014 | Kandil | Contrast: enhancement in arterial phase. | NA | NA |
| 35  | 2014 | Sato | 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 |
| No. | Year | Author      | CT findings | MRI findings                                                                 | Angiography                                                                 |
|-----|------|-------------|-------------|-------------------------------------------------------------------------------|----------------------------------------------------------------------------|
| 36  | 2014 | Tinoco [39] | NA          | Hypervascular lesion                                                           | NA                                                                         |
|     |      |             |             | Contrast: homogeneous enhancement in arterial phase, with                    |                                                                             |
|     |      |             |             | lavage in the portal phase and equilibrium                                     |                                                                             |
| 37  | 2015 | Grambow [40]| Contrast: hypervascular mass with enhancement typical for HCC              | NA                                                                          |                                                                             |
|     |      |             |             | Pre-contrast T1-W: slightly hyperintense                                      |                                                                             |
|     |      |             |             | Pre-contrast T2-W: slightly hyperintense                                      |                                                                             |
|     |      |             |             | Post-contrast T2-W: hypointense during arterial phase and                    |                                                                             |
|     |      |             |             | hypointense during the portal phase                                           |                                                                             |
| 38  | 2015 | Li [41]     | Contrast: strong homogeneous enhancement in arterial phase and            | NA                                                                          |                                                                             |
|     |      |             | hypodense during portal 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                                                     |                                                                             |
| 39  | 2015 | Liu [6]     | NI          | T2-W: intermediate-to-high signal intensity                                   | NA                                                                         |
| 40  | 2015 | Tamm [42]   | Non-contrast: slightly hypodense                                            | Na                                                                          |                                                                             |
|     |      |             | Contrast: hypodense during arterial phase and hypodense during            |                                                                             |
|     |      |             | portal venous phase                                                         |                                                                             |
| 41  | 2015 | Toktas [43]| Isodense with spleen                                                        | 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]   | Contract: early arterial enhancement with                                  | Pre-contrast T1-W: hypointense                                              |                                                                             |
|     |      |             | contract washout in delayed phase                                           | Pre-contrast T2-W: hyperintense                                             |                                                                             |
|     |      |             |             | Post-contrast T2-W: enhancement in arterial phase followed by               |                                                                             |
|     |      |             |             | washout in delayed phase                                                     |                                                                             |
| 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                                                               |                                                                             |
| 45  | 2016 | Jeeb [47]   | Contrast: hypodense lesions in portal phase                                | Post-contrast T1-W: hypointense in both arterial and late phase              |                                                                             |
|     |      |             |             | Post-contrast T2-W: hypointense 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                                               | NA                                                                         |
|     |      |             |             | Post-contrast T1-W: heterogeneous enhancement during arterial phase,        |                                                                             |
|     |      |             |             | more homogeneous in portal and delayed phase                                |                                                                             |
| 48  | 2017 | Wang [5]    | Non-contrast: hypodense                                                     | Pre-contrast T1-W: slightly hypointense                                     |                                                                             |
|     |      |             | Contrast: strong homogeneous enhancement in arterial phase and            | Pre-contrast T2-W and DWI: high signal intensity                            |                                                                             |
|     |      |             | hypodense during portal phase                                               | Post-contrast T2-W: uneven enhancement with decreased signal during         |                                                                             |
|     |      |             |             | the delayed phase                                                           | NA                                                                         |
| No. | Year | Author          | CT findings                                                                 | MRI findings                                                                 | Angiography |
|-----|------|-----------------|------------------------------------------------------------------------------|-------------------------------------------------------------------------------|-------------|
| 49  | 2017 | Wang [50]       | Contrast: marked homogeneous enhancement in arterial and portal venous phase | Pre-contrast T1-W: hypointense                                                | NA          |
|     |      |                 | with diminished enhancement in the equilibrium phase                         | Pre-contrast T2-W: hyperintense                                               |             |
|     |      |                 | Post-contrast: moderate homogeneous enhancement with marked                 | delayed ring enhancement mimicking a pseudocapsule similar to                 |             |
|     |      |                 | delayed enhancement                                                       | hepatocellular carcinoma (HCC) in equilibrium phase                          |             |
| 50  | 2018 | Aramoana        | Contrast: enhancement in arterial phase                                      | Post-contrast T2-W: peak enhancement at 60 s and washout                      | NA          |
|     |      | [51]            |                                                                               | at 10 min                                                                     |             |
| 51  | 2018 | Budak [52]      | NA                                                                           | T2-HASTE: hyperintense                                                       | NA          |
|     |      |                 | Post-contrast T1-W: hepatic lesion showed marked enhancement                 | in arterial phase. Multiple nodule formations in peritoneal cavity            |             |
|     |      |                 | similarly showed similar contrast uptake pattern                            |                                                                               |             |
| 52  | 2018 | Guzman [53]     | NI                                                                           | NI                                                                            | NA          |
| 53  | 2018 | Smolen [54]     | Non-contrast: multiple isodense lesions                                      | NA                                                                            | NA          |
|     |      |                 | Contrast: hyperenhancement in arterial phase, isodense to                   |                                                                                |             |
|     |      |                 | hypoenhancement in portal and delayed phase                                | Carcinoma could not be ruled out                                             |             |
| 54  | 2018 | Teles [55]      | NI                                                                           | NI                                                                            | NA          |
| 55  | 2018 | Varghese [56]  | Contrast: heterogeneous “arciform” enhancement in arterial phase,          | NA                                                                            | NA          |
|     |      |                 | with continued homogeneous enhancement in delayed phase with slow          |                                                                                |             |
|     |      |                 | washout                                                                      |                                                                                |             |
| 56  | 2018 | Vergara [57]    | Contrast: mild enhancement in arterial phase                                | Pre-contrast T1-W: low signal intensity                                       | NA          |
|     |      |                 |                                                                               | Pre-contrast T2-W: slightly hyperintense                                      |             |
|     |      |                 |                                                                               | Post-contrast T1-W: lower enhancement compared surrounding                   |             |
|     |      |                 |                                                                               | liver parenchyma                                                             |             |
| 57  | 2018 | Xuan [58]       | Non-contrast: slightly hypodense                                             | Pre-contrast T1-W and T2-W: slightly hypointense                              | NA          |
|     |      |                 | Contrast: inhomogeneous enhancement during arterial phase and               | DWI: slightly hyperintense                                                    |             |
|     |      |                 | diminished enhancement during the portal and equilibrium phase             | Post-contrast: strongly heterogeneous and hypointense during the arterial     |             |
|     |      |                 |                                                                               | phase and relatively hypointense during the portal                          |             |
| 58  | 2019 | Guedes [59]     | NA                                                                           | Pre-contrast T1-W: hypointense                                                | NA          |
|     |      |                 |                                                                               | Pre-contrast T2-W: hyperintense                                               |             |
| 59  | 2019 | Luo [4]         | Non-contrast: multiple hypodense lesions                                     | Post-contrast: increased vascularity and washed out during late               | NA          |
|     |      |                 | Contrast: enhancement during arterial phase with hypodense rim              | venous phase                                                                  |             |
|     |      |                 | surrounding lesion. Lesions washed out in portal venous phase              |                                                                               |             |

CT – computed tomography, DWI – diffusion-weighted imaging, Gd-OTA – gadolinium-diethyltriaminopentaacetic 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 HJS [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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