Non-contrast MR lymphography of the lymphatic system of the liver

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NON-CONTRAST MR LYMPHOGRAPHY OF THE LYMPHATIC SYSTEM OF THE LIVER

Abstract

This review shows the images obtained with non-contrast MR lymphography in different pathologic conditions affecting the liver. Non-contrast MR lymphography is obtained with a free-breathing 3D high spatial resolution fast-recovery fast spin-echo sequence similar to that used for 3D MR cholangiopancreatography. The liver is the largest lymph-producing organ generating approximately half of the body's lymphatic fluid, and is the most important part of the lymphatic system from a functional point of view. Therefore, understanding the anatomy, physiology, and physiopathology of the lymphatics of the liver is important. However, its anatomy and pathology are relatively unknown because of the absence of commonly used imaging techniques.

We describe the anatomy, the physiology, and the pathophysiology of the lymphatic system of the liver and the possibility of identifying dilated lymphatic vessels in various liver diseases and conditions.

Disruption of normal lymphatic structure and function is observed in various disease conditions. Liver lymph flow is directly correlated with portal venous pressure. Therefore, a dilatation of liver lymphatics is observed in portal hypertension as well as in increased pressure in hepatic veins. After liver transplantation, ligation of lymphatic vessels at the hilum reduces chylous ascites and results in lymphatic dilatation which is easily observed. In severe long-standing biliary stenosis, dilated lymphatic vessels are commonly demonstrated with non-contrast MR lymphography. In hepatocellular carcinoma, intrahepatic cholangiocarcinoma, and some metastases, lymphatic vessels are abundant in the immediate vicinity of the tumour. These various lymphatic abnormalities can be demonstrated with non-contrast MR lymphography.

Key words

Lymphatic system

Liver

Abnormalities, lymphatic

Magnetic resonance

Key points

Anatomy and pathology of the lymphatics of the liver are relatively unknown, partly because of lack of current imaging technique.

Non-contrast MR lymphography is obtained with a free-breathing 3D high spatial resolution fast spin-echo sequence similar to that used for 3D MR cholangiopancreatography.

Various lymphatic liver abnormalities can be commonly demonstrated with non-contrast MR lymphography.

Non-contrast MR lymphography may participate to the understanding of several abnormal liver conditions including portal hypertension, biliary diseases, and malignant hepatic tumours.

Abbreviations

HCC Hepatocellular carcinoma

ICC Intrahepatic cholangiocarcinoma

VEGF Vascular Endothelial Growth Factor

Introduction

Presently, as pointed out by Iwakiri in their editorial in *Hepatology*, lymphology is experiencing a large renewal of interest, and the importance of lymphatics in diseases is gaining more recognition outside the field of limb lymphedema and cancer biology to also include acute and chronic inflammation [1–3]. The lymphatic system may be divided in three parts: soft tissue lymphatics, intestinal lymphatics, and liver lymphatics [4–6]. Soft tissue lymphatics are involved in the most common lymphatic disease, i.e. primary and secondary lymphedema [7]. In both primary and secondary lymphedema of upper and lower limbs, non-contrast magnetic resonance (MR) lymphography has demonstrated its interest for positive diagnosis, evaluation of severity, classification, and follow-up [8, 9]. Contrast-enhanced MR lymphangiography may also be performed for analysis of the lymphatic system and is notably useful from a functional point of view (10).

Compared to the vascular system, the lymphatic system anatomy is markedly complex and exhibits a lot of variants [11]. Most of the lymphatic channels are very small, and, together with lymph nodes, they create a complex network of interlacing vessels. This complexity and variability are, in part, explained by the embryology of the lymphatic system [1, 4, 11]. The lymphatic system originates from several locations in the body which later fuse together during the development of the embryo. There are multiple lymphatico-venous connections in different locations of the body. In addition, functional alteration or anatomical obstruction of the lymphatic vessels can result in the opening of new lymphatico-venous communications [6, 12, 13].

For these reasons, classical anatomical research methods such as dissection and casting are difficult. This represents a challenge for the interpretation of clinical imaging [14]. Normal lymphatic vessels of the liver are not visualised in classical cross-sectional studies such as ultrasonography, computed tomography (CT), and classical MR imaging because of their small size. We present the images obtained with non-contrast MR lymphography in different pathologic conditions affecting the liver.

Non-contrast MR lymphography

Though non-contrast MR lymphography has already been used for the demonstration of lymphatic vessels of the retroperitoneum and of upper and lower limbs, it has never been used to describe the analysis of lymphatic vessels of the liver [8, 9, 15]. Non-contrast MR lymphography is obtained with a free-breathing 3D high spatial resolution fast-recovery fast spin-echo sequence similar to that used for 3D MR cholangiopancreatography (Table 1). Four hundred millilitres of pineapple juice are given 30 minutes before non-contrast MR lymphography, as a negative oral contrast agent to decrease bowel content signal intensity. The main difference between MR lymphography and MR cholangiopancreatography include field of view, plane orientation, and slice thickness. To include retroperitoneal lymphatic vessels and anterior retrosternal thoracic lymphatic vessels, field of view should be larger than that used for MR cholangiopancreatography. As an alternative to coronal plane, MR lymphography may be performed with axial source images which precisely demonstrate both anterior and posterior lymphatic vessels. Because of the small size of lymphatic vessels, very thin section source images (millimetric or submillimetric) are used. Scan time varies from 3 to 5 minutes, depending on the number of source images. Post-processing of the data is performed to obtain maximum intensity projection (MIP) images and multiplanar reformatted (MPR) images. Imaging at 3 Tesla results in improved signal-to-noise ratio that allows for the improvement of spatial resolution. However, motion artefact, susceptibility effect, and local field inhomogeneity distributed throughout the full set of images may decrease image quality.

Other techniques that can be used for imaging of lymphatic vessels of the liver are uncommonly performed. Under certain conditions, such as congestion in patients with cirrhosis or after liver transplantation, hepatic lymphedema and dilated lymphatic vessels may be demonstrated as periportal thickening on CT, ultrasonography, or MR imaging [16–18].

In 1968, Clain and McNulty reported the results of a radiological study of the lymphatics of the liver by direct injection of contrast material within liver parenchyma [19]. In normal liver, no lymphatic drainage of contrast material was seen. On the other hand, in case of liver disease, they demonstrated the presence of efferent hepatic lymph channels. Lymphatic vessels in the liver appeared as fine vessels which filled rapidly with contrast material draining medially in tortuous fashion to the hilum of the liver and regional lymph nodes, or less commonly towards the diaphragm [19, 20]. The cisterna chyli and thoracic duct were uncommonly opacified [19]. However, the technique is hampered by the opacification of hepatic veins, portal veins, and biliary ducts. In addition, transhepatic liver lymphangiography has been performed in order to allow liver

lymphatic embolisation in case of hepatic lymphorrhea and protein-losing enteropathy (21, 22). However, direct transhepatic lymphography remains a very specialised technique [21–23].

Recently, Yamada et al. evaluated visualisation of periportal lymphatics and lymph nodes on Gd-EOB-DTPA-enhanced MR imaging using fat suppressed T2-weighted sequences. Images were acquired after the biliary phase following intravenous administration of Gd-EOB-DTPA, which causes signal loss in the bile duct, to facilitate the visualisation of the periportal lymphatic system [24]. However, only the largest periportal lymphatic vessels were demonstrated (24).

Delivery of gadolinium chelates by intranodal injection allows demonstration of central lymphatic vessels with dynamic ability (10). The intestinal and hepatic lymphatic vessels are outside the pathway of contrast injected in the lower extremities either by bipodal or nodal lymphangiography (10).

Anatomy

The lymph of the liver originates in the perisinusoidal space of Disse [12, 25]. This space lies between the basal surface of hepatocytes, the basal surface of the endothelial cells, and Kupffer cells that line the sinusoids (10, 26). Electron microscopy has demonstrated that sinusoidal endothelium is characterised by many intercellular openings and transcellular fenestrations [25]. Hepatic lymph results from plasma components of blood filtered through fenestrations of liver sinusoidal endothelial cells [13, 27, 28]. Drainage continues into small lymphatic channels around the portal tracts, which leave the liver for the systemic lymphatic system. The only lymphatic vessels in the hepatic acinus are in the portal tracts. Therefore, Pupulim et al. underlined that, although portal triad is a convenient term, it is a misnomer, as one or more lymph vessels travel with the vein, artery, and bile duct [14]. The structure of these lymphatic vessels is similar to that of blood vessels, and in the absence of specific lymphatic markers, it is difficult to distinguish them from blood vessels [4, 29, 30]. The initial lymphatic capillaries are characterised by a single layer of lymphatic endothelial cells and the absence of a continuous basement membrane. The contractility of the larger collecting lymphatic vessels is related to the presence of surrounding smooth muscle cells, which constitute the main driving force of the lymphatic circulation [31].

The lymphatics of the liver can be divided into a superficial and a deep system, as proposed by the French anatomist Rouvière in 1932 [32]. The superficial lymphatic system is mainly situated near the liver capsule. At the superior surface of the liver, it drains into the mediastinal lymph nodes whereas at the inferior surface of the liver, it drains into the hepatic and coeliac lymph nodes. The deep lymphatic system can be divided into two groups: the periportal lymphatic system and the perihepatic vein lymphatic system [Fig. 1]. The periportal lymphatic vessels emerge at the liver hilum and most lymphatic vessels course through the hepatic lymph nodes [7, 11, 32]. The periportal lymphatic system communicates with duodenal, superior pancreatic, and coeliac lymphatic nodes, or directly with the retroperitoneal lymphatic trunks and the thoracic duct.

The perihepatic vein lymphatic system runs along the terminal portion of the inferior vena cava. The lymphatic system relative to the hepatic veins differs from the lymphatics relative to the portal vein system in that it constitutes a dense network adjacent to the wall of the veins and do not converge in large lymphatic vessels even when leaving the liver [4, 13]. With non-contrast MR lymphography, deep lymphatic vessels of the liver are easily demonstrated in conditions resulting in lymphatic dilatation. They are easily recognised because of the characteristic alternating bands of constriction (lymphatic valves) and dilatation [Figs. 1c,d,f]. Furthermore, signal intensity of lymphatic vessels is usually lower than that of biliary ducts, possibly due to the high protein

concentration of hepatic lymph [4, 30]. More than 80% of hepatic lymph drains via the deep system.

Intrahepatic lymphatic vessels of the superficial system on the superior convex surface of the liver, which drain the capsule and adjacent liver tissue, run not only toward the falciform ligament but also to the right and left triangular ligaments, and most of them communicate with the diaphragmatic lymphatics to join the mediastinal lymph nodes [4, 13] [Fig. 2]. With non-contrast MR lymphography, normal size superficial lymphatic system is not visible but is commonly demonstrated in conditions resulting in lymphatic dilatation [Figs. 2c,e]. While there is no segmental delineation of lymphatic drainage, the two systems are extensively interconnected.

The lymphatic system has a major role in maintaining tissue fluid homeostasis through reabsorption of interstitial fluid and transporting lipids and waste materials [1, 2, 4]. It also contributes to the transport of immune cells and to the coordination of immune response. Hydrostatic pressure is the most relevant factor for the plasmatic components to move from sinusoid to the interstitial space of Disse. Therefore, haemodynamic changes in the sinusoids correlate with the amount of lymph production. For instance, production of lymph increases in cirrhosis with portal hypertension as a result of elevated sinusoidal pressure [33–36] [Figs. 1,2]. Obstruction of the hepatic veins or increased pressure related to congestive right ventricle failure has the same consequences [12, 33, 34]. The lymphatic drainage in normal adult liver varies from one to three litres/24 h. Experiments performed in rabbits and rats have demonstrated marked dilatation of lymphatic vessels and lymphatic oedema in the connective tissue and perisinusoidal spaces of Disse after ligation of the lymphatic vessels in the liver hilum [27, 28, 37, 38]. In man, Dumont and Mulholland demonstrated by thoracic duct cannulation that the thoracic lymph flow was three to six times higher in cirrhotic patients compared to a normal rate of about 1 mL/min in non-cirrhotic patients [34] [Figs. 1,2].

Anatomically, the increased lymph pressure is followed by the dilatation of lymphatic vessels in both superficial and deep lymphatic systems [Figs. 1,2] [28, 37, 38]. Liver lymph flow is directly correlated with portal venous pressure [39]. The number of lymphatic channels is correlated with the severity of fibrosis around the portal tract. There is an increase of lymphangiogenesis inducers in cirrhosis. Insufficiency of this lymphatic drainage system may cause hepatic lymph to spill into the peritoneal cavity, resulting in ascites. Furthermore, dilated lymphatics have been described at autopsy in patients with cirrhosis [20].

Besides participating in tissue fluid homeostasis, lymphatic vessels have a major role in collecting fat and waste materials in the intestinal system. In non-alcoholic fatty liver disease, it is logical to consider that maintenance of normal lymphatic function could have a positive impact in maintaining a healthy liver [40]. In addition, lymphangiogenesis helps immune cells to be discharged from inflamed sites, thus determining the resolution of inflammation [Fig. 1b-d]. One can assume that controlled lymphangiogenesis may participate in reducing inflammation in early stages of liver injury and preventing development of liver fibrosis [2]. Finally, tumour lymphangiogenesis is also implicated in lymph node metastasis and distant metastasis [41]. Peri-

hepatic lymph nodes are easily demonstrated with MR imaging, but non-contrast MR lymphography may eventually demonstrate communication of lymph nodes with lymphatic channels [Fig. 3] [1, 3].

Ligation of the lymphatic vessels of the liver at the hilum results in a lymphostatic condition of the liver which is histologically characterised by dilatation of the interstitial space of Disse [28, 37, 38]. Similar results are seen after liver transplantation when the lymphatic vessels are ligated. After liver transplantation, ligation of lymphatic vessels at the hilum reduces chylous ascites and results in lymphatic dilatation [42] (Fig. 4). This lymphatic dilatation is reversible because of the development of drainage routes via perihilar lymphangiogenesis and via peripheral routes available from pericapsular and omental adhesions. Chylous ascites and lymphatic dilatation generally resolve within weeks following liver transplantation by reestablishment of lymphatic drainage (Fig. 7). Similar lymphatic changes may also be observed after major liver surgery with extensive dissection of lymphatic vessels [4]. Dilated hepatic lymph vessels due to impaired lymphatic drainage have been shown to appear on CT as lucent areas surrounding peripheral and central portal veins and lucent rims around the intrahepatic vena cava [16–18]. Non-contrast MR lymphography directly demonstrates both hepatic lymphedema and dilated lymphatic vessels (Fig. 4).

In cholestasis, bile is regurgitated via the lymphatic vessels of the liver. The passage of bile into the lymph is possible from the bile canaliculi to the interstitial space of Disse, from the periphery of the parenchyma to the terminal lymph vessels, from bile ducts to lymphatic vessels, or, finally, from the multiple lymphatic vessels of the gallbladder to the lymphatic vessels of the liver [43]. It has been demonstrated that hepatic lymph flow is increased up to three times its normal value when ligation of the bile duct is performed and that the concentration of bilirubin rose faster in lymph than in blood plasma [4]. Dilated lymphatics have been shown at the hilum of the liver at surgery for obstructive jaundice [20]. In severe long-standing biliary stenosis, dilated lymphatic vessels are commonly demonstrated with non-contrast MR lymphography. Some of these channels are particularly visible around and along the biliary stenoses [Fig. 5].

In hepatocellular carcinoma (HCC) and some metastases, lymphatic vessels are abundant in the immediate vicinity of the tumour. Lymphatic vessels are more developed in fibrous areas that circumscribe tumours but absent in the core of tumours [41]. Lymphatic involvement in hepatic cancer is a well-known prognostic factor. HCC is the most common primary liver cancer which is not characterised by a high rate of lymph node metastasis. Incidence of lymph node metastasis in patients who have undergone hepatectomy for HCC has been reported between 2.5 and 7.5%. (26). On the other hand, intrahepatic cholangiocarcinoma (ICC) has a high risk of lymph node metastasis.

Incidence of lymph node involvement in patients with resected ICC has been reported between 20 and 50% [Fig. 3 g–i] [2, 4, 41]. With increasing knowledge of lymphatic vessels of the liver and the role of lymphangiogenesis in cancer, there is a potential role for an antilymphangiogenic agent. Today, no antilymphangiogenic therapy is in clinical use. On the other hand, the monoclonal antibody against Vascular Endothelial Growth Factor (VEGF), namely bevacizumab, has been approved for different metastatic cancer, and this antiangiogenic agent is also known to inhibit lymphangiogenesis [41, 44–46]. Nagy et al. first demonstrated that over-expression of VEGF-A induces new lymphatic vessel formation in mice [47]. These neo-lymphatics were structurally and functionally abnormal, similar to hyperplastic lymphatic vessels found in malformations [47]. Finally, uncommon diseases of the liver, such as cystic lymphangiomas of the liver may be demonstrated with non-contrast MR lymphography. Multiloculated appearance of cystic lymphangiomas is rather different from simple hepatic cyst [Fig. 6]. Specific immunohistochemical staining, including D2-40 and podoplanin, is warranted for a definite diagnosis, as cystic lymphangiomas may mimic liver haemangioma in histology [48].

Conclusion

Development of new lymphatic imaging techniques including non-contrast-, contrast-enhanced-MR lymphography, and transhepatic liver lymphangiography could improve our understanding of the hepatic lymphatic system which may open new routes for prevention, diagnosis, and treatment of liver diseases notably in fields of liver cancer, liver inflammation, portal hypertension, and biliary diseases. Visualisation of dilated lymphatic vessels of the liver which is easily performed with non-contrast MR lymphography could have a prognostic value in different liver diseases. For instance, Daher et al. recently demonstrated that portal lymphadenopathy, as assessed by CT/MRI, was significantly associated with advanced stages of non-alcoholic steatohepatitis (49). Such lymphatic dilatation is also observed in severe liver inflammation, portal hypertension, and biliary diseases. However, results of MR lymphography of the liver are mostly preliminary and should be confirmed by further specific studies.

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Figure 1:

Deep lymphatic system of the liver.

(a) Schematic representation of lymphatic drainage by periportal (black arrows) and perihepatic vein (white arrows) systems.

(b,c,d) 25-year-old woman with spleen and liver tuberculosis. On T2-weighted MR image (b) multiple nodules are demonstrated within liver parenchyma. Larger nodules hyperintense to spleen parenchyma are demonstrated within spleen. High signal intensity halo is seen around portal vein (PV) and inferior vena cava (IVC). MR lymphography (volume MIP reconstruction) (c) demonstrates several periportal lymphatic vessels (long arrow) around main biliary duct (arrowhead). Retroperitoneal lymphatic vessels (short arrow). Periportal lymphatic vessels (long arrows) are well demonstrated on 10-mm-MIP reconstruction (d). Main biliary duct (short arrows), pancreatic duct (arrowheads).

(e,f) 52-year-old man with portal hypertension related to post-viral C cirrhosis. On T2-weighted MR image (e), high signal intensity halo is demonstrated around portal vein (PV) and in front of aorta (A). On MR lymphography (30-mm-MIP reconstruction) (f) deep lymphatic vessels are well demonstrated on around portal vein (long arrow). Superficial lymphatic vessels are demonstrated around falciform ligament (arrowhead). Collecting lymphatic vessels are demonstrated in retroperitoneal location (short arrow). MBD, main biliary duct

Figure 2:

Superficial lymphatic system of the liver

(a) Schematic representation of lymphatic drainage by superficial system demonstrating drainage to mediastinal lymph nodes at the superior surface of the liver and to hepatic and coeliac lymph nodes at the inferior surface of the liver.

(b, c) 45-year-old woman with portal hypertension related to alcoholic cirrhosis. Peripheral lymphatic vessels are well demonstrated on T2-weighted MR images (b). On MR lymphography (c) peripheral lymphatic vessels with characteristic alternating bands of constriction (lymphatic valves) and dilatation are well demonstrated when they leave the liver to join the perihepatic lymphatic vessels (arrows).

(d,e) 65-year-old man with portal hypertension related to alcoholic cirrhosis. Peripheral lymphatic vessels are well demonstrated on T2-weighted images (d) and on MR lymphography (e) (arrows). Other deep perihepatic lymphatic vessels (short arrow) are demonstrated around inferior vena cava

(V). In their central portion, dilated lymphatic vessels may mimic peribiliary cysts (arrowhead).
Brauch-duct IPMN (I).

Figure 3:

Perihepatic lymph nodes

(a–c) 69-year-old man with primary biliary cholangitis. Retroportal, perihepatic, and coeliac lymph nodes (N) are well demonstrated on fat suppressed T2-weighted MR images (a). Corresponding MR lymphography (b, c) demonstrates several dilated periportal (long arrow) and peripheral lymphatic vessels (short arrow). Pancreatic duct crosses the main biliary duct (pancreas divisum).

(d–f) 85-year-old woman with metastatic pancreatic adenocarcinoma. Large retroportal metastatic lymphadenopathy (N) is well demonstrated on T2-weighted MR image (d) and diffusion-weighted MR images (e). On MR lymphography (f) normal structure of lymph node of high signal intensity (arrows) is replaced by a metastatic deposit (M).

(g–i) 82-year-old woman with metastatic cholangiocarcinoma (CCA). On T2-weighted MR images metastatic lymph nodes (N) are demonstrated around portal vein (PV) and inferior vena cava (C) (g).

Perihepatic lymphatic extension is well demonstrated on MR lymphography (h) with multiple metastatic deposits around portal vein (long arrow) and in a retroperitoneal location (short arrow). A metastatic diaphragmatic lymph node (N) is demonstrated.

Metastatic diaphragmatic lymph node (N) is well demonstrated on 20-mm-MIP reconstruction (i) with communicating dilated afferent and efferent lymphatic vessels (long arrows).

Figure 4:

42-year-old man, 15 days after liver transplantation performed for hepatocellular carcinoma. On T2-weighted MR image, high signal intensity halo is demonstrated around right (R) and left (L) portal veins (a). On MR lymphography (b), lymphedema and lymphatic vessels (long arrow) are demonstrated around main biliary duct (B). Markedly dilated thoracic duct (short arrows). Dilatation of periportal lymphatic vessels is well demonstrated (long arrows) on the 10-mm-MIP reconstruction (c).

Follow-up MR lymphography performed 3 months later (d) demonstrates disappearance of dilatation of periportal lymphatic vessels and decrease of diameter of thoracic duct (short arrow).

Figure 5:

Dilatation of lymphatic vessels in biliary stenosis.

(a) 53-year-old man with primary sclerosing cholangitis. MR lymphography demonstrates the stenosis of both main biliary ducts (M) and intrahepatic biliary ducts (arrowhead). Marked dilatation of lymphatic vessels (arrows) is well demonstrated.

(b) 36-year-old woman with primary sclerosing cholangitis. MR lymphography demonstrates severe stenosis of main biliary duct and intrahepatic biliary ducts (arrowheads). Marked dilatation of lymphatic vessels (arrows) is well demonstrated.

Figure 6:

53-year-old woman with pathologically proved cystic lymphangioma of the left liver lobe. Multiloculated high signal intensity lesion (arrow) is well demonstrated on T2-weighted MR image (a). There is no enhancement of the lesion after contrast injection on this portal phase (b). Multiloculated lesion is well demonstrated on MR lymphography (c). Multiloculated appearance of cystic lymphangiomas is rather different from simple hepatic cyst.

(d) Pathologically, the sponge-like lesion is composed of cysts lined by attenuated endothelium.

(e) Immunohistochemical staining with D2-40 shows the well-demonstrated lining endothelium.

Inferior vena cava lymph nodes

Hepatic lymph nodes

Coeliac lymph nodes

PV

IVC

PV

A

MBD

<4-10>

R

P

<6-58>

R

P

<4-15>

R

P

<5-1>

R

V

P

N

M

R

N

N

< 1308 - 53 >

RP

Table 1

Acquisition parameters of non-contrast MR lymphography

MR unit	Signa HDxt or Optima MR 450 w
Constructor	General Electric Healthcare
Field strength	1.5 T
Sequence	3D High spatial resolution fast-recovery fast spin-echo (FRFSE)
Plane	Coronal / Axial
TR (ms)	3500 – 4000
TE (ms)	700 – 884
Number of averages	1
Flip angle	90°
Matrix acquisition size	512 x 288
FOV (mm)	400 x 400
Number of slices	124 – 316
Slice thickness (mm)	0.8 – 1.4
Spacing (mm)	0
Anatomical area	Liver
Gating	Free breathing with respiratory gating
Acquisition time (minutes)	3 – 5