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Case Report

Adult form of Langerhans cell histiocytosis with pulmonary and hepatic involvement mimicking malignancy in a patient with chronic hepatitis C infection

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ABSTRACT

Langerhans cell histiocytosis (LCH) is a myeloid neoplasm with inflammatory properties. There are few published reports of adult LCH with liver involvement, which is still poorly understood, but shows high morbidity and mortality. We report a case of a 37-year-old woman suffering from hepatitis C showing a LCH affecting the lung as well as the liver. Consistent with histology, we found an early stage of a proliferative/granulomatous phase of hepatobiliary LCH, whereas pulmonary findings showed a nodular stage of adult pulmonary LCH. Although hepatocellular carcinoma is a common malignancy in patients suffering from hepatitis C, it is crucial to keep in mind differential diagnosis for newly appearing liver lesions.

Introduction

Langerhans cell histiocytosis (LCH) is a myeloid neoplasm with inflammatory properties [1]. It most often affects the bones in children, with a peak between the age of 1 and 4 years old [2,3]. LCH can affect single (unifocal) or multiple organs of the human body (systemic) [4,5]. Mortality is increased in patients suffering from multiorgan involvement, especially when the reticuloendothelial system is involved

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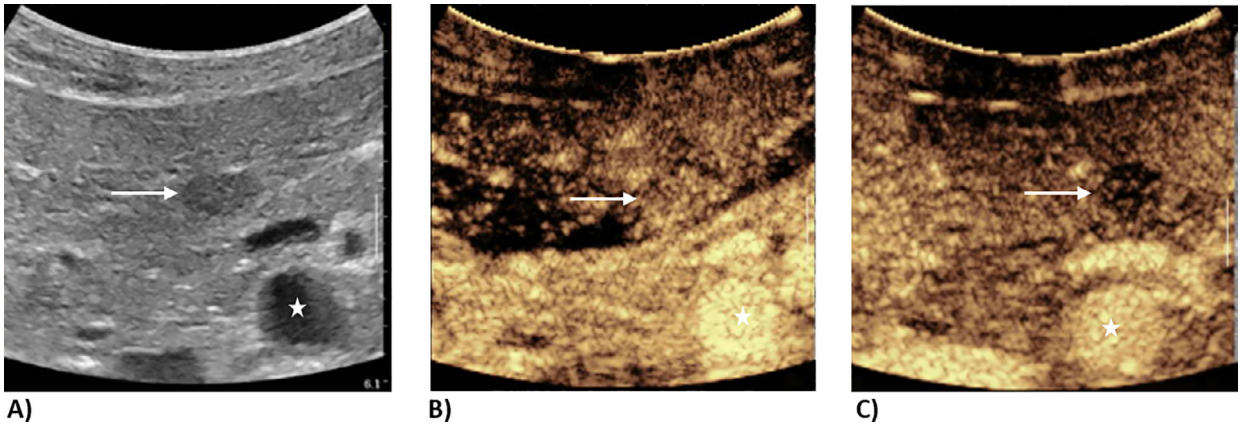

Fig. 1 – Contrast-enhanced ultrasound (CEUS) of one of the hepatic lesions (white arrow). (A) *Gray scale image with hypoechogenic lesion in liver segment III; (B) late arterial phase showing contrast enhancement of the lesion with venous wash-out in (C). Please note contrast enhancement of the aorta as a reference to recognize the arterial and the venous phase (asterisk).*

(spleen, liver, bone marrow) [6,7]. The presence of a BRAF-mutation is an important prognostic factor associated with systemic LCH and poor survival [8,9].

The adult form of LCH is rare, the exact incidence is unknown. Some authors estimate an incidence of 1-2 cases of LCH per million adults per year, while the pulmonary form occurs most frequently, being associated with smoking [10–13]. In a series of 502 open lung biopsies for chronic diffuse infiltrative lung disease in 1980, diagnosis of pulmonary LCH was made in 17 patients (3.4%) [14]. There are few published reports of adult LCH with liver involvement, which is still poorly understood, but may show high morbidity and mortality [15]. We report a case of a 37-year-old woman suffering from LCH affecting the lung as well as the liver.

Case presentation

A 37-year-old woman known for a low replicative chronic hepatitis C (HCV) infection was seen for a follow-up in our outpatient clinic. HCV infection was due to an intravenous drug abuse in the past. She was asymptomatic and in good general condition. Besides being an active smoker (15 py), she had a history of intravenous drug abuse but stopped many years ago. She was under substitution therapy with buprenorphine and took the antidepressant bupropion as well as vitamin D3. She was vaccinated for hepatitis A and B and HIV negative. Up until this date, the patient had not been treated for HCV due to normal liver tests, low and declining replication status (max copies measured 3295 IU/mL 2015, 520 IU/mL 2017, and 38 IU/mL 2019) and no signs of fibrosis or cirrhosis in fibroscan and ultrasound. Routine liver enzyme tests, blood count, and inflammatory markers were normal. In search for signs of fibrosis and focal liver lesions, abdominal sonography was performed. It revealed a liver with a normal parenchymal aspect and no signs of portal hypertension. Surprisingly, one small hypoechoic lesion with 10 × 13 mm in size was seen in segment III. For better characterization of the lesion, contrast-enhanced ultrasound was performed, showing an arterial contrast enhancement and a venous was-hout (Fig. 1A-C), typical features of a neoplastic lesion.

Subsequently, an MRI of the liver was performed, which confirmed the sonographic findings. A noncirrhotic liver parenchyma with several small T1w hypointense, T2w hyperintense lesions (≤15 mm) in both liver lobes with predominance in the right lobe was seen. No macroscopic or microscopic fat was present on the fat-saturated images and on the T1 Dixon in and out of phase acquisitions. After intravenous administration of gadoxetic acid (Primovist), the lesions showed a rim-like enhancement in the arterial phase and central hypointensities in the venous and hepatobiliary phase, as well as diffusion restriction (Fig. 2A-F). T1 reduction rate (ΔT1) in the hepatobiliary phase based on T1-mapping was 84%, consistent with normal hepatocellular liver function (T1 relaxation time pre contrast = 916 ms, T1 relaxation time in the hepatobiliary phase = 149 ms, considering ΔT1 ≥60% as a normal liver function) [16] (Fig. 3A and B). Intra- and extrahepatic bile tracts were normal.

Characteristics of the hepatic lesions were similar to those of a multifocal hepatocellular carcinoma (HCC) with diffusion restriction, arterial phase enhancement, and central hypointensity in the venous and hepatobiliary phase. However, our patient was young and despite chronic hepatitis C, there were no signs of liver fibrosis or cirrhosis. Therefore, further investigations were necessary. The tumor markers alphafeto protein (HCC) and chromogranin A II (neuroendocrine tumor) were negative. Gastroscopy and colonoscopy were normal. To rule out metastatic disease, a thoracoabdominal CT was performed, showing no visible tumor of the pancreas, kidneys or gastrointestinal tract, and no identifiable lymphadenopathy. However, multiple pulmonary nodules (≤8 mm) with upper lobe predominance and sparing of the subpleural space were found. Many of those nodules exhibited cystic changes, raising the suspicion of pulmonary LCH (Fig. 4 A and B). The surrounding pulmonary parenchyma showed no alterations and there was no thoracic lymphadenopathy. The differential diagnosis of the radiological findings included septic emboli and fungal affection in a patient with a history of intravenous drug abuse. However, as our patient had not been an active

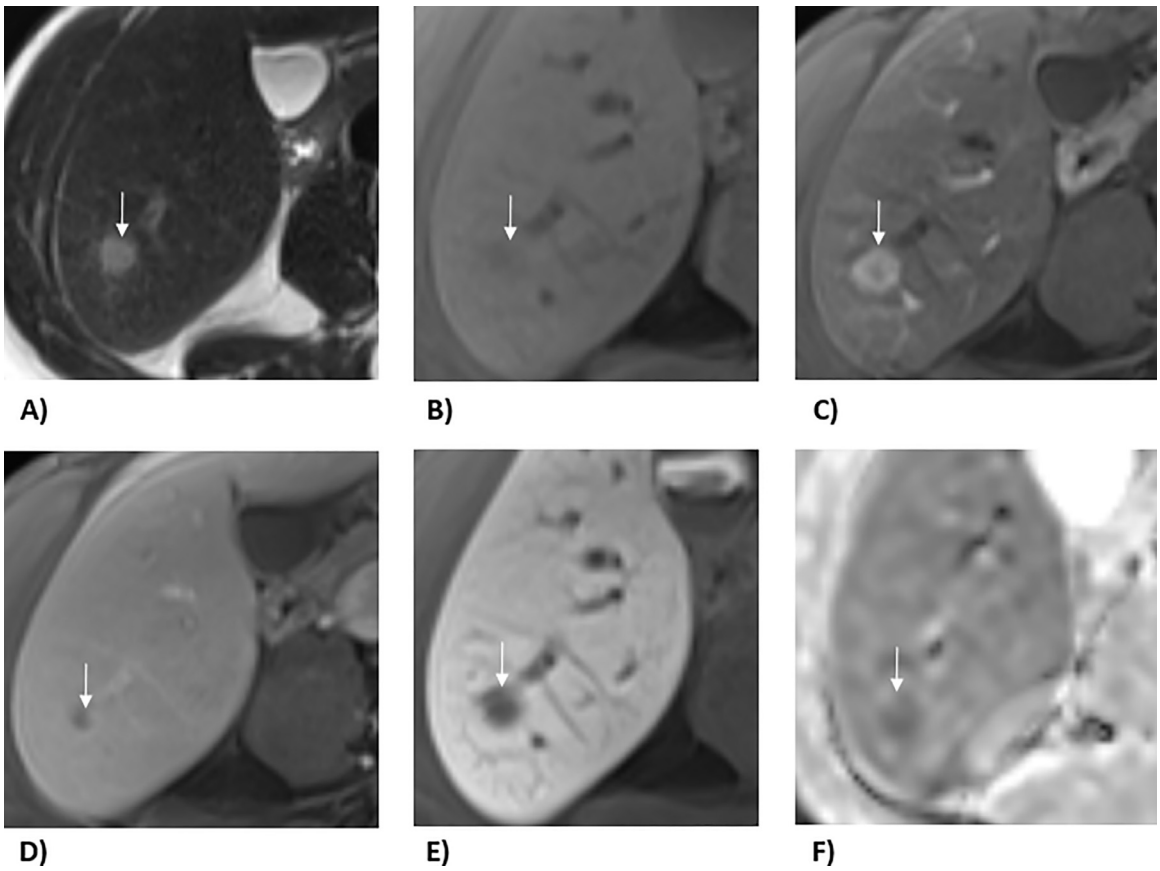

Fig. 2 – MRI of the liver with one liver lesion in segment VI. The lesion is slightly hyperintense on T2-weighted images (A). On T1-weighted images, the lesion is hypointense before contrast administration (B) and shows an avid rim-like enhancement in the arterial phase (C) with central hypointensity in the venous phase (D) and no gadoxetic acid uptake in the hepatobiliary phase (E). Diffusion-weighted imaging shows diffusion restriction (F).

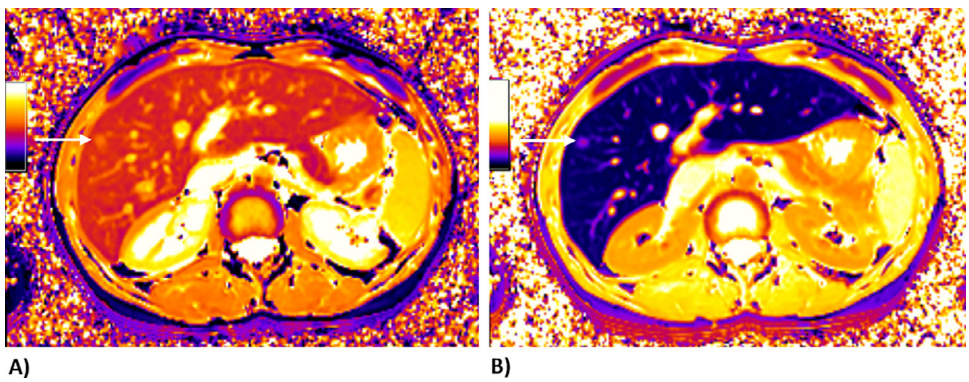

Fig. 3 – shMOLLI T1 – mapping images with the lesion. (A) Precontrast (B) postcontrast in the hepatobiliary phase, 20 minutes after intravenous administration of gadoxetic acid. T1 relaxation time of the liver pre contrast was 916 ms and 149 ms in the hepatobiliary phase, with a calculated T1 reduction rate (ΔT1) of 84%, consistent with a normal hepatocellular function of the liver. Please note a hepatic lesion in liver segment V with longer precontrast T1 relaxation time as compared to the adjacent liver parenchyma. The lesion shows a reduced T1 shortening after gadoxetic acid administration, consistent with a nonhepatocellular lesion (white arrow).

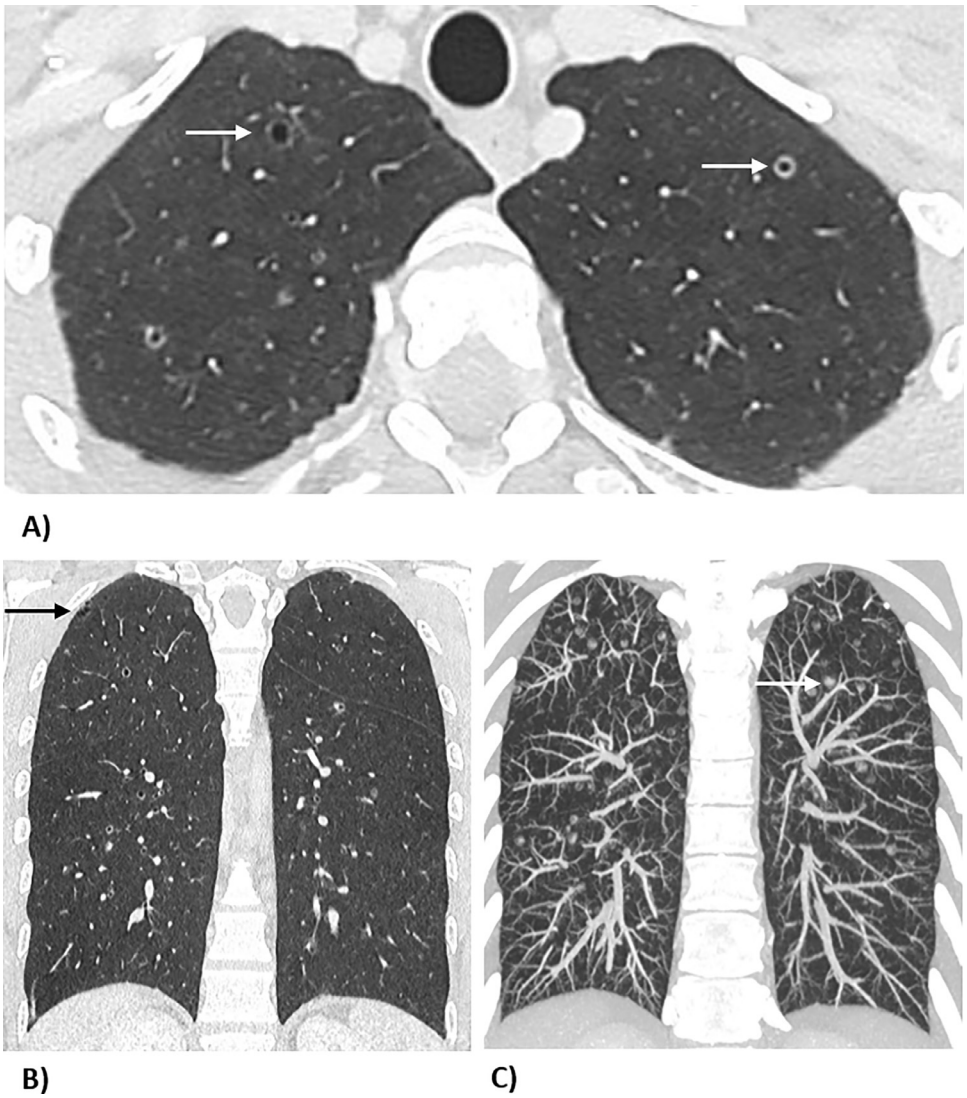

Fig. 4 – CT scan showing multiple pulmonary nodules with upper lobe predominance. On the axial (A) and coronal images (B) multiple cystic changes are seen (white arrows). Please note paraseptal emphysema (black arrow in B) in this patient with a history of smoking, but no signs of pulmonary fibrosis. Maximum intensity projection (MIP) reconstructions illustrate the upper lobe predominance of the pulmonary nodules (C).

intravenous drug abuser for many years, this was unlikely in the clinical context.

After discussion in our multidisciplinary board, we decided to perform a liver biopsy to exclude HCC and metastasis and to confirm our suspicion of a rare case of LCH with pulmonary and hepatic involvement. On histology, circumscript infiltrates of atypical histiocytic cells were found (Fig. 5A), intermingled with eosinophilic granulocytes, and lymphocytes (Fig. 5C). Immunohistochemistry showed positivity for CD1a in the histiocytic cells (Fig. 5 B to D). No BRAF (V600E) mutation was found in immunohistochemistry. Taken together, these findings established the diagnosis of LCH in the liver. As pulmonary radiological findings were compatible with LCH, the diagnosis of LCH with pulmonary and hepatic involvement was made. Our examinations showed no further organ manifestations (skin, lymph nodes or bones). After another discussion in our multi-disciplinary board, a watch and wait strategy was chosen for this asymptomatic patient presenting in a non-fibrotic stage of LCH.

The patient was encouraged to discontinue smoking, since the effect of nicotine abuse stimulating recurrence or progression of pulmonary LCH is well described [17]. Whether chronic hepatitis C was an additional factor for LCH development in the liver is unclear (see discussion). As the association of chronic hepatitis C in other hematological tumors is known (foremost non-Hodgkin-lymphoma [18]) and the oncogenic Ras-ERK pathway signaling in LCH pathogenesis is described in many cases [1,19], also having a link to the mechanism of hepatitis C [20], we favored to treat the patient for hepatitis C.

In the follow-up consultation 4 months later, the patient was still asymptomatic, she quit smoking, liver enzymes were normal and the liver lesion in segment III was smaller in size

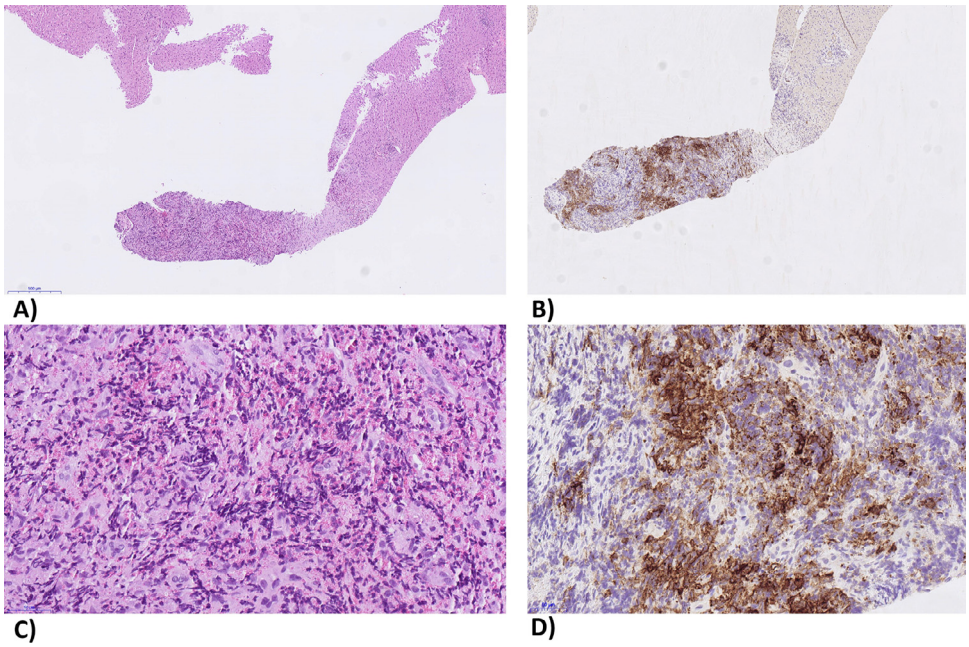

Fig. 5 – Histology showing circumscript infiltrates of atypical histiocytic cells (A to C). Immunohistochemistry for CD1a demonstrate (brown-stained areas) positive staining in Langerhans cells (B to D). (A to B) are shown with a 2 × magnification, (C to D) with a 20 × magnification. Scale bars (500 μm and 50 μm) are included on the bottom left of the images.

(10 mm in diameter compared to 13 mm previously). Interestingly enough, she had spontaneously and persistently cleared the hepatitis C virus.

Discussion

We present a case with a challenging diagnostic process of an adult form of LCH with pulmonary and hepatic involvement. This case shows that arterial enhancing nodules with central hypointensity in the venous phase in the liver are not always consistent with HCC. Especially in cases of a noncirrhotic liver, differential diagnosis such as metastatic, infectious, and systemic diseases should be considered, while other imaging findings can lead to the correct diagnosis. Here, partially cavitary nodules (≤8 mm) of the lungs with upper lobe predominance and sparing of the subpleural space raised suspicion of an adult form of LCH with predominant pulmonary, but also hepatic involvement [21].

Lung

Pulmonary LCH shows variable appearance and is associated with nicotine abuse [17]. Significantly enlarged mediastinal lymph nodes and pleural effusion are rarely observed in patients suffering from LCH [3,22]. Early during disease, LCH presents in a nodular stage, histologically characterized by interstitial Langerhans-cellular infiltrates centered on the walls of bronchioles. On CT, the typical findings are small, sometimes with cystic changes (1-10 mm) with peribronchovascular distribution, sparing the costophrenic angle, and upper lobe predominance [23–25]. In the early phase, no significant fibrotic alterations of the surrounding parenchyma are seen. In the late, fibrotic course of LCH, formation of pulmonary cysts occurs. Pathophysiologically it is assumed that the formation of thin walled cysts is due to a check-valve bronchial obstruction by the nodules, causing dilatation of distal airways, and the occurrence of interstitial fibrosis with architectural distortion. Those irregular shaped cysts may have diameters up to 2-3 cm and may coalesce to bronchiectasis or emphysema [13]. Histologically, various appearances can occur, such as focal scarring, confluent fibrosis or diffuse honeycombing, which may be difficult to distinguish from honeycombing in patients having other interstitial diseases. In the late fibrotic course of disease, spontaneous pneumothoraces can occur [3]. In a series of 102 adults with histologically proven adult pulmonary LCH, Vassallo et al found an extrapulmonary involvement in 17 patients (involvement of the pituitary gland in 8 patients, bone in 4 patients, skin in 4 patients and lymph nodes or liver in 4 patients) with an estimated median survival of 12.5 years [26].

Liver

Hepatic involvement of LCH is rare in adults and is usually seen along with pulmonary involvement in the adult form of LCH [27]. Generally, there are 4 histological stages of hepatic LCH with corresponding imaging features: proliferative, granulomatous, xanthomatous, and fibrous phase, which may lead to liver failure [3]. During the proliferative and granulomatous phase, histology shows periportal infiltration of Langerhans cells and other inflammatory cells, causing periportal inflammation with edema. Ultrasound shows

hypoechoic band like or nodular areas with periportal distribution. Similarly, hypodense lesions are visible on CT, while T1-weighted hypointense and T2-weighted hyperintense lesions are visible on MRI [3]. The xanthomatous stage of disease is characterized by histiocytes ingesting fat containing cell membrane debris, leading to a foamy consistency of the histiocytes. Accordingly, imaging shows linear periportal fatty lesions. On Ultrasound they appear hyperechoic, while on CT scan they are hypodense, and on native T1w-MRI without fat suppression the appearance is hyperintense [28,29,3]. In the fibrous phase, liver parenchyma shows dysmorphic and nodular alterations, due to extensive periductal fibrosis, secondary causing portal hypertension [28,30,31]. In imaging, primary or secondary sclerosing cholangitis leads to biliary irregularities with segmental narrowing and dilatation, resulting in a beaded appearance of the bile ducts at conventional cholangiography, ERCP, or MR cholangiopancreatography [3]. Liver fibrosis may be characterized with transient elastography (Fibroscan) or MR-elastography.

Hepatitis C and LCH

Hepatitis C (HCV) is a risk factor for developing hepatocellular carcinoma, mostly in the setting of advanced fibrosis/cirrhosis of the liver. Recently, more data were published on the possible molecular mechanisms. One of those is the activation of the pro oncogenic MEK/ERK pathway [20].

This pathway seems to be crucial in the development of LCH as well [19], suggesting hepatitis C infection being a risk factor for LHC in the liver. However, due to the rareness of the disease, there is no association described besides some scarce case reports found in the literature [32,33].

After the novel direct-acting antiviral agent (DAA) was introduced in clinical practice, concern was expressed that this therapy may increase the risk of de novo HCC [34]. This was based on descriptive studies observing a higher than historically expected proportion of patients who developed HCC after antiviral treatment. The biological mechanism that was proposed was that rapid viral clearance with DAAs could lead to reduced cancer immune surveillance and antitumor activity. Studies that are more recent provide evidence that DAA-induced eradication of hepatitis C reduces HCC risk [35]. This discussion was a factor making us more alert as to whether the treatment of the hepatitis C in our patient would be of benefit or could even provoke harm due to the change of local immunity.

Hepatitis C virus is not only a hepatotropic, but also a lymphotropic virus and HCV-associated non-Hodgkin lymphomas are a well-described entity. Hematologic remission in HCV-associated indolent lymphoma can be achieved by treating HCV [18]. Therefore, we decided to treat the patient with DAA for the hepatitis C. However, interestingly the patient had a negative HCV RNA in 2 subsequent follow-up visits and therefore cleared the HCV spontaneously.

Conclusion

We present a rare case of adult LCH with synchronous hepatic and pulmonary involvement in a nonfibrotic stage of disease. Consistent with histology, we found an early stage of a proliferative/granulomatous phase of hepatobiliary LCH without any fat containing liver lesions, normal hepatocellular function, and no significant fibrotic liver remodeling. This is consistent with the pulmonary findings, showing a nodular stage of adult pulmonary LCH without any signs of architectural distortion or pulmonary fibrosis.

Statement

Written, informed consent for publication of her case was obtained from the patient.

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