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Human immunodeficiency virus (HIV) infection and tuberculosis (TB)

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Introduction

Human immunodeficiency virus (HIV) infection and tuberculosis (TB) are two diseases that are frequently seen together. The twin epidemics especially affect Sub-Saharan Africa, but they are synergistic in other areas of the world as well [(1)]. Besides socio-economic causes, there are biological explanations for this concurrence. With HIV disease progression, the probability of reactivation of latent TB infection increases; the incidence of active TB has been found to be increase more than twentyfold in those who are HIV-positive compared with HIV-negative individuals [(2, 3)]. Furthermore, HIV infection increases the risk of progression to active TB after primary infection [(4)]. At the same time, active TB favours early viral replication and dissemination and therefore contributes to the progression of HIV-1 infection [(5)]. As both diseases frequently affect patients simultaneously, their ultrasound findings will be covered together in this chapter.

Human Immunodeficiency Virus (HIV)

Introduction

HIV is a chronic infection mainly affecting the T-helper cells ('CD4 cells'). In untreated infections, destruction of CD4 T-helper lymphocytes leads to an increasing degree of immune suppression, especially when the CD4 count falls below 350 cells/mm³. While infections with HIV have become a manageable chronic condition in Europe where effective antiretroviral treatment (ART) has made severe immunosuppression a rarity, it is still a major cause of morbidity and mortality in tropical countries, especially in sub-Saharan Africa. The programmatic roll-out of ART is successfully advancing and the Global Burden of Disease Study, published in in October 2016 [(6)], showed a significant increase in life expectancy between 2005 and 2015 in many African countries (e.g. patients in Malawi gained life expectancy of 13.7 years for females and 10.5 years for males) mainly due to ART. Recent changes in the WHO guidelines have seen a move towards people starting ART at higher CD4 counts and since 2016 the recommendation has been to treat all HIV positive patients in all settings irrespective of their CD4 count [(7)]. The *test-and-treat strategy* carries the optimism that 'sick patients' can be prevented. Despite the guideline changes a substantial proportion

of people do not get diagnosed or initiated on ART until their CD4 counts are very low, which prompted further WHO guidelines on the management of these 'advanced patients' [(8)]. When CD4 counts fall below 200 cells/mm³, a variety of opportunistic infections and malignancies affect the patient who is then diagnosed with acquired immunodeficiency syndrome (AIDS) [(9)].

Ultrasound is useful in the diagnosis of a wide array of HIV associated diseases and infections in various organ systems, predominantly in diagnosing opportunistic infections in severely immunosuppressed patients, but also in patients with longstanding HIV infection on ART [(10, 11)]. In addition, it is widely used to guide diagnostic needle biopsies for histological or microbiological investigations [(12)]. The use of point-of-care ultrasound is being recorded in an increasing number of regions [(13, 14)]. This section is an overview of ultrasound findings that may be seen in the organs of patients with HIV.

Abdominal ultrasound

Liver

Diffuse pathologies

Hepatomegaly is one of the most frequent findings in patients who are HIV-positive and was found in up to 35% of patients screened in the Democratic Republic of Congo and Zambia [(15, 16)]. The causes of hepatomegaly in HIV-positive patients are numerous, but the most frequent are concomitant hepatitis B and C virus infection, cytomegalovirus (CMV) infection, granulomatous hepatitis *e.g.* due to tuberculosis [(17)], *Mycobacterium tuberculosis*, atypical mycobacteria infection (MOTT, mycobacteria other than tuberculosis, *e.g.* mycobacterium avium complex (MAC) or *Mycobacterium kansasii*) and diffuse lymphomatous infiltration [(18, 19)]. Visceral leishmaniasis, presenting with fever and hepatosplenomegaly, is also more common in people infected with HIV and is an important differential in endemic areas [(20)]. In Asia, *Talaromyces* (formerly *Penicillium*) *marneffe* is a common opportunistic infection causing hepatosplenomegaly and generalised lymphadenopathy, as well as typical skin lesions [Figure 1].

Figure 1 Diffuse hepatomegaly (a) and splenomegaly (b) (17 cm) in a patient with *Talaromyces marneffe* infection. Typical umbilicated skin lesion on the forearm (c).

a



b

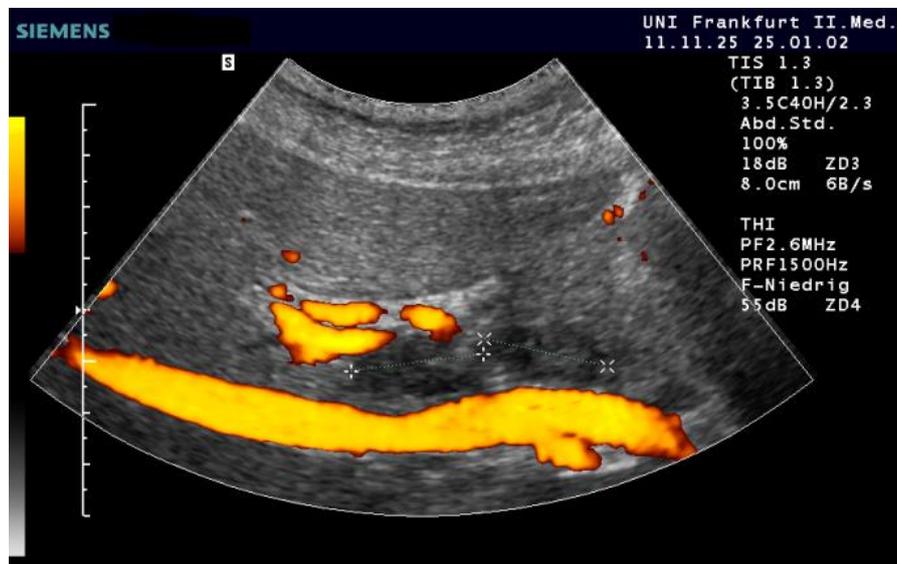


c



Often no specific cause of hepatomegaly is found. Ultrasound-guided liver biopsy helps to narrow down the differential diagnosis. Small lymph nodes are frequently detectable within the hepatoduodenal ligament in patients with chronic HIV. Enlarged lymph nodes can be found in HIV-positive patients with or without chronic hepatitis C virus [(21-23)] and in other inflammatory liver diseases such as primary biliary cholangitis and autoimmune hepatitis [(19, 24-26)], as well as in lymphoma [Figure 2].

Figure 2 Enlarged perihepatic lymph nodes in the dorsal hepatoduodenal ligament (between markers) in an HIV-positive patient with chronic hepatitis C and hepatic tuberculosis.



Focal pathologies

Focal pathologies of the liver are a common finding in patients with HIV. The echo-pattern of the liver lesions may be described as hypoechoic, hyperechoic or of mixed echogenicity. Diseases commonly presenting with hypoechoic liver lesions are lymphoma, *Mycobacterium tuberculosis* infection and abscesses [(27)]. AIDS-related lymphomatous lesions may vary largely in size from a few to several centimetres [Figure 3] and in some instances they may appear echo-free and can be confused with cystic lesions [Figure 4]. Bacterial abscesses often show irregular borders and may contain small gas bubbles [Figure 5].

Figure 3 Complex lesion in the left lobe of the liver in a patient with HIV: lymphoma.

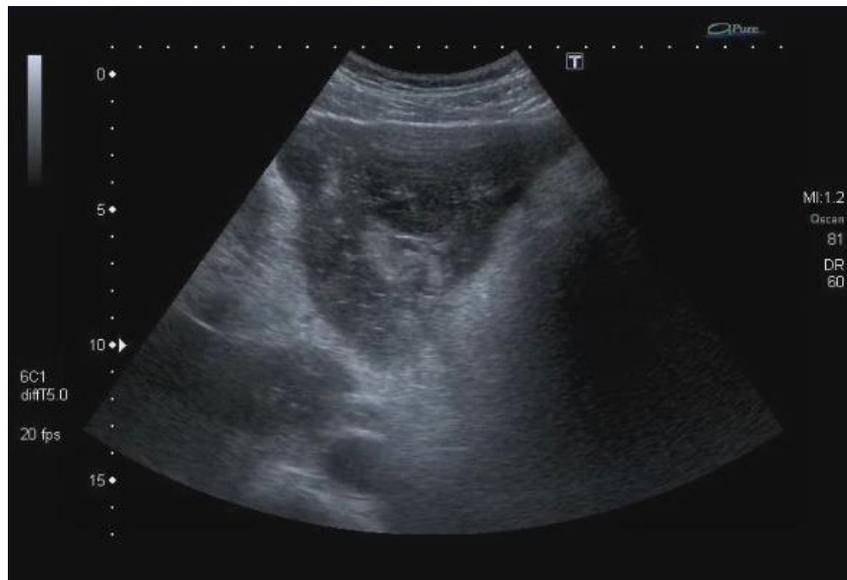


Figure 4 Round hypoechoic lesion in the liver of an HIV positive patient: non-Hodgkin lymphoma (biopsy result).

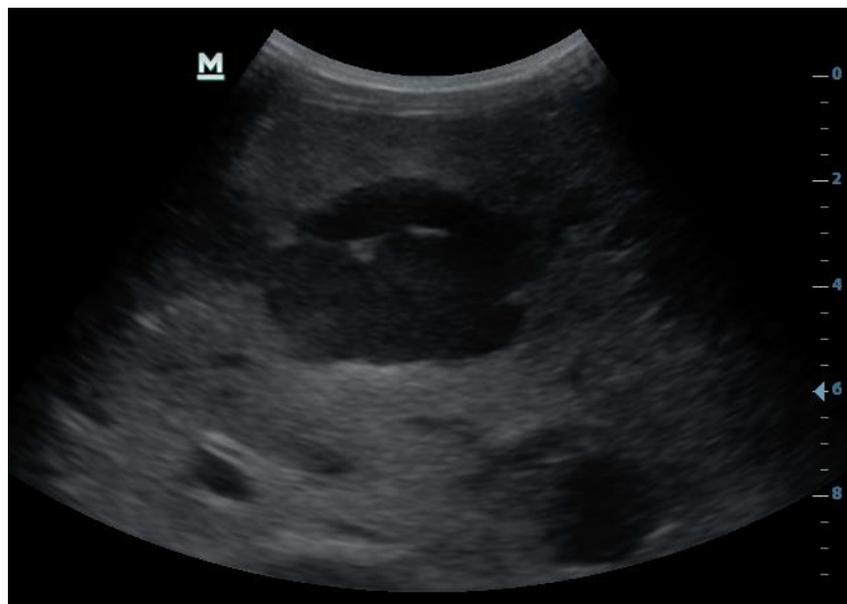


Figure 5 Bacterial abscess of the liver.



Fungal microabscesses can have a bulls-eye appearance; in particular, this morphology has been described in *Candida albicans* infections and mucormycosis [(11)] [Figure 6].

Disseminated Kaposi's sarcoma (KS) presents with hyperechoic, disseminated lesions, 5–10 mm in size, which can be found even in the absence of cutaneous lesions [Figure 7]. In larger KS lesions, a complex echo-pattern with hyper- and hypoechoic areas is observed.

Figure 6 'Bull's eye' sonographic appearance of a fungal abscess in the liver of an HIV-positive young drug user [(11)].

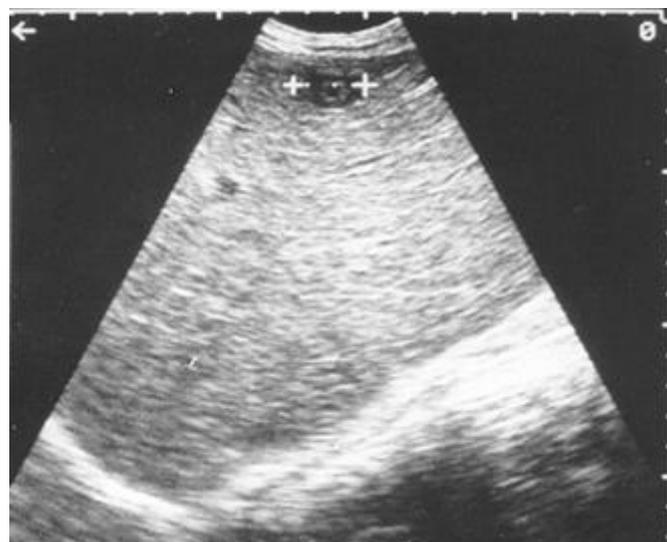
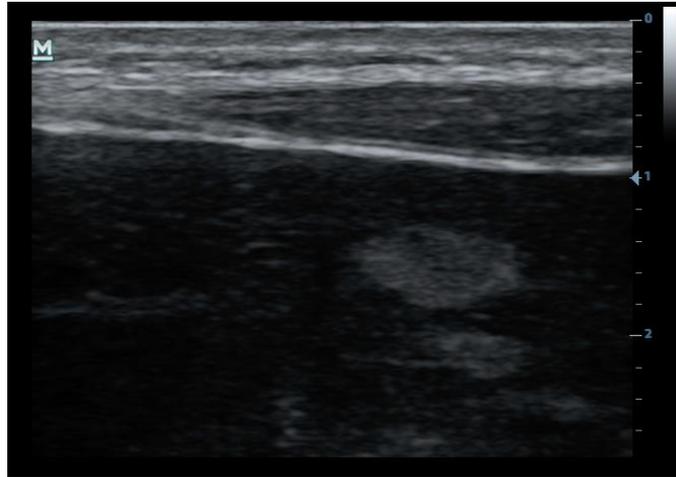


Figure 7 Hyperechoic liver lesion in an HIV positive patient with disseminated Kaposi's sarcoma: liver KS (the lesion disappeared after chemotherapy).



Small hyperechoic liver lesions are seen in disseminated MAC and *Pneumocystis jirovecii* infections. Bacillary peliosis or bacillary angiomatosis is characterised by cystic, blood-filled vasoproliferative lesions and spaces in the liver. This is linked to opportunistic infection with *Bartonella henselae* and has a sonographic appearance of multiple heterogeneous, more often hyper- but sometimes also hypoechoic, hypervascular focal liver lesions [Figure 8] [(28)]. Multiple, diffuse small echogenic lesions in the liver or spleen are seen as a 'snowstorm pattern'. Although this was initially described with *Pneumocystis jirovecii* infections [(11)], other organisms such as *Candida* and *Aspergillus* can be a cause. Histological features include foci of calcification, but their frequency is not sufficient to explain the multiple echogenic foci. The interfaces caused by the fibrosis could be largely responsible for the snowstorm appearance [(29)]. Ultrasound guided biopsy is used to determine the diagnosis [(12, 30)].

Hepatocellular carcinoma (HCC) is a common cancer in HIV-positive patients, mainly driven by hepatitis C virus co-infection. A focal lesion in a cirrhotic liver is highly suggestive of HCC [Figure 9]. The lesions are mostly hypoechoic, but hyperechoic lesions also occur especially if small. A mosaic pattern is typical, but rare [(31)]. Biannual ultrasound screening is

recommended for all patients with cirrhosis and those who are infected with hepatitis C with additional risk factors (family history of HCC, Asians and Africans) [(32, 33)]. Recent evidence suggests that more frequent screening may be beneficial in cirrhotic patients with HIV, in particular those with a detectable HIV viral load [(34)].

In patients at risk of HCC, the Liver Imaging Reporting and Data System (LI-RADS) can be used for classification. The American College of Radiology introduced LI-RADS to standardise the reporting and data collection of CT, MR and US imaging for hepatocellular carcinoma (HCC) [(35-37)]. LI-RADS is an algorithm which categorises observations from LR-1, a definitely benign lesion through to LR-5, reflecting a confident diagnosis of HCC. LR-M suggests a malignant lesion without specificity for HCC and LR-V suggests tumour thrombus in the portal vein. Between LR-1 and LR-5 are all the other possible observations reflecting the process of carcinogenesis including LR-2, a probably benign observation, LR-3 an observation of intermediate probability for HCC and LR-4, a highly suspicious observation for HCC. The categories LR-3 to LR-5 tend to roughly reflect the progression from large regenerative nodules (>4 mm) to mature HCC, paralleled by a derangement of intratumoural vascularisation.

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