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Ultrasound in tropical medicine. Human Immunodeficiency Virus (HIV) Infection

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Introduction

Infection with human immunodeficiency virus (HIV) is a major cause of morbidity and mortality in tropical countries, especially sub-Saharan Africa. In untreated infection, destruction of CD4 T-helper lymphocytes leads to an increasing degree of immune suppression, especially when the CD4 counts fall below 350 cells/mm$^3$. When CD4 falls below 200 cells/mm$^3$, opportunistic infections and malignancies affect the patient who is then defined as having acquired immunodeficiency syndrome (AIDS).

Ultrasound can be used to diagnose a wide array of diseases and infections in various organ systems [(1, 2)]. It is also widely used to guide diagnostic needle biopsies for histological or microbiological investigations.

This chapter is an overview of ultrasound findings that may be seen in the organs of patients with HIV.
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 patient screened in the Congo and Zambia [(3)]. Causes of hepatomegaly in HIV-positive patients are numerous, but the most frequent are concomitant hepatitis B and C virus infections, cytomegalovirus (CMV) infections, granulomatous hepatitis e.g. due to *Mycobacterium tuberculosis*, atypical mycobacteria (*mycobacterium avium complex-MAC- M. kansasii*) infections and diffuse lymphomatous infiltration. Often no specific cause of hepatomegaly is found. Ultrasound-guided liver biopsy helps to narrow the differential diagnosis. Lymph nodes are detectable within the hepatoduodenal ligament in almost all patients with chronic HIV. Enlarged lymph nodes can be found in HIV-positive patients with or without chronic virushepatitis C [(4)] and other inflammatory liver diseases but also in lymphoma [Figure 1].

Figure 1  Enlarged perihepatic lymph nodes in the dorsal hepatoduodenal ligament (in between markers) in a HIV-positive patient finally with the diagnosis of chronic virushepatitis C and hepatic tuberculosis. For more details of perihepatic lymphadenopathy with and without HIV, see chapter on the Liver.

Focal pathologies
Focal pathologies of the liver are common findings in patients with HIV. The echo-pattern of the liver lesions may be described as hypoechoic, hyperechoic or of mixed echogenecity.
Diseases commonly presenting with hypoechoic liver lesions are lymphoma, *M. tuberculosis* infection and abscesses. AIDS-related lymphomatous lesions may vary in size from a few to several centimetres [Figure 2], and in some instances they may appear echo-free and can be confused with cystic lesions [Figure 3].

**Figure 2**  Complex lesion in the left lobe of the liver in a patient with HIV: lymphoma.

![Complex lesion in the left lobe of the liver in a patient with HIV: lymphoma.](image)

**Figure 3**  Round hypoechoic lesion in the liver of a patient with AIDS during fine-needle biopsy: lymphoma.

![Round hypoechoic lesion in the liver of a patient with AIDS during fine-needle biopsy: lymphoma.](image)

Bacterial abscesses often show irregular borders and may contain small gas bubbles. Fungal micro-abscesses can have a bull-eye appearance; in particular, this morphology has been described in disseminated *Candida albicans* infections.
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. In larger KS lesions, a complex echo-pattern with hyper- and hypoechoic areas is observed. Small hyperechoic liver lesions are seen in disseminated MAC and *Pneumocystis jirovecii* infections. Bacillary peliosis or bacillary angiomatosis is characterized 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 hyperechogenic hypervascular liver lesions [(5)]. Multiple, diffuse small echogenic lesions in the liver or spleen are seen as a “snowstorm pattern”. Although this has been initially described with *P. jirovecii* infections, 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 [(6)]. Fine-needle biopsy is used to determine the diagnosis.

**Gallbladder and bile ducts**

Gallbladder wall thickening is a frequent finding in patients with HIV; however, in the majority of patients this is an incidental finding. A thick-walled and distended gall bladder, which shows the “sonographic Murphy’s sign” (tenderness on probe pressure in the gallbladder area), may point to cholecystitis. In contrast to immune-competent individuals, this may develop in the absence of gallstones (“acalculous cholecystitis”) [Figure 4]. Gallbladder thickening is a short-life sonographic phenomenon of early phase acute hepatitis in approximately 50% of patients. This must not be confused with acute cholecystitis where there is no circumscribed pain under ultrasound visualized palpation [(7)].
Irregular or smooth dilatation of intrahepatic bile ducts and concentric thickening of the intra- and extrahepatic biliary tree (sclerosing cholangitis) may be seen in patients with HIV. Extrahepatic strictures, as well as papillary stenosis, have been described. Biliary-tract infections can be caused by various organisms, but cryptosporidia and CMV are the most frequently reported.

**Spleen**

Splenomegaly is found in about a third of patients with HIV in Africa [(3)]. This can be a non-specific finding in general infection, but can also be accompanied by diffuse echogenic infiltration e.g. lymphoma.

Focal lesions can be due to infections such as pyogenic abscesses (generally hypoechoic) [Figure 5], mycobacterial micro-abscesses (hypoechoic) [Figure 6] or toxoplasmosis (calcifications of a few millimetres in size with a posterior acoustic shadow).
Figure 5  Hypoechoic lesions in the spleen with a possible mycobacterial aetiology.

Figure 6  Tuberculosis of the spleen with small hypoechoic lesions in a HIV-positive patient. Similar images can be seen in other infectious (fungal) disease, hemophagocytosis-syndrome and lymphoma.

The snowstorm pattern has also been described (see liver section). The most frequent neoplastic focal lesions of the spleen are lymphomas, commonly hypoechoic, ill-defined lesions of varying size. Contrast enhanced ultrasound is helpful in delineating small infiltrations including hemophagocytosis lesions [(8)] and extramedullary hematopoesis [Figure 7].
Figure 7  Extramedullary hematopoiesis. Extramedullary hematopoiesis can be seen in a variety of neoplastic and infectious diseases in association with HIV-infection.

Burkitt’s lymphoma lesions tend to be larger and may have a complex echo-structure [(9)]. KS tends to be echogenic and may vary in size from a few millimetres to a large lesion occupying a large area of the spleen.

Pancreas

Although pancreatic involvement is frequently found in patients with HIV, it is rarely symptomatic and is usually in the context of disseminated infections. Pancreatitis may be seen owing to strictures induced by opportunistic infections, similar to the cholangitic changes already described. Tuberculosis of the pancreas might be diffuse or circumscribed [Figure 8]. In addition, focal masses of the pancreatic head due to tuberculosis or primary pancreatic lymphoma may cause obstruction of the pancreatic duct leading to secondary pancreatitis.

Figure 8  Tuberculosis of the pancreas. Ductal adenocarcinoma was suspected by computed tomography. Ultrasound-guided biopsy revealed the final diagnosis of tuberculosis of the head of the pancreas. Elastography revealed softer tissue whereas in the more advanced stages harder elasticity is predominant [(10)].
Kidney

Focal-segmental glomerulosclerosis is the most frequent renal pathology found on ultrasound. The kidneys are typically normal or increased in size and the parenchyma is hyperechoic [Figure 9]. This appearance is non-specific and can be seen in other renal diseases such as diabetic glomerulosclerosis or other forms of chronic glomerulonephritis. The sonographic finding should prompt an assessment of proteinuria. In some cases renal biopsy might be indicated to determine the exact diagnosis.

Figure 9    Hyperechogenic kidney in a patient with AIDS.
Nephrocalcinosis with circumscribed renal calcifications might be seen in generalised MAC and histoplasmosis infections, as well as patients taking medication such as sulfadiazine, acyclovir and in particular indinavir, which can induce renal stone-like structures. Abscess formation is typical in tuberculosis [Figure 10]. Retroperitoneal masses like lymphadenopathy can obstruct the ureters and result in hydronephrosis.

**Figure 10** Renal tuberculosis in HIV-infected patients. The infiltration patterns vary from larger abscesses (b,c) to tiny infiltration (c). Contrast enhanced ultrasound is helpful in delineating non-vascularized abscesses (b) [(11)]. Nierenrinde: cortex of the kidney.
**Gastrointestinal tract**

The intestinal tract is particularly prone to opportunistic infections owing to its large surface area and the presence of lymphoid tissue in the bowel wall. Inhomogeneous masses may be observed, but commonly the pathology presents as thickened (up to 2cm) hypoechoic bowel wall that is similar to that seen in colitis. Often a central hyperechoic, gas-containing lumen is visible ("target sign").Rare intestinal diseases in HIV-positive patients have been described [(12) (13)]. Again, there is a wide differential diagnosis, including opportunistic infections and neoplasms. Endoscopy may be used to obtain diagnostic tissue samples, but because of the submucosal location of the lesions this does not always allow diagnosis. Percutaneous ultrasound-guided biopsy of the bowel wall was shown to be a safe way to obtain tissue samples [(14)].

**Ascites**

Ascites is a relatively common finding that is encountered in up to 1 in 5 patients in some African studies [(3)]. Ascites may be due to portal hypertension, especially in co-infected patients (with hepatitis C or B virus) or those with alcoholic liver disease. Exudates may be due to infections or tumours and numerous causes have been described. Ultrasound helps to identify even small amounts of intraperitoneal fluid and can assist paracentesis. Microbiological culture and PCR (polymerase chain reaction) may yield results
of *M. tuberculosis*, MAC and CMV, but in rare cases organisms such as *C. albicans*, *Coccidiodes immitis*, *P. jirovecii*, *T. gondii* and *Encephalitozoon cuniculi* have been found. Malignant ascites is seen less frequently and should be suspected in culture-negative exudative peritoneal fluid. KS and lymphoma should be considered. Primary effusion lymphoma associated with human herpes virus 8 (HHV-8) is a subgroup of AIDS-related B-cell lymphoma affecting body cavities in patients with HIV.

**Lymph nodes**

Enlarged lymph nodes are frequently seen in patients with HIV and imply a wide differential diagnosis. Intra-abdominal lymph nodes larger than 1.5 cm are commonly considered pathological, and are often round and plump and can occasionally become very large [Figure 11].

![Figure 11](image)

**Figure 11** Enlarged lymph nodes encasing the coeliac axis, common hepatic artery and splenic artery (transverse section).

Often the nodes appear hypoechoic and have a disrupted architecture with absence of the “hilum fat sign” and, sometimes, have liquid, necrotic areas. The differential diagnosis includes tuberculosis, MAC, toxoplasmosis, CMV, as well as generalised KS and lymphoma. Castleman’s disease is another lymphoproliferative disease associated with HHV-8 in HIV patients presenting with fever and lymphadenopathy. Ultrasound-guided fine-needle biopsy can often help make a diagnosis.
**Parotid**

5–10% of patients with HIV-1 infection have parotid swellings, most commonly due to cystic lymphoepithelial lesions of the salivary gland. Sonographic examination shows unilaterally or bilaterally enlarged glands with cystic lesions. The size of the sonolucent areas may vary from a few millimetres to a few centimetres, cyst number varies from a single cyst to numerous and represent lymphoepithelial cysts, intraparotid lymphadenopathies and parenchymal lymphoproliferation [(15)].

If necessary, the diagnosis can be confirmed through fine-needle aspiration, treatment modalities include simple aspiration, surgical resection or radiotherapy; most cases that are treated with antiretroviral therapy show regression.

**Heart**

HIV-associated cardiomyopathy is reported in 9–57% of patients who are HIV-positive in Africa [(16)]. Variation in study design, population and a lack of a clear definition for cardiomyopathy may account for this wide range.

If biopsies are obtained in these patients, myocarditis due to *T. gondii, C. neoformans* and *M. avium intracellulare* have been shown; cardiotropic viruses are seen more frequently in developed countries.

A direct HIV-associated cardiac inflammation is also common. A relationship between the degree of immunosuppression and the likelihood of cardiomyopathy seems to exist; antiretroviral therapy prevents immunosuppression, but it is unclear whether it reverses cardiomyopathy.

Abdominal sonographic views may show the typically enlarged, dilated ventricle (diastolic diameter more than 5.5 cm) with globally reduced contractility; this may prompt further investigation by echocardiography.

**Tuberculosis**

Infections with *M. tuberculosis* commonly affect the lungs and are diagnosed by a chest radiography as well as by sputum microscopy (acid-fast bacilli, AFB) and culture. Nevertheless, because this is a systemic disease, extrapulmonary manifestations are seen regularly and in cases of concomitant HIV infection these are even more frequent.
As material for microscopy and culture is not readily obtainable in extrapulmonary tuberculosis (EPTB), diagnosis often depends on aspiration of suspicious fluids or on clinical case definitions in high prevalence settings. Ultrasound helps to provide significant information that leads to diagnosis and treatment [(17)]. Standard treatment for all forms of EPTB is similar to pulmonary tuberculosis (TB); usually 4 antibiotics (rifampicin, isoniazid, ethambutol and pyrazinamid) are given for 2 month followed by 4 month of rifampicin and isoniazid.

**Pericarditis**

TB pericarditis is one of the acutely life-threatening manifestations of EPTB owing to the possibility of cardiac tamponade [(18)]. It is the most common cause of pericarditis in Africa, in a South African series TB pericarditis accounted for up to 70% of cases referred for diagnostic pericardiocentesis [(19)] [Figure 12].

![Figure 12](image)

Figure 12  
Enlarged cardiac silhouette on a chest radiograph in tuberculosis pericarditis.

TB pericarditis usually develops by retrograde lymphatic spread of *M. tuberculosis* from peribronchial or mediastinal lymph nodes; the immune response to viable acid-fast bacilli penetrating the pericardium is responsible for morbidity. Non-specific signs and symptoms such as fever, night sweats and weight loss are observed, and chest pain, a cough and breathlessness are common. In African patients, chronic cardiac compression mimicking congestive heart failure is another common presentation.
Sonographically, two forms of disease can be differentiated: pericardial effusion and constrictive pericarditis. Effusion is characterized by a large, anechoic-rim around the heart; it should be assessed if the effusion impairs the normal filling of the right ventricle or atrium, which would suggest cardiac tamponade [Figure 13].

**Figure 13** Massive pericardial effusion seen on ultrasound (curvilinear probe).

Often a thickened pericardium with fibrinous strands and exudative coating material are observed floating in the effusion. If aspirated, the effusion is typically exudative and may yield positive results in mycobacterial culture or PCR. At the same time AFB should be looked for in sputum. In cases of constrictive pericarditis a thick fibrinous exudate is seen in the pericardial sac, which is associated with reduced movement of the surface of the heart. The pericardial exudate condenses into a thick skin surrounding the heart, and this can usually be distinguished from the myocardium [(20)].

Corticosteroids may be given in addition to antibiotic treatment, although their impact on outcome is still controversial. In any case, a statistically non-significant, but potentially large reduction in mortality was observed in one randomised trial [(21)] and patients experience a more rapid clinical improvement, therefore we prescribe it for 6 weeks, especially in cases with tamponade.

**Pleuritis**

The pleura may be affected by TB in different ways:

- Effusion that develops usually a few months after primary infection (hypersensitivity reaction).
Effusion developing as a result of lung disease in older adults, which might develop into purulent effusion (empyema).

Rupture of a cavity and escape of bacteria and air into the pleural space, from which empyema and pyopneumothorax may result.

Complicating miliary TB that involves polyserositis.

In all of the above, effusions can be observed sonographically, and fibrin strands may be seen [(22)]. Ultrasound may guide aspiration, and if a total white blood cell count higher than 500 cells/mm$^3$ and protein more than 2.5g/dl are found in the aspirate, empyema can be diagnosed. This can be further differentiated clinically between “thin empyema” (possible to mobilize through cannula) and “thick empyema” (which may need a transthoracal drain to be mobilized). Antibiotic therapy is highly effective.

**Peritonitis**

TB peritonitis is probably caused by haematogenous spread and reactivation of long-latent foci or mesenteric lymph nodes [(23)], but contiguous spread from bowel or fallopian tube is also possible. Ultrasound findings are ascites (clear or complex), fixed membranes, septae, strands, floating debris, omental thickening (“omenta cake”), thickened mesentery and abdominal lymphadenopathy [Figure 14].

**Figure 14** Circumscribed peritoneal thickening in a HIV-positive patient with peritoneal tuberculosis.
Ascites is usually straw-coloured, sometimes (10% of cases) blood stained, protein content is usually more than 2.5 g/dl and leukocytes with lymphocytic predominance can be seen. Direct microscopy is usually AFB negative, cultures are also only positive in approximately 20% of cases. Laparoscopy-guided peritoneal biopsy has a higher diagnostic yield but is more invasive. “Blind” peritoneal biopsy using an endoscopy biopsy forceps has been successfully used as an alternative [(24)].

**Disseminated abdominal infection (lymph nodes and spleen)**

HIV positive patients may present with disseminated abdominal TB, affecting abdominal lymph nodes and the spleen. Signs and symptoms are usually weight loss, abdominal pain and diarrhoea. Abdominal lymph node enlargement and ascitis are the most common findings, and hypoechoic lesions of the spleen are seen in about 50% of patients. [Figure 15]. These represent “miliary” micro-abscesses, although patients frequently show no miliary pattern on a chest radiograph [(25)].

These splenic hypoechoogenic foci may suggest *M. tuberculosis* infection rather than nontuberculous mycobacteria, as they are rarely seen in the latter. A marked lymphadenopathy is far more frequent in TB cases.

**Figure 15** Hypoechogenic tuberculous nodules seen with a linear probe in the lower splenic pole.
Liver
Involvement of the liver in TB is common (up to 80% in autopsies of PTB), while clinical manifestations of this involvement are not. Sonographically, two forms exist: an enlarged liver with a homogenous bright echo-pattern points towards hepatic granulomatous disease (often wrongly described as granulomatous hepatitis when the liver cells are unaffected). The diagnosis is reached by ultrasound-guided liver biopsy. Focal tuberculomas present as “abscess-like” masses, which are usually hypoechoic, may be single or multiple and may vary in size from 0.5–12 cm. Tuberculosis infection may present with an enormous heterogeneity [Figures 16]. It should be noted that these lesions (as all tuberculous lesions) during successful treatment can initially increase in size as the improved immunological response increases the inflammatory reaction. This does not point to treatment failure and it should be observed.

Figure 16  Tuberculosis of the liver with granulomatous infiltration of the liver parenchyma and bile ducts (in between markers).

Gastrointestinal tract
Although tuberculosis can involve any region of the gastrointestinal tract, in about 90% of cases it affects the ileocecal valve, and the adjacent ileum and colon [(17)]. Sonographic appearance in most patients is a heterogenous and asymmetric bowel-wall thickening with typical intramural necrosis [Figure 17], often with mesenteric enlargement of regional lymph nodes and the so-called white bowel appearance [(26)] [Figure 18]. In some cases matted
masses are observed, which represent conglomerates of thickened bowel loops, thickened mesentery, abscess formation [Figure 19], complex ascites and enlarged lymph nodes.

**Figure 17** Gastrointestinal tuberculosis in a HIV-positive patient with intramural abscess formation in between markers.

**Figure 18** Gastrointestinal tuberculosis in a HIV-positive patient with complex inflammation of the lymphatic vessels resulting in so-called white bowel. App: Appendix. Coe: coecum.
Figure 19  Gastrointestinal tuberculosis in a HIV-positive patient with complex infiltration, fistula (arrow) and abscess (abs) formation (panoramic imaging).

Renal and urinary tract

Genito-urinary TB is seen more commonly in Caucasians than in Africans patients. The pathogenesis involves the haematogenous spread of *M. tuberculosis* followed by seeding in the renal cortex in which a high oxygen tension exists. During reactivation, granuloma form that spread into the medulla and can lead to necrosis of renal papillae, and renal obstruction may occur. Bacilluria can lead to ureter and bladder involvement with fibrosis and reflux. Sonography may show renal calcifications, papillary irregularities and intrarenal masses. Hydronephrosis due to strictures, thickening and dilatation of the ureter and bladder abnormalities (wall thickening and masses) may also be seen [(27)]. Diagnosis is usually made with a urine culture.

Scrotal involvement in the form of a swelling due to “cold abscesses” in the epididymis and testis are well described. Focal areas of decreased echogenicity can be demonstrated on ultrasound. Differentiation from tumours may be difficult, so image-guided aspiration is often needed.

Patients with TB involvement of the female genital tract often present with chronic pelvic pain, infertility and vaginal bleeding. Most patients have abnormal hysterosalpingograms with endometrial adhesions, fallopian tube constrictions and small calcifications in the adnexal area. Ultrasound may show tubo-ovarian abscesses, extension of these collections to extraperitoneal areas can suggest TB, so often the diagnosis is made by aspiration and microbiological investigation of the material [(28)].