

Abdominal Sonographic Findings in Severely Immunosuppressed Human Immunodeficiency Virus-Infected Patients Treated for Tuberculosis

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Abstract

Objective: We describe the abdominal sonographic findings among patients with HIV-tuberculosis (TB) co-infection with advanced immune suppression before initiation of ART and relate these findings to the patients' abdominal symptoms and CD4 T-cell count. **Methods:** Consecutive HIV-TB co-infected patients, qualifying for ART, were prospectively enrolled in a cohort study at the Mulago National Tuberculosis and Leprosy Programme clinic in Kampala, Uganda. An abdominal ultrasound was performed at enrolment. **Results:** A total of 209 HIV-TB co-infected patients (76% with pulmonary, 19% with extra-pulmonary TB and 5% with extra-pulmonary and pulmonary TB) underwent an abdominal ultrasound scan. Only 49 patients (23.4%) had a normal abdominal ultrasound. The following sonographic abnormalities were found: multiple lymphadenopathy (38%), splenomegaly (18%), renal abnormalities (14%), gastro-intestinal tract abnormalities (thickened bowel loops, appendicitis) (13%), splenic abscesses (13%) and ascites (6%). The commonest groups of enlarged lymph nodes were in the porta-hepatis (19%) and peri-pancreatic

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(17%) area and 80% of the enlarged lymph nodes were hypo-echoic. Conclusion: Most patients with advanced immune suppression and HIV-TB co-infection have sonographic evidence of generalized TB with abdominal involvement, therefore Ultrasound may assist in the early diagnosis of disseminated TB.

Keywords

Abdominal Sonography, Severe Immunosuppression, HIV-TB Co-Infection

1. Introduction

The prevalence of HIV in patients with tuberculosis (TB) in sub-Saharan African countries ranges from 20% to 67%. The most common cause of death in persons with HIV infection in the tropics is TB, which is disseminated in up to 70% of patients with CD4 counts of less than 100 cells/mm³ [1] [2]. Abdominal symptoms are frequent complaints of HIV-TB co-infected patients, especially in advanced stages of immunosuppression [3]-[5].

Traditionally the diagnosis of TB depends on the demonstration of acid-fast bacilli in the sputum. This diagnostic process is however considerably less sensitive in cases of HIV co-infection due to the fact that TB is often extra-pulmonary and when TB infects the lungs it is much more likely to be smear-negative. Therefore, ultrasound examination of the abdomen has been used in a number of centers to assist in diagnosing disseminated TB in patients with advanced HIV disease. A number of ultrasonographic findings such as lymphadenopathies with a central hypo-echoic region and splenic micro-abscesses have been regarded useful in the diagnosis of TB [6] [7].

In this manuscript, we describe the baseline abdominal sonographic findings in patients with TB-HIV co-infection before initiation of ART. In addition, we correlate the abdominal ultrasound findings to the patients' abdominal symptoms and to CD4 T-cell count.

2. Methodology

2.1. Study Setting and Population

From December 17th 2007 to 31st December 2009, consecutive HIV-TB co-infected patients, qualifying for ART according to National ART treatment guidelines, were prospectively enrolled in a cohort to study the incidence of the immune reconstitution inflammatory syndrome at the National Tuberculosis and Leprosy Programme clinic [8].

2.2. Data Collection

Study eligibility criteria included adults (>18 yrs), living within a 20 kilometre radius of the hospital, with a positive TB diagnosis as defined by microbiology or by the WHO criteria [9], starting TB treatment or having taken TB treatment for less than two months and were eligible for ART initiation according to the Uganda national ART treatment guidelines (CD4+ T-cell counts \leq 250 cells/ μ l) [10]. Exclusion criteria were liver function abnormalities (alanine and aspartate transaminases greater than five times the upper limit of normal) and renal failure.

All patients were subjected to a detailed clinical history, physical examination, and laboratory investigations. Other investigations were performed based on clinical indications and their CD4 counts.

Patient characteristics (age, gender), haemoglobin, CD4 counts measurement were obtained at study enrolment and relevant specimens (sputum, lymph node aspirate, pleural effusion, etc.) were examined by Ziehl Nielsen (ZN) stain and Lowenstein Jensen (LJ) culture for TB (details of the microbiological findings have been published elsewhere) [11].

2.3. Imaging

A chest X-ray and an abdominal ultrasound were performed at enrolment. An abdominal ultrasound was conducted for evaluation of the abdomen. Two radiologists (HNK, MGK), certified by the National Medical Asso-

ciation Board and each with more than ten years of experience, performed the abdominal ultrasound scans with the patient in supine position. Each sonogram was obtained using a sonography unit (Philips HD7, China), with a broad band (2 - 5 MHz) curve-linear and high a frequency (7.5 - 10 MHz) linear transducer.

A complete abdominal sonographic examination was performed included a detailed evaluation of the liver, gallbladder, bile ducts, spleen, pancreas, kidneys, mesentery, bowel loops, aorta and inferior vena cava. Findings recorded included organ enlargement, altered echogenicity and echo-texture, presence of focal masses (single or multiple), fluid collections, lymphadenopathy, hollow visceral thickening, gut wall matting and vascular assessment. Color flow Doppler was used to further analyze an area or lesion of interest in case of need. After all organs and their contiguous structures were individually examined, a diagnosis was formulated. If no pathology was found a limited number of standard hard copy images were recorded. All sono-images were stored electronically.

2.4. Definitions

Lymphadenopathy: nodes larger than 1 cm in diameter [12] [13] splenomegaly: spleen more than 13 cm in its maximum length [13] [14], hepatomegaly: longitudinal measurement of the liver at the mid-clavicular line measures more than 15 cm [15], Centri-lobular/“starry sky” pattern of the liver: decreased echogenicity of the liver with apparent increase in the number of portal vein walls with more than 10 such vessels per image [15]-[17]. The fatty-fibrotic/bright liver pattern: increased echogenicity of liver parenchyma and sound attenuation with decreased definition of portal vein walls [16] [18]. Normal gallbladder wall: ≤ 3 mm [19].

2.5. Statistical Analysis

Medians and interquartile range (IQR) were calculated for continuous variables. The chi-squared test or the Fisher Exact test was used to compare proportions of patients with and without sonographic abnormalities as indicated. The analysis was performed using STATA 12 software (Stata, East College Station, TX).

2.6. Ethical Approval

The University Research and Ethics Committee, the Committee on Human Research, the Hospital Institutional Review Board and the National Council for Science and Technology approved the protocol. Informed consent was obtained for screening and for enrolment into the study.

3. Results

A total of 209 HIV-TB co-infected patients underwent an abdominal ultrasound scan (Table 1). The median age of the patients was 34 years (interquartile range (IQR) 27 - 39). The majority of patients had advanced HIV infection with a median CD4+ T-cell count of 48 cells/mm³ (IQR 19 - 128) and most patients had a diagnosis of pulmonary TB at baseline.

Abdominal sonographic findings among HIV-TB co-infected patient starting anti-retroviral therapy (ART) are presented in Table 2.

Differences in sonographic findings between patients with and without abdominal complaints are presented in Table 3.

There were no significant statistical differences in the abdominal sonographic findings between those with and without symptoms, as well as patients with CD + T-cell count < 50 cells/mm³ and ≥ 50 cells/mm³ (Table 4).

4. Discussion

4.1. Background

Abdominal TB accounts for 15% - 20% of all TB cases in Africa [20]. Patients with abdominal TB tend to present with abdominal pain, weight loss and fevers [5] [7] [11] [21]-[24]. However, a definitive diagnosis in developing countries with high prevalence of HIV is often a challenge due to but not limited to: low sensitivity and specificity of the clinical symptoms, the paucity of radiological and diagnostic modalities, and difficulties in accessing the affected tissues for a diagnostic specimen [6] [7] [23] [25]-[27].

A number of studies have found that a combination of clinical features and sonographic characteristics may

Table 1. Demographic and clinical characteristics of 209 HIV-TB co-infected patients starting anti-retroviral therapy (ART).

| Patient characteristic (N = 209) | n (%) |
|---|-------------------------|
| Female (%) | 100 (47.9) |
| Median age (IQR), years | 34 (27 - 39) |
| Localization of tuberculosis | |
| Pulmonary TB | 230 (76.2) |
| Extra-pulmonary TB | 58 (19.2) |
| Pulmonary and extra-pulmonary TB | 14 (4.6) |
| Clinical symptoms | |
| Cough | 131 ^a (72.4) |
| No abdominal symptoms | 48 (26.5) |
| Abdominal pain | 27 (12.9) |
| Abdominal swelling | 2 (1) |
| Diarrhea | 6 (2.9) |
| Yellowing of eyes | 2 (1) |
| Skin nodules | 4 (1.9) |
| Laboratory results | |
| Median initial CD4 (IQR), cells/mm ³ | 48 (19 - 128) |
| Hemoglobin < 12 g/dL | 191 (91.8) |

^aOut of 181 patient with available data.**Table 2.** Abdominal sonographic findings among HIV-TB co-infected patient starting anti-retroviral therapy (ART).

| Abdominal sonographic findings (n = 209) | n (%) |
|---|-----------|
| Total | n (%) |
| Normal abdominal scan | 49 (23.4) |
| Hepatomegaly | 6 (2.9) |
| Focal liver mass(es) | 3 (1.4) |
| Diffuse liver parenchymal disease (fatty-fibrotic pattern) | 8 (3.8) |
| Centri-lobular pattern | 1 (0.5) |
| Biliary tract abnormalities [†] | 15 (7.1) |
| Pancreatic abnormalities [*] | 2 (1.0) |
| Splenomegaly | 37 (17.7) |
| Splenic abscesses | 27 (12.9) |
| Renal abnormalities [‡] | 30 (14.4) |
| Ascites | 12 (5.7) |
| Lymphadenopathy | 79 (37.8) |
| Gastro-intestinal abnormalities (thickened bowel loops, appendicitis) | 4 (13.4) |

[†]Biliary abnormalities included cholangiopathies, bile duct thickening and or dilatation (n = 3), cholelithiasis with or without cholecystitis (n = 12),^{*}Pancreatic abnormalities: 1 case of chronic calcific pancreatitis with a pancreatic pseudocyst and one case of acute pancreatitis, [‡]Renal abnormalities: 26 cases of nephropathy (diffuse enlarged kidneys with diffuse increased echogenicity), 2 cases of cortical renal cysts, 1 case of obstructive hydronephrosis due to a pelvic abscess and 1 case focal renal masses.

Table 3. Lymphadenopathy distribution.

| Lymphadenopathy (N = 79*) | |
|---------------------------------|-----------|
| Number | n (%) |
| Solitary lymphadenopathy | 16 (20.3) |
| Multiple lymphadenopathy | 63 (79.7) |
| Site | |
| Para-aortic lymphadenopathy | 28 (35.4) |
| Porta-hepatis lymphadenopathy | 39 (49.4) |
| Mesenteric lymphadenopathy | 25 (31.7) |
| Iliac lymphadenopathy | 15 (19.0) |
| Peri-pancreatic lymphadenopathy | 36 (45.6) |
| Splenic hilum | 4 (5.1) |
| Echogenicity | |
| Hypo-echoic | 79 (100) |
| Caseation | 34 (43.0) |

*Stands for the number of patients with lymph nodes, some patients had lymph nodes occurring in more than one site.

Table 4. Sonographic findings stratified according to abdominal symptoms and CD4 cell count among HIV-TB co-infected patients.

| Abdominal sonographic findings | Abdominal Complaints n (%) | No abdominal complaints n (%) | P-value | CD + T-cell count < 50 cells/mm ³ | ≥50 cells/mm ³ | P-value |
|---|----------------------------|-------------------------------|---------|--|---------------------------|---------|
| Total number of patients | 28 (13.4) | 181 (86.6) | | | | |
| Normal abdominal scan | 4 (14.3) | 45 (24.9) | 0.34 | 23 (21.7) | 26 (25.2) | 0.5 |
| Biliary tract abnormalities | 2 (7.1) | 13 (7.2) | 1.00 | 5 (4.7) | 10 (9.7) | 0.2 |
| Splenomegaly | 8 (28.6) | 29 (16.0) | 0.12 | 19 (17.9) | 18 (17.5) | 0.9 |
| Renal abnormalities | 6 (21.4) | 24 (13.3) | 0.25 | 14 (13.2) | 16 (15.5) | 0.6 |
| Ascites | 4 (14.3) | 8 (4.4) | 0.06 | 7 (6.6) | 5 (4.9) | 0.6 |
| Lymphadenopathy | 9 (32.1) | 70 (38.7) | 0.54 | 42 (39.6) | 37 (35.9) | 0.6 |
| Gastro-intestinal abnormalities (thickened bowel loops, appendicitis) | 2 (7.1) | 2 (1.1) | 0.09 | 3 (2.8) | 1 (1.0) | 0.3 |

help to diagnose abdominal TB early and therefore lead to earlier treatment and improved survival [5]-[7] [21] [22] [24] [26]-[28]. In resource constrained countries, abdominal sonography is traditionally performed very selectively to evaluate specific abnormalities discovered at clinical examination or when the patient has abdominal complaints. However, the signs and symptoms of the disease may be masked by concurrent illness and weak immune response, reducing the sensitivity of relying on the tradition clinical assessment [24]. In addition, abnormal ultrasound findings have been documented in this and other previous studies in patients with HIV-TB co-infection without abdominal symptoms, especially in patients with severe immune deficiency [6] [7] [24] [26] [27].

Therefore a screening abdominal ultrasound scan especially in severely immunosuppressed HIV-TB co-infected patients, would be useful before initiation of ART to detect pathology that would be missed just by physical examination or by performing ultrasound only in selected symptomatic patients. Current advances in ultrasound technology and scan heads allow greater spatial and contrast resolution, for early detection of comorbid-

ities among patients with HIV-TB co-infection even before they become clinically apparent [6] [27] [28].

In addition, the decrease in prices for ultrasound equipment makes this imaging modality easily available and a cost effective screening and diagnostic tool especially in resource constrained countries.

Abdominal sonographic findings of TB in patients with advanced immune deficiency include: mesenteric hypo-echoic lymphadenopathy [21] [22] [28]-[31] ascites [21] [26] [27], multiple splenic hypo-echoic nodules and thickened matted bowel loops. Some studies however have found ascites to be more common in HIV negative patients [6] [7] [32]. Evidence of TB elsewhere, like in this study may provide circumstantial evidence in favor of a diagnosis.

4.2. Lymphadenopathy

Multiple lymphadenopathy, the commonest finding observed in 38% of the studied patients is much lower than the 55.3% - 96.7% reported in studies that only included patients with extra-pulmonary TB. These tend to be poorly vascularised (**Figure 1(a)**) and undergo caseation (**Figure 1(b)**). The lack of retroperitoneal lymphadenopathy despite extensive mesenteric and peritoneal involvement in TB may be explained by the fact that mesenteric lymph nodes drain direct into thoracic duct via the cistern chيلي [22].

4.3. Ascites

The presence of ascites should raise the suspicion of TB. Different sonographic patterns of ascites in abdominal TB have been described including free or loculated, with or without stranding/septations like violin strings or lattice appearance (**Figure 2**) [26] [27] [33]-[35].

4.4. Liver and Spleen

Variable incidences of hepatomegaly and splenomegaly in HIV-TB co-infection have been described ranging from 19% - 85% [6] [7] [26] [27]. The most common encountered liver abnormality is a diffuse fatty-fibrotic pattern, often due to fatty degeneration of the liver. A study of abdominal ultrasound in adults with AIDS in Zambia and Zaire found 14 cases of TB out of 42 ultrasound guided liver biopsies among patients with focal parenchymal lesions [6]. TB lesions in the spleen may present as multiple small hypo-echoic nodules of 5 - 10 mm, best demonstrated by using the high-frequency probe for better resolution (**Figure 3**) [21] [26] [27] [30] [36].

4.5. Gastrointestinal Tract (GIT)

We observed bowel thickening with loss of architecture and definition of the five layers (**Figure 4(a)**), depicting the “pseudokidney appearance” (**Figure 4(b)**), but with no increased blood flow. Other studies record bowel

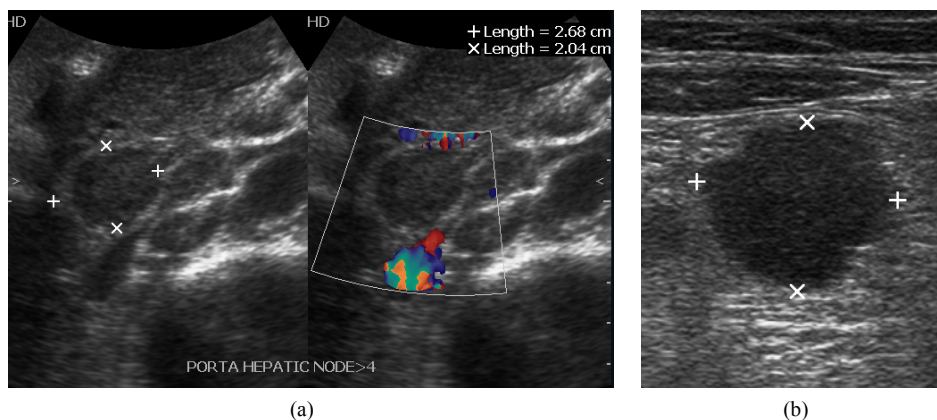


Figure 1. HIV-TB coinfectd 30-year-old female with CD4+ T-cell count of 3 cells/mm⁻³ and extrapulmonary tuberculosis. (a) Hypo-echoic peripancreatic, porta-hepatis and para-aortic poorly vascularised lymphnodes. (b) Hypo-echoic mesenteric lymphnode with posterior enhancement, a sign of semi-solid nature of the nodes due to caseation.

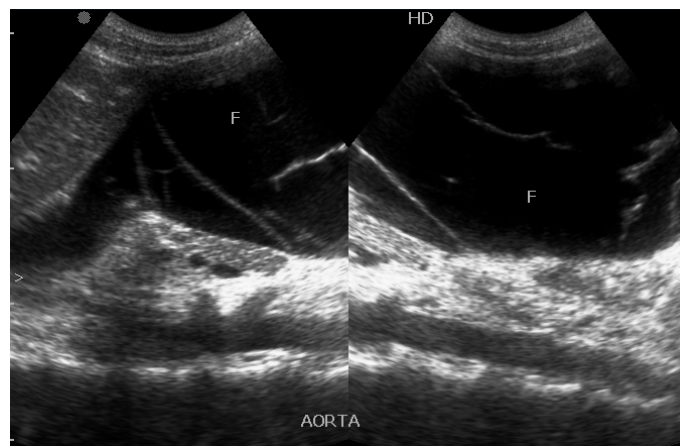


Figure 2. A 45-year-old male with HIV-TB coinfected with CD4+ T-cell count of 196 cells/mm³ with disseminated tuberculosis. The sonograms show ascites with fibrinous band opacities.

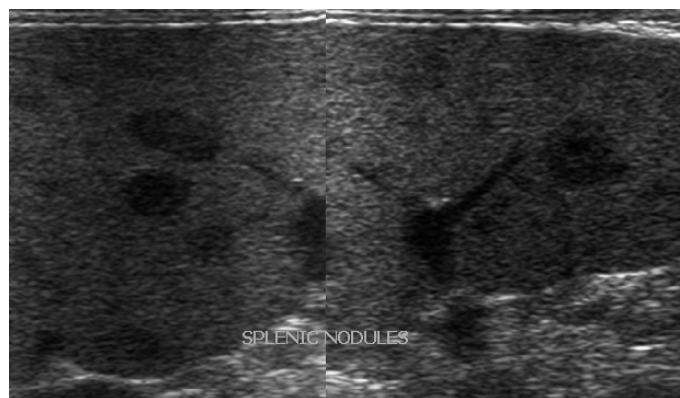


Figure 3. HIV-TB coinfected patient with CD4+ T-cell count of 122 cell·mm⁻³ with no abdominal symptoms. Sonograms of the spleen shows multiple small intraparenchymal illdefined masses less than 10 mm.

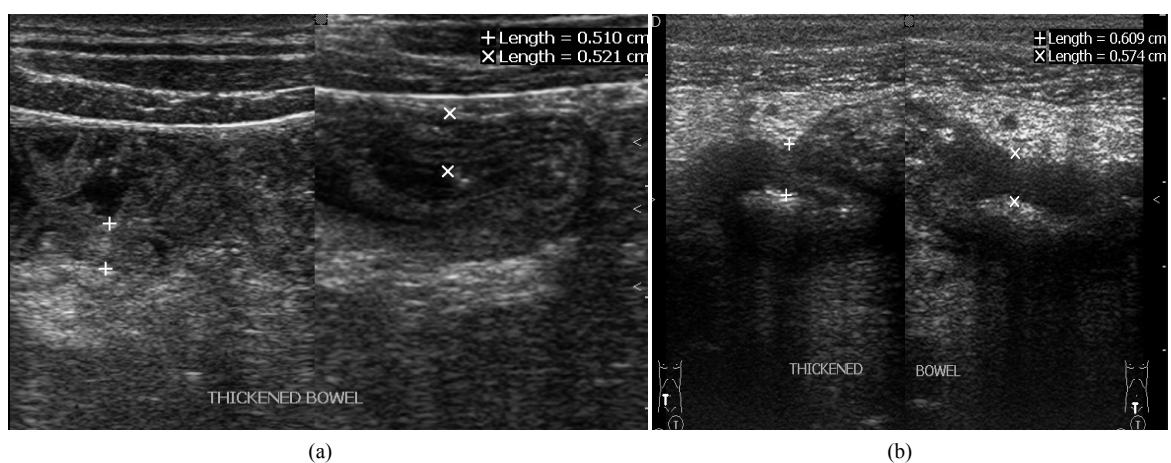


Figure 4. (a) Longitudinal scans shows an inflamed appendix with thickened edematous walls and intraluminal echocomplex collection in a 33-year-old male with right iliac fossa pains and CD4+ T-cell count of 194 cells·mm⁻³. (b) shows hypoechoic thickened wall with loss of definition of the five layers and an echogenic center, the lumen; depicting the “pseudokidney appearance”.

thickening and matting, obstruction and fistula formation [26] [27] [29] [32] [37]. Mesenteric thickening of 15 mm or more, has been attributed to TB [22].

4.6. Renal Changes

In the kidneys, *Mycobacterium tuberculosis* produces multiple hypo-echoic small abscesses, calcified foci and hydronephrosis due to obstruction by retroperitoneal masses [6] [26] [27] [29] [33]. All these changes tend to resolve with TB therapy.

4.7. Limitations

The main limitation of our study is the lack of microbiological or histological confirmation of abdominal TB. We used circumstantial evidence of tuberculosis elsewhere in favor of diagnosis. We can thus not be certain that all the observed abnormal sonographic findings were caused by TB.

5. Conclusion

In resource constrained settings, ultrasound is a cost effective easily available screening tool in severely immune suppressed HIV-TB co-infected patients initiating ART. The following criteria should trigger ultrasound screening for co-morbidities like extra pulmonary TB: severe immune suppression (CD4 cell count less than 100), abdominal symptoms, and weight loss.

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