Rwanda Medical Journal RMJ

ORIGINAL RESEARCH Open Access

Pathological features seen on medical imaging in hospitalized patients treated for tuberculosis in a reference hospital in Rwanda

Authors: L. Bitunguhari[1,2,*], O. Manzi[1], T. Walker[3], J. Mukiza[4,5], J. Clerinx[6]

Affiliations: *[1]Department of Internal Medicine, University Teaching Hospital of Kigali (CHUK), Rwanda; [2]School of Medicine and Pharmacy, University of Rwanda; [3]Faculty of Health and Medicine, University of Newcastle, Australia; [4]School of Edcation, College of Education, University of Rwanda, Rwanda; [5]Facult of Nursing, University of Gitwe, Rwanda; [6]Department Clinical Sciences, Institute of Tropical Medicine Antwerp, Belgium*

ABSTRACT

BACKGROUND: Tuberculosis (TB) and HIV are major causes of morbidity and mortality worldwide. Abdominal ultrasound and Chest X-ray may reveal suggestive features of TB disease in hospitalized sputum AFB negative patients treated for TB.
This study describes the pathological features seen on Chest X-ray and abdominal ultrasound in inpatients treated for TB and their association with bacteriological TB diagnosis and HIV co-infection.
METHODS: All patients being initiated on TB treatment during hospitalization were included. TB was confirmed when acid-fast bacilli were found in sputum or elsewhere, and probable when composite clinical, laboratory and radiological findings were consistent with TB disease. Disseminated TB was defined on medical imaging criteria. HIV testing was done in all.

RESULTS: Of 199 patients included, TB was confirmed in 80 (40%) and 125 people (63%) were co-infected with HIV. Lesions consistent with TB were seen in 148/187 (87%) on Chest X-ray and in 156/183 (85%) on abdominal ultrasound. Pulmonary TB and/or concurrent pulmonary/extrapulmonary TB was seen in 130 (65%), and isolated extrapulmonary TB in the remaining 69 (35%) patients. Disseminated TB was seen in 121/199 (61%) patients. HIV co-infection was associated with disseminated TB, abdominal TB and miliary TB, but inversely associated with TB pleurisy. Bacteriological TB confirmation was not associated with HIV co-infection nor with TB dissemination.

CONCLUSION: Pathological features on medical imaging were seen in the vast majority of hospitalized patients treated for TB, and disseminated TB in more than half. TB dissemination is more frequently seen in HIV co-infection. Abdominal ultrasound is essential to reveal the true extent of TB dissemination.

Key words (MeSH): Medical Imaging; Disseminated tuberculosis; abdominal ultrasound; chest X-ray.

BACKGROUND

Human infection by Mycobacterium tuberculosis (MTB) and HIV have been globally identified as widespread causes of morbidity and mortality [1, 2]. Tuberculosis (TB) associated mortality remains considerable, despite the administration of antiretroviral treatment [3]. Africa alone counts for 2.59 million cases (52%) of the world's TB burden in 2016 [4]. In Rwanda, TB incidence rate currently stands at 50/100.000 persons p.a., but only one-quarter occurs in persons living with HIV (PLWH) [4]. In contrast the incidence rate of TB in South Africa is about 10 times higher, of whom the majority were PLWH. Among hospitalized patients at the Kigali University Teaching Hospital (CHUK), HIV co-infection rates declined from 89% in 1992 to 68% in 2008 [5]. In Rwanda during

***Corresponding author:** Dr. Leopold Bitunguhari, Email: drbitunga@gmail.com; **Potential Conflicts of Interest (CoI):** All authors: no potential conflicts of interest disclosed; **Funding:** All authors: no funding was disclosed; **Academic Integrity.** All authors confirm that they have made substantial academic contributions to this manuscript as defined by the ICMJE; **Ethics of human subject participation:** The study was approved by the local Institutional Review Board. Informed consent was sought and gained where applicable;
Originality: All authors: this manuscript is original has not been published elsewhere; **Type-editor**: Haley Sessions (USA)
Review: This manuscript was peer-reviewed by three reviewers in a double-blind review process;
Received: 26th May 2019; **Initial decision given:** : 27th July 2019; **Revised manuscript received:** 19th August 2019; **Accepted: :** 11th November 2019.
 Publisher: Rwanda Biomedical Centre (RBC)/Rwanda Health Communication Center, P.O.Box 4586, Kigali.
ISSN: 2079-097X (print); 2410-8626 (online)

Citation for this article: L. Bitunguhari, O. Manzi, T. Walker et al. Pathological features seen on medical imaging in hospitalized patients treated for tuberculosis in a reference hospital in Rwanda. Rwanda Medical Journal, Vol 76, no 4, pp 1-9, 2019

the last decade, HIV prevalence remained stable at 2,5% (adults 15-49 years), but HIV incidence rates and mortality rates have declined substantially. In 2018, 87% of PLWH were on antiretroviral treatment [1].

Clinical studies in African inpatients with TB have primarily focused on PLWH. In this population, extrapulmonary TB (EPTB), a lower sputum Acid-Fast Bacilli (AFB) smear positivity rate, and disseminated disease with mycobacteremia was more frequently seen [6,7]. EPTB was the main cause of pleural, pericardial, and peritoneal effusions, as well as sputum AFB negative pulmonary infiltrates [8-10]. Miliary TB is clearly associated with HIV coinfection and poorer outcomes [11]. In severely immune suppressed PLWH, TB has been grossly underreported [12]. The role of abdominal ultrasound in TB diagnosis has only recently been appreciated [10-14]. A concise ultrasound (US) protocol (Focused Assessment by Sonography in HIV, "FASH") has been proposed to identify the main pathological features of TB of the abdominal, pleural and pericardial space [15]. Systematic US to refine TB diagnosis has been adopted at the Department of Internal Medicine of the CHUK since 2007 [5].

In the present study we focused on the pathologic features of TB seen on Chest X-ray (CXR) and Abdominal Ultrasound (US) in hospitalized patients treated for TB, with attention to multifocality, overlapping features, TB dissemination, and its relationship with HIV co-infection.

PATIENTS AND METHODS

Permission for this study was obtained from CHUK Research Committee and the Rwandan School of Medicine Ethics committee. Patients were counseled regarding the study and gave informed consent before inclusion. The study data were collected on a specific study file. Only the principal investigator and data manager had access to the data. All data were disassociated from full patient identifiers.

This study was part of a more comprehensive prospective cohort study, conducted among adult inpatients on TB treatment in the Department of Internal Medicine of CHUK during 2013. Consecutive, consenting hospitalized adult patients were recruited upon starting anti-TB treatment in hospital. The main collected data included sex, HIV-1 status, and a sputum Ziehl-Neelsen staining for AFB (and Xpert MTB/RIF analysis where available) in those who could expectorate., as well as Chest X-ray and Abdominal Ultrasund readings.

Diagnosis of TB was made on bacteriological evidence of MTB in sputum or on tissue biopsy ("confirmed TB"), or on a composite definition combining clinical, laboratory and CXR and US findings ("probable TB").
Patients were considered having probable TB when presenting with fever and having infiltrates and/or cavities on CXR not responding to current antibiotics for Community Acquired Pneumonia (CAP) in the context of a febrile disease lasting for more than a week (Table 1). Likewise, febrile patients with longstanding fever for more than one week and presenting with a pericardial effusion, a nonpyogenic pleurisy, free abdominal fluid, intrasplenic nodules and/or deep seated paravascular adenopathy were considered having TB until proven otherwise.

Febrile patients showing hepatosplenomegaly or hepatic nodules were considered as having probable TB when other diagnoses like hepatic abscess, typhoid fever or chronic malaria were excluded during TB treatment. Finally, some patients were considered as having TB by clinical expert opinion after case discussion by the specialists.

Patients presenting with a chronic lymphocytic meningitis with a negative cryptococcal antigen test, a low glucose level and a high protein level were considered as having TB meningitis. Diagnosis of peripheral TB adenopathy, osteoarticular TB, renal TB and skin TB were established on indirect radiologic, histologic and laboratory criteria, or on bacteriological evidence of MTB.
Patients were excluded when another diagnosis was established as the cause of the illness.

A CXR and US exam were part of the diagnostic workup, and were interpreted by the radiologist and/or by the principal investigator.

Table 1. Criteria for clinical diagnosis of probable TB

Patients with fever of > 1 week, not responding to first-line antibiotics and having any of the following:
Pulmonary infiltrates and/or cavities and/or miliary pattern on CXR
Pleurisy and/or pericardial effusion on US and/or CXR
Deep seated abdominal adenopathy and/or ascites and/or nodular splenic infiltrates on US
Hepatomegaly and/or splenomegaly
Clinical meningitis with mononuclear pleiocytosis, low glucose and raised protein, and negative cryptococcus antigen test and not having another identified cause of fever

CXR: Chest X-ray; US: Abdominal Ultrasound

US readings followed those of the FASH criteria described by Heller et al.: deepseated abdominal adenopathy, free abdominal fluid, splenic and hepatic nodules, pleural and pericardial effusion. We added three additional criteria: hepatomegaly and/or splenomegaly, and thickened gut wall [15]. Note that miliary TB was reclassified as concurrent PTB/EPTB because of its hematogenic spread and its association with AFB in sputum samples [11, 16].

Disseminated TB was defined on imaging data, without confirmation by tissue biopsy, bone marrow aspiration or blood culture [17]. TB was considered disseminated when at least two noncontiguous pathologic sites consistent with TB coexisted, with at least one above, and one below the diaphragm. Miliary TB, and TB meningitis associated with another noncontiguous TB focus were also considered as disseminated TB [11].

Data were collected on an individual Clinical Record Form (CRF). Data were analyzed using Epi-info and Stata, with Chi-square (Mantel Haenszel correction of Fisher exact) test for categorical variables, and a Mann-Whitney-Wilcoxson non-parametric test comparing means of continuous variables, using a $p<0.05$ as the threshold of significance.

RESULTS

From January to December 2013, 206 eligible TB patients were recruited. Five patients were
excluded because of another definitive diagnosis, and data were insufficient in two. Baseline Characteristics of the TB Cohort are presented in Table 2.

Table 2. Baseline characteristics of the study population

Variable	N/n	%
Male sex	120/199	60
HIV co-infected	125/199	63
On ARV treatment prior to TB treatment	73/117	62
Medical imaging (Chest X-ray and/or Ultrasound)	194/199	97
Chest X-ray	166/199	83
Abdominal Ultrasound	183/199	92
Pulmonary Tuberculosis or combined PTB/EPTB	130/199	65
Isolated Pulmonary Tuberculosis	22/199	11
Isolated Extrapulmonary Tuberculosis	69/199	34
Disseminated Tuberculosis	121/199	61
Confirmed TB by microbiology	79/199	40
Sputum Acid Fast Baccili on microscopy	71/148	48
Age in years (median; IQR) (N=199)	35; 28-43	
CD4 count per µL (median; IQR) (N=125)	71; 29-171	

Medical imaging features of TB associated pathology was seen on CXR and/or by US in 187/194 (96%) patients: thoracic TB features in 146/166 (87%) CXR and abdominal TB manifestations in 130/183 (71%) US exams. TB associated medical imaging features are shown in Table 3 and 4.

Table 3. Pathologic features on Chest X-ray in hospitalized TB patients

Variable	N/n	%
Abnormal Chest X-ray	145/166	87
Pulmonary infiltrates	104/165	63
Pulmonary Cavity	35/165	21
Bilateral diffuse infiltrates	74/165	45
Miliary TB pattern (part of previous)	39/166	23
Pleurisy (pleural effusion and/or thickening)	63/165	38
Mediastinal/perihilar gross adenopathy	11/165	7

Upon examination of CXR, pulmonary infiltrates predominated (105/166; 63%), mostly with bilateral infiltrates (74/105;72%) of whom 39/74 (53%) had a miliary pattern. In contrast, pulmonary cavities were seen in only 35/165 (21%). Deep-seated adenopathy and ascites predominated on US.E TB pathology was found by US in 41 patients with either normal CXR (n=18) or lacking CXR (n=23). PTB was diagnosed in 115 patients having either infiltrates (N=105) and/or cavities (N=36) on CXR and in 16 sputum AFB positive patients lacking a CXR.

Table 4. Pathologic features on Abdominal Ultrasound in hospitalized TB patients

Variable	N/n	%
Abnormal abdominal Ultrasound*	155/183	85
Ascites	50/174	29
Deep seated enlarged abdominal lymph nodes	73/178	41
-Perihilar hepatic	18/167	11
-Perihilar splenic	5/162	3
-Paravascular	49/173	29
-Mesenteric	48/170	28
Hepatomegaly	50/177	28
Hepatic nodules	10/170	6
Splenomegaly	30/179	17
Splenic nodules	25/173	14
Thickened intestinal wall	9/160	6
Pleural effusion	60/172	35
Pericardial effusion[$]	40/170	24

**Number of radiologic examinations with specific information on site, available for interpretation*
[$]Pericardial pathology documented by abdominal US only

In 157 patients for whom both CXR and US data were available, TB associated pathology was found in 153 (96%), and thoracic TB abnormalities were largely concurrent with abdominal pathology. For pleural disease, readings of CXR (61/147) and US (56/147) were discordant: in 17 cases, pleurisy was present on CXR while absent on US, and US detected a pleural effusion in 12 not having pleurisy on CXR. US exams demonstrated a pleural and/or pericardial effusion in 26 patients without abdominal TB pathology. The relative proportion and the extent of overlap of the main TB-associated pathology seen on Ultrasound by "FASH" assessment is shown in Figure 1. Free abdominal fluid (ascites) is mostly seen together with either pleural and/or pericardial effusion and/or with abdominal adenopathy.

Among 14 patients with TB meningitis, pulmonary infiltrates were seen in 4/9 (43%), and associated TB pathology was seen in 7/10 US exams. Osteoarticular TB was seen in 4, renal TB in 1 and skin TB in 1. AFB were demonstrated in peripheral lymph node aspirates of 2 patients. TB was multifocal in 145/199 (73%) patients, and was disseminated in 121/199 (61%), and in 103/199 (52%) when dissemination was restricted to the FASH criteria on US. When the definition of disseminated TB was restricted to miliary TB as the classic clinical and radiological expression of hematogenous spread, only 39/199 (19,5%) fulfilled these criteria.

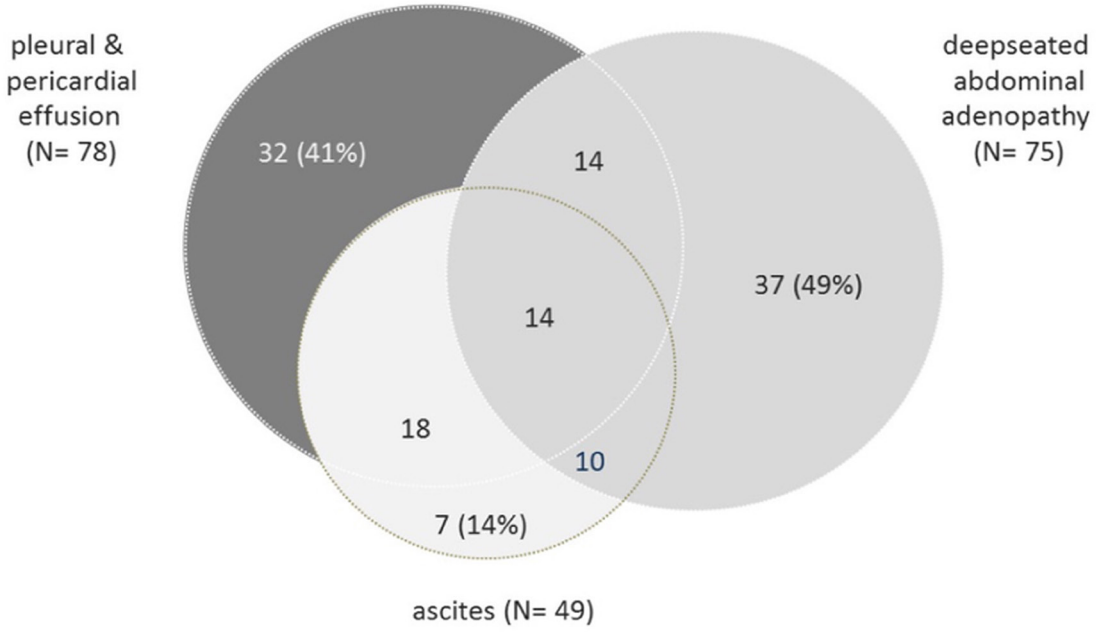

Figure 1: Main pathologic ultrasound features of TB by "FASH" assessment (n=183)

Association of clinical features of TB and HIV co-infection in hospitalized patients

Concurrent PTB/EPTB was the main clinical presentation of TB (77/125, 61%) in PLWH. It was less frequent (31/74, 42%) in HIV negative patients (p = 0.01), with whom EPTB was predominant.

Figure 2 shows the shift in clinical presentation of TB in relation with HIV co-infection. In both groups, only a fraction of patients presents with pulmonary tuberculosis not associated with another extrapulmonary site of TB. Concurrent PTB and EPTB is the predominant presentation in HIV co-infected patients.

No specific pathologic features on CXR or US were exclusively

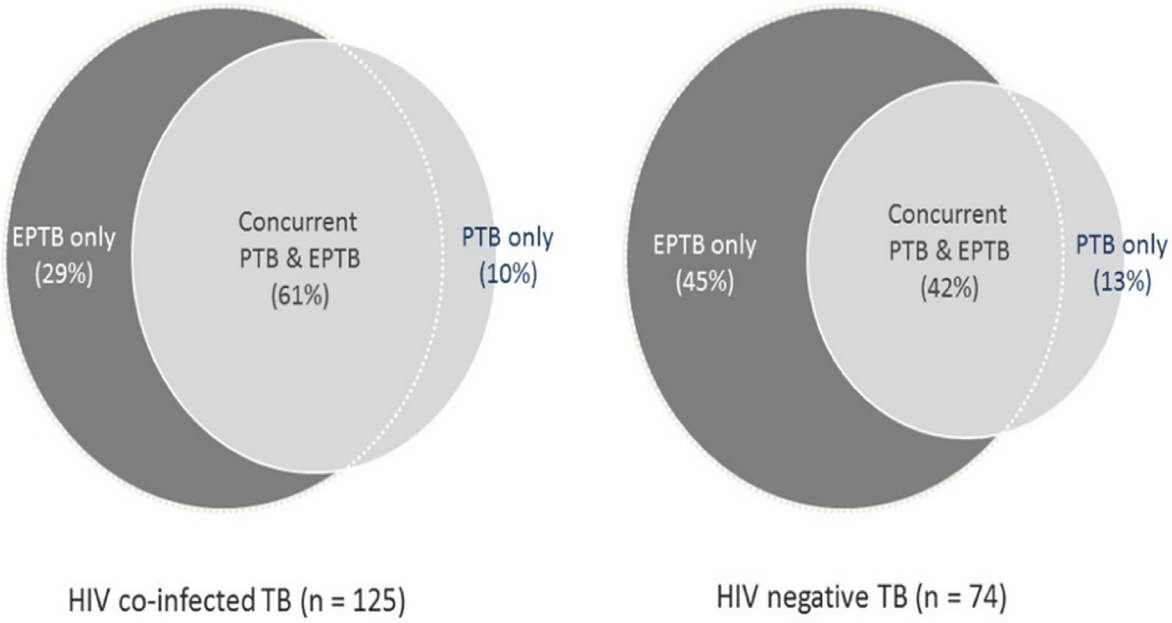

Figure 2: Main clinical presentations of TB in 199 hospitalized patients in relation with HIV co-infection

seen in PLWH (Table 5). Miliary TB, deep-seated abdominal adenopathy and intrasplenic nodules were significantly associated with HIV co-infection, but pleural disease was more frequently associated with a HIV negative status.

Disseminated TB was significantly associated with HIV co-infection (p < 0.001) as shown in Table 6. Hospitalized HIV co-infected patients on TB treatment tend to be of older age than HIV uninfected TB patients.

Table 5. TB presentation on Chest X-ray and Abdominal Ultrasound in relation with HIV coinfection

Variable	HIV Pos (n=125) N /n (%)	HIV Neg (n=74) N /n (%)	p	OR (95%CI)
Chest X-ray features associated with TB				
Pulmonary infiltrates	73/103 (71)	31/62 (50)	ns	
Miliary pattern	34/103 (33)	5/63 (8)	<0.001	5.66 (2.18 – 17.27)
Pleurisy*	41/122 (34)	39/72 (54)	0.008	0.43 (0.24 – 0.78)
Pericarditis*	26/120 (22)	16/72 (22)	ns	
Abdominal pathology associated with TB detected by Abdominal Ultrasound				
Abdominal TB	96/117 (82)	33/66 (50)	<0.001	4.53 (2.31 – 9.03)
Ascites	38/112 (34)	12/62 (19)	0.05	2.13 (1.03 – 4.62)
Deepseated abdom. ADP	61/114 (54)	12/64 (19)	<0.001	4.94 (2.42 – 10.58)
Hepatomegaly	39/112 (35)	11/65 (17)	0.02	2.61 (1.24 – 5.77)
Splenomegaly	22/115 (19)	8/64 (13)	ns	
Splenic nodules	21/110 (19)	4/63 (6)	0.03	3.46 (1.19 – 12.30)

** Chest X-ray and Abdominal Ultrasound findings combined; ns: not significant; ADP: adenopathy*

Table 6. General data and dissemination status of TB in relation with HIV co-infection

Variable	HIV pos (n=125) N /n (%)	HIV Neg (n=74) N /n (%)	p	OR (95%CI)
General patient data				
Male sex	72/125 (58)	48/74 (65)	ns	
TB sputum AFB pos. (n=148)	48/92 (52)	23/56 (41)	ns	
Age (Median, IQR)	37.0 (30.5-70)	29.5 (24-48)	0.012	
TB dissemination status (n = 199)				
>1 anatomical site affected	100/125 (80)	45/74 (60)	0.005	2.56 (1.34 – 4.91)
Disseminated TB	90/125 (72)	31/74 (42)	<0.001	3.54 (1.94 – 6.55)
Disseminated TB FASH criteria	78/125 (62)	25/74 (34)	<0.001	3.23 (1.78 – 5.97)

ns: not significant

DISCUSSION

This study demonstrates that abdominal US provides a useful adjunct to CXR and sputum AFBs in the categorization of TB among a referral hospital patient population undergoing treatment for TB in Rwanda [18]. While ultrasound findings were frequently concordant with CXR and other clinical markers, in many patients additional useful clinical data were obtained.

Medical imaging features associated with TB disease

Among the hospitalized patients treated for TB in our cohort, disease presentation was multifocal and PTB and EPTB was concurrent in most of the cases. While differences in definitions of TB diagnosis and dissemination make comparison between published studies difficult, CXR and sputum AFB microscopy are still the mainstay of TB diagnosis [18]. Classic presentations of TB on CXR, such as alveolar infiltrates in the upper lung segments and cavitation, are predominant among outpatients. In contrast, as this study demonstrates, hospitalized patients present with more extensive lung disease, with diffuse bilateral infiltrations, often coexisting with cavitation. On CXR, PTB may resemble a community acquired bacterial pneumonia [19].

A miliary pattern is commonly associated with HIV co-infection and with signs of dissemination elsewhere, as was demonstrated in this study as well [11]. On a CXR, a pleural effusion is sometimes difficult to differentiate from pleural thickening, but is correctly identified by US, which is more sensitive to detect small amounts of pleural fluid. This probably explains the discordant findings on pleural effusion between CXR and US in this study. Most patients in this study demonstrate pleural effusion coexisting with pulmonary infiltrates, and sometimes with atypical infiltrates. A normal CXR does not rule out sputum AFB positive PTB in clinically suspected patients, but we did not observe that in this hospital-based cohort [20].

In developing countries with high TB burden, few studies incorporated US in the workup of hospitalized patients suspected of having TB, and those published enrolled almost exclusively PLWH with low immunity [10-14,21]. This particular population frequently presents US features of EPTB [21,22]. The most common signs of abdominal TB are deep-seated adenopathies and ascites, often concurring [10]. Deep-seated adenopathy may be subtle or widespread, and may form gross coalescent masses measuring several centimeters in diameter.

In peritoneal TB, free abdominal fluid appears gradually and may not be clinically apparent until late in the disease stage. Hence, an abdominal ultrasound exam is key in detecting free abdominal fluid at an early stage. Multiple splenic nodules are a less common, but almost pathognomonic sign of disseminated TB, and as this study reveals, not exclusively seen in HIV co-infection [23]. A similar hepatic nodular pattern may occasionally be found, often concomitantly with splenic nodules. A thickened bowel wall is a suggestive, albeit a less frequent and more subtle sign of intestinal TB involvement. Renal TB shows up on US only when lesions are extensive and is therefore less frequently reported than a molecular diagnosis by urine Xpert MTB/RIF suggest [24]. Perhaps the least specific abdominal features of disseminated TB are hepatomegaly and splenomegaly. Both these features were not part of the FASH criteria, as many other infectious diseases may cause similar changes [25]. However, in this study, hepatomegaly and splenomegaly were more frequently associated with disseminated TB. Hepatomegaly, but not splenomegaly, was also more frequently found in patients with miliary TB [16]. This suggests that hepatomegaly may be associated with hematogenic spread and possibly with persistent mycobacteremia [26]. Splenomegaly is also a feature of chronic malaria with low parasitemia (hyperreactive malaria splenomegaly). Splenomegaly not associated with another medical imaging feature suggestive for TB should therefore be considered of malarial origin, or of another infectious disease of which splenomegaly is a prominent feature, such as bacteriaemic salmonellosis, or visceral leishmaniasis in specific endemic regions.

Several authors have stressed that the ultrasound diagnosis of EPTB involves less than 10 different sites and presentations, and that detection of these is well within reach of a physician taking care of TB patients in resource-poor settings [15,27]. At present, almost all district hospitals in Rwanda are equipped with a suitable ultrasound system, but it is so far underused.

The impact of HIV co-infection on the clinical presentation of TB

In sub-Saharan Africa, TB is the most common cause of disease in hospitalized patients and is amplified by the ongoing HIV epidemic [4]. HIV co-infected TB inpatients are vastly overrepresented compared with the HIV prevalence in the general population. In outpatients, PTB predominates and mortality rates are low, whereas in inpatients, disseminated TB is frequent and with high mortality rates [28-30]. Hospitalized TB patients thus represent a distinct group of patients with advanced disease, in whom sputum AFB negative status is associated with a prolonged disease duration [6, 31]. This study clearly demonstrates that in this group, TB is disseminated and multifocal, and that the imaging findings are similar regardless of HIV coinfection (Table 3, 4). Autopsy studies conducted early in the course of the HIV epidemic demonstrated that severe immune depression facilitated hematogenic mycobacterial dissemination often from established pulmonary foci [29]. In severely immune supressed PLWH infected with TB, tissular reactions against mycobacteria are reduced. Therefore, extrapulmonary manifestations are often clinically inapparent, and mycobacteremia is frequent [26, 30-33]. Miliary TB is a classic example of hematogenous spread [11]. The majority of our patients with miliary TB were HIV co-infected and had concurrent abdominal, pleural and/or pericardial TB associated pathology on US (Table 4). In this study, most HIV co-infected TB patients were taking antiretrovirals prior to hospitalization and had a relatively high CD4 count. Neither miliary TB, nor nodular spleen lesions on US nor TB dissemination were associated with a lower CD4 count compared to other TB manifestations. With increasing access to antiretroviral and better immunity, the clinical presentation of TB may resemble the one seen in HIV negative TB patients [34]. Antiretroviral treatment has both increased the phenomenon of TB associated immune reconstitution inflammatory syndrome (TB IRIS) in patients treated for TB, and has "unmasked" latent TB in HIV infected patients with severe immune depression [35].

Definition of disseminated TB

A robust clinical definition of disseminated TB is needed, without the requirement for each pathologic site or blood cultures to be bacteriologically explored. Disseminated TB is largely the consequence of intermittent or continuous hematogenous spread, as ascertained by mycobacterial blood culture or bone marrow sampling [17]. These diagnostic techniques, as well as pleural and pericardial biopsy, are beyond the means of most clinical settings in Africa. Mycobacterial culture of pleural, pericardial and abdominal free fluid lacks sensitivity. Therefore a definition of disseminated TB based on clinical and medical imaging criteria may be a useful substitute. Following Iseman's criteria that TB dissemination implies hematogenous spread to noncontiguous anatomic sites, and considering that the diaphragm is an effective barrier to contiguous or lymphatic spread from a pulmonary or extrapulmonary focus, we postulated that TB is likely to be disseminated when TB associated pathology is present on either side of the diaphragm, i.e. concurrent thoracic and abdominal lesions. As a consequence, multifocal TB on one side of the diaphragm, such as concurrent pulmonary and pericardial TB and/or TB pleurisy is not synonymous with disseminated TB.
The impact of US in finetuning the clinical definition of disseminated TB cannot be ignored. In most settings where US or abdominal CT-scan is not available in the context of TB, the clinical diagnosis of disseminated TB is mainly based on miliary TB seen on CXR.

Disseminated TB using mycobacterial blood culture as the gold standard is strongly associated with HIV co-infection [7, 26]. Likewise, disseminated TB based on our medical imaging definition was also associated with HIV co-infection (Table 3). Whether disseminated TB based on our proposed medical imaging criteria is an independent predictor of TB associated excess mortality has yet to be determined.

Study limitations

This clinical study has important limitations. First, a TB diagnosis was only bacteriologically confirmed in less than half of the patients included, while a clinical diagnosis of TB was based on a composite case definition as in standard clinical practice. Second, diagnosis of disseminated tuberculosis was not underpinned neither by mycobacterial blood culture nor by bacteriological evidence from all the affected anatomical sites. Third, this study was conducted in hospitalized patients with proven or probable TB, who present mainly with clinically severe disease, and its conclusions may not apply to outpatients with TB.

CONCLUSION

Medical imaging is a powerful tool to detect multiple pathological foci associated with a TB etiology in hospitalized patients treated for TB. When based on medical imaging data, disseminated TB is surprisingly common, seen in most hospitalized TB patients and associated with, but not limited to HIV co-infection. Performing US in hospitalized patients with suspected and proven TB overwhelmingly reveal multiple pathologic features consistent with TB. In this population, US is an essential tool in the workup of a TB diagnosis and staging, in addition of a CXR and a sputum exam. Whether disseminated TB based on medical imaging criteria might be a useful predictor of adverse outcome is still unclear.

REFERENCES

1. Lawn SD, Zumla AI. Tuberculosis. Lancet. 2011;378(9785):57-72. doi:10.1016/S0140-6736(10)62173-3.

2.Dheda K, Barry CE, Maartens G. Tuberculosis. Lancet.2016;387(10024):1211-1226.doi:10.1016/S0140-6736(15)001518.

3. Mahmud O, Dates C, Akil L, Ahmad HA. HIV and tuberculosis trends in the United States and select Sub-Saharan Africa countries. Int J Environ Res Public Health. 2011;8(6):2524-2532. doi:10.3390/ijerph8062524.

4. WHO. WHO Global Tuberculosis Report 2016.; 2016. doi:ISBN 978 92 4 1565394.

5. Lorent N, Sebatunzi O, Mukeshimana G, den Ende J, Clerinx J. Incidence and Risk Factors of Serious Adverse Events during Antituberculous Treatment in Rwanda: A Prospective Cohort Study. PLoS One. 2011;6(5).doi:10.1371/journal.pone.0019566.

6. Harries AD. Tuberculosis in Africa: Clinical presentation and management. Pharmacol Ther. 1997;73(1):1-50. doi:10.1016/S0163-7258(96)00115-5.

7. Munseri PJ, Talbot EA, Bakari M, Matee M, Teixeira JP, Von Reyn CF. The bacteraemia of disseminated tuberculosis among HIV-infected patients with prolonged fever in Tanzania.Scand J Infect Dis.2011;43(9):696-701. doi:10.3109/00365548.2011.577802.

8. Batungwanayo J, Taelman H, Allen S, Bogaerts J, Kagame A, Vande Perre P. Pleural effusion, tuberculosis and HIV-1 infection in Kigali, Rwanda. AIDS. 1993;7(1):73-79.doi:10.1097/00002030-199301000-00011.

9. Mayosi BM, Wiysonge CS, Ntsekhe M, et al. Clinical characteristics and initial management of patients with tuberculous pericarditis in the HIV era: The Investigation of the Management of Pericarditis in Africa (IMPI Africa) registry. BMC Infect Dis. 2006;6. doi:10.1186/1471-2334-6-2.

10. Sinkala E, Gray S, Zulu I, et al. Clinical and ultrasonographic features of abdominal tuberculosis in HIV positive adults in Zambia. BMC Infect Dis. 2009;9:1-8. doi:10.1186/1471-2334-9-44.

11. Sharma SK, Mohan A, Sharma A, Mitra DK. Miliary tuberculosis: new insights into an old disease. Lancet Infect Dis. 2005;5(7):415-430. doi:10.1016/S1473-3099(05)70163-8.

12. Wong EB, Omar T, Setlhako GJ, et al. Causes of Death on Antiretroviral Therapy: A Post-Mortem Study from South Africa. PLoS One. 2012;7(10). doi:10.1371/journal.pone.0047542.

13. Patel MN, Beningfield S, Burch V. Abdominal and pericardial ultrasound in suspected extrapulmonary or disseminated tuberculosis. South African Med J. 2011;101(1):39-42.doi:10.7196/SAMJ.4201.

14. Spalgais S, Agarwal U, Sarin R, Chauhan D, Yadav A, Jaiswal A. Role of routine abdominal ultrasonography in intensified tuberculosis case finding algorithms at HIV clinics in high TB burden settings. BMC Infect Dis. 2017;17(1). doi:10.1186/s12879-017-2433-6.

15. Heller T, Wallrauch C, Goblirsch S, Brunetti E. Focused assessment with sonography for HIV-associated tuberculosis (FASH): A short protocol and a pictorial review. Crit Ultrasound J. 2012;4(1):1-9.doi:10.1186/2036-7902-4-21.

16. Mert A, Arslan F, Kuyucu T, et al. Miliary tuberculosis: Epidemiological and clinical analysis of large-case series from moderate to low tuberculosis endemic Country. Medicine (Baltimore). 2017;96(5):1-7. doi:10.1097/MD.0000000000005875.

17. Iseman MD. Extrapulmonary tuberculosis in adults. In: A Clinician's' Guide to Tuberculosis. 1st ed. Philadeliphia: Williams & Wilkins; 2000:p.145-97.

18. World Health Organization. Implementing the Stop TB Strategy.World Health Organ.2008;(April):2008. doi:WHO/HTM/TB/2008.401.

19. Zhang ZX, Sng L-H, Yong Y, et al. Delays in diagnosis and treatment of pulmonary tuberculosis in AFB smear-negative patients with pneumonia. Int J Tuberc Lung Dis. 2017;21(5):544-549.doi:10.5588/ijtld.16.0667.

20. Pepper T, Joseph P, Mwenya C, et al. Normal chest radiography in pulmonary tuberculosis: Implications for obtaining respiratory specimen cultures. Int J Tuberc Lung Dis.2008;12(4):397-403.

21. Giordani MT, Brunetti E, Binazzi Ret al. Extrapulmonary mycobacterial infections in a cohort of HIV-positive patients: Ultrasound experience from Vicenza, Italy. Infection. 2013;41(2):409-414. doi:10.1007/s15010-012-0336-4.

22. Heller T, Mtemang'ombe EA, Huson MAM, et al. Ultrasound for patients in a high HIV/TB prevalence setting -A needs assessment and review of focused applications for sub-Saharan Africa. Int J Infect Dis. 2016.doi:10.1016/j.ijid.2016.11.001.

23. Sharma SK, Smith-Rohrberg D, Tahir M, Mohan A, Seith A. Radiological manifestations of splenic tuberculosis: A 23-patient case series from India. Indian J Med Res.2007;125(5):669-678.

24. Peter JG, Theron G, Muchinga TE, Govender U, Dheda K. The diagnostic accuracy of urine-based Xpert MTB/RIF in HIV-infected hospitalized patients who are smear-negative orsputum scarce. PLoS One.2012;7(7):1-8. doi:10.1371/journal.pone.0039966.

25. HellerT, GoblirschS, Bahlas S, etal. Diagnostic value of FASH ultrasound and chestX-ray in HIV-co-infected patients with abdominal tuberculosis. Int J Tuberc Lung Dis.2013;17(3):342-344. doi:10.5588/ijtld.12.0679.

26. Jacob ST, Pavlinac PB, Nakiyingi L, et al. Mycobacterium tuberculosis Bacteremia in a Cohort of HIV-Infected Patients Hospitalized with Severe Sepsis in Uganda-HighFrequency, Low Clinical and Derivation of a Clinical Prediction Score. PLoS One.2013;8(8). doi:10.1371/journal.pone.0070305.

27. Heller T, Wallrauch C, Lesseils RJ, Goblirsch S, Brunetti E. Short report: Short course for focused assessment with sonography for human immunodeficiency virus/tuberculosis: Preliminary results in a rural setting in South Africa with high prevalence of human immunodeficiency virus and tuberculosis. Am J Trop Med-Hyg.2010;82(3):512-515. doi:10.4269/ajtmh.2010.09-0561.

28. Kyeyune R, den Boon S, Cattamanchi A, et al. Causes of early mortality in HIV- infected TB suspects in an East African referral hospital. J Acquir Immune Defic Syndr. 2010;55(4):446-450. doi:10.1097/QAI.0b013e3181eb611a.

29. Gupta RK, Lucas SB, Fielding KL, Lawn SD. Prevalence of tuberculosis in post- mortem studies of HIV-infected adults and children in resource-limited settings: a systematic review and meta-analysis. AIDS. 2015;29(15):1987-2002. doi:10.1097/QAD.0000000000000802.

30. Cox JA, Lukande RL, Nelson AM, et al. An autopsy study describing causes of death and comparing clinico-pathological findings among hospitalized patients in Kampala, Uganda. PLoS One. 2012;7(3):1-8.doi:10.1371/journal.pone.0033685.

31. Lorent N, Mugwaneza P, Mugabekazi J, et al. Risk factors for delay in the diagnosis and treatment of tuberculosis at a referral hospital in Rwanda. Int J Tuberc Lung Dis.2008;12(4):392-396.

32. Reyn CF, Kimambo S, Mtei L, et al. Disseminated tuberculosis in human immunodeficiency virus infection: ineffective immunity, polyclonal disease and high mortality. Int J Tuberc Lung Dis. 2011;15(8):1087-1092.doi:10.5588/ijtld.10.0517.

33. Nakiyingi L, Ssengooba W, Nakanjako D, et al. Predictors and outcomes of mycobacteremia among HIV-infected smear- negative presumptive tuberculosis patients in Uganda. BMC Infect Dis. 2015;15(1).doi:10.1186/s12879-015-0812-4.

34. Hoogendoorn JC, Ranoto L, Muditambi N, et al. Reduction in extrapulmonary tuberculosis in context of antiretroviral therapy scale-up in rural South Africa. Epidemiol Infect. 2017;145(12):2500-2509. doi:10.1017/S095026881700156X.

35. Meintjes G, Lawn SD, Scano F, et al. Tuberculosis-associated immune reconstitution inflammatory syndrome: case definitions for use in resource-limited settings Europe PMC Funders Group. Lancet Infect Dis. 2008;8(8):516-523. doi:10.1016/S1473- 3099(08)70184-1.