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# Ultrasound findings in cases of extrapulmonary TB in patients with HIV infection in Jeddah, Saudi Arabia

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### PEER REVIEW

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#### Comments

This is a well written article about a small retrospective study, illustrating the importance of including US in diagnostic algorithms for tuberculosis. It is an interesting piece of work contributing to the literature, as not much is published on this issue from this region.

Details on Page 17

### ABSTRACT

**Objective:** To report ultrasound (US), laboratory and chest radiograph (CXR) findings of patients with extra-pulmonary tuberculosis (EPTB) and discuss the diagnostic relevance of US in high-risk individuals.

**Methods:** In this retrospective study, we described a cohort of 39 patients with a primarily immigrant background diagnosed with HIV and EPTB in Saudi Arabia and evaluated the role of US in their clinical management. All inpatient files of those diagnosed with EPTB who were HIV positive and had at least one US exam and one CXR exam performed were identified; results and outcomes were extracted.

**Results:** Thirty-nine patients were diagnosed with HIV-associated EPTB between January 2008 and March 2012 and fulfilled the search criteria. Disseminated TB was diagnosed in 32 patients, pleural TB in 15, TB meningitis in 9 and TB pericarditis in 5. Enlarged abdominal lymph nodes were the single most frequent US finding seen in 61%, followed by pleural effusions (38%), liver (36%) and spleen (31%) lesions. CXR were normal in 38% of the patients.

**Conclusions:** As EPTB infections in HIV positive patients can be treated effectively if diagnosed early, we suggest that US should be integrated in diagnostic algorithms for EPTB.

### KEYWORDS

HIV, Extra-pulmonary tuberculosis, Ultrasound, Diagnosis

## 1. Introduction

HIV infected patients are at high risk of co-infection with tuberculosis; diagnostic approaches as well as treatment efforts must therefore consider the dual infection. When immunosuppression is severe, the probability of extrapulmonary tuberculosis (EPTB) rises and the risk of mortality increases[1]. Delayed diagnosis can be assumed

as a contributing factor for this excess mortality and rapid, simple and accurate diagnostic tests are needed as many of the patients have negative acid-fast bacilli smears. World Health Organisation (WHO) guidelines with diagnostic algorithms for smear-negative and EPTB exist and emphasize clinical as well as imaging results, in particular chest X-rays (CXR) for the diagnosis of EPTB in HIV-infected patients[2].

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In recent years, ultrasound (US) has emerged as an additional imaging modality that is rapid, cheap and available in many settings where HIV/TB patients are diagnosed. In the appropriate clinical setting, US imaging results were found to be specific enough to make empiric treatment of TB<sup>[3]</sup> and consequently of HIV infection warranted. Abbreviated US protocols similar to point-of-care US used in emergency medicine departments were developed to widen access to US in resource-poor settings<sup>[4]</sup>. The findings suggestive of EPTB include pericardial effusion, pleural effusion and in some patients ascites. Enlarged abdominal lymph nodes and focal hypoechoic lesions in the spleen and liver were also described as highly suggestive of disseminated TB in HIV patients<sup>[5]</sup>.

In this study, we examined the results of US in different forms of EPTB in a series of HIV co-infected patients from different geographic providence in a university hospital in Jeddah, Saudi Arabia.

## 2. Materials and methods

### 2.1. Patient population and methods

The King Abdulaziz University Hospital (KAAUH) is a 700-bed teaching hospital in Jeddah, Saudi Arabia. It provides free health service to patients and is the main treatment hospital for both the Saudi population and expatriate workers and their families.

A retrospective search of the inpatients of KAAUH between January 2008 and March 2012 was performed; all files of patients diagnosed with EPTB who were HIV positive and had at least one US exam and one CXR performed were identified.

Information was systematically reviewed using a standardized questionnaire. Demographic information (age, sex and country of origin) were recorded. Patients were grouped according to their ethnic background as Arab (Saudi, Yemeni), African (Somali, Nigerian, Chadian) or Asian (Burmese, Pakistani). Immunological and laboratory data as well as information from reports of US and CXR exams were extracted.

Location of EPTB was grouped following definitions in WHO guidelines<sup>[3]</sup>: Pleural TB was diagnosed by the presence of pleural effusion, pericardial TB by the presence of pericardial effusion, tuberculous meningitis was diagnosed by cerebrospinal fluid analysis showing high protein and lymphocytosis. Disseminated TB was defined as the presence of enlarged abdominal lymph nodes and/or focal lesions in the spleen or liver suggestive of tuberculomata, this definition differed from the WHO suggestion which is based on purely clinical findings.

The diagnosis of TB was confirmed in 24 patients: 15 patients had positive sputum smear or culture results. In 13 patients (9 additional patients) lesions were diagnostically biopsied which confirmed the EPTB diagnosis. The remaining 13 patients were considered as possible TB diagnosis as they had typical signs and symptoms which improved with TB treatment<sup>[4]</sup>.

### 2.2. Data analysis

Statistical analysis was carried out using SPSS 17.0 for

Windows (SPSS Inc., Chicago, IL). Proportions, the estimated 95% confidence interval (CI) and for quantitative data the median and the inter-quartile range given were needed. Conventional  $\chi^2$ - and Fischer's exact tests were used to analyze qualitative association in exploratory univariate analysis. Binary logistic regression was used to analyze association of multiple variable with hospital mortality. *P*-values <0.05 were taken to indicate statistically significant results.

## 3. Results

### 3.1. Demographic and laboratory data

Thirty-nine patients were identified that were diagnosed with HIV associated EPTB and fulfilled the search criteria of having a CXR and a US result documented. Seventeen patients (43%) were male, and 22 (57%) were female. The median age of the male patients was 38 years (IQR 34.5–52.0), the median age of the female patients was lower (33 years, IQR 24.5–43.5); the difference was not significant. Twelve patients (31%) were Saudi Arabian citizens, 27 patients (69%) were immigrants or expatriate workers. A total of 54% of the patients were of African origin (Chadian 13, Somali 7, Nigeria 1), 36% Arab (Saudi 12, Yemeni 2) and 10% Asian (Pakistani 2, Burmese 2).

The median CD4 count was 60 cells/ $\mu$ L (IQR 32–111); there were no significant differences between the different ethnic groups. The median ESR was 108 mm (IQR 70–125 mm). Results of hepatitis serology were available for 36 patients. Thirty-four patients (89%) had normal serology results, 2 (5.5%) tested positive for hepatitis B Ag, and 2 (5.5%) showed antibodies for hepatitis C.

### 3.2. Location of TB and diagnostic data

The location of EPTB was defined according to the above-mentioned case definitions. Disseminated TB was diagnosed in 32 patients, pleural TB in 15, TB meningitis in 9 and TB pericarditis in 5. Results of the US exams are summarized in Table 1. Enlarged abdominal lymph nodes were the single most frequent US finding in patients with EPTB seen in 61% (95% CI 46%–75%), followed by pleural effusions (38%, 95% CI 25%–54%) and liver lesions (36%, 95% CI 23%–52%).

**Table 1**

Ultrasound findings in HIV positive patients with extrapulmonary TB.

Location of EPTB	<i>n</i>	Pericardial effusion	Pleural effusion	Lymph nodes	Spleen lesions	Liver lesions	Ascites
Disseminated/abdominal	33						
only	17	0	0	12	5	9	4
+pleural	9	0	9	7	5	3	5
+pericardial	1	1	0	1	0	0	1
+meningitis	2	0	0	1	0	1	0
+pleural,+pericardial	2	2	2	2	1	0	0
+pleural,+meningitis	1	0	1	1	1	0	0
+pericardial,+meningitis	1	1	0	0	0	1	0
Others	6						
meningitis	3	0	0	0	0	0	0
meningitis,+pleura	2	0	2	0	0	0	1
pleural,+pericardial	1	1	1	0	0	0	0
Total	39	5	15	24	12	14	11
		12% (6%–27%)	38% (25%–54%)	61% (46%–75%)	31% (18%–46%)	36% (23%–52%)	28% (17–44%)

Results of different diagnostic procedures (laboratory and imaging investigations) according to the site of disease location are given in Table 2. As some patients fulfilled more than one of the definitions for disease location, they were recorded multiple times. Smear stains for acid-fast bacilli were positive in 28% of all patients and in only 11% of the patients with TB meningitis. Chest X-ray results were suggestive of TB in 24 patients (62%), the remaining 15 (38%) had a normal CXR. Chest X-rays were positive in all patients with pleural disease, in 64% of the patients with abdominal TB and in 60% of the patients with pericardial disease. Abdominal US findings (enlarged lymph nodes, focal liver and/or spleen lesions) were present in 85% of the patients.

**Table 2**

Diagnostic findings in HIV/TB co-infected patients.

Location of EPTB	n	Pericardial effusion	Pleural effusion	Abdo findings <sup>1</sup>	CXR <sup>2</sup> +	AFB smear +	Biopsy <sup>3</sup> +
Disseminated	33	4 (12%)	12 (36%)	33 (100%)	21 (64%)	10 (30%)	13 (39%)
Pleural	15	3 (20%)	15 (100%)	12 (80%)	15 (100%)	6 (40%)	4 (27%)
Pericardial	5	5 (100%)	3 (60%)	4 (80%)	3 (60%)	3 (60%)	2 (40%)
Meningitis	9	1 (11%)	2 (22%)	4 (44%)	6 (66%)	1 (11%)	1 (11%)
All	39	5 (12%)	15 (38%)	33 (85%)	24 (61%)	11 (28%)	14 (38%)
		(6%–27%)	(25%–54%)	(70%–93%)	(46%–75%)	(16%–44%)	(25%–54%)

<sup>1</sup>US abdo findings: enlarged abdominal lymph nodes, focal liver and/or spleen lesion; <sup>2</sup>CXR was positive if the presence of infiltrates or cavities, hilar lymph nodes, pleural effusions, or miliary lesions were noted; <sup>3</sup>Site of biopsy: lymph node, liver, bone marrow.

### 3.3. Outcome

Eleven patients died during their hospital stay; total in-patient mortality was 28.3% (95% CI 16.5%–43.8). The mortality of the 33 patients with disseminated/abdominal TB was 27.3% (95% CI 15.1–44.2). Of the 15 patients with pleural TB the mortality was 33.3% (95% CI 15.2–58.3) and of the 9 patients with meningeal TB it was 55.6% (95% CI 26.7–81.1). None of the patients with pericardial TB died (0%, 95% CI 0.0–43.5). In univariate analysis, the location of the TB was not associated with statistically increased mortality, only patients with meningitis had significantly higher mortality than patients without meningitis (55.6% vs. 20.0%, Fischer Exact test  $P=0.052$ ). As many patients had more than one disease location, interaction effects between the locations were assumed. A binary logistic regression analysis controlling for other disease locations (pleural, pericardial) showed a significant higher mortality for patients with meningeal TB (hazard ratio HR=5.69, 95% CI 1.01–31.91,  $P=0.048$ ). There was no association between CD4, positive smear, culture or biopsy and mortality.

## 4. Discussion

HIV and TB are global problems leading to massive morbidity and mortality, especially in Sub-Saharan countries. The prevalence of HIV infections in Saudi Arabia is comparatively lower than in Western countries and substantially lower than in Africa<sup>[6]</sup>. Despite the low total prevalence, numbers are continuously increasing<sup>[7]</sup>. The highest prevalence of HIV infections is reported from the area of Jeddah with a prevalence of 70 cases/100 000 inhabitants compared to an average of 29 cases/100 000 inhabitants in the other regions of Saudi Arabia<sup>[8]</sup>. The incidence of TB, a

frequent opportunistic infection in HIV infected individuals, is known to be high in Saudi Arabia. The western region, where Jeddah is located, has historically the highest incidence in the country<sup>[9]</sup>.

Previous studies from Jeddah have shown that bacterial infections are the main cause of opportunistic infections in HIV infected in-patients with *Mycobacterium tuberculosis* being the single most common cause of bacterial infection. Fifty percent of all HIV/TB co-infected patients in this published case series showed extra-pulmonary disease, which underlines the importance of the extrapulmonary location in HIV patients<sup>[10]</sup>.

As can be seen from the results of our study, the conventional diagnostic approach of sputum smears is frequently not helpful in patients with EPTB. In smear-negative TB, WHO guidelines would suggest CXR as next step in the work-up of the patient<sup>[2]</sup>. However, our results show CXR is also non-suggestive of tuberculosis in more than a third of the patients. These findings are in accordance with findings from other geographical regions<sup>[11]</sup>.

In these individuals, US plays a pivotal role as changes like abdominal lymph nodes and focal lesions of liver and spleen are frequently found. It has been shown that in individuals with a clinically high risk of tuberculosis, these findings are sufficiently specific to initiate anti-TB treatment<sup>[3]</sup>. Nevertheless, in settings outside Sub-Saharan Africa and other settings with limited resources, it seems prudent to perform US-guided biopsy and aspiration of the lesions for bacteriological confirmation of the diagnosis<sup>[12]</sup>. In our series, biopsy/aspiration was the diagnostic procedure in 14 patients (38%).

Pericardial effusions and pleural effusions can be diagnosed easily by US and it is common practice to rapidly screen for free fluid in body cavities in trauma victims, but it can be used in analogy for TB infection<sup>[13]</sup>. In HIV patients, pericardial effusion is a highly suggestive finding for pericardial TB<sup>[14]</sup>. Pleural effusions, especially when unilateral, are common findings in tuberculosis and particularly so in HIV/TB co-infected patients<sup>[13]</sup>. Simple screening protocols for these findings exist, are simple to apply and take minimal time to perform<sup>[4]</sup>.

Approximately one in three of our patients with HIV/TB co-infection died during their hospital stay. Meningeal involvement of the disease is associated with increase risk for poor outcome. The high mortality underlines the severe immunosuppression and the advanced stage of the disease at presentation. Additionally, delayed treatment due to missing the diagnosis by physicians as well as the described difficulties in diagnostic work-up may further worsen prognosis. Of particular interest is the finding that patients with TB meningitis frequently also have abnormal findings on abdominal or thoracic ultrasound. This underlies the fact that in HIV patients with severe immune-suppression EPTB is often a multi-organ disease where distant organ systems are affected.

The number of patients in our study was low limiting possibility to generalize the results. Nevertheless, as the results are in good accordance with other reported patient populations they seem valid. Another problem of the retrospective design is that the patients were preselected to have had a abdominal ultrasound, probably due to clinicians suspicion of findings. This might cause a selection bias

and increase the rate of findings. A further limitation of our study is that there was no comparison group and thus no measurement of the performance (sensitivity/specificity) of the ultrasound as a diagnostic tool for extra pulmonary TB.

Disseminated mycobacterial infections in HIV positive patients carry a high mortality, however can be treated effectively if diagnosed early. US frequently can detect findings supporting the diagnosis of TB in HIV patients. We suggest that US should be integrated in diagnostic and screening algorithms for EPTB in high-risk individuals.

### Conflict of interest statement

We declare that we have no conflict of interest.

### Comments

#### Background

TB is still the most common opportunistic infection in HIV patients. Diagnosis of TB in HIV-infected patients remains cumbersome; sputum smears are often negative and patients with severe immunodeficiency often present with extrapulmonary TB.

#### Research frontiers

This is a retrospective review of case records in a teaching hospital in Saudi Arabia, illustrating the importance of ultrasound in diagnosis of extrapulmonary TB in HIV patients. This has been shown before in other populations, but as far as I know, this is the first report from the Middle East.

#### Related reports

This article described a retrospective cohort of HIV patients with EPTB, who underwent US and CXR. Similar studies have been performed in Italy (in mainly immigrants) and South Africa, where similar results have been found. To that end, this article is another confirmation on the usefulness of ultrasound in diagnosing TB in HIV infected patients. It contributes to the discussion on introducing US as diagnostic tool in diagnostic algorithms.

#### Innovations & breakthroughs

As stated above, this is the first report on the use of US in diagnosing TB in HIV patients in this setting in the Middle East. It shows that similar data are found in endemic settings around the world.

#### Applications

This report shows again that US is very useful and should be implemented in diagnostic algorithms for TB in HIV infected patients. In certain setting, it can be used for decision making on empiric initiation of anti tuberculous treatment in HIV patients.

#### Peer review

This is a well written article about a small retrospective study, illustrating the importance of including US in diagnostic algorithms for tuberculosis. It is an interesting piece of work contributing to the literature, as not much is published on this issue from this region.

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