

Changes of FASH ultrasound findings in TB-HIV patients during anti-tuberculosis treatment

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SUMMARY

Ultrasound findings of extra-pulmonary tuberculosis (TB) have been well-described, particularly in human immunodeficiency virus (HIV) co-infected patients, and are often used as a basis of diagnosis in high-prevalence settings. Changes in findings during anti-tuberculosis treatment are less well documented. We present a single-centre case series of 21 TB-HIV co-infected individuals with typical ultrasound findings present at baseline. In 16/21 (76%) patients, all findings had resolved by

month 3 of treatment. In patients with persistent ultrasound findings at 3 months, non-adherence, drug resistance, chronic disease, immune-reconstitution inflammatory syndrome and alternative diagnoses were identified. Follow-up ultrasound at month 3 may help identify high-risk cases.

KEY WORDS: HIV; EPTB; ultrasound; FASH; treatment changes

IN MANY PARTS OF THE WORLD, particularly in sub-Saharan Africa, the human immunodeficiency virus (HIV) and tuberculosis (TB) epidemics have led to substantial increases in extra-pulmonary TB (EPTB).¹ Ultrasound is a widely available imaging modality increasingly seen as an addition to chest X-ray to aid in the diagnosis of TB.² Pericardial and pleural effusions are highly suggestive of EPTB and can be diagnosed by ultrasound.³ Intra-abdominal involvement is another frequent presentation of EPTB in HIV-positive patients. Typical ultrasound findings include retroperitoneal and mesenteric lymphadenopathy (node diameter >2 cm), multiple splenic hypoechoic nodules (0.5–2 cm) and patterns of ascites.³ Hyper- or hypoechoic hepatic lesions, retroperitoneal abscesses and thickening of the bowel walls are also seen, although less frequently. In areas with high HIV and TB co-infection prevalence, ultrasound findings may be specific enough to initiate anti-tuberculosis treatment even in the absence of bacteriological or histological confirmation.⁴ As ultrasound findings of EPTB are relatively easy to recognise even by less experienced sonographers, protocols for point-of-care focused assessment for HIV-associated TB (FASH) have been developed.³ The FASH protocol is taught to clinicians in the field,⁵ and is now widely used in emergency settings in Southern Africa.⁶

For patients undergoing repeat follow-up investi-

gations, it is important to know the natural history of sonographic changes, particularly in settings with a high burden of TB drug resistance and in HIV settings, where immune reconstitution inflammatory syndrome (IRIS) may lead to a worsening of findings despite adequate treatment.

To investigate temporal changes in ultrasound findings during anti-tuberculosis treatment, we studied a cohort of HIV-infected patients with EPTB using serial ultrasound examinations.

METHODS

HIV-positive patients with culture-proven diagnosis of EPTB at the San Bortolo Hospital, Vicenza, Italy, were reviewed.⁷ Those with EPTB ultrasound findings and follow-up ultrasounds performed to reassess the initial findings were included. All patients had abdominal ultrasound examinations performed 1, 3, 6 and 12 months after diagnosis. Ultrasound examinations were performed by one examiner (MTG) using an Aplio XG (Toshiba, Tokyo, Japan) with a 3.5 MHz convex and a 8-MHz linear probe.

Patients were treated for TB according to international standards. Treatment regimens using rifampicin (RMP), isoniazid (INH), ethambutol and pyrazinamide were most frequently used; in case of antimicrobial resistance or intolerance, treatment was adapted accordingly. Patients who were not

already on antiretroviral therapy (ART) were offered treatment. The choice of ART and the timing of initiation were at the discretion of the treating physician. Tenofovir/emtricitabin, abacavir/lamivudine and zidovudin/lamivudine in combination with efavirenz were most frequently used.

As all data had been previously collected and analysed retrospectively, ethical approval was not required for this study.

RESULTS AND DISCUSSION

Twenty-one patients seen between 2005 and 2013 for HIV-associated TB had a diagnostic ultrasound scan and additional follow-up ultrasound examinations. The median patient age was 31 years (interquartile range [IQR] 29–42), 12 (57%) were male and 14 (67%) were of African origin. The median CD4 count on admission was 73 cells/ μ l (IQR 20–134); 18 (86%) had CD4 counts <350 cells/ μ l and 13 (62%) <100 cells/ μ l. The viral load (VL) on admission was available for 18 patients; the median VL was 109 000 copies/ μ l; 53% of the patients had VL >100 000 copies/ μ l. Eight patients underwent ART before the TB diagnosis, 12 started ART treatment within 2 weeks of the TB diagnosis, and one patient did not start ART (CD4 count 342 cells/ μ l, VL <50 copies/ μ l). VL measurements within the first 3 months were available for 13 patients; all were virologically suppressed (VL < 100 copies/ μ l).

Lymph node enlargement, pleural effusion and splenic lesions were the most frequent findings at diagnosis. Changes in ultrasound findings during the course of anti-tuberculosis treatment are shown in Table 1. The majority of the findings, especially effusions, disappeared within the first month of initiating anti-tuberculosis treatment. All ultrasound findings had disappeared in 10 patients by month 1 (48%) and in 16 patients by month 3 (76%). All of these patients underwent successful anti-tuberculosis treatment, and follow-up was uneventful. Effusions and ascites resolved in all patients. Lymph nodes and

splenic abscesses persisted in three patients, while enlarged lymph nodes persisted only in two. Three of the five patients with persistent ultrasound findings (summarised in Table 2) eventually died, illustrating the high mortality in this group.

Several reasons may account for persistent ultrasound findings during treatment. Failure to take treatment due to miscommunication or non-adherence should be considered; this is especially common when patients report a subjective feeling of improved health.⁸ Multidrug-resistant TB (MDR-TB, defined as TB resistant to at least INH and RMP), seen in an increasing number of pulmonary TB and EPTB cases, is another reason.¹ Diagnostic material for resistance testing should be obtained, e.g., via image-guided aspiration tools, whenever MDR-TB is suspected. Wrong or additional diagnoses, particularly lymphoma or Kaposi's sarcoma, are other possible causes of persistently enlarged lymph nodes. This is particularly true in settings where treatment is started empirically. Although the ultrasound morphology of malignant lymph nodes differs from inflammatory nodes as in EPTB, findings overlap considerably, and a final differentiation based on imaging alone is not possible.⁹

IRIS is well described in TB-HIV co-infected patients;¹⁰ the risk increases when ART is started. Only one patient in our series showed IRIS, and clinical trials have shown that the benefit of early ART clearly outweighs the potential risks of IRIS.¹¹ Even in the absence of the abovementioned causes, some patients may show protracted lymph node enlargement. Serial chest computed tomography (CT) scans assessing enlarged mediastinal lymph nodes in 58 TB patients reported slow (reduced size after month 3, but residual nodes after year 1) or no (no change in size after treatment) response to anti-tuberculosis treatment in up to 29 patients,^{12,13} similar to the course seen in our patient 3. The substantially higher rate of persistence of lymph nodes in this study may be due to the mediastinal

Table 1 Sonographic findings of extra-pulmonary tuberculosis in 21 HIV co-infected patients: changes in findings during the course of anti-tuberculosis treatment

	Present at time of diagnosis*	Disappeared by (cumulative %) [†]				Persisted for >12 months
		Month 1	Month 3	Month 12	>12 months	
	<i>n</i>	<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)	
Abdominal lymph nodes	18	10 (55)	13 (72)	14 (78)	4 (22)	
Spleen abscess	8	5 (67)	6 (78)	—	2 (22)	
Liver abscess	2	1 (50)	2 (100)	—	—	
Ascites	8	6 (78)	8 (100)	—	—	
Pleural effusion	12	11 (92)	12 (100)	—	—	
Pericardial effusion	1	1 (100)	—	—	—	
Bowel thickening	6	5 (83)	6 (100)	—	—	

* Several patients showed more than one finding at the time of diagnosis.

[†] Findings were considered to have disappeared when they were not visible on ultrasound (no visible fluid, lymph nodes <1 cm, no focal lesions in the liver or spleen, bowel wall thickness 3–5 mm).

HIV = human immunodeficiency virus.

Table 2 Course and complications of HIV-EPTB disease in patients with persistent sonographic findings at month 3 of anti-tuberculosis treatment

No	Ultrasound findings	Clinical course	Death	Problem
1	ALN persisted > 3 months, SL and HL developed between months 1 and 3	Treatment was not initiated due to miscommunication between laboratory, physician and patient. After treatment was started all findings disappeared within 1 month	No	Missing treatment
2	ALN persisted >12 months	MDR-TB was grown on follow-up aspirate from ALN, and treatment was changed. The patient developed renal failure, stopped treatment and eventually died	Yes	MDR-TB
3	Ascites and bowel thickening disappeared after 1 month, ALN and SL persisted >12 months	Anti-tuberculosis treatment was continued > 2 years; repeat culture showed no resistance. Treatment was eventually completed	No	Chronic TB
4	ALN persisted > 12 months	Lymph node aspiration grew <i>M. tuberculosis</i> . Initial clinical improvement; the patient continued treatment, then deteriorated. Histology showed Castleman's disease. The patient died after 16 months	Yes	Additional diagnosis
5	ALN and SL increased in size, showed more anechoic areas and persisted >12 months	The patient developed additional neck and psoas TB abscesses, IRIS was assumed. In the further course of treatment the patient showed non-adherence and died after 14 months. No post mortem	Yes	IRIS and non-adherence

HIV = human immunodeficiency virus; EPTB = extra-pulmonary tuberculosis; ALN = abdominal lymph nodes; SL = spleen lesions; HL = hepatic lesions; MDR-TB = multidrug-resistant tuberculosis; IRIS = immune reconstitution inflammatory syndrome.

location of the lymph nodes or to higher sensitivity of CT scans.

Ours was a single-centre study with a limited number of patients; nevertheless, it has the advantages of good standardisation of examinations and no inter-observer differences. The case series illustrates that in a large majority of patients treated for EPTB, characteristic ultrasound findings disappeared by month 3 of treatment. A follow-up FASH ultrasound at this time can help to pick-up non-response and identify patients with treatment complications that should be monitored closely, as such patients have a higher mortality.

Conflict of interest: none declared.

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RESUME

Les échographies des tuberculoses (TB) extrapulmonaires ont été bien décrites, surtout chez les patients présentant une coinfection avec le virus de l'immunodéficience humaine (VIH), et elles sont souvent utilisées comme un critère diagnostique dans les contextes de prévalence élevée. Les modifications des échographies en cours de traitement sont en revanche moins bien documentées. Nous présentons ici une série de cas de 21 patients coinfectés par le VIH dans un centre unique avec des résultats échographiques typiques

lors du premier bilan. Chez 16/21 (76%) patients, toutes les anomalies des échographies ont disparu après 3 mois de traitement. Chez les patients présentant encore des anomalies échographiques à 3 mois, nous avons identifié soit une non-adhésion au traitement, soit une résistance aux médicaments, soit une maladie chronique, soit un syndrome inflammatoire lié à la reconstitution immunitaire, ou enfin, un diagnostic alternatif. Un suivi échographique à 3 mois pourrait permettre d'identifier les cas à haut risque.

RESUMEN

Los hallazgos ecográficos en los casos de tuberculosis (TB) extrapulmonar se han descrito ampliamente, sobre todo en pacientes coinfectados por el virus de la inmunodeficiencia humana (VIH) y con frecuencia constituyen la base del diagnóstico en los entornos con alta prevalencia. Las modificaciones de las imágenes en curso de tratamiento están menos documentadas. En el presente artículo se presenta una serie de 21 pacientes coinfectados por la TB y el VIH de un centro único, cuyas características ecográficas iniciales fueron

clásicas. En 16/21 (76%) pacientes, todas las imágenes ecográficas habían regresado al tercer mes de tratamiento. En los pacientes con imágenes persistentes, se observó incumplimiento terapéutico, farmacorresistencia, enfermedad crónica, síndrome de inflamatorio de reconstitución inmunitaria y errores diagnósticos o diagnósticos asociados. El seguimiento ecográfico a los 3 meses de tratamiento puede detectar los casos con alto riesgo de una evolución desfavorable.
