

# ROLE OF ULTRASOUND IN THE DIAGNOSIS OF EXTRAPULMONARY TB: AN OVERVIEW

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## Abstract

Extrapulmonary TB (EPTB) is rare, but its incidence is increasing with the increasing prevalence of HIV and pulmonary TB infections. It can affect any organ or system in the body and may mimic numerous disease entities. This often results in delayed diagnosis and treatment, which in turn increases morbidity and mortality. Diagnosis of EPTB is often difficult, requires a high index of suspicion and should be one of the differentials in areas where TB is endemic. It is important to be familiar with the various spectrum of radiological manifestations. In this review, we illustrate and describe the ultrasound findings of cervical lymphadenitis, abdominal TB involving the liver, spleen, adrenal glands, peritoneum and kidney, as well as discuss the role of ultrasound in the diagnosis.

## Cervical Lymphadenitis

- Most common manifestation of EPTB
- Local manifestation of systemic disease
- Affects peripheral lymph nodes
- Maybe discrete or may coalesce
- Important to assess distribution, size, shape, hilum, echogenicity, border, presence of necrosis and calcification
- Must be differentiated from malignant or metastatic nodes (Refer to Table. 1)

## Introduction

According to WHO data, tuberculosis (TB) is a top infectious disease killer worldwide. In 2014, 9.6 million people fell ill with TB and 1.5 million died from the disease. Over 95% of TB deaths occur in low and middle-income countries. An estimated 1 million children became ill with TB and 140,000 children died of TB (1). TB can affect any organ or system in the body and with increasing prevalence of HIV infection more and more cases of extra pulmonary tuberculosis (EPTB) are reported. The most commonly involved sites of EPTB are the lymph nodes, specifically in the cervical area (67%), but may also involve any other organs especially in the abdomen (2, 3, 4, 5, 6).

There are several articles in the literature that illustrate the importance of including ultrasound (US) in the diagnostic algorithm for EPTB (8, 9). The diagnosis of EPTB is often difficult as it can mimic numerous other disease entities. Thus, it is important to be familiar with the various US features of EPTB, as it is an affordable diagnostic modality and readily available worldwide. In this review, we will illustrate and describe US findings of cervical lymphadenitis, abdominal TB involving the liver, spleen, adrenal glands, peritoneal and renal tuberculosis as well as discuss the role of ultrasound in the diagnosis.

## Cervical Lymphadenitis

Tuberculosis involving the lymph nodes usually affects the peripheral lymph nodes, most commonly the cervical lymph nodes. It is a local manifestation of systemic disease by hematogenous and lymphatic dissemination. Initially, the nodes are discrete but due to periadenitis, results in matting and fixation of the nodes. Sometimes they coalesce and perforate the deep fascia forming a "collar stud" abscess (8).

Tuberculous lymphadenitis / adenitis remains a diagnostic dilemma as it is hard to differentiate from malignant lymphoma and metastatic lymph nodes. It is important to differentiate the three as the treatment is quite different. The role of high-resolution ultrasound in the assessment of cervical lymph nodes is well established. The grey scale features like distribution, size, shape, hilum, border, echogenicity, micronodular appearance, intranodal necrosis and calcification are assessed. Adjacent soft tissue edema and matting are particularly useful to identify tuberculosis. Power Doppler features includes vascular pattern and displacement of vascularity. It has a high sensitivity (98%) and specificity (95%) when used in conjunction with fine needle aspiration cytology (10).

### Renal TB

- Genitourinary TB is the second most common manifestation of EPTB
- Classification based on US:
  1. Parenchymal granuloma
  2. Mass with cavitation and/or calcifications
  3. Papillary involvement/necrosis
  4. Sloughing of papillae
  5. Focal caliectasia
  6. Renal TB abscess

### Adrenal TB

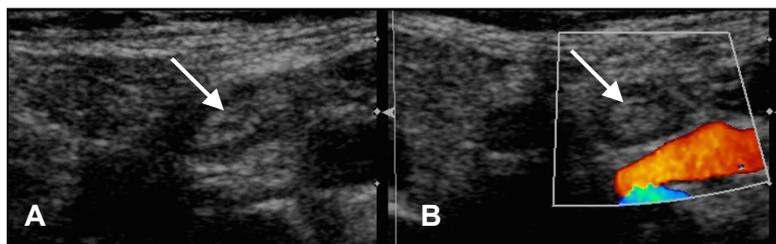
- Seen in up to 6% with active TB, almost always bilateral
- Leads to inflammation, necrosis, and destruction of adrenal tissue
- Ultrasound features:
  - Diffuse enlargement
  - Hypoechoic in acute stage but becomes echogenic and develops calcification in chronic stage

### Liver TB

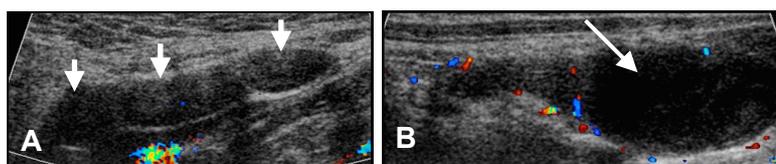
- Often associated with miliary TB
- Spectrum of ultrasound findings:
  - Hepatomegaly without lesions
  - Hypoechoic nodules
  - Hyperechoic micronodular pattern (calcifications) seen in chronic state
  - Large mass-like nodules
- Image-guided biopsy is often required for definitive diagnosis

**Table 1. Differences Between Tuberculous Adenitis versus Malignant / Metastatic Nodes**

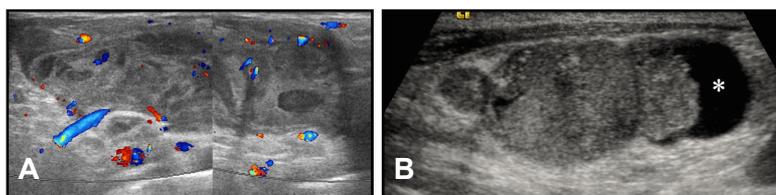
Ultrasound Features	TB Adenitis	Malignant LN/ Metastasis
Distribution (5)	Posterior triangle and supraclavicular fossa	Site specific
Size	Relatively smaller	Larger
Shape (11)	Round with uniformly thickened cortex	Round with eccentric cortical thickening due to intranodal tumor infiltration
Borders (11)	Unsharp due to adenitis	Sharp due to tumor infiltration and reduced fatty deposition within LNs
Echogenicity (15)	Hypoechoic	Hyperechoic
Echogenic hilum (12, 13, 14)	With central echogenic hilum	No central echogenic hilum
Calcification (15,16,17)	May exhibit dense calcifications post treatment	Punctate and peripherally located
Intranodal necrosis (15,16,17)	Cystic necrosis	Cystic necrosis
Vascular pattern (15,16,17)	May or may not have vascularity in the central hilum	May have irregular pattern of vessels from the capsule/cortex
Vascular Resistance (18,19)		Have higher PI and RI than reactive lymph nodes



**Figure 1. Normal lymph node.** Longitudinal (A) and transverse (B) views of a normal ovoid shaped hypoechoic lymph node with echogenic center representing fatty hilum (arrow).



**Figure 2. TB Adenitis in two different patients.** A few lymph nodes without normal fatty hilum (small arrows) at the posterior triangle of the neck (A) and a lymph node with cystic necrosis (large arrow) in the anterior neck (B).



**Figure 3. TB Adenitis versus Malignant Node.** TB lymphadenitis in a patient with TB meningitis reveals a heterogenous lymph node with cystic necrosis and abscess formation (A), compared with an enlarged, hyperechoic submandibular lymph node with microcalcifications and necrosis (asterisk) in a patient with papillary thyroid carcinoma (B).

## Splenic TB

- Uncommon form of TB usually seen in immunocompromised
- Spectrum of ultrasound findings:
  - Splenomegaly without lesions
  - Small hypoechoic nodules representing tuberculomas
  - Splenic abscesses
  - Hyperechoic micronodular pattern (calcifications) seen in chronic state
- Image-guided biopsy is often required for definitive diagnosis

## Peritoneal TB

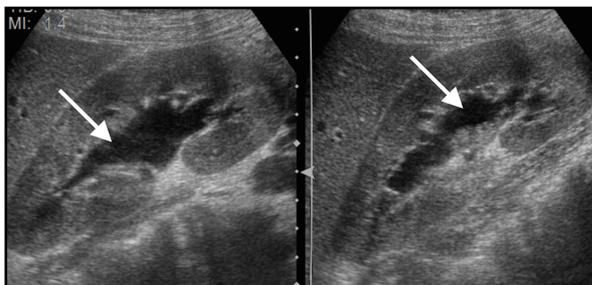
- Associated with widespread intraabdominal TB disease
- Could be from hematogenous disease, from rupture of lymph node or spread from adjacent diseased organ
- Ascites is a common manifestation of peritoneal TB
- Thickened peritoneum with hyperemia can be seen
- Three forms:
  - Wet type - most common (90%), diffuse or loculated viscous fluid
  - Fibrotic/fixated - 60% of cases, large omental cake-like masses
  - Dry/plastic - 10% of cases, fibrous peritoneal reaction, thickening, adhesions, and nodules

## Renal TB

Genitourinary TB is the second most common manifestation of EPTB after lymph node involvement (79, 80) and the kidneys are the primary organ infected in urinary disease. Due to hematogenous dissemination of TB, bilateral involvement of the kidneys is a potential risk. A timely diagnosis and treatment is necessary to avoid complications such as renal failure. Thus imaging plays an important role (26).

US is a readily available technique for demonstrating the various morphologic abnormalities found in renal TB (20, 21, 22), and is a convenient method as a guide in fine needle aspiration cytology (FNAC) (23, 24). Masses may be missed if its echogenicity is similar to the renal parenchyma on US, and with diffuse involvement, the kidney may be normal looking (25). A normal kidney on US in the presence of a non-functioning kidney is considered typical of TB, although parenchymal infiltration usually causes loss of corticomedullary differentiation (26).

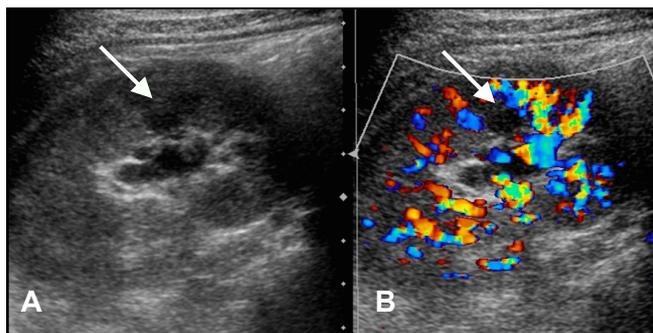
The literature describes two patterns of GUTB (27): 1) the infiltrative pattern with its more common feature of increased echogenicity due to calcifications, infected debris, and/or abscesses; and the other pattern which is 2) hydronephrosis or pyonephrosis, with dilated calyces and a small renal pelvis [Fig. 4] (28,29). Unfortunately, the demarcation between the two is often not very clear, and the picture is often a combination of both processes.



**Figure 4. Pyohydronephrosis.** Patient with known TB disease demonstrating dilated calyces (arrow) and small renal pelvis, proven to be due to TB infection. Note that the fluid within the dilated calyces appears demonstrate floating debris.

### Types of Renal TB based on US features as proposed by Rui and colleagues (30):

1. Parenchymal granuloma is the most frequently encountered parenchymal abnormality in US; small (5-15 mm) focal lesions are either echogenic or have an echogenic border with central area of low echogenicity; larger focal lesions (>15 mm) have mixed echogenicity and poorly defined borders (31, 26). These can be better appreciated on color flow study, with a 'cut off' of the vasculature highlighting the presence of granulomas [Fig. 5].



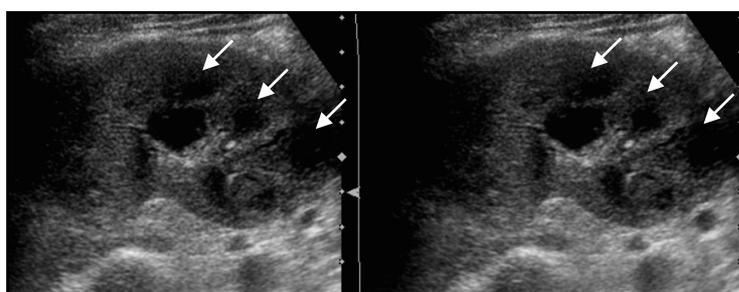
**Figure 5. Renal Parenchymal Granuloma.** Grey scale sagittal ultrasound of the kidney (A) and with color doppler (B) demonstrates a focal hypoechoic renal lesion with “cut-off” of the vascular flow on color flow imaging (arrow).

2. Masses with cavitation and multiple punctate calcifications. Caseation within the masses leads to parenchymal cavities, which could rupture into the pelvicalyceal system (32) [Fig. 6]. Important differentials for Renal TB includes acute focal bacterial nephritis, xanthogranulomatous pyelonephritis, and small benign and malignant tumors which may have the same appearance as TB on US (34). An US-guided FNAC may be performed to confirm the diagnosis, especially in patients with negative urine cultures. US-guided FNAC also aids in defining the nature of sonographically visible lesions in patients with positive urine cultures (31, 33).



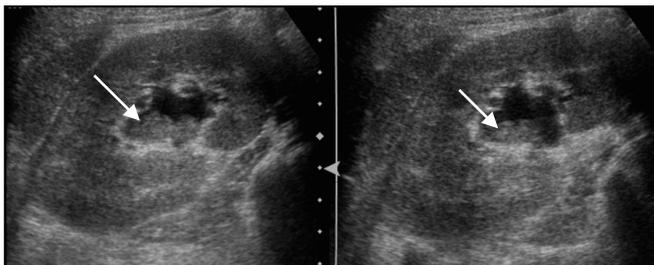
**Figure 6. Renal TB as Parenchymal Mass.** Renal ultrasound in longitudinal (A) and transverse views (B) demonstrate a hypoechoic mass in the renal parenchyma. Ultrasound of another patient demonstrates lobulated kidney with multifocal hypoechoic masses that ruptured into the pelvicalyceal system (C).

3. Papillary involvement may be seen as an echogenic non-shadowing medullary mass in close proximity to the calyces, into which it commonly ruptures, to produce a cavitory lesion that communicates with a calyx via a thin or wide anechoic tract [Fig. 7] (31,35).



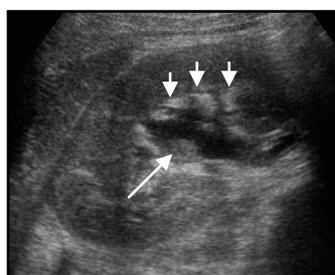
**Figure 7. Renal TB and Papillary Necrosis.** Contiguous sagittal ultrasound images reveal swollen and bulbous renal papilla in the lower pole of the kidney (arrows).

4. Sloughing is accompanied by an echogenic flap, which is separated from the calyceal wall. Intracalyceal filling defects may be caused by sloughed papillae as well as blood clots, fungal balls, or other debris; however, other features of renal TB help distinguish the cause [Fig. 8]. In doubtful cases, FNAC may be performed (31).



**Figure 8. Renal TB with Intracalyceal Debris.** Contiguous sagittal renal ultrasound images show echogenic debris within the major calyx (arrow) compatible with sloughed papillae.

5. Focal caliectasia resulting from infundibular stenosis often accompanied by varying degrees of urothelial thickening [Fig. 9] may create a fairly characteristic sonographic pattern of a focally dilated collecting system containing debris (36). When the renal pelvis and ureter are involved by TB, the hydronephrosis becomes severe because the pelvis is usually scarred (40,41). The pattern of diffuse uneven caliectasia (without renal pelvic dilatation) accompanied by urothelial thickening is a good pointer of renal TB, especially in the absence of a renal pelvic calculus (37,38,39).



**Figure 9. Caliectasia with Debris and Urothelial Thickening.** Sagittal renal ultrasound image show caliectasia with echogenic debris (long arrow) as well as thickened urothelium (short arrows).

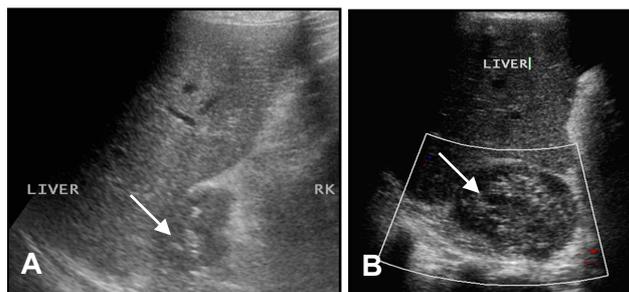
6. In renal TB, the renal size is generally maintained. A TB renal abscess may be noted as an irregular cavity, with a semi-solid echogenicity and a thick ill-defined wall. Necrotic debris and scattered echogenic foci may be seen. The abscess can extend outward and may rupture, which may lead to a perinephric abscess and later to a cutaneous fistula (41, 42).

A thorough analysis of the retroperitoneal compartments, in particular, the psoas muscle sheath, is required as these are possible sites of migrating abscess. Restriction of renal movement is a good US pointer toward perinephric spread. US, being a rapid, dynamic, and safe modality, can also be used to detect the presence of TB elsewhere in the abdomen. Findings of omental caking, especially in conjunction with septated ascites and peritoneal, mesenteric, or bowel wall thickening and lymphadenopathy, are virtually diagnostic of abdominal TB (43).

## Adrenal TB

Adrenal TB are seen in up to 6% of patients with active tuberculosis and are almost always bilateral due to hematogeneous or lymphomatous routes with an Addisonian type of clinical picture (44, 45). There is often a delay in diagnosis; and patients may first present with a life-threatening crisis (46, 47, 48). Tuberculosis of the adrenal glands leads to inflammation, necrosis and destruction of adrenal cortical tissue and should be part of the differentials in endemic regions (48). Diagnostic modality of high relevance for this disease includes CT, MRI, and ultrasound.

Sonographic findings of adrenal inflammatory disease are diffuse enlargement or hypoechoic nodules of the glands in the acute phase and calcification in the chronic stage. Calcification in adrenal glands can be diffuse, localized or punctate and increases with course of the illness (49) [Fig. 10]. However, adrenal gland calcification maybe seen in both benign and malignant lesions, necessitating histopathological study to direct proper management and treatment.



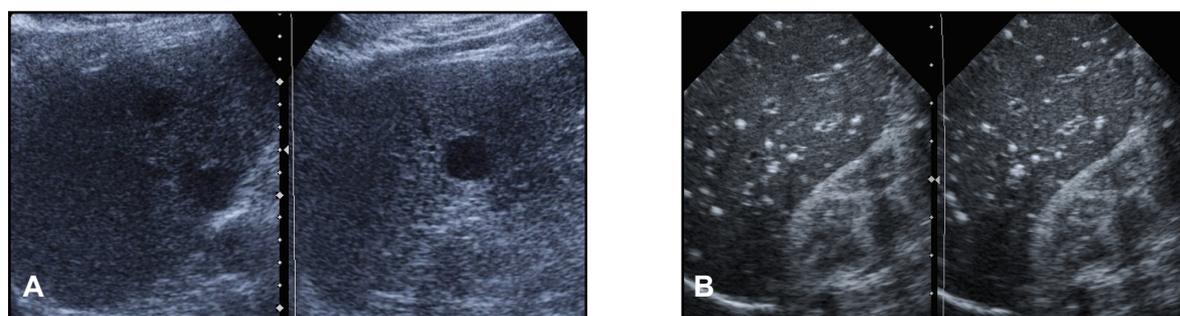
**Figure 10. Adrenal TB.** Sagittal (A) and transverse (B) ultrasound images of the right suprarenal area reveals an enlarged, mass-like adrenal gland with heterogenous echogenicity (arrow).

## Liver TB

Hepatobiliary TB is uncommon, is often associated with miliary TB, and occurs more often in immunocompromised patients (50, 51, 52, 53, 54, 55). Pre-operative diagnosis of hepatic TB is difficult and can be confirmed on histopathological examination of excised specimen (8). Hepatic TB was classified in the literature into miliary TB (part of generalized disease) and localized disease. Localized hepatic TB could be further divided into focal or nodular TB (including hepatic abscess or tuberculomas) and into tubular form (intrahepatic duct involvement) (56, 57, 58, 59).

In small nodular hepatic lesions that are below the resolution of US or CT, the only imaging finding is hepatomegaly. US may demonstrate tiny hypoechoic lesions with a “bright liver pattern” [Fig.11 A]. Calcifications may be detected when chronic [Fig. 11 B]. The differential diagnosis of micronodular hepatic TB includes metastases, lymphoma, leukemic cell infiltration, sarcoidosis, and fungal infection (56, 60, 61, 62, 63). Larger TB nodules are rare and are probably secondary to conglomeration of miliary granulomas and may be demonstrated in US as hypoechoic lesions or complex masses.

Important differentials include pyogenic abscess, metastases, and primary liver tumors such as cholangiocarcinoma and hepatocellular carcinoma. Image-guided biopsy is often required to obtain a definitive histological diagnosis. Hepatic tuberculomas eventually tend to calcify, and the presence of calcified granulomas in patients with known risk factors and in the absence of a known primary tumor should raise suspicion for TB (37, 56, 58, 60, 61, 62, 84).

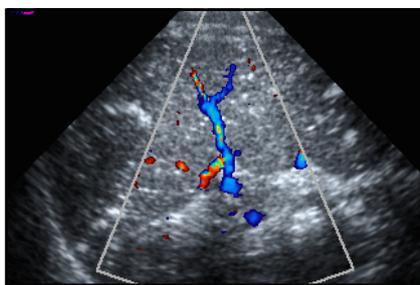


**Figure 11. Hepatic TB.** Sagittal and transverse ultrasound images of the liver (A) demonstrate small round hypoechoic nodules later proven as TB nodules. Contiguous ultrasound images of the liver in another patient with miliary TB (B) demonstrate innumerable calcified TB granulomas throughout the liver.

## Splenic TB

Splenic TB is a rare form of abdominal TB and is usually seen in immunocompromised individuals or as a part of disseminated TB (63,64,65,66). However, spleen can be the only site of tuberculous infection (isolated splenic TB) (67,68). TB of the spleen can present as splenomegaly which may occur in patients with disseminated/miliary tuberculosis and may also present as splenomegaly, splenic abscess or as a solitary splenic lesion (69).

Abdominal US may demonstrate multiple small hypoechoic lesions in the spleen representing tuberculomas (85,86) which may calcify in chronic cases [Fig.12]. These may also present as multiple abscesses and even as normal if the lesions are too small and below the resolution of US. Concurrent ascites on US may also be seen in some patients (69,70,71,72). Perisinusoidal inflammation and perisinusoidal fibrosis may develop in relation to tubercular granulomas, which may lead to progressive obstruction to venous drainage that may further result in splenomegaly (72,73,74). Pre-operative diagnosis of splenic tuberculosis is difficult and the diagnosis can be confirmed on histopathological examination of excised specimen (8).



**Figure 12. Splenic TB.** Splenic ultrasound image of a 2-year-old with disseminated TB reveals splenomegaly with multiple small calcified nodules throughout the spleen.

## Peritoneal TB

Isolated peritoneal TB is rare and is usually associated with widespread intraabdominal disease. Spread is usually hematogenous but may also be due to ruptured lymph node, gastrointestinal deposit or fallopian tube infection. The patient may present with abdominal pain, abdominal distension or fever (45). It is the most common clinical manifestation of abdominal TB affecting 1/3 of all patients (45).

The common ultrasound findings in peritoneal TB include detection of ascites, with involvement of peritoneal layers, mesentery and omentum. Color Doppler should be performed to evaluate thickening of the peritoneum and to identify hyperemia. US is more sensitive than CT in the detection of diffuse peritoneal thickening, especially in the presence of ascites, characteristically found in chronic inflammation. According to the WHO, in the case of high suspicion of TB, antibiotic therapy must be given, and in this sense, ultrasound could be very useful in monitoring the response to the therapy (75). There are three forms described and they are as follows: 1) Wet - most common (90%) [Fig.13]; presents with copious diffuse or loculated viscous fluid with medium level echo floaters due to high protein and water content. 2) Fibrotic/ fixed - 60% of the cases; characterised by large omental cake-like masses, tethered bowel and mesentery, occasional ascites. 3) Dry/ plastic - 10% of the cases; characterised by fibrous peritoneal reaction, dense adhesions, mesenteric thickening and caseous nodules (rare). There can be considerable overlap between the three types (76). US, being a rapid, dynamic, and safe modality, can also be used to detect omental caking, especially in conjunction with septated ascites and peritoneal, mesenteric, or bowel wall thickening and lymphadenopathy which are virtually diagnostic of abdominal TB (77).



**Figure 13. Peritoneal and Pleural TB.** Ultrasound image showing copious pleural effusion (PE) and diffuse intraperitoneal fluid (ASC) with medium level echo floaters due to high protein content in the fluid.

## Conclusion

A high degree of suspicion is required for the diagnosis of extra pulmonary TB. Conventional diagnostic techniques provide varying degrees of sensitivity and specificity according to location and bacterial load. Invasive methods are often needed to obtain samples for microbiological and histological testing (9) and ultrasound plays an important role as a noninvasive and radiation negative tool for guided aspiration for cytology. The recognition of the imaging manifestations of extra pulmonary TB is important, because of its increasing incidence and its propensity to mimic a variety of neoplastic and non-neoplastic conditions, which in most cases delays the diagnosis and treatment.

Major advantages of US, aside from being a radiation negative tool, are that it is inexpensive, readily available, and can be used to serially follow up patients post treatment. The major limitation of US, however, is that it is operator-dependent.

## Recommendations

While US and CT scan are widely available, they have limitations. In patients who have persistent lesions on CT or US, but it is suspected that TB has resolved, it may be useful to follow these up with magnetic resonance imaging MRI and positron emission tomography (PET) scanning. These imaging modalities (MRI and PET) are better capable of resolving stable, fibrotic lesions versus persistent active lesions. PET is especially suitable for detecting the activity of the lesions, and its role may expand as it becomes more accessible. This will be crucial in better assessing when to terminate treatment, which is currently very difficult. Although both options are limited in resource-poor settings, these may be useful in select circumstances when available. Further study of these modalities is warranted as they become more widely available (83, 84, 85).

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