The use of imaging to increase the level of confidence in the diagnosis of smear negative and disseminated tuberculosis

ABSTRACT
The incidence of smear negative pulmonary and extra-pulmonary tuberculosis has increased substantially in countries where both tuberculosis and HIV are prevalent and this represents a significant impediment to addressing the TB/HIV epidemic. HIV positive, smear negative pulmonary and extra-pulmonary TB patients have inferior outcomes, including higher mortality rates as compared with HIV positive smear positive patients. The optimal usage of available imaging modalities can increase the level of confidence of a diagnosis of tuberculosis in smear negative patients. An approach to the use of imaging in this setting is discussed. Increasing the level of confidence for a diagnosis of tuberculosis can enable treatment to be commenced without having to wait for the results of sputum culture, which can take up to six weeks; during which time patients may succumb to tuberculosis if left untreated. A further important consideration is that untreated smear negative patients remain infective.

Key words: smear negative tuberculosis, disseminated tuberculosis, diagnosis, imaging, chest X-ray, CT scan, sonar, ultrasound

INTRODUCTION
Tuberculosis (TB) is the most common opportunistic infection in HIV positive patients in Africa and world-wide and accounts for approximately one third of all AIDS related deaths. TB can occur at any stage of HIV infection and accelerates its course. The clinical presentation varies according to the stage of the HIV infection. Early in the course of the retroviral infection, with relatively preserved cell mediated immunity, pulmonary TB resembles the HIV negative picture; i.e. upper lobe infiltration with cavitation on chest X-ray. The tuberculin test is positive and acid fast bacilli (AFB) are usually detectable on direct sputum examination. However, as the cell mediated immunity worsens, the picture becomes atypical with direct sputum examination and tuberculin tests often negative; and the chest X-ray features atypical; thus making the diagnosis difficult. In addition, extra-pulmonary tuberculosis becomes common. Smear negative individuals may continue to spread tuberculosis. In various series, extra-pulmonary TB alone or in combination with pulmonary disease has been documented in 40 to 60% of HIV positive cases. The most common extra-pulmonary forms are lymphatic, disseminated, pleural and pericardial. In the gold mining industry, there is a high incidence of silicosis in a population that also has a high prevalence of HIV. This presents a particular diagnostic dilemma as these patients frequently present with atypical changes on chest X-ray and have a higher prevalence of smear negative TB.

The incidence of smear negative pulmonary and extra-pulmonary TB has increased substantially in countries where both TB and HIV are prevalent. This increase in smear negative cases strains already overloaded laboratories and erodes the predictive value of microscopy. For a number of reasons, HIV positive, smear negative pulmonary TB patients have inferior treatment outcomes, including higher mortality rates, compared with HIV positive smear positive pulmonary TB patients and HIV negative TB patients. In the absence of an easily applied, rapid diagnostic test that is more sensitive than AFB smear microscopy, diagnostic algorithms that include a trial of broad spectrum antibiotics have been recommended. These algorithms have been developed through consensus; a sound evidence-base does not yet exist. Most algorithms extend a patient’s evaluation over several weeks, during which time many HIV infected patients may die from undiagnosed TB. Autopsy studies have found disseminated TB in 40 to 54% of HIV infected people in countries with a high burden of HIV and TB. In many of these patients, disseminated TB was undiagnosed prior to death.

An urgent need exists to develop more rapid and accurate TB diagnostic tests, but while such tests are being developed and validated, clinical practice and policy should be modified to improve the diagnosis and management of smear negative pulmonary and extra-pulmonary TB. Speedy diagnosis and treatment of smear negative pulmonary and extra-pulmonary TB is needed, particularly in resource-constrained settings where HIV is prevalent. The optimal usage of available imaging modalities can increase the level of confidence of a diagnosis of tuberculosis in smear negative patients. This paper discusses an approach to the use of imaging in this setting.

MAXIMISING INFORMATION FROM THE CHEST RADIOGRAPH
1. The most useful adjunct to a current chest X-ray is a previous chest X-ray for comparison, which allows the following:
• The ability to determine whether or not lung parenchymal changes on the current film are new or of longstanding.
• If present on the old film, it can be determined whether there has been progression.
• The old film can also serve as a control, particularly for assessing the width of the mediastinum. Mediastinal and hilar lymphadenopathy, without any visible lung parenchymal lesion (the pattern of tuberculosis commonly seen in children) is now recognised as a relatively common presentation in immunocompromised adult patients. In these patients (who are frequently sputum negative), both the hilar and the mediastinal lymphadenopathy may be subtle. However, comparison of the width of the upper mediastinum between the old and new films will often allow an increase in the mediastinal width on the current chest radiograph (indicating the presence of mediastinal lymphadenopathy) to be recognised.

2. Obtaining apical views will often allow lesions which are partially obscured by the clavicle or by ossification of the first costal cartilage to be better assessed.

CT Scan

Although accessibility has in the past been limited, access to CT scanning is increasingly becoming available in South Africa. In countries which are less resource constrained than those in sub-Saharan Africa, CT scanning has become a valuable tool in the diagnosis and evaluation of pulmonary tuberculosis and is regarded as playing an important role in the detection of TB in patients in whom the chest radiograph is normal or inconclusive. The use of CT scanning in the following situations is particularly relevant to the current HIV/TB epidemic, in smear negative patients.

1. Limited CT scan through an upper zone or apical lesion

2. High resolution CT scan. CT scanning has a greater sensitivity for the detection of fine miliary nodulation than chest radiographs and is able to detect miliary tuberculosis that is not visible on a standard chest X-ray. It is well recognised that very fine miliary nodules may not be visible on a standard chest radiograph. (High resolution CT also has the advantage of being far more sensitive than chest X-ray in detecting ground glass opacification, which is a classic finding of PCP.) High resolution CT scans are more expensive than limited CT scans but the fact that they do not require intravenous contrast, increases their affordability.

3. Spiral CT scan of the chest with contrast. The ability of CT scan to accurately demonstrate hilar and mediastinal lymphadenopathy can provide a high level of diagnostic certainty in the diagnosis of intra-thoracic lymphadenopathy. The lymph nodes of tuberculous lymphadenitis demonstrate a characteristic pattern of enhancement, with dense enhancement along the perimeter of the node, and no enhancement of the central portion. When seen, this pattern of lymphadenopathy is virtually diagnostic of tuberculosis. This examination is useful where mediastinal widening is minimal or equivocal. Spiral CT scan with intravenous contrast is however an expensive examination and where there is unequivocal widening of the mediastinum on the chest radiograph, in the presence of strong clinical suspicion of tuberculosis, spiral CT would in most instances, not be cost-effective; despite its substantial diagnostic potential.

It is important to note that patients with both tuberculous lymphadenopathy and miliary tuberculosis are frequently sputum negative. Miliary and disseminated disease are both strongly associated with immunosuppression.

SONAR/ULTRASOUND

1. Sonar examination of the thorax. Sonar is generally of little value in the assessment of parenchymal lung disease and its primary use in the thorax is in the diagnosis and assessment of pleural and pericardial effusions. With pleural effusions, the finding of a lattice like-distribution of fibrin strands within a pleural effusion is virtually diagnostic of tuberculous pleurisy. Using a sub-sternal approach, the pericardium can be routinely assessed as a component that is of indeterminate activity on chest X-ray. The greater sensitivity of CT scanning will often show early cavitation, the presence of clusters of nodules or nodular aggregation that is not recognisable on the chest X-ray. The finding of a tree-in-bud appearance is very strong evidence of active infection. Although the tree-in-bud appearance is not specific for a particular infecting organism, its presence in association with early cavitation or nodulation makes the probability that the infection is due to TB, very high. As this examination requires only a limited number of images through a relatively small area of the lung and does not require intravenous contrast, it is relatively inexpensive.

Figure 1. Intra-abdominal tuberculous lymphadenitis. The typical sonographic appearance of multiple enlarged lymph nodes in the central upper abdominal region due to tuberculous lymphadenitis is shown. [L/n = lymph node; Ao = Aorta]
of the sonar examination of the abdomen and this is
discussed in further detail below.

2. Sonar examination of the abdomen. Sonar examination of
the abdomen can be of immense value in the diagnosis
of disseminated tuberculosis, particularly when the patient
has an unexplained pyrexia. In our hospital and in our
sister hospital (West Vaal Hospital, Orkney), sonar exami-
nation of the abdomen is extensively used for patients
where a diagnosis of tuberculosis is clinically suspected
but where the chest radiograph is normal and the sputum
is smear negative. Evaluation is carried out according to
the method as described by Emby and Hunter, where the
finding of one or more of two criteria (namely abdominal
lymphadenopathy or splenic micro-abscesses) is regarded
as sufficient criteria for a presumptive diagnosis of dissemi-
nated tuberculosis. (A typical pattern of lymphadenopathy,
including the peri-pancreatic region was recognised in
the majority of patients where this finding was positive.
Less commonly there was involvement of the splenic
hilum, which when present, was highly associated with
disseminated TB.) In addition, the finding of a pericardial
effusion greater than 5 mm in width was regarded as
strong presumptive evidence of tuberculous pericarditis.
A pericardial effusion greater than 10 mm in width, in the
absence of any other explanation for the presence of
pericardial fluid, or the presence of fibrin, was regarded
as diagnostic of tuberculous pericarditis. An important
additional observation was that a significant pericardial
effusion may be found in patients where the cardiac density
on the chest radiograph is not enlarged.

In a series of 35 patients examined at our hospital between
October 2009 and September 2010, who were diagnosed
as having disseminated TB on sonar criteria, 25 were sub-
sequently found to be positive for TB on sputum culture and
a further three yielded positive direct smears on repeated
sputum examination. The presence of tuberculosis was thus
confirmed in 28 of the 35 patients giving a correlation between
diagnosis on sonar criteria and laboratory confirmation of TB
of 80%. All patients were started on treatment for tuberculosis
immediately following the sonar diagnosis and were closely
clinically monitored. All 35 patients showed a good response to
the TB treatment. As it can take up to six weeks to obtain culture
results, it is highly likely that deaths would have occurred while
waiting for culture results, had the patients not been started
on treatment following the positive sonar findings. Invasive
investigations such as bone marrow or liver biopsy (with their
associated additional cost), are no longer considered neces-
sary in these patients.

The typical appearance of tuberculous lymphadenitis
and splenic micro-abscesses as demonstrated at sonar are
shown in Figures 1 and 2 respectively. Figure 3 demonstrates
a pericardial effusion with fibrin deposition along the visceral

![Figure 2. Splenic micro-abscesses. Sonar image showing multiple micro-abscesses within the spleen in a case of disseminated tuberculosis.](image-url)
REFERENCES


LESSONS LEARNED

1. Tuberculosis in HIV positive patients is often extra-pulmonary, which makes diagnosis difficult. Diagnosis of pulmonary TB is also challenging as changes on chest X-rays are frequently atypical and there is a higher likelihood that the infection will be smear negative.

2. The optimal usage of available imaging modalities can increase the level of confidence of a diagnosis of tuberculosis in smear negative patients.

3. Comparison of a current chest X-ray with a previous chest X-ray enables the determination of whether lung parenchymal changes on the current film are new or of longstanding, whether there has been progression, and the old film can be a control, particularly for assessing the width of the mediastinum.

4. The use of CT scanning can be particularly relevant to the current HIV/TB epidemic, in smear negative patients.

5. Pericardial and abdominal ultrasound are valuable as supplementary investigations in the diagnosis of suspected extra-pulmonary or disseminated TB.

CONCLUSION

The diagnosis of tuberculosis where sputum examination for acid fast bacilli is negative (smear negative tuberculosis) presents an important challenge in overcoming the current HIV/TB epidemic. As previously noted, smear negative individuals may continue to spread tuberculosis and there is significant mortality in immunocompromised individuals in whom a diagnosis of TB, and hence the commencement of TB treatment, is delayed. Furthermore, the high incidence of silicosis together with the high prevalence of HIV amongst gold miners poses a particular diagnostic dilemma as these patients frequently present with atypical changes on chest X-ray and have a higher prevalence of smear negative TB. The optimal use of imaging modalities, which have the potential to increase the level of diagnostic confidence to a point where commencement of TB treatment becomes justified, is described. As with all patients in whom any form of treatment is commenced, it is essential that the clinical response to treatment is closely monitored. This is especially important when smear negative individuals are started on TB treatment.