The role of abdominal ultrasound in the investigation of suspected extrapulmonary and disseminated tuberculosis

by

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Dedication

This work is dedicated to all the staff at G F Jooste Hospital for their commitment towards improving the lives of their patients.

Abstract

Infection with tuberculosis (TB) is a widespread problem in South Africa, particularly in the Western Cape. Added to this burden, is the increasing prevalence of co-morbid human immunodeficiency virus (HIV) infection. HIV-infected individuals are more likely to have extrapulmonary TB (EPTB), disseminated TB and/or smear-negative TB. These presentations of TB are difficult to diagnose and are associated with an increased mortality.

Prompt diagnosis and appropriate treatment is important in the control of TB. Smear microscopy of appropriate samples can make the diagnosis rapidly, but in smear-negative cases, culture results have to be awaited and they can take up to 8 weeks. This delay may be averted if there are other supportive features of TB.

Aim: To prospectively assess the role of abdominal ultrasound examination in the investigation of patients with suspected tuberculosis.

Objective: The primary objective was to undertake a prospective study in order to determine whether abdominal lymphadenopathy detected at ultrasound examination could be used as an indicator of the presence of active extrapulmonary and/or disseminated TB.

Method: A prospective cross-sectional study including descriptive and analytic components was designed and performed during 2004. Abdominal ultrasound examinations were done sequentially on 300 patients admitted to G F Jooste Hospital, a secondary level hospital in Cape Town.

The entry criterion was a clinical diagnosis of suspected disseminated tuberculosis. The abdominal ultrasound, chest radiography findings, final microbiological and serologic data were recorded and analysed.

Results: After patients with inadequate laboratory specimens for TB were excluded, a final sample size of 267 patients was analysed. The study population was made up of 174 women and 93 men, with a mean age of 36.4 years. Within this sample, 91% were HIV-positive, with a mean CD4 count of 110 cells/μl. Seventy percent of these patients had World Health Organisation (WHO) clinical stage 4 HIV disease.

Of the 267 patients, a final diagnosis of active tuberculosis (by smear, culture, elevated adenosine deaminase or histology) was determined in 67.8% (n= 181) of patients, and 77.3% of those with TB were also HIV positive.

Ultrasonically visible deep lymphadenopathy (peri-pancreatic, peri-portal, para-aortic and/or splenic hilar) with nodes greater than 1 cm in size correlated significantly with active tuberculosis [odds ratio (OR) = 2.79, 95% confidence interval (CI) = 1.56 – 4.99, probability (p) = 0.0001]. Nodes were present in 54.7% of patients diagnosed with active TB (by smear, culture, elevated ADA and histology). The mean abdominal node size in the patients with adenopathy was 15.3 mm.

In addition, the presence of sonographically detected pericardial effusions [OR = 3.54, 95% CI = 1.95 – 6.45, p = 0.000005], ascites [OR = 3.40, 95% CI = 1.71 – 6.83, p = 0.0001] or splenic lesions [OR = 1.89, 95% CI = 1.02 – 3.55, p = 0.030] also increased the likelihood of active TB.

On chest radiography, 90% of cases had detectable pathology. Unilateral consolidation, bronchogenic nodular patterns, pleural effusion and/or thoracic nodes were the commonest findings. Of these, only the presence of thoracic nodes and pleural effusion correlated significantly with active tuberculosis [OR = 2.93, p = 0.0011]. Active TB (by smear, culture, elevated ADA and histology) was diagnosed in 71.6% of abnormal chest films.

Sputum smear diagnosis was only 43% sensitive when compared with culture, highlighting the need for other diagnostic procedures in the workup of patients with suspected disseminated or extrapulmonary TB.

Interpretation: Ultrasound examination of the abdomen is a valuable investigation in the workup of suspected disseminated tuberculosis when smears are negative and accessible sites for aspiration/biopsy are lacking.

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Table of contents

List of tables

List of figures

Glossary of abbreviations

ADA	Adenosine Deaminase
AFB	Acid-fast Bacilli
AIDS	Acquired Immune Deficiency Syndrome
CI	Confidence Interval
CMV	Cytomegalovirus
CNS	Central Nervous System
CRP	C-Reactive Protein
CSF	Cerebrospinal Fluid
CT	Computed Tomography
CXR	Chest X-ray
EPTB	Extrapulmonary Tuberculosis
FNA	Fine Needle Aspiration
HIV	Human Immunodeficiency Virus
IVC	Inferior Vena Cava
MAC	Mycobacterium Avium Complex
MRI	Magnetic Resonance Imaging
MOTT	Mycobacteria other than Tuberculosis
OR	Odds Ratio
p	Probability
PA	Posteroanterior
PCP	Pneumocystis Carinii Pneumonia
PCR	Polymerase Chain Reaction
PGL	Persistent Generalised Lymphadenopathy
TB	Tuberculosis
WHO	World Health Organisation
ZN	Ziehl-Neelson

Chapter 1: Introduction and literature review

1.1 Introduction

Tuberculosis (TB) has been present for millennia and its association with man predates written history. The disease is ubiquitous in developing countries, primarily associated with poverty, malnutrition and overcrowding. The offending pathogen is the bacillus, *Mycobacterium tuberculosis*. It typically causes a pulmonary-acquired infection that can spread to other parts of the body, and may be fatal.

Despite TB having become treatable, curable and preventable over time, it is still a serious health problem worldwide. The TB epidemic today is worse than at any other time in history. Currently, one-third of the world's population is infected and approximately 25 000 people develop active tuberculosis every day.[1, 2] Globally, TB results in 3 million deaths per year, and 95 to 98% of these deaths are occurring in developing countries.[3]

In 2003, the global incidence of TB was growing at approximately 0.4% per year, but was faster in sub-Saharan Africa.[2] Table 1.1 demonstrates the significant increase in the number of tuberculosis cases in South Africa over a 14-year period: in 2004, 36% of new pulmonary cases and 45% of new and relapsed cases were sputum smear-positive; 15% of new and relapsed cases were extrapulmonary.[2] The TB case fatality rate in South Africa for 2004 was 79 per 100000, a rate which is twice as high as the global TB fatality average of 32 per 100000.[2]

TABLE 1.1: ESTIMATED BURDEN OF TUBERCULOSIS IN SOUTH AFRICA : 1990 AND 2004 [2]

	Incidence of all forms of TB	Incidence of smear-positive TB	Prevalence of all forms of TB	Mortality from all forms of TB
1990*	98 944	42 204	271 070	32 711
2004*	339 078	138 099	316 260	63 529
2004 HIV + **	144 857	50 700	72 428	36 884

*Incidence, prevalence and mortality estimates include patients with HIV. Estimates labelled HIV+ ** are for HIV-positive adults (aged 15-49 years).

The effect of the human immunodeficiency virus (HIV) pandemic on tuberculosis is overwhelmingly significant. According to the 2006 United Nations report, an estimated 38.6 million people worldwide were living with HIV at the end of 2005.[4, 5] The greatest concentration of HIV infection was in sub-Saharan Africa and the Acquired Immune Deficiency Syndrome (AIDS) epidemic in South Africa was marked as one of the worst: in 2005 there were approximately 5.5 million people infected with HIV in South Africa.[5, 6, 7]

The lifetime risk of developing active TB if co-infected with TB/HIV is approximately 60% (compared to 10% in patients infected with TB alone).[8, 9] TB has been found to precede the diagnosis of AIDS in 67% of patients.[1] HIV-infected individuals are also more likely to experience a recurrence of TB after completion of treatment, and more commonly present with extrapulmonary tuberculosis (EPTB), disseminated disease and smear-negative TB. EPTB occurs in 15% of non-HIV patients and in up to 70% of HIV-positive patients.[10, 11, 12] TB may also speed the progression of HIV infection to AIDS in dually infected individuals.[9] In 2005, the World Health Organisation (WHO) estimated the TB/HIV co-infection rate in South Africa at 250 per 100 000 population.[2]

The principal gold standard in the diagnosis of TB is a positive culture of the bacterium, but this can take up to 8 weeks. Earlier confirmation is possible via smear microscopy, where the acid-fast TB bacilli are demonstrated by specific staining on appropriate samples. The problem rests with smear-negative results. In such cases curative treatment may have to be delayed while awaiting culture results; morbidity and mortality may be increased and disease transmission and progression could continue.[13] In addition, EPTB is difficult to diagnose and invasive procedures may be required to obtain adequate specimens.[14]

Based on this background, the current study evaluated the role of abdominal ultrasound in the diagnosis of tuberculosis and its impact on clinical practice at G F Jooste Hospital. The study objectives are outlined as follows:

The primary objective of this project was to undertake a prospective study in order to determine whether ultrasonically detected abdominal lymphadenopathy could be used as an indicator of the presence of active disseminated tuberculosis or EPTB.

Subsidiary objectives were: -

1. To document and evaluate the role of abnormal abdominal ultrasound findings besides lymphadenopathy e.g. splenic micro-abscesses and ascites
2. To correlate tuberculosis culture results of sputa, urine, peripheral node fine needle aspiration (FNA) etc. with the abdominal ultrasound findings
3. To review the chest X-ray (CXR) findings and their relevance with respect to
    a. suspected mediastinal or hilar adenopathy
    b. air-space disease
    c. pleural disease
    d. enlarged cardiac shadow
4. To correlate the CXR findings with the abdominal ultrasound findings

G F Jooste Hospital, where the current study was conducted, is a secondary level health care institute. It serves sub-districts in Cape Town with high unemployment and low-income levels and a high burden of TB/HIV co-infection.[15, 16]

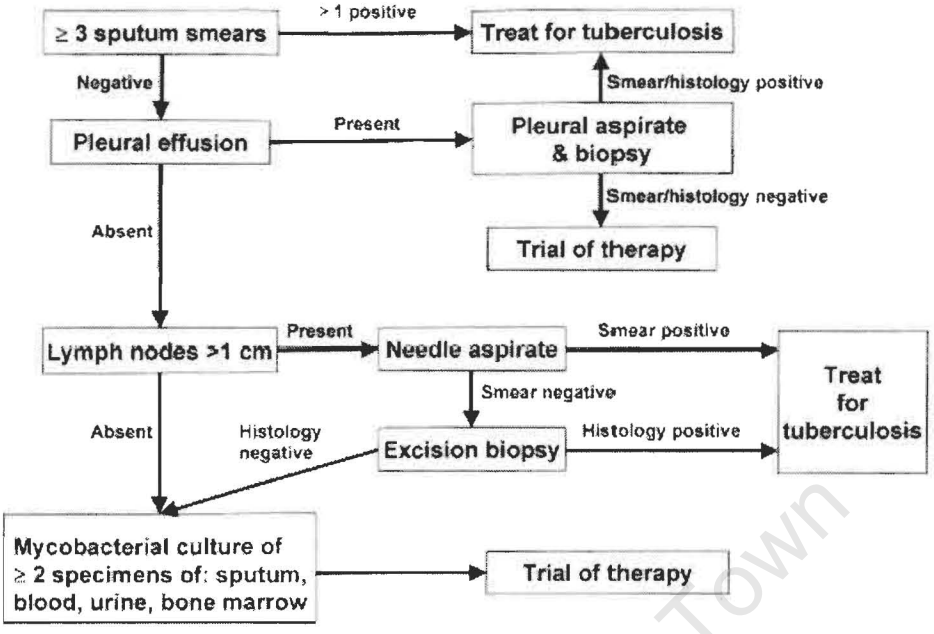
The adverse consequences of diagnostic delay in establishing TB in the face of smear-negative patients are clearly documented.[17,18] A prior study at G F Jooste found a mean delay of 70 days in establishing the diagnosis and commencing treatment of TB patients requiring admission.[19] Consequently, a policy at G F Jooste Hospital was formulated to accelerate the initiation of tuberculosis therapy in patients with suspected disseminated tuberculosis. In the presence of peripheral or deep (thoracic or abdominal) lymphadenopathy where a diagnosis of disseminated

tuberculosis is clinically highly likely, anti-tuberculous treatment is commenced empirically, based on the opinion of the consultant physician. The final decision to complete 6 months of therapy is deferred until culture results become available (typically 8 weeks later), using markers such as weight, C-reactive protein (CRP) and haemoglobin to influence the clinician's final decision if culture results are negative. Although this management plan is also advised in the South African Tuberculosis guidelines,[20] the role of sonographically detected enlarged abdominal nodes has not yet been scientifically validated. In addition, the significance of other abnormal abdominal ultrasound findings (for example hepatomegaly, splenomegaly, ascites, splenic lesions) in the setting of EPTB has not been extensively investigated.

Supporting this, work by Wilson[21] has suggested that in the setting of smear-negative disease, the diagnosis of pulmonary TB and EPTB can be accelerated if clinical case definition criteria are expanded and therapeutic trials are used, with assessments of the treatment responses at 8 weeks. In doing so, he found that the positive predictive value for the most common case definitions ranged from 89% to 96%, and that there were significant improvements in treatment responses in the subjects with subsequently confirmed TB [probability (p) less than 0.001]. Similarly, Harries et al also suggested a trial of therapy in situations where diagnostic facilities are limited.[22]

Hudson and Wood in their study on 141 patients at another Cape Town hospital noted that alternative methods of diagnosis that have a high diagnostic yield, such as lymph node and pleural biopsies, were being under-utilised.[23] They also noted that costs could be reduced if repeated smear examinations were used, rather than repeated cultures, since the cumulative yield from repeated smears was higher. The following is their proposed diagnostic algorithm in HIV patients with suspected tuberculosis. (Figure 1.1)

Figure 1.1: Algorithm for the diagnosis of tuberculosis [23]



Abdominal ultrasound may facilitate early treatment without having to wait 6 to 8 weeks for culture results.

The aim of the current study is therefore to prospectively assess the role of abdominal ultrasound examination in the investigation of patients with suspected disseminated or extrapulmonary smear-negative TB.

Specifically the study aims to:

1. document abnormal abdominal ultrasound findings in patients with suspected EPTB or disseminated TB, including hepatomegaly, splenomegaly, splenic micro-abscesses, lymphadenopathy, ascites and pericardial effusions;
2. correlate these abnormal ultrasound findings with laboratory evidence of active TB, including positive smears [Ziehl-Neelson (ZN) stained], positive TB cultures and elevated adenosine deaminase (ADA) levels obtained from

samples of sputum, urine, FNA of peripheral lymph nodes, cerebrospinal fluid (CSF), ascitic fluid, pleural fluid or pericardial fluid; and,

3. correlate the abnormal ultrasound findings with abnormal CXR findings, including nodules, air-space consolidation and pleural effusions in patients with laboratory evidence of active TB.

In this chapter, a brief overview of the literature relevant to the primary aims of the study is given. The overview focuses mainly on the radiological investigation of TB and laboratory diagnosis of pulmonary and EPTB. Chapter 2 describes the research methods and data analysis. The study results are described in Chapter 3 and chapter 4 follows with a discussion of the results. The concluding comments, including a brief discussion of the limitations of the study and further research needed, are presented in chapter 5.

1.2 Pathogenesis of tuberculosis

Infection results when the host inhales airborne droplets that contain viable tuberculous bacilli. The bacterium then induces an immune response from the host that attempts to control the infection. If this response is adequate, immunity develops and granulomatous lesions or tuberculomata form.[24, 25] Healing occurs by caseous necrosis, fibrosis and/or dystrophic calcification, but bacilli can remain viable and dormant within these lesions in the host.[25, 26]

1.2.1 Primary tuberculosis

This initial infection is also known as primary TB. It is often localised to the mid and lower zones of the lungs, accompanied by hilar and paratracheal lymphadenopathy (Ghon complex). Pleural involvement occurs as a hypersensitivity response to

tuberculoprotein.[24, 27] The majority of cases heal spontaneously, but with impaired immunity, clinical disease can develop. If this occurs, the initial lesion enlarges and may form cavities, or causes collapse, bronchial obstruction, and haematogenous (miliary TB) or extrapulmonary dissemination.[25, 27]

1.2.2 Post-primary tuberculosis

Post-primary TB is also known as secondary TB, adult-type TB or reactivation TB. It results from endogenous reactivation of dormant infection, or as a result of exogenous re-infection. Although later progression of latent disease can occur at any seeded site, there is a predilection for the upper lung zones, where a higher oxygen tension exists and lymphatic drainage is impaired. Pleural effusions can result from rupture of a cavity or an adjacent parenchymal focus. Consequently, a large number of organisms are commonly present in the fluid.[24, 25, 27]

1.2.3 Miliary or disseminated tuberculosis

Miliary spread can occur during primary or post-primary disease, resulting from spread of bacilli via erosion into a blood or lymph vessel. These viable bacilli seed into the capillary beds of multiple organs, where they may grow.[27]

The term 'disseminated TB' refers to TB that involves multiple body systems. It results from acute haematogenous or lymphatic spread of TB. By definition, all miliary tuberculosis is disseminated, but not all disseminated TB is miliary.[28]

1.2.4 Extrapulmonary tuberculosis

Extrapulmonary tuberculosis is defined as TB of organs other than the lungs and results from lympho-haematogenous dissemination of the tubercle bacilli during primary tuberculosis infection. The bacilli can seed to solid organs or serosal surfaces, with spread of disease to adjacent structures. The disease tends to target

highly vascular areas such as lymph nodes, meninges, spleen, kidneys, spine and the growing ends of bones. Additional sites of involvement include the pleura, pericardium, peritoneum, liver, gastrointestinal tract, genitourinary tract and skin. The gastrointestinal tract can also be directly involved through ingestion of bacilli, usually as a result of swallowing organisms coughed up from cavitatory pulmonary disease.[11, 17]

1.2.4.1 Tuberculous lymphadenitis

This is the commonest extrapulmonary form of tuberculosis and occurs in approximately one-third of HIV-infected patients.[17]

Nodal sizes range between 2 to 3 cm.[29] The nodes are classically discrete, firm and painless, but inflammation and pain may also be present. In time, the nodes develop into a firm matted mass, which may become fluctuant and drain spontaneously if left untreated. They can also progress into a nodal abscess, which can spontaneously perforate and discharge onto the skin via a fistula, or into the mediastinum, bronchus or pleural space.[30 - 33]

The nodes usually occur in the cervical and supraclavicular regions but any lymph node group can be involved.[29, 30] They have a predilection for the mesenteric, peri-pancreatic, peri-portal and retro-peritoneal locations, and often surround the mesenteric vessels [29, 30, 31]

In non-HIV-infected patients, metastases, Whipples disease and Crohn's need to be considered as causes for lymphadenopathy.[29]

1.2.4.2 Abdominal tuberculosis

Abdominal tuberculosis may involve the gastrointestinal tract, peritoneum, mesenteric lymph nodes or genitourinary tract. Peritoneal tuberculosis is the

commonest form, more frequent in HIV infection. Three types are described: the wet type is distinguished by a large amount of free or loculated fluid; the fibrotic and dry types are far less frequent.[30, 34]

Enteric tuberculosis can affect any portion of the gastrointestinal tract, but ileocaecal TB involvement occurs in 80 to 90% of abdominal TB. The ileocaecal valve enlarges, the caecal wall thickens and shallow linear or stellate ulcers form. Fistulae and sinus tracts are rare.[29, 34]

The liver, spleen and adrenal glands are usually only affected by miliary dissemination.[11]

1.2.4.3 Genitourinary tuberculosis

Genitourinary tuberculosis can affect any part of the urinary tract, and accounts for approximately 15% of all EPTB.[30]

1.2.4.4 Pleural tuberculosis

Tuberculous pleuritis is the second commonest form of EPTB after lymph node TB.[32] In HIV-infected individuals, tuberculous pleuritis is more often seen in advanced disease.[27]

1.2.4.5 Cardiovascular tuberculosis

Pericardial involvement is the most common manifestation of cardiovascular TB. Fibrin strands develop, and the visceral or parietal pericardium becomes thickened.[35]

1.2.4.6 Central nervous system (CNS) tuberculosis

CNS TB accounts for 5% of extrapulmonary disease, often affecting young children and HIV-infected individuals.[29]

1.3 Radiology

The range of radiographic findings in tuberculosis varies significantly, depending on whether the infection is primary or post-primary, on the patient's age and most importantly, on the individual's level of immunity.[36] Extensive radiological changes can be present with minimal clinical symptoms or signs; conversely, TB can also present with minimal or no changes radiographically.[27, 37]

Chest radiography is used as an adjunct to laboratory investigations. Although chest radiography can be suggestive of tuberculosis, treatment should preferably only be commenced once there is a positive smear or culture.

1.3.1 Chest radiography

1.3.1.1 Primary tuberculosis

Lymphadenopathy is the radiologic hallmark of primary TB, typically located in the right paratracheal and hilar regions.[25, 38]

In addition to the nodes, parenchymal opacities also occur. Commonly this may be in the form of homogeneous, segmental or lobar consolidation, but multi-focal, patchy, linear, nodular and mass-like forms have all been described.[25, 39]

Pleural effusion is an uncommon manifestation of primary TB, usually observed in association with parenchymal and nodal abnormalities. It tends to be unilateral and located on the same side as the parenchymal changes, but bilateral effusions can occur.[11, 25]

1.3.1.2 Post-primary tuberculosis

Parenchymal opacities in the apical and posterior segments of the upper lobes and the superior segment of the lower lobes, often with associated cavitation, are the typical radiographic manifestations of post-primary TB. Usually more than one segment is affected and atypical sites may be involved.[37, 39, 40]

The opacities are heterogeneous and ill-defined and may have nodular and linear components. Solitary or multiple tuberculomata can also occur, often with calcification and adjacent 'satellite' nodules. Cavitation is evident in 40% to 45% of cases, with varying wall thicknesses.[25, 39, 40]

Bronchogenic spread of disease occurs when an area of caseous necrosis liquefies and communicates with the bronchial tree. It is seen in approximately 20% of cases, manifesting as multiple, ill-defined, 5 to 10 mm nodules in a segmental or lobar distribution.[39]

Hilar and mediastinal lymphadenopathy are not common in post-primary TB, occurring in only 5% of cases. Tuberculous pleural effusions occur in up to 19% of cases, usually unilateral and typically loculated.[38, 40]

Evidence of previous tuberculosis can take the form of calcified nodes or nodules and fibrotic and/or cystic changes.[39] As these findings can also occur in active disease, they are not specific for treated disease.

1.3.1.3 Miliary tuberculosis

On CXR, there are innumerable, 0.5 to 2 mm non-calcified nodules scattered diffusely throughout both lungs. In 25 to 40%, the initial radiograph may be normal, with the miliary lesions only becoming visible 3 – 6 weeks after haematogenous dissemination.[25, 27]

1.3.2 Abdominal ultrasound

A constellation of radiological findings is often more helpful than a single feature.

Ultrasound features of abdominal tuberculosis include:

1. Enlarged conglomerate nodal masses, typically heterogeneous and predominantly hypoechoic.[31]
2. Increased "through-transmission" of ultrasound by the abdominal nodal mass is highly suggestive of caseating necrosis, but is not specific.
3. With the Duplex Doppler ultrasound technique, tuberculous nodes can be seen to display abnormal internal vascularity. Necrotic nodes lack any internal Doppler flow.[41, 42]
4. Calcifications within the lymph nodes are seen as "dirty" shadows.
5. Other findings associated with abdominal tuberculosis include bowel wall thickening [especially in the ileocaecal junction], peritoneal nodules, mesenteric thickening and clear or complex "dirty" ascites.
6. Visceral involvement may be seen as organomegaly or as multiple small abscesses in solid organs, particularly within the spleen and liver.[31]

1.3.3 Other modalities

Pulmonary TB

Computed tomography (CT) and magnetic resonance imaging (MRI) of the chest can be performed in patients with suspected tuberculosis.[32, 43] Tuberculous nodes

may be differentiated from lymphoma at MRI.[44] High-resolution CT of the chest is useful when radiographs are normal.

Abdominal TB

Other diseases that mimic abdominal TB include Crohn's disease, intestinal lymphoma and disseminated Kaposi's sarcoma. CT and MRI can be helpful in differentiating these conditions. Ascites is easily recognized at CT. Associated omental and mesenteric thickening may be noted. Peritoneal involvement in carcinomatosis, mesothelioma and non-tuberculous peritonitis can have similar appearances.[29, 30, 34]

1.4 Tuberculosis in HIV-infected individuals

Almost 70% of AIDS patients suffer some form of respiratory disease during the course of their illness.[45] In HIV infection, the level of immunity determines the type of infection that occurs. With CD4 levels above 500 cells/μl, the more virulent organisms such as bacterial pneumonias and TB predominate.[45] When the CD4 count drops below 200 cells/μl, Pneumocystis carinii pneumonia (PCP) and disseminated TB infection are common, and in the very advanced stages (CD4 counts below 50 cells/μl), patients are at high risk for Mycobacterium avium complex (MAC), cytomegalovirus (CMV) and fungal infections, as well as AIDS-related lymphoma and Kaposi's sarcoma, all potentially fatal.[45 - 47]

The radiologic manifestations of tuberculosis are also immune dependent. With intact cellular immune function, the radiographic findings of pulmonary TB are similar to those of non HIV-infected individuals. However, at severe levels of immune suppression, atypical manifestations are more frequent: normal radiographs are found in 10% to 20%; the features of primary tuberculosis

predominate regardless of a prior TB exposure; parenchymal infiltrates are typically basal; cavitation is less frequent; and miliary dissemination is common.[36, 45 - 48]

Radiologically, other bacterial infections cannot be differentiated from tuberculosis. Mycobacteria other than tuberculosis (MOTT) infections can present with a normal CXR in up to 14% of cases, but the typical findings are an interstitial infiltrate with adenopathy.[49] Cryptococcal infection is often disseminated and, consequently, concomitant meningitis is present in up to 86% of cases. Radiographic findings of cryptococcosis include a coarse, asymmetric, nodular or interstitial infiltrate, alveolar consolidation or a normal film.[49, 50] Based on radiological criteria alone, miliary tuberculosis cannot be distinguished from pulmonary cryptococcosis and other causes of a miliary pattern.[45, 49]

Tuberculous lymphadenopathy must be differentiated from persistent generalised lymphadenopathy (PGL), which occurs in up to 80% of HIV-infected individuals. PGL occurs in individuals with early disease and does not require any treatment. These nodes are symmetrical, non-tender and less than 2 cm in size.[10] With progressive immunosuppression, PGL lymphadenopathy tends to regress. Thus the development of any new nodes in advanced HIV infection usually suggests another pathological process such as TB or lymphoma.[51]

Other causes for enlarged nodes in the HIV population include lymphoma [non-Hodgkin's], Kaposi's sarcoma, MAC and CMV infection. Lymphoma tends to affect the lower abdominal nodes more frequently. Also mesenteric nodal involvement occurs more frequently in disseminated (80%) and non-disseminated TB (52%), than in patients with untreated non-Hodgkin disease (6%).[52]

According to several studies, intra-abdominal TB adenopathy and visceral lesions are more common in HIV-infected patients, whilst omental thickening and ascites occur more frequently in non-HIV infected patients.[29, 31]

The differential diagnosis for splenic abscesses includes bacterial and fungal infections, including candida. Leukaemia and lymphoma are non-infective causes.[53] In hepatosplenic AIDS-related Kaposi's sarcoma, small hyperechoic nodules may be seen in the liver and the spleen on ultrasound.[54]

In CNS disease, alternative conditions to consider in HIV infection would be cryptococcal meningitis, toxoplasmosis and CNS lymphoma.[29]

1.5 Laboratory diagnosis of tuberculosis

The diagnosis of active tuberculosis is made on clinical, microbiological and radiological grounds, but the gold standard is a positive culture of the *Mycobacterium tuberculosis* bacterium.

Active EPTB is diagnosed in the presence of at least one culture-positive specimen from the extrapulmonary site, histological evidence, or strong clinical evidence.[14, 55]

The steps towards diagnosing TB are the same in HIV-infected and immune-competent individuals, but due to the defective immune response in co-infected patients, the standard diagnostic tests for tuberculosis are less valuable.[9]

1.5.1 Types of samples collected for laboratory investigation

Specimens are collected depending on the site or sites of involvement. Some sample types are displayed in Table 1.2.

TABLE 1.2: TYPES OF SAMPLES COLLECTED	
SPUTUM	Early morning specimens with the sample originating from the tracheo-bronchial tree and not the mouth are crucial.[10] Sputum production can be promoted through saline nebulisation.
GASTRIC WASHINGS	A nasogastric tube is used to obtain early morning gastric contents (swallowed sputum).
URINE	Mid-stream early morning specimens are collected.
CEREBRO-SPINAL FLUID	Fluid is acquired by lumbar puncture.
PLEURAL, PERICARDIAL AND ASCITIC FLUID	Samples are collected by aspiration, either blindly or with ultrasound guidance.
FINE NEEDLE ASPIRATES AND BIOPSY SAMPLES	Palpable nodes greater than 1 cm in diameter are amenable to aspiration with large bore needles. Deep thoracic and abdominal nodes, or focal lesions in solid organs, are sampled with ultrasound or CT guidance or surgically.
BONE MARROW	Core biopsies can be obtained from the iliac bone or other sites.

1.5.2 Tests performed

1.5.2.1 Smears - sputum

Sputum smear microscopy is the quickest method of diagnosing pulmonary TB. Slide specimens are prepared, stained with the specific dye using the ZN method, and microscopically examined for the characteristic acid-fast rod-shaped bacilli (AFB). This test can be performed in most laboratories and plays a pivotal role in most TB control programmes. In HIV-infected patients with early disease (CD4> 200 cells/μl), AFBs are usually detectable on sputum samples. However, in advanced disease, the sensitivity and specificity of sputum-microscopy is poor.[9] In addition, discrimination from non-tuberculous pathogenic mycobacteria (also AFBs) is not possible by microscopy alone.[56 - 58]

Approximately 5,000 to 10,000 mycobacteria/ml are necessary in a sputum sample for routine microscopic detection of acid-fast bacteria. The sputum is AFB-positive in approximately 5 percent of cases where no infiltrates are visible on CXR.[33]

Smears – other

Examination for AFBs can also be performed on other samples, including FNA specimens, bronchoalveolar lavage material, biopsy cores, serous fluid, CSF and urine.

Fine needle aspiration is more consistent in patients with HIV because of their higher mycobacterial burden.[11, 58]

1.5.2.2 Culture

Culture is the gold standard, central to the confirmation and identification of the specific mycobacterium species. It is also required for drug susceptibility testing. Microbiological tests using liquid (2-4 weeks) or solid (3-5 weeks) media can be used. The bacillus is identified based on its morphology, growth and biochemical characteristics. A culture will be considered "negative" only if no bacteria are identified after 6 to 8 weeks. Incidentally, non-tuberculous mycobacteria grow much faster than *M tuberculosis* and are often identified within two weeks.[10, 22]

Initial negative smear specimens can produce positive cultures later.[22] Almost 50% of all patients with culture-positive pulmonary tuberculosis have no detectable AFBs on examination of three consecutive sputum samples.[33]

1.5.2.3 Histology

In active TB, histology reveals granulomatous caseous necrosis and giant cells, and may show AFBs. Since CD4+ T-lymphocytes are required for granuloma

formation, these features are usually absent in advanced stage HIV-infected patients.[33]

Pleural, pericardial and peritoneal biopsies often yield a definitive diagnosis more frequently than serous fluid alone.[11, 58]

1.5.2.4 Adenosine Deaminase levels and biochemistry of fluid samples

The ADA levels in serous fluid from the pleural, pericardial and peritoneal spaces can be determined. Pleural, pericardial and ascitic fluid levels greater than 30U/l are suggestive of tuberculosis. However, low or normal values may not have a high negative predictive value in countries with an increased TB prevalence.[11, 56]

The aspirates are usually exudative, lymphocyte predominant and have protein levels greater than 30g/L.[10, 11] A diagnostic tap of tuberculous ascites typically reveals straw-coloured or bloodstained fluid.

Cerebrospinal fluid findings typical of tuberculous meningitis include elevated lymphocyte counts, increased protein and decreased glucose levels. CSF ADA levels over 6 U/l are supportive, but non-specific, as this could occur with either tuberculous or cryptococcal meningitis.[11, 55, 58]

1.5.2.5 Other investigations

Using rapid gene probes, polymerase chain reaction (PCR) testing is possible. The sensitivities and specificities for different specimens vary significantly.[11]

Table 1.3 displays the various tests performed and the diagnostic yields from some of these investigations.

TABLE 1.3: TESTS PERFORMED

SAMPLE	DIAGNOSTIC YIELD	ZN SMEAR	CULTURE	ADA	HISTO-LOGY
SPUTUM	Direct sputum smear microscopy: sensitivities 25 to 65%, specificity 98%; sensitivities improve with serial examinations. Culture increases the number of diagnosed TB cases by 30 to 50%.[59]	✓	✓		
URINE	In genitourinary TB, positive culture of the *Mycobacterium tuberculosis* yields the diagnosis in 90% of cases.[11]	✓	✓		
CEREBRO-SPINAL FLUID	The yield of AFBs in CSF is in the range of 10 to 90%.[11, 60] CSF cultures are positive in 45 to 90%.[11]	✓	✓	✓	
PLEURAL, PERICARDIAL AND ASCITIC FLUID	The yield of positive pleural fluid culture is 20 to 40%. Smears and cultures are usually positive in tuberculous empyema, where a large number of bacilli are present.[10, 11, 25]	✓	✓	✓	
FINE NEEDLE ASPIRATES AND BIOPSY SAMPLES	In tuberculous lymph nodes, AFBs are seen in 50% of cases.[57] The yield from pleural biopsies is in the range of 65 to 70%.[25] Peritoneal biopsy is diagnostic in over 90%.[58]	✓	✓		✓
BONE MARROW	Bacilli are often identified in the bone marrow in cases of miliary TB.[28]	✓	✓		✓

Chapter 2: Methods

2.1 Study design

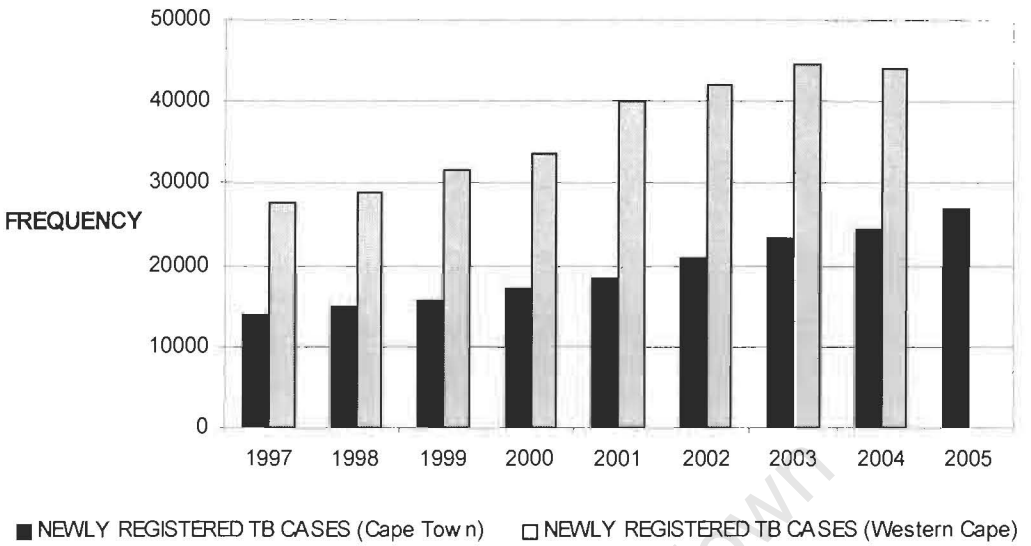
A prospective cross-sectional study design was used to determine which abdominal ultrasound markers were of value in patients with proven tuberculosis. The study included both descriptive and analytic components.

2.2 Study participants

G F Jooste Hospital, a 200-bed acute care hospital, located 18km from central Cape Town, serves approximately 1.3 million of the Cape Town Metropole population of 3.4 million people.[61] The Western Cape has the highest population rate of TB in South Africa, 810 cases per 100 000 population (2003).[62] Recent data indicate that the frequency of TB is increasing further.[63] (see Figure 2.1) Over the last 7 years, the total TB caseload has increased by 66% in Cape Town. In 2005, there were 25 000 people with active TB in Cape Town and two thirds of these were co-infected with HIV.[64] The high burden sub-districts were Khayelitsha, Nyanga and Oostenberg.[16]

In 2002/2003, HIV and/or AIDS accounted for the greatest number of all deaths in Cape Town, with tuberculosis as the third commonest cause after ischaemic heart disease. Mortality figures from sub-districts have revealed that deaths from TB and HIV were highest in Khayelitsha and Nyanga, both of which are areas served by G F Jooste Hospital.[61]

Figure 2.1: Number of newly registered TB cases in Cape Town and in the Western Cape from 1997 to 2005 [63]



Given this situation, G F Jooste Hospital admits a significant number of acutely ill new TB patients every month. A survey in 2003 indicated that the average number of medical admissions per month amounted to 550 patients. Thirty percent of these patients had a diagnosis of TB at outcome and up to 40% had advanced HIV infection i.e. WHO clinical stage 3 or 4.[65] Up to 56 inpatient HIV-related deaths occurred monthly, 57% of which are due to TB.[13]

Based on the survey data, approximately 1500 admissions were expected over a three-month period, with at least 30%, i.e. 450, of these likely to be investigated for disseminated tuberculosis. A sample size of 306 was calculated using a 95% confidence interval and an estimated TB positivity rate of 15% (based on previous non-published audits), with a 4% margin of error.

The study was performed on 300 consecutive patients admitted to the medical wards at G F Jooste Hospital (during August 2004 to October 2004) with a clinical diagnosis of suspected disseminated tuberculosis. Suspected disseminated tuberculosis was defined as TB in any two extrapulmonary sites of tuberculosis e.g. lymph nodes, pericardium, peritoneum, nervous system, etc.

Investigations included an abdominal ultrasound, CXR, prospective data capture of selected clinical parameters, as well as tests for tuberculosis, including ZN stains and culture of samples, fluid ADA and CSF evaluation.

2.3 Ultrasound examination of the abdomen

All of the study subjects underwent an abdominal ultrasound scan with a Toshiba Eccocee machine, using a 3.5 to 5.0 MHz convex probe, as well as a 7.5 MHz linear probe where indicated.

Routine abdominal ultrasound scans were performed. Scans were obtained in deep inspiration in co-operative patients. The size of the right lobe of liver was measured craniocaudally in the mid-clavicular line; an upper limit of 15cm was used to define right hepatic enlargement.[66, 67] The pericardium was assessed through the epigastrium or intercostally in the left parasternal region for the presence of fluid (any fluid more than 5mm was documented), pericardial thickening (greater than 2mm) and pericardial stranding.

The gallbladder, pancreas and bile ducts were assessed in the usual manner. The spleen was examined for size (a midclavicular craniocaudal dimension of greater then 12cm was defined as splenomegaly)[67] and any focal lesions or abscesses. The 7.5 MHz linear probe was used for improved resolution as required. The kidneys were evaluated for renal size (greater than 12.5cm defined as enlarged) and renal echogenicity, in addition to structural abnormalities. Nodes were actively sought in the para-aortic, peri-pancreatic, peri-portal, splenic hilar, mesenteric and inguinal regions. Nodes greater than 10mm were considered significant and their location was documented, in addition to their appearances and the minimum and maximum nodal dimensions, measured in the short axis diameter. The presence of

ascites and pleural effusions were noted, as was any significant small bowel wall thickening over 3mm.

2.4 Chest radiograph review

To avoid any bias, two radiologists reviewed the patients' chest radiographs independently. The CXR's were reviewed systematically, evaluating for cardiomegaly, thoracic nodes, air-space disease and pleural disease. Parenchymal involvement was categorised as focal or diffuse and location was noted as right or left and lobar or zonal. Any nodular patterns were defined according to nodule sizes. A miliary pattern required 0.5 to 2mm nodules, small nodules were 2 to 5mm and bronchogenic pattern for opacifications over 5mm; any distortion, fibrosis, cavitation and bronchiectasis were also recorded.

2.5 Laboratory investigations

At the discretion of the supervising clinician(s), microbiological samples, including sputum, urine, serous fluid and CSF were sent to the laboratory for tuberculosis microscopy and culture. The principal investigator captured these laboratory results as they became available.

2.6 Ethical considerations

Ethics approval was obtained from The University of Cape Town's Health Sciences Research Ethics Committee. (ref 279/2004 – Appendix 1). Permission was also

requested and obtained from the Clinical Executive of G F Jooste Hospital. (Appendix 2)

Informed consent was not considered to be required as the study was designed in order to validate current clinical practice in the Department of Medicine at G F Jooste Hospital.

Routine HIV testing did not form part of the study protocol. Similarly, the CXR and all laboratory tests performed formed part of the routine clinical work-up of patients with suspected tuberculosis at G F Jooste Hospital. All tests were requested at the discretion of the clinician(s). No additional tests were performed.

Confidentiality and anonymity were strictly respected at all times. All of the recorded personal and clinical patient details were kept confidential throughout the investigations and will remain undisclosed. The collated data was correlated and described independently, using numerical codes only. The published information is not traceable to the individual patients involved in the project.

2.7 Data capture and analysis

The principal investigator conducted a review of the patients' clinical records to capture relevant data (see data capture form at the end of the document – Appendix 3). A pilot study (n = 25) was performed prior to initiating the main study to evaluate the applicability of the draft data capture sheet and to determine the duration of time required for the ultrasound examination.

Data from the ultrasound findings, clinical records, radiographic findings and laboratory investigations was collected and entered into an Access database. (Table 2.1) The primary cohort was then stratified according to the various outcome

measures. The data was extracted from the database onto an Excel spreadsheet and analyzed using STATA (StataCorp. 2001. Stata Statistical Software: release 7.0 College Station, TX). Frequency and two-by-two tables were generated. Odds ratios (OR) and 95% confidence intervals (CI) were calculated, and Chi-squared and Fisher's exact tests were used for comparing proportions. A probability-value (p) of less than or equal to 0.05 was considered significant. A logistic regression analysis, using a model building technique, was performed to determine which of the ultrasound variables predicted TB infection.

TABLE 2.1: OUTCOME MEASURES

ABDOMINAL ULTRASOUND	Abdominal lymphadenopathy • Location : retroperitoneal or mesenteric • Node size • Nodal appearance Ascites Pleural effusions Pericardial effusions Hepatic abnormalities Splenic abnormalities Pancreatic abnormalities Abdominal abscess or collection
CHEST RADIOGRAPH	Cardiac size and configuration Air-space disease Mediastinal lymphadenopathy Pleural effusions
CLINICAL RECORDS	Peripheral lymphadenopthy HIV status, if known WHO clinical HIV stage (Appendix 4[68])
LABORATORY*	Sputum TB smear and culture Urine TB smear and culture Peripheral node FNA, TB smear and TB culture Bone marrow histology and TB culture Ascitic fluid ADA and TB culture Pleural fluid ADA and TB culture Pleural biopsy TB culture and histology CSF TB culture

* Not all tests were performed in all subjects. Tests were advised at the discretion of the clinician managing the patient.

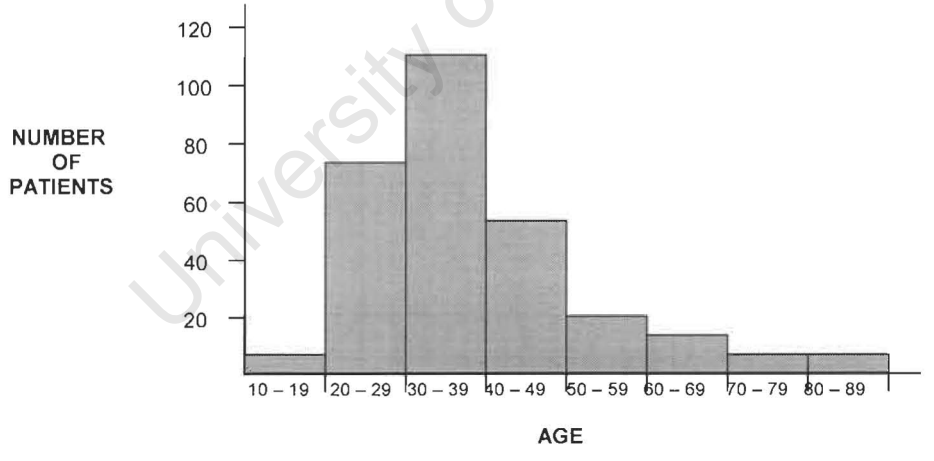
Chapter 3: Results

A final study population of 300 patients was obtained over the three-month period. Only 267 of the 300 patients (89%) had adequate laboratory specimens for the evaluation of active TB. The 33 patients with inadequate samples were therefore excluded from this analysis. (The statistical data is displayed in Appendix 7)

3.1 Patient demographics

Patients who presented with suspected tuberculosis were aged between 15 and 86 years, with a mean age (± standard deviation) of 36.4 years (± 10.8 years). The frequency of patients in each age group is displayed in Figure 3.1. Most patients were between the ages of 20 and 49. A total of 174 (65.2%) were females.

Figure 3.1: Histogram of age distribution of patient cohort



3.1.1 HIV status

The HIV status was known in 221 (82.7%) patients and of these, 201 (91%) were HIV-positive. Twenty-eight percent (28.4%) of the HIV-positive sample was aged

between 20 and 29 years, 46.8% between 30 and 39 years and 18.4% between 40 and 49 years.

Thirty percent of the HIV-positive patients were classified as WHO clinical stage 3 and 70% as WHO clinical stage 4. Active TB (diagnosed by smear, culture, elevated ADA or histology) was present in 140 HIV-positive patients and 11 HIV-negative patients; the difference was not statistically significant. [OR = 1.88, 95% CI = 0.67 – 5.20, p = 0.179].

3.2 Clinical features

Palpable peripheral lymphadenopathy (nodes 1cm or greater in size) was present in 80 patients, of whom 87.5% had cervical nodes, 28.8% axillary nodes and 7.5% inguinal nodes. Seventy-four percent (74.3%) of patients with cervical nodes and 82.6% with axillary nodes were diagnosed with active TB (by smear, culture, elevated ADA or histology). The correlations were not statistically significant.

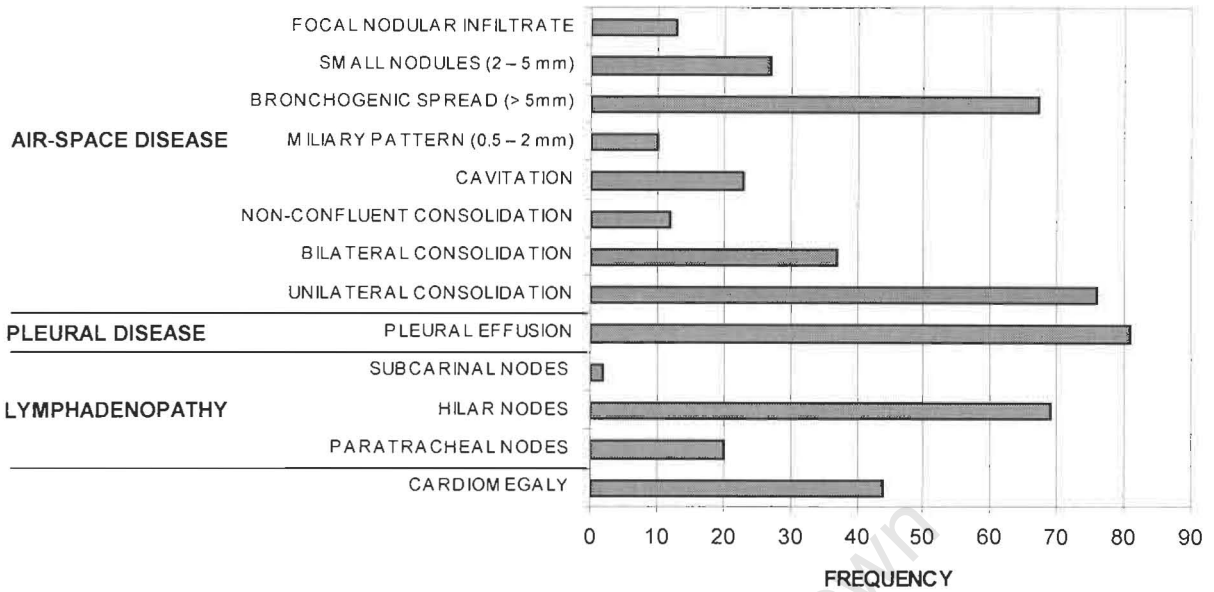
3.3 Chest radiograph findings

There were 262 chest radiographs available for review and of these, 90.1% were abnormal. A wide range of findings was observed (Figure 3.2).

3.3.1 Thoracic lymphadenopathy

Thoracic nodes were noted in 29.4% of cases, with the majority (89.6%) being hilar in location; paratracheal nodes were present in 26% only.

Figure 3.2: Frequency of findings on CXR



3.3.2 Air-space and pleural disease

Unilateral consolidation and a bronchogenic pattern were the most frequently observed parenchymal findings, noted in 32.2% and 28.4% respectively. Cavitation was seen in 9.7% and pleural effusions were present in 34.3%.

Of the abnormal radiographs, 71.6% were finally diagnosed with active tuberculosis by smear, culture, elevated ADA or histology, and the association between the abnormal CXR and TB positivity was significant [OR = 5.13, 95% CI = 2.12 – 12.60, p = 0.00002]. Ten patients (5.6%) with active tuberculosis had normal chest radiographs; 7 of these were HIV-positive and the HIV status was unknown in the remaining 3.

3.3.3 CXR findings and active tuberculous infection

Logistic regression analysis, together with a forward stepwise selection procedure, was performed in order to determine the chest radiograph findings that best correlated with active TB. The variables that fitted the model best included thoracic hilar nodes and pleural effusion, with a decreased deviance of 24.63 and 5%

significance. The model showed that the presence of thoracic nodes was associated with a 2.9 times increased risk of active TB [OR = 2.93, 95% CI = 1.44 – 6.04, p = 0.0011] and pleural effusion with a 3.6 fold risk of active TB [OR = 3.63, 95% CI = 1.76 – 7.62, p = 0.0001].

Forty-seven percent (47.5%) of patients with an abnormal CXR were diagnosed with active pulmonary tuberculosis by sputum smear or culture. The chest radiograph finding that correlated most significantly with a positive sputum smear or culture was the presence of hilar lymphadenopathy [OR = 4.31, 95% CI = 1.59 – 12.30, p = 0.0011]. Radiographic bronchogenic spread did not correlate significantly [OR = 2.09, 95% CI = 0.92 – 4.86, p = 0.056].

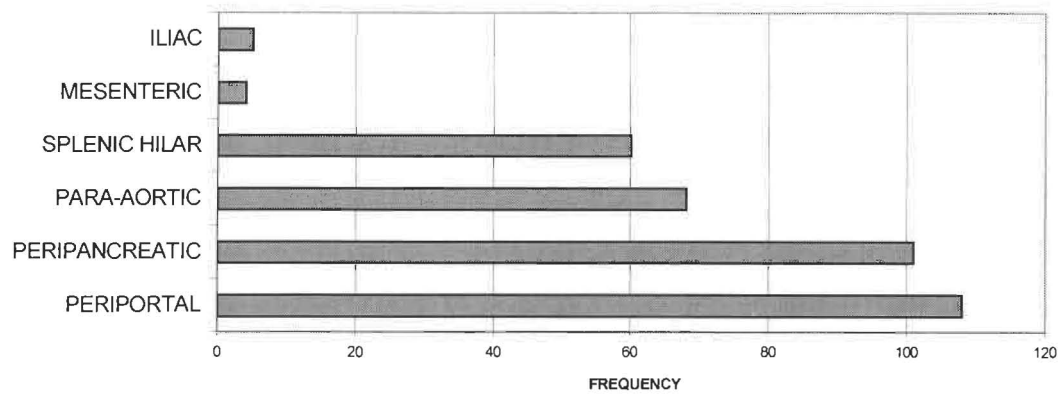
The features of primary TB were evident in 26.3% of abnormal radiographs, and of these, 70.97% were diagnosed with active pulmonary or pleural TB (by sputum or pleural fluid smear or culture, or elevated pleural fluid ADA); 88.7% were HIV-positive and in 5 (8.1%) of the 62 cases, the HIV status was unknown. The presence of thoracic lymphadenopathy and parenchymal consolidation in combination correlated significantly with active tuberculosis (diagnosed by smear, culture, ADA or histology) [OR = 3.59, 95% CI = 1.14 – 12.55, p = 0.014].

3.4 Ultrasound findings

3.4.1 Abdominal lymphadenopathy

Enlarged abdominal lymph nodes were noted on ultrasound in 125 cases (46.8%). A hypoechoic appearance was evident in 98.4%, whilst 13.6% were cystic or necrotic. The mean maximum node size was 15.3 ± 5.5mm and the mean minimum node size was mean 9.7± 2.8mm. The locations of the enlarged abdominal lymph nodes are shown in Figure 3.3; nodes in the peri-portal and peri-pancreatic areas were most frequent.

Figure 3.3: Frequency of nodal locations



Deep abdominal lymphadenopathy correlated significantly with active TB diagnosed by smear, culture, elevated ADA or histology [OR = 2.79, 95% CI = 1.56 – 4.99, p = 0.0001]. In total, 54.7% of the patients with active tuberculosis (diagnosed as above) had abdominal lymphadenopathy on ultrasound. The splenic hilar, para-aortic, peri-portal and peri-pancreatic nodal locations all corresponded significantly with active TB [OR = 2.23 – 2.86, 95% CI = 1.06 – 5.83, p = 0.0002 – 0.021].

The presence of abdominal lymphadenopathy was significantly associated with palpable, enlarged cervical nodes [OR = 2.06, 95% CI = 1.14 – 3.73, p = 0.0100] and with the presence of enlarged thoracic nodes on CXR [OR = 4.04, 95% CI = 2.20 – 7.47, p = 0.000008].

In 23 patients, ultrasound examination detected abdominal lymphadenopathy, but tuberculosis could not be confirmed in these cases.

3.4.2 Pericardial effusion

A pericardial effusion was shown at ultrasound in 125 cases. The mean effusion size was 11.4mm (± 6.0), with a range of 5.8 to 46.6mm. Stranding was noted in 4 cases only and the pericardium was thickened by more than 2mm in 9 cases. More

notably, the presence of an effusion correlated significantly with active tuberculosis (diagnosed by smear, culture, elevated ADA or histology) [OR = 3.54, 95% CI = 1.95 – 6.45, p = 0.000005] and with radiographic cardiomegaly [OR = 4.27, 95% CI = 1.95 – 9.51, p = 0.00004].

3.4.3 Liver

The mean size of the right lobe of the liver was 13.7cm (± 1.7), with a minimum length of 8cm and a maximum of 18.7cm. Using a cut-off of 15cm, 21.3% of cases had an enlarged liver. No significant observations were evident when comparing liver size with HIV status and tuberculosis.

3.4.4 Spleen

The mean splenic size was 9.8cm (± 1.7), ranging from 6 to 16.7cm. Thirty patients had a splenic size over 12cm; the correlations of splenomegaly with TB and HIV were not significant.

Splenic lesions were observed in 86 patients. The mean lesion size was 5.6mm (± 2.6); minimum 2.3mm, maximum 15.6mm. The correlation between splenic lesions and active TB (diagnosed by smear, culture, elevated ADA or histology) was significant [OR = 1.89, 95% CI = 1.02 – 3.55, p = 0.030]. Splenic lesions were more frequent in HIV-positive patients [OR = 11.8, 95% CI = 1.62 – 241, p = 0.002].

3.4.5 Ascites

Ascites was present in 32.2% (86) of cases and correlated significantly with active tuberculosis (diagnosed by smear, culture, elevated ADA or histology) [OR = 3.40, 95% CI = 1.71 – 6.83, p = 0.0001].

3.4.6 Ultrasound findings and active tuberculous infection

Logistic regression analysis, together with a forward and backward stepwise selection procedure (with a decreased deviance of 30.05 and significance at the 5% level of p=0.0000) determined that abdominal lymphadenopathy and pericardial effusion were the ultrasound variables with the best predictive value for active tuberculosis (diagnosed by smear, culture, elevated ADA or histology). The model showed that the presence of abdominal nodes was associated with a 2.8 times increased risk of active TB and pericardial effusion with a 3.5 times increased risk.

The combinations of abnormal ultrasound findings that correlated significantly with active tuberculosis (diagnosed by smear, culture, elevated ADA or histology) are displayed in table 3.1. Other combinations were not statistically relevant.

TABLE 3.1: COMBINATIONS OF ULTRASOUND FINDINGS

ULTRASOUND FINDINGS	RISK OF ACTIVE TB			FREQUENCY OF TB PATIENTS WITH THIS FINDING	
	OR	95% CI	p value		
SPLENIC LESIONS AND LYMPHADENOPATHY	2.12	1.09 – 4.16	0.017	41.44%	(75/181)
SPLENIC LESIONS AND ASCITES	3.09	1.08 – 9.48	0.019	18.78%	(34/181)
SPLENIC LESIONS AND LYMPHADENOPATHY AND ASCITES	3.91	1.25 – 13.61	0.008	18.23%	(33/181)

All of the documented ultrasound findings were present in two cases and both of these were diagnosed with active tuberculosis by culture.

3.5 CXR and ultrasound findings in active tuberculosis

In combination, the CXR and abdominal ultrasound findings that correlated significantly with active tuberculosis (diagnosed by smear, culture, elevated ADA or histology) were thoracic lymphadenopathy and abdominal lymphadenopathy [OR = 4.61, 95% CI = 1.79 – 12.58, p = 0.0003], pleural effusion and ascites [OR = 6.13,

95% CI = 1.73 – 25.89, p = 0.001] and parenchymal consolidation and abdominal lymphadenopathy [OR = 2.47, 95% CI = 1.08 – 5.79, p = 0.019].

3.6 Laboratory diagnosis of tuberculosis

In total, 181 (67.8%) of the 267 analysed patients were diagnosed with active TB by smear, culture, elevated ADA or histology; of these, 140 (77.3%) were HIV-positive. A microbiological diagnosis of *Mycobacterium tuberculosis* (culture positive) was present in 134 patients. The laboratory findings are displayed in Table 3.2.

TABLE 3.2: FREQUENCY OF LABORATORY FINDINGS

SAMPLE (NUMBER OF SAMPLES)	SMEAR POSITIVE (%)		CULTURE POSITIVE (%)	
SPUTA (191)	72	(37.7%)	120	(62.8%)
CSF (18)	0		3	(16.7%)
URINE (104)	6	(5.8%)	24	(23.1%)
FNA (60)	30	(50.0%)	8	(13.3%)
GASTRIC WASHINGS (5)	1	(20.0%)	1	(20.0%)
PERITONEAL FLUID (9)	0		5	(55.6%)
PLEURAL FLUID (51)	3	(5.9%)	30	(58.8%)
PERICARDIAL FLUID (2)	0		2	(100.0%)

The sputum smear was 94% specific, but 43% sensitive for active tuberculosis. Seventy-three patients had two sputum samples sent to the laboratory, whilst 103 had only a single sputum sample.

The pleural, peritoneal and pericardial ADA findings are displayed in Table 3.3.

TABLE 3.3: ADA LEVEL

SAMPLE	NUMBER OF SAMPLES (% > 30 u/L)	
PLEURAL FLUID	51	(82.4%)
PERITONEAL FLUID	9	(71.4%)
PERICARDIAL FLUID	2	(100.0%)

A total of 78 CSF specimens were analysed. Twelve cases were diagnosed with tuberculous meningitis (CSF findings of 3 or more lymphocytes per high power field, protein greater than 0.45 g/l and decreased glucose less than 2.2 mmol/l. Positive tuberculosis CSF cultures were noted in 3 cases only.

A bone marrow biopsy was performed in 5 patients. Tuberculosis was proven by culture in one of these samples only.

In 86 patients the diagnosis of tuberculosis could not be ascertained by means of smear, culture or ADA. However, 7 of these patients had typical CSF biochemistry findings for TBM and 6 cases had radiological changes suggestive of tuberculosis. Of the remaining cases, 33 patients were diagnosed with alternative conditions (Table 3.4); in the rest of the patients the diagnosis was unknown at the time of the study.

TABLE 3.4: NUMBER OF CASES WITH ALTERNATIVE FINDINGS	
CRYPTOCOCCAL MENINGITIS	9
CARDIAC DISORDER	4
PROBABLE PCP (CLINICAL + CXR)	5
PROBABLE KAPOSI'S SARCOMA (CLINICAL + CXR)	2
LUNG CARCINOMA ON HISTOLOGY	2
BACTERIAL SEPTICAEMIA	2
BACTERIAL MENINGITIS	1
PULMONARY CANDIDIASIS	1
MOTT	1

3.7 Other laboratory parameters

3.7.1 CD4 counts

A total of 89 CD4 counts were measured, with a mean value of 109.8 ± 133.1cells/μl, ranging from 1 to 570cells/μl. Sixty-two (69.6%) patients were found

to have CD4 values less than 200cells/μl and 43 (48.3%) of these were diagnosed with tuberculosis by smear, culture, elevated ADA or histology.

3.7.2 CRP measurements

Of the 119 CRP measurements recorded, the mean value was 134.5 (± 80.0), with a range of 1 to 360. CRP levels over 10 were present in 79 (69.3%) patients diagnosed with tuberculosis (by smear, culture, elevated ADA or histology), and in 93 (81.6%) of the HIV-positive sample.

3.8 Mortality

The in-patient mortality was 3.7%. Of the 11 patients that died, 7 had stage 4 HIV disease. The HIV status in the other 4 patients was unknown.

Chapter 4: Discussion

This study of 267 patients, evaluating the role of abdominal ultrasound investigation in the workup of patients with suspected extrapulmonary or disseminated tuberculosis, is the largest study on this subject conducted in South Africa to date. In 2002, local authors suggested in a letter that abdominal ultrasound might be an appropriate method to diagnose tuberculosis in the setting of repeatedly negative sputum smears, but made no mention of their study sample size.[35] In another study, Hudson and Wood reported on a total of 35 ultrasound scans in patients with HIV and abdominal pain. They found that a final diagnosis of tuberculosis was made in 12 cases and concluded that the role of ultrasound in the diagnosis of tuberculosis was limited.[69] Similarly, other local researchers have also concentrated on HIV and TB, but none have investigated the role of ultrasound examination of the abdomen in the diagnosis of smear-negative TB.[13, 19, 21, 23,

In the present study, a final sample of 181 patients (67.8% of patients with suspected tuberculosis) was diagnosed with active tuberculosis on the basis of smear, culture, elevated ADA or histology. At least 77% of these patients were co-infected with HIV infection. Lymphadenopathy greater than 10 mm at abdominal ultrasound, was associated with a 2.8 times increased risk of active tuberculosis, and was present in 54.7% of these cases. Although abdominal lymphadenopathy is a well-described manifestation of tuberculosis, the importance of this ultrasound finding in more than two-thirds of patients with proven disseminated TB in our study highlights the value of abdominal ultrasound examination in the investigation of patients with suspected disseminated or extrapulmonary TB, specifically in smear-negative cases. In the appropriate clinical context, abdominal lymphadenopathy found at ultrasound examination could be used as a surrogate marker of TB while awaiting specimen culture results. (Appendix 5)

Ultrasound is a cheap, non-invasive radiological modality. Although interpretation by the ultrasonographer is subjective and experience necessarily develops with

time, the technique of scanning, especially in the abdomen, is readily taught, and can be widely practised. It could be especially useful in centres where the burden of tuberculosis is high, particularly disseminated smear-negative TB in HIV-positive patients.

The ultrasound features of enlarged lymph nodes due to tuberculosis, observed in this study, were similar to those described in the literature. The typical hypoechoic, matted appearance and the characteristic vascular encasement, previously described ultrasonographically, were noted;[31, 41, 70] as was a mean nodal size of 15.3mm, correlating with other studies where mean sizes ranged from 15 to 18mm.[70, 71, 72] The peri-portal, peri-pancreatic and para-aortic locations were the most frequently involved in other reports as well, and were statistically significant in the prediction of tuberculosis. [14, 71, 72]

In this study radiographic thoracic nodes, present on posteroanterior (PA) chest films, were recorded in 29.4% of patients, and also correlated significantly with active tuberculosis. [OR = 2.93, 95% CI = 1.44 – 6.04, p = 0.0011] The hilar region was most frequently involved. Mediastinal nodes are however not always easily recognized radiographically.[39]

Since a significant association was found between active TB and thoracic and/or abdominal nodes [OR = 4.61, 95% CI = 1.79 – 12.58, p = 0.0003], it seems appropriate to suggest that enlarged deep nodes (thoracic or abdominal) may serve as a very useful indicator of active TB in patients clinically suspected of having extrapulmonary or disseminated disease.

Peripheral cervical lymphadenopathy, present in 28.7% of the active TB sample, is in keeping with other work published.[11, 14] Barthwal et al determined that peripheral and retroperitoneal lymph nodes in EPTB were the commonest findings (each present in 52% of the patients), followed by mediastinal nodes (present in 16%).[14]

Primary pulmonary tuberculosis is a common presentation in more severely immune-compromised individuals. In this study, radiological features of primary TB were evident in 26.3% of abnormal radiographs, and at least 88.7% of these were HIV positive. Other studies on TB in HIV-infected patients have also reported a high incidence of a primary tuberculous pattern, in the region of 38%.[73, 74] The remaining patients had features of post-primary tuberculosis or atypical manifestations. Unilateral consolidation and bronchogenic nodular patterns (greater than 5mm) were the commonest parenchymal findings. In fact, a nodular pattern with nodules less than 1cm is documented as a frequent presentation of tuberculosis in patients with AIDS.[75] Of the patients with diagnosed tuberculosis, 5.6% had normal chest radiographs and 70% of these were known to be HIV positive. The reported frequency of normal radiographs in patients with TB/HIV ranges from 5 to 12%, and in one series was up to 33%.[18, 39, 73, 76] A normal chest radiograph in the presence of active disease in HIV-positive patients further stresses the need for determining other useful indicators for active tuberculosis, such as ultrasound examination of the abdomen.

In the setting of suspected EPTB or disseminated TB, the presence of pericardial fluid was associated with a 3.5 times increased risk of TB and should be routinely sought when performing abdominal ultrasound examination on patients with suspected EPTB or disseminated TB. This was particularly true of patients with enlarged cardiac silhouettes on the CXR (OR = 4.27, 95% CI = 1.95 – 9.51, chi=16.71, p = 0.00004). A study at Tygerberg Hospital in Cape Town on patients with pericardial effusions of 10mm or more in size found that tuberculous pericarditis was present in 53% and that 100% had a cardiothoracic ratio that was enlarged and 45.5% were HIV positive.[77]

Hepatomegaly and splenomegaly were not found to be consistent findings in patients with active extrapulmonary tuberculosis, as claimed in the literature.[27, 58, 78] However, splenic lesions correlated significantly with active TB [OR = 1.89, 95% CI = 1.02 – 3.55, p = 0.030]. This finding emphasizes the need for earlier diagnosis

since the presence of splenic microabscesses in TB is known to be associated with increased mortality.[14, 79] Using a linear high frequency ultrasound probe to clearly demonstrate the presence or absence of splenic lesions should be routine when ultrasound examinations are performed on these patients.

Ascites has been recognised as a common occurrence in abdominal tuberculosis and smear or culture tests on ascitic fluid are useful.[78, 80] In the present study, ascites was recorded in 32.2% of cases and the presence of ascites was associated with a 3-fold increased risk of active tuberculosis. This study also found that elevated ascitic fluid ADA was more frequently suggestive of active tuberculosis than was smear or culture. Generally, smears are positive in less than 5% of cases.[11]

It is well known that in the setting of advanced immune compromise, extrapulmonary or disseminated TB occurs more frequently.[81, 82] The findings in this study support this, since abdominal nodes, thoracic nodes and splenic lesions, indicative of EPTB, were often present in HIV-positive patients with TB.

Whilst CD4 levels were not measured in all of the patients, the majority of tested patients had a CD4 under 200 cells/μl (69.6%). This corresponds with the large number of study patients (n = 141) with WHO stage 4 clinical disease. Part of the reason for this bias is the fact that all patients included in this study were ill enough to require hospital admission. Patients less ill and probably less immune compromised are usually seen in an ambulatory contact at the primary health care level; secondly, the CD4 measurements were only performed in selected patients; more ill patients may have been investigated more aggressively.

Approximately 18% (23/125) of patients had abdominal lymphadenopathy that could not be confirmed to be of tuberculous origin. In these patients an alternative diagnosis for the abdominal lymphadenopathy was probable. This could have included systemic candidiasis, mycobacteria other than tuberculosis, Kaposi's

sarcoma, disseminated cryptococcosis and lymphoma. Direct sampling of these nodes were not undertaken to confirm an alternative diagnosis or establish TB not proven by the other samples submitted in the study.

Sputum, CSF, pleural fluid and urine samples were obtained most frequently. Overall, sputum smear tests had a poor sensitivity for tuberculosis (43%). A comparative study found similar results, with sputum smears positive in less than 50%; by contrast, urine were cultures positive in 70%; CSF and pleural fluid samples were rarely smear positive and positive culture yields from diagnostic nodal aspirates were in the range of 50 to 90%.[17]

Bearing this in mind, it is concerning to note that sputum microscopy is still the principal diagnostic tool in areas of the world with scarce resources, despite its poor sensitivity.[82] Consequently, the need for laboratory cultures is becoming increasingly important in the management of tuberculosis, particularly in high HIV prevalence settings like South Africa.[2]

Chapter 5: Conclusion

5.1 Projected study benefits

- The finding that sonographically detected abdominal lymphadenopathy is a statistically significant predictor of active tuberculosis supports the use of ultrasound as a useful diagnostic tool in the workup of smear-negative patients with suspected tuberculosis.

- Other ultrasound features are also significant predictors, including splenic lesions, ascites and pericardial effusions.

- The role of ultrasound is likely to be especially relevant at the primary and secondary health care centres, where the load of tuberculosis is the highest and investigative resources are limited.

- The chest radiograph is also shown to be a significant tool with regards to detection of hilar lymphadenopathy and cardiomegaly in patients with pericardial effusions, and could be used as a screening tool where ultrasound is not available.

- The prospective method of investigation of this study ensured that data capture was as complete as possible. The sample size was sufficient to predict statistically significant findings.

- Secondly, the study was conducted by a single investigator, thus limiting subjective variations of the interpretation of ultrasound findings.

- The results from this will be beneficial to health care workers in Southern Africa, and possibly further afield. The information obtained may alter

current clinical management practices and will hopefully improve the early treatment of suspected tuberculosis prior to the availability of culture results. This is particularly important in smear-negative immune compromised HIV-positive patients who require a more aggressive approach to the early detection and treatment of disseminated tuberculosis.

5.2 Study limitations and suggestions

- Fine needle aspiration biopsies of the abdominal nodes were not performed, even though the procedure is no more invasive than lumbar puncture, peripheral node aspiration or serous fluid aspiration. Consequently the definitive pathology of the abdominal nodes was not determined and instead, the diagnosis of disseminated tuberculosis was inferred from the results of samples from other relevant accessible sites.
- An invasive study with formal lymph node pathology would have been more specific.

- Ultrasound is cheap and non-invasive, but is reliant on subjective operator dependant interpretation.
- Training of operators could however improve the yield of tests.
- In Cape Town, patients have to present to a secondary or tertiary level centre for the test to be performed. Most patients are seen at the primary level and studies need to be conducted to improve the pick up rate at this level as well, including motivation for facilities to acquire portable ultrasound machines. Alternatively, outreach programmes can be performed from level 2 and 3 hospitals to level 1 care in order to make the findings of this study accessible to those in need.

- The chest radiograph interpretations were also subjective, although bias was reduced through independent double reporting.
- CT scanning may be a less subjective way of investigating lymphadenopathy but radiation, cost and restricted availability limit widespread use. For similar reasons MRI would also not be practical as a clinically useful tool for large-scale use in the public sector.

- The high pre-test probabilities of HIV and TB may have influenced the results, based on Bayesian principles.

5.3 Conclusion

Ultrasound should be considered an appropriate tool in the setting of suspected tuberculosis when sputum smears are negative and aspiration or biopsy is not feasible. Ultrasound can confirm the presence or absence of intra-abdominal lymphadenopathy, ascites, pericardial effusions and splenic lesions and should probably become more widely used within the hospital setting for difficult-to-diagnose cases, particularly in HIV-infected individuals.

HIV and TB present the most serious challenges to public health across the world and need to be addressed urgently. By improving the index of suspicion of a diagnosis of active tuberculosis, abdominal ultrasound may prevent unnecessary delays in initiation of therapy, thus limiting further disease transmission, curbing the development of multidrug-resistant TB and reducing morbidity and mortality, particularly in smear-negative patients with disseminated tuberculosis. Ultrasound can also be of value in the follow-up of these patients.

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Appendix 1: The University of Cape Town's Health Sciences Research Ethics Committee ethics approval. (ref 279/2004)

UNIVERSITY OF CAPE TOWN

Research Ethics Committee
E53 Room 44.1, Old Main Building
Groote Schuur Hospital, Observatory, 7925
Queries : Xolile Fula
Tel : (021) 406-6492 Fax: 406-6411
E-mail : Xfula@curie.uct.ac.za

20 September 2004

REC REF: 279/2004

Dr MN Patel
Radiology
GSH

Dear Dr Patel

ABDOMINAL LYMPHADENOPATHY AS A SURROGATE FINDING FOR TUBERCULOSIS: A PROSPECTIVE CROSS-SECTIONAL ANALYSIS OF THE ROLE OF ABDOMINAL ULTRASOUND IN PATIENTS WITH SUSPECTED TUBERCULOSIS

Thank you for submitting your study to the Research Ethics Committee for reviewal.

It is a pleasure to inform you that the Research Ethics Committee has formally approved the above mentioned study.

Please quote the REC. REF in all your correspondence

Yours sincerely

PROF. T. ZABOW
CHAIRPERSON

Appendix 2: Permission from the Clinical Executive of G F Jooste Hospital.

ENQUIRIES
NAVRAE
IMIBUZO
Dr GM Perez

TELEPHONE
TELEFOON
IFOWUNI
021-6901002

REFERENCE
VERWYSING
ISALATHISO

DATE
DATUM
UMHLA
01/09/2004

PROVINCIAL ADMINISTRATION: WESTERN CAPE
DEPARTMENT OF HEALTH

PROVINSIALE ADMINISTRASIE: WES-KAAP
DEPARTEMENT VAN GESONDHEID

ULAWULO LWEPHONDO: INTSHONA KOLONI
ISEBE LEZEMPILO

ABDOMINAL LYMPHADENOPATHY AS A SURROGATE FINDING FOR TUBERCULOSIS – RESEARCH PROTOCOL

Dear Dr Patel

Thank you for the copy of your research protocol. Permission is hereby granted for the proposed research to be conducted at GF Jooste Hospital. This research is especially relevant to GF Jooste, where abdominal ultrasound is used in the work up of patients with suspected non-pulmonary tuberculosis.

We look forward to receiving the results of your research.

Sincerely

Dr GM Perez
Senior Medical Superintendent

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Appendix 3: Data Collection Sheet

DATA COLLECTION SHEET DISSEMINATED TUBERCULOSIS STUDY	PATIENT LABEL	Code
STUDY NO : ☐☐☐		G M :
DATE OF ADMISSION : ..... / ..... / 2004		P
		A

CLINICAL INFORMATION

1. MENTAL STATUS
Awake & Co-operative ☐ Awake but Unco-operative ☐ Obtunded ☐

2. HIV STATUS
Positive ☐ Negative ☐ Unknown ☐
WHO stage 1 ☐ WHO stage 2 ☐ WHO stage 3 ☐ WHO stage 4 ☐ N / A ☐
Disseminated Zoster ☐ Kaposi's sarcoma ☐ Oral candida ☐ PCP ☐ Crypto meningitis ☐ Severe wasting ☐
Recent CD4 count : .....
Weight : ... Kg
Hb : ..... g/dL
CRP : .....

3. COUGH
Productive cough ☐ Non-productive cough ☐ Unable to cough ☐

4. PERIPHERAL NODES (1cm or more i.e. suitable for FNAB)
Cervical ☐ Axillary ☐ Inguinal ☐

ULTRASOUND

1. NODES
Absent ☐ Obscured ☐ Hypoechoic ☐
Max node size : ..... mm Min node size : ..... mm Cystic /necrotic ☐
Periportal ☐ Peripancreatic ☐ Mesenteric ☐
Paraaortic ☐ Splenic hilar ☐ Iliac ☐

2. CHEST
RT pleural effusion ☐ LT pleural effusion ☐
Pericardial effusion : ..... mm Pericardial thickness > 2mm ☐ Stranding ☐

3. ABDOMEN
Liver size : ..... cm Spleen size : . cm Splenic lesions : ..... mm Ascites ☐
RT kidney size : ..... cm Echogenicity ↑ ☐ Echogenicity normal ☐ Psoas abscess ☐
LT kidney size : ..... cm Echogenicity ↑ ☐ Echogenicity normal ☐ Psoas abscess ☐
Other :

CXR

Heart size normal ☐ Cardiomegaly ☐ Pericardial effusion ☐
Paratracheal nodes ☐ Hilar nodes ☐ Subcarinal nodes ☐
RT pleural effusion ☐ LT pleural effusion ☐ Consolidation ☐
Cavitation ☐ Miliary ☐ Bronchogenic spread ☐
Other :

LABORATORY RESULTS

Sample	Dates	Sample no	Smear (+ / -)	TB Culture (+ / -)	Other
Sputum					
Sputum					
Urine					
CSF					See below
FNAB nodes					
Gastric washings					
Bone Marrow					
Peritoneal fluid					ADA :
Pleural fluid					ADA :
Pleural biopsy					
CSF analysis	Lymphs :	Glucose :	Protein :	CLAT - / +	VDRL - / +

F/U wt : ..... Kg	F/U Hb : ..... g/dL	F/U CRP :	Height : ..... m

Appendix 4: WHO Clinical Classification System[68]

WHO Asymptomatic

WHO Stage 1

This includes the acute retroviral syndrome of initial infection, the asymptomatic and those with persistent generalised lymphadenopathy.

WHO Symptomatic

This has been divided into two areas;

WHO Stage 2

- Weight loss < 10% of body weight
- Mucocutaneous manifestations such as seborrhoeic dermatitis, prurigo, fungal nail infections, recurrent oral ulcerations, angular cheilitis.
- Herpes zoster
- Recurrent upper respiratory tract infections such as bacterial sinusitis.

WHO Stage 3

- Weight loss > 10% of body weight
- Unexplained chronic diarrhoea > 1 month.
- Unexplained prolonged fever (intermittent or constant > 1 month).
- Candidiasis, oral.
- Candidiasis, vulvovaginal for > 1 month.
- Oral hairy leukoplakia.
- Pulmonary tuberculosis
- Severe bacterial infections such as pneumonia or pyomyositis.
- Bed ridden for < 50% of the day during the last month.

WHO Stage 4 / WHO – AIDS

- Bed ridden for > 50% of the day during the last month.
- Candidiasis of the oesophagus, trachea, bronchi or lungs
- Cryptococcus, extrapulmonary
- Cryptosporidiosis with diarrhoea for > 1 month.
- Cytomegalovirus disease of an organ other than the liver, spleen or lymph nodes.
- Herpes simplex infection, mucocutaneous for > 1 month or visceral for any duration.
- HIV dementia
- Isosporiasis with diarrhoea for > 1 month.
- Kaposi's sarcoma
- Lymphoma
- Mycobacterium tuberculosis – extrapulmonary
- Mycobacteriosis – atypical and disseminated.
- Mycosis – disseminated histoplasmosis or coccidiodomycosis.
- Pneumocystis carinii pneumonia.
- Progressive multifocal leukoencephalopathy.
- Salmonella septicaemia (non-typhoidal)
- Toxoplasmosis of the brain.
- Wasting syndrome due to HIV.

Appendix 5: Basic modified diagnostic flow chart

INVESTIGATING THE PATIENT WITH SUSPECTED DISSEMINATED OR EXTRAPULMONARY TUBERCULOSIS

Examine the CXR for the following

- ✓ Hilar or mediastinal nodes
- ✓ Parenchymal changes
- ✓ Pleural disease
- ✓ Cardiac size

and

Send samples to the laboratory for AFB smears, ADA and culture or histology

- ✓ Sputum x 2 or
- ✓ Peripheral node FNA or
- ✓ Pleural, peritoneal or pericardial fluid or
- ✓ Urine or CSF, etc

↓

If smears are positive, treatment for TB can be commenced

↓

If smears are negative, proceed to ultrasound examination of the abdomen and assess for

- ✓ Abdominal lymphadenopathy ≥ 10mm
- ✓ Splenic micro-abscesses
- ✓ Ascites
- ✓ Pericardial effusion

↓

Commence TB treatment if the ultrasound features are suggestive of tuberculosis and wait for culture results

Appendix 6: Image gallery and case reports

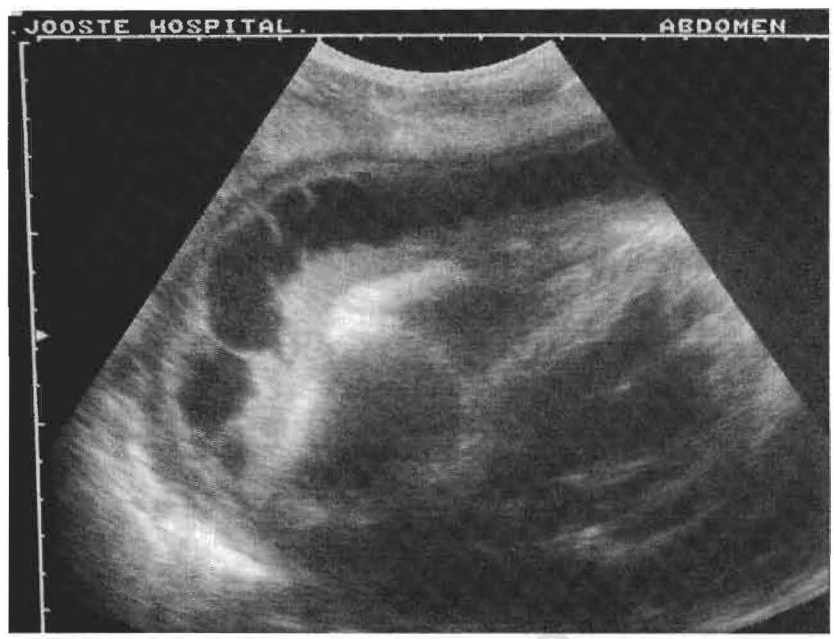
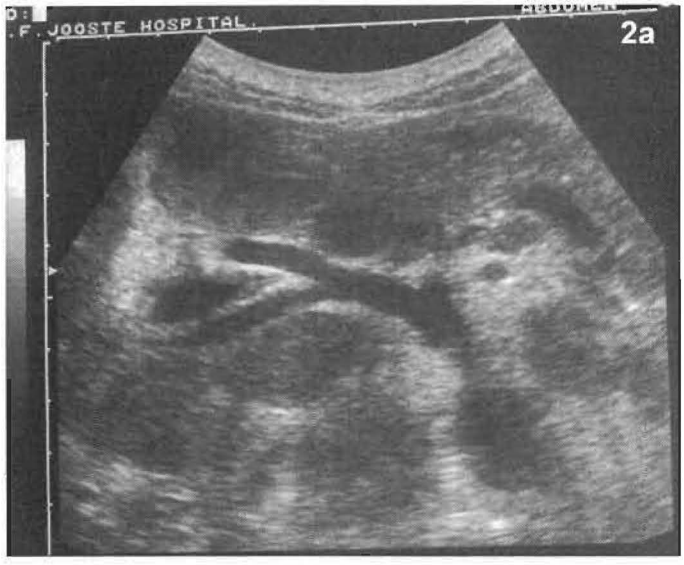
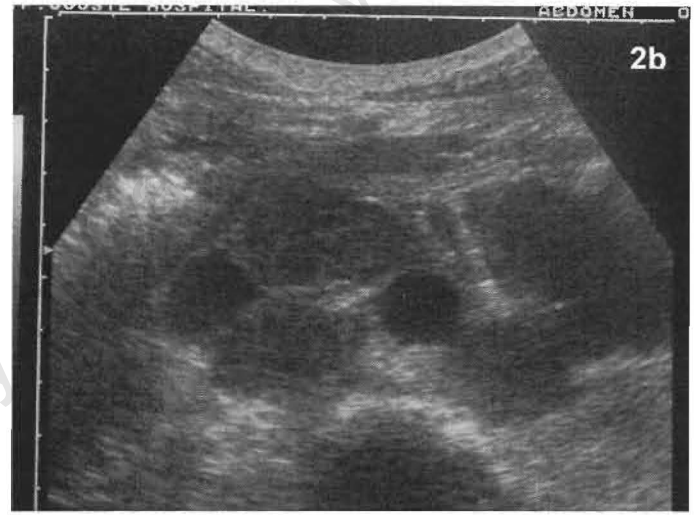


Image 1:

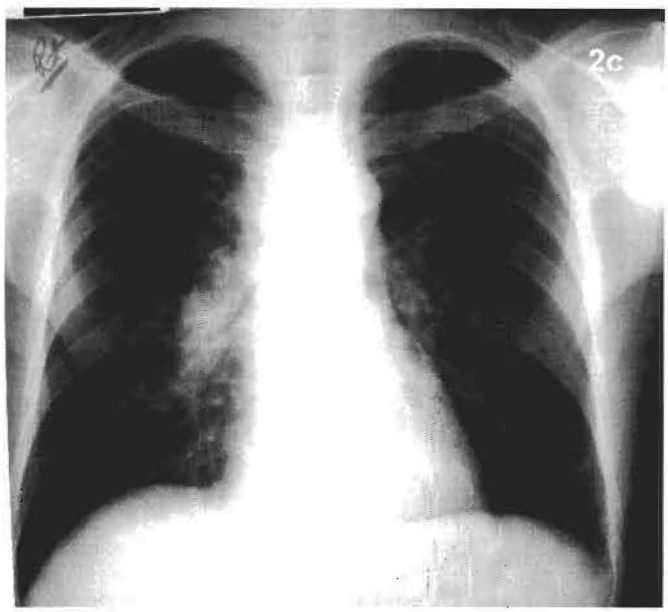
Transverse ultrasound view of the heart demonstrating a 26mm pericardial effusion with associated fibrinous stranding and pericardial thickening, typical of tuberculosis. The patient was a 40-year-old female with stage 4 retroviral disease. In addition to the cardiac involvement, she also had hypoechoic abdominal nodes on abdominal ultrasound, ranging from 10.1 to 14.8mm in the peri-portal and peri-pancreatic regions. There was no hepatosplenomegaly, nor any splenic lesions or ascites. Her CXR revealed cardiomegaly, unilateral consolidation without cavitation and a pleural effusion. She was diagnosed with active tuberculosis on the basis of a positive sputum culture and elevated pleural fluid ADA at 66IU.

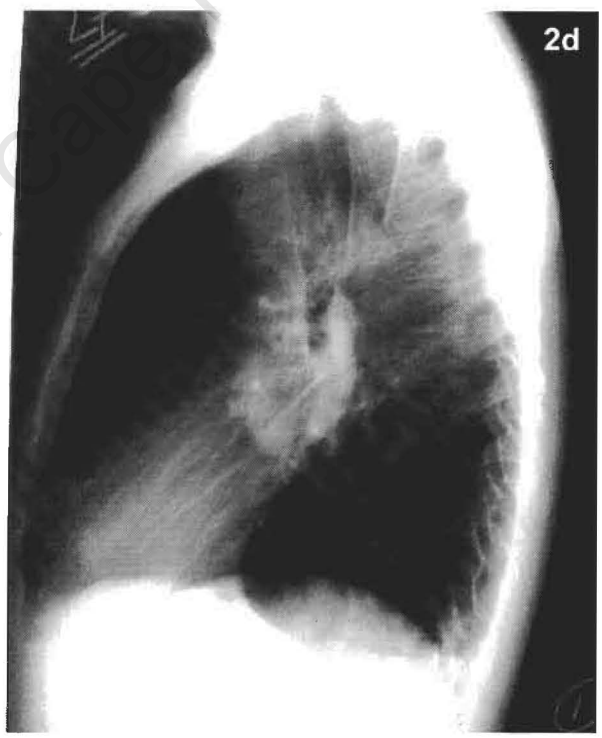




Images 2a and 2b:

Transverse ultrasound views at the level of the upper abdomen (2a) and lower inferior vena cava (IVC)/aorta (2b) demonstrate large hypoechoic lymph nodes in the para-aortic region, extending along the hepatic branch of the celiac axis (2a). In image 2b the interaortocaval nodes are separating the great vessels. The maximum nodal short axis diameter was 28.2mm. Nodes were also present in the peri-pancreatic and splenic hilar regions. This patient was a 34-year-old male with stage 4 retroviral disease and a CD4 count of 35. Other findings included a 10mm pericardial effusion, hepatomegaly at 18.6cm, splenomegaly at 12.4cm, splenic lesions and ascites.





Images 2c and 2d

The chest radiographs in the same patient showed lobulated right hilar fullness on the PA view and increased opacification in the subcarinal region on the lateral view, both suggestive of lymphadenopathy. There were no parenchymal changes and no pleural disease was evident.

Active disseminated tuberculosis was confirmed in this case by positive sputum culture.

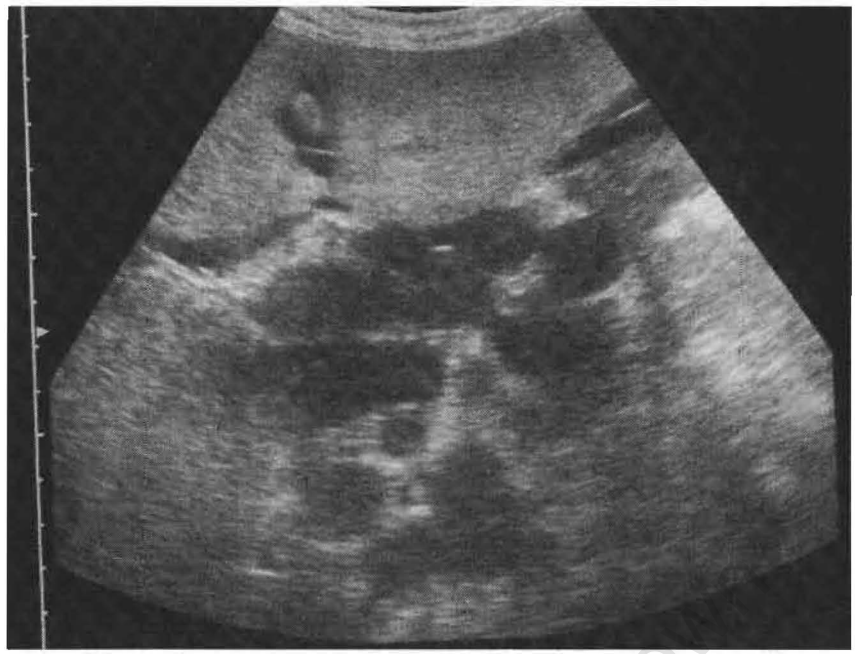


Image 3:

This oblique ultrasound view through the epigastrium shows multiple hypoechoic nodes around the porta. Nodes were also present in the peri-pancreatic, para-aortic and splenic hilar regions, with nodal sizes ranging from 19.7 to 25mm. The spleen was not enlarged but there were multiple splenic lesions, the largest measuring 12.7mm. The kidneys were normal in size and appearance. Ascites was noted.

The patient was a 57-year-old female, HIV positive with stage 4 disease clinically and palpable cervical lymphadenopathy. Her CXR revealed hilar nodes and diffuse bilateral bronchogenic spread.

Active disseminated tuberculosis was diagnosed by positive urine smear and culture and positive FNA smear from the cervical lymph node.

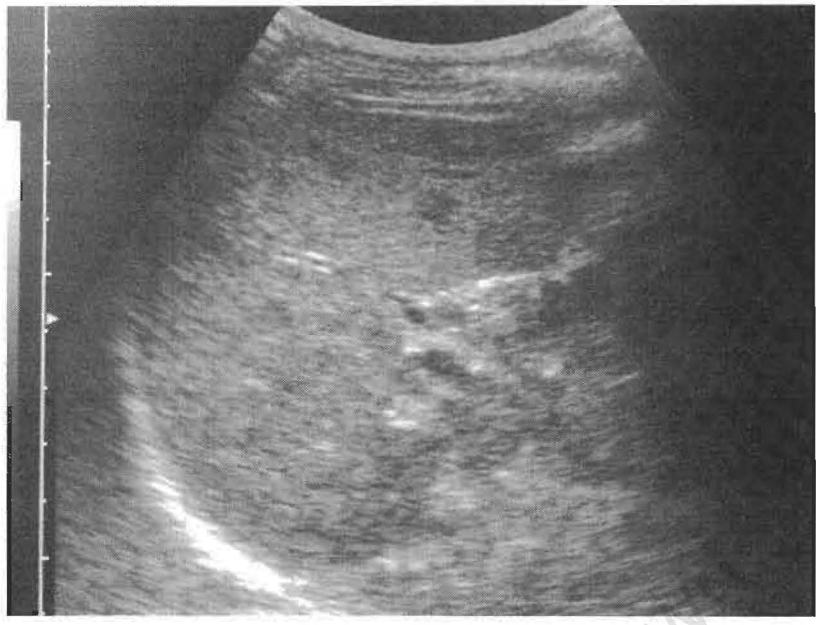


Image 4:

Multiple focal hypoechic lesions are evident in the spleen when scanning with the curvilinear probe in this 31-year-old HIV positive male. The patient had palpable cervical lymphadenopathy, hilar nodes on CXR and 15mm abdominal nodes on ultrasound. The kidneys were echogenic, but not enlarged. There were no parenchymal changes in the chest.

The diagnosis of active disseminated TB was made from a positive sputum smear and a positive urine culture.

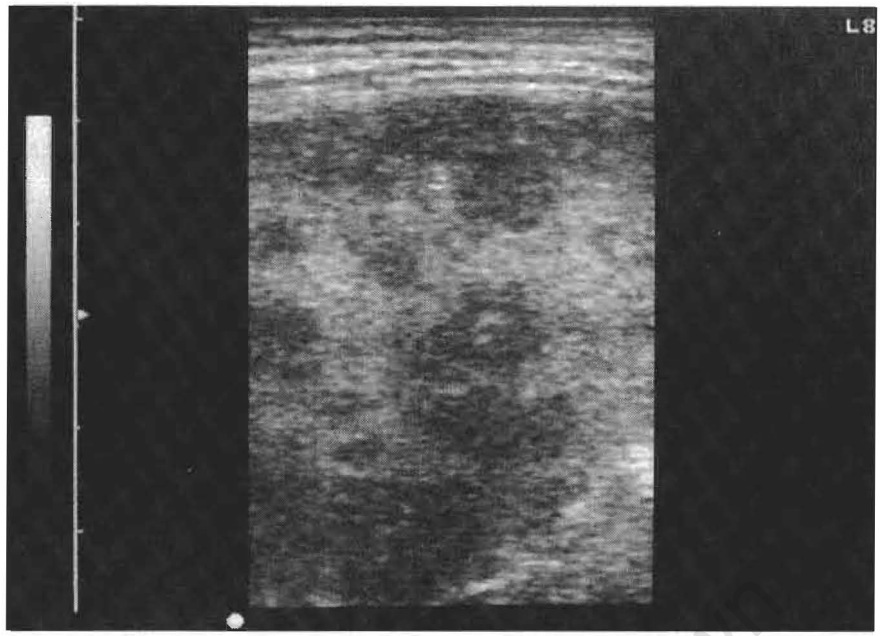
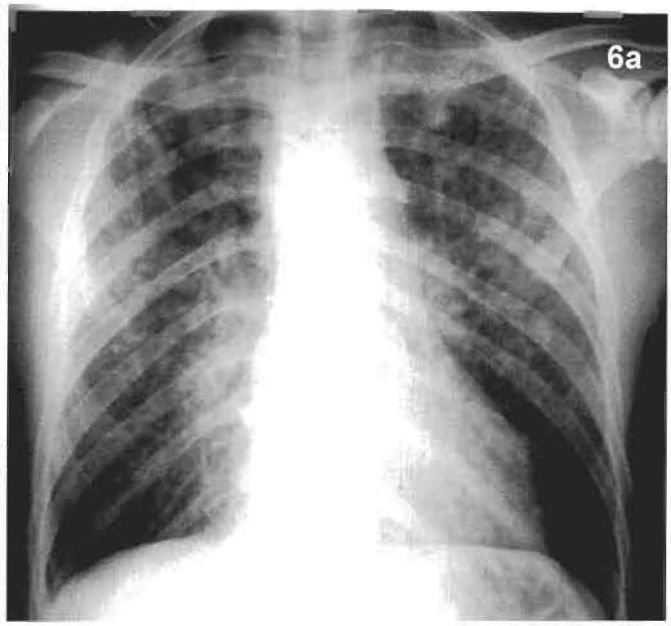


Image 5:

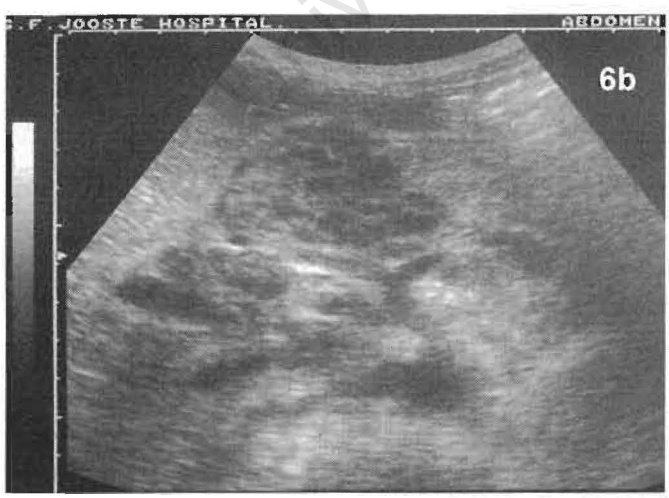
In comparison to image 4, by using the linear probe, the hypoechoic splenic lesions are more clearly defined in this 27-year-old female. The largest splenic lesion measured 14mm in size. She also had cervical lymphadenopathy and 13 to 20mm abdominal lymphadenopathy in the peri-portal, peri-pancreatic, para-aortic and splenic hilar regions. There was no hepatosplenomegaly, but ascites was present. A small pleural effusion was noted on her CXR.

The patient was diagnosed with stage 4 retroviral disease and active tuberculosis based on histological caseous necrosis in a cervical lymph node.

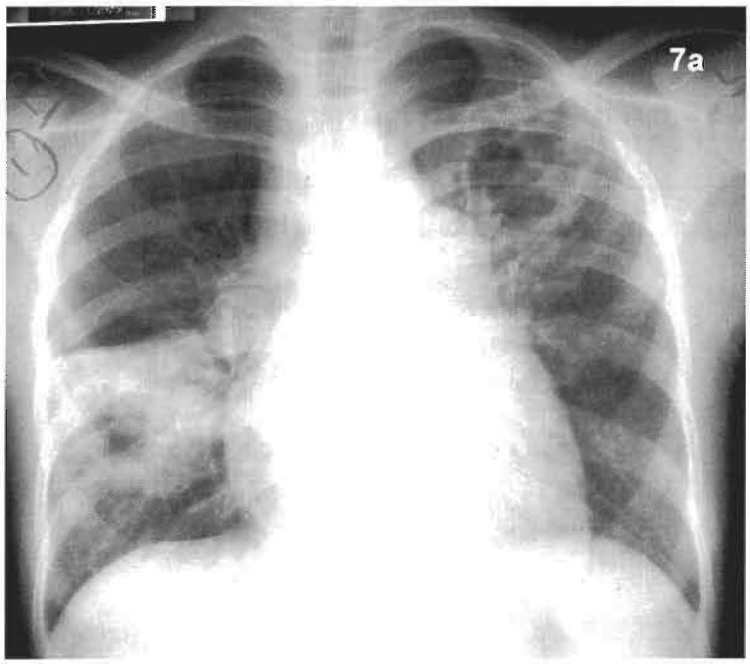


Images 6a and 6b:

Posteroanterior CXR (6a) of a 40-year-old male with stage 4 retroviral disease demonstrates a bilateral upper and mid zone bronchogenic infiltrate, as well as increased opacification in the right paratracheal region suggestive of adenopathy. The patient presented with a productive cough and was sputum smear and culture positive for TB.

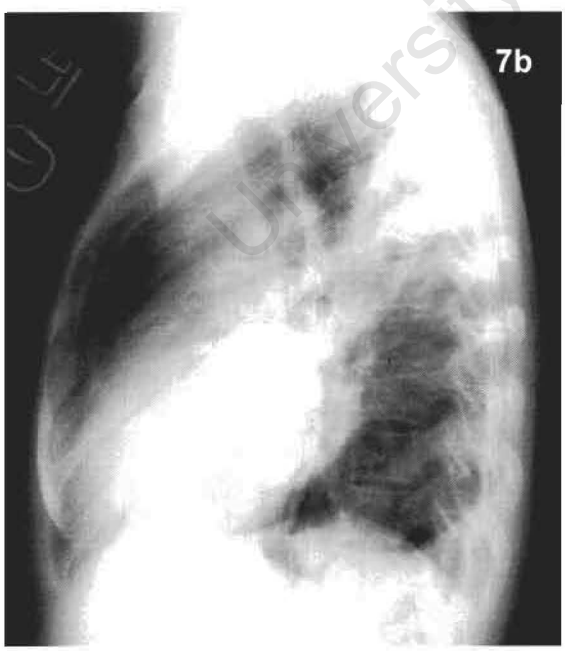


At abdominal ultrasound (6b), the same patient had several hypoechoic and cystic/necrotic lymph nodes, up to 30 mm in size. The nodes were peri-portal, peri-pancreatic and para-aortic in location, and ascites was present.

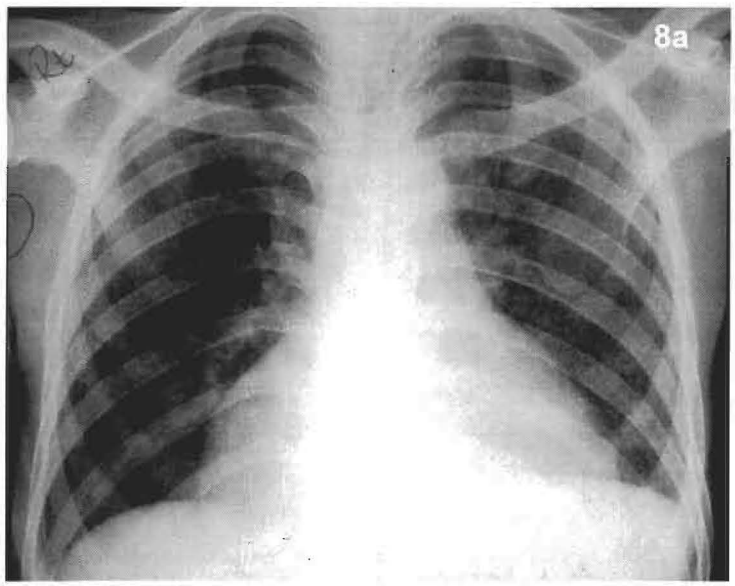


Images 7a and 7b:

PA (7a) and lateral (7b) views of the chest show focal consolidation with breakdown in the lateral segment of the right middle lobe and cavitation in the left upper lobe with peripheral patchy consolidation. In addition, there are lobulated opacities in the right paratracheal and hilar regions suggestive of thoracic lymphadenopathy. The patient was a 20-year-old female with retroviral disease.

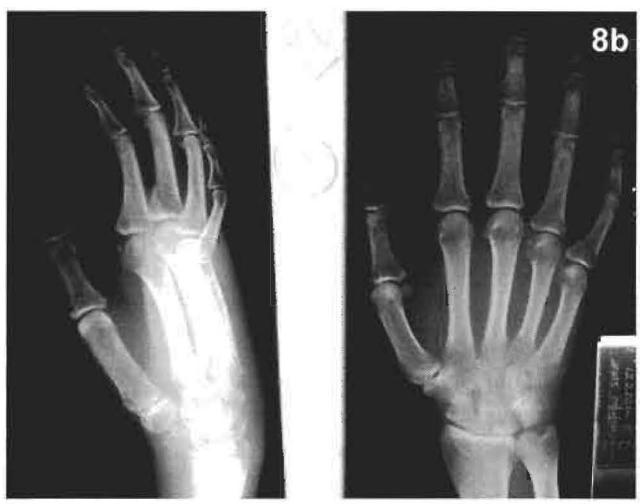


She was diagnosed with disseminated active TB by positive sputum culture. On abdominal ultrasound, there were hypoechoic nodes in the peri-portal, peri-pancreatic and splenic hilar regions. Focal splenic lesions were noted and she had a 9mm pericardial effusion.

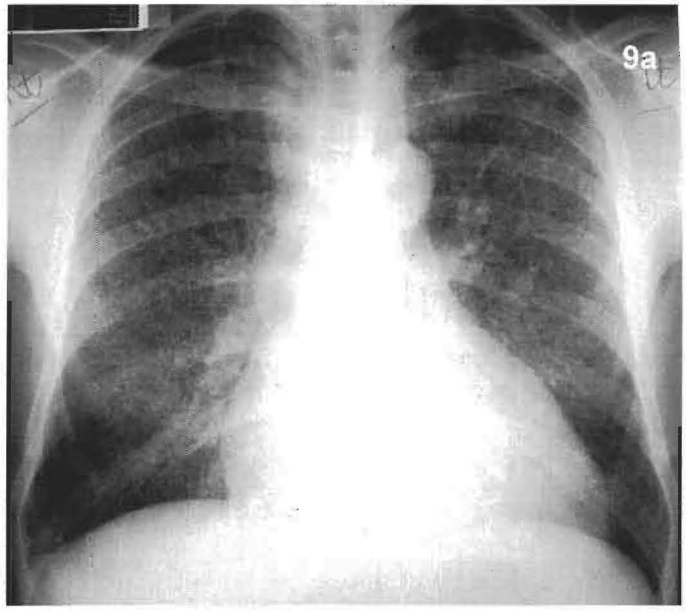


Images 8a and 8b:

PA radiograph of the chest (8a) in a 27-year-old female with stage 4 retroviral disease. The film shows cardiomegaly and a small left-sided pleural effusion with patchy basal opacification; a small nodular pattern is evident throughout the lungs, more prominent on the left. There was no identifiable thoracic adenopathy. Abdominal ultrasound found 16mm hypoechoic nodes and a 10.5mm pericardial effusion without any stranding. The liver and spleen were normal; ascites was noted. The patient had a palpable axillary node which was aspirated. The sample was culture positive for TB. There was no history of previous tuberculosis.

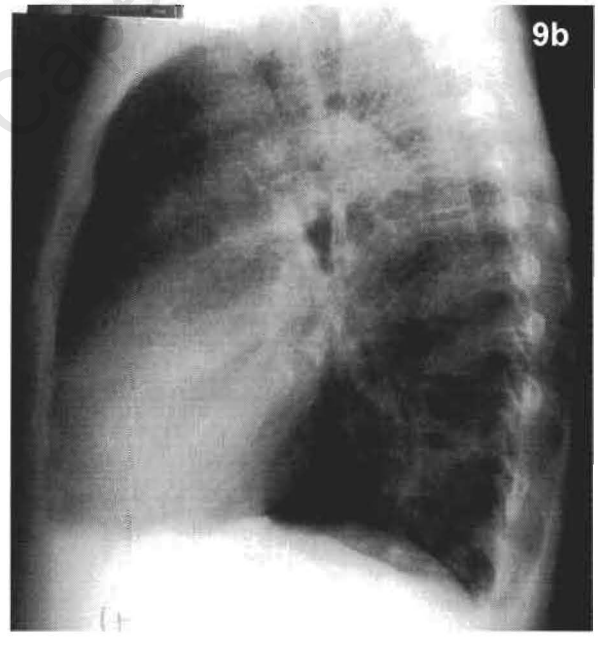


The same patient complained of a painful right wrist - radiographs (8b) revealed juxtaarticular osteopaenia in the region of the wrist with loss of clarity of the carpal bone margins and soft tissue swelling. In the setting of disseminated tuberculosis, these findings most likely represent inflammatory TB of the wrist.



Images 9a and 9b:

PA (9a) and lateral (9b) chest views demonstrating numerous small nodules (2 to 5mm) distributed throughout both lungs. Mild cardiomegaly is also present. The patient was a 34-year-old male, HIV positive, with stage 3 disease. No abdominal lymphadenopathy was present on ultrasound, but there was a 13mm pericardial effusion and a 17cm hepatomegaly.



The sputum smear and culture were positive for active tuberculosis.

Appendix 7: Odds ratio tables

ULTRASOUND FINDINGS (n = 267)		TB SPECIMENS																	
		SMEAR (n = 92)			CULTURE (n = 134)			SEROUS FLUID ADA (n = 47)			SMEAR or CULTURE (n = 170)			SMEAR or CULTURE or SEROUS FLUID ADA or HISTOLOGY (n = 181)			SMEAR or CULTURE or SEROUS FLUID ADA or CSF BIOCHEMISTRY or HISTOLOGY (n = 188)		
		+ ve	- ve	OR 95% CI p-value	+ ve	- ve	OR 95% CI p-value	+ ve	- ve	OR 95% CI p-value	+ ve	- ve	OR 95% CI p-value	+ ve	- ve	OR 95% CI p-value	+ ve	- ve	OR 95% CI p-value
LYMPHADENOPATHY (n = 125)	+ ve	51	74	1.70 0.99 - 2.92	71	54	1.65 0.99 - 2.76	28	97	1.87 0.94 - 3.72	94	31	**2.63 1.51 - 4.60**	99	26	**2.79 1.56 - 4.99**	102	23	**2.89 1.59 - 5.28**
	- ve	41	101	0.040	63	79	0.042	19	123	0.053	76	66	**0.0002**	82	60	**0.0001**	86	56	**0.0001**
HEPATOMEGALY (n = 58)	+ ve	14	44	0.53 0.26 - 1.08	26	32	1.76 0.41 - 1.42	12	46	1.30 0.58 - 2.84	32	26	0.63 0.34 - 1.19	35	23	0.66 0.34 - 1.25	36	22	0.61 0.32 - 1.18
	- ve	78	131	0.061	108	101	0.356	35	174	0.485	138	71	0.128	146	63	0.170	152	57	0.115
SPLENOMEGALY (n = 30)	+ ve	9	21	0.80 0.32 - 1.93	17	13	1.34 0.59 - 3.08	3	27	0.49 0.11 - 1.79	22	8	1.65 0.66 - 4.24	23	7	1.64 0.63 - 4.42	23	7	1.43 0.55 - 3.86
	- ve	83	154	0.585	117	120	0.451	44	193	0.245	148	89	0.242	158	79	0.269	165	72	0.425
SPLENIC LESIONS (n = 86)	+ ve	41	45	**2.32 1.32 - 4.10**	43	43	0.99 0.57 - 1.71	13	73	0.77 0.36 - 1.62	63	23	**1.89 1.04 - 3.46**	66	20	**1.89 1.02 - 3.55**	67	19	1.75 0.93 - 3.32
	- ve	51	130	**0.001**	91	90	0.966	34	147	0.462	107	74	**0.024**	115	66	**0.030**	121	60	0.064
ASCITES (n = 86)	+ ve	38	48	**1.86 1.06 - 3.28**	51	35	1.72 0.99 - 2.99	24	62	**2.88 1.46 - 5.69**	65	21	**2.24 1.22 - 4.15**	72	14	**3.40 1.71 - 6.83**	73	13	**3.22 1.59 - 6.62**
	- ve	54	127	**0.021**	83	98	0.040	23	158	**0.0007**	105	76	**0.005**	109	72	**0.0001**	115	66	**0.0003**
PERICARDIAL EFFUSION (n = 125)	+ ve	46	79	1.22 0.71 - 2.08	75	50	**2.11 1.26 - 3.55**	35	90	**4.21 1.98 - 9.12**	95	30	**2.83 1.62 - 4.96**	102	23	**3.54 1.95 - 6.45**	104	21	**3.42 1.85 - 6.35**
	- ve	46	96	0.449	59	83	**0.002**	12	130	**0.00002**	75	67	**0.00008**	79	63	**0.000005**	84	58	**0.00001**
LYMPHADENOPATHY and/or SPLENIC LESIONS (n = 136)	+ ve	56	80	**1.85 1.07 - 3.19**	75	61	1.90 0.90 - 2.50	29	107	1.70 0.85 - 3.41	101	35	**2.59 1.50 - 4.49**	106	30	**2.64 1.50 - 4.66**	109	27	**2.66 1.48 - 4.77**
	- ve	36	95	**0.018**	59	72	0.098	18	113	0.103	69	62	**0.0002**	75	56	**0.0002**	79	52	**0.0003**
LYMPHADENOPATHY, SPLENIC LESIONS and/or ASCITES (n = 163)	+ ve	65	98	**1.89 1.07 - 3.36**	91	72	**1.79 1.06 - 3.04**	38	125	**3.21 1.41 - 7.52**	118	45	**2.62 1.52 - 4.54**	127	36	**3.27 1.85 - 5.78**	130	33	**3.12 1.75 - 5.59**
	- ve	27	77	**0.019**	43	61	**0.021**	9	95	**0.002**	52	52	**0.0002**	54	50	**0.000009**	58	46	**0.00002**
LYMPHADENOPATHY, SPLENIC LESIONS, ASCITES and/or PERI-CARDIAL EFF (n = 190)	+ ve	71	119	1.59 1.86 - 2.97	105	85	**2.04 1.15 - 3.65**	42	148	**4.09 1.47 - 12.3**	135	55	**2.95 1.64 - 5.29**	144	46	**3.38 1.87 - 6.14**	149	41	**3.54 1.94 - 6.48**
	- ve	21	56	P=0.115	29	48	**0.009**	5	72	**0.002**	35	42	**0.00008**	37	40	**0.00001**	39	38	**0.000006**
ANY OF THE ABOVE (n = 205)	+ ve	76	129	1.69 0.86 - 3.36	111	94	**2.00 1.07 - 3.74**	43	162	**3.85 1.25 - 13.23**	142	63	**2.74 1.47 - 5.10**	151	54	**2.98 1.59 - 5.60**	157	48	**3.27 1.73 - 6.18**
	- ve	16	46	0.101	23	39	**0.018**	4	58	**0.008**	28	34	**0.0005**	30	32	**0.0001**	31	31	**0.00005**

COMBINATION FINDINGS ULTRASOUND		TB SPECIMENS																	
		SMEAR (n = 92)			CULTURE (n = 134)			SEROUS FLUID ADA (n = 47)			SMEAR or CULTURE (n = 170)			SMEAR or CULTURE or SEROUS FLUID ADA or HISTOLOGY (n = 181)			SMEAR or CULTURE or SEROUS FLUID ADA or CSF BIOCHEMISTRY or HISTOLOGY (n = 188)		
		+ ve	- ve	OR 95% CI p-value	+ ve	- ve	OR 95% CI p-value	+ ve	- ve	OR 95% CI p-value	+ ve	- ve	OR 95% CI p-value	+ ve	- ve	OR 95% CI p-value	+ ve	- ve	OR 95% CI p-value
SPLENIC LESIONS and LYMPHADENOPATHY (n = 75)	+ ve	36	39	**2.24 1.25 - 4.03 0.003**	39	36	1.11 0.63 - 1.95 0.711	12	63	0.85 0.39 - 1.84 0.667	56	19	**2.02 1.07 - 3.82 0.019**	59	16	**2.12 1.09 - 4.16 0.017**	60	15	**2.00 1.01 - 4.00 0.031**
	- ve	56	136		95	97		35	157		114	78		122	70		128	64	
SPLENIC LESIONS and ASCITES (n = 34)	+ ve	20	14	**3.19 1.44 - 7.12 0.001**	17	17	0.99 0.46 - 2.16 0.918	6	28	1.00 0.35 - 2.76 0.994	27	7	2.43 0.96 - 6.41 0.041	29	5	**3.09 1.08 - 9.48 0.019**	30	4	**3.56 1.14 - 12.39 0.014**
	- ve	72	161		117	116		41	192		143	90		152	81		158	75	
SPLENIC LESIONS and LYMPHADENOPATHY and ASCITES (n = 33)	+ ve	20	13	**3.46 1.54 - 7.84 0.0007**	17	16	1.06 0.48 - 2.34 0.870	6	27	1.05 0.36 - 2.89 0.925	27	6	**2.86 1.07 - 8.07 0.020**	29	4	**3.91 1.25 - 13.61 0.008**	30	3	**4.81 1.35 - 20.44 0.005**
	- ve	72	162		117	117		41	193		143	91		152	82		158	76	
HEPATOMEGALY and SPLENIC LESIONS (n = 25)	+ ve	10	15	1.30 0.52 - 3.24 0.540	9	16	0.53 0.21 - 1.32 0.136	4	21	0.88 0.24 - 2.91 0.825	15	10	0.84 0.34 - 2.12 0.688	17	8	1.01 0.39 - 2.68 0.981	17	8	0.88 0.34 - 2.35 0.781
	- ve	82	160		125	117		43	199		155	87		164	78		171	71	
HEPATOMEGALY and LYMPHADENOPATHY (n = 34)	+ ve	9	25	0.65 0.27 - 1.55 0.294	17	17	0.99 0.46 - 2.16 0.981	8	26	1.53 0.59 - 3.88 0.331	22	12	OR=1.05 (CI=0.47-2.39) P=0.893	24	10	OR=1.16 (CI=0.50-2.75) P=0.708	24	10	OR=1.01 (CI=0.43-2.40) P=0.980
	- ve	83	150		117	116		39	194		148	85		157	76		164	69	
HEPATOMEGALY and ASCITES (n = 23)	+ ve	7	16	0.82 0.29 - 2.22 0.671	13	10	1.32 0.52 - 3.39 0.525	7	16	2.23 0.77 - 6.26 0.090	17	6	OR=1.69 (CI=0.60-4.98) P=0.285	19	4	OR=2.40 (CI=0.74-8.66) P=0.111	19	4	OR=2.11 (CI=0.65-7.60) P=0.180
	- ve	85	159		121	123		40	204		153	91		162	82		169	75	
HEPATOMEGALY and PERICARDIAL EFFUSION (n = 31)	+ ve	7	24	0.52 0.19 - 1.33 0.138	18	13	1.43 0.63 - 3.26 0.350	10	21	**2.56 1.03 - 6.30 0.022**	21	10	1.23 0.52 - 2.94 0.616	24	7	1.73 0.67 - 4.62 0.222	24	7	1.51 0.58 - 4.04 0.363
	- ve	85	151		116	120		37	199		149	87		157	79		164	72	
HEPATOMEAGLY and SPLENIC LESIONS and ASCITES (n = 10)	+ ve	6	4	2.98 0.72 - 12.97 0.083	4	6	0.65 0.15 - 2.68 0.369	2	8	1.18 0.00 - 6.29 0.551	8	2	2.35 0.45 - 16.34 0.228	9	1	4.45 0.56 - 95.24 0.113	9	1	3.92 0.50 - 84.05 0.150
	- ve	86	171		130	127		45	212		162	95		172	85		179	78	
HEPATOMEAGLY and SPLENIC LESIONS and LYMPHADENOPATHY (n = 23)	+ ve	9	14	1.25 0.47 - 3.23 0.621	9	14	0.61 0.23 - 1.58 0.267	4	19	0.98 0.27 - 3.28 0.620	14	9	0.88 0.34 - 2.30 0.770	16	7	1.09 0.40 - 3.07 0.848	16	7	0.96 0.35 - 2.69 0.925
	- ve	83	161		125	119		43	201		156	88		165	79		172	72	
HEPATOMEAGLY and LYMPHADENOPATHY and ASCITES (n = 16)	+ ve	6	10	1.15 0.36 - 3.59 0.791	9	7	1.30 0.43 - 4.00 0.616	4	12	1.61 0.42 - 5.75 0.304	13	3	2.59 0.67 - 11.79 0.131	14	2	3.52 0.74 - 22.98 0.081	14	2	3.10 0.65 - 20.24 0.098
	- ve	86	165		125	126		43	208		157	94		167	84		174	77	
HEPATOMEGALY and ASCITES and PERICARDIAL EFF (n = 15)	+ ve	4	11	0.68 0.18 - 2.39 0.513	10	5	2.06 0.63 - 7.16 0.188	6	9	**3.43 1.02 - 11.30 0.030**	12	3	2.38 0.60 - 10.92 0.175	14	1	7.13 0.96 - 147.64 0.021	14	1	6.28 0.84 - 130.12 0.034
	- ve	88	164		124	128		41	211		158	94		167	85		174	78	

CXR FINDINGS (n = 262)		TB SPECIMENS																	
		SMEAR (n = 92)			CULTURE (n = 134)			SEROUS FLUID ADA (n = 47)			SMEAR or CULTURE (n = 170)			SMEAR or CULTURE or SEROUS FLUID ADA or HISTOLOGY (n = 181)			SMEAR or CULTURE or SEROUS FLUID ADA or CSF BIOCHEMISTRY or HISTOLOGY (n = 188)		
		+ ve	- ve	OR 95% CI p-value	+ ve	- ve	OR 95% CI p-value	+ ve	- ve	OR 95% CI p-value	+ ve	- ve	OR 95% CI p-value	+ ve	- ve	OR 95% CI p-value	+ ve	- ve	OR 95% CI p-value
THORACIC LYMPHADENOPATHY (n = 77)	+ ve	40	37	**2.92 1.62 - 5.27 0.0001**	46	31	1.64 0.92 - 2.91 0.072	10	67	0.60 0.26 - 1.34 0.177	62	15	**3.01 1.53 - 5.99 0.0004**	64	13	**2.93 1.44 - 6.04 0.0011**	65	12	1.69 0.86 - 3.36 0.101
	- ve	50	135		88	97		37	148		107	78		116	69		120	65	
CONSOLIDATION (n = 120)	+ ve	45	75	1.21 0.71 - 2.08 0.457	61	59	0.98 0.58 - 1.64 0.926	22	98	1.05 0.53 - 2.07 0.878	77	43	0.94 0.55 - 1.62 0.822	85	35	1.16 0.66 - 2.04 0.573	87	33	1.07 0.60 - 1.90 0.805
	- ve	47	95		73	69		25	117		93	49		96	46		101	41	
NODULES (n = 116)	+ ve	53	63	**2.31 1.33 - 4.01 0.001**	55	61	0.78 0.46 - 1.31 0.313	13	103	0.42 0.20 - 0.87 0.011	79	37	1.29 0.75 - 2.23 0.330	83	33	1.23 0.70 - 2.17 0.441	84	32	1.06 0.60 - 1.89 0.832
	- ve	39	107		79	67		34	112		91	55		98	48		104	42	
CAVITATION (n = 23)	+ ve	10	13	1.53 0.59 - 3.92 0.334	12	11	1.05 0.41 - 2.66 0.917	2	21	0.41 0.06 - 1.91 0.226	16	7	1.28 0.47 - 3.60 0.595	18	5	1.71 0.57 - 5.49 0.300	18	5	1.55 0.52 - 4.98 0.399
	- ve	80	159		122	117		45	194		153	86		162	77		167	72	
PLEURAL EFFUSION (n = 81)	+ ve	18	63	0.43 0.23 - 0.82 0.005	54	27	2.53 0.41 - 4.53 0.0007	44	37	**70.56 19.57 - 301.9 0.00000**	59	22	1.73 0.94 - 3.20 0.059	69	12	**3.63 1.76 - 7.62 0.0001**	69	12	**3.22 1.56 - 6.79 0.0005**
	- ve	72	109		80	101		3	178		110	71		111	70		116	65	
CARDIOMEGALY (n = 44)	+ ve	12	32	0.67 0.31 - 1.45 0.278	23	21	1.06 0.53 - 2.12 0.869	12	32	1.96 0.86 - 4.43 0.076	27	17	0.85 0.42 - 1.75 0.633	30	14	0.97 0.46 - 2.07 0.934	31	13	0.99 0.46 - 2.14 0.980
	- ve	78	140		111	107		35	183		142	76		150	68		154	64	
CONSOLIDATION and/or NODULES (n = 195)	+ ve	72	123	1.59 0.83 - 3.09 0.134	99	96	0.94 0.52 - 1.70 0.835	30	165	0.53 0.26 - 1.11 0.066	128	67	1.21 0.66 - 2.23 0.511	137	58	1.33 0.71 - 2.48 0.342	140	55	1.24 0.66 - 2.36 0.472
	- ve	18	49		35	32		17	50		41	26		43	24		45	22	
CONSOLIDATION, NODULES and/or PLEURAL EFFUSION (n = 215)	+ ve	75	140	1.14 0.56 - 2.37 0.679	116	99	1.89 0.95 - 3.79 P=0.051	46	169	**12.52 1.78 - 250.6 0.0018**	145	70	**1.99 1.00-3.94 0.033**	156	59	**2.53 1.27 - 5.08 0.003**	159	56	**2.29 1.14 - 4.62 0.011**
	- ve	15	32		18	29		1	46		24	23		24	23		26	21	
CONSOLIDATION and/or PLEURAL EFFUSION (n = 157)	+ ve	52	105	0.87 0.50 - 1.52 0.608	90	67	**1.86 1.10 - 3.17 0.014**	46	111	**43.1 6.23 - 855.9 0.00000**	107	50	1.48 0.86 - 2.56 0.131	118	39	**2.10 1.19 - 3.70 0.005**	120	37	**2.00 1.12 - 3.55 0.011**
	- ve	38	67		44	61		1	104		62	43		62	43		65	40	
ANY OF THE ABOVE (n = 233)	+ ve	85	148	2.76 0.95 - 8.58 0.039	127	106	**3.77 1.45 - 10.13 0.002**	46	187	6.89 0.96 - 139.5 0.031	159	74	**4.08 1.70 - 9.97 0.0003**	170	63	**5.13 2.12 - 12.60 0.00002**	174	59	**4.83 2.02 - 11.67 0.00004**
	- ve	5	24		7	22		1	28		10	19		10	19		11	18	

COMBINATION FINDINGS CXR		TB SPECIMENS																	
		SMEAR (n = 92)			CULTURE (n = 134)			SEROUS FLUID ADA (n = 47)			SMEAR or CULTURE (n = 170)			SMEAR or CULTURE or SEROUS FLUID ADA or HISTOLOGY (n = 181)			SMEAR or CULTURE or SEROUS FLUID ADA or CSF BIOCHEMISTRY or HISTOLOGY (n = 188)		
		+ ve	- ve	OR 95% CI p-value	+ ve	- ve	OR 95% CI p-value	+ ve	- ve	OR 95% CI p-value	+ ve	- ve	OR 95% CI p-value	+ ve	- ve	OR 95% CI p-value	+ ve	- ve	OR 95% CI p-value
THORACIC NODES and CONSOLIDATION (n = 32)	+ ve	17	15	**2.44 1.09 - 5.49 0.016**	20	12	1.70 0.75 - 3.89 0.170	5	27	0.83 0.26 - 2.44 0.715	26	6	2.64 0.98 - 7.46 0.034	28	4	**3.59 1.14 - 12.55 0.014**	28	4	**3.25 1.03 - 11.39 0.025**
	- ve	73	157		114	116		42	188		143	87		152	78		157	73	
THORACIC NODES and NODULES (n = 39)	+ ve	22	17	**2.95 1.40 - 6.25 0.001**	18	21	0.79 0.38 - 1.65 0.499	6	33	0.81 0.28 - 2.19 0.652	30	9	2.01 0.86 - 4.82 0.078	31	8	1.92 0.80 - 4.8 0.115	32	7	2.09 0.83 - 5.48 0.089
	- ve	68	155		116	107		41	182		139	84		149	74		153	70	
THORACIC NODES and CONSOLIDATION and PLEURAL EFFUSION (n = 13)	+ ve	5	8	1.21 0.33 - 4.23 0.480	8	5	1.56 0.45 - 5.67 0.441	5	8	3.08 0.83 - 11.08 0.062	9	4	1.25 0.34 - 4.98 0.483	11	2	2.60 0.53 - 17.43 0.168	11	2	2.37 0.48 - 15.89 0.209
	- ve	85	164		126	123		42	207		160	89		169	80		174	75	
NODULES and PLEURAL EFFUSION (n = 27)	+ ve	9	18	0.95 0.38 - 2.36 0.906	14	13	1.03 0.43 - 2.45 0.938	13	14	**5.49 2.20 - 13.73 0.0001**	19	8	1.35 0.53 - 3.51 0.501	23	4	2.86 0.89 - 10.12 0.051	23	4	2.59 0.81 - 9.20 0.079
	- ve	81	154		120	115		34	201		150	85		157	78		162	73	
CONSOLIDATION and PLEURAL EFFUSION (n = 44)	+ ve	11	33	0.59 0.26 - 1.29 0.152	25	19	1.32 0.65 - 2.66 0.409	20	24	**5.90 2.71 - 12.86 0.0000002**	29	15	1.08 0.52 - 2.25 0.830	36	8	2.31 0.97 - 5.70 0.039	36	8	2.08 0.87 - 5.15 0.073
	- ve	79	139		109	109		27	191		140	78		144	74		149	69	
CARDIOMEGALY and PLEURAL EFFUSION (n = 21)	+ ve	4	17	0.42 0.12 - 1.40 0.123	13	8	1.61 0.60 - 4.43 0.303	12	9	**7.85 2.82 - 22.11 0.00002**	15	6	1.41 0.49 - 4.25 0.489	18	3	2.93 0.78 - 12.89 0.079	18	3	2.66 0.71 - 11.72 0.113
	- ve	86	155		121	120		35	206		154	87		162	79		167	74	

CXR and ULTRASOUND		TB SPECIMENS																	
		SMEAR (n = 92)			CULTURE (n = 134)			SEROUS FLUID ADA (n = 47)			SMEAR or CULTURE (n = 170)			SMEAR or CULTURE or SEROUS FLUID ADA or HISTOLOGY (n = 181)			SMEAR or CULTURE or SEROUS FLUID ADA or CSF BIOCHEMISTRY or HISTOLOGY (n = 188)		
		+ ve	- ve	OR 95% CI p-value	+ ve	- ve	OR 95% CI p-value	+ ve	- ve	OR 95% CI p-value	+ ve	- ve	OR 95% CI p-value	+ ve	- ve	OR 95% CI p-value	+ ve	- ve	OR 95% CI p-value
THORACIC NODES and ABDOMINAL NODES (n = 54)	+ ve	29	25	**2.80 1.45 - 5.40**	33	21	1.66 0.87 - 3.21	10	44	1.05 0.45 - 2.41	46	8	**3.97 1.70 - 9.63**	48	6	**4.61 1.79 - 12.58**	49	5	**5.18 1.87 - 15.52**
	- ve	61	147	**0.0007**	101	107	0.100	37	171	0.900	123	85	**0.0003**	132	76	**0.0003**	136	72	**0.0002**
NODULES and SPLENIC LESIONS (n = 44)	+ ve	27	17	**3.91 1.90 - 8.10**	18	26	0.61 0.30 - 1.23	5	39	0.54 0.17-1.54	31	13	1.38 0.65 - 2.97	34	10	1.68 0.74 - 3.86	35	9	1.76 0.76 - 4.19
	- ve	63	155	**0.00003**	116	102	0.136	42	176	0.212	138	80	0.365	146	72	0.178	150	68	0.153
PLEURAL EFFUSION and ASCITES (n = 37)	+ ve	9	28	0.57 0.24 - 1.34	25	12	**2.22 1.01 - 4.95**	24	13	**16.21 6.80 - 39.26**	27	10	1.58 0.69 - 3.69	34	3	**6.13 1.73 - 25.89**	34	3	**5.55 1.56 - 23.48**
	- ve	81	144	0.165	109	116	**0.031**	23	202	**0.000**	142	83	0.245	146	79	**0.001**	151	74	**0.002**
CONSOLIDATION and ABDOMINAL NODES (n = 51)	+ ve	20	31	1.30 0.66 - 2.55	29	22	1.33 0.69 - 2.58	14	37	2.04 0.93 - 4.42	38	13	1.79 0.86 - 3.77	42	9	**2.47 1.08 - 5.79**	43	8	**2.61 1.11 - 6.38**
	- ve	70	141	0.414	105	106	0.362	33	178	0.048	131	80	0.096	138	73	**0.019**	142	69	**0.016**