



# Unusual Presentations of Tuberculosis: A Case Series

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## Abstract

**Introduction:** Tuberculosis (TB) is an air-borne infection caused by the organism *Mycobacterium Tuberculosis* that can affect any organ though it commonly involves infection of the lungs. Given the nature of Extra-Pulmonary Tuberculosis (EPTB) that has various form of clinical manifestation, diagnosing EPTB remains a challenge. **Background:** This report discusses three cases of EPTB that posed diagnostic and management challenges. The first case presented as pleural effusion and TB was diagnosed on pleural biopsy. The second case presented with abdominal pain and mass in the right iliac fossa. Final diagnosis of tuberculous colitis was made post-laparotomy and he underwent successful anti-tuberculous treatment. The third case presented with a single enlarged cervical lymph node and a typical history. Investigations were suggestive of tuberculous lymphadenitis and patient showed a positive response to anti-tuberculous treatment. **Conclusion:** EPTB has various forms of clinical manifestation, which imposes diagnostic and treatment challenges. Thus, it is crucial to always include tuberculosis as part of working diagnosis especially in regions where tuberculosis is endemic until proven otherwise. Hence it is imperative to start treatment early to ensure better response.

## Keywords

Extra-Pulmonary Tuberculosis, Pleural Effusion, Colitis, Lymphadenitis

**Subject Areas:** Infectious Diseases

## 1. Introduction

Tuberculosis (TB) is an air-borne infection caused by the organism *Mycobacterium Tuberculosis* which can affect any organ though it commonly involves infection of the lungs [1]. TB is further classified into Pulmonary

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Tuberculosis (PTB) and Extra-Pulmonary Tuberculosis (EPTB) based on the site of infection as per the name suggests. EPTB makes up at least 20% of TB cases worldwide [2]. Although the most common site of infection of EPTB is lymph node, other sites of infection include pleura, urogenital tract, bones and joints, meninges, central nervous system, bowel and/or peritoneum, pericardium, and skin [3]. Studies conducted in Netherlands and United States have established that EPTB commonly affects women, ethnic minorities and foreigners [4]. In addition, various studies have proven that immunocompromised status especially having retroviral disease along with other less common factors like diabetes mellitus, malnourishment, extremes of age groups and prolonged chemotherapy or steroid treatment are frequently associated with EPTB infection [5] [6]. Despite having significant risk factors, an effective algorithm in identifying, diagnosing and managing EPTB still remains a challenge. This is mainly contributed by the nature of EPTB that could mimic other common pathologies [7] [8]. Besides that, various clinical manifestation of EPTB imposes difficulties in obtaining relevant sample of specimen for diagnostic purposes [9]. Thus, EPTB remains a challenging diagnosis given its dependency on a very high clinical suspicion. Besides that, varying clinical expertise of the clinicians, limited access to diagnostic measures and a lack of experience in managing EPTB impose great limitations in diagnosing and treating EPTB.

## 2. Case Presentation

### 2.1. Case 1: Tuberculosis of the Pleura

The first case presentation is based on a 22 years old male of Malay descent, a contractor who presented to the hospital with a three day history of non-productive cough associated with right sided pleuritic chest pain and high fever associated with chills and rigors. However he denied any hemoptysis. With regards to his fever, it had been consistently high over the three days that worsened at night as well. He denied having night sweats. In addition, he also experienced headache and fatigue. However, he had no previous medical or surgical history. He is not currently on any medication. He had no history of smoking, alcohol use or any form of illicit drug abuse. The patient had no recent history of travel but had been in consistent contact with foreign workers from Bangladesh, Indonesia and Nepal. Besides that, he had history of tuberculosis patient contact with his sister three weeks prior to presentation.

Upon physical examination, he was febrile at a temperature of 39.4°C. On examination of the chest, there was an obvious reduction of chest wall expansion on the right side. Percussion note revealed stony dullness on right lower zone of the lung. Upon auscultation, air entry was absent on the right lower zone.

Further investigations (refer [Table 1](#)) revealed mildly elevated white blood cell count and a high erythrocyte sedimentation rate. Sputum smear results were negative for acid-fast bacilli and sputum culture revealed no growth. A chest X-Ray (refer [Image 1](#)) revealed a right-sided pleural effusion, which was followed by pleurocentesis and pleural biopsy. The pleural fluid smear and culture results were both negative. Pleural fluid biochemistry on the other hand revealed an exudative effusion (refer [Table 2](#)). Histopathological examination of the pleural biopsy was reported as granulomatous inflammation and thus raised a high suspicion of tuberculosis given that the patient did not respond to initial treatment of intravenous Ceftriaxone 2grams once daily for seven days (choice and dosage of antibiotics were adopted from the National Antibiotics Guidelines 2014, Malaysia).

Thus, patient was diagnosed with tuberculosis of pleura. He was started on standard anti-tuberculous treatment which consisted of two months of intensive therapy followed by 7 months of maintenance therapy. He was treated with four oral drugs during the intensive phase which were isoniazid, rifampicin, ethambutol and pyrazinamide. The maintenance phase of treatment incorporated two oral drugs which were isoniazid and rifampicin. Oral pyridoxine supplementation was given throughout the treatment course to prevent the development of isoniazid induced peripheral neuropathy. At the end of his treatment, patient completely recovered from his clinical symptoms and has gained weight from 56 kg to 63 kg. His post treatment chest X-Ray showed clear lung fields with right lower subpleural thickening ([Image 2](#)).

### 2.2. Case 2: Tuberculous Colitis

A 64-year-old male of Chinese descent presented with a history of loss of weight, loss of appetite and low-grade fever of uncertain duration. He however did not experience any altered bowel habits or haematochezia. There were no significant risk factors. In addition, patient was a non-smoker although he consumed alcohol occasionally. He did not have any significant family or past medical history. Besides, there was no recent travel history or contact with tuberculosis patients.



**Image 1.** Chest X-Ray at presentation (before treatment) shows right sided pleural effusion.



**Image 2.** Chest X-Ray post completion of treatment shows resolution of right sided pleural effusion with right lower subpleural thickening.

**Table 1.** Blood investigations.

Parameters	Values
Haemoglobin	14.7 g/dL
Total White Cell	$11 \times 10^9/L$
Platelet	$353 \times 10^9/L$
ESR	62 mm/hr (raised)
Urea	3.8 mmol/L
Creatinine	89 $\mu\text{mol/L}$
AST	27 U/L
HIV	Non reactive
Hep B	Non reactive
Hep C	Non reactive

**Table 2.** Pleural fluid analysis.

Parameters	Values (normal)
Total Protein	59 g/l (pleural:serum Total protein >0.5)
Lactate Dehydrogenase	1220 U/L (pleural:serum LDH ratio >0.6)
Glucose	4.5 mmol/L
Amylase	37 U/L
Urea	3 mmol/L
Creatinine	73 umol/L
Albumin	34 g/L
Culture	No growth

Upon physical examination, patient's vital signs were stable. His significant examination findings included mildly distended abdomen with a positive fluid shift but negative fluid thrill. A localized mass was palpable in the right iliac fossa, which was tender on palpation.

The blood parameters are as shown in **Table 3**. Further, peritoneal fluid was tapped and analyzed; findings include scattered mesothelial cells and abundant inflammatory cells predominantly polymorphs, lymphocytes and histiocytes, which were highly suggestive of inflammatory yield. However, malignant cells were not observed. A colonoscopy was then performed at a different center (refer **Image 3**) and the macroscopic appearance of the lesion was suggestive of a tumor and biopsied.

Thus, patient underwent an exploratory laparotomy and a right-hemicolectomy was performed. The specimen was sent for further histopathology examination, which showed granulomatous enterocolitis and epithelioid histiocytes, multinucleated Langhan's type giant cells, lymphocytes and fibrosis.

This led to a suspicion of tuberculous colitis and thus patient was started on anti-tuberculosis treatment which consisted of two months of intensive therapy followed by seven months of maintenance treatment. During the two months of intensive phase, he was given four oral drugs which were isoniazid, rifampicin, ethambutol and pyrazinamide. The seven month maintenance phase consisted of oral isoniazid and rifampicin. Oral pyridoxine supplementation was added throughout the course of treatment to prevent isoniazid induced peripheral neuropathy. Patient showed improvement of clinical symptoms including progressive weight gain upon commencement of anti-tuberculosis treatment which was completed over a duration of nine months.

### 2.3. Case 3: Tuberculous Cervical Lymphadenitis

A 40-year-old female patient presented to the local general practitioner clinic complaining of swelling on her right side of the neck for 1 month. This was associated with loss of appetite, loss of weight and night sweats. However she did not experience any episodes of fever or prolonged cough although she had positive tuberculosis contact history. She has a background history of type 2 diabetes mellitus, for which she is on oral anti-diabetic medication. She is a non-smoker and has no history of illicit drug use or alcohol consumption.

Upon physical examination, patient was comfortable and alert. She was afebrile. Significant findings included an enlarged right cervical lymph node. This measured to approximately 1 cm × 1 cm, non-tender upon palpation, and appeared matted.

The blood investigations are as shown in **Table 4**. Her ESR upon presentation to the GP was raised at 110 mm/hr with normal full blood examination parameters except for her monocyte count, which was raised at 13%. Her chest X-ray was normal. The tuberculin skin test was raised to 25mm at 72 hours. She was then started on standard anti-tuberculous medications which consisted of two months of intensive therapy incorporating four oral drugs which were isoniazid, rifampicin, ethambutol and pyrazinamide. The maintenance treatment consisted of seven month therapy of two oral drugs which were isoniazid and rifampicin. Oral pyridoxine supplementation was added throughout the course of treatment. Symptomatic improvement was noticed in the first month with significant weight gain, better appetite and she stopped having night sweats. The lymph node remained same in size after the first month of treatment. There were no new enlarged lymph nodes.



**Image 3.** A mass lesion on lower end of ascending colon on colonoscopy.

**Table 3.** Investigation findings.

Parameters	Values
Haemoglobin	14.0 g/dL
Red Blood Cell Count	$5.1 \times 10^6/\text{ml}$
Platelet Count	$500 \times 10^9/\text{L}$
Erythrocyte Sedimentation Rate (ESR)	39 mm/hr
Total White Cell Count	$5.0 \times 10^9/\text{L}$
Urea	2.0 mmol/L
Creatinine	61 micromol/L
Total protein	67 g/L
Albumin	31 g/L
ALT	18 U/L
AST	19 U/L
Alkaline Phosphatase	72 U/L

### 3. Discussion

#### 3.1. Tuberculous Pleural Effusion

Tuberculous pleural effusion is an accumulation of fluid at pleural space due to a delayed hypersensitivity reaction that is either a manifestation of a primary Mycobacterium Tuberculosis infection or secondary to reactivation of the disease. Tuberculous pleural effusion being the second most common type of extra pulmonary tuberculosis makes up 5% of the total Mycobacterium Tuberculosis infection [10]. The incidence of tuberculous pleural effusion however, varied from 4% in United States to 23% in Spain despite a higher frequency of Tuberculosis patient in the Asian continent [11] [12].

The pathogenesis of tuberculous pleural effusion is initiated by the rupture of subpleural caseous focus of the lung into the pleural space [13]. This is followed by hypersensitivity reaction mediated by predominantly CD4 T

**Table 4.** Blood investigations.

Parameters	Values
Haemoglobin	11.3 g/dl
Red Blood Cell Count	$4.0 \times 10^6/\text{ml}$
Haem Indices ( PCV, MCV, MCH, MCHC)	PCV 35%
	MCV 88 fl
	MCH 28 pg/cell
	MCHC 32 %
Platelet Count	$267 \times 10^9/\text{L}$
Erythrocyte Sedimentation Rate (ESR)	110 mm/hr
Total White Cell Count	$7.0 \times 10^9/\text{L}$
Differential Count	Polymorphs 66%
	Lymphocytes 20%
	Monocytes 13%
	Eosinophils 1%
	Basophils 0%
Peripheral Blood Film	Normal Blood Film

helper lymphocytes that occurs approximately 6 - 12 weeks after the primary infection [14] [15]. As a consequence, the adenosine deaminase (ADA) and gamma-interferon will be markedly elevated in the tuberculous pleural fluid [16]. The accumulation of fluid in pleural space in primary disease is due to increase in permeability of the capillaries and occlusion of pleural stomata that impairs lymphatic clearance of protein and fluid in pleural space whereas in tuberculous pleural effusion secondary to reactivation of the disease, this is mainly associated with parenchymal damage [17] [18].

Thus, patients with tuberculous pleural infection usually present as acute illness with common clinical symptoms of non-productive cough, pleuritic chest pain and fever for less than one week [19] [20]. Previous studies have demonstrated that the mean age of primary tuberculous pleuritis is 28 years old whereas in secondary reactivation, the mean age is 54 years old [21]. However, a newer study has established a higher median age of 56 years old in all patients presenting with tuberculous pleuritis [22]. Thus, the diagnosis of pleural tuberculosis should be considered in any adult or elderly patient presenting with unilateral pleural effusion [23]. Besides that, the incidence of tuberculous pleural effusion is higher among patients with HIV positive although being a hypersensitivity reaction; the rate of pleural tuberculosis should be lower in immuno-compromised state [24]. However, a study has proven that tuberculous pleural effusion is more common in HIV patients with higher CD4+ counts [25]. Besides, HIV positive patients presenting with tuberculous pleuritis are usually older and have a higher incidence of disseminated disease [26].

Although tuberculous pleuritis may resolve spontaneously without aggressive treatment, studies have proven that subsequently, as much as 65% of tuberculous pleural effusion patients have developed some form of active tuberculosis regardless of the nature and severity of their initial presentation [27]. This emphasizes the need to diagnose and manage tuberculous pleural effusion effectively. A study in Malaysia has concluded that a good overall treatment outcome of pleural tuberculosis is determined by early detection of the disease and implementing measures to ensure high adherence rate [28]. Thus, the major challenge in managing pleural tuberculosis remains in effective diagnosis.

Firstly, the pleural fluid in tuberculosis infection is invariably an exudate where its protein levels are almost always more than 5 g/dL and small lymphocytes makes up more than 50% of the content [20]. Besides that, if a patient presents within two weeks of infection, the pleural fluid would predominantly contain polymorphonuclear leucocytes [29]. Other than that, glucose of pleural fluid would either be lower or equivalent to the levels

of glucose in serum whereas the LDH levels would be higher in pleural fluid [30]. Although the pH levels of pleural fluid maybe lower, in general the pH levels would be always higher than 7.30 [31]. In order to exclude tuberculosis as a differential diagnosis, although many studies have concluded that eosinophil levels are more than 10% will rule out tuberculosis infection, one study has articulated that this may not be the case anymore given that a Spanish study has established that 15.6% of eosinophilic pleural effusion in 45 patients was due to tuberculosis infection [31] [32]. Besides, this rule is also an exception in patients with pneumothrax or previous thoracentesis as blood or air in the pleural space would invariably trigger eosinophilia [31] [32].

Various studies have conferred that one of the easiest and effective ways diagnosing tuberculous pleuritis is by demonstrating pleural fluid adenosine deaminase (ADA) level of more than 40 U/L and an elevated pleural fluid interferon gamma levels [33]. In fact, meta analysis has concluded that the combined specificity and sensitivity for pleural fluid ADA and interferon gamma levels in diagnosing tuberculosis pleural effusion is 93% and 96% respectively [34]. A cost analysis study in India has established that pleural fluid interferon gamma levels are more sensitive compared to pleural ADA levels in diagnosing tuberculosis pleural effusion [35]. However, the same study has concluded that, the cost of performing this additional test in diagnosis one tuberculous pleuritis patient is equivalent to the cost of anti-tuberculosis treatment of six patients [28]. Thus, in developing countries where resources of medical treatment are limited, these tests may not be cost effective [35].

Other than that, sputum smear and culture that are routinely done to diagnose pulmonary tuberculosis is rather underutilized in diagnosing tuberculous pleural effusion [33]. Studies have shown that as many as 35 out of 64 pleural tuberculosis patients (55%) whose sputum has been induced have positive sputum study despite having a clear chest X-Ray except for unilateral pleural effusion [36]. Although routine pleural fluid smear may not be useful, pleural fluid culture especially using BACTEC system has been proven to provide higher yields and faster results in diagnosing tuberculous pleural effusion [20] [37] [38]. Blind needle biopsy of the parietal pleura still is one of the effective method of diagnosing tuberculous pleural effusion [39]. Demonstrating granulomatous pleuritis on parietal pleural biopsy is sufficient to raise the suspicion of tuberculous pleural effusion as 95% of granulomatous pleuritis is due to mycobacterium tuberculosis infection [39].

In terms of treating tuberculous pleurisy, a standard six-month treatment regimen is adequate in most of the cases [40]. This six month course is divided into 2 months of intensive treatment with isoniazid, rifampicin and pyrazinamide which followed by a four months of maintenance treatment with isoniazid and rifampicin only [41]. In countries where isoniazid resistance is prevalent, ethambutol or streptomycin should be added [42]. Other than that, surgical drainage, debridement, decortication and rib resection which used in treating patients with extensive pleuropulmonary disease is now rarely indicated except for thoracoscopy to make a definite diagnosis [40]. Besides that, another major concern is residual pleural thickening that occurs in at least 50% of patients, 6 - 12 months post-treatment especially in patients presented with loculated pleural effusion [43]. The use of fibrinolytic agent like urokinase has been proven to reduce residual pleural thickening [44]. Besides that, paradoxically worsening of pleural effusion upon commencement of treatment may occur which has been postulated to be due to isoniazid induced lupus pleuritis [45]. Some patients may also develop peripheral lung nodule, which will resolve upon completion of anti-tuberculous treatment [46]. Other than that, the role of corticosteroid is not indicated as studies have shown that there are no significant differences in patients treated with corticosteroid in terms clinical outcome, rate of absorption of pleural fluid, pleural sequelae and lung capacity at the end of treatment [47]. Besides that, although early drainage of pleural fluid confers better clinical treatment outcome, repeated drainage or complete drainage of pleural effusion does not confer any added advantages [48].

### 3.2. Tuberculous Colitis

On the other hand, tuberculous enteritis is tuberculous infection that can affect any part of the gastrointestinal tract though it commonly affects the ileocaecal junction [49]-[52]. Although tuberculous colitis is rather rare in developed countries, the incidence of such cases are on the rise for the past two decades where it accounts for up to 1% - 3% of tuberculosis worldwide [49] [53]-[55]. Age, sex, socioeconomic status, immune status and Mycobacterium Tuberculosis genotype are major contributing factors towards a widely variable epidemiology of tuberculous colitis worldwide [56]. Studies have shown a predominance of female and young adults in regions with higher incidence of tuberculous colitis like Pakistan, Turkey, and West Africa [56]. However, in regions of lower incidence namely China, Singapore, India and the United Kingdom, such gender predominance is either equal or more towards male patients [56]. Besides that, studies have established immunocompromised status in

particular retroviral disease as a strong risk factor for developing tuberculous colitis just like any other extra-pulmonary tuberculosis in whole [57]. It is very important to note that tuberculous may mimic any gastrointestinal condition, which include Crohn's Disease and carcinoma of the colon and thus, impose great diagnostic challenges [57] [58].

The etiology of tuberculous enteritis is usually due to ingestion of bacterium; *i.e.* through food particles or bronchiole secretions in patients with existing pulmonary tuberculosis [55] [58]. Besides that, spread from adjacent organs or via haematogenous spread is also another common etiology [59]. The terminal ileum particularly ileocaecal junction is the commonest site of infection tuberculosis which accounts for up to 90% of tuberculous colitis cases [50]-[52] [59]. The abundance of lymphoid tissue at terminal ileum, the stasis of intestinal content at the ileocaecal valve and the relatively longer transit time of intestinal contents with the mucosa at terminal region is the major contributory factors that facilitate the tuberculous infection at this region [60]-[63]. Besides that, tuberculous colitis less commonly affects ascending and descending colon as well [51].

Clinically, tuberculous colitis patients present with non-specific symptoms, which predominantly includes abdominal pain and weight loss [64]-[66]. Besides that, less than 50% of 69 tuberculous patients in a study presented with fever, followed by per rectal bleed in 20% of patients and less commonly, abdominal mass was seen in only 6.4% patients [59]. However, another study by Palmer et al. has shown up to 43% of tuberculous colitis patients presented with abdominal mass [67]. Various studies have also established that endoscopic features of tuberculosis of the colon is usually non-specific where it may show segmental ulcers, polyps, tumors, inflammatory stricture and rarely tuberculous colitis which could potentially mimic inflammatory bowel disease and malignancy of the colon [64] [66]-[69]. In addition, one retrospective review of 86 cases of tuberculous colitis showed 98% of participants with elevated ESR levels, 64% had microcytic anemia with reduction of albumin in 73% of patients [70]. Besides that, an estimated 15% - 20% of patients with tuberculous colitis did not show any significant chest X-ray findings [51]. Thus, this explains the challenges in diagnosing tuberculous colitis.

Looking at evidences supporting more effective diagnostic measures of tuberculous colitis, Han et al studied tuberculous colitis cases using double-contrast barium enema and concluded that a finding of circular or transverse ulcer was more characteristic of tuberculous colitis [71]. Another study conducted in France established that in tuberculous colitis cases, the ileocaecal valve is usually rigid and incompetent while the caecum might be retracted [51] [72]. The study had also established that CT scan findings of tuberculous colitis involves asymmetrical and thickened wall of the colon which was in the presence of enlarged lymph node with a hypoattenuating centre which is a result of necrotic caseation [51] [72]. In addition, CT scan of the abdomen has shown to have a 67% of sensitivity in diagnosing tuberculous colitis [73]. In contrary, common diagnostic measure of demonstrating acid-fast bacilli or caseating granuloma on histological specimen has rather low sensitivity of 32% and 50% respectively [73]. In addition, the significance of mycobacterium tuberculosis culture and sensitivity in diagnosing tuberculous colitis is rather questionable given varying findings by previous studies [74]-[76]. On the other hand, laparotomy and laparoscopy have the highest rate of success in diagnosing TB with 100% and 94.5% cases being confirmed respectively although this imposes its own risk given its invasive nature and higher cost [70]. Lastly, a therapeutic trial of anti-TB treatment has shown to be effective in diagnosing and treating tuberculous infections in endemic areas like in Malaysian setting [77].

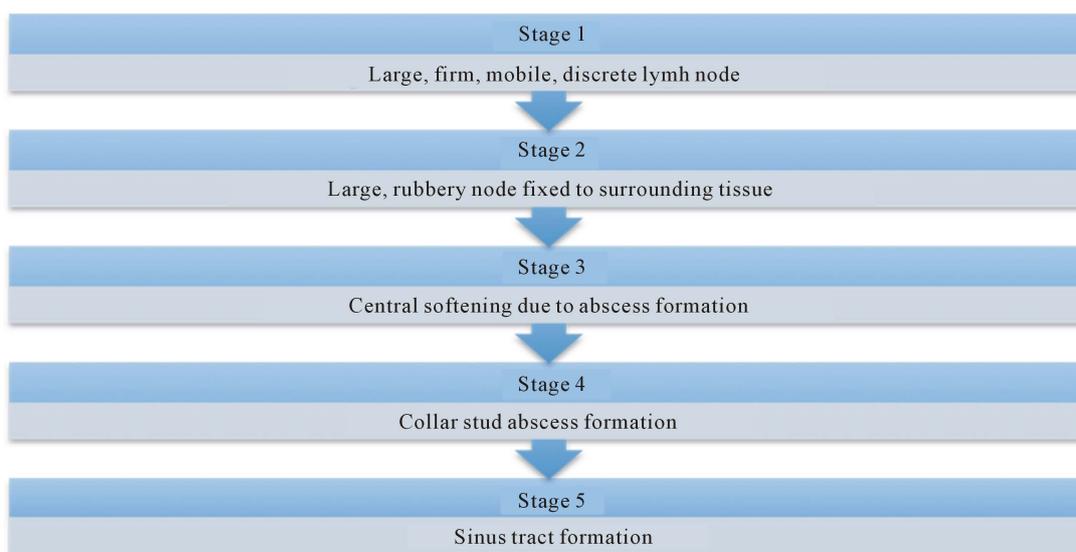
Majority of tuberculous colitis patients have responded to anti-tuberculosis treatment and delay in treatment imposes higher mortality and morbidity rate [59] [78]. Common diagnostic and management dilemma in tuberculosis colitis is given its nature of clinical presentation that usually mimics Crohn's disease and carcinoma of the colon [59] [75]-[78]. Although there are risks of falsely labeling a patient with tuberculous colitis given that anti-inflammatory properties of anti-tuberculosis treatment may resolve lesions in inflammatory bowel disease patient, study has shown that this is not a common occurrence [59] [74]. Besides that, starting anti-tuberculosis treatment in inflammatory bowel disease or malignancy of the bowel does not confer adverse effects as it does by starting immunosuppressive chemotherapy in patients with underlying tuberculosis where it leads to dissemination of the tuberculosis [59]. This is especially important clinically in areas with higher prevalence of tuberculosis as compared to inflammatory bowel disease or malignancy of the bowel. Thus, it is worthwhile to treat patient with anti-tuberculous treatment based on a high clinical suspicion given that tuberculosis is curable provided appropriate treatment is implemented. In addition, endoscopy post anti-tuberculosis treatment in 69 patients with tuberculous colitis has shown close to 100% improvement of the lesions [59]. This had led to the clinical implication that does not require repeated endoscopy in order to monitor anti-tuberculous treatment response in patients with tuberculous colitis provided their clinical symptom improves [59].

### 3.3. Tuberculous Cervical Lymphadenitis

Tuberculous lymphadenitis makes up 35% of the extra pulmonary tuberculosis incidence worldwide out of which cervical lymph node is the commonest site of infection, which makes up 60% - 90% of the cases [79] [80]. This incidence is higher among HIV positive patients as they make up 53% - 62% of the extra-pulmonary tuberculosis cases [81] [82]. Tuberculous lymphadenitis is usually more common among African Americans and Asians, particularly in their second decade although tuberculous lymphadenitis can occur across any age group [82] [83]. Many studies have established a tendency in female patients [82] [83]. The commonest cause of tuberculous lymphadenitis is Mycobacterium Tuberculosis whereas non-tuberculous lymphadenitis is often caused by Mycobacterium Avium-Intracellular complex [79].

Tuberculous lymphadenitis may occur as a primary infection or as a result of reactivation of a dormant foci as well as a direct entry from a contagious focus [79]. In primary infection, the inhaled droplet nuclei are small enough to pass across muco-ciliary defenses in bronchi and lodge in the terminal lung alveoli [79]. The bacilli that multiply in the Ghon focus of the lungs would then be drained by lymphatic drainage into the hilar lymph nodes and thus forming the primary complex [84]. Hilar, mediastinal and paratracheal lymph nodes are the primary regional lymph nodes that would be infected from where the lymphatic drainage can spread into any part of the lymphatic system [84]. Cervical tuberculous lymphadenitis being the commonest site of infection occurs when the bacilli from the primary focus spread into tonsils, adenoid sinusoids and osteomyelitis of ethmoid bones [85] [86]. Initially, progressive multiplication of the bacilli will be followed by delayed hypersensitivity reaction where there will be marked hyperemia, swelling, necrosis and caseation of the centre of the lymph node [85] [86]. Progressive inflammation will lead to further swelling and mothing of several nodes where adhesion to adjacent skin may cause induration and purple discoloration [86] [87].

Tuberculous cervical lymphadenitis may present as unilateral, single or multiple mass or masses commonly at the posterior cervical margin which is usually a non-tender slow growing mass over weeks to months [88] [89]. Up to 10% of patients may present with fistula formation [90] [91]. Besides that, 21.8% of tuberculous lymphadenitis patients have presented with a history of previous tuberculosis patient contact whereas as high as 16.1% of patients have had previous tuberculosis infection [91] [92]. Studies have shown that tuberculous lymphadenitis would also present with systemic symptoms commonly low grade fever, weight loss, fatigue and less commonly night sweats although cough is rather not prominent [92] [93]. However, 57% of patients may not present with any systemic symptoms [87] [92] [93]. In addition, multiplicity, caseation and matting are some of the diagnostic features in tuberculous lymph node [79]. It is also important to note that the patient may present with tender lymph node swelling if there is a secondary bacterial infection, in a rapidly growing mass as well as in if they are HIV positive [87]. The features of the lymph node may vary according to the stages as explained in **Figure 1** based on Jones and Campbell criteria [94].



**Figure 1.** Jones and Campbell description on stages of tuberculous lymphadenitis [94].

When it comes to diagnosing and treating cervical tuberculous lymphadenitis, a very high suspicion index is required as the differential diagnosis is extensive [95] [96]. This includes various infections, neoplasms, non-specific reactive hyperplasia, sarcoidosis, toxoplasmosis, collagen vascular disease, cat-scratch fever and reticuloendothelial disease [95] [96]. A study in United Kingdom has established an algorithm to diagnose and manage tuberculous cervical lymphadenitis [97].

Patients presenting with enlarged lymph node should be investigated with tuberculin skin test, fine needle aspiration (FNA) of the lymph node, HIV screening test and a chest X-Ray if they have risk factors of developing tuberculosis [97]. Patients with FNA results consistent with tuberculosis should be started on anti-tuberculous treatment while waiting for the culture result [97]. If patients show no improvement upon commencement of treatment and culture results are negative, these patients could be followed up with an excisional biopsy after anti-tuberculous treatment is either completed or an alternative diagnosis is considered based on the biopsy results [97].

However, if the first line investigations are inconclusive or if a patient is immunocompromised, they should be further investigated with excisional biopsy to assist in the diagnosis [97]. Anti-tuberculous treatment can be started if findings are consistent with tuberculosis while culture results are still pending [97]. Clinical response, positive culture and/or emergence of new enlarged lymph node warrants repeat FNA, cytology and culture [97]. If patients have enlarged lymph node post anti-tuberculous treatment, these patients require short-term observation where a repeated diagnostic and treatment measures should be implemented where it is necessary [97].

#### 4. Conclusion

EPTB has various forms of clinical manifestation, which imposes diagnostic and treatment challenges. Thus, it is crucial to always include tuberculosis as part of working diagnosis especially in regions where tuberculosis is endemic until proven otherwise. Hence it is imperative to start treatment early to ensure better response.

#### Conflict of Interests

The authors have no conflict of interests.

#### Informed Consent

Informed consent was obtained from the three patients prior to publication of this report.

#### Ethical Approval

Ethical approval was obtained from the relevant authority.

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