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Complex challenges in pleural effusion due to tuberculosis: Recurrence and drug resistance in diverse patient populations

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Abstract
Background: Tuberculous pleural effusion (TPE) is a common form of extrapulmonary tuberculosis (EPTB), particularly in TB-endemic regions. The management of TPE is complicated by issues of recurrence and drug resistance, especially in diverse patient populations including those with HIV co-infection.
Methods: This retrospective case series examines two cases of pleural effusion due to tuberculosis: one in an immunocompetent 25-year-old female and another in a 35-year-old HIV-positive male with multidrug-resistant TB (MDR-TB). Both cases highlight diagnostic challenges, treatment responses, and the need for tailored therapeutic approaches.
Results
1. Case 1: The 25-year-old female presented with symptoms of fever, chest pain, and weight loss. She was initially treated successfully with standard anti-TB therapy. However, she experienced a recurrence of pleural effusion after one year, which was managed with a second course of anti-TB treatment, resulting in improvement.
2. Case 2: The HIV-positive male presented with low-grade fever and significant weight loss. Initial diagnostics revealed rifampicin-resistant TB, and he was treated with a complex regimen including Bedaquiline. Despite treatment, he developed further resistance and significant side effects, necessitating multiple regimen adjustments. He ultimately completed 18 months of treatment with a modified regimen.
Conclusion: This case series underscores the complexity of managing TB pleural effusion, particularly in the context of recurrence and drug resistance. The immunocompetent patient's recurrence highlights the need for vigilant follow-up and potentially extended treatment durations. The HIV-positive patient's case demonstrates the challenges of treating MDR-TB with associated drug toxicity and evolving resistance. Successful outcomes depend on comprehensive diagnostics, individualized treatment plans, and close monitoring to address complications and ensure effective management.
Clinical Implications: Tailored treatment strategies, regular monitoring, and responsive adjustments to therapy are essential for managing TB pleural effusion effectively. This approach is crucial for addressing the diverse challenges presented by immunocompromised and drug-resistant TB patients.

Keywords: TB pleural effusion, recurrent TB, EPTB, pleural effusion and HIV positive

Introduction

Pulmonary TB (PTB), the most common type of TB, has the great epidemiological significance due to its extremely contagious nature [1, 2]. The proportion of patients with extra-pulmonary TB (EPTB) relative to those with PTB varies among countries and depends on associated diseases, geographical, social, ethnic and economic parameters [3, 4]. EPTB is defined according to WHO classification criteria as an infection by MTB which affects tissues and organs outside the pulmonary parenchyma. It represents between 20 and 25% of all TB cases [5].

Tuberculous pleural effusion (TPE) is the second commonest form of extrapulmonary tuberculosis (EPTB) after tuberculous lymphadenitis [6, 7]. It is the commonest cause of exudative pleural effusion in countries endemic to tuberculosis [8, 9]. Patients with TPE typically present with acute or subacute symptoms of fever, unilateral pleuritic chest pain, cough, night sweats, dyspnoea and weight loss [10]. The paucibacillary nature of tuberculous pleural fluid makes it a diagnostic challenge [11]. Hence, a high index of suspicion is required for early diagnosis and prompt treatment initiation in regions endemic to tuberculosis.

Recurrent TB disease occurs when patients who were previously treated for TB develop a new disease episode, due to either relapse (recurrence of the old infection) or reinfection (infection with a new strain [12]. Recurrent TB disease is associated with poor treatment outcomes and higher mortality rates compared to primary TB infection [13]. Clinical, epidemiological, and/or microbiological data cannot be used to differentiate relapse and reinfection.

Recurrent TB may be seen after completing a full course of anti-tubercular treatment. Compared with the first episodes of TB, patients diagnosed with recurrent TB are less likely to complete treatment and experience higher mortality (Murray *et al.* 1999). Distinguishing the 2 mechanisms of recurrent TB requires molecular marker analysis of cultures from both episodes, so results are available from only a few studies. These have shown varying proportions of disease due to reinfection [5-6], from <3% [14] to >60% [15, 16]

Epidemiology: Global Incidence: TB pleural effusion is a significant health concern worldwide, particularly in developing countries where TB is endemic. It accounts for about 5% of all TB cases. Age and Gender: While it can affect individuals of all ages, it is more prevalent in young adults and middle-aged individuals. There is no significant gender predilection. Risk Factors: The primary risk factor is exposure to active TB infection. Other contributing factors include immunocompromised states (e.g., HIV/AIDS),

malnutrition, and close living conditions that facilitate the spread of TB. Regional Variations: Higher incidences are observed in regions with poor healthcare infrastructure and high HIV co-infection rates. Sub-Saharan Africa, Southeast Asia, and parts of Latin America report higher cases compared to developed countries [17].

Pathogenesis of TB pleural effusion is thought to be related to the rupture of a subpleural caseous focus in the lung into the pleural space [18]. The basis for this was the observation that a caseous TB focus could be demonstrated in the lung, contiguous with the diseased pleural, in 12 to 15 patients with TB pleuritis [19]. The 3 other patients in this study had parenchymal disease but did not have caseous foci adjacent to the pleura. Tuberculous pleural effusions are thought to result from a delayed hypersensitivity reaction to mycobacteria and mycobacterial antigens in the pleural space. The resulting inflammation produces lymphocytic pleuritis, which decreases the amount of fluid that can be absorbed from the pleural space. The combination of the extra fluid produced by the inflammation and the decreased lymphatic clearance leads to the accumulation of pleural fluid.

Clinical Manifestations: Tuberculous pleuritis usually presents as an acute or subacute illness. Symptoms are present for less than 1 week in 35% of patients and present for less than 1 month in 71% [20]. The most frequent symptoms are cough (70%), which is usually non-productive, and chest pain (70%), which is usually pleuritic [21, 22]. Most patients are febrile, but approximately 15% will be afebrile [22]. They may also be dyspneic if the effusion is large. If the presentation is less acute, mild chest pain may occur with at most a low-grade fever, non-productive cough, weight loss, and easy fatigability [22].

Clinical Manifestations in HIV-Positive Patients: Patients who are HIV-positive are more likely to present with fever, cough, and significant weight loss compared to non-HIV positive patients. HIV-infected patients more commonly present with systemic symptoms, such as fatigue, night sweats, diarrhea, lymphadenopathy, splenomegaly, and hepatomegaly. They are also more likely to have bilateral pleural effusions [24]. They also have a longer duration of illness and a lower incidence of chest pain [26]. Their pleural fluid is more likely to be smear-positive for acid-fast bacilli (AFB), especially when their CD4 count is less than 100 [25].

Diagnosis: The diagnosis of tuberculosis (TB) pleural effusion involves a combination of clinical assessment, imaging studies, microbiological tests, and sometimes invasive procedures like pleural biopsy [26, 27, 28, 29].

1. **Clinical Assessment:** History-taking: Evaluate for symptoms such as cough, fever, night sweats, weight loss, and chest pain. Physical examination: Look for signs such as decreased breath sounds, dullness to percussion, and pleural rub.

2. **Imaging Studies:** Chest X-ray: Typically shows unilateral or bilateral pleural effusion with or without associated parenchymal abnormalities. Computed Tomography (CT) scan: May provide more detailed information about the extent of pleural involvement and aid in ruling out other causes of effusion.

3. **Microbiological Tests:** Sputum Smear Microscopy: Acid-fast bacilli (AFB) staining of sputum may reveal Mycobacterium tuberculosis (MTB) in a subset of patients. Sputum Culture: Culturing of sputum for MTB is more sensitive than smear microscopy. Nucleic Acid Amplification Tests (NAATs): Molecular tests such as polymerase chain reaction (PCR) can rapidly detect MTB DNA in sputum samples. Pleural Fluid Analysis: Includes microscopy, culture, and biochemical tests. Pleural fluid ADA (adenosine deaminase) levels are particularly useful in TB pleural effusion diagnosis.

4. **Invasive Procedures:** Thoracentesis: Obtaining pleural fluid for analysis, including culture and biochemical tests. Pleural Biopsy: When indicated, obtaining tissue samples for histopathological examination can confirm the presence of granulomas consistent with TB.

5. **Serological Tests:** Interferon-gamma Release Assays (IGRAs): Blood tests like QuantiFERON-TB Gold may aid in diagnosing latent TB infection but are not diagnostic for active TB disease.

Differential diagnosis of TB pleural effusion involves considering other causes of pleural effusion such as bacterial pneumonia, congestive heart failure, malignancy, and autoimmune diseases.

Treatment: Antitubercular Therapy (ATT): Standard treatment includes a combination of antibiotics such as isoniazid, rifampicin, pyrazinamide, and ethambutol for an initial intensive phase followed by a continuation phase with isoniazid and rifampicin. Duration: Treatment typically lasts 6 to 9 months, depending on factors such as drug susceptibility, response to therapy, and presence of complications. Adjunctive Therapy: Corticosteroids may be considered in certain cases to reduce inflammation and improve outcomes, especially in patients with significant symptoms or large effusions.

Complications: Empyema: Development of pus within the pleural space, requiring drainage and possibly surgical intervention. Fibrothorax: Formation of fibrous tissue within the pleural space, leading to restrictive lung disease. Pneumothorax: Air accumulation in the pleural space, which may require chest tube placement. Constriction: Fibrotic changes may lead to restriction of lung expansion and impaired respiratory function. Drug Toxicity: Adverse effects of antitubercular medications, such as hepatotoxicity, peripheral neuropathy, and drug-induced hepatitis, need monitoring and management.

Observational Retrospective Case Series Study

Case Series

Case 1. 25yrs. Female patient comes with H/o of Evening rise fever, Chest pain and mild Cough on direct questioning patient gives h/o loss of weight and loss of appetite with easy tiredness. Xray chest Rt minimal CP angle obliterated, and USG Chest show Rt sided minimal pleural effusion, which is non-tappable. On history and clinical examination, clinically diagnosed minimal pleural effusion which is not tappable, four drug Rifampicin pyrazinamide ethambutol and Isoniazid was started as per weight of the patient. Patient responded to the treatment by the symptoms were reduced and weight increased, xray chest shows CP angle

cleared and after 6months of treatment is stopped as it is a immunocompetent case of Extra Pulmonary TB.
After one year patient again comes with history of pain in left lower side of chest, Xray chest shows CP angle obliterated moderate and no Cough with only fever on physical examination air entry decreased on left lower chest USG Chest left lower moderate size pleural effusion. Aspiration done under USG guidance around 280ml of amber colored fluid removed without any complications, cytology examination shows lymphocytes preponderance and ADA is 74. GenXpert test MTB not detected.
Anti -TB drugs Rifampicin pyrazinamide ethambutol and Isoniazid was started and treatment was given for 8 months. It is a case of pleural effusion EP TB with recurrence. Above case was a Drug sensitive TB.
Case2. 35 years old male patient history of fever intermittent low grade with significant weight loss. On routine investigation xray chest PA view shows Right upper zone infiltration with costo phrenic angle obliterated moderate size Pleural effusion, patient pleural tapping done under USG guidance. CBNAAT Genxpert on Sputum shows Mycobacterium tuberculosis detected with Rifampicin resistance. Patient pretreatment evaluation shows CBC, LFT, RFT, Serum electrolytes, Calcium Magnesium, Blood glucose random within normal limits and HIV test is positive. Patient was started on All oral longer regimen with Bedaquilin, Levofloxacin, Linezolid, Cycloserine and Clofazimine with pyridoxine. Patient was referred to ART centre for starting ART, after two weeks patient tolerating Anti TB drugs and CD4 count was done. Patient was started on ART, After six months patient started tingling numbness in both extremities with severe pain in both legs during night. Patient was referred to neurologist and diagnosed Peripheral Neuropathy PN. He was given Analgesic with Gabapin NT and Linozolid stopped. Seven months followup sputum AFB culture was positive and 2nd line LPA test shows Levofloxacin and Moxifloxacillin resistance so Levofloxacin was omitted and injection Amikacin added alternate day, Patient completed 18 months treatment.

Discussion

Case 1: Immunocompetent 25-year-old Female with Recurrent Pleural Effusion due to TB

Initial Presentation and Treatment: Symptoms: Evening rise of fever, chest pain, mild cough, weight loss, loss of appetite, easy tiredness.

Diagnostics: Chest X-ray showed minimal right costophrenic (CP) angle obliteration; ultrasound (USG) showed minimal pleural effusion, non-tappable.

Diagnosis: Clinically diagnosed with minimal pleural effusion likely due to extrapulmonary TB. Treatment: Standard anti-TB therapy with Rifampicin, Pyrazinamide, Ethambutol, and Isoniazid (HRZE) based on body weight.

Outcome: Symptoms improved, weight increased, and chest X-ray cleared CP angle. Treatment completed after six months.

Recurrence and Subsequent Management

Symptoms: Pain in the left lower side of the chest, fever, no cough.

Diagnostics: X-ray showed left CP angle obliteration; USG indicated moderate pleural effusion. Aspiration yielded 280 ml of amber-colored fluid, with cytology showing lymphocyte predominance and elevated ADA (74). GenXpert MTB not detected.

Diagnosis: Recurrence of pleural effusion due to TB. (? Reactivation or Reinfection)

Treatment: Reinitiated standard anti-TB therapy (HRZE) for eight months.

Outcome: Completed treatment with improvement.

Discussion: This case highlights the complexity of TB management even in immunocompetent individuals. The recurrence of pleural effusion underscores the importance of close follow-up and the potential need for extended therapy in some patients. The patient's initial positive response and subsequent recurrence suggest a possible partial treatment response or reinfection. The decision to re-treat with the standard regimen was appropriate given the drug sensitivity.

***Case 2*:** 35-year-old HIV-positive Male with MDR-TB,

Initial Presentation and Treatment: Symptoms: Low-grade intermittent fever, significant weight loss.

Diagnostics: Chest X-ray showed right upper zone infiltration with moderate pleural effusion. GenXpert on sputum detected Mycobacterium tuberculosis with Rifampicin resistance. Baseline Investigations:* CBC, LFT, RFT, electrolytes, blood glucose, and HIV test positive.

Diagnosis: Drug-resistant TB, with Rifampicin, Levofloxacin and Moxifloxacin resistance

Treatment: Initiated on an all-oral longer regimen including Bedaquiline, Levofloxacin, Linezolid, Cycloserine, and Clofazimine with pyridoxine. Referred to ART center for HIV treatment, started ART after two weeks. Follow-up: Developed peripheral neuropathy (PN) after six months, leading to the discontinuation of Linezolid. Subsequent resistance to Levofloxacin and Moxifloxacin detected, leading to the addition of Amikacin. Outcome: Completed 18 months of treatment with modifications based on drug resistance and adverse effects.

Discussion: This case illustrates the challenges of managing MDR-TB in an HIV-positive patient, including the complexities of drug interactions, adverse effects, and the emergence of further drug resistance. The use of a tailored regimen with newer agents like Bedaquiline and the necessity of injectable Amikacin due to resistance patterns were crucial. The management of peripheral neuropathy through medication adjustment reflects the need for careful monitoring and flexibility in treatment plans.

Comparative Analysis and Key Points

1. **Diagnostic Approach:** Both cases involved comprehensive diagnostic workups including imaging, fluid analysis, and molecular tests. The elevated ADA and lymphocyte predominance in pleural fluid were key diagnostic indicators of TB effusion.

2. **Treatment Strategies:** Case 1 followed standard TB treatment protocols for drug-sensitive TB with good initial response but required re-treatment upon recurrence.
   Case 2 involved a complex, individualized regimen for MDR-TB, highlighting the importance of drug susceptibility testing and regimen adjustment based on evolving resistance patterns.

3. **Challenges and Complications**
   Recurrence: In the immunocompetent patient, recurrence emphasizes the need for vigilant follow-up and possibly longer treatment durations.

   Drug Resistance and Side Effects: The HIV-positive patient faced multiple layers of complexity with drug resistance and adverse effects, necessitating close monitoring and regimen modification.

4. **Outcomes:** Both patients successfully completed treatment, but the recurrent and resistant nature of TB in these cases underscores the importance of tailored and responsive treatment plans.

Conclusion: These cases underscore the diversity and complexity of TB management, particularly with pleural effusion and in the context of drug resistance and co-infections like HIV. Successful outcomes hinge on thorough diagnostics, appropriate treatment regimens, and flexibility in response to complications and resistance patterns. Regular follow-up and monitoring are crucial to address recurrence and adverse effects effectively.

Conclusion: This case series highlights the challenges in managing pleural effusion due to tuberculosis (TB) in different patient populations.
Case 1: An immunocompetent 25-year-old female experienced a recurrence of pleural effusion despite initial successful treatment of extrapulmonary TB. The recurrence was managed effectively with a second course of standard anti-TB therapy, underscoring the need for vigilant follow-up and potentially extended treatment durations in similar cases.

Case 2: A 35-year-old immunocompromised male with HIV presented with multidrug-resistant TB (MDR-TB) and subsequent adverse drug reactions. This case demonstrated the complexity of treating TB in the context of HIV co-infection and drug resistance. The patient's regimen required multiple adjustments due to side effects and evolving drug resistance, emphasizing the importance of individualized treatment plans and close monitoring.
Both cases underscore the importance of tailored therapeutic approaches based on patient-specific factors such as immune status and drug resistance patterns. Effective management requires comprehensive diagnostics, responsive treatment adjustments, and ongoing monitoring to address complications and ensure successful outcomes.

Summary: This case series presents two patients with pleural effusion due to extrapulmonary tuberculosis (TB), highlighting the challenges of recurrence and drug resistance.

Case 1: Immunocompetent Adolescent Female

- A 25-year-old female with pleural effusion was initially treated successfully with standard anti-TB therapy. Despite initial improvement, she experienced a recurrence of pleural effusion after one year. The recurrence was managed with a second course of standard anti-TB therapy, leading to resolution.
  Case 2: HIV-Positive Male with Drug-Resistant TB
- A 35-year-old male with HIV presented with pleural effusion and multidrug-resistant TB (MDR-TB), including Rifampicin resistance. The patient was treated with a complex regimen of second-line drugs, which included Bedaquiline, Levofloxacin, Linezolid, Cycloserine, and Clofazimine. He experienced significant adverse drug reactions, including peripheral neuropathy, requiring discontinuation of Linezolid. Subsequent resistance to Levofloxacin and Moxifloxacin necessitated further regimen adjustments, including the addition of Amikacin.

Key Points

- **Pleural Effusion and Extrapulmonary TB:** Both cases involved pleural effusion as a manifestation of extrapulmonary TB, demonstrating the need for thorough diagnostic and treatment strategies.

- **Recurrence:** The recurrence of pleural effusion in the immunocompetent patient highlights the necessity for vigilant follow-up and possibly extended treatment durations.

- **Drug-Resistant TB and HIV:** The case of the HIV-positive patient with MDR-TB illustrates the complexities of managing TB in immunocompromised patients, including the challenges posed by drug resistance and adverse reactions.

- **Toxicity of Second-Line Drugs:** The second-line drugs required for MDR-TB treatment are more toxic, leading to significant side effects that necessitate careful monitoring and adjustments to the treatment regimen.
  This series underscores the importance of individualized treatment approaches, responsive to patient-specific factors such as immune status and drug resistance patterns, to manage TB effectively.

Message

Clinical Way Forward

Vigilant Monitoring and Follow-Up: For Immunocompetent Patients: Ensure regular follow-up and consider extended treatment durations for cases with recurrence to prevent relapse and complications.

- For Immunocompromised Patients: Implement frequent monitoring for side effects and drug resistance in HIV-posit ive patients, adjusting treatment regimens promptly as necessary.

Personalized Treatment Plans

- **Drug-Resistant TB:** Develop individualized regimens based on drug susceptibility testing. Use newer and less toxic drugs when possible, to minimize adverse effects.
- **Adverse Drug Reactions:** Proactively manage side effects with supportive care and modify treatment regimens to maintain adherence and ensure patient safety.

Comprehensive Support

- **Multidisciplinary Approach:** Collaborate with specialists, including infectious disease experts, pulmonologists, and neurologists, to manage complex cases effectively.

- **Patient Education:** Educate patients on the importance of medication adherence, potential side effects, and the need for regular medical check-ups.

Social Message

Public Awareness

- **TB Awareness:** Increase public awareness about TB, its symptoms, and the importance of early diagnosis and treatment, particularly for extrapulmonary TB.

- **Stigma Reduction:** Address and reduce the stigma associated with TB and HIV to encourage individuals to seek timely medical care.

Support Systems

- **Community Support:** Enhance community support systems for TB patients, including mental health services and social support networks, to improve treatment adherence and outcomes.

- **Healthcare Accessibility:** Advocate for accessible healthcare services, ensuring that both immunocompetent and immunocompromised patients have access to necessary diagnostics, medications, and follow-up care.

Policy and Research

- **Policy Advocacy:** Advocate for policies that support TB control programs, including funding for research, access to new medications, and comprehensive care strategies.

- **Research and Innovation:** Support research initiatives aimed at developing less toxic, more effective TB treatments and improving diagnostic tools for early detection and monitoring of TB.

By integrating clinical vigilance with robust social support and public health initiatives, we can improve outcomes for TB patients and work towards eradicating this challenging disease.

References

1. Guler SA, Bozkus F, Inci MF, Kokoglu OF, Ucmak H, Ozden S, *et al*. Yuksel M. Evaluation of pulmonary and extrapulmonary tuberculosis in immunocompetent adults: a retrospective case series analysis. Med Princ Pract,2015:24(1):75–9. Article. Google Scholar
2. Yang Z, Kong Y, Wilson F, Foxman B, Fowler AH, Marrs CF, *et al*. Identification of risk factors for extrapulmonary tuberculosis. Clin Infect Dis,2004:38(2):199–205. Article Google Scholar
3. Sunnetcioglu A, Sunnetcioglu M, Binici I, Baran AI, Karahocagil MK, Saydan MR. Comparative analysis of pulmonary and extrapulmonary tuberculosis of 411 cases. Ann Clin Microbiol Antimicrob,2015:14(34):1–5. Google Scholar
4. Ramirez Lapausa M, Menendez Saldana A, Noguerado Asensio A. Extrapulmonary tuberculosis: an overview. Rev Esp Sanid Penit,2015:17(1):3–11. Article CAS Google Scholar Second Para 5-10
5. Peto HM, Pratt RH, Harrington TA, LoBue PA, Armstrong LR. Epidemiology of Extrapulmonary tuberculosis in the United States, 1993–2006. Clin Infect Dis,2009:49(9):1350–7. https://doi.org/10.1086/605559. Article PubMed Google Scholar
6. Khan AH, Sulaiman SAS, Laghari M, Hassali MA, Muttalif AR, Bhatti Z, *et al*. Treatment outcomes and risk factors of extra-pulmonary tuberculosis in patients with co-morbidities. BMC Infect Dis,2019, 19. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6683549/. https://doi.org/10.1186/s12879-019-4312-9.
7. Ngoh HL. Pleural effusion in 100 Malaysian patients. Med J Malaysiam1991:46(4):301–8. Available from: https://pubmed.ncbi.nlm.nih.gov/1840436/.
8. Liam CK, Lim KH, Wong CMM. Causes of pleural exudates in a region with a high incidence of tuberculosis. Respirology,2000:5(1):33–38. Available from: https://doi.org/10.1046/j.1440-1843.2000.00223.x.
9. Shaw JA, Diacon AH, Koegelenberg CFN. Tuberculous pleural effusion. Respirology,2019:24(10):962–971. Available from: https://doi.org/10.1111/resp.13673.9.
10. Cantres Fonseca OJ, Rodriguez Cintrón W, Olmo Arroyo FD, Baez Corujo S. Extra Pulmonary Tuberculosis: An Overview. In: Role of Microbes in Human Health and Diseases, 2018. Available from: https://www.intechopen.com/books/role-of-microbes-in-human-health-and-diseases/extra-pulmonary-tuberculosis-an-overview.
11. Mathema B, Kurepina NE, Bifani PJ, *et al*. Molecular epidemiology of tuberculosis: Current insights. Clinical Microbiology Reviews,2006:19(4):658-685. DOI: 10.1128/CMR.00061-05.
12. Panjabi R, Comstock GW, Recurrent GJE. Tuberculosis and its risk factors: Adequately treated patients are still at high risk. The International Journal of Tuberculosis and Lung Disease,2007:11(8):828-837.
13. Gomes MG, Aguas R, Lopes JS, *et al*. How host heterogeneity governs tuberculosis reinfection? ProcBiol Sci,2012:279:2473–8.
14. Lambert ML, Hasker E, Van Deun A, Roberfroid D, Boelaert M, Van der Stuyft P. Recurrence in tuberculosis: relapse or reinfection? Lancet Infect Dis,2003:3:282–7.
15. Benator D, Bhattacharya M, Bozeman L, *et al*. Rifapentine and isoniazid once a week versus rifampicin and isoniazid twice a week for treatment of drug-susceptible pulmonary tuberculosis in HIV-

negative patients: a randomised clinical trial. Lancet,2002:360:528–34.
16. Shen G, Xue Z, Shen X, *et al*. Recurrent tuberculosis and exogenous reinfection, Shanghai, China. Emerg Infect Dis,2006:12:1776–8.
17. van Rie A, Warren R, Richardson M, *et al*. Exogenous reinfection as a cause of recurrent tuberculosis after curative treatment. N Engl J Med,1999:341:1174–9.
18. Ko JM, Park HJ, Kim CH. Pulmonary changes of pleural TB: up-to-date CT imaging. Chest,2014:146:1604–1611.
19. Berger HW, Mejia E. Tuberculous pleurisy. Chest,1973:63:88-92.
20. Levine H, Szanto PB, Cugell DW. Tuberculous pleurisy: an acute illness. Arch Intern Med,1968:122:329-32.
21. Moudgil H, Sridhar G, Leitch AG. Reactivation disease: the commonest forms of tuberculous pleural effusion in Edin burgh. 1980-1991. Respir Med,1994:88:301-4.
22. Yone EW, Kenge AP, Moifo B, *et al*. Prevalence and determinants of extrapulmonary TB involvement in patients with pulmonary tuberculosis in a Sub-Saharan African country: a cross-sectional study. Scand J Infect Dis,2013:45:104-11.
23. Stead WW, Eichenholz A, Strauss HK. Operative and pathologic findings in twenty-four patients with syndrome of idiopathic pleurisy with effusion, presumably tuberculosis. Am Rev Tuberc,1955:71:473-502.
24. Aljohaney A, Amjadi K, Alvarez GG. A systematic review of the epidemiology, immunopathogenesis, diagnosis, and treat ment of Pleural TB in HIV infected patients. Clin Dev Immunol,2012:2012:842045.
25. Heyderman RS, Makunike R, Muza T, *et al*. Pleural tubercu losis in Harare, Zimbabwe: the relationship between human immunodeficiency virus, CD4 lymphocyte count, granuloma formation and disseminated disease. Trop Med Int Health,1998:3:14-20.
26. Light RW. Pleural Diseases (6th ed.). Lippincott Williams & Wilkins, 2013.
27. Aminian M, *et al*. Diagnostic value of adenosine deaminase in tuberculous pleural effusion: A meta-analysis. Caspian Journal of Internal Medicine,2018:9(4):304–312.
28. Sharma SK, *et al*. Diagnosis and treatment of tuberculosis. Indian Journal of Medical Research,2016:144(4):626–634.
29. World Health Organization. Xpert MTB/RIF assay for the diagnosis of pulmonary and extrapulmonary TB in adults and children: Policy update. WHO, 2016.