Tuberculose pleural effusion
TPE

Dr.M Shaheen

Tuberculosis (curable) is one of the most frequent causes of **pleural effusions**, especially in developing countries.

TPE is the second most common form of **extrapulmonary tuberculosis**.

The pleural fluid is an **exudate** that usually has predominantly **lymphocytes**.

The proportion of patients with tuberculosis who have **pleural effusions** has varied from population to population.

In the USA, although the total number of patients with **TPE** decreased between 1993 and 2003, the proportion of patients with **TPE** compared to the total number of tuberculosis cases remains relatively stable (**3.6 %**).

The proportion of TPE in total pleural effusions.

Country	n	TPE (%)
China	833	40
South Africa	51	82.4
India	68	23.5
New Zealand	51	5.9
United Kingdom	56	5.6
Spain	93	3.2
France	149	2.7
Denmark	146	2.1
United States	51	0

Clinical manifestations

TPE predominates in men more than women **2:1** .

Epidemiological analysis from the USA, the mean age of patients with **TPE** is **49** years: about **50 %** were younger than **45** years and **30 %** were over **65** years .

In contrast, **TPE** affects mainly younger individuals (mean age =**34** years) in **higher tuberculosis burden areas**.

TPE usually manifests as an **acute illness**, especially in younger patients who are more immunocompetent.

Symptoms had been present for less than a month (**71 %**) and for less than **1** week (**35 %**).

TPE is usually unilateral and can be of any size.

333 patients, pleural fluid occurred on the left side in **38.1%**, on the right in **48.4%**, and both sides were affected in **13.5%** .

In unilateral or bilateral effusion, **20.4%** small size, **19.2%** moderate size , and **60.4%** large size of pleural effusions.

Approximately **20 %** of patients with TPE have coexisting parenchymal disease on chest radiograph (CT Scan).

The most frequent symptoms of TPE are :

- **Nonproductive cough**.
- **Pleuritic chest pain** (the pain usually precedes).
- Most patients are **febrile** but approximately **15 %** will be afebrile.
- **Dyspnea** can be present in some **TPE** patients with large effusion.
- Other symptoms include **night sweats**, **weight loss**, **malaise**.

Diagnosis

- Demonstration of ***Mycobacterium tuberculosis*** in the **sputum**, **pleural fluid**, or **pleural biopsy specimens**.
- Demonstrating ***granuloma*** in the parietal pleura.
- **adenosine deaminase** (ADA) in pleural fluid.
- Elevated concentrations of **interferon-γ** in pleural fluid.

Tuberculin skin tests

In **low tuberculosis prevalence areas**, or **no vaccination**:
A **positive** tuberculin skin test result is supportive evidence in the diagnosis of **TPE**.
A **negative** result can be seen in **1/3** of patients.

Since a negative test **does not rule out** the diagnosis of **TPE**, tuberculin skin test is being utilized less and less in patients suspected of having **TPE**, especially in high tuberculosis burden countries.

If the patient is **immunosuppressed with HIV infection** or is **severely malnourished**, the skin test is always **negative**.

Mycobacterial stain and culture

It is necessary to obtain **sputum** in addition to **pleural fluid** for the acid-fast bacilli smear and ***Mycobacteria tuberculosis*** culture in patients with suspected **TPE**, even in the absence of parenchymal involvement.

Prospectively evaluated **84** patients with **TPE** :
Smear positive in **12 %** and **culture-positive** in **52 %** of cases .

In a study of **254** patients with **TPE**, **93** patients (**36.6 %**) had positive of pleural fluid cultures for ***Mycobacteria tuberculosis*** in the Löwenstein-Jensen medium.

Thus, **pleural fluid cultures** should be performed in any patient with an **undiagnosed** pleural effusion.

The combination of **pleural fluid** and **sputum** cultures in the diagnostic workup of **TPE** seems a reasonable initial approach, with a combined diagnostic yield of **79%** .

Adenosine deaminase

ADA is a predominant T-lymphocyte enzyme that catalyzes the conversion of adenosine to inosine and deoxyadenosine deoxyinosine.

ADA in pleural fluid for the early diagnosis of **TPE**.
Easy and **inexpensive** method for diagnosing **TPE**.

Meta-analysis of **63** studies for high levels of **ADA** in pleural fluid in the diagnosis of TPE → **Sensitivity: (92 %) …. Specificity: (90 %).**

ADA levels in pleural fluid are also elevated in **HIV patients** even with very low $CD4^+$ T cells.

Almost all patients with **TPE** have a pleural fluid **ADA > 40 U/L**, which is the accepted value for the diagnosis of **TPE.**

The higher the level, the greater the chance of patients having **TPE.**

the lower the level the lesser the chance of the patient having **TPE.**

Instances with high pleural fluid ADA:

- ❑ parapneumonic effusions.
- ❑ Empyemas.
- ❑ Brucellosis.
- ❑ Q fever.
- ❑ Lymphomas.
- ❑ Rheumatoid arthritis.

2/3 of **empyemas** and **1/3** of **parapneumonic effusions: ADA** > 40U/L.

The differential diagnosis of **TPE** from these conditions is not difficult:

Both **clinical picture** and **polymorphonuclear leukocytes** predominant pleural fluid of patients with parapneumonic effusions and empyemas are total different from those of patients with TPE.

ADA has two molecular forms, ADA1 and ADA2:

- **ADA1** is found in lymphocytes and monocytes.
- **ADA2** is found only in monocytes.

ADA2 is responsible for the increased total **ADA** in **TPE**, whereas high **ADA** in nontuberculose effusions is due to an increase in the **ADA1**.

ADA2 isoenzyme is as sensitive and more specific than total **ADA** for diagnosing **TPE** .

pleural fluid **ADA** is routinely employed in the diagnostic workup of pleural effusions in **high tuberculosis burden countries**.

Interferon-gamma

Interferon-γ is a cytokine released by activated $CD4^+$ T cells that increases the mycobactericidal activity of macrophages.

Meta-analysis of 22 studies of **782** patients with **TPE** and **1,319** patients with **nontuberculous effusions**:
The **sensitivity** of the **interferon-γ** was **89%**.
The **specificity** was **97%**.

The long historical success of **ADA** and the fact that it is **simpler** and **less expensive** than the **interferon-γ** makes it the preferred test.

There are now two commercially available **interferon-γ**: (**QuantiFERON-TB Gold** and **T-SPOT.TB**) for clinical use.

These tests are good at identifying patients who have been infected with ***Mycobacterium tuberculosis***, but they are much less useful in identifying patients with **TPE**.

Nucleic acid amplification tests

Amplification of ***Mycobacterium tuberculosis*-specific nucleic acid** from specimens such as sputum and pleural fluid.

Systematic review and **meta-analysis** of **40** studies assessing the use of pleural fluid **nucleic acid amplification tests** for diagnosing **TPE** : .

high specificity (97%).

poor and variable sensitivity (62%).

The low sensitivities of nucleic acid amplification techniques may be due to:

- The presence of inhibitory substances in pleural fluid.
- The small amount of ***Mycobacterium tuberculosis*** in pleural fluid.
- Technical defect of nucleic acid extraction.

So:
The inconsistent results of different studies and the high cost of **nucleic acid amplification** tests limit their use to investigational settings.

Other biochemical tests

B-cell response, complement activation, leptin, lysozyme, and the other cytokines.

The evidence does not support the use of this biomarkers for the diagnosis of **TPE** because of their low **sensitivity** or/and **specificity**.

Interleukin 27 in **TPE** is higher than those in **pleural effusions with the other etiologies** → **Pleural Interleukin 27** levels can be used for diagnosing **TPE**, with **sensitivity**: **92.7%** and **specificity**: **98.8%** .

Pleural biopsy

- **Caseating granulomas**.

- **Blind needle biopsy** of the pleura.

Study of **248** patients with **TPE** with Blind needle biopsy:

- **Granulomas** in **80%** of patients,
- **Acid-fast bacilli** stain was positive in **25.8%**.
- ***Mycobacteria tuberculosis*** culture was positive in **56%** .

Sometimes we need more invasive procedures like **medical thoracoscopy** when one or more **thoracenteses** or/and **blind needle biopsy** fail to reach definite diagnosis.

Meta-analysis

- No **mortality** with medical thoracoscopy.
- An the rates of **major complications**: **1.5%** and **minor complications**: **10.5%**.
- **Very safe procedure** in the diagnosis of exudative pleural effusions.

In the largest series of **333** patients with **TPE**:
Medical thoracoscopy with pleural biopsies yielded tuberculosis pathology in **330** (**99.1%**) patients by demonstration of one or more of following histological abnormalities in pleural biopsy specimen:

- **Acid-fast bacillus**.
- **Caseating granulomas**.
- **Epithelioid cell granuloma** with **no** evidence of other granuloma diseases.

Treatment

In many cases, **TPE** is a **self-limited disease** → Spontaneous resolution in **4** to **16** weeks.

About **half** of **untreated patients** would develop some form of the **active disease**.

The goals of the treatment of TPE

- **Prevent** the occurrence of active tuberculosis.
- **Relieve** the symptoms of TPE.
- **Avoid** the presence of a fibrothorax.

- With appropriate treatment, the symptoms and radiological abnormalities of patients with **TPE** gradually abate.

- Patient becomes **afebrile** within **2** weeks, but temperature elevations may persist for **2** months.

- The mean time for the **complete resorption of pleural fluid** is approximately **6** weeks, but it can be as long as **12** weeks.

- There is no reason to keep the patient at **bed rest** and the patient needs to be **isolated** only if the sputum is positive for ***Mycobacteria tuberculosis***.

Anti-tuberculosis chemotherapy

- **(2HRZ/4HR) for 6 months** .
- **(HR)** for **9** months may be effective when the organisms are fully susceptible to the drug.
- Directly observed therapy (**DOTS**).
- **16%** to **49%** of all patients do not complete the regimen.

Recommended doses of first-line anti-tuberculosis drugs for adults

Drug	Recommended dose			
	Daily		3 times per week	
	Dose and range (mg/kg body weight)	Maximum (mg)	Dose and range (mg/kg body weight)	Daily maximum (mg)
Isoniazid	5 [4–6]	300	10 [8–12]	900
Rifampin	10 [8–12]	600	10 [8–12]	600
Pyrazinamide	25 [20–30]	–	35 [30–40]	–
Ethambutol	15 [15–20]	–	30 [5–35]	–

- In the case of resistance to isoniazid → **6-months** of **fluoroquinolone** (**levofloxacin** or **moxifloxacin**).

- **6-month (R-Moxifloxacin-PYZ-ETH)** for **2** months, **followed** by **(R-Moxifloxacin)** for **4** months, may be effective .

- When **TPE** is caused by **multidrug-resistant *Mycobacteria tuberculosis*** confirmed by either by **culture** or with **DNA**, the initial treatment regimen should be individually tailored according to the **results of drug-susceptibility testing**.

- In the absence of this information, **empirical regimens** can be used, but as soon as the results of drug susceptibility testing become available, the treatment regimen should be adjusted.

Therapeutical thoracentesis

- **Dyspnea** because of a large pleural effusion → Therapeutical thoracentesis is recommended.

- The complete clearance of pleural fluid pigtail drainage to an effective anti-tuberculosis regimen **does not** appear significantly to decrease the incidence of **residual pleural thickening** and **other clinical symptom**.

Fibrinolytics

- **Fibrinolytic agents** may decrease the degree of residual pleural thickening in patients with loculated **TPE**.

- **Fibrinolytics**, in addition to **anti-tuberculosis medication**, in patients with symptomatic loculated tuberculosis effusions may reduce the incidence of **residual pleural thickening**.

Corticosteroids

- The role of corticosteroids in the treatment of **TPE** is controversial.
- Corticosteroids through their **antiinflammatory** action may hasten fluid resorption and prevent pleural thickening.
- **3 Randomized trials** showed early resolution of **clinical symptoms and signs**, but there was no difference in residual lung function and incidence of residual pleural thickening.

- In selected patients who continue to have severe systemic symptoms (e.g., **fever**, **malaise**, **pleuritic chest pain**) after **2** weeks of anti-tuberculosis treatment and therapeutic thoracentesis, a **short course of corticosteroids may be beneficial**.

A recent **Cochrane** review concluded that there are **insufficient data to support evidence-based recommendations** regarding the use of adjunctive corticosteroids in people with tuberculous pleurisy.

- The use of corticosteroids in **HIV-positive individuals** may increased the risk of opportunistic infections.

- Randomized study of **197** patients with **HIV** associated **TPE**, the administration of **prednisolone** was associated with an increased risk of **Kaposi sarcoma**.

- Because there is a **lack of survival benefit** and **increased risk of Kaposi sarcoma**, the use of **steroids** in **HIV** associated **TPE** is not currently recommended.

Tuberculose empyema

- Uncommon chronic, active infection of the pleural space, which is characterized by the presence of **thick pus** and the **visceral pleura is usually calcified**.
- **Acid-fast bacilli smears** and cultures are usually **positive**.
- **Penetration of anti-tuberculosis** drugs is impaired, and **surgical drainage** is often needed to control the situation.
- In addition to a standard anti-tuberculosis regimen **thoracocentesis**, **extrapleural pneumonectomy** or **thoracoscopy**.

CONCLUSION

The gold standard for the diagnosis of TPE :

- **Detection of *Mycobacterium tuberculosis*** in pleural fluid, or **pleural biopsy** specimens, either by microscopy and/or culture.
- **Histological demonstration of caseating granulomas in the pleura.**
- **Adenosine deaminase.**
- **Interferon-γ** in pleural fluid.

- It can be accepted that in areas with **high tuberculosis prevalence**, the easiest way to establish the diagnosis of TPE in a patient with a **lymphocytic pleural effusion** is to generally demonstrate a **Adenosine Deaminase** **level above 40 U/L.**

- The recommended treatment for TPE is a regimen with **HRP** for **2** months followed by **4** months of two drugs, **Isoniazid** and **Rifampin**.

THANK YOU