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MODERN APPROACHES AND ALGORITHMS OF DIAGNOSIS OF TUBERCULOUS PLEURISY

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Annotation: Tuberculous pleurisy (TP) remains one of the most significant causes of exudative pleural effusion worldwide, particularly in regions with a high prevalence of tuberculosis, where it accounts for 30% to 70% of all cases . Despite advances in diagnostics, verifying the etiology of pleurisy remains a challenging clinical task. Late or misdiagnosis can lead to the formation of adhesions, the development of pleural empyema, and the need for surgical intervention . This review systematizes current data on the pathogenesis, clinical manifestations, and, most importantly, a comprehensive differential diagnostic algorithm for suspected tuberculous pleurisy, examining both routine and high-tech verification methods.

Introduction: Epidemiological and clinical significance

Tuberculous pleurisy is a specific inflammation of the pleural sheets caused by *Mycobacterium tuberculosis* (MBT), which can occur as an independent form of the disease or complicate other forms of pulmonary tuberculosis . TP accounts for 8–14% of respiratory tuberculosis cases. Its epidemiological significance varies: in developed countries (USA, EU countries), TP accounts for 3–5% of cases of pleural effusions, while in endemic regions (South Africa, China, Kyrgyzstan), this figure reaches 40–82%. The disease most often affects young and middle-aged individuals (under 40 years), although in countries with low incidence, it shifts toward older age groups .

Pathomorphogenesis and clinical-pathogenetic forms

The development of TP is based on the immune response of a sensitized organism to mycobacterial antigens in the pleural cavity. Three main mechanisms of MBT penetration into the pleura are distinguished: contact (from subpleural foci), lymphogenous (from intrathoracic lymph nodes), and hematogenous . Rupture of a subpleural caseous lesion, releasing its contents into the pleural cavity, is considered the key event triggering the cascade of delayed-type hypersensitivity reactions.

In clinical practice, it is customary to distinguish three main forms of TP, which are important for differential diagnosis:

1. **Allergic (paraspecific) pleurisy** : acute onset with high fever, rapid accumulation of serous exudate, severe dyspnea, and tachycardia. Characteristic of primary tuberculosis in individuals with hypersensitivity to tuberculin .
2. **Perifocal pleurisy** : develops subacutely or gradually with the spread of inflammation from a subpleural pulmonary lesion. It is characterized by pain, a dry cough, and fluctuating low-grade fever. Exudate may be scanty or moderate .
3. **Pleural tuberculosis itself** results from hematogenous or lymphogenous dissemination. It is characterized by prolonged intoxication and the formation of serous, serous-purulent, or purulent effusion (empyema). The course is persistent, often with the formation of dense pleural deposits .

Comprehensive algorithm for differential diagnostics

Differential diagnosis of TP is based on the sequential application of methods aimed first at establishing the nature of the effusion and then at verifying its specific etiology. The algorithm includes several mandatory steps.

1. Primary clinical, anamnestic and instrumental examination

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- **Clinical presentation** : TP is characterized by an acute or subacute onset with pleuritic pain, nonproductive cough, fever, night sweats, weight loss, and dyspnea, the intensity of which depends on the volume of effusion . However, similar symptoms are observed in parapneumonic pleurisy, pulmonary embolism, viral pleurisy, and malignant pleural lesions.
- **Imaging (X-ray, CT, ultrasound)** : Standard radiography reveals effusion, which is unilateral in 80–95% of cases . Concomitant pulmonary infiltrates or signs of primary tuberculosis complex are detected in 20–50% of cases based on X-ray findings, but computed tomography (CT) increases this sensitivity to 86%. CT also allows visualization of changes characteristic of tuberculosis: enlarged lymph nodes with caseous necrosis and "tree-in-bud" areas. Ultrasound (US) is critical for assessing the location of effusion (especially encapsulated), identifying fibrin bands and septa, and for navigation during diagnostic puncture .

2. Laboratory analysis of pleural fluid: differentiating exudate and transudate.

The first step in laboratory diagnosis is differentiating exudate from transudate. Exudative effusion is absolutely characteristic of pleural effusion. The most widely used **criteria are Light's** :

- The ratio of pleural fluid protein to serum protein is > 0.5.
- The ratio of pleural fluid LDH to serum LDH is > 0.6.
- The LDH level in pleural fluid exceeds two-thirds of the upper limit of normal for serum.

The presence of at least one criterion indicates an exudative nature of the effusion (sensitivity 98%, specificity 83%). Detection of transudate (e.g., in heart failure, cirrhosis) virtually excludes pulmonary fibrosis and requires adjustment of therapy for the underlying disease .

Table 1. Main laboratory characteristics of pleural effusion in the differential diagnosis of TP

Parameter	**Tuberculous pleurisy**	**Parapneumonic pleurisy / Empyema**	**Malignant pleurisy**	**Rheumatic pleurisy (RA, SLE)**
Appearance	Serous, less often serous-hemorrhagic	Cloudy, purulent	Often hemorrhagic	Serous, cloudy (in RA – “tea-colored”)
Predominant cells	**Lymphocytes (>80-90%)**	**Neutrophils**	Lymphocytes, possibly tumor cells	Lymphocytes, neutrophils
pH	Usually >7.3 (lower in empyema)	**Often <7.2** (indication for drainage)	May be <7.3 in case of massive damage	**Often <7.2** (especially in RA)
Glucose	Normal or moderately reduced	**Sharply reduced (<3.33 mmol /l, with empyema ≈0)**	It may be reduced	**Sharply reduced (especially in RA)**
Key biomarkers	**ADP >40 U /L** , IFN-γ increased	Procalcitonin and CRP are elevated	Tumor markers (CYFRA, CEA)	RF, antinuclear antibodies, low complement

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Parameter	Tuberculous pleurisy	Parapneumonic pleurisy / Empyema	Malignant pleurisy	Rheumatic pleurisy (RA, SLE)
Diagnostic standard	Pleural biopsy (granulomas), PCR, culture	Fluid culture, response to antibiotics	Cytology, pleural biopsy	Combination with systemic manifestations, serology

3. Specific diagnostics of tuberculous etiology

After establishing the lymphocytic nature of the exudate, the diagnostic search is narrowed to confirming the tuberculous etiology.

- **Direct microbiological and histological methods** :

o **Microscopy and culture** : Direct pleural fluid culture for acid-fast mycobacteria (AFB) has low sensitivity (<10%) in immunocompetent patients . Culture on liquid culture media (e.g., BACTEC) increases sensitivity to 30–70% but requires up to 8 weeks. It is important to culture not only pleural fluid but also **induced sputum or bronchial washings** , as even in the absence of radiographic changes in the lungs, their diagnostic value can reach 55%.

o **Pleural biopsy** is **the gold standard** for diagnosis. Blind pleural biopsy (using Kopp or Abrams needles) with histological examination detects caseous granulomas in 80% of cases, while a combination of histology and biopsy culture increases sensitivity to 91%. **Video-assisted thoracoscopy** (medical thoracoscopy) is the method of choice in complex cases, providing visual control, targeted biopsy of the most altered areas, and the ability to perform therapeutic procedures. Its diagnostic sensitivity and specificity approach 100%.

- **Molecular genetic methods and biomarkers** :

o **Polymerase chain reaction (PCR)** : Has high specificity (97%), but variable and often low sensitivity (62–76%) when working with pleural fluid due to the presence of inhibitors and low numbers of MTB . The use of PCR (including the Xpert MTB/RIF system) on pleural biopsy tissue significantly increases diagnostic value.

o **Adenosine deaminase (ADP)** : An enzyme actively released by T lymphocytes during the cellular immune response. ADP levels in pleural fluid >40 U /L in a clinical context are highly sensitive (92%) and specific (90%) for T cell transplantation. However, elevated ADP levels can also be observed in empyemas (neutrophilic exudate), lymphomas , and rheumatoid pleurisy, requiring differential assessment based on a combination of data.

o **Interferon-gamma (IFN-γ)** : A cytokine that directly reflects the activation of Th1 lymphocytes in response to MBT. High levels of IFN-γ in pleural effusion have diagnostic characteristics comparable to ADP .

Differential diagnosis with underlying diseases

1. **Parapneumonic pleurisy and pleural empyema** : The key difference is neutrophilia Cytosis in the exudate, more severe intoxication, and a connection with pneumonia. pH <7.2 and low glucose levels (<2.22 mmol /L) are prognostic markers of a complicated course and an indication for drainage . ADP may be elevated, but clinical and laboratory findings and the response to standard antibacterial therapy usually allow differentiation.
2. **Malignant pleurisy (metastatic, mesothelioma)** : Typically found in older patients, often with hemorrhagic effusion. Cytological examination is the initial diagnostic method, but its sensitivity does not exceed 60%. Thoracoscopy with biopsy is crucial . Unlike tuberculous pleurisy, neoplastic pleurisy is often associated with normal or slightly elevated ADP levels.
3. **Pleurisy in systemic diseases of connective tissue** :

o **Rheumatoid arthritis** : Effusion with very low glucose levels (<1.67 mmol /L), pH <7.2, and elevated rheumatoid factor titer in the pleural fluid. History of typical articular syndrome .

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- **Systemic lupus erythematosus** : Detection of LE cells or high titer of antinuclear antibodies in the effusion.

4. **Pleurisy associated with pulmonary embolism (PE)** : Acute pain, shortness of breath, and signs of right ventricular failure. The effusion may be serous or hemorrhagic, with a predominance of both neutrophils and lymphocytes. The diagnosis is confirmed by CT angiography and D- dimer testing .

The integrated diagnostic algorithm for a patient with pleural effusion is as follows:

1. Clinical and anamnestic assessment + radiation diagnostics (X-ray, ultrasound, CT scan if indicated).
2. Diagnostic thoracentesis : analysis according to Light criteria , cytosis , biochemistry (pH , glucose, LDH).
3. If lymphocytic exudate is detected: determination of the level of ADP and/or IFN-γ.
4. **If the ADP level is >40 U /L and the clinical picture is characteristic in a region with a high prevalence of tuberculosis, a diagnosis of TP can be established and therapy can be started.**
5. **If the result is questionable, the ADP level is <40 U /L or confirmation is needed (especially in regions with low incidence), a pleural biopsy (preferably video-assisted thoracoscopic) is indicated** with histological, microbiological and molecular genetic (PCR, Xpert) examination of the obtained material.

Conclusion and Prospects

Differential diagnosis of tuberculous pleurisy requires a comprehensive approach based on an understanding of its pathogenesis and consistent application of a diagnostic algorithm. Current strategies include the integration of clinical data, imaging results, pleural fluid analysis (with mandatory determination of ADP as a highly informative screening marker), and, in non-obvious cases, invasive methods, among which video-assisted thoracoscopic biopsy remains the "gold standard." Future prospects lie in the improvement of molecular genetic rapid tests (e.g., improved versions of Xpert MTB/RIF) for pleural fluid and biopsy specimens , as well as the search for new highly specific immunological and proteomic assays. biomarkers that will minimize the need for invasive procedures and reduce the time it takes to verify a diagnosis.

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