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# Primary Tuberculosis in Adults: Diagnostic Errors

***Objective*** — to study the frequency and causes of diagnostic errors in primary pulmonary tuberculosis (PrPTB) in adults.

***Materials and methods.*** The frequency and causes of diagnostic errors in verifying PrPTB in adults were studied by analyzing the pathomorphosis aspect of a specific process. Sectional material from 200 adult deaths due to primary forms of tuberculosis (PrFTB) over a period of 45 years (1974—2020) was analyzed. The study period was divided into three periods: the first period spanned from 1974 to 1988, during which three antimycobacterial drugs (isoniazid, streptomycin, and PASC) were used; the second period ranged from 1989 to 2005, during which rifampicin, ethambutol, and pyrazinamide were added to the treatment regimen; and the third period covered from 2005 to 2020, during which aminoglycosides, fluoroquinolones, linezolid, and other antimycobacterial drugs were widely utilized.

***Results and discussion.*** Studies conducted on clinical and pathological material from 200 deaths related to primary forms of tuberculosis (PrFTB) over the last 45 years (1974—2020) based on data from prosectures in Lviv indicate a significant decrease in the number of deaths from primary pulmonary tuberculosis (PrPTB) among the adult population. This decline is attributed to the widespread adoption of modern antimycobacterial therapy for patients with pulmonary tuberculosis (PTB). The predominant clinico-pathological form of PrPTB is tuberculosis of the intrathoracic lymph nodes (TBILN), which manifests with various progression variants. Complications of a specific nature (such as miliary TB, TB meningitis, and TB sepsis) prevail among the direct causes of death. However, diagnosing PrPTB in adults poses significant challenges in modern conditions, with an increasing frequency of underdiagnosis over the years. Diagnostic errors most commonly occur in general diagnostic hospitals during the verification of TBILN and its complications in patients over 30 years old.

***Conclusions.*** The frequency of underdiagnosing PrPTB has increased due to its atypical course, likely resulting from the pathomorphosis of a specific process. The discrepancy between clinical and pathoanatomical diagnoses, attributable to the unique clinical course of PrPTB, was observed in 7.3 % of cases in the first period, 27.2 % in the second, and 40.0 % in the third. Several factors contribute to the underdiagnosis of PrPTB, including short-term hospital stays, the atypical course of PrPTB due to the pathomorphosis of a specific process, inadequate patient examination, the lack of urgency for phthisiological evaluation in general medical institutions and incorrect interpretation of clinical, radiological and laboratory data.

**Keywords**

Primary tuberculosis in adults, diagnosis, errors.

The frequency of underdiagnosing PrPTB has increased due to its atypical course, likely resulting from the pathomorphosis of a specific process. The discrepancy between clinical and pathoanatomical diagnoses, attributable to the unique clinical course of PrPTB, was observed in 7.3 % of cases in the first period, 27.2 % in the second, and 40.0 % in the third. Several factors contribute to the underdiagnosis of PrPTB, including short-term hospital stays, the atypical course of PrPTB due to the pathomorphosis of a specific process, inadequate patient examination, the lack of

urgency for phthisiological evaluation in general medical institutions and incorrect interpretation of clinical, radiological and laboratory data. Disseminated caseous lymphadenitis, extensive pulmonary lesions and pronounced vascular reactions resulted in tuberculous bacteremia and rapid progression of the specific process, leading to large and miliary forms of lymphogenous and hematogenous dissemination. Additionally, the formation of a primary pulmonary cavern facilitated bronchogenic dissemination [1—7, 14, 16].

Nevertheless, significant changes in the clinic of primary forms (PrF) of tuberculosis have occurred due to the pathomorphosis of a specific process. According to studies by M.I. Sakhelashvili et al. [4, 5], the generalised forms and accompanying irreversible specific complications of primary tuberculosis (PrTB) have almost completely disappeared. This has led to an increase in the frequency of diagnostic errors in verifying primary forms of tuberculosis (PrFTB) in both children and adults [1, 8—16].

In modern conditions, PrTB has shifted from being primarily a childhood problem to being frequently encountered in adults. Verification of primary pulmonary tuberculosis (PrPTB) poses significant challenges for adults. Despite this, recent medical literature has devoted little attention to this issue [9—16].

**Objective** — to study the frequency and causes of diagnostic errors in PrPTB in adults.

## Materials and methods

To investigate the frequency and causes of diagnostic errors in verifying primary pulmonary tuberculosis (PrPTB) in adults, considering the pathomorphosis of the specific process, we conducted an analysis of sectional material from 200 fatal cases of primary forms of tuberculosis (PrFTB) in adults over a 45-year period (1974—2020).

The study period was divided into three periods: the first period, from 1974 to 1988, during which three antimycobacterial drugs (AMBDs) — isoniazid, streptomycin and PAS (para-aminosalicylic acid) — were used; the second period, from 1989 to 2005, saw the addition of rifampicin, ethambutol and pyrazinamide to the treatment regimen; and the third period, from 2005 to 2020, witnessed the widespread use of aminoglycosides, fluoroquinolones, linezolid and other AMBDs.

## Results and discussion

The group of deceased individuals consisted of 102 (51.0 %) men and 98 (49.0 %) women. Among them, 65 (32.5 %) deaths occurred between 18 and 22 years old, 69 (34.5 %) between 21 and 30 years old, 21 (10.5 %) between 31 and 40 years old, 17 (8.5 %) between 40 and 50 years old and 28 (14.0%) were over 50 years old.

Our studies revealed a gradual decrease in the frequency of deaths from primary forms of respiratory tuberculosis (RTB) among the adult population over the years. In the first period, 109 out of 200 patients died; in the second period — 63; and in the third period — 28 (54.5, 31.5% and 14.0 %, respectively).

Out of 200 patients, 127 (64.4 %) were hospitalised in anti-tuberculous institutions (Anti-TBIs), while 73 (36.5 %) were admitted to general medical hospitals (GMHs). Specifically, in the first period, 91 (63.2 %) patients were referred to an Anti-TBI, in the second period, 55 (69.6 %) and in the third period, 12 (34.2 %). The remaining patients were mistakenly hospitalised in GMHs. These findings indicate that in the third period, diagnostic errors occurred at the first stage of patient examination in 65.8 % of cases. Moreover, in the third period, PrTB was not recognised in Anti-TBIs in 33.3 % of cases, compared to only 3.3 % in the first period. Conversely, in non-specialised hospitals, PrTB was not recognised in 69.5 % of cases in the third period, compared to 24.4 % in the first period.

Among the 200 deaths from PrTB, clinical and pathoanatomic diagnoses coincided in 118 cases (59.0 %), while differences in the clinical form and genesis of the specific process were observed in 39 cases (19.5 %). Complete discrepancy of diagnosis was noted in 43 cases (21.3 %). Diagnostic mistakes were most commonly made in individuals over 30 years old (79.0 %). Additionally, an increase in the frequency of diagnostic errors was observed over the years, particularly in adult patients over the age of 30, for primary pulmonary tuberculosis (PrPTB) in specialised institutions.

To determine the increase in the frequency of undiagnosed PrPTB in adults, a further analysis of the clinical and anatomical material was conducted for 60 deceased individuals (26 in the first period, 20 in the second and 14 in the third period) who had an unrecognised specific process during their lifetime. Among them, 33 (55.0 %) were men, with an average age of (41.2 ± 3.1) years.

The distribution of age among the deceased individuals was as follows: 15 (25.0 %) were between 18 and 20 years old, 12 (20.0 %) were between 21 and 30 years old, 12 (20.0 %) were between 31 and 40 years old, 11 (18.3 %) were between 41 and 50 ears old and 10 (16.7 %) were over 51 years old. A similar age distribution was observed among deceased women.

Regardless of gender, patients predominantly died at a young age. Among men, 27 out of 33 (81.8 %) deaths occurred in individuals under 30 years old,

Table. **Distribution of deaths from primary tuberculosis**

| Pathologoanatomical diagnosis | Number of deaths | | | | Average age, years |
|---|---|---|---|---|---|
| | General number | | Including women | | |
| | Abs. | % | Abs. | % | |
| Primary tuberculosis complex | 18 | 30.0 | 12 | 40.0 | 25.1 ± 1.2 |
| Tuberculosis of intrathoracic lymphatic nodes | 37 | 61.6 | 22 | 59.4 | 28.4 ± 2.4 |
| Chronic primary tuberculosis | 5 | 8.4 | 2 | 50.0 | 31.0 ± 2.6 |

while among women, 24 out of 27 deaths (88.9 %) were in the same age group ($p > 0.05$).

In the clinical and pathomorphological structure of those who died from PrPTB, acute forms predominated, accounting for 60.0 % compared to 40.0 % for chronic forms ($p < 0.05$). Only 5 (8.4 %) of the deceased were diagnosed with a chronic course of PrPTB (Table).

It should be noted that there was a 53.8 % increase in the number of deceased males and a 34.0 % increase in individuals over 30 years old with undiagnosed TB in the third period compared to the first. Presumably, changes in the age structure of those who died from TB, particularly the increasing age of the deceased, along with a lack of phthisiological awareness, were the main reasons for the increased frequency of diagnostic errors in this disease.

The disease typically manifested acutely in the majority of patients (66.7 %), with rapid progression observed. A third of these patients were admitted to the hospital in a serious condition. Regardless of whether the disease onset was acute or gradual, all patients died within one month of hospital admission with unrecognised tuberculosis (TB) in the first period; this proportion increased to 70.0 % in the second period and 85.7 % in the third period. These findings indicate a concerning trend in modern conditions, with an increasing number of patients admitted to the hospital in a serious condition and experiencing fatal outcomes within the first month of their hospital stay.

The analysis of the sectional material revealed that the primary cause of death among patients was the emergence of severe progressive forms of tuberculosis affecting the intrathoracic lymphatic nodes (TBILNs), miliary tuberculosis, tuberculosis meningitis and tuberculosis sepsis, among others, occurring more frequently during the third period compared to the first and second periods. Notably, tuberculosis sepsis often developed in conjunction with severe comorbidities, wherein various immunosuppressants were utilised in treatment, or when the primary specific process coincided with HIV/AIDS infection [14, 16].

40.0 % of patients were examined and treated in several medical institutions, some were consulted by phthisiologists, oncologists, hematologists, surgeons, but the diagnosis was established only on autopsy.

The spectrum of diagnostic errors in the verification of PrFTB of the respiratory system and its forms of progression was quite wide. In particular, out of 60 patients whose PrTB was detected during autopsy, they were mistakenly treated for nonspecific lung diseases (15 patients — 25.0 %), malignant processes in the lungs or in other organs (11 patients — 18.3 %), diseases of the cardiovascular system (7 patients — 11.7 %), central nervous system (8 patients — 13.3 %), urinary-sexual (5 patients — 8.3 %), hematological (6 patients — 10.0 %), septic state (5 patients — 8.3 %), peritonitis (2 patients — 3.4 %) and typhoid fever (1 patients — 1.7%) [11, 12, 15]. The main reason for these errors was the pathomorphosis of the specific process, contributing to the development of an atypical course of PrFTB and the appearance of 'masks' of the PrPTB course, such as arthralgia (23.3 %), myalgia (23.3 %), vegetodystonia (23.3 %), vasculitis (16.7 %), heart pain (16.7 %), erythema nodosum (16.7 %), anemia (6.7 %), TB-allergic chorio-retinitis (6.7 %), TB-allergic keratoconjunctivitis (3.4 %), etc. All of these factors significantly influenced the referral of these patients to GMIs rather than to Anti-Tuberculosis Institutions (Anti-TBI) [4, 7, 13].

When analysing the reasons for the difference in clinical and pathoanatomical diagnosis, it was established that 16 (26.7 %) of patients with PrFTB were not diagnosed correctly due to their short hospital stays. In 15 cases (25.0 %), there was defective examination due to the lack of phthisiological awareness among general physicians. Additionally, in 16 cases (26.7 %), the unique course of PrTB in adults contributed to misdiagnosis, and in 8 cases (13.3 %), incorrect interpretation of clinical and radiological data was identified [1, 8, 9, 12, 14, 16].

It should be noted that in the third period, there was an increase in the frequency of hypodiagnosing PrTB, presumably due to its atypical course, possibly related to pathomorphosis of a specific process.

Additionally, there was an observed increase in the incidence of TB cases developing against the backdrop of severe comorbidities and immunodeficiency conditions. If in the first period, a complete difference between clinical and pathoanatomical diagnoses, due to the peculiarities of the clinical course of PrTB, was ascertained in 7.3 % of cases, in the second period, it was 27.2 %, then in the third period, it rose to 40.0%.

## Conclusions

The analysis of clinical and pathological data from 200 fatalities attributed to PrFTB over the past 45 years (1974—2020), based on data from autopsies in Lviv, reveals a notable decline in PrTB-related mortality among adults. This trend can be attributed to the widespread implementation of modern antimycobacterial therapy for individuals with PTB.

In adults, primary tuberculosis (PrTB) can present itself under the guise of non-specific lung diseases. Symptoms such as arthralgia (23.3 %), myalgia (23.3 %), vegetodystonia (23.3 %), vasculitis (16.7 %), pain in the heart (16.7 %), erythema nodosa (16.7 %), anemia (6.7 %), TB-allergic chorioretinitis (6.7 %), TB allergic keratoconjunctivitis (3.4 %) and others may be observed.

The frequency of cases of hypodiagnosing of PrTB has increased due to its atypical course, which is presumably a result of the pathomorphosis of a specific process. If in the first period a complete difference between clinical and pathoanatomical diagnosis, due to the peculiarities of the clinical course of PrTB, was ascertained in 7.3 % cases, in the second period it was observed in 27.2 %, and in the third period it rose to 40 % of cases.

Hypodiagnosing of PrTB is caused by several factors, including the short-term stay of the patient in the hospital, the atypical course of PrTB resulting from the pathomorphosis of a specific process, defective examination of the patient, lack of phthisiological urgency in the GMIs, incorrect interpretation of clinical-radiological and laboratory data.

**No conflict of interests.**
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# Первинний туберкульоз у дорослих: діагностичні помилки

***Мета роботи*** — вивчити частоту і причини діагностичних помилок при первинному туберкульозі (ПТБ) легень у дорослих.

***Матеріали та методи.*** Для вивчення частоти і причин діагностичних помилок при верифікації ПТБ легень у дорослих (за патоморфозом специфічного процесу) провели аналіз секційного матеріалу 200 померлих у дорослому віці від первинних форм туберкульозу (ТБ) за понад 45 років (1974—2020). Досліджуваний період розділили на три періоди: перший — 1974—1988 рр., коли використовували три протитуберкульозних препарати (ізоніазид, стрептоміцин і парааміносаліцилова кислота), другий — 1989—2005 рр., коли до схеми лікування додавали рифампіцин, етамбутол і піразинамід, третій — 2005—2020 рр., коли широко використовували аміноглікозиди, фторхінолони, лінезолід та інші протитуберкульозні препарати.

***Результати та обговорення.*** Дослідження клінічно-патологічного матеріалу 200 померлих від первинних форм ТБ у 1974—2020 рр. за даними прозектур м. Львова свідчать про суттєве зменшення кількості випадків смерті від ПТБ серед дорослого населення. Це зумовлено широким впровадженням сучасної антимікобактеріальної терапії хворих на туберкульох легень. Клініко-патологоанатомічною формою ПТБ, яка домінувала, був ТБ внутрішньогрудних лімфатичних вузлів із різними варіантами прогресування. Серед причин смерті переважали ускладнення специфічного характеру (міліарний ТБ, туберкульозний менінгіт і туберкульозний сепсис). У сучасних умовах виникають труднощі з діагностикою ПТБ у дорослих. Частота гіподіагностики цього захворювання збільшується. Найчастіше діагностичні помилки реєструють у загальносоматичних стаціонарах при верифікації ТБ внутрішньогрудних лімфатичних вузлів та його ускладнень у хворих віком понад 30 років.

***Висновки.*** Збільшилася частота випадків гіподіагностики ПТБ через його атиповий перебіг, що, імовірно, зумовлено патоморфозом специфічного процесу. У перший досліджуваний період відмінність клінічного і патологоанатомічного діагнозів, зумовлена особливостями клінічного перебігу ПТБ, зареєстровано в 7,3 % випадків, у другий період — у 27,2 % випадків, у третій період — у 40,0 % випадків. Гіподіагностика ПТБ спричинена кількома чинниками: нетривалим перебуванням пацієнта в стаціонарі, атиповим перебігом ПТБ унаслідок патоморфозу специфічного процесу, неповноцінним обстеженням пацієнта, відсутністю фтизіатричної настороженості в лікарів загальної мережі, неправильною інтерпретацією клініко-рентгенологічних і лабораторних даних.

***Ключові слова:*** первинний туберкульоз у дорослих, діагностика, помилки.

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