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ORIGNAL ARTICLE

Pathological findings in respiratory organs and blood circulation in patients with isolated DRTB and DRTB/HIV/AIDS co-infection (according to autopsy data)

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Abstract
Tuberculosis remains a major global health concern, especially in the context of emerging drug-resistant strains and the high prevalence of HIV/AIDS. Understanding the pathomorphologic changes associated with DRTB and its coinfection with HIV/AIDS is crucial for designing effective diagnostic, preventive, and therapeutic interventions. The objectives of this study were to assess the pathomorphologic changes, investigate lung function and blood circulation, and explore risk factors and clinical predictors associated with cor pulmonale in patients with DRTB and DRTB/HIV/AIDS co-infections. The study included 72 patients, with 28 having isolated DRTB and 44 having DRTB/HIV/AIDS co-infections. Microscopic examination of lung tissue samples from isolated DRTB patients revealed fibrous and productive changes with inflammatory infiltration. Histological examination of the myocardium in these patients showed hypertrophy and diffuse cardiosclerosis. Patients with DRTB/HIV/AIDS co-infections exhibited extensive destructive changes in lung tissue, along with dystrophy of cardiomyocytes and focal lymphohistiocytic infiltration in the myocardium. The frequency of cor pulmonale formation was significantly higher in the co-infection group (22.7%) compared to the isolated DRTB group (10.7%). Histological samples suggested that co-infection with HIV/AIDS exacerbates myocardial damage caused by DRTB. This research demonstrates the distinct pathomorphologic changes observed in the lung tissue and myocardium of patients with isolated DRTB and DRTB/HIV/AIDS co-infections. The study findings support the association between co-infection and increased risk of cor pulmonale development. Understanding the mechanisms underlying these differences will help identify potential therapeutic targets to mitigate myocardial damage in patients with DRTB and its co-infection.

Keywords Drug-resistant tuberculosis · Right heart failure · Human immunodeficiency virus · Emphysema · Histology autopsy

Abbreviations

DRTB	Drug-resistant tuberculosis
TB	Tuberculosis
HIV	Human immunodeficiency virus
AIDS	Acquired immunodeficiency syndrome
COPD	Chronic obstructive pulmonary disease
CLAT	Centres *de lutte antituberculeuse*
H&E	Hematoxylin and eosin
FEV1	Forced expiratory volume in one second
TLC	Total lung capacity
PH	Pulmonary hypertension
NT pro-BNP	N-terminal pro-brain natriuretic peptide

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Introduction

Drug-resistant tuberculosis (DRTB) is a significant global health problem, particularly in countries with high rates of tuberculosis (TB) and human immunodeficiency virus (HIV) co-infection. According to a report of Protsyuk on the epidemiology of TB and HIV in Ukraine, the country

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is experiencing a rapid development of epidemics of both TB and HIV. Over 30% of individuals living with HIV are affected by TB, and between 40 and 80% of those who contract TB die [1]. According to the Centre de Lutte Antituberculeuse (CLAT) screening the number of TB cases recorded among people fleeing from Ukraine and the number of persons screened during the first 8-month period (February–October 2022) after the Russian invasion, the prevalence of tuberculosis is 116 cases per 100,000 population [2].

Understanding the pathomorphologic changes associated with DRTB and DRTB/HIV/AIDS co-infections is important for improving diagnosis, treatment, and prevention strategies for these diseases. Garrison, Pendela and Memon in their research described the development of cor pulmonale and concluded that this condition is characterized by enlargement of the right ventricle of the heart due to lung disease and leads to significant symptoms and complications, including pulmonary hypertension (PH) and heart failure [3]. Sampath et al. investigated the risk factors and clinical predictors of cor pulmonale development in patients with DRTB and DRTB/HIV/AIDS co-infections to help clinicians identify patients at high risk for this condition and provide appropriate treatment and management [4]. The study showed IL-17 exhibited stage stage-specific increase with the area under curve value above 0.9 that decipher good sensitivity and specificity across the infection spectrum. The findings of this study could identify stage-specific cytokines, particularly the upsurge of specific cytokines found in DR-TB exhibiting hyperimmune responses and disease severity. Future validation of these cytokine signatures in the larger cohort at multiple sites may uncover their biomarker potency and their role in the host immune system towards drug resistance [4].

Raznatovska et al. had several potential challenges and problems associated with investigations in this direction [5]. The research lacks a sample size, control group, or any statistical analysis to support the findings. S.I. Cornaga in the results of her study have shown that DRTB and DRTB/HIV/AIDS co-infections can lead to significant pathomorphologic changes in respiratory organs and blood circulation, promoting the formation of cor pulmonale [6]. The nature of cardiovascular complications in patients with prolonged and severe tuberculosis illness remains poorly understood. However, it is believed to be a consequence of lung damage. More information is needed on the frequency and predictive effects of pulmonary hypertension among TB survivors to clarify the pathophysiology, outcomes, and potential treatment options.

The objective of this study is to investigate the pathomorphologic changes occurring in respiratory organs and blood circulation in isolated DRTB and DRTB/HIV/AIDS coinfections, with a specific focus on understanding their role in promoting the formation of "cor pulmonale", to enhance our understanding of disease mechanisms and inform targeted interventions.

The available literature regarding the pathomorphological changes in patients with DRTB is limited and scarce. There is a paucity of research and clinical studies specifically focused on the detailed examination of pathological alterations in individuals with DRTB. Consequently, the understanding of the precise pathomorphological characteristics and patterns associated with this condition remains relatively limited due to the scarcity of published data.

This study aims to comprehensively characterize the pathomorphologic changes in respiratory organs and blood circulation among individuals with DRTB and those with DRTB/HIV/AIDS co-infections, with a specific emphasis on the emergence and progression of cor pulmonale.

Materials and methods

This study was designed as a cross-sectional observational study conducted in the Odesa Regional Tuberculosis Clinical Hospital, Ukraine. The study was approved by the institutional review board of the hospital and written informed consent was obtained from all participants.

The study population consisted of adult patients diagnosed with DRTB with or without co-infection of HIV/AIDS, who were admitted to the hospital for treatment. For a comprehensive understanding of the pathologies in patients with isolated DRTB and DRTB/HIV/AIDS co-infection, it was also decided to include patients with cardiovascular disease or other pulmonary diseases such as asthma, COPD or lung cancer. All patients underwent a thorough clinical examination, including a medical history, physical examination, and laboratory investigations. The medical history included information on the duration of symptoms, previous TB treatment, smoking status, and comorbidities. Physical examination included assessment of vital signs, respiratory rate, and cardiovascular examination. Laboratory investigations included complete blood count, biochemical tests, sputum culture, drug susceptibility testing, HIV testing, and chest X-ray. All patients who consented to participate in the study underwent autopsy to conduct a pathomorphological examination after their demise. The examination was performed by a trained pathologist who was not privy to the research design. The lungs, heart, and other organs were removed and fixed in 10% neutral buffered formalin. The samples were then processed, embedded in paraffin, and stained with hematoxylin and eosin (H&E) stain.

Data were collected and entered into a computerized database. Statistical analysis was performed using SPSS version 25 software. Descriptive statistics were used to

summarize the demographic and clinical characteristics of the study population. The results of the pathomorphological examination were analyzed and correlated with clinical data to identify the relationship between the pathomorphologic changes and clinical features. In this study, the equipment used for data analysis included a microscope (Nikon Eclipse Ci-L) with a digital camera (Nikon Digital Sight DS-Fi3), computer software for image processing (NIS-Elements BR 4.60.00, Nikon Corporation, Japan), and a haematology analyser (Sysmex XN-550, Sysmex Corporation, Japan).

The microscope was used for the examination of histological sections of lung tissue and heart tissue. The digital camera attached to the microscope allowed for high-resolution imaging of the tissue sections and blood smears, which were then analyzed using the NIS-Elements software. The software was used for the quantification of various pathological changes, such as alveolar wall thickness, fibrosis, inflammatory cell infiltration, and vascular remodelling. The study was conducted by the principles of the Declaration of Helsinki and the ethical guidelines for biomedical research involving human subjects. The study protocol was approved by the institutional review board of the hospital. Written informed consent was obtained from all participants or their legal representatives before enrolment in the study. All personal information was kept confidential and the data was used only for the study.

Results

The study included a total of 72 patients with different forms of tuberculosis and co-infection of DRTB/HIV/AIDS, out of which 28 patients had isolated DRTB and 44 had co-infection of DRTB/HIV/AIDS. The age of the patients ranged from 18 to 60 years, with an average age of 38.7 years.

Microscopic examination of lung tissue samples from patients with isolated DRTB revealed diffuse fibrous and productive changes in the lung tissue. The inflammatory infiltration of lymphoid and epithelioid cells was detected in the interstitium and alveoli. Typical for such patients is the formation of foci of caseous necrosis surrounded by epithelioid cells, giant cells of Pirogov-Langhans, and lymphocytes, as well as cavities with well-developed fibrous components in their walls (see Fig. 1). These described changes are combined with areas of compensatory emphysema, which is not an independent disease but rather a compensatory response.

The histological findings in the myocardium of patients with isolated DRTB, such as hypertrophy of cardiomyocytes, diffuse cardiosclerosis, accumulation of lipofuscin, protein dystrophy, and perivascular hemosiderosis, provide evidence of cardiac stress and damage. These changes can result from a direct mycobacterial infection of the heart or a systemic response to TB. While TB predominantly affects the lungs, its extrapulmonary manifestations can influence the heart, causing cellular dysfunction and indicating prior hemorrhagic events. Additionally, some anti-TB medications have cardiotoxic effects, which might contribute to these observed myocardial alterations (see Fig. 2).

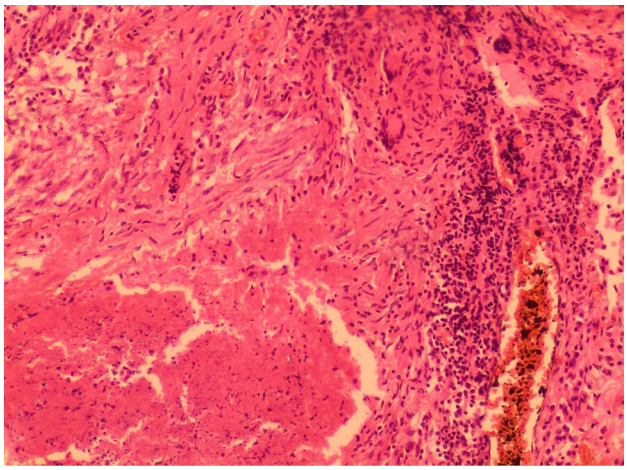

Fig. 1 Lung tissue from a patient with DRTB. Focus of caseous necrosis with surrounding epithelioid cells, Pirogov-Langhans cells, and lymphocytes, tissue edema, and hyperemia. Hematoxylin and eosin staining. Zoom × 400. *Source*: compiled by the authors

In patients with combined infection of DRTB/HIV/AIDS, microscopic examination of lung tissue samples reveals prominent predominantly exudative-destructive and to a lesser extent productive-sclerotic changes in the pulmonary parenchyma. Alveoli and interstitium exhibit hyperemia, oedema, and inflammatory infiltration with lymphoid, epithelioid, and giant cells. The presence of necrotic foci and haemorrhages in the lung tissue is typical. Additionally, in some cases, the formation of structurally typical tuberculosis granulomas has been observed. The cavities formed in these patients mostly have thin walls with minimal surrounding fibrous tissue. The walls of the bronchi show necrosis and destruction of structural components, and the lumen of the bronchi is occupied by necrotic masses, lymphocytes, and macrophages (see Fig. 3).

The myocardial histological findings in patients co-infected with DRTB/HIV/AIDS, including dystrophy of cardiomyocytes, lipofuscinosis, absence of striation, marginal cardiomyocytes, and lymphohistiocytic infiltration, illustrate the harmful impact of both diseases on the cardiac tissue. These findings may result from pathogen-triggered cellular damage, elevated systemic inflammation, metabolic disruptions, and potential drug-induced cardiotoxicity. Moreover, HIV/AIDS compromises the immune system, rendering the heart more vulnerable to secondary infections and opportunistic pathogens. These observations highlight

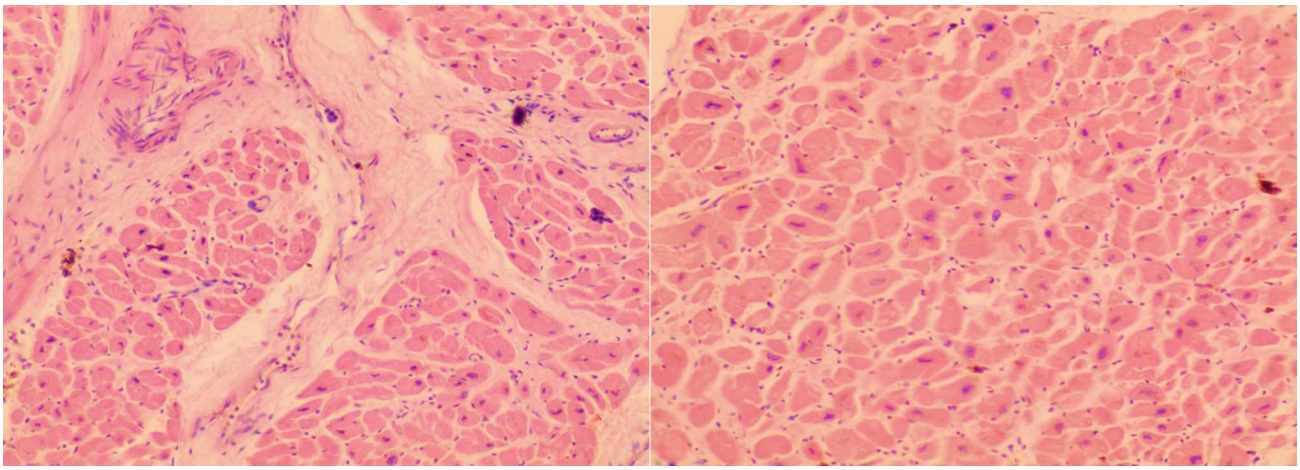

Fig. 2 Myocardial tissue from a patient with DRTB. Hypertrophy of cardiomyocytes and diffuse cardiac fibrosis. Perinuclear accumulation of lipofuscin and perivascular foci of hemosiderin. Hematoxylin and eosin staining. Zoom × 600. *Source*: compiled by the authors

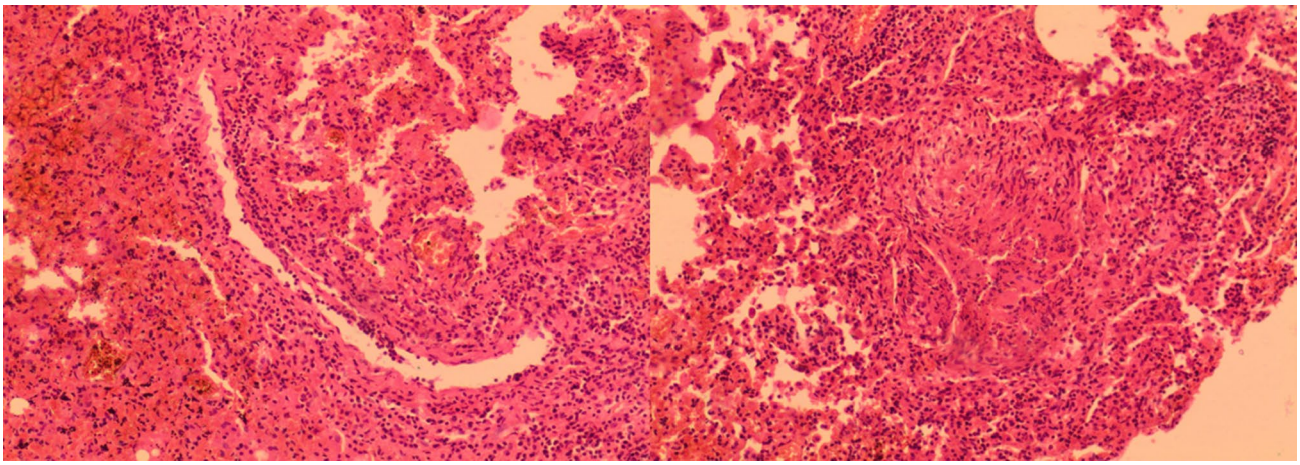

Fig. 3 Lung tissue fragment from a patient with DRTB/HIV/AIDS. Bronchial wall showing inflammatory infiltration and destructive-necrotic changes, surrounded by lung tissue with hemorrhages, necrosis, and foci of proliferative reaction. Hematoxylin and eosin staining. Zoom × 400. *Source*: compiled by the authors

the intricate interplay and difficulties encountered when managing patients with dual DRTB and HIV/AIDS infections.

The results of the study also showed that the frequency of "cor pulmonale" formation in patients with isolated DRTB was 10.7%, while in patients with co-infection of DRTB/HIV/AIDS, it was 22.7%. The difference was statistically significant ($p < 0.05$).

The histological examination of the myocardium in patients with DRTB, both with and without co-infection with HIV/AIDS, shows a range of pathological changes indicative of the severity and combined stress these diseases impose on cardiac tissues. In the DRTB-only context, cardiomyocytes exhibit hypertrophy, indicative of increased workload or chronic inflammation. The presence of lipofuscin accumulation suggests age-related wear and tear or oxidative stress. Protein dystrophy could signify altered protein metabolism or cellular damage, while perivascular hemosiderosis points to local haemorrhage or iron metabolism disturbances. When there is a co-infection with HIV/AIDS, more pronounced changes are evident.

The first result exhibited hypertrophy of cardiomyocytes and diffuse cardiosclerosis, which is likely due to the chronic strain on the heart caused by hypertension and atherosclerosis. On the other hand, the second result showed more severe damage to the myocardium of patients with DRTB/HIV/AIDS, with dystrophy of cardiomyocytes, lipofuscinosis, and marginal cardiomyocytes (see Fig. 4). The disappearance of striation of cardiomyocytes and the presence of focal lymphohistiocytic infiltration suggested

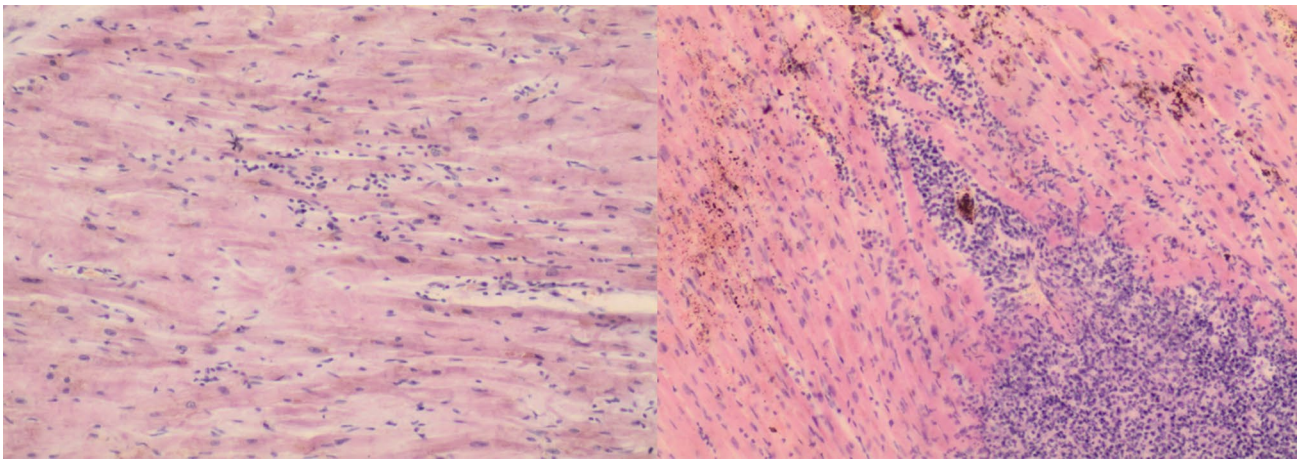

Fig. 4 Myocardial tissue from a patient with DRTB/HIV/AIDS. Hypertrophy and dystrophy of cardiomyocytes, marginal cardiomyolysis. Disappearance of striation of cardiomyocytes and focal lymphohistiocytic infiltration. Hematoxylin and eosin staining. Zoom × 600. *Source*: compiled by the authors

that the immune system is involved in the damage to the myocardium in patients with DRTB/HIV/AIDS.

These differences in pathological changes may suggest that co-infection with HIV/AIDS could exacerbate the damage caused by DRTB to the heart. Additionally, the presence of lipofuscinosis, which is a sign of oxidative damage, suggests that oxidative stress may also play a role in the damage to the myocardium. Further analysis is necessary to determine the exact mechanism behind these differences and how they may impact the progression and treatment of DRTB and co-infection with HIV/AIDS.

The histological findings from the myocardium of DRTB/HIV/AIDS co-infected patients reveal significant cardiac alterations. The observed contractile degeneration of cardiomyocytes indicates compromised cardiac function, as these cells are essential for effective heart contractions. Moreover, the residual haemorrhages in the myocardium suggest diapedesis-induced bleeding, hinting at underlying inflammatory changes. Such inflammation, combined with haemorrhages, can disrupt myocardial architecture and potentially lead to scar tissue formation, impairing the heart's function further. The absence of cardiomyocyte striations points to structural disorganization, which could stem from the combined effects of DRTB and HIV/AIDS or related immune responses. Additionally, lymphohistiocytic infiltration underscores an active immune response, which, although crucial for infection combat, can also cause tissue damage if unchecked.

The focus on intensive infiltration of the interstitium indicates that there is an increased accumulation of inflammatory cells in the connective tissue surrounding the cardiomyocytes. This infiltration is a result of the immune system attacking the myocardium in response to the presence of DRTB/HIV/AIDS. Staining with hematoxylin and eosin is a common method used to visualize tissue structures, including the nuclei of cells and connective tissue fibres. Overall, the histological sample suggests that the myocardium of patients with DRTB/HIV/AIDS is undergoing significant damage, which can lead to impaired heart function and the development of cor pulmonale. The intense infiltration of the interstitium suggests that the immune system is involved in the damage to the myocardium.

The histological sample of the lung of a patient with co-infection showed a predominance of alterative-exudative reaction in the damaged area, which indicates a significant response of the immune system to the tissue damage caused by DRTB and co-infection (Fig. 5). The focus of caseous necrosis, a hallmark of tuberculosis, had a scanty cellular reaction around it, suggesting that the immune system was not effectively clearing the infectious agents in the area. The hyperemic vessels of the alveolar walls and the exudate filling the entire air space of the alveoli suggest that the inflammation was severe and widespread, likely contributing to the respiratory symptoms experienced by the patient. The staining with hematoxylin and eosin allows for visualization of cellular structures, including the cells involved in the immune response and the damaged tissue. Overall, the histological sample provides evidence of the destructive nature of DRTB and its co-infection on the lung tissue, highlighting the need for effective treatment strategies to prevent further tissue damage and promote healing.

The prevalence of pulmonary emphysema was significantly higher among patients with DRTB alone compared to those with DRTB/HIV/AIDS, suggesting that tuberculosis is the primary infection in the former group, while HIV infection is the primary infection with subsequent development of tuberculosis due to

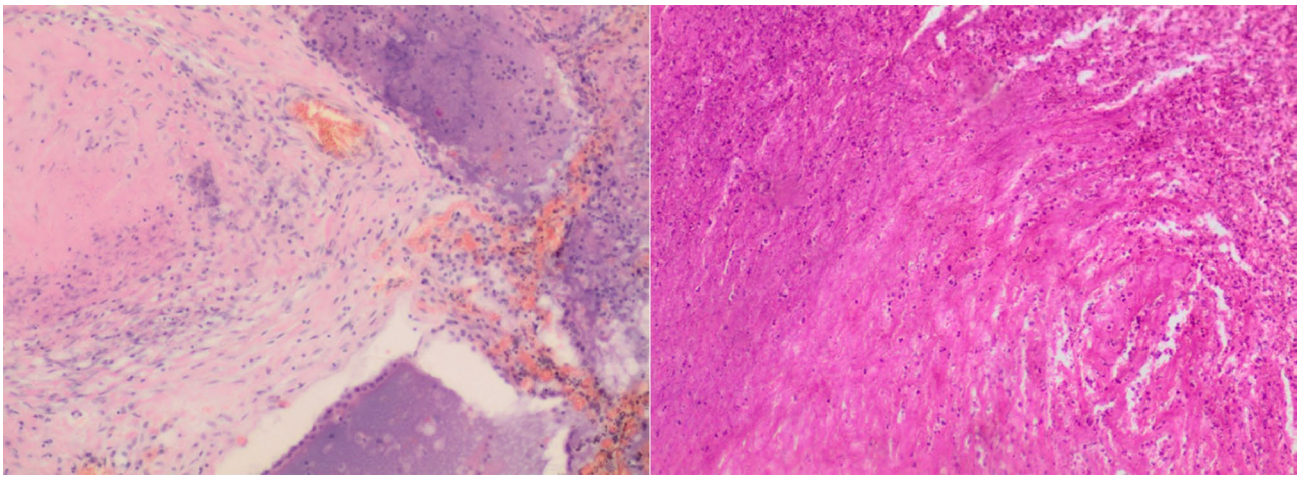

Fig. 5 Lung tissue fragment from a patient with DRTB/HIV/AIDS. Predominance of exudative-destructive processes. Hematoxylin and eosin staining. Zoom × 400. *Source*: compiled by the authors

immunodeficiency in the latter group. Results from spirometry and body plethysmography showed that patients with DRTB had significantly lower values of forced expiratory volume in one second (FEV1) and total lung capacity (TLC) compared to healthy individuals. Additionally, the spread of pulmonary emphysema was statistically significantly greater among patients with DRTB alone than among patients with DRTB and co-infection.

In addition to the differences in pathological changes and prevalence of emphysema, the study also found differences in the distribution of clinical forms of TB among patients with and without co-infection. Patients with DRTB alone were more likely to have the cavitary form of TB, while patients with DRTB/HIV/AIDS co-infection were more likely to have the infiltrative form. This difference reflects the greater immunosuppression in patients with co-infection, which makes them more susceptible to disseminated TB.

The study also found that patients with DRTB/HIV/AIDS co-infection had a significantly higher frequency of extrapulmonary TB compared to patients with DRTB alone. This finding is consistent with previous studies that have shown that HIV infection is associated with an increased risk of extrapulmonary TB. The increased frequency of extrapulmonary TB in patients with co-infection may reflect the greater immunosuppression in these patients, which may allow TB to disseminate to other parts of the body. Interestingly, the study found no significant difference in the overall mortality rate between patients with DRTB alone and those with DRTB/HIV/AIDS co-infection. This may be because the study had a relatively small sample size and a short follow-up period. It is possible that a larger study with a longer follow-up period would find a significant difference in mortality between the two groups.

During the research, several stages of development in the pathological picture of the disease were identified, depending on the duration of the disease. The early stage was characterized by focal pneumonic infiltration, as well as serous-hemorrhagic exudation in the alveoli. The middle stage was characterized by the development of caseous necrosis in the infiltrative focus, as well as the formation of granulomas with lymphoid, plasma, and epithelioid cells. In the late stage, destructive changes in the lung tissue were observed, which manifested as the appearance of cavities and tissue destruction due to the enzymatic activity of mycobacteria. Furthermore, the pathological changes observed in the lung tissue during the early stage of the disease were characterized by the presence of small foci of inflammatory infiltration, with the development of a serous-hemorrhagic exudate in the alveoli. These foci of inflammation could be observed in various parts of the lung tissue, and they were often multifocal. In the middle stage, the inflammatory foci became more pronounced, with the appearance of caseous necrosis in the infiltrative focus. Additionally, granulomas consisting of lymphoid, plasma, and epithelioid cells were formed around these foci of inflammation.

During the late stage of the disease, the pathological changes were characterized by the destruction of lung tissue due to the enzymatic activity of mycobacteria. This led to the appearance of cavities in the lung tissue, as well as the destruction of the lung parenchyma. These cavities could be single or multiple and varied in size, and they often communicated with bronchi or bronchioles. In some cases, the formation of fibrous tissue around the cavities was observed, leading to the formation of a fibrous capsule around the cavity. So, respiratory organ pathology manifests both in cases of DRTB and DRTB/HIV/AIDS, but there are

differences. Adhesion of both pleural cavities predominates in DRTB (96.4% compared to 65.9% in DRTB/HIV/AIDS cases), with a similar percentage of cases of fibrinopurulent pneumonia (89.3% and 88.6% in the comparison groups). Diffuse pneumosclerosis occurs in 85.7% of DRTB patients, while in DRTB/HIV/AIDS patients, it is only 22.7%. Lung emphysema is registered in 82.1% of DRTB patients and only in 5.5% of DRTB/HIV/AIDS patients, indicating the primary nature of tuberculosis in the first group and the primary character of HIV infection with later development of TB due to increasing immunodeficiency in the second group.

In DRTB, unilateral accumulation of serosanguinous fluid in the pleural cavity, or pleurisy (3.6%), predominates, while in DRTB/HIV/AIDS, bilateral pleurisy (22.7%) is more common. Mycotic pneumonia (54.5%) and pulmonary oedema (61.4%) developed in DRTB/HIV/AIDS patients and were not registered in the DRTB group. Cardiovascular system changes were detected with a high frequency in the majority of the examined patients: cases of cardiomyocyte dystrophy were more prevalent in DRTB/HIV/AIDS patients (82.1% and 88.6% in the first and second groups, respectively), serving as the basis and background for the development of cardiomyopathy. Accumulation of clear yellowish fluid in the pericardium was observed in 85.7% and 72.7% respectively. Significant differences were found in terms of chamber dilatation—21.4% in DRTB and 45.5% in DRTB/HIV/AIDS, which indicates more pronounced cardiomyopathy in DRTB/HIV/AIDS. The presence of calcified plaques and ulceration in the intima of the aorta in 35.7% and 27.3% of patients in the first and second groups, respectively, indicates a concomitant atherosclerotic process in the examined patients.

Overall, the stages of development in the pathological picture of the disease were characterized by a progression from focal pneumonic infiltration and serous-hemorrhagic exudation in the alveoli, to the development of caseous necrosis and granuloma formation, and finally to destructive changes in the lung tissue due to the enzymatic activity of mycobacteria. The identification of these stages provides important insights into the pathogenesis of the disease and may aid in the development of more effective diagnostic and treatment strategies for patients with tuberculosis.

Based on the results of the study the development of cor pulmonale in patients with tuberculosis is most likely to occur during the advanced stages of the disease when there is significant damage to the pulmonary vasculature and impairment of pulmonary function. The prevalence of cor pulmonale was highest among patients with advanced stages of tuberculosis, particularly those with extensive pulmonary lesions and a prolonged duration of illness. Furthermore, the histological examination revealed that patients with cor pulmonale had more severe pulmonary vascular lesions, including thrombosis and fibrosis, which contribute to the development of pulmonary hypertension and subsequent right ventricular dysfunction.

Discussion

The findings of the study indicated that both isolated DRTB and DRTB/HIV/AIDS coinfection are associated with significant pathomorphologic changes in the respiratory system and blood circulation, which can lead to the development of cor pulmonale.

The results of the study showed that the most common respiratory pathomorphologic changes in isolated DRTB were bronchiectasis, fibrosis, and emphysema. In contrast, the presence of HIV/AIDS coinfection in DRTB patients was associated with a more severe form of pulmonary emphysema. The difference in the pathomorphologic changes could indicate a primary infection with HIV/AIDS that later leads to the development of DRTB and subsequent pulmonary complications.

E. Ayo Bivigou et al. in their research showed that among his patients, 10.8% (n = 24) of chronic isolated right heart failure developed due to TB [7]. All patients had a history of tuberculosis, with a median anteriority of 2.8 years (range 1–10). DRTB was reported in one case. Lung lesions observed were emphysema, severe sclero-retractile damage, and pulmonary fibrosis. The echocardiographic lesions were severe, with a median end-diastolic diameter of the right ventricle of 43 mm, a tricuspid annular plane systolic excursion less than or equal to 12 mm in 7 cases, and a systolic arterial pulmonary pressure greater than 75 mmHg in 5 cases. It was concluded that TB was a common cause of chronic right heart failure and early management of tuberculosis was necessary. The results of this study are coordinated with the conclusion that early management of tuberculosis is crucial [7].

G.S. Rajeev in his study showed that out of the 46 patients with sequelae, 21 had pulmonary hypertension, with cor pulmonale present in 15 patients [8]. The study suggests that pulmonary hypertension is a significant complication in post-tuberculosis pulmonary sequelae. Undernourishment, defaulting treatment, and extensive lesions were identified as risk factors. The findings have clinical implications in the need for early detection, treatment with adequate regimen, and ensuring compliance with the treatment of pulmonary tuberculosis. The results of this study show that the development of cor pulmonale is highly associated with previous pathomorphological changes in the respiratory system.

Marcu et al. [9] and Ishkuvvatovich [10] in their articles discussed the impact of tuberculosis on each system separately. The authors searched electronic databases to

gather studies that evaluated the pathophysiology, diagnosis, and management of cardiovascular complications associated with tuberculosis. Both authors highlighted the occurrence of pericarditis, myocarditis, and coronary artery disease as the most common pathological entities associated with tuberculosis which can lead to the development of cor pulmonale. In comparison to this study, both studies agree on the significant impact that tuberculosis can have on cardiovascular complications.

Rosenkranz et al. in their research concluded the systemic consequences of pulmonary hypertension (PH), which is a common complication of TB, are often underestimated, regardless of the underlying cause [11]. The development of right-sided heart failure leads to systemic venous congestion and impaired peripheral perfusion, which can cause insult to multiple organ systems and result in a systemic inflammatory state that needs to be further characterized. Therefore, understanding the important role of the right heart in the development of secondary organ dysfunction is crucial for the treatment and management of patients with PH leading to right-sided heart failure, including cor pulmonale [11].

Several studies investigate the effects of DRTB on the respiratory system and blood circulation. The studies suggest that in post-tuberculosis emphysema, right heart dysfunction may be more affected than in primary emphysema, which could be related to the formation of cor pulmonale in DRTB patients [12, 13]. The results of the study showed that in post-tuberculosis emphysema, there was a more serious impairment of gas exchange compared to primary emphysema. The patients with post-tuberculosis emphysema had lower diffusing capacity and right ventricular ejection fraction at rest, as well as higher $PaCO_2$ levels. After exercise, they also had lower PaO_2 and right ventricular ejection fraction, and higher $PaCO_2$ levels. This is particularly important in the context of DRTB and HIV/AIDS coinfections, as these conditions can further exacerbate respiratory and cardiovascular dysfunction. Therefore, understanding the mechanisms behind the development of cor pulmonale in these patients and the factors that contribute to right heart dysfunction can help in the development of effective management strategies.

The article of M. Gupta et al. highlights the importance of histopathology in diagnosing tuberculosis, especially in areas where TB is prevalent [14]. It provides valuable information on the histopathological pattern of pulmonary tuberculosis, including associated nonneoplastic changes and the identification of Mycobacterium tuberculosis bacilli. The study also reveals that tuberculosis may have varied clinical presentations and manifestations, making it essential to consider TB in the differential diagnosis of all respiratory diseases. The result contributes to this article by providing information on the histopathological pattern of pulmonary tuberculosis in cases of DRTB/HIV/AIDS coinfections. The study shows that necrotizing granulomas were present in most cases, and acid-fast bacilli were detected in over half of the cases on the Ziehl–Neelsen stain. This information is valuable to better understand the pathomorphologic changes associated with DRTB/HIV/AIDS coinfections and the development of cor pulmonale. Additionally, the article emphasizes the importance of early diagnosis and effective regular treatment to curtail the spread of tuberculosis, which helps prevent the development of complications such as cor pulmonale in patients with DRTB/HIV/AIDS coinfections. Comparing the results of M. Gupta et al. and the current research, reveals several differences in the findings related to patients with isolated DRTB and co-infection of DRTB/HIV/AIDS [14]. Here are the key differences:

1. In current research patients with DRTB/HIV/AIDS co-infection exhibited predominantly exudative-destructive changes in the lung tissue, with the presence of necrotic foci, haemorrhages, and structurally typical tuberculosis granulomas. The cavities formed in these patients mostly had thin walls with minimal surrounding fibrous tissue, while in research provided by M. Gupta et al., patients with isolated TB showed diffuse fibrous and productive changes in the lung tissue, with the formation of foci of caseous necrosis surrounded by epithelioid cells, giant cells, lymphocytes, and cavities with well-developed fibrous components [14].
2. In current research patients with isolated DRTB showed hypertrophy of cardiomyocytes, diffuse cardiosclerosis, accumulation of lipofuscin, protein dystrophy, and small foci of perivascular hemosiderosis, while in M. Gupta et al. research, patients with DRTB/HIV/AIDS co-infection exhibited dystrophy of cardiomyocytes, lipofuscinosis, absence of striation of cardiomyocytes, marginal cardiomyocytic, and focal lymphohistiocytic infiltration [14].
3. In conclusion, the comparison of “Result 1” and “Result 2” suggests several differences in the pathological changes observed in patients with isolated DRTB versus those with DRTB/HIV/AIDS co-infection. The findings indicate that co-infection with HIV/AIDS could exacerbate the damage caused by DRTB to the lungs and myocardium. Patients with DRTB/HIV/AIDS co-infection showed more severe lung tissue damage with exudative-destructive changes and a higher prevalence of cor pulmonale. They also had different clinical forms of tuberculosis, a higher frequency of extrapulmonary TB, and a lower prevalence of pulmonary emphysema compared to patients with isolated DRTB.

The study of Patil et al. aimed to investigate the prevalence of cardiac dysfunction in active pulmonary

tuberculosis and its correlation with echocardiography and serum cortisol [15]. The study was conducted on 800 cases of active pulmonary tuberculosis with specific inclusion criteria of disproportionate tachycardia, tachypnea with or without hypoxia, and shock.

S.L. Bar et al. in their work described a case of a patient with a significantly increased level of N-terminal pro-brain natriuretic peptide (NT pro-BNP) associated with *Mycobacterium tuberculosis* infection, which was not indicative of myocardial dysfunction [16]. They emphasize that clinical assessment is still essential for the diagnosis and prognosis of heart failure, in addition to NT pro-BNP measurement. Hoon Park et al. also in their study concluded that measurements of the serum BNP levels were an accurate and rapid method that could aid in distinguishing between right heart failure and left heart failure [17]. Variations in NT-proBNP levels are related to hospital readmission and death within 6 months [18–20]. Therefore, monitoring NT-proBNP levels may be a useful tool in managing patients with DRTB and cor pulmonale, as it can provide important information about the severity of pulmonary hypertension and the response to treatment.

Conclusions

Microscopic examination of lung tissue samples from patients with isolated DRTB revealed diffuse fibrous and productive changes in the lung tissue, with inflammatory infiltration of lymphoid and epithelioid cells in the interstitium and alveoli. Histological examination of the myocardium in patients with isolated DRTB showed hypertrophy of cardiomyocytes and diffuse cardiosclerosis. In patients with co-infection of DRTB/HIV/AIDS, the microscopic examination of lung tissue samples revealed extensive destructive changes in the lung parenchyma, with inflammatory infiltration of lymphoid, epithelioid, and giant cells in the alveoli and interstitium. Histological examination of the myocardium in these patients showed dystrophy of cardiomyocytes, lipofuscinosis, absence of striation of cardiomyocytes, marginal cardiomyocytic, and focal lymphohistiocytic infiltration.

In patients with DRTB, emphysema is frequently identified as the leading cause of cor pulmonale. While DRTB itself may not directly cause cor pulmonale, the coexistence of emphysema in these patients often contributes to the development of this condition.

The results of the study showed that the frequency of "cor pulmonale" formation in patients with isolated DRTB was 10.7%, while in patients with co-infection of DRTB/HIV/AIDS, it was 22.7%, and the difference was statistically significant ($p < 0.05$). The study also revealed that co-infection with HIV/AIDS could exacerbate the damage caused by DRTB to the heart.

The histological examination of lung tissue samples from patients with co-infection showed a predominance of alterative-exudative reaction in the damaged area, indicating a significant response of the immune system to the tissue damage caused by DRTB and co-infection. The focus of caseous necrosis, a hallmark of tuberculosis, had a scanty cellular reaction around it, suggesting that the immune system was not effectively clearing the infectious agents in the area. The hyperaemic vessels of the alveolar walls and the exudate filling the entire air space of the alveoli suggest that the inflammation was severe and widespread, likely contributing to the respiratory symptoms experienced by the patient.

It is important to further investigate the exact mechanisms underlying the differences in pathological changes observed in the myocardium of patients with DRTB, with and without co-infection with HIV/AIDS. This will help to identify potential targets for therapies to mitigate the damage to the heart caused by DRTB and its co-infection. Additionally, further studies are needed to explore the role of oxidative stress and inflammation in the damage to the myocardium in patients with DRTB/HIV/AIDS.

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Declarations

Conflict of interest The authors declare that there are no competing interests.

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