ABSTRACT: Introduction: Tuberculosis (TB) is an infectious disease caused by the bacterium Mycobacterium tuberculosis (Mtb), a strictly aerobic, non-encapsulated, and non-sporulating bacillus. Objective: To gather effects of Mtb infection on the lungs and the immune system. Method: An integrative review was conducted between May and June 2023, using PubMed database with the following search strategies: “Tuberculosis, Pulmonary” AND Necrosis; “Mycobacterium tuberculosis” AND “lung injury”; “Mycobacterium tuberculosis” AND “immune system” AND Inflammation. Original articles published between 2018 and 2023 that met the review’s objective were selected. Results: A total of 134 articles were obtained from the search, 126 were excluded after reading the title, abstract, and full text, remaining 8 articles selected to compose this review. The studies indicated that Mtb infection stimulates the production of cytokines such as TNF-α, IFN-γ, and IL-10, inducing variations in their serum levels depending on the stage of the disease and the spread of infection. Additionally, there were changes in the rates of B lymphocyte growth factors and the production of anti-TB antibodies, leading to the formation of granulomas and macroscopic lung lesions. Conclusion: The effects of Mtb infection on the lung and the immune system are inferred to be instigated by the action of various cytokines, which will modulate the inflammatory and immune response against the bacterium.

KEY WORDS: Inflammation; Mycobacterium tuberculosis; Lung; Immune System; Tuberculosis.

RESUMO: Introdução: Tuberculose (TB) é uma doença infectocontagiosa causada pela bactéria Mycobacterium tuberculosis (Mtb), um bacilo aeróbio estrito, não encapsulado e não esporulante. Objetivo: Compilar os efeitos da infecção por Mtb no pulmão e no sistema imune. Método: Revisão integrativa realizada entre maio e junho de 2023, na base de dados PubMed, com as seguintes estratégias de busca: “Tuberculose, Pulmonar” AND Necrose; “Mycobacterium tuberculosis” AND “lesão no pulmão”; “Mycobacterium tuberculosis” AND “sistema imune” AND Inflamação. Foram selecionados artigos originais publicados entre 2018 e 2023 que atendessem ao objetivo desta revisão. Resultados: Obteve-se um total de 134 artigos com a busca, dos quais foram excluídos 126 após leitura do título, do resumo e da leitura na íntegra, restando 8 artigos selecionados para compor esta revisão. Os estudos indicaram que a infecção por Mtb estimula a produção de citocinas, como TNF-α, IFN-γ e IL-10, e induz variações em seus níveis séricos conforme o estágio da doença e disseminação da infecção, além de alterações nas taxas de fatores de crescimento de linfócitos B e na produção de anticorpos anti-TB, formando granulomas e lesões macroscópicas pulmonares. Conclusão: Depende-se que os efeitos da infecção por Mtb no pulmão e no sistema imune são instigados pela ação de diversas citocinas, que irão modular a resposta inflamatória e imune contra a bactéria.

PALAVRAS-CHAVE: Inflamação; Mycobacterium tuberculosis; Pulmão; Sistema Imunitário; Tuberculose.
INTRODUCTION

Tuberculosis (TB) is an infectious disease caused by the bacterium Mycobacterium tuberculosis (Mtcb). It is estimated that the first cases of tuberculosis in Brazil occurred during Portuguese colonization in 1549. Although there were several cases of tuberculosis, it was not until 1882 that the physician Heinrich Hermann Robert Koch proved the idea that TB was caused exclusively by the bacillus of the genus Mycobacterium and that its transmission occurred with the elimination of the bacterium from the body through sneezing, saliva droplets and phlegm. In addition, it is noteworthy that the bacterium is more prevalent in individuals in situations of extreme vulnerability - low levels of income, education and inadequate housing - that, in the absence of adequate health care, there is an increase in the spread of the disease.

Mtcb is a strict, non-encapsulated, non-spore-forming aerobic bacillus that retains basic fuchsin in its cell wall, even in the presence of alcohol and acid - a fact that characterizes it as an acid-fast bacillus (AFB) - and that proliferates inside macrophages. The action of Mtcb in the body begins, most of the time, through the inhalation route, in which the nasal cilia, the cough reflex and mucociliary clearance try to eliminate the bacilli by physical mechanisms and, if this is not possible, the bacteria settles. After about three to four weeks, the pulmonary focus begins.

Upon reaching the lungs, Mtcb will be phagocytosed by type II pneumocytes and alveolar macrophages, which release chemokines that attract and activate neutrophils, monocytes, lymphocytes and other inflammatory cells that conjugate to destroy them. Although they are not efficient in fighting the bacterium, the joint action with tumor necrosis factor-alpha (TNF-α), which induces reactive nitrogen intermediates (RNI) and caseous necrosis, and interferon gamma (IFN-γ), make the medium lethal for Mtcb.

In this context, the influence of CD4+ T lymphocytes can be perceived, in which the TH1 subgroup inhibits BK growth by regulating the immune response. It is from the T lymphocytes that the granulomatous lesion characteristic of TB begins through the formation of a granuloma, which contains epithelioid cells and Langhans giant cells and, in its envelope, CD4+ and CD8+ T lymphocytes. Therefore, with the development of cellular immunity, this center of the granuloma undergoes a process of caseous necrosis, which can also be induced by BK, through TNF-α and lipopolysaccharin glycoprotein (LAM), which is present on the surface of the bacilli that mediates the interaction between mannose receptors and BK.

Thus, the pathophysiology of TB is characterized in the primary phase as asymptomatic and mild, with a Ghon’s lesion, a calcified nodule, and, as the disease progresses, patients develop daytime fever, night sweats, weight loss, anorexia, malaise, weakness, and cough with occasional massive hemoptysis. Therefore, TB is treated with antibiotics, such as rifampicin, isoniazid, pyrazinamide, and ethambutol, and one of the forms of prevention is through the BCG vaccine.

A high incidence of tuberculosis in Brazil, with 66,796 new cases reported in 2016 and 12,809 in retreatment, with the highest prevalence in illiterate patients aged 30-39 years. Also in 2019, 73,864 new cases were registered with the occurrence of 6,760 deaths, which corresponds to a mortality coefficient of 3.17 deaths per 100 thousand inhabitants. It is worth noting that the Notifiable Diseases Information System (SINAN) records only after the diagnosis is confirmed, made through clinical history, chest X-ray, chest computed tomography, bronchoscopy, tuberculin skin test, or Mantoux reaction.

When looking at the epidemiological data of TB in Brazil from 2018 to 2022, the severity of the disease is noted, since 470,915 cases were reported, and one person is capable of infecting about 10 to 15 other individuals per year in the country. It was observed that during the Covid-19 pandemic, there was a decrease in TB cases, which can be justified by the increased use of masks, hand hygiene, and distancing. Another relevant factor was that infected patients develop neutralizing antibodies after 2-4 weeks, which help fight TB. Therefore, it is essential to approach this topic in order to understand how Mtcb acts on the immune system and its form of containment. And therefore, this study aims to compile the effects of Mycobacterium tuberculosis infection on the lung and immune system.

METHODS

This is a literature review following an integrative methodology. The following guiding question was used to guide the conduction of the review: “What are the effects caused by Mtcb infection on the lung and the immune system?”

The descriptors “Tuberculosis, Pulmonary”, “Necrosis, Mycobacterium tuberculosis”, “Lung injury”, “Immune system” and “Inflammation”, extracted from the Health Sciences Descriptors (DeCS/MeSH) database, were used to formulate the three search strategies used in the PubMed database, between May and June 2023. “Tuberculosis, Pulmonary” AND Necrosis, Mycobacterium tuberculosis AND Lung injury”, “Mycobacterium tuberculosis” AND “immune system” AND Inflammation. The criteria used to include the articles in the review were: published between 2018 and 2023; written in English or Portuguese; available in full. Articles that did not answer the guiding question, meta-analyses, and other literature reviews were excluded from the review. The criteria were employed by two different researchers, who selected the articles first by reading the title and abstract and then by reading the article in its entirety. A complementary manual search was performed in order to add new articles, obtained from other databases and without applying the same criteria, in order to improve the discussion of the results.

RESULTS

By using the three search strategies described in the method and after applying the filters, a total of 134 articles were found. After excluding articles by reading the title and abstract, 13 articles were obtained, which were read in full, and thus, another five articles were excluded because they did not deal with the theme of this review, totaling the inclusion of 9 articles, which are shown in Table 1.

Table 1 - Studies included in the review and their background information.

<table>
<thead>
<tr>
<th>Study Title</th>
<th>Author(s)</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Altered circulating levels of B cell growth factors and their modulation upon anti-tubercular drug treatment in pulmonary tuberculosis and tuberculosis lymphadenitis</td>
<td>KATHAMUTHU et al.</td>
<td>2018</td>
</tr>
<tr>
<td>Sex influences the association between haemostasis and the extent of lung lesions in tuberculosis</td>
<td>TAN et al.</td>
<td>2019</td>
</tr>
<tr>
<td>Immunochemical host responses as surveillance and prognostic markers in tubercular lymphadenitis</td>
<td>WAGHMARE et al.</td>
<td>2019</td>
</tr>
<tr>
<td>Mycobacterium tuberculosis exploits focal adhesion kinase to induce necrotic cell death and inhibits reactive oxygen species production</td>
<td>AFRIYIE-ASANTE et al.</td>
<td>2021</td>
</tr>
<tr>
<td>Mycobacterium tuberculosis load in host cells and the antibacterial activity of alveolar macrophages are linked and differentially regulated in various lung lesions of patients with pulmonary tuberculosis</td>
<td>UFM-TSEVA et al.</td>
<td>2021</td>
</tr>
<tr>
<td>Changes of TH1 and TH2 cytokines levels in patients with active pulmonary tuberculosis</td>
<td>KIREEV et al.</td>
<td>2021</td>
</tr>
<tr>
<td>Pathology of pulmonary tuberculosis: has the tiger changed its stripes?</td>
<td>DESAI et al.</td>
<td>2022</td>
</tr>
<tr>
<td>B cells promote granulomatous inflammation during chronic Mycobacterium tuberculosis infection in mice</td>
<td>CHEN et al.</td>
<td>2022</td>
</tr>
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</table>

Source: Prepared by the authors (2023)

TNF plays an important role in the immune response to TB, the main one being to ensure the latency of bacterial infection. Kireev et al., based on blood collection from 45 patients with TB and 150 without TB, analyzed the serological levels of TNF and anti-TNF autoantibody by means of enzyme-linked immunosorbent assays (ELISA). Their study found similar levels of TNF between TB patients and healthy individuals. However, when comparing TNF levels among TB patients, it was found that disseminated infection (infection occupying more than two segments) is linked to a higher TNF value than localized infection (infection occupying one or two segments). Patients with more severe manifestations, with the pathogen isolated by bronchoscopy, also demonstrated higher levels of TNF. Regarding the titration of serum levels of the anti-TNF autoantibody, the IgG class showed significantly higher levels in TB patients than in healthy patients, unlike immunoglobulin M (IgM) and immunoglobulin A (IgA). The immunoglobulin G3 (IgG3) subclass was elevated in tuberculosis patients when compared to healthy individuals, while immunoglobulin G1 (IgG1) and immunoglobulin G2 (IgG2) remained stable. Among patients with disseminated infection in whom Mtcb was isolated by bronchoscopy, IgG, IgG1 and IgA levels were elevated.

The retrospective study by Desai et al. described macroscopic and microscopic patterns and Ziehl-Neelsen staining and TB complications. Over a three-year period, 120 autopsies of patients who died after TB infection were conducted. Among the macroscopic morphological alterations, non-cavitary bronchopneumonia was the most present in 47 of the cases (36.15%), followed by miliary lesions in 34 cases (26.15%), nodular lesions in 19 cases (14.62%) and fibrocavitary lesions in 17 cases (12.08%); bronchopneumonia with cavitation in 12 cases (9.23%), and pleuritis in only one case (0.77%). In addition, TB complications were analyzed, including vasculitis, in 55 cases (42%), observed with bronchopneumonia, in 16 cases diffuse alveolar hemorrhage, in cases (2.3%), diffuse alveolar damage, in 11 cases (8.4%) and pulmonary thromboembolism, in two cases (1.5%).

Blood samples from 145 individuals, including 85 patients with recent TB (58.6%), 25 in follow-up with TB (17.2%), and 35 in a healthy control group (24.1%), measured plasma levels of the cytokines interleukin 10 (IL-10), TNF-α, and IFN-γ in the study by Abdul-Aziz et al. The diagnosis of the disease was made based on Ziehl-Neelsen staining (for recent disease) and PCR test (for disease under follow-up). In patients with new TB cases, serumological IFN-γ levels were significantly higher than in the healthy control group and the follow-up group.

No significant differences were found between IL-10 and TNF-α in patients recent TB, healthy control group, and ongoing TB.

The research by Kathamuthu et al. examined the magnitude of the importance of proliferation-inducing ligand (APRIL) and B-cell activating factor (BAFF) as B-type lymphoid cell growth factors in patients with active pulmonary tuberculosis (PTB); latent tuberculosis infection (LTB), tuberculous lymphadenitis (LTB), and in a healthy control group (CH), each of the groups with 44 individuals. APRIL was found to be significantly reduced in PTB patients relative to the other two clusters, with 130.1 pg/mL in PTB, 2869 pg/mL in LTB, 2582 pg/mL in LTB, and 2582 pg/mL in HC. On the other hand, circulating levels of BAFF were found to be elevated in PTB and LTB.
LTB, with 571.7 pg/mL and 795.9 pg/mL, respectively, when compared with LTB (290.7 pg/mL) and CH (283.2 pg/mL). The study also revealed decreases in the levels of APRIL and BAFF in serum IgG antibody levels. T. Bacteria were observed in the sputum in 46.5% of the male patients and in 25.6% of the female patients, but there was no difference between the sexes in relation to the positive response in both the anti-TB antibody and the TSPOT test. BT. During evaluating differential lung lesions, it was found that men had greater lung damage, with more cavitory lesions (70.5% versus 37.2%, P < 0.001) associated with emphysema-scarring, pleural thickening, bronchovascular distortion, and parenchymal bands. In addition, regardless of gender and age, low lymphocyte counts were related to higher sputum bacterial counts 14.

Blood samples were collected from patients with TB relapse (group 1), patients undergoing antituberculosis (RTA) treatment (group 3) and healthy controls (group 4) to assess the level of serum cytokines and chemokines in the study by Waghmare et al. The study revealed low means of TNF-α and IL-6 treated with RTA - with the exception of the individual who had high levels of TNF-α (102.36 pg/ml) - and values in patients with TB relapse. The cytokine IL-10 showed a significant difference between almost all groups, except controls group 1 and 2, where it remained at low levels. In addition, when comparing the groups and the Bonferroni test, a significant difference in TNF-α was revealed between all groups, with low mean levels in group 1 and high levels in the group that comprised TB and IL-10 with a difference between groups 2 and 3 14.

The study by Afriky-Asante et al. evaluated the influence of Mtb infection on the expression of Focal Adhesion Kinase (FAK) in THP-1 macrophages and THP-1 cells, as well as in wild-type control cells, with an mc 26206 strain of Mtb H37Rv. In the analysis carried out over four days, it was observed that the total levels of FAK decreased during infection (reached approximately 25% compared to wild-type control cells) and that this reduction is related to the The level of mRNA transcription of PTK2 (the gene encoding FAK), an enzyme that regulates the host immune response by inducing apoptosis of infected cells22. The cytokine to play an active role in the death of host cells. This divergence may be due to the different variables between the groups studied that were not taken into account in the studies, requiring further research.

Kireev et al. analyzed TNF levels and described that there were no relevant changes between healthy individuals and those diagnosed with tuberculosis. However, in cases of disseminated tuberculosis (involving more than two lung segments) in which Mtb was isolated on bronchoscopy (Mtb+), elevated TNF levels were observed in comparison with other cases of tuberculosis. These high levels of cytokine serve to explain the greater lung tissue damage and loss of organ function, in this case of the lung22. In contrast, the levels found in patients with recent tuberculosis. This may be due to the different variables between the groups studied that were not taken into account in the studies, requiring further research.

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with its low levels in the active picture of tuberculosis, it can serve as an indicator for the severity of the infection, as well as other cytokines. IFN-γ acts on both innate and adaptive immunity, regulating phagocytosis, activating defense cells, stimulating the killing of Mtb by neutrophils and macrophages, among other functions31. Abdul-Aziz et al. found elevated levels of IFN-γ in patients who had recently manifested TB. A decrease in the values of those who underwent treatment was also observed29, findings that are corroborated by Waghmare et al., who found high levels of the cytokine in active tuberculosis28.

Thus, the role of IFN-γ in the control of tuberculosis is clear, and its reduction is common after treatment and recovery.

Seeking to analyze the relationship between different stages of tuberculosis and the levels of the cytokines BAFF and APRIL, Kathamathu et al. found high levels of BAFF in cases of active and latent tuberculosis and reduced levels in those who underwent treatment. B-cell activating factor plays an essential role in fighting Mtb infection, which is consistent with its reduced levels after treatment and elevated during the immune response. The rates of APRIL in active tuberculosis were significantly decreased compared to the other study populations, which may be explained by the role of APRIL in stimulating BAFF action, thus, low APRIL rates would be a possible cause for the active stage of the disease32.

Maglione et al. observed the role of B cells in the response against Mtb infection, demonstrating that they regulate the production of cytokines and chemokines, controlling the inflammatory response and granuloma formation, although the exact mechanisms by which this happens are still unclear33. Thus, B-cell growth factors are essential in modulating this integral part of the immune response against tuberculosis, making it clear why the presence of the bacterium promotes changes in its concentrations.

Chen et al. also evaluated B lymphocytes in rats, but specifically the inflammatory response in chronic tuberculosis. The study found that the B-cell-deficient mouse line showed a decreased Th1 response, with a consequent reduction in the granulomatous response. The pMφ rats survived longer than the control group, which is consistent with the other articles in this review, since there is an absence of an uncontrolled and harmful inflammatory response, and the lesions caused by this exaggerated response caused by the bacillus would occur in smaller quantities34. The data also pointed to higher levels of IL-10 in the B-cell-deficient mice, which confirms a role of these cells in inhibiting its production.

Mtb infection leads to the inhibition of FAK in the macrophage, contributing to the lower production of ROS, which participates in the elimination of pathogens by this cell20. This progressive inhibition of FAK favors a pattern of cell death by necrosis, to the detriment of apoptosis. Apoptosis is a programmed cell death pathway, which aims to minimize inflammation, containing cellular debris in apoptotic bodies surrounded by membrane, easily phagocytosed and digested by defense cells. The persistence of cell lesions, in the inactivation of the apoptotic pathways, which are inhibited, leads to a pattern of cell dissolution characteristic of necrosis, leading to the exacerbation of the adjacent inflammatory response. In addition, Mtb acts by necroptosis mechanisms, in which pyroptosis signaling elements, such as TNF receptors, and cell dissolution are present, with the participation of receptor interaction proteins (RIP) and pyroptosis, in which chemical agents or cytosolic proteins called inflammasomes induce an apoptotic response that leads to the release of inflammatory and pyrogenic cytokines35. Thus, the inhibition of FAK is related to the worsening of the inflammatory response over time19.

Figure 1 exemplifies some of the mechanisms related to the immune system’s response to Mtb infection, more specifically the action of several cytokines involved in this process.

**Figure 1 - Mechanism involved in the activation of macrophages and T lymphocytes by mycobacteria.**


**CONCLUSION**

This review synthesized the effects of Mycobacterium tuberculosis infection on the lungs and the immune system, and showed its link with the action of several cytokines, especially TNF-α, IL-10 and IFN-γ, which will modulate the inflammatory and immune response against the bacterium. In this sense, it is observed that the formation of areas of caseous necrosis, which leads to tissue loss and lung damage, depends on high levels of these proteins. It is also observed that at the macroscopic level, in the lung tissue, there are small necrotic nodules with fibrotic encapsulation of up to 5 mm, a marked manifestation of TB. At the microscopic level, in the Zielh-Neelsen histological examination, granulomas, a central region surrounded by a thick border of fibrous tissue, which contains macrophages, fibroblasts, a small amount of Langhans giant cells and the absence of neutrophils, appear. In addition, it is found that the inhibition of FAK in the macrophage promoted by the bacterium results in a lower production of reproductive species.


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