Literature Review

Immunopathogenesis of Silicotuberculosis: A Literature Review

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Submitted: June 18th, 2023
Accepted: July 18th, 2023
Published: October 28th, 2023

Respir Sci. 2023; 4(1): 40-53
https://doi.org/10.36497/respirsci.v4i1.103

Abstract

Silicotuberculosis is a tuberculosis infection that emerges as a silicosis complication. A silicosis patient is 2.8 to 39 times more likely to develop pulmonary tuberculosis (TB). Moreover, the fibrotic condition caused by silicosis may exacerbate the symptoms and worsen the clinical outcome of silicotuberculosis patients. The current report suggests that the immune system plays an important role in the pathogenesis of this disease. Silicosis or silica exposure might interfere with the immunological response, especially the macrophages, which permit the *Mycobacterium tuberculosis* to infect the host. In this literature review, we will discuss the definition, epidemiology, and immunopathogenesis of silicotuberculosis.

Keywords: *Mycobacterium tuberculosis*, silica, silicotuberculosis

INTRODUCTION

A pneumoconiosis called silicosis, one of the oldest industrial diseases, is brought on by breathing in inorganic dust for an extended period that has high concentrations (>10%) of free crystalline silica (SiO_2).[1] Inflammation, the development of silicotic nodules, and fibrosis which are gradual and irreversible-define this interstitial lung disease.[2]

There are various names for this illness, including Potter's rot, Grinder's asthma, and Miner's pthisis.[2,3] Silicosis is brought on by the prolonged inhalation and deposition of silica crystals (SiO_2/silicon dioxide).[4] Hippocrates noted the link between silica dust exposure and respiratory diseases in 430 BC, and Agricol discovered it in the 16th century. Rammazini's studies in 1713 using postmortem silicotic nodules established the connection even more.[1]

Depending on the length of time and the severity of exposure to silica dust, the latency period for silicosis can last anywhere from a few years to many decades. Due to the prolonged latency period in several occupational pulmonary diseases, such as silicosis, mesothelioma, and asbestosis, the diagnosis may be delayed, which can have detrimental effects on the course of the disease.[5]

The majority of the earth's crust, 59%, is composed of the mineral silica. In order to be inhaled and reach the alveoli,

silica crystal particles typically have a diameter of less than 5 μm.[6] This size results from industrial work procedures such as cutting, crushing, and grinding materials. This is the reason why people who work in the building construction industry, glass industry, jewelry industry, gold mining, ceramics industry, and other industries frequently get silicosis.[7]

Individuals inhaling silica crystals may be at risk for cardiovascular, COPD, autoimmune, and tuberculosis (TB) illnesses.[8] Patients with silicosis can develop silicotuberculosis, a TB infection, as a secondary illness. Patients with silicosis have a 2.8 to 39-fold increased chance of contracting pulmonary TB and a 3.7-fold increased risk of contracting extrapulmonary TB.[8,9]

Understanding the immunopathogenesis of silicotuberculosis is crucial because it helps us better understand how the human immune system contributes to the development of post-silicosis TB infection.

EPIDEMIOLOGY

It is challenging to estimate the prevalence of silicotuberculosis on a global scale. In countries with poor economic levels, silicosis and silicotuberculosis are more common. This is a result of inadequate training in the use of safety equipment and compliance with occupational safety laws.[9] Silica crystal inhalation may also increase a person's risk of developing autoimmune diseases, neoplasms, cardiovascular issues, chronic obstructive pulmonary disease (COPD), and TB infections.[10]

According to a 2015 study on 3,121 employees in Iran, there were 917 cases of silicosis for every 100,000 people, and there were 172 cases of silicotuberculosis for every 100,000 people in the same group.[11] Additionally, among those who had been exposed to silica but did not have silicosis, there were 69 cases of TB infection per 100,000 people. The study found that smoking, being older than 30, and having worked for more than ten years are all risk factors for developing silicotuberculosis.[11,12]

Research conducted in the United States also showed an increase in the mean Odds Ratio (OR) of 2.48 in the group of workers who had prolonged exposure to silica.[9] Several other risk factors, such as male gender, HIV infection, smoking, COPD, migration, and the severity of silicosis can be triggers for silicotuberculosis.[13]

BASIC IMMUNOLOGY

The body's defense responses are mediated by the immune system, which is made up of many cells, tissues, and chemicals.[10] The immune system defends the body from harmful foreign substances like bacteria, viruses, cancer cells, and poisons. Innate immunity and adaptive immunity are the two main divisions of the immune system.[14]

The body's initial line of defense against infections that enter the body is innate immunity, sometimes referred to as

natural or naive immunity. The non-specific defense mechanisms of innate immunity might become active right away or several hours after being exposed to antigens.[15] The particular immune system or acquired immune system are other names for adaptive immunity. After antigen exposure, adaptive immunity requires some time to respond at its best.[14]

INNATE IMMUNOLOGY

The body's first line of defense against diseases or foreign objects is innate immunity, which has a quick response. By producing cytokines, innate immunity works to draw immune cells to areas of infection and inflammation. Small proteins called cytokines serve as intermediaries between immune cells.[14,15]

Antibodies, proteins, and glycoproteins are released as a result of cytokine synthesis, activating the complement system. Dead cells and foreign bodies found in organs, tissues, blood, and lymph are removed during this process. Antigen-presenting cells (APC), which present antigens to adaptive immunity, help the innate immune system activate adaptive immunity.[15,16]

Anatomical defenses, physiological defenses, endocytic-phagocytic defenses, and inflammatory processes make up the four types of defenses that compose innate immunity.[15] Anatomical defenses include skin and mucosa, while physiological defenses include temperature, pH, and chemical mediators. The skin and mucosa's epithelial barrier is the first line of defense in innate immunity, stimulated by microorganisms. Other defense mechanisms include phagocytic cells, lymphoid cells, plasma proteins, and complement system.[16,17]

ADAPTIVE IMMUNOLOGY

Ineffective innate immunity prevents pathogen removal, while adaptive immunity identifies antigens, eliminates pathogens, and develops immunologic memory.[17] Humoral and cellular immunity involve B lymphocytes producing antibodies for homing immunity.[17–19] T-lymphocyte activation leads to cellular immunity as APC phagocytosis and binding to MHC molecules activate T-lymphocytes, triggering cytokine production and immune system regulation.[18,19]

Table 1. Aspects of Innate Immunity Cells

Cell	Function
Phagocytes	Includes neutrophils and macrophages, function to phagocytose of foreign bodies. Granules seen in neutrophils destroy harmful organisms.
Dendritic Cells	Phagocytosis and APC have a role in mediating innate and adaptive immunity.
Mast Cells	Function to start an immediate inflammatory reaction. The connective tissue contains these cells.
Basophils	Possess the same purpose as mast cells but are found in the bloodstream.
Eosinophils	Phagocytic, able to eat parasites that are too big to fit within its cells.
Natural Killer (NK)	By producing porphyrins and granzymes that cause apoptosis, this enzyme contributes to the rejection of tumors and the killing of virus-infected cells.

In the bone marrow, hemopoietic stem cells give rise to B lymphocytes. All antigens can be recognized by B cells, which do not function as APC. In addition to producing antibodies, B cells participate in the humoral immune response. B lymphocytes generate five distinct antibody subtypes.

SILICA

Silica, a common mineral, can be crystalline or amorphous, causing lung and organ toxicity after inhalation. Quartz, tridymite, and cristobalite are crystalline forms.[19,20] The resulting silica crystal dust often has no color and smell. Silica crystals smaller than 5 μm can be breathed in until they reach the alveoli, and those larger than 10 μm can pass through the airway. Silica that is crystalline is more harmful than non-crystalline silica. Silica, a common mineral like silica, quartz, tridymite and cristobalite cause lung and organ toxicity.[20]

Piezoelectricity in crystalline silica increases cytotoxicity due to electrical polarity and the formation of reactive silica crystals, causing increased reactive oxygen species production.[21] Crystalline silica is more harmful than non-crystalline silica, causing lung and organ toxicity.[22]

SILICOTUBERCULOSIS

Silicosis is a lung condition that damages lung tissue and progresses without cure. Reaching the silicosis elimination goal by 2030 is challenging due to workplace concerns in 13 middle- to low-income countries.[23,24]

One of the most frequent comorbidities linked to silicosis is pulmonary TB, which is more prevalent in underdeveloped nations. Silico-TB is silicosis with active TB on top. According to estimates, people with silicosis had a 2.8 relative risk of getting pulmonary TB.[24] One-fourth of individuals with silicosis and coal workers' pneumoconiosis, which are frequently characterized by "eggshell calcification" of peripheral lymph nodes, have silico-TB.[25]

Severe silicosis increases TB risk; exposure to silica dust increases risk.[24,25] Experimental studies show that silica crystals inhibit macrophage function, increasing vulnerability to TB infection and increasing the reactivation risk.[25]

IMMUNOPATHOGENESIS

Respirable silica particle inhalation causes mineral deposits, inflammatory pulmonary tissue reactions, and fibrosis. The severity and pathogenicity of the disease depend on the amount and duration of exposure. Long-term exposure can lead to repeated airway injuries and deplete airway epithelial stem cells, causing pulmonary silicosis.[26]

When someone breathes in silica, their immune system is activated. Numeorus studies have concentrated on early silica exposure, lung cells, and modifications in the innate immune cell response.[27] There are five primary ways in which silica can harm an object (Figure 1). Alveolar macrophages and broncho-alveolar epithelial cells come into contact

with silica crystals that have entered the alveoli. Due to their piezoelectricity, which can result in electrical polarity, silica crystals can inflict immediate injury when they come into contact. Inflammation and lipid peroxidation of bronchoalveolar cells are the results of this.[28,29]

Alveolar macrophages will also phagocytize silica crystals. This scenario results in a respiratory burst and increased oxygen consumption, which raises the levels of ROS, reactive nitrogen species (RNS), and inducible nitric oxide synthase (iNOS).[29]

The amino acid L-arginine is changed by the presence of iNOS into L-citrulline, which interacts with superoxide to produce peroxynitrite, which harms mitochondria and deoxyribonucleic acid (DNA). After dying, macrophage cells will once again release silica crystals. Other alveolar macrophage cells will once more phagocytize silica crystals that are not completely destroyed.[29]

An inflammatory process is brought on by the interaction of silica, macrophages, and epithelial cells, which activate neutrophils and lymphocytes in the injured area. The creation of Interleukin (IL)-1, which promotes nuclear factor kappa beta (NF-κB) translocation from the cytoplasm to the nucleus and binds to DNA, is the following process. Pro-IL-1 is then translated and transcriptionally transcribed (Figure 1). Additionally, inflammatory cytokines such as leukotriene B4, Fas Ligand (FasL), macrophage inflammatory protein (MIP)-1, MIP-2, tumor necrosis factor (TNF)-, interferon (IFN), and IL-6 are released.[30,31]

Scavenger Receptor (SR)-A and Macrophage Receptor with Collagenous Structure (MARCO) on macrophages are additional receptors that can identify and phagocytose foreign objects to be eliminated from the alveoli. One of the pattern recognition receptors (PRR) is called MARCO.[28–30]

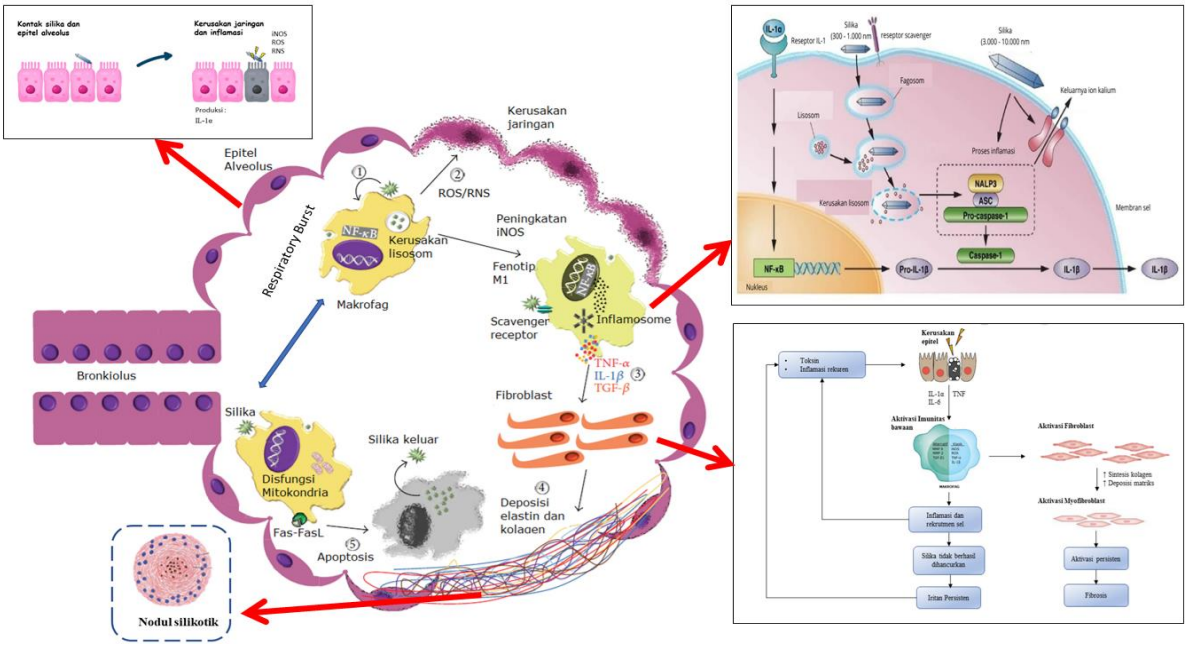

Figure 1. Immunopathogenesis of Silicosis

Macrophages that engulf silica crystals will damage the phagosome and discharge their contents into the cytoplasm. Adipose-derived stem cells (ASC), pro-caspase-1, and nicotinamide adenine dinucleotide phosphate (NALP-3) inflammasomes are all activated as a result. Pro-inflammatory IL-1 is created when inflammasomes break down pro-IL-1. IL-18 production and intracellular potassium ion release are also triggered by NALP-3 inflammasome activation.[28–30] Additionally, interactions between lymphocytes can readily activate NALP-3 inflammasomes. In this route, T cells express T-lymphocyte antigen 4 (TLA-4) IL-10, and transforming growth factor (TGF)-β.[30]

During the silicosis process, increased TNF expression results in fibroblast recruitment and proliferation. TGF causes fibroblasts to assemble in the injured area, where it induces collagen deposition and enhanced elastin production. The lung parenchyma undergoes structural alterations as a result of increased expression of metalloproteinase (MMP)-2 & MMP-9 and tissue inhibitors of metalloproteinase (TIMP)-1 & TIMP-2.[32]

Fibrosis and lung remodeling are caused by an increase in silica-induced tissue injury, extracellular matrix degradation by MMPs, and concentric aggravation of collagen deposition (Figure 1).[28,32] Nodular lesions will develop if free silica crystals are encircled by fibroblasts and collagen. These silica nodules are made up of fibroblasts and collagen surrounding an acellular zone loaded with silica in the center.[30,32]

Apoptosis induction in macrophages is a potential consequence of silica exposure. It is well known that TNF and FasL interact with cell death receptors to start the apoptotic cascade. Dysfunction of the mitochondrial caspase is the cause of apoptosis. Oxidative stress, which lowers mitochondrial potential, leads to mitochondrial malfunction.[29,30]

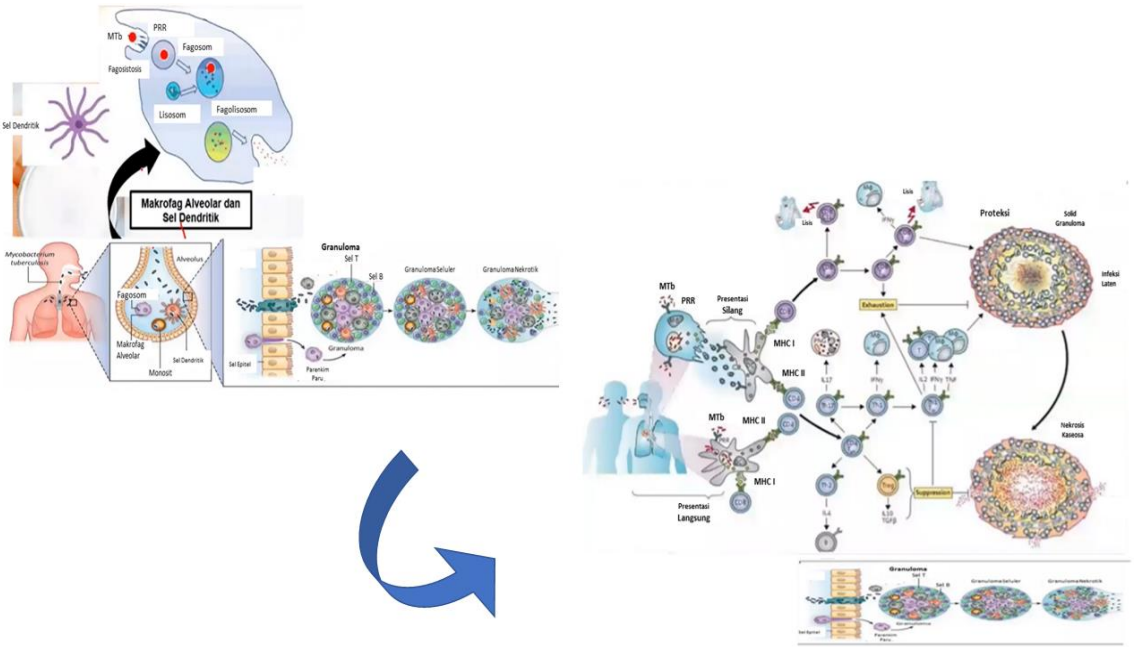

Figure 2. Immunopathogenesis of Tuberculosis

DNA fragmentation and caspase-9 and caspase-3 activation are caused by this mechanism. In addition to re-secreting silica crystals and chemotactic substances that worsen the already present inflammation, macrophage cells will undergo death.[29,30]

Dendritic cells increased as a result of the apoptosis that occurred following silica exposure, which reduced the number of alveolar macrophages. It is well established that non-specific interference with the inflammatory response lowers dendritic cell viability and activity.[33] In addition to interfering with the function of dendritic cells and macrophages, silica particles also have an impact on neutrophil cells. Similar to macrophages, neutrophils have lower vitality and phagocytic capacity.[13,33] A study found that NK cells grew more in spleens that had been exposed to silica nanoparticles.[34]

The inhalation of MTB-containing droplets or aerosolization actions is the first step in the MTB infection process, which is supported by several risk factors.[33] Human Immunodeficiency Virus (HIV) and other immunocompromising disorders, those taking long-term immunosuppressant medications, smokers, drinkers, children under the age of five, contact with active TB patients, and slum surroundings are some of the risk factors that affect MTB transmission.[35]

The number of organisms present, their concentration, and the amount of time a person spends breathing contaminated air are some of the variables that affect MTB transmission in the air.[33–35]

MTB has a complicated component structure under the microscope, and its cell wall contains 40% mycolic acid. The cell wall of MTB is made of mycolic acid, which makes it exceedingly robust and challenging to study via gram staining. MTB is characterized as an Acid Resistant Bacillus (Acid-Fast Bacilli/AFB) because of its bacillus shape and the mycolic acid component, a fatty acid with a role in cell wall impermeability. Additionally, MTB contains barriers against macrophage phagocytosis[32]

The immune system of the body is formed by MTB intake through the upper airways in a complex manner, beginning with the innate immune system and stimulating the activation of the adaptive immune system (Figure 2).[35] The mucosa in the airway will react to MTB inhalation into the airway first. Alveolar macrophages and mucosal immune cells, specifically dendritic cells, will interact at the same time (Figure 2).[35,36]

Macrophages will identify MTB as PAMPs (pathogen-associated molecular patterns) via the mucosal antigen receptor PRR. The body's battle to get rid of MTB is carried out by macrophages phagocytosing it. The three stages of this process are antigen adhesion to the cell membrane, lysosomal enzyme harvesting, and breakdown.[35,36]

Hepsoprotein (HSP) is one of MTB's defense mechanisms. A hit-shock response is the result of MTB with HSP, and it stresses the cells in the body. Additionally, MTB damages its link with lysosomal enzymes, neutralizes phagosomes by

reducing pH, and is resistant to lysosomal enzymes. The ability of macrophages to eradicate MTB reaches a threshold due to the MTB resistance mechanism. Adaptor proteins are recruited by NF-κB positive macrophage components to activate pro-inflammatory cytokines, chemokines, and other antimicrobial compounds. Additionally, through MHC I and MHC II, macrophages that serve as APC will trigger adaptive immunity.[35,36]

When adaptive immunity is engaged, all pro-inflammatory cytokines are released and assembled into solid granulomas (Figure 2). Caseous necrosis will arise by encapsulating solid granulomas.[35] The immune system performs this process because MTB is an aerobic organism that requires oxygen and nutrients to exist in the body. However, at this time, MTB can also dormant and create a latent TB infection. The reactivation of MTB and the hematogenous or lymphogenous propagation of the infection will be influenced by host risk factors.[36,37]

MTB infection is more likely to occur in those who have silicosis or have been exposed to silica crystals (Figure 3). Droplets of less than 5 µm in size that contain MTB nuclei can enter the alveoli when breathed in. The MTB will come into contact with other APC and alveolar macrophages. The PAMP structure of MTB can be recognized by APC PRRs. One PRR that is crucial to the development of bacterial infection is the toll-like receptor (TLR). The macrophages will then identify MTB and phagocytize it.[36]

With the assistance of host risk factors for silicosis and TB, this process will mark the onset of silicotuberculosis (Figure 3). Repeated occurrence of this mechanism will result in a clinical course that progresses along with the concurrent creation of silicotic nodules and caseous necrosis.[36,37]

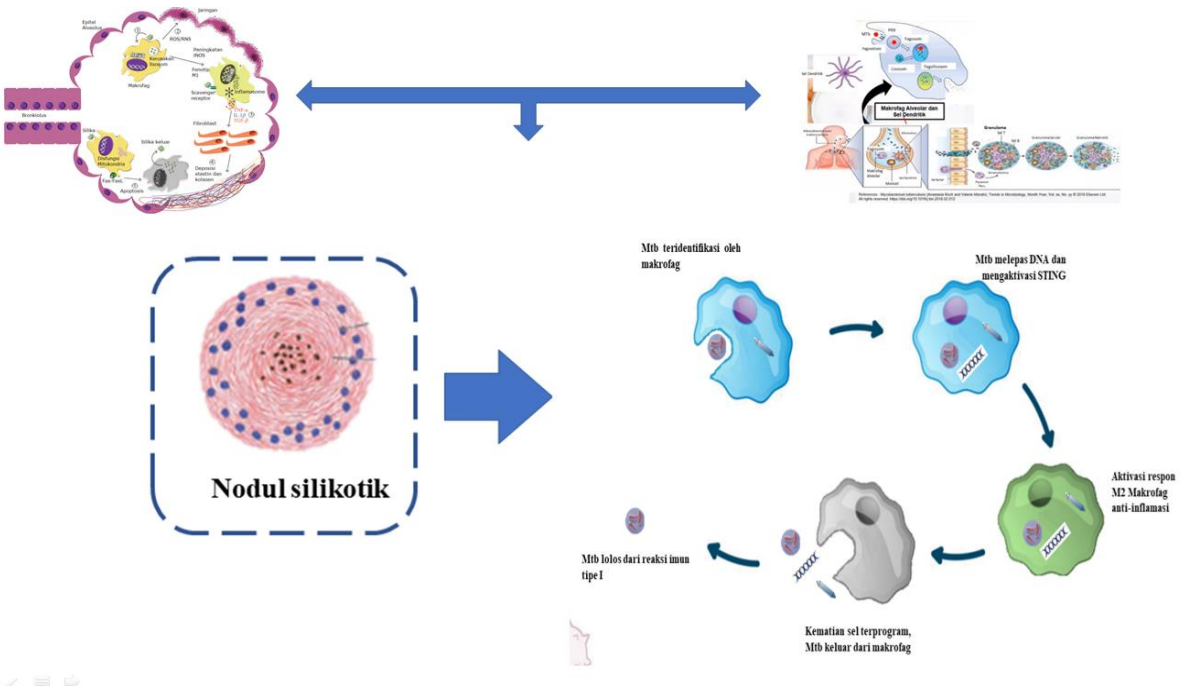

Figure 3. Immunopathogenesis of Silicotuberculosis

The cytosolic surveillance mechanism uses cyclic guanosine monophosphate (cGMP)-AMP Synthase (cGAS) to identify DNA released by MTB residing in macrophages. A type I IFN response is brought on by this process, which also activates the adaptor molecule Stimulator of IFN Genes (STING).[36]

The presence of silica crystals boosts MTB DNA's ability to polarize macrophages into the anti-inflammatory M2 phenotype. Type 2 cytokines like IL-10, which are secreted by M2 macrophages, block type I cytokines including TNF-, IFN, and IL-12. Through the production of reactive oxygen intermediates (ROI) and reactive nitrogen intermediates (RNI) in the late phase of phagosomes, the IFN cytokine is crucial in the elimination of MTB. MTB bacteria may survive when the release of IFN cytokines is inhibited (Table 2). MTB can persist in silicotic nodules in addition to macrophages.[33,34]

Through the synthesis of the eicosanoids prostaglandin E2 (PGE2) and lipoxin A4 (LXA4), surviving MTB will cause programmed cell death. Cell DNA and MTB will be released from within the cell and enter the extracellular milieu as a result of this process. Due to this mechanism, MTB can avoid the type I immune response, which is the body's main line of defense against eliminating pathogenic invaders.[37] APCs include dendritic cells and alveolar macrophage cells. These cells can identify antigens and connect to T lymphocytes in the adaptive immune system.[37,38]

Reduced macrophage viability and function are the result of macrophage apoptosis, which is the outcome of the silicosis mechanism. As a result, the MTB infection's ability to penetrate and harm the lung parenchyma increases. Both cells are prevented from delivering MTB antigens to T lymphocytes as a result of this mechanism.[39] As a result, the adaptive immune system's ability to activate normally will be compromised, which makes it impossible to stop the spread of MTB.[40]

Table 2. Immune Responses to Silica Exposure and Silicotuberculosis

Immune System	Silica	Silicotuberculosis
Macrophages	Apoptosis induction, the development of fibrotic nodules, the activation of inflammatory and chronic anti-inflammatory pathways, and the creation of ROS and RNI	Research on impaired MTB response is still needed
Dendritic cells	Lessening viability	Still requiring research
Neutrophils	decreased viability and phagocytosis	Still requiring research
Natural killer	A rise in NK	Still requiring research
Antigens	There is still conflicting evidence.	Still requiring research
CD 4+, CD 8+, δγ T cells	Apoptosis is elevated, Th1/Th2 responses are altered, T-reg is activated, and T cell inhibitory activity is decreased in response to increased FAS ligand.	Research is still needed because the evidence is inconsistent and intermittent.
B cells	B cell activity both increasing and decreasing, increased autoantibodies	Still requiring research

Further research must be carried out to determine the precise mechanism of this process. A future study is required to completely understand the role of different immune cell components in the immunopathogenesis of silicotuberculosis (Table 2).[32,39]

A mixed pathological state of silicotic nodules and caseous necrosis can result from silicosis plus MTB infection. According to certain journals, MTB can also persist in silicotic nodes and result in caseous necrosis. MTB will survive and wait to reactivate until the host immunity factor drops. This is the reason of a patient's clinical state who is suspected of having silicotuberculosis cannot be determined by radiologic evaluation. Chest pain, severe shortness of breath, and a cough with phlegm that may or may not contain blood are signs of silicotuberculosis. Complaints of coughing may be a sign that the lung parenchyma has developed cavities.[13,41]

This immunopathologic silicotuberculosis series can be used as a guide in the clinical setting to identify occupational lung disease. To determine the exact cause of silicotuberculosis cases and the process of the disease, more testing is necessary. To establish the presence of silicosis and TB, a number of supportive investigations can be carried out, including thoracic photos, computed tomography (CT-scan), and histopathological testing. By using samples obtained from bronchoalveolar lavage (BAL) testing along with histopathological investigation, recommendations can be made to confirm both diseases. Caseous necrosis or the presence of silicotic nodules might be noticed on a histopathologic examination.[13,41]

For the purpose of obtaining a histopathologic image of the silicotuberculous lung, a lung dissection study for silicotuberculosis in BALB/c mice was performed (Figure 4). To create a mouse model of silicotuberculosis, intratracheally exposed BALB/c mice were injected with MTB 107 colony-forming units (CFU).[41]

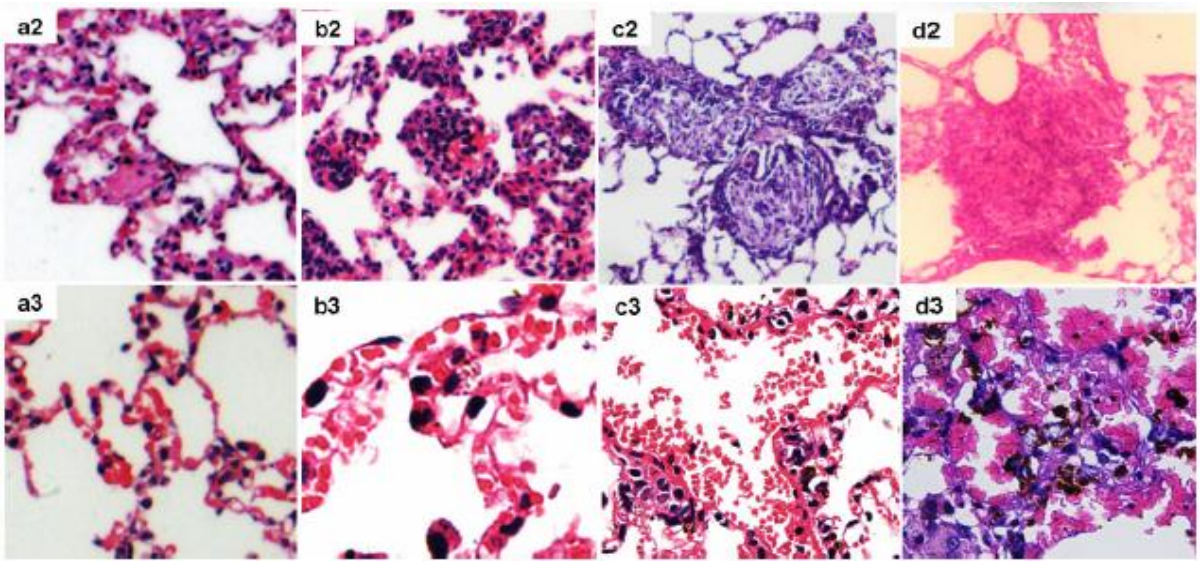

Figure 4. Silicotuberculosis histopathologic characteristics in BALB/c mice

Microscopic analysis of the lungs of mice that had been simultaneously exposed to silica and MTB revealed the development of tuberculoid epithelial cells, macrophage accumulation, and tubercle formation, as well as leukocyte infiltration around them. In the lung tissue, there was also caseous necrosis and a scattering of Langerhans cells. On the other hand, mice who received MTB injection on day 50 after silica exposure had distinct traits.[41]

The primary pathologic characteristic of lung tissue is exudation. Large fibrous nodules (tertiary silicon nodules) with thick walls can also be seen, together with concentrically and circularly ordered endothelial cell growth (Figure 4).[40]

The details in Figure 4 are represented by several microscopic pictures, including the dispersion of Langerhans cells in image part a2 and the principal silicotic nodules in image part b2. Other pictures' findings include a depiction of secondary silicotic nodules in image c2, tertiary silicotic nodules in image part d2, lung interstitial tissue in image part a3, pulmonary capillary dilatation in image part b3, and lung congestion in image part c3.[40,41]

Additionally, image part d3 shows hemosiderin and red blood cell accumulation in the lung cavities. Because airway mucosal cells are the first line of defense for the body's response to these two mechanisms, collecting examination samples by BAL is also a sensible option.[40,41]

CONCLUSION

Innate immunity and adaptive immunity, which each contain different immune cell components, make up the human immune system. The main risk factors for silicotuberculosis with recurrent silica exposure are occupational and environmental variables. One of the body's immune cells, called macrophages, plays a crucial role in the development of silicotuberculosis. Increased ROS, elastin and collagen deposition, as well as macrophage apoptosis, are all effects of silica that can directly harm lung tissue. In silicotuberculosis, anti-inflammatory M2 phenotype macrophages are activated, preventing MTB from being eliminated by macrophages. As they cannot completely remove MTB, macrophages cannot function as APCs for adaptive immunity. Future studies are therefore required to determine how additional immune cells contribute to the immunopathogenesis of silicotuberculosis.

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