CASE REPORT

Unveiling Risk Factors in a Patient with Silicotuberculosis: A Case Report

Rahel Yuana Sadikim[1,2], Helmia Hasan[2*], Agus Hidayat[2], Garinda Alma Duta[2], Farah Fatma Wati[2,3]
[1]Dr. Soetomo General Academic Hospital, Surabaya, Indonesia.
[2]Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia.
[3]Graduate Institute of Biomedical Science, China Medical University, Taiwan.

ARTICLE INFO

Article history:
Received 2 December 2024
Received in revised form
12 December 2024
Accepted 30 December 2024
Available online 30 January 2025

Keywords:
Holistic approach,
Risk factors,
Silicotuberculosis,
Tuberculosis.

Cite this as:
Sadikim RY, Hasan H, Hidayat A, *et al*. Unveiling Risk Factors in a Patient with Silicotuberculosis: A Case Report. *J Respi* 2025; 11: 62-69.

ABSTRACT

Introduction: Silicosis, an occupational lung disease caused by crystalline silica dust, is often complicated by tuberculosis. The epidemiological triad suggests that disease results from imbalanced interactions between the host, agent, and environment.
Case: A 63-year-old underweight male presented with decreased consciousness after swallowing capsules, chronic cough, low-grade fever, weight loss, and lower urinary tract symptoms. The patient had a medical history of smoking, drug abuse, and alcohol consumption. He had worked as a construction worker for 33 years without personal protective equipment (PPE). The patient lived in a substandard housing, and three neighbors had a history of tuberculosis (TB). Urine toxicology was positive for amphetamines, while abdominal ultrasound showed prostate enlargement. A chest X-ray showed fibroinfiltrates, cavities, and reticulogranular patterns. A high-kV chest X-ray revealed profusion levels of 1/2 S/S and 1/1 P/P. Contrast chest CT showed tree-in-bud patterns, reticulogranular patterns, small nodules, and fibrosis, while brain CT was normal. GeneXpert sputum confirmed *Mycobacterium tuberculosis* and bronchoalveolar lavage (BAL) spectrophotometric detected 38.90 ppm silica. The patient was diagnosed with amphetamine intoxication, benign prostatic hyperplasia, and silicotuberculosis. Haloperidol, tamsulosin, and anti-tuberculosis therapy were administered, although no specific treatment was administered for silicosis. He was advised to transition to a job with minimal silica exposure and planned to receive housing renovation assistance from the Health Office of Surabaya City. The patient was declared cured after completing six months of TB treatment.
Conclusion: The host factors included nutritional status, comorbidity, and personal habits; the agent factor was *Mycobacterium tuberculosis*; and the environmental factors included inadequate ventilation, high housing density, close contact with TB patients, and occupational conditions. A holistic identification of host, agent, and environmental risk factors is essential for understanding the development, prevention, and diagnosis of silicotuberculosis.

INTRODUCTION

Pneumoconiosis encompasses a group of occupational lung diseases caused by the prolonged inhalation of specific mineral dust. The global incidence of pneumoconiosis rose by 66%, from 36,186 cases in 1990 to 60,055 cases in 2017, with silicosis contributing to 39% of cases.[1] Silicosis is an occupational lung disease caused by the inhalation of crystalline silica or silicon dioxide (SiO2) dust. It is commonly associated with occupations such as mining, pottery, stone carving, excavation, drilling, tunneling, and sandblasting.[2] The 2019 Global Burden of Disease (GBD) reported that the incidence of silicosis is 1.65 cases per 100,000 population annually across 204 nations and regions.[3]

Tuberculosis (TB) is the predominant complication of silicosis, presenting a risk factor that is 2.8 to 39 times greater than in individuals without silicosis.[4] Tuberculosis infections associated with silicosis frequently occur among men over 30 years of

*Corresponding author: helmi.hasan@fk.unair.ac.id

Jurnal Respirasi, p-ISSN: 2407-0831; e-ISSN: 2621-8372.
Accredited No. 79/E/KPT/2023; Available at https://e-journal.unair.ac.id/JR. DOI: 10.20473/jr.v11-I.1.2025.62-69

age, smokers, those with compromised health, those who are HIV-positive, and patients with acute or accelerated silicosis, particularly in low- and middle-income countries and regions with high tuberculosis prevalence.[5,6]

The epidemiological triad, a fundamental concept in epidemiology, posits that disease arises from a disruption in the interaction between three critical elements: host, agent, and environment.[7] Risk factors for silicotuberculosis comprise host factors such as nutritional status, immunity, socioeconomic status, comorbidities, and personal habits including smoking, alcohol abuse, and drug use; agent factors such as *Mycobacterium tuberculosis* (MTB); and environmental factors such as unhealthy housing conditions, contact with TB patients, and working conditions.[2,8–12] A holistic identification of the risk factors is crucial for understanding the progression, prevention, and diagnosis of silicotuberculosis. This case report highlights silicotuberculosis in an adult male patient with multiple associated risk factors.

CASE

A 63-year-old male presented to the emergency department with a sudden decrease in consciousness since the previous day, accompanied by a headache and incoherent speech after taking capsules. The capsules were provided by a close friend, who claimed they were painkillers. The patient also reported a persistent cough for two months, low-grade fever, and weight loss. Additionally, he had a history of incomplete and infrequent urination over the past two years, but had not sought medical treatment.

The patient had a 30-year history of smoking, drug abuse, and alcohol consumption. He worked as a construction worker for 33 years, especially working on stone breaking, cement mixing, and ceramic cutting, without any personal protective equipment (PPE). He was of a lower-middle socioeconomic status. His housing conditions did not meet the criteria for a healthy home, marked by inadequate ventilation (one window of 1.2 m², only 4.3% of the floor area) and high housing density (a single 4 m² bedroom shared by two individuals) (Figure 1). Furthermore, significant close contact was observed, as three neighbors living five meters away suffered from tuberculosis, with their treatment status remaining unknown.

Physical examination revealed poor general condition, somnolence (GCS 4-3-5), and underweight (BMI 18.02 kg/m²). Chest examination and other neurological findings were within normal limits. However, psychiatric assessment revealed dysphoric mood/affect, diminished desires, and heightened psychomotor activity, including agitation and aggression.

Figure 1. The patient's housing conditions

The specific composition of the capsules could not be identified due to the unavailability of drug samples, preventing the forensic team from conducting a toxicological analysis. However, urine toxicology was positive for amphetamines and brain CT scan was normal, supporting a diagnosis of decreased consciousness due to amphetamine intoxication. A chest X-ray showed fibroinfiltrates, multiple cavities, and reticulogranular patterns, raising the possibility of concurrent pulmonary tuberculosis and silicosis (Figure 2A). Differential diagnoses included lymphangitic pulmonary metastasis secondary to suspected prostate carcinoma. Additional investigations, such as HIV testing, prostate-specific antigen (PSA), GeneXpert MTB sputum, high-KV chest X-ray, abdominal ultrasound, and contrast chest CT scan, were performed to clarify the diagnoses. HIV tests were non-reactive. PSA levels were slightly elevated (30.06) and abdominal ultrasound indicated prostate enlargement. These findings ruled out prostate carcinoma, resulting in a diagnosis of benign prostatic hyperplasia. GeneXpert sputum confirmed the presence of MTB.

A high-kV chest X-ray conducted at 125 kV, 320 mA, and 32 ms revealed profusion levels of 1/2 S/S and

1/1 P/P based on the International Labour Organization (ILO) classification, indicative of silicosis (Figure 2B, 2C). Contrast chest CT scan showed tree-in-bud patterns, reticulogranular patterns, multiple small nodules, and fibrosis, effectively excluding pulmonary metastasis (Figure 3). Spectrophotometric analysis of bronchoalveolar lavage (BAL) specimens confirmed silicosis with a silica content of 38.90 ppm SiO_2. These findings confirmed a diagnosis of silicotuberculosis, hence ruling out the possibility of pulmonary metastasis.

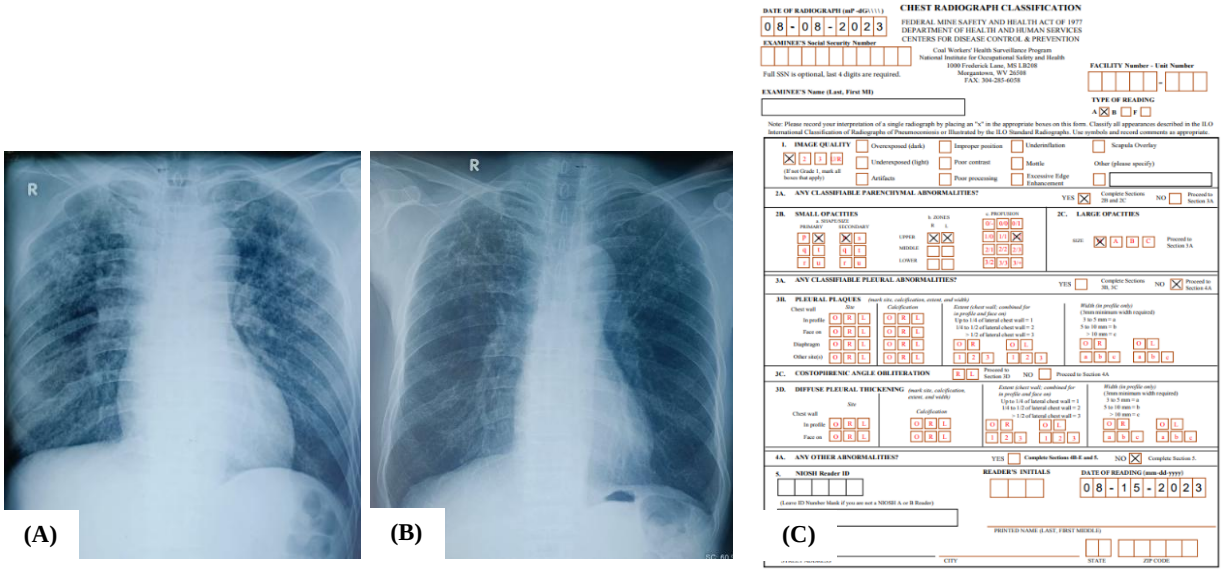

Figure 2. A) Chest X-ray in anterior-posterior position on the first day of hospitalization; B) a high-kV chest X-ray two months following tuberculosis therapy; and C) the International Labour Organization reading sheet

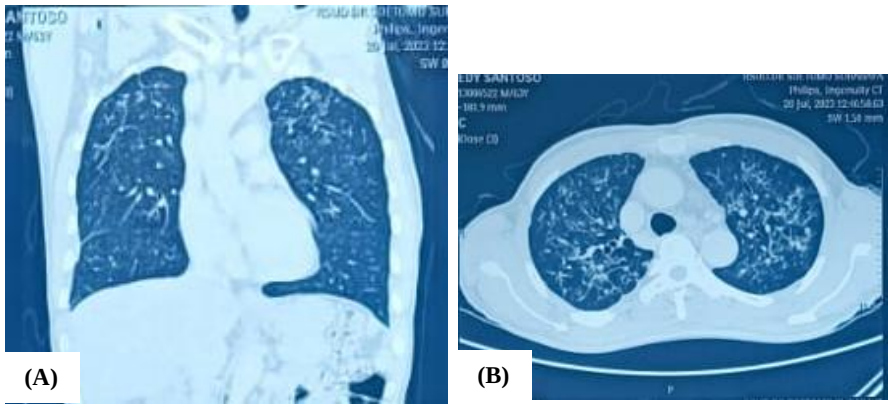

Figure 3. A) Coronal and B) axial contrast chest computed tomography scan showed tree-in-bud patterns, reticulogranular patterns, multiple small nodules, and fibrosis

During hospitalization, the patient received haloperidol, tamsulosin, and anti-tuberculosis therapy. His consciousness improved and he was discharged with plans for outpatient follow-up care. The patient was scheduled for psychotherapy via motivational interviewing at the mental health clinic due to amphetamine intoxication. However, he never attended the session. After six months of TB treatment, the patient exhibited clinical improvement and was declared cured. Nonetheless, no specific therapy for silicosis was available. The patient was advised to change occupations to minimize silica exposure and was arranged to receive complimentary housing renovation assistance from the Health Office of Surabaya City.

DISCUSSION

The epidemiological triad states that disease arises from a disruption in the interaction between three critical elements: host, agent, and environment.[7] Risk factors for silicotuberculosis included host factors such as nutritional status, comorbidity of silicosis, smoking, and substance abuse (alcohol and drugs); agent factors such as *Mycobacterium tuberculosis* (MTB); and environmental factors such inadequate ventilation, high housing density, close contact with TB patients, and occupational exposure to silica dust (Figure 4).

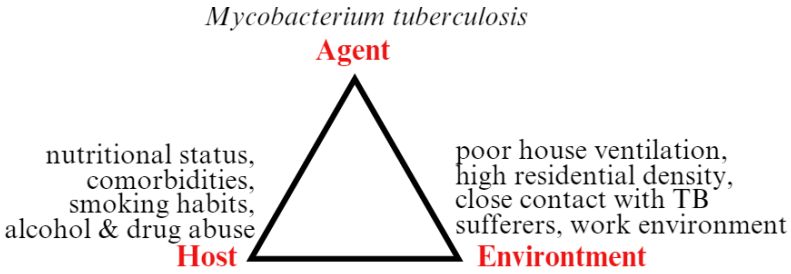

Figure 4. The epidemiological triad related to risk factors for silicotuberculosis in this case

Malnutrition, both micro- and macronutrient deficiencies, elevates the risk of tuberculosis (TB) by six- to 10-fold. The risk of tuberculosis increases by 13.8% with each unit decrease in body mass index (BMI). Malnutrition compromises the innate immune response to MTB, characterized by decreased secretion of TNF-α, IFN-γ, and IL-12, alongside the suppression of macrophage phagocytosis. Additionally, it impairs the induction of T-helper type 1 (Th-1) cells as an adaptive immunological defense against intracellular infections. Micronutrient deficiencies further affect immune response to TB. For instance, vitamin D insufficiency weakens immunomodulatory defenses, while deficiencies in zinc and copper reduce mycobactericidal activity. Alterations in body composition or compromised gastrointestinal function resulting from malnutrition can influence the pharmacokinetics and pharmacodynamics of anti-TB therapy, leading to treatment failure or increased toxicity.[10] Both active and passive smoking increase the risk of tuberculosis by 1.5- to 2-fold. Cigarette smoke decreases the quantity and obstructs the movement of cilia and increases the production of viscous mucus, thereby restricting mucociliary clearance. Smoking also impairs both innate immunity by reducing the expression of receptors such as TLR2 and MARCO on alveolar macrophages crucial for recognizing and phagocytosing MTB; and adaptive immunity, as evidenced by CD4+ lymphopenia.[9,11,13] Individuals with an alcohol use disorder face a 2.9-fold higher risk of developing active TB. The mechanisms include abnormalities in the immune system, such as mucociliary dysfunction, synthesis of surfactant and GM-CSF in alveolar epithelial cells, oxidative stress, and impaired maturation and phagocytosis of alveolar macrophages due to increased cytokines such as IL-13 and TGF-β (Figure 5). Alcohol abuse also disrupts the absorption and metabolism of TB drugs (isoniazid, rifampicin, and fluoroquinolones), delays access to healthcare, and causes non-compliance with treatment. These factors exacerbate the severity and transmission risk of tuberculosis due to social marginalization and suboptimal treatment outcomes.[12]

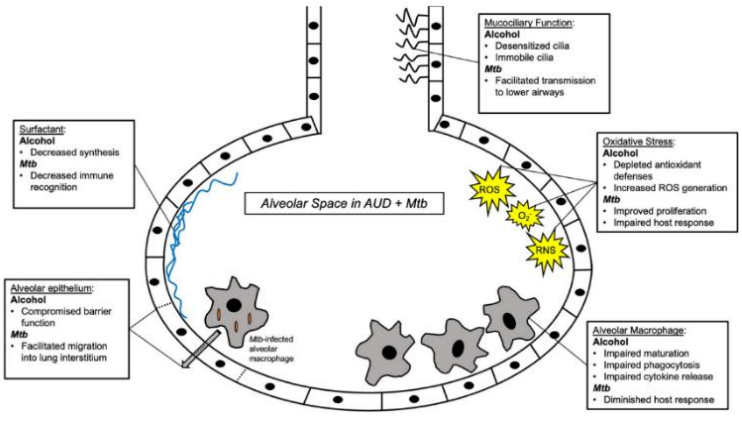

Figure 5. The effects of alcohol abuse on *Mycobacterium tuberculosis* pathophysiology[12]

The patient had a 30-year history of drug use and presented with amphetamine intoxication. This diagnosis was supported by symptoms such as heightened alertness, restlessness, and irritability which manifested shortly after the ingestion of capsules, along with a positive result for amphetamines in urine toxicology. The diagnostic criteria for amphetamine intoxication include clinical and physical findings during or shortly after the use of high doses of amphetamines or related compounds while excluding alternative physical or mental disorders. Amphetamines, as stimulant drugs, enhance central nervous system

activity, resulting in symptoms such as hyper-alertness, anxiety, and irritability.[14,15] The risk of active TB infection among drug users is 5-10% within 2-5 years post-exposure, accompanied by a two-fold increase in smear-positive TB cases. High transmission rates and disease severity are attributed to social marginalization and delayed diagnosis because of suppressed cough reflexes in opioid users and limited health awareness among cannabis and sedative users.[9]

The infectious agent *Mycobacterium tuberculosis* (MTB) is eliminated within minutes of direct exposure to heat, sunlight, and ultraviolet (UV) radiation. MTB in sputum can survive for approximately one week at temperatures between 30 and 37 °C. MTB can enter a dormant state in unfavorable conditions and reactivate in favorable environments. This adaptability is attributed to its 4.41 Mb genome and 4,009 genes associated with lipogenesis and lipolysis for bacterial cell wall synthesis.[16,17]

Parameters for healthy housing conditions, including ventilation, occupancy density, lighting intensity, floor type, humidity levels, and temperature, influence the risk of pulmonary tuberculosis.[8] Ventilation facilitates air exchange and allows the entry of UV rays and sunlight. Adequate ventilation, at least 10% of the floor area, can eliminate most bacteria within minutes to two hours. In contrast, insufficient ventilation reduces lighting and increases humidity, enabling MTB to survive longer in droplet nuclei and propagate easily. This significantly raises the risk of tuberculosis by 15-fold.[18] A minimum bedroom area of 8 m^2 per individual is recommended, as MTB risk increases 6.42-fold due to high housing density. High housing density and close contact within a 10-meter radius facilitate TB transmission and progression.[19]

Silicosis is an occupational lung disease caused by the inhalation, retention, and pulmonary reaction to crystalline silica or silicon dioxide (SiO2) dust, characterized by progressive inflammation and irreversible pulmonary fibrosis. Industries commonly associated with a high risk of silicosis include mining, pottery, stone carving, excavation, drilling, tunneling, and sandblasting.[2] Exposure to crystalline silica dust can lead to numerous complications, with silicotuberculosis being the most prevalent. Due to a lack of surveillance and inadequate access to health services, the infection continues to affect exposed workers, especially in developing countries. The risk of TB is 2.8- to 39-fold higher in individuals with silicosis than in healthy population.[4] TB is most frequently associated with acute and accelerated types of silicosis.[5]

The mechanism that increases the susceptibility of silicosis patients to TB is the harmful effects of silica on macrophages, which act as the primary defense against TB. Respirable silica particles accumulate in the lower respiratory tract and alveoli, where they are recognized by the macrophage receptor with collagenous structure (MARCO) and subsequently engulfed by macrophages, resulting in lysosomal impairment. Damaged particles generate free radicals, including reactive oxygen species (ROS) and reactive nitrogen intermediates (RNI), along with the release of pro-inflammatory cytokines such as TNF-α, IL-18, IL-1α, and IL-1β. These induce mitochondrial dysfunction, increased expression of FasL with TNF, and accelerated macrophage death. Silica particles are released into the extracellular space and phagocytosed by additional macrophages, which subsequently undergo apoptosis. The impaired lysosome hinders the degradation of MTB within macrophages, facilitating intracellular proliferation. The accelerated macrophage death facilitates the escape of MTB from macrophages. Moreover, silica promotes the Th2 response, which inhibits Th1 cells, thereby limiting the management of TB infection and deteriorating the patient's condition.[20]

The diagnosis of silicosis is based on the patient's occupational history including current and past silica exposure (e.g., exposure duration, detailed job descriptions, technical protective measures, and measurement of respirable dust using Cumulative Total Dust (CTD)), distinctive radiological findings, and the exclusion of alternative underlying causes (Figure 6).[21] Silicosis can be classified according to the amount of inhaled particles and the duration of exposure: (1) acute silicosis results from high levels of respirable dust over a period of several months to five years with severe and progressive clinical manifestations; (2) accelerated silicosis results from heavier exposures over five to 10 years and develops more rapidly than chronic silicosis; (3) chronic silicosis develops after more than 15 to 20 years of exposure, generally involving low levels of silica. Simple or classical chronic silicosis is frequently identified unintentionally, as patients typically show no symptoms. Conversely, complicated chronic silicosis or progressive massive fibrosis (PMF) is frequently associated with various complications.[2]

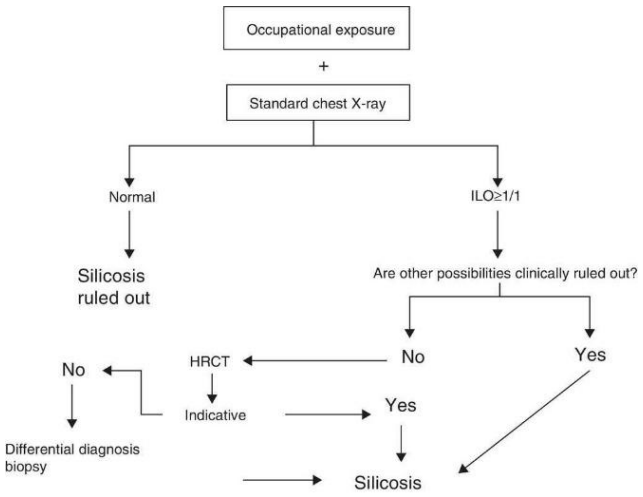

Figure 6. Diagnostic algorithm for silicosis[21]

The classic radiographic findings of silicosis on a high-kV chest X-ray, according to the International Labour Organization (ILO) reading sheet, include rounded opacities less than 10 mm, symmetrical (mainly types "q" and "r"), or linear/irregular opacities located in the upper lung zones (apical and posterior lobes). A hallmark feature is "eggshell" calcification of the hilar lymph nodes, observed in only 10% of cases. PMF presents as large conglomerate nodules (>10 mm), resulting in lung parenchymal distortions. Acute silicosis generally manifests as diffuse interstitial patterns, with infrequent nodular opacities, and air bronchograms may be detected.[21] High-resolution computed tomography (HRCT) has greater sensitivity than standard chest X-rays and is applied in cases of clinical or radiological ambiguity.[5] Chest CT scans show improved visual detail, especially for complicated silicosis. A definitive diagnosis is established using mineral dust analysis or metabolic assessment of samples collected via sputum, BAL, or if required, transbronchial or open lung biopsy.[2]

The patient had worked as a construction worker for 33 years without using protective masks and exhibited no symptoms. A reticulogranular pattern on a standard chest X-ray raised concern for potential diagnoses, particularly silicosis and pulmonary metastases from prostate cancer. However, contrast chest CT scan excluded pulmonary metastases. A high-kV chest X-ray showed profusion levels of 1/2 S/S (irregular opacities <1.5 mm with a density of 1/2) and 1/1 P/P (small rounded opacities <1.5 mm with a density of 1/1). The spectrophotometric analysis of BAL revealed a silica content of 38.90 ppm SiO_2. Neither HRCT nor biopsy was conducted because the clinical presentation and high-kV chest X-ray findings were sufficient for diagnosis. The patient was diagnosed with simple chronic silicosis based on the clinical condition, inhaled particle load, and period of exposure.

Chest X-ray progression and smear sputum examination are the backbones of diagnosing active pulmonary tuberculosis in silicosis patients. Radiological findings suggestive of silicotuberculosis include asymmetric nodules or consolidation, effusions, cavities, and focal or rapid deterioration. Chest CT scans are conducted when standard chest X-ray and sputum examination results are inconclusive. BAL and biopsies may be performed when the diagnosis of active tuberculosis remains unclear, as silica fibrosis obstructs the release of tubercle bacilli into sputum.[6] The patient, exhibiting chronic symptoms, close contact with TB patients, and chest CT scan findings including tree-in-bud and multiple cavities, along with GeneXpert sputum results showing MTB detection, was diagnosed with TB complication, namely silicotuberculosis.

Prevention is the primary strategy in the management of silicosis. According to the National Institute for Occupational Safety and Health (NIOSH) in 1974, the permissible exposure limit for inhalable crystalline silica is 50 μg/m³, averaged over a 10-hour workday. Prolonged exposure to low concentrations presents a greater risk for silicosis than short-term exposure to higher concentrations with the same cumulative dose. [2] Primary prevention involves implementing policies to ensure airborne dust concentrations remain under acceptable exposure thresholds. Secondary prevention focuses on early disease detection via health surveillance every one to three years. Tertiary prevention targets individuals diagnosed with silicosis to prevent disease progression and complications.[21]

Currently, no effective treatment is available.[21] Management primarily focuses on disease complications and may include symptomatic therapies such as oxygen supplementation, bronchodilators, antitussives, and antibiotics for infections. Corticosteroids may be utilized in acute silicosis. Nevertheless, prolonged treatment elevates the risk of infection. The efficacy of antifibrotic drugs remains unclear. Lung transplantation is an option for younger patients with end-stage silicosis despite relatively low post-transplant survival rates.[2]

The management of tuberculosis in silicosis presents unique challenges because of impaired alveolar macrophage function from silica exposure, reduced drug penetration in fibrotic nodules, and a 1.55-fold increased incidence of TB recurrence. Anti-tuberculosis therapy may be extended to eight months to decrease the risk of recurrence. Prophylactic regimens consist of isoniazid 300 mg/day for 24 weeks, isoniazid 300 mg/day combined with rifampin 600 mg/day for 12 weeks, rifampin 600 mg/day for 12 weeks, or weekly administration of rifapentine with isoniazid for 12 weeks. These regimens can be prescribed to silicosis

patients after excluding active TB and can decrease the likelihood of developing active TB by 50%.[2,6] The patient received TB treatment for six months due to a diagnosis of silicosis complicated by active TB.

CONCLUSION

Pneumoconiosis remains a major global occupational health hazard and illness, with silicosis being the most common form. The clinical symptoms of silicosis are typically nonspecific, with the majority of patients being asymptomatic and commonly diagnosed accidentally. A comprehensive occupational history, particularly concerning current and past exposure to silica, is essential for suspecting a diagnosis of silicosis. A high-kV chest X-ray, as outlined in the International Labour Organization (ILO) reading sheet, can be utilized as a diagnostic instrument to support the diagnosis of silicosis. The presence of silica confirms the definitive diagnosis via spectrophotometric analysis in BAL or biopsy specimens.

TB is the most frequent complication in patients with silicosis, as silica impairs the ability of macrophages to inhibit the growth of *Mycobacterium tuberculosis*. The epidemiological triad states that disease arises from a disruption in the interaction between three essential components: the host, the agent, and the environment. This highlights the importance of identifying risk factors for silicotuberculosis to enhance understanding of disease development, prevention, and diagnosis.

Currently, no validated effective treatment exists for silicosis. Consequently, prevention is the principal approach to disease management. As clinicians, our responsibilities extend beyond treating patients to educating them, particularly regarding the management of several risk factors, which is crucial for minimizing complications and delaying disease progression.

Consent

Written informed consent was obtained from the patient.

Acknowledgments

None declared.

Conflict of Interest

The authors declared there is no conflict of interest.

Funding

This study did not receive any funding.

Authors' Contributions

All authors contributed and approved the final version of the manuscript.

REFERENCES

1. Shi P, Xing X, Xi S, et al. Trends in global, regional and national incidence of pneumoconiosis caused by different aetiologies: An analysis from the Global Burden of Disease Study 2017. *Occup Environ Med* 2020;77(6):407–414. [PubMed]
2. Stansbury RC, Sangani RG, Parker JE. Coal Workers' Lung Diseases and Silicosis. In: Fishman's Pulmonary Diseases and Disorders. McGraw-Hill Education; 2022. p. 11–33. [Book]
3. Liu X, Jiang Q, Wu P, Han L, Zhou P. Global incidence, prevalence and disease burden of silicosis: 30 years' overview and forecasted trends. *BMC Public Health* 2023;23(1):1–8. [Journal]
4. Shafiei M, Ghasemian A, Eslami M, Nojoomi F, Rajabi-Vardanjani H. Risk factors and control strategies for silicotuberculosis as an occupational disease. *New Microbes New Infect* 2019;27:75–77. [PubMed]
5. Go L, Cohen R. Pneumoconiosis. In: Murray & Nadel's Textbook of Respiratory Medicine. Elsevier; 2022. p. 1409–1422. [Book]
6. Lanzafame M, Vento S. Mini-review: Silico-tuberculosis. *J Clin Tuberc Other Mycobact Dis* 2021;23:1–4. [PubMed]
7. Satyarup D, Kumar M, Mohanty S, Dalai RP, Rathor KR. Theories of Disease Causation: An Overview. *Indian Journal of Forensic Medicine & Toxicology* 2020;14(4):8075–8079. [ResearchGate]
8. Jannah RZ, Azizah R, Jalaludin JB, Sulistyorini L, Lestari KS. Meta-Analysis Study: Environmental Risk Factors of Tuberculosis (TB). *Jurnal Kesehatan Lingkungan* 2023;15(2):84–91. [Journal]
9. Nguipdop-Djomo P, Rodrigues LC, Smith PG, Abubakar I, Mangtani P. Drug misuse, tobacco smoking, alcohol and other social determinants of tuberculosis in UK-born adults in England: a community-based case-control study. *Sci Rep* 2020;10(1):1–10. [PubMed]
10. Ockenga J, Fuhse K, Chatterjee S, et al. Tuberculosis and malnutrition: The European perspective. *Clinical Nutrition* 2023;42(4):486–492. [PubMed]
11. Feldman C, Theron AJ, Cholo MC, Anderson R. Cigarette Smoking as a Risk Factor for Tuberculosis in Adults: Epidemiology and Aspects of Disease Pathogenesis. Pathogens. 2024;13(2). [PubMed]
12. Wigger GW, Bouton TC, Jacobson KR, Auld SC, Yeligar SM, Staitieh BS. The Impact of Alcohol Use Disorder on Tuberculosis: A Review of the Epidemiology and Potential Immunologic Mechanisms. *Front Immunol* 2022;13:1–13. [PubMed]
13. Hapsari BAP, Wulaningrum PA, Rimbun R. Association between Smoking Habit and Pulmonary Tuberculosis at Dr. Soetomo General Academic Hospita. *Biomolecular and Health Science Journal* 2021;4(2):89. [Journal]
14. Maramis W, Maramis A. Ketergantungan Zat. In: Catatan Ilmu Kedokteran Jiwa. Surabaya: Airlangga University Press; 2009. p. 369–383. [Book]

15. Kementerian Kesehatan RI. Buku Saku Penatalaksanaan Kedaruratan Adiksi NAPZA. 1st ed. Jakarta: Kementrian Kesehatan Republik Indonesia; 2022. [Book]
16. Tobin E, Tristram D. Tuberculosis [Internet]. StatPearls Publishing. 2024 [cited 2024 Oct 28]; Available from: https://www.ncbi.nlm.nih.gov/books/NBK441916/ [PubMed]
17. Perhimpunan Dokter Paru Indonesia (PDPI). Tuberkulosis. 2nd ed. Jakarta: PDPI; 2021. [Book]
18. Noerhalimah T. Cakupan PHBS Skala Rumah Tangga dan Proporsi Rumah Sehat dengan Kejadian Tuberkulosis di Jawa Barat. 2020;4(1):28–42. [Journal]
19. Yuniar I, Wahyono A, Purnomo H. Relationship of House Building Materials, Lighting and Occupational Density to the Incidence of Tuberculosis. In: Proceedings of the 3rd Borobudur International Symposium on Humanities and Social Science 2021. Banjarnegara: Atlantis Press SARL; 2023. p. 378–382. [Proceeding]
20. Konečný P, Ehrlich R, Gulumian M, Jacobs M. Immunity to the dual threat of silica exposure and mycobacterium tuberculosis. *Front Immunol* 2019;10(3069):1–11. [PubMed]
21. Fernandez Alvareza R, Martinez Gonzaleza C, Martineza AQ, et al. Normative for the diagnosis and follow-up of silicosis. *Arch Bronchoneumol* 2015;51(2):86–93. [PubMed]