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Case Report

Occupationally Triggered Fibrosing Sarcoidosis: A Case Report

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ABSTRACT: (1) Sarcoidosis is a systemic granulomatous disease of multifaceted etiology, characterized predominantly by pulmonary parenchymal involvement. While genetic susceptibility represents a foundational prerequisite, environmental and occupational xenobiotics are increasingly recognized as pivotal etiologic triggers. In cosmetic formulation environments, prolonged inhalation of mineral micro- and nanoparticles—such as titanium dioxide, talc, and fine silicates—alongside volatile organic solvents, provides a persistent antigenic stimulus that can drive aberrant granulomatous cascades toward aggressive, fibrosing phenotypes. (2) A 54-year-old female industrial worker presented with a 17-year history of occupational exposure in cosmetic manufacturing (handling airborne inorganic powders, titanium dioxide, talc, and organic vehicles without certified particulate respiratory protection), exhibiting progressive dyspnea, marked asthenia, and weight loss. Examination revealed inspiratory crackles at the pulmonary apices, violaceous nasal plaques consistent with lupus pernio, subcutaneous nodules, and sarcoid acropathy. Imaging and histology confirmed stage IV systemic sarcoidosis with fibrosing interstitial lung disease and multiple deep lymphadenopathies. Biologically and histologically, sarcoidosis was confirmed. Complete cessation of occupational exposure was achieved through workplace reassignment. Following combination therapy with oral corticosteroids and mycophenolate mofetil, the patient demonstrated clinical stabilization, resolution of hypercalcemia, and static lung function at 6-month follow-up. (3) This case underscores the importance of considering occupational exposures, including handling cosmetic products, in the pathogenesis and progression of fibrosing sarcoidosis. Early recognition and multidisciplinary management, integrating immunosuppressive therapy and occupational health interventions, are critical to limit irreversible organ damage.

Keywords: Sarcoidosis; Occupational exposure; Cosmetic industry; Granulomatous inflammation; Fibrosing interstitial lung disease; Immunosuppressive therapy

1. Introduction

Sarcoidosis is a systemic non-caseating granulomatous disorder of cryptogenic etiology, characterized by an exaggerated cellular immune response to uneliminated environmental or occupational antigens in genetically susceptible hosts [1]. While historically viewed through an idiopathic lens, expanding epidemiological and molecular frameworks identify inhaled xenobiotics—ranging from inorganic micro-

and nanoparticles to industrial volatile vehicles—as critical etiologic catalysts [2]. These occupational inhalants do not merely act as transient irritants; they bypass mucociliary clearance, disrupt lysosomal machinery in alveolar macrophages, and initiate self-perpetuating granulomatous networks that drive disease progression toward chronic fibrosing phenotypes [1,2].

Rather than following the conventional trajectory of classic bilateral hilar lymphadenopathy, severe disease can rapidly escape homeostatic containment. In these high-risk subsets, persistent particulate retention converts local inflammation into a destructive vascular, cutaneous, and parenchymal remodeled network. The concurrent presentation of Stage IV fibrosing interstitial lung disease (ILD), lupus pernio, and sarcoid acropathy forms a formidable «triple phenotype». This triad is not a random confluence of features, but an inflammatory signature reflecting chronic, multi-organ antigenic trapping that resists conventional monotherapy [1–3].

This report describes an exceptionally complex presentation of advanced fibrosing pulmonary sarcoidosis featuring this rare triple phenotype in a patient with a 17-year history of occupational exposure in cosmetic formulation. By mapping the immunopathogenic convergence between airborne cosmetic particulates (titanium dioxide, talc, and fine silicates) and refractory granulomatous remodeling, this case highlights the crucial imperative for systematic occupational exposure profiling in severe sarcoidosis phenotypes.

2. Case Presentation

2.1. Admission and Detailed Occupational History

A 54-year-old woman, employed as a production laborer in a cosmetic manufacturing facility for 17 years, presented with a 9-month history of insidious, progressive exertional dyspnea (mMRC grade III), severe asthenia, and unquantified weight loss, in the absence of febrile episodes. Her occupational duties entailed daily manual mixing, sifting, filling, and packaging of raw cosmetic ingredients, exposing her to dense airborne clouds of fine cosmetic powders, titanium dioxide dust, talc, silicates, and volatile organic solvent vapor vehicles used in hair care and skincare products. Personal protective equipment (PPE) during her 17-year employment was markedly inadequate, restricted to non-certified, loose-fitting surgical masks without respiratory filtration capabilities (such as certified N95, FFP2, or elastomeric particulate respirators).

On physical examination, her resting oxygen saturation was 95% on room air, with a respiratory rate of 16 breaths/min. A standardized 6-min walk test demonstrated significantly impaired functional exercise tolerance accompanied by exertional desaturation. Auscultation of the lungs revealed dry inspiratory crackles localized to the bilateral pulmonary apices.

Dermatological examination revealed an indurated, violaceous, telangiectatic plaque over the nasal alae and tip, pathognomonic of lupus pernio (Figure 1). Scattered subcutaneous nodules were noted on the forearms. Inspection of the extremities revealed fusiform swelling of the distal phalanges of the hands (Figure 2a) and forefeet (Figure 2b), characteristic of sarcoid acropathy. Lower extremity varicosities were graded as C2 according to the CEAP classification.

Lymph node examination revealed firm, mobile, non-tender right laterocervical and supraclavicular lymphadenopathies measuring up to 15 × 15 mm, as well as a right axillary lymph node measuring 20 × 20 mm. Other lymph node regions were unremarkable. Breast, abdominal, neurological, and musculoskeletal examinations were normal.

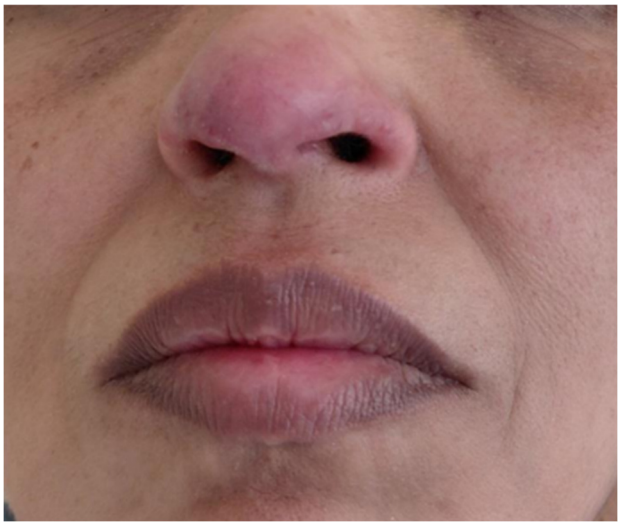
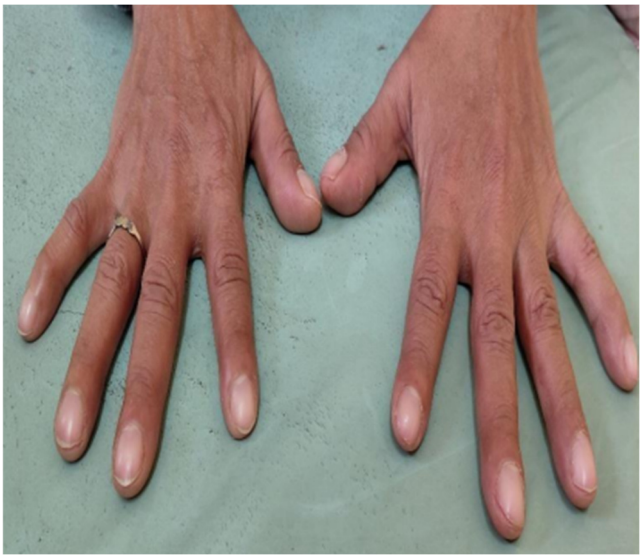
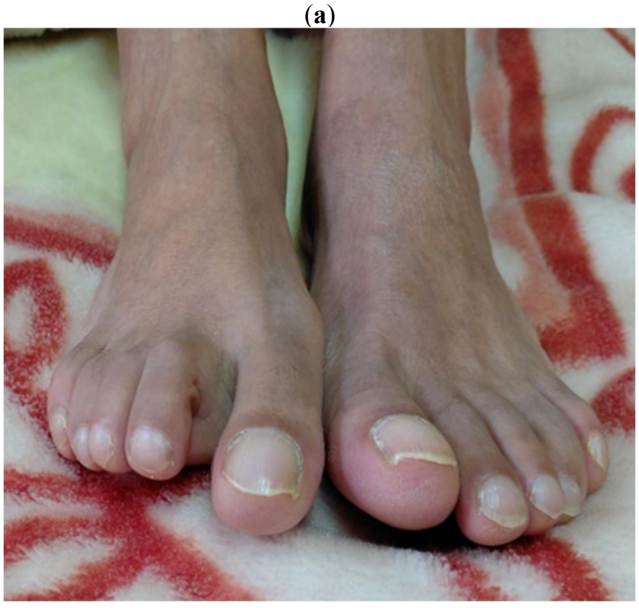


Figure 1. Lupus pernio lesions on the nose, characterized by violaceous and indurated plaques typical of chronic cutaneous sarcoidosis.



(**a**)



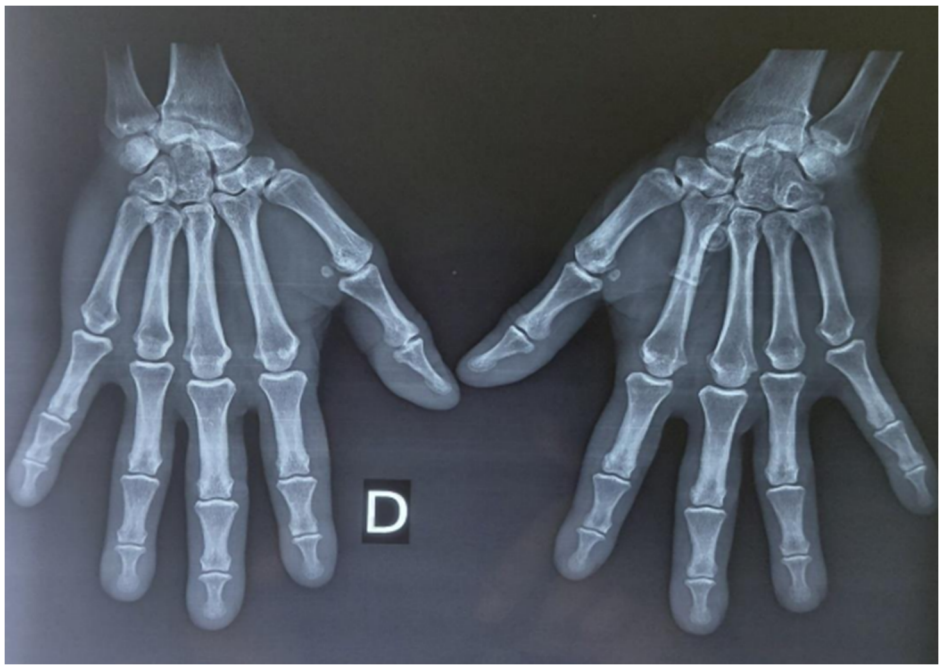
(**b**)

Figure 2. (**a**) Hands showing digital swelling and clubbing. (**b**) Toes with similar distal phalangeal swelling.

2.2. Diagnostic Evaluation

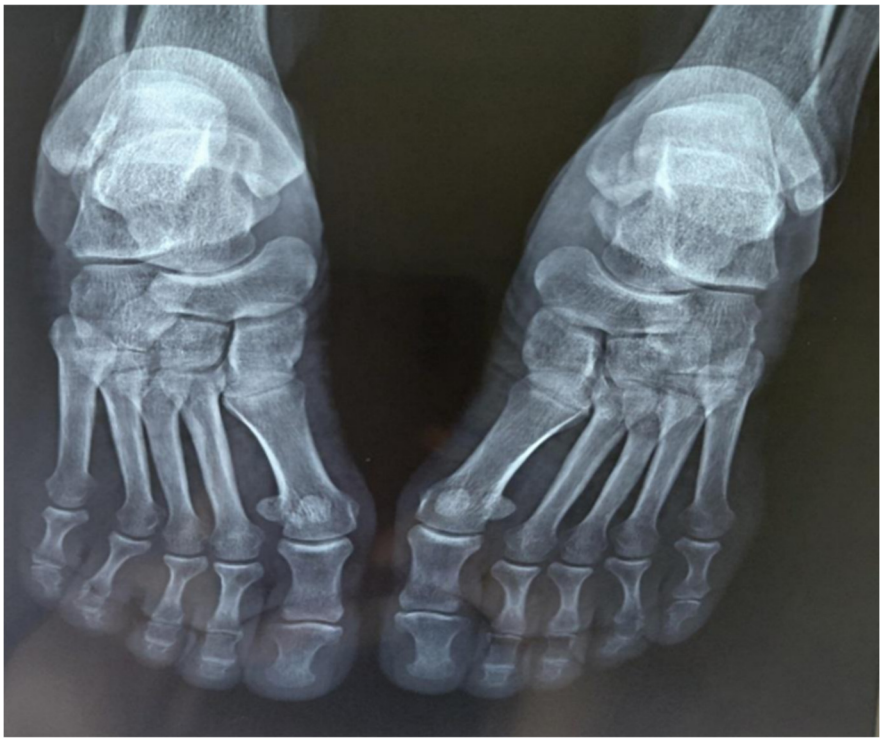
Laboratory analyses revealed marked elevation of serum angiotensin-converting enzyme (ACE) at 110 IU/L (reference range: 20–70 IU/L), corrected hypercalcemia at 114 mg/L (reference range: 85–102 mg/L), and elevated 24-h urinary calcium excretion at 420 mg/24 h (reference range: 100–300 mg/24 h). Hepatic biochemical evaluation demonstrated an isolated cholestatic pattern without cytolysis (alkaline phosphatase: 212 IU/L [reference: 40–130 IU/L]; gamma-glutamyl transferase: 193 IU/L [reference: 8–61 IU/L]). Serological testing for viral hepatitis B and C was negative. Abdominal magnetic resonance imaging (MRI) excluded biliary tree obstruction but identified non-necrotic, enlarged lymphadenopathies within the hepatic hilum, celiac axis, retroperitoneum, and renal hila. Clinical examination of the breast, abdominal, neurological, and musculoskeletal systems was unremarkable.

Infectious etiologies were systematically ruled out. Serial microscopic examinations and polymerase chain reaction (PCR) assays of sputum and urine for *Mycobacterium tuberculosis* yielded negative results, and an interferon-gamma release assay (IGRA) was non-reactive. Targeted radiographs of the hands (Figure 3a) and feet (Figure 3b) confirmed sarcoid acropathy, demonstrating distal phalangeal soft-tissue expansion, periarticular erosions, and typical "lace-like" trabecular bone restructuring. Excisional biopsy of enlarged, firm, mobile right laterocervical and axillary lymph nodes pathologically confirmed well-formed, non-caseating epithelioid and multinucleated giant cell granulomas, solidifying the diagnosis of systemic sarcoidosis. The initial tissue biopsy was performed at an external surgical center prior to specialized referral. Due to institutional archival constraints at the referring center, original histological slides and paraffin blocks could not be retrieved for high-resolution microphotography; definitive diagnosis was established via official institutional histopathological reports.



(a)

Note: D denotes *droite*, the French word for "right".



(**b**)

Figure 3. (**a**) Radiograph of the hands demonstrating sarcoid acropachy, with distal phalangeal soft tissue swelling, mild periarticular erosions, and periosteal changes typical of granulomatous involvement. (**b**) Sarcoid acropachy of the toes, demonstrated by distal phalangeal swelling and periarticular changes on radiography.

High-resolution chest computed tomography (HRCT) revealed stage IV pulmonary sarcoidosis, characterized by fibrosing interstitial lung disease with architectural distortion, traction bronchiectasis, and subpleural reticulation consistent with a non-specific interstitial pneumonia (NSIP) pattern (Figure 4), associated with confluent, partially calcified mediastinal and hilar lymphadenopathies. Pulmonary function testing (PFT) demonstrated a moderate restrictive ventilatory defect (Forced Vital Capacity [FVC]: 62% predicted) paired with a severely reduced diffusing capacity of the lung for carbon monoxide (DLCO: 44% predicted).

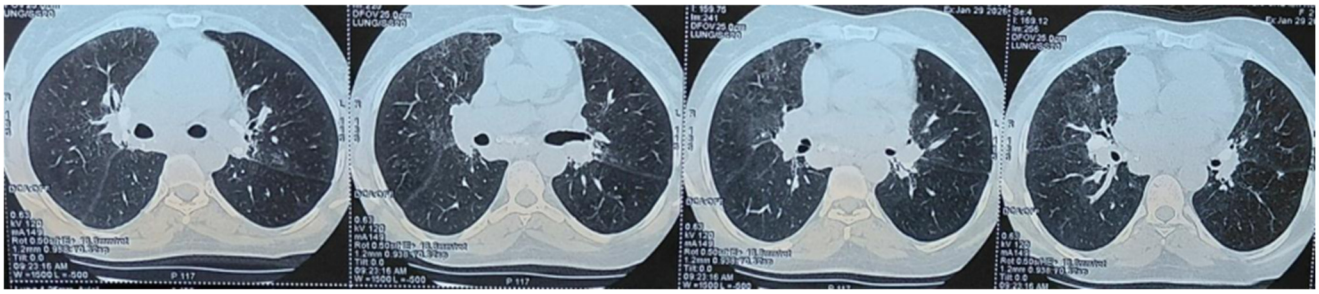


Figure 4. Chest computed tomography, axial slices in parenchymal window, showing fibrosing interstitial lung disease.

2.3. Therapeutic Management and Clinical Trajectory

The patient was managed with systemic immunosuppression consisting of oral prednisone (60 mg/day), 1 mg/kg/day) combined with mycophenolate mofetil (2 g/day) as a steroid-sparing agent. Given the progressive fibrosing parenchymal phenotype, she was referred for specialized multidisciplinary evaluation regarding adjunctive antifibrotic therapy (nintedanib). Crucially, an occupational medicine evaluation was completed. Complete elimination of airborne industrial exposures was achieved through permanent administrative reassignment to a clean office environment within the enterprise.

At the 6-month follow-up, the patient exhibited clinical improvement, with dyspnea stabilizing at mMRC grade I. Laboratory investigations confirmed normalization of serum calcium (94 mg/L) and reduction of serum ACE levels to 48 IU/L. Repeat physiological testing confirmed functional stabilization (FVC: 64% predicted; DLCO: 46% predicted), with no evidence of radiological progression on serial chest imaging.

3. Discussion

Sarcoidosis has traditionally been defined as an idiopathic granulomatous disorder; however, accumulating evidence increasingly supports the concept that it results from an exaggerated immune response to environmental or occupational antigens in genetically predisposed individuals. The predominance of pulmonary involvement strongly suggests an inhalational route of exposure, making occupational factors particularly relevant in disease pathogenesis. Recent epidemiological data indicate that a substantial proportion of sarcoidosis cases (estimated at up to 30%) may be linked to occupational exposures, including inorganic dusts, metals, and chemical agents [1–3]. These findings challenge the classical "idiopathic" paradigm and instead position sarcoidosis as a heterogeneous syndrome with potentially identifiable triggers.

The pathophysiological cascade begins when inhaled xenobiotic micro- or nanoparticles bypass mucociliary clearance and lodge deep within the alveolar acini. Resident alveolar macrophages phagocytose these non-degradable particles. However, the inability to digest inorganic materials leads to lysosomal disruption and cytosolic leakage, triggering downstream assembly of the NLRP3 inflammasome. This innate immune activation generates an initial wave of pro-inflammatory cytokines, specifically IL-1beta, TNF-alpha, and IL-18, establishing a persistent local inflammatory state. As antigen-presenting cells present processed fragments via HLA Class II molecules to naive CD4+ T lymphocytes, the response transitions to an adaptive immune response dominated by Th1 and Th17 cell populations. The ongoing secretion of IFN-gamma and IL-12 drives the continuous recruitment of peripheral monocyte-derived macrophages, which differentiate into epithelioid cells and multinucleated giant cells. Because the occupational antigen cannot be degraded, the immune response fails to self-regulate or clear, maintaining non-caseating granulomas indefinitely. Over time, chronic activation leads to macrophage-to-myofibroblast transdifferentiation (MMT), promoting excessive extracellular matrix collagen deposition, Stage IV fibrotic remodeling, and systemic manifestations [4–6]. The step-by-step immunopathogenic cascade linking occupational particulate exposure to granuloma assembly and subsequent fibrotic remodeling is illustrated in Figure 5.

The simultaneous convergence of Stage IV fibrosing interstitial lung disease, lupus pernio, and sarcoid acropathy represents an extraordinarily rare "triple phenotype" that delineates a distinct, high-mortality clinical subset. Rather than viewing these extra-thoracic features as isolated physical findings, current literature highlights them as high-yield clinical biomarkers of persistent, treatment-refractory systemic granulomatous disease driven by uncleared xenobiotic antigen loads [7,8].

- Lupus Pernio as a Molecular & Prognostic Marker: Violaceous, indurated plaques involving the central face are pathognomonic for chronic, fibrosing sarcoidosis. Epidemiological cohorts demonstrate that lupus pernio is tightly linked with upper respiratory tract involvement (URTI) and progressive fibrotic pulmonary decay. At the tissue level, these chronic cutaneous lesions exhibit dense, non-caseating granulomatous infiltrates characterized by high local TNF-alpha and IL-1beta expression, reflecting a state of non-resolving inflammatory drive.

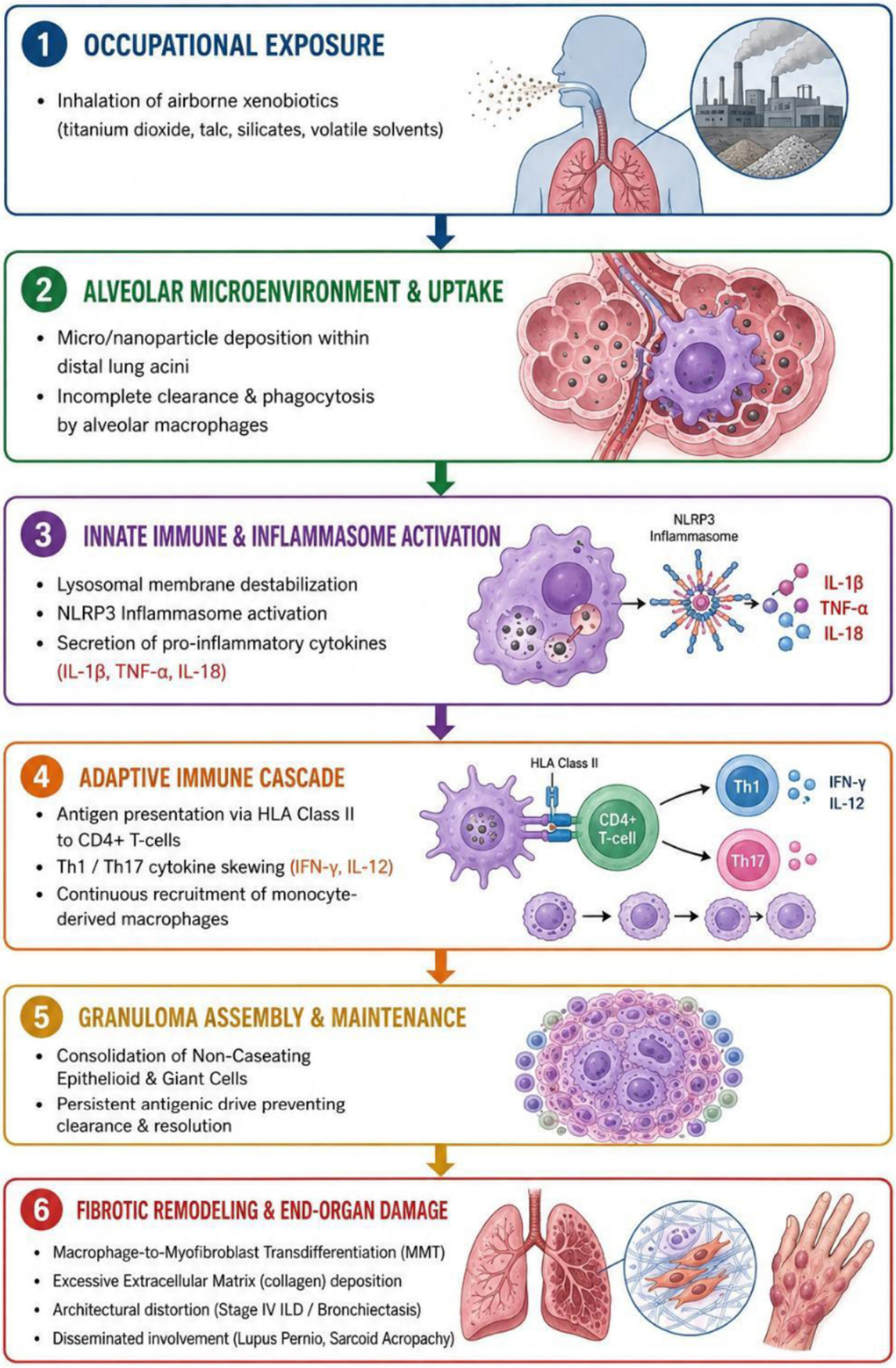


Figure 5. Schematic representation of the immunopathogenesis of occupationally triggered sarcoidosis.

- Sarcoid Acropachy as a Hallmark of Systemic Chronicity: Occurring in less than 1% of sarcoidosis cases, sarcoid acropathy—manifested by digital clubbing, soft-tissue swelling, and classic "lace-like" periosteal bone resorption—is almost exclusively encountered in patients with advanced, multi-organ disease. Its presence strongly correlates with severe cutaneous involvement (predominantly lupus pernio) and end-stage pulmonary fibrosis, signaling longstanding, unmodulated systemic vascular and osteoclast activation.
- Stage IV Fibrotic Remodeling & Antigenic Persistence: Pulmonary fibrosis accounts for the vast majority of sarcoidosis-attributable mortality. When persistent inorganic micro-particulates (such as titanium dioxide, talc, and silicates) remain trapped within alveolar acini, they act as continuous triggers for MMT. This ongoing transdifferentiation bypasses standard anti-inflammatory checkpoints, driving excessive extracellular matrix collagen deposition, traction bronchiectasis, and irreversible architectural distortion.

Recognizing this phenotypic triad early is crucial, as it mandates immediate cessation of exposure and aggressive, dual-targeted therapy that combines potent immunosuppression with early antifibrotic intervention. One of the major challenges highlighted by the literature is the underrecognition of occupational sarcoidosis. In routine clinical practice, occupational history is often insufficiently explored, leading to misclassification of exposure-related cases as idiopathic. This gap has important implications, as identifying a causative exposure allows for targeted interventions, including exposure cessation, which may alter the disease trajectory. Moreover, failure to recognize occupational etiology may result in continued exposure and ongoing immune stimulation, thereby promoting chronicity and fibrosis [9].

Therapeutic management of advanced and occupationally triggered sarcoidosis remains challenging and is evolving toward a more personalized, mechanism-based approach. While systemic corticosteroids continue to represent the cornerstone of treatment for active and progressive disease, their long-term toxicity necessitates early integration of steroid-sparing immunosuppressive agents such as methotrexate, azathioprine, or mycophenolate mofetil, articularly in chronic fibrosing phenotypes [10].

In patients with persistent inflammatory activity or refractory disease, biologic therapies targeting tumor necrosis factor-alpha, such as infliximab, have demonstrated efficacy in controlling ranulomatous inflammation and improving extrapulmonary manifestations, especially in severe ystemic forms [11]. The current ERS-based treatment approach specifically identifies infliximab and adalimumab as TNF antagonists that can be considered as glucocorticoid-sparing therapy in selected sarcoidosis patients [12]. Importantly, the recognition of a progressive fibrosing phenotype has opened new therapeutic horizons, with antifibrotic agents such as nintedanib showing promise in slowing functional decline in non-idiopathic interstitial lung diseases, including sarcoidosis [13].

Beyond pharmacologic therapy, a critical yet often underestimated component of management in occupational sarcoidosis is the identification and elimination of the causative exposure, which may reduce ongoing antigenic stimulation and favorably influence disease trajectory. This integrative strategy (combining immunomodulation, antifibrotic therapy, and occupational intervention) represents a paradigm shift toward comprehensive care that not only controls inflammation but also prevents irreversible organ damage and improves long-term outcomes.

4. Conclusions

This case illustrates a severe form of systemic sarcoidosis with fibrosing pulmonary involvement, inaugurated by characteristic cutaneous lesions and acropathy. It highlights the potential role of chronic occupational exposure in cosmetic manufacturing as a contributing factor in disease development and progression. Early recognition and appropriate immunosuppressive treatment are essential to limit irreversible pulmonary damage. A multidisciplinary approach, including occupational health interventions, remains crucial in managing such complex cases.

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Author Contributions

C.Z.: Conceptualization, data curation, clinical investigation, writing—original draft preparation. M.M., K.E. and H.E.: Data curation, investigation, writing—review and editing. All authors have read and agreed to the published version of the manuscript.

Ethics Statement

The study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical review and approval were waived for this case report in accordance with institutional policies, as it involves a single patient and no experimental intervention.

Informed Consent Statement

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Data Availability Statement

Data supporting the findings of this study are included within the article. Additional details may be available from the corresponding author upon reasonable request, in accordance with ethical and privacy considerations.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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