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SYSTEMATIC REVIEW

Systematic review of Pulmonary Manifestations by Thermophilic Actinomycetes: A Biological, Clinical and Pathological Analysis

Revisión sistemática de manifestaciones Pulmonares por Actinomicetos Termófilos: Un Análisis Biológico, Clínico y Patológico desde 2015-2024 en América

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ABSTRACT

Bacterial species of the genus Thermoactiomyces are aerobic, Gram-positive, endospore-forming bacteria belonging to the order Bacillales. These bacteria are common in both indoor (as humidifiers) and outdoor (soil and pasture) environments, especially in agricultural settings. A notable characteristic of these bacteria is their ability to produce endospores containing dipicolinic acid, a component that confers resistance to high temperatures and desiccation conditions when grown on organic substrates, the associated pathophysiological process begins when the spores are inhaled and reach the pulmonary alveoli. There, a cell-mediated immune response is triggered, particularly through the activation of T lymphocytes and the release of proinflammatory cytokines. This inflammatory response can lead to lung diseases such as hypersensitivity pneumonitis, characterized by symptoms such as cough, shortness of breath and fever, associated with exposure to these microorganisms. To analyze the biological and pathophysiological characteristics of bacteria of the Thermoactiomyces genus and their relationship with the development of lung diseases, particularly hypersensitivity pneumonitis, in order to understand the immune response mechanisms and their impact on human health in agricultural and occupational environments.

Keywords: Hypersensitivity Pneumonitis; Farmer's Lung; Humidifier Lung; Thermophilic Actinomycetes; Emphysema; Cor Pulmonale; Fibrosis; Granuloma.

RESUMEN

Las especies bacterianas del género Thermoactiomyces son aerobias, formadoras de endosporas y Gram positivas, pertenecientes al orden de los Bacillales. Estas bacterias son comunes tanto en ambientes interiores (como humidificadores) como en exteriores (suelo y pastos), especialmente en entornos agrícolas. Una característica notable de estas bacterias es su capacidad para producir endosporas que contienen ácido dipicolínico, un componente que les confiere resistencia a altas temperaturas y condiciones de desecación cuando crecen sobre sustratos orgánicos, el proceso fisiopatológico asociado comienza cuando las esporas son inhaladas y alcanzan los alvéolos pulmonares. Allí, se desencadena una respuesta inmunitaria mediada por células, particularmente a través de la activación de linfocitos T y la liberación de citoquinas proinflamatorias . Esta respuesta inflamatoria puede provocar enfermedades pulmonares como la neumonitis por hipersensibilidad, caracterizada por síntomas como tos, dificultad respiratoria y fiebre, asociados a la exposición a estos microorganismos. El objetivo general de esta investigación Analizar las características biológicas y fisiopatológicas de las bacterias del género Thermoactiomyces y su relación con el desarrollo de enfermedades pulmonares, particularmente la neumonitis por hipersensibilidad, con el fin de comprender los mecanismos de respuesta inmunitaria y su impacto en la salud humana en ambientes agrícolas y ocupacionales.

Palabras clave: Neumonitis por Hipersensibilidad; Pulmón de Granjero; Pulmón de Humidificador; Actinomicetos Termófilos; Enfisema; Cor Pulmonale; Fibrosis; Granuloma.

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INTRODUCTION

Bacterial species of Thermoactinomyces are Gram-positive, endospore-forming, aerobic bacteria belonging to the order Bacillales. They are frequently isolated both indoors (humidifiers) and outdoors (soil, pastures), as well as in agricultural environments.[1] They produce endospores containing dipicolinic acid, the component responsible for their resistance to high temperatures and desiccation when grown on organic substrates.[2]

Thermophilic actinomycetes in solid artificial media do not aerolyze sufficiently for inhalation. Still, when it occurs spontaneously in nature, directly on hay, heaters, and on outdoor surfaces, the actinomycete produces more dense spores that are aerolized easily and favor their spread. The pathophysiological process begins when the spores are inhaled and reach the pulmonary alveoli.

Once there, they can induce a cell-mediated immune response characterized by the activation of T lymphocytes and the release of proinflammatory cytokines.[3]

Objective

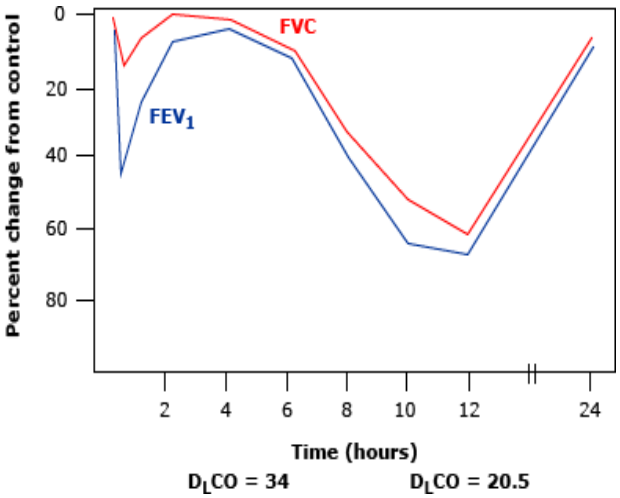
To describe the clinical, biological, and pathological characteristics of pulmonary manifestations caused by thermophilic actinomycetes in patients exposed to this microorganism.

METHOD

In preparation for this article, an exhaustive review of the available articles on the topic of interest—pulmonary manifestations associated with bacteria of the genus Thermoactinomyces—was carried out. Initially, 60 scientific articles related to the topic were identified using medical databases such as PubMed, NCBI, and other open-access sources.

Thus, we avoided topics such as other types of microorganisms and comorbidities, and only selected 30 studies that provided the most pertinent and up-to-date information. These articles were analyzed in detail to extract data relevant data on the biology of Thermoactiomyces.

RESULTS



Source: Schlueter DP, Am J Med 1974; 57:476

Figure 1. Typical two-stage clinical and physiological response to inhalation challenge with an extract of thermophilic actinomycetes

Thermophilic actinomycetes can cause lung damage mainly through the induction of hypersensitivity pneumonitis (HP). This condition is an inflammatory response of the lung to inhalation of antigens from these microorganisms, commonly found in agricultural environments and water-damaged buildings.Exposure to aerosols containing thermophilic actinomycetes, such as Micropolyspora faeni and Thermoactinomyces vulgaris, can trigger an immune reaction in the lung. This reaction is T-cell mediated and is characterized by granuloma formation and an interstitial inflammatory response. Clinical symptoms may include dyspnea, cough, and fever, and in chronic cases, it may lead to pulmonary fibrosis.[33]

Studies have shown that the presence of these microorganisms in dust from water-damaged buildings is associated with respiratory symptoms and alterations in lung function, such as a decrease in FEV1/FVC ratio and forced expiratory flow.[31] This suggests that thermophilic actinomycetes may contribute to granulomatous lung diseases and asthma.

Hypersensitivity Pneumonitis

Thermophilic actinomycetes-related hypersensitivity pneumonitis (HP) is an immune-mediated interstitial lung disease characterized by a complex inflammatory response that can lead to pulmonary fibrosis.

Inflammation

Exposure to thermophilic actinomycetes triggers an immune response involving both humoral and cellular immunity, with the production of specific IgG antibodies and the activation of T-helper type 1 (Th1) cells. This response leads to a predominantly

lymphocytic inflammatory pattern, with infiltration of mononuclear cells in the pulmonary interstitium.[4,5]

The activation of these T cells leads to the release of proinflammatory cytokines and chemokines, which are mediated by signaling pathways such as the activation of the protein kinase D1 (PKD1).[6] In addition, CD103 expression on the cells of the dendritic cells a mechanisms that regulate the severity of the inflammatory response, playing a crucial role in maintaining homeostasis and regulating the inflammatory response resulting in lymphocytic alveolitis granulomatous, characteristic of the HP(hypersensitivity pneumonitis).[7]

T helper cells, particularly Th1 and Th17, play a crucial role in the inflammatory response and fibrosis in hypersensitivity pneumonitis (HP) caused by thermophilic actinomycetes. Th1 cells are associated with producing proinflammatory cytokines such as interferon gamma (IFN-γ), which mediate the initial immune response against inhaled antigens.[4]

The transition from a Th1 to Th17 environment and dysfunction of regulatory T cells (Tregs) may promote a proinflammatory environment that favors fibroblast growth and extracellular matrix synthesis, contributing to fibrosis.[8,5] Th17 cells, through IL-17 production, promote chronic inflammation and pulmonary fibrosis, facilitating epithelial-mesenchymal transition and collagen accumulation.[32,9]

Dysfunction of Tregs can exacerbate this process by failing to adequately regulate the immune response, allowing persistent inflammation and fibroblast activation.[5,10] The change in this pattern of cytokine and cellular activity is essential for the progression of PH to a fibrotic form, where abnormal remodeling of lung tissue and accumulation of extracellular matrix result in structural and functional damage to the lung.[8]

Granuloma formation

Granulomas in PH are typically small and poorly formed, composed of clusters of epithelioid histiocytes and multinucleatedgiant cells, surrounded by lymphocytes. These granulomas in the peribronchiolar interstitium may be associated with organizing pneumonia.[4]

Granuloma formation in response to thermophilic actinomycetes is a complex process involving innate and adaptive immunity. Granulomas are organized aggregates of macrophages and other immune cells that form when individual macrophages cannot eradicate a persistent, infectious, or non-infectious stimulus.[12]

The process begins with activating antigen-presenting cells (APCs), such as macrophages and dendritic cells, through Toll-like receptors (TLRs), which recognize microbial components. This initial activation of the innate immune system is crucial for the subsequent activation of the adaptive immune response.[13] T helper cells, especially Th1 cells, play an essential role in regulating the adaptive response, promoting the formation of granulomas through the production of proinflammatory cytokines.[13]

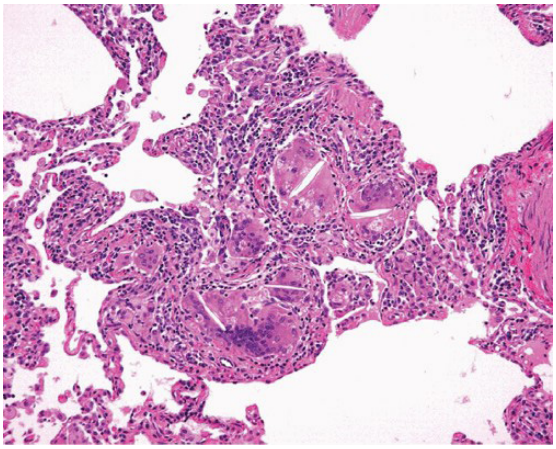
Proinflammatory cytokines that promote lung granuloma formation in response to thermophilic actinomycetes include tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6).[14] TNF-α is crucial for granuloma formation and maintenance, as it regulates cell migration and the expression of chemokines necessary to organize these structures.[15] IL-6 also plays a vital role in the granulomatous response, contributing to the inflammation and maintenance of granulomas.[15] These cytokines facilitate macrophage activation and immune cell organization at the site of infection, which is essential to contain and control infection.

Macrophage polarization is a key component in granuloma formation. Macrophages can shift their metabolism towards glycolysis under hypoxic conditions, indispensable for their activation and function within the granuloma.[16] The mTOR signaling pathway in macrophages influences their differentiation and granuloma function.[16]

The humoral immune system also regulates granulomatous inflammation, coordinating fundamental physiological processes in macrophages that facilitate granuloma formation.[18]

These processes include activation of the immune, phagocytosis, the metabolism and tissue remodeling, Which dictate the functionality of macrophages during granuloma formation.[18]

Granuloma formation in response to thermophilic actinomycetes is a dynamic process involving the interaction of multiple immune and metabolic pathways, with both protective and pathological implications, characteristic of actinomycete infection.[12]



Source: Barrios R et al.[36]

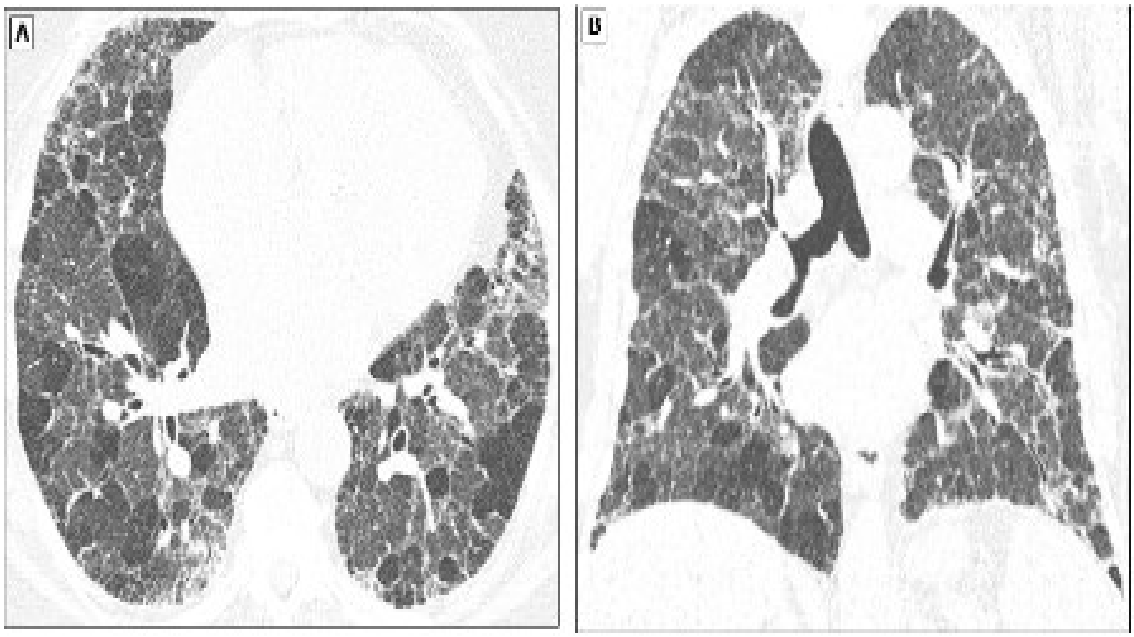
Figure 2. A high magnification view shows a poorly defined “loose” granuloma

Potential fibrosis

Infection by thermophilic actinomycetes contributes to pulmonary fibrosis by developing hypersensitivity pneumonitis (HP), inflammation, and granuloma formation. This process is mediated by key cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-17 (IL-17).

Progression to fibrosis in Hypersensitivity Pneumonia (HP) is mediated by a shift in the cytokine milieu from Th1 to Th17, Th17 mainly producing interleukin-17 (IL-17) which plays an essential role in lung inflammation and fibrosis, retention of interleukins together with fibroblast activation and extracellular matrix synthesis leads to abnormal lung tissue remodeling and fibrosis.[19] In addition, neutrophils and macrophages are the primary sources of IL-17A, contributing to a chronic inflammatory environment.[9]

The production of Proinflammatory and pro-fibrotic cytokines, such as transforming growth factor beta (TGF-β) and tumor necrosis factor alpha (TNF-α), are also central to the Granuloma formation and initial inflammatory response. It facilitates macrophage and lymphocyte activation, promoting the formation of granulomas that attempt to contain the antigen, contributing to collagen synthesis and fibrosis progression.[20] This dysfunction of regulatory T cells promotes fibroblast growth and differentiation and extracellular matrix synthesis, leading to abnormal lung tissue remodeling. Fibrosis can manifest as a pattern of usual interstitial pneumonia (UIP) or nonspecific interstitial pneumonia (NSIP).[20]



Source: Nestor Muller, M.D.[17]

Figure 3. Transverse (A) and coronal (B) CT images show random reticular opacities, extensive ground-glass and lobar areas of decreased attenuation and vascularity in all lobes. A three-density pattern is observed in both inferior lobes

Cor pulmonale

The key factors to analyze the relationship between hypersensitivity pneumonitis and cor pulmonale are to follow the natural evolution of the disease, which is the establishment of pulmonary fibrosis, with hypoxemic respiratory failure and pulmonary hypertension in the absence of therapeutic intervention.[21] In cases NH, prolonged exposure to inhaled antigens such as thermophilic actinomycetes can cause pulmonary fibrosis, stiffening, and thickening of lung tissue. This structural alteration can lead to increased resistance in pulmonary blood flow, which increases pressure in the pulmonary artery and, over time, overloads the right ventricle of the heart, resulting in cor pulmonale.[24] This can lead to pulmonary fibrosis.

This process is particularly relevant in the chronic phase of NH, when symptoms such as dyspnea and cough worsen, and fibrosis leads to respiratory and cardiac failure.[23]

Among patients with chronic PH, the development of symptomatic pulmonary hypertension correlates with the severity of interstitial lung disease and portends worse survival.[17]

The distinction between the classical stages of the disease is often complicated since different forms can coexist in the same individual, being different stages of the same disease. For this reason, an alternative classification has been proposed by dividing patients into 2 clusters:

Cluster 1: patients with recurrent systemic symptoms (general malaise, chills) after 4-8h since antigenic exposure, with a radiological study without findings; prognosis after antigenic avoidance would be favorable. Cluster 1 includes those with acute and subacute clinical forms.

Cluster 2: patients with persistent symptoms, development of acropaquia, hypoxemia, restrictive pattern in the pulmonary function study and presence of fibrosis in the radiological study. The prognosis of this subgroup of patients is unfavorable and corresponds to the chronic form of the disease.

	Clínica	Patrón radiológico en TCAR	Patrón histológico
NH aguda.			
Duración de los síntomas pocas semanas/meses < 6 meses (≈ 24 semanas)	Reversible Resolución completa posible Síntomas relacionados con la exposición al agente causal que pueden resolverse completamente después de la evitación antigénica (frecuentemente observada en NH ocupacional)	Patrón micronodular centrílobular difuso y opacidades de vidrio predominantemente en lóbulos superiores y medios, nódulos centrilobulares mal definidos; patrón en mosaico, atrapamiento aéreo o raramente consolidación	NH Inflamatoria (celular): Infiltrado linfoplasmocítico/mononuclear (macrófagos) Infiltrado linfocitico centrado en vía aérea/ peribronquiolar Granulomas poco formados Células gigantes multinucleadas NINE celular-like
NH crónica			
Duración de los síntomas generalmente mas de 6 meses (>≈ 24 semanas)	Potencialmente reversible Riesgo de progresión	Fibrosis predominantemente en lóbulos superiores y medios, fibrosis peribroncovascular, panalización, mosaico, atrapamiento aéreo, nódulos centrilobulares y relativa preservación de bases	NH fibrótica: NIU like NINE fibrótica –like Fibrosis centrada en vía aérea Inclasificable Los signos histológicos de NH inflamatoria pueden presentarse sobre una base fibrótica.

Source: Vasacova M et al.[34]

Figure 4. Clinical-Radiological and Histological Comparison of Acute and Chronic Hypersensitivity Pneumonitis

Table 1 Demographic characteristics, types of HP, and baseline pulmonary function data in patients with and without PH

Variables	sPAP < 50 mmHg	sPAP ≥ 50 mmHg	*P*
No. patients	59	14	
Age (years)	61.9 ± 10.2	67.5 ± 7.9	0.033
Male/female	27/32	4/10	0.37
Types of HP			
Bird-related HP	46	12	0.64
Farmer's lung	6	0	
Home-related HP[a]	6	2	
Others	1	0	
Pulmonary function measurements			
% FVC	63.9 ± 21.5	54.3 ± 18.6	0.13
% FEV_1	68.4 ± 21.1	58.6 ± 18.2	0.11
FEV_1/FVC	88.6 ± 7.9	89.3 ± 7.4	0.77
% TLC	67.7 ± 19.3	62.3 ± 20.0	0.35
% DLCO	42.2 ± 18.4	34.0 ± 17.8	0.25
PaO_2 (mmHg)	61,7 ± 14.8	48.0 ± 10.3	0.002
$PaCO_2$ (mmHg)	39.1 ± 5.5	43.1 ± 9.8	0.16

[a] HP caused by inside molds due to a damp and moldy home environment

Source: Koschel DS et al.[35]

Figure 5. Demographic characteristics, types of HP, and baseline pulmonary function data in patients whit and without PH

In a retrospective study of 120 patients with hypersensitivity pneumonitis seen at two different respiratory care centers over a 5-year interval, pulmonary hypertension (PAPs ≥ 50 mmHg) was detected in 14 patients and was associated with an increased risk of

death, with a median survival of 23 to 98 months, patients with pulmonary hypertension were older and had a significantly reduced PaO2.[35]

Emphysema

The clinical presentation of hypersensitivity pneumonitis is divided into acute, subacute, and chronic, depending in part on the duration of antigen exposure. Chronic hypersensitivity pneumonitis, resulting from continuous or recurrent low-level exposure to the causative antigen, is often associated with progressive pulmonary fibrosis and the development of emphysema. Although it is not known in detail how emphysema occurs, risk factors associated with its development can be identified.[27]

The duration of exposure to inhaled antigens has been observed in diseases such as farmer's lung, where continuous exposure to antigens specific can lead to emphysematous changes in the lung.[26]

In addition, chronic inflammation induced by an exaggerated immune response to these antigens is a key mechanism, as it can lead to the destruction of alveolar tissue and the formation of abnormally large air spaces abnormally characteristic of emphysema.[28] Importantly, emphysema in hypersensitivity pneumonitis can develop regardless of smoking history; studies have shown that patients with emphysema may be nonsmokers.[29,30]

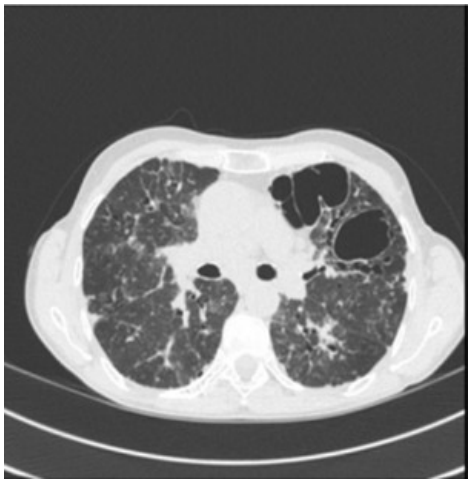


Figure 6. CT scan of the chest of a 68-year-old man with chronic hypersensitivity pneumonitis presenting with bullae in the left upper lobe

The patient presents with large bullae and evidence of emphysema, which has a predilection for the upper and middle lungs. The extent of involvement is greater in these areas than in the lower lungs. Radiological tests showed fibrosis, characterized by intralobular lines, irregular thickening of the interlobular septum and traction bronchiectasis. In addition, chronic hypersensitivity pneumonitis was diagnosed, which may be the result of acute or subacute hypersensitivity pneumonitis.[29]

DISCUSSION

Exposure to thermophilic bacteria of the genus Thermoactiomyces presents a significant risk to pulmonary health, particularly in agricultural environments where conditions favor the proliferation and aerosolization of these spores. Although in controlled environments inhalation is unlikely, direct contact with natural sources such as hay and hot surfaces facilitates spore dispersal, increasing the likelihood of exposure.

Inhaled spores trigger a significant immune response in the pulmonary alveoli, which, in many cases, manifests as hypersensitivity pneumonitis. This condition underscores the importance of identifying and mitigating risks where agricultural activities and handling organic materials facilitate spore release.

RECOMMENDATIONS

Use of personal protective equipment: we recommend the use of face masks or respirators in high-risk environments, such as farms or agricultural areas where hay, grass, or compost is handled, to avoid inhaling spores.

Improve ventilation in indoor environments: in places where humidifiers or other equipment that may facilitate the proliferation of bacteria are used, promote good ventilation to avoid the accumulation of spores in the air.

Maintenance and cleaning of agricultural and industrial equipment: recommend regular cleaning of equipment such as humidifiers, fans and machinery agricultural land that can accumulate organic material, to reduce the presence of spores in the environment.

Environmental monitoring and control: establish workplace monitoring protocols to measure the concentration of spores and other biological contaminants in the air, implementing corrective measures if levels are hazardous.

Training and awareness: provide training to workers and exposed persons on the risks associated with Thermoactiomyces and the importance of preventive measures, including early recognition of symptoms of hypersensitivity pneumonitis.

Early medical intervention: recommend immediate medical consultation at the onset of respiratory symptoms (such as cough, fever or shortness of breath) after.

CONCLUSIONS

Hypersensitivity pneumonitis (HP) associated with thermophilic actinomycetes represents a significant challenge to respiratory health, especially in agricultural and moisture-affected buildings. This article has highlighted the complexity of the T cell-mediated immune response and the transition from Th1 to Th17 environment, which contributes to chronic inflammation, granuloma formation, and subsequent pulmonary fibrosis. The dysfunction of regulatory T cells (Tregs) has been identified as a critical factor in the exacerbation of inflammation and progression to fibrosis.

FINANCING

None.

CONFLICT OF INTEREST

Authors declare that there is no conflict of interest.

AUTHORSHIP CONTRIBUTION

Conceptualization: Anlly Añez, José Penido, Lyra Hsieh, Mariano Guerra, Luis Aparicio.
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Drafting - original draft: Anlly Añez, José Penido, Lyra Hsieh, Mariano Guerra, Luis Aparicio.
Writing - proofreading and editing: Anlly Añez, José Penido, Lyra Hsieh, Mariano Guerra, Luis Aparicio.

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