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Case Report

Disseminated paracoccidioidomycosis under biological therapy

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Abstract

Introduction: Paracoccidioidomycosis is an endemic mycotic infection caused by *Paracoccidioides* spp., prevalent in Central and South American countries. Anti-tumor necrosis factor (TNF) alpha agents, commonly used for autoimmune diseases, increase the risk of severe infections. We present a case of anti-TNF alpha-related paracoccidioidomycosis in a 71-year-old male farmer from Colombia.

Case presentation: The patient had oral lesions and chronic cough. A biopsy showed granulomatous inflammation with multinucleated giant cells but no microorganisms. Negative microbiological stains and tests for other infections prompted further investigations. A positive serum immunodiffusion test for *Paracoccidioides* antibodies at a 1:256 titer led to mediastinoscopy and lung biopsy, which revealed budding yeast in a "captain's wheel" formation. Treatment with liposomal amphotericin B and itraconazole was initiated.

Conclusions: This case highlights the risk of opportunistic infections under anti-TNF alpha therapy and raises awareness of paracoccidioidomycosis associations. Early diagnosis and management are essential for better patient outcomes.

Key words: paracoccidioidomycosis; immunosuppression; opportunistic; infections.

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Introduction

Paracoccidioidomycosis is an endemic mycotic infection caused by a fungus belonging to the *Paracoccidioides* spp. in Central and South American countries [1]. The infection primarily occurs when individuals inhale the fungi during activities related to soil exposure [2]. Upon inhalation, about 10% of cases progress to an acute pulmonary infection, while in others, the immune system effectively combats the infection through a TH1 immune system-related response, resulting in either complete elimination of the fungi, or containment in granulomas without dissemination [3].

Anti-tumor necrosis factor (TNF) alpha agents—a type of biological therapy—have been widely used to treat various autoimmune diseases and related conditions, including rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. However, their use comes with the drawback of an increased risk of severe infections, particularly in vulnerable subgroups such as older individuals or those receiving concomitant therapies like systemic steroids [4].

There are a growing number of reported cases in recent literature that describe endemic mycotic infections associated with the use of anti-TNF alpha agents. Among the well-known fungi linked to this therapy are *H. capsulatum*, *B. dermatitidis*, and *Coccidioides* spp [5]. Here, we report a case of anti-TNF alpha related paracoccidioidomycosis infection.

Case presentation

A 71-year-old male farmer; residing in a rural area of Antioquia, Colombia; came to our clinic with complaints of chronic cough and oral lesions on his palate (Figure 1). The patient's past medical history included psoriasis, diagnosed 25 years ago. He was initially treated with methotrexate, but due to refractoriness, he was switched to anti-TNF alpha therapy with adalimumab 11 years ago.

A previous biopsy of the oral lesions demonstrated chronic granulomatous inflammation. However, specialized staining techniques, including Ziehl-Neelsen, modified Ziehl-Neelsen, and Grocott-Gomori methenamine silver stain, failed to detect any microorganisms.

The presence of right inguinal adenopathy was noted upon physical examination. However, no other palpable lymph nodes were detected. Despite the absence of any other evident physical abnormalities, a high-resolution computed tomography (HRCT) of the chest showed multiple pulmonary nodules, as well as intraparenchymal lymph node and subpleural ground-glass opacities in the middle lobe and lingula.

A subsequent biopsy of the inguinal lymph node

revealed chronic granulomatous inflammation with multinucleated giant cells, consistent with the prior findings from the oral lesions. Despite performing microbiological stains on the inguinal lymph node biopsy, no evidence of fungi or mycobacteria was detected.

Furthermore, testing for cryptococcal antigen in serum, *Histoplasma* urine antigen, and *Mycobacterium tuberculosis* polymerase chain reaction (PCR) on urine samples yielded negative results. However, a serum immunodiffusion assay for fungal pathogens demonstrated a positive result for *Paracoccidioides* antibodies, with a titer of 1:256.

A mediastinoscopy and lung biopsy were performed to investigate further. Silver staining from the biopsy revealed the characteristic presence of *Paracoccidioides* budding yeast arranged in the distinctive "captain's wheel" formation (Figure 2).

Treatment and outcome

Initial antifungal therapy with amphotericin B deoxycholate was started, but due to concerns regarding nephrotoxicity, it was transitioned to liposomal amphotericin B after a few doses. Itraconazole was later introduced for consolidation therapy.

Discussion

Paracoccidioidomycosis, formerly known as "South American blastomycosis", is caused by a fungus belonging to *Paracoccidioides* spp. which is endemic to South and Central America. This infection presents as a granulomatous disease, similar to *Mycobacterium tuberculosis* infections or histoplasmosis [6]. The most common form of the disease occurs in older adult patients and is characterized by chronic infection with pulmonary, cutaneous, or adrenal gland lesions, often accompanied by constitutional symptoms [7].

Figure 2. Paracoccidioides budding yeast seen upon silver staining of lung tissue biopsy, and appearing as characteristic budding yeast exhibits of round to oval shape surrounded by a clear halo known as the "captain's wheel" or "Mariner's wheel" formation. This unique pattern is created by multiple small daughter cells budding from the larger parent cell, resembling the spokes of a wheel, and it is a hallmark feature of Paracoccidioides species.

Figure 1. Oral lesions on hard palate of patient, consisting of two painless 0.5 cm diameter ulcers with white fibrine exudate base and surrounding active erythematous border.

The typical mode of acquisition of paracoccidioidomycosis is through the inhalation of the yeast during soil manipulation in an endemic area [8]. Unlike other mycotic infections, it is relatively common to find paracoccidioidomycosis in apparently healthy individuals. However, the infection tends to be more extensive in immunocompromised patients. In the past, human immunodeficiency virus (HIV) patients with severe immunodeficiency syndrome, characterized by CD4 counts below 150 cells/mL, have been documented to experience extensive disseminated infections with high mortality rates [9].

TNF is a soluble proinflammatory cytokine primarily expressed by immune cells, especially macrophages, to combat intracellular infections [10].

Anti-TNF alpha agents are a group of antibodies used for treating various inflammatory conditions; including rheumatoid arthritis, psoriasis, and intestinal inflammatory diseases [11].

As expected, the introduction of anti-TNF treatments is associated with an increased incidence of opportunistic infections. A systematic review and meta-analysis published in 2006 that involved 5,014 patients treated with anti-TNF alpha medications revealed a higher risk of severe infections (odds ratio, OR 2.0; 95% confidence interval, 1.3–3.1) [12]. Notably, opportunistic infections were found to be a significant concern, with viral etiologies (such as herpes zoster, varicella zoster, disseminated herpes simplex, and cytomegalovirus) being the most common, followed by fungal infections (including pneumocystis, invasive aspergillosis, and cryptococcosis) accounting for approximately 22% of cases.

There is a scarcity of medical literature regarding the association between anti-TNF alpha agents and paracoccidioidomycosis. However, an increasing number of case reports have been published, raising awareness of this potential risk and emphasizing the importance of early diagnosis and appropriate treatment for better patient outcomes.

Conclusions

This case serves as a reminder of the heightened risk of opportunistic infections in patients receiving anti-TNF alpha agents. Therefore, it is crucial for healthcare providers to exercise caution when prescribing these therapies, and carefully assess the risk-benefit ratio for each individual patient. Paracoccidioidomycosis should be considered in individuals residing in endemic regions who have occupational exposure to soil and present with chronic lesions accompanied by granulomatous inflammation, particularly in the skin or respiratory system. Moreover, as demonstrated in this patient's case, individuals with some form of immunosuppression, which impairs their natural defense mechanisms against infections, are more susceptible to such fungal infections. Early suspicion and timely diagnosis of paracoccidioidomycosis can significantly impact patient outcomes and guide appropriate management strategies.

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Conflict of interests

No conflict of interests is declared.

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