EJCRIM
European Journal
of Case Reports
in Internal Medicine

SHOULD HISTOPLASMOSIS BE SCREENED FOR BEFORE INITIATION OF TUMOUR NECROSIS FACTOR ALPHA INHIBITORS?

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Received: 15/03/2024 **Accepted:** 25/03/2024 **Published:** 16/04/2024

Conflicts of Interests: The Authors declare that there are no competing interests.
Patient Consent: Written consent was obtained from the patient.

How to cite this article: Edupuganti S, Chirumamilla Y, Upadhyay M, Osterholzer D. Should histoplasmosis be screened for before initiation of tumour necrosis factor alpha inhibitors? *EJCRIM* 2024;**11**:doi:10.12890/2024_004467

ABSTRACT

Histoplasmosis is a soil-based dimorphic fungus endemic to the Midwest and Southeastern United States and is responsible for infection through inhalation of conidia. Infection is usually asymptomatic, as the fungal growth is contained by formation of granulomas. However, dissemination can occur in immunocompromised hosts due to the lack of optimal activity of interferon gamma, tumour necrosis factor alpha (TNF-alpha) and interleukin-17. There is a significant overlap between the symptomatology of histoplasmosis and granulomatosis with polyangiitis (GPA). We report a case of a 48-year-old female who presented with high-grade fever, worsening generalised weakness and tachycardia. She had a previous history of bilateral cavitary lung lesions for which she was evaluated at an outside facility. As her entire infectious investigation was negative and found to be positive for antineutrophil cytoplasmic antibody (ANCA), a diagnosis of GPA was made, and she was initiated on rituximab infusions 7 weeks prior to her presentation to our facility. Repeat infectious investigations at our facility were positive for (1-3)-β-D-glucan test and urine histoplasma antigen. Prompt discontinuation of rituximab and initiation of systemic antifungal therapy led to clinical improvement. Based on this experience, we highlight the association of histoplasma with ANCA positivity along with the importance of closely monitoring these patients for possible clinical worsening after the initiation of TNF-alpha inhibitors, despite the negative infectious work-up. Also routine screening or pre-emptive therapy for histoplasmosis before the initiation of TNF-inhibitors is not recommended.

KEYWORDS

Histoplasmosis, GPA, ANCA positivity, TNF-alpha inhibitors

LEARNING POINTS

- Histoplasmosis is associated with ANCA positivity.
- Despite the negative investigations for histoplasmosis and criteria for GPA being met, patients should be closely monitored for possible clinical worsening after the initiation of immunosuppressive therapy, especially TNF-alpha inhibitors.
- Current guidelines are not recommending routine screening or pre-emptive therapy for histoplasmosis before initiation of TNF-alpha inhibitors.

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European Federation of Internal Medicine

Publisher
smc media srl

INTRODUCTION

Histoplasma capsulatum is the most prevalent endemic mycosis in the United States, first described by an Army physician Samuel Darling in Panama, in 1906. *H. capsulatum* proliferates best in soil contaminated with bird or bat droppings and the infection is acquired through the inhalation of conidia. Excavation, building, demolition, remodelling, woodworking and cleaning buildings coated in bat or bird excrement are among the activities that have been commonly linked to exposure[1]. While most infections are asymptomatic or self-limited, some individuals develop acute pulmonary infections or severe and progressive disseminated infections. Due to remarkable similarity in the clinical picture, histoplasmosis is often misdiagnosed as granulomatosis with polyangiitis (GPA). We present a case of a 48-year-old female who was treated for GPA which led to significant morbidity, and she was eventually diagnosed with histoplasmosis.

CASE DESCRIPTION

The patient was a 48-year-old female with a past medical history of heart failure with reduced ejection fraction, asthma, sleep apnoea and Factor V Leiden mutation on chronic anticoagulation, as well as antineutrophilic cytoplasmic antibody (ANCA)-associated vasculitis and necrotising granulomatous lesions of the lower extremities diagnosed at an outside facility. She presented to the Emergency Department with complaints of worsening weakness.

One year earlier, she was evaluated at a different facility for fever, shortness of breath, chest pain and fatigue. A computerised tomography (CT) scan at that time revealed cavitary lung lesions measuring 51 mm in the right upper lobe, 51 mm in the right lower lobe and 41 mm in the left upper lobe. Borderline to mild mediastinal lymphadenopathy was noted as well, the most prominent being a paratracheal node that measured 11 mm. Bronchoalveolar lavage was performed which revealed benign bronchial cells, squamous cells, macrophages, and mixed inflammatory infiltrates. Following that, the patient underwent a CT guided lung biopsy which revealed patchy chronic granulomatous inflammation, histiocytic reaction, and focal necrosis. Keeping a broad differential diagnosis, she had further work-up which yielded a mildly elevated rheumatoid factor at 32 (reference range: 0–20 IU/ml), erythrocyte sedimentation rate of 88 (reference range <20 mm/hr), negative angiotensin-converting enzyme (ACE), antinuclear antibody (ANA), ANCA, cyclic citrullinated peptide (CCP), QuantiFERON tuberculosis, urine histoplasma antigen and Coccidioides antibodies. At a multidisciplinary conference with pulmonologists, thoracic radiologists, and pathologists, it was determined that there was the presence of large cavitary lesions, necrotising granulomas, and necrotic neutrophils along with the absence of giant cells. As this is not consistent with sarcoidosis, the two most likely aetiologies were thought to be a granulomatous infection, either

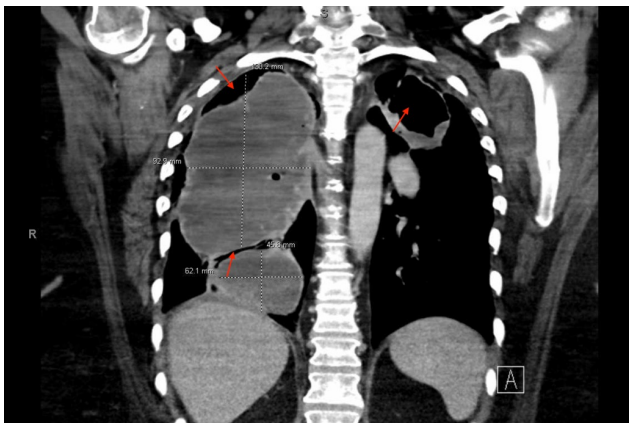

Figure 1. Multiple cavitary lesions in the bilateral lungs with air fluid levels – PA view.

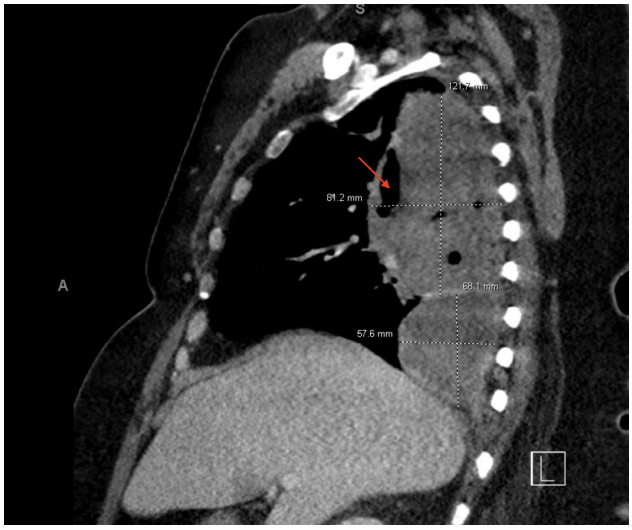

Figure 2. Multiple cavitary lesions in the right lung with air fluid levels – lateral view.

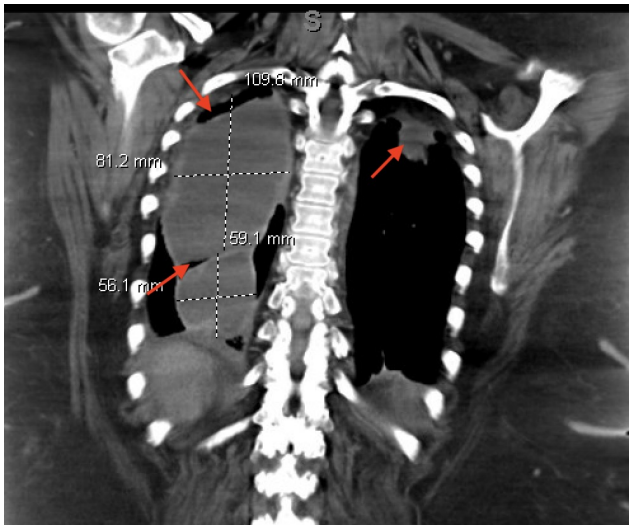

Figure 3. Cavitary lesions with decreasing size and resolving air fluid levels – PA view.

mycobacterial or fungal, or vasculitis. Given the negative fungal markers and tuberculosis screening, vasculitis was considered to be the more likely diagnosis, specifically ANCA-negative vasculitis. The patient was referred to rheumatology for further confirmation of whether she

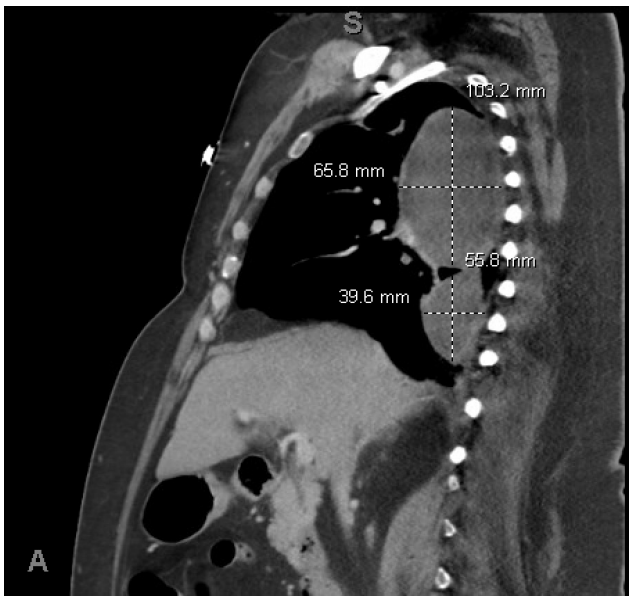

Figure 4. Cavitary lesions with decreasing size and resolving air fluid levels – lateral view.

met the criteria for ANCA-negative vasculitis and in the meantime was continued on daily prednisone therapy. On visiting her rheumatologist, she had repeat laboratory work done which revealed a positive cytoplasmic ANCA and proteinase 3 antibody. At that time, she also had bullous lesions developing on bilateral lower extremities and biopsy from these lesions revealed necrotising vasculitis, thought to be consistent with her previous lung vasculitis. Hence, she was given methylprednisolone and rituximab infusions, and ultimately discharged on an expedited prednisone taper.

Eight weeks after receiving the rituximab infusions she arrived at our facility with generalised weakness, and her vital signs were significant for a temperature of 39°C and tachycardia. Her laboratory evaluation revealed leukocytosis with a white blood cell count of 12.2 (reference range: 4.5 to 11.0 × 10^3/µl). An abbreviated respiratory panel was positive for SARS-CoV-2, and she was started on treatment. As she was meeting the systemic inflammatory response syndrome criteria in the setting of her recent immunosuppression, further infectious work-up was done and broad-spectrum antibiotics and antifungal medications were initiated. She underwent a CT of the chest, abdomen, and pelvis, which showed worsening bilateral lung abscesses, two in the posterior right lung and one in the posterior superior left upper lobe *(Fig. 1 and 2)*. Her (1-3)-β-D-glucan test was elevated at 254 pg/ml (reference range <54 pg/ml). Urine histoplasma antigen and blastomyces antigen were positive at 2 ng/ml (reference range <0.2 ng/ml) and 0.38 ng/ml (reference range <0.2 ng/ml) respectively. She was ultimately diagnosed with pulmonary histoplasmosis and began oral itraconazole treatment. She was advised to remain on treatment for a minimum of one year.

She continued follow-up as an outpatient with an Infectious Disease clinic and reported an improvement in the cough, decreased sputum production, shortness of breath and absence of fever. The following months after azole initiation, serial CT chest imaging *(Fig. 3 and 4)* were done which showed a reduction in the lung cavity size and resolving air fluid levels.

DISCUSSION

Histoplasmosis is a soil-based dimorphic fungus endemic to the Midwest and Southeastern states of the USA and is responsible for infection through inhalation of conidia. Our patient lived in a damp basement in western Michigan, which most likely led to exposure. Histoplasma exposure is usually asymptomatic because the fungal growth is contained by the formation of granulomas. However, dissemination can occur in immunocompromised hosts due to the lack of optimal activity of interferon gamma, TNF-alpha and interleukin-17. Presenting symptoms included high fever, malaise, weight loss, headache, a non-productive cough, chest pain and arthralgias similar to GPA[2,3].

Our patient presented with similar symptoms to those described above and a CT chest scan revealed lung nodules with cavitary lesions and several borderline mildly enlarged mediastinal lymph nodes. Hilar and mediastinal adenopathy as seen in our patient are more prominent in granulomatous diseases such as sarcoidosis and pulmonary histoplasmosis, but not in GPA[4]. The histopathology picture with patchy chronic granulomatous inflammation, histiocytic reaction and focal necrosis also looked fuzzy, reminiscent of necrosis due to fungal infection. These findings are consistent with pulmonary histoplasmosis rather than GPA. The classic features of GPA such as fibrinoid necrosis of small to medium sized vessels and mononuclear infiltrate mainly with necrotic neutrophils that result in intense basophilic staining were absent[4-6]. Unexpectedly, histoplasma yeasts were not identified in the lung biopsy specimen with the Grocott methenamine silver stain. Biopsy of the lower extremity ulcers had also yielded similar findings.

The scenario took an interesting turn when an antineutrophil cytoplasmic antibody (c-ANCA) test resulted positive at the subsequent visit. As per ELK (ears, nose and throat or upper respiratory tract, lung and kidney) criteria, given her typical manifestations along with the c-ANCA positivity, she now fitted the diagnosis of GPA and was treated with rituximab infusions[3]. Looking into the existing literature, two documented cases have been identified highlighting the correlation between ANCA positivity and histoplasmosis. The first patient is an 81-year-old man with oral ulcers while the second patient is a 6-year-old immunocompetent boy, making both the cases quite unique. However, during the diagnostic process this detail is usually overlooked[7,8].

After receiving rituximab infusions our patient did not follow up for 8 weeks, and eventually returned with worsening symptoms and enlarging cavitary nodules in comparison with previous imaging. There is existing literature stating the increased risk of new onset or dissemination of the early-stage histoplasmosis after the use of TNF-alpha blockers including rituximab[9]. As the infectious work-up this time revealed elevated (1-3)-β-D-glucan and urine histoplasma

antigen, rituximab was stopped immediately and she was initiated on systemic antifungal therapy which improved her symptoms. In retrospect, extensive counselling of the patient regarding the importance of close follow-up after the initiation of TNF-alpha inhibitors and monitoring her for clinical worsening would have significantly reduced her morbidity in this case. Even though there is a high risk of unmasking latent histoplasmosis in patients who are being initiated on TNF-alpha inhibitors, routine screening or pre-emptive therapy for histoplasmosis is not recommended in these situations based on the existing literature[10,11].

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