Chronic wrist monoarthritis in an immunocompetent patient: an unexpected fungal culprit

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Submitted: 14/09/2026

Accepted: 16/09/2026

Running title - Articular histoplasmosis: a case based review

Accepted manuscript

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as an 'Accepted Article'

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Abstract

Aims: To describe articular histoplasmosis as the presenting feature of disseminated infection in an immunocompetent host, and to review the musculoskeletal manifestations of histoplasmosis.

Methods: Case report and narrative review of the literature.

Results: A 73-year-old immunocompetent man, whose only exposure was military service in Africa fifty years earlier, presented with a bleeding gingival lesion and left wrist monoarthritis. Acute phase reactants, autoantibodies and HIV serology were negative. Ultrasound-guided synovial biopsy yielded *Histoplasma capsulatum* on both mycological culture and histopathology. Computed tomography, magnetic resonance imaging and echocardiography disclosed adrenal infiltration and pericardial effusion, establishing disseminated disease. Itraconazole was complicated by rhabdomyolysis arising from interaction with simvastatin; after amphotericin B for fourteen days and twelve months of itraconazole, the arthritis resolved within six weeks.

Conclusions: Infection should be considered in unexplained monoarthritis irrespective of immune status. Ultrasound-guided synovial biopsy was decisive here, and articular disease may be the only clue to disseminated histoplasmosis, warranting a systemic search.

Keywords: Monoarthritis; Histoplasmosis; Disseminated histoplasmosis; Ultrasound guided-synovial biopsy; Ultrasonography.

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Introduction

Histoplasmosis is a fungal infection caused by *Histoplasma capsulatum*, variant *capsulatum* or *duboisii*, first described in 1905. It is a thermally dimorphic pathogen, often found as spores in areas with bird or bat droppings, and frequently transmitted in relation to spelunking, farming or excavation. It is considered the most prevalent mycosis in the United States[1]. It is endemic in certain regions, particularly the Ohio and Mississippi River valleys in the United States, parts of Central and South America, Africa and Southeast Asia[2]. Infection results from the aerosolisation of infectious spores of *H. capsulatum*, which are inhaled into the lower airways. The spores are then phagocytised by macrophages and, at higher temperatures, converted into their infectious form, yeasts[1,2].

Most cases of histoplasmosis are subclinical and self-limited, with primary pulmonary histoplasmosis being the most common manifestation[3]. The musculoskeletal manifestations of histoplasmosis, which are rare and often overlooked, may appear as the primary manifestation. Recognising them can prompt swift diagnosis and therapeutic intervention, reducing the morbidity and mortality related to disseminated infection[3].

Case report

In March 2024, a 73-year-old man presented to the Stomatology clinic of a tertiary hospital with a bleeding exophytic gingival lesion that had developed over the previous three months. In May 2024 he presented to the Rheumatology clinic with a left wrist monoarthritis.

The patient reported having served in Africa during the Portuguese Colonial War in the 1970s. His medical history included ischaemic heart disease, for which he underwent stent placement in 2004, as well as hypertension, a history of smoking and degenerative lumbar spine disease. His medication comprised perindopril and amlodipine (4 + 5 mg once daily), bisoprolol (5 mg twice daily), calcium carbonate and cholecalciferol (1500 mg + 400 IU), cyanocobalamin (0.2 mg daily), pyridoxine (200 mg daily), thiamine (100 mg daily), pregabalin (50 mg twice daily) and simvastatin (40 mg daily).

Blood tests were unremarkable, without elevation of acute phase reactants, and with negative results for rheumatoid factor, anti-cyclic citrullinated peptide antibodies and human leukocyte antigen B27. Serologies for human immunodeficiency virus and for hepatitis B and C viruses were also negative.

An orthopantomogram revealed bone destruction beneath the gingival lesion, leading to an incisional biopsy that confirmed the presence of *H. capsulatum*. Radiography of the left wrist

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revealed reduced bone mineral density within the carpal bones, irregularity of the bone contour at the distal extremity of the radius and soft tissue thickening in the surrounding area. Ultrasound revealed synovitis of the radiocarpal joint as well as tenosynovitis of the flexor and extensor tendons of the fingers. Ultrasound-guided needle biopsy of the wrist was performed and the material was sent for microbiological culture and for histopathological examination. Bacteriological and mycobacteriological cultures were negative. Mycological culture was positive for *H. capsulatum*. Histopathology documented small, uniform, oval yeasts with narrow-based budding and eccentric, acorn-like nuclei, clustering within histiocytes, morphologically compatible with *H. capsulatum* (Figures 1 and 2), confirming articular involvement.

The patient was admitted to the Infectious Diseases department and underwent a body computed tomography scan, which revealed mild diffuse bronchial wall thickening and nodularity in both adrenal glands. To characterise these findings further, abdominal magnetic resonance imaging was performed, demonstrating diffuse bilateral thickening of the adrenal glands suggestive of bilateral infiltration. Transthoracic echocardiography identified a moderate pericardial effusion in the right posterior auricular region.

Disseminated histoplasmosis was diagnosed, with definite involvement of the joints and gingiva and possible involvement of the adrenal glands and pericardium. The patient was started on itraconazole and discharged.

A month later, in June 2024, he was readmitted with rhabdomyolysis and myopathy, attributed to a drug interaction between simvastatin and itraconazole. Simvastatin was stopped and he received amphotericin B for 14 days, followed by itraconazole for one year. He completed treatment in June 2025 without new symptoms attributable to histoplasmosis, his arthritis having resolved completely after one and a half months of antifungal therapy.

Discussion

Although histoplasmosis is primarily an opportunistic infection, it can affect both immunocompromised and immunocompetent individuals[1,3,4], as seen in this case.

Patients with conditions that compromise cellular immunity, such as acquired immunodeficiency syndrome, immunosuppression for organ transplantation or similar conditions, and the use of tumour necrosis factor (TNF) inhibitors, are more susceptible to disseminated histoplasmosis, as are the elderly and young children[2]. In murine models, TNF has been hypothesised to be a major factor in the immune defence against *H. capsulatum*, along with cell-mediated immunity[5]. In patients receiving TNF inhibitors, histoplasmosis is the second

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most frequent opportunistic infection after tuberculosis[2]. Clinical presentation may also vary depending on inoculum size or the patient's comorbidities[6].

Most people exposed to *H. capsulatum* are asymptomatic[3,5]. In those who develop symptoms, respiratory involvement is the most frequent, particularly in immunocompromised individuals, usually presenting as flu-like symptoms as well as lymphadenopathy, hepatomegaly, splenomegaly and gastrointestinal manifestations[2,5]. Mediastinal histoplasmosis, pericarditis, pulmonary nodules, and subacute and chronic pulmonary histoplasmosis are also possible presentations[2]. Progressive disseminated histoplasmosis is defined by haematogenous dissemination of *H. capsulatum* leading to extrapulmonary involvement. It may have an acute onset or develop many years after the initial pulmonary infection, through reactivation of latent disease. Patients with impaired immunity, especially cellular, are at greatest risk[2,7].

Musculoskeletal manifestations are very rare. A series of 111 patients with disseminated histoplasmosis did not report any case of rheumatic manifestations[7]. Another series of 381 patients detected musculoskeletal manifestations in 24, with only 6 presenting with arthritis[8]. The first description of joint involvement was reported in 1942 in a patient with knee arthritis[9]. Four main groups of musculoskeletal involvement have been described: reactive arthritis; musculoskeletal infection (arthritis, tenosynovitis, myositis, panniculitis, osteomyelitis)[8]; systemic infection resembling rheumatic disease; and superinfection in individuals treated with immunosuppressive agents[2, 10]. Arthritis is rare and presents most frequently as monoarthritis, with the knee the most common site[2,4,5]. Polyarthritis may be additive or migratory[2]. Tenosynovitis predominantly affects the volar aspects of the fingers and wrists[1]. Carpal tunnel syndrome, osteomyelitis, spondylodiscitis and prosthetic joint involvement are also described[1,2,5,10].

Some authors propose that the musculoskeletal manifestations of histoplasmosis relate to a systemic inflammatory response to the infection rather than to the direct virulence of *H. capsulatum*[5].

While the presumptive diagnosis of joint histoplasmosis was high in this case, articular histoplasmosis can be the initial manifestation of disseminated disease, which makes the diagnosis challenging. The gold-standard approach involves microbiological isolation and histological confirmation with haematoxylin and eosin and either periodic acid-Schiff or Grocott methenamine silver staining[2,3]. Demonstration of antigen in serum or urine by enzyme-linked immunosorbent assay, or positive serology, may also support the diagnosis[2]. A case series and literature review proposes that patients with atypical presentations of inflammatory arthritis

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that do not respond to immunosuppressive therapy, particularly those with a travel history to endemic regions or with immunocompromised status, should undergo tissue biopsy with samples sent for culture and histopathological examination[3]. It is also crucial to exclude immunosuppressive conditions such as HIV infection, and comorbidities such as diabetes mellitus[4].

For treatment, itraconazole is the preferred antifungal, particularly in mild cases, typically administered for a minimum of 12 months, and may be preceded by amphotericin B in moderate or severe disease[2,3]. In immunosuppressed patients, lifelong itraconazole may be required[3]. Other authors suggest voriconazole as a possible alternative, with no resistance to treatment identified so far[11]. The rhabdomyolysis seen in this patient is a reminder that azoles inhibit cytochrome P450 3A4, and that concomitant statin therapy should be reviewed before a prolonged course is started.

This case-based review presents an elderly patient with no risk factors other than remote exposure, who presented with disseminated histoplasmosis and arthritis, highlighting the need for infectious aetiologies to be considered and thoroughly assessed in patients presenting with monoarthritis. Synovial biopsy has a preponderant role in the diagnosis of such conditions. Timely recognition is essential for effective treatment, particularly in individuals who are immunocompromised or who have concurrent rheumatic conditions and are undergoing immunosuppressive therapy.

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Tables and Figures

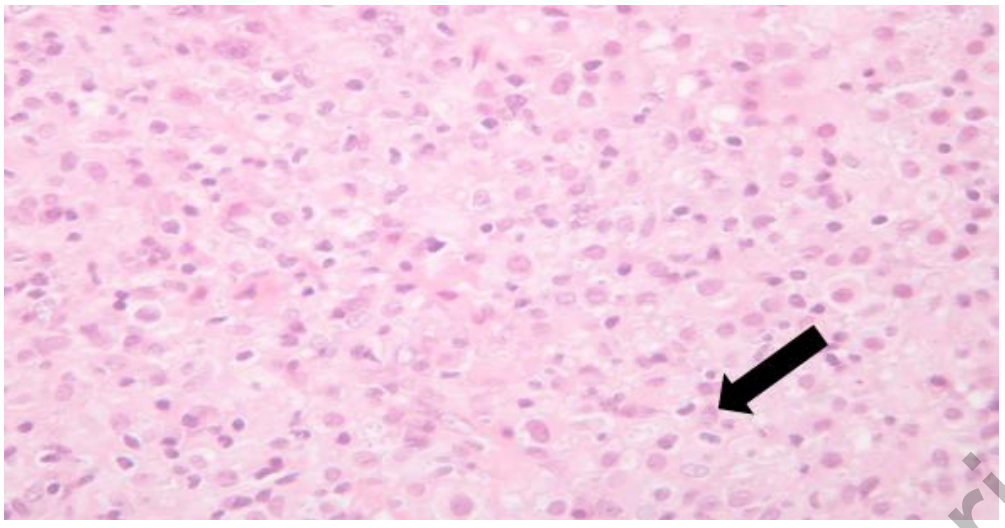


Figure 1. Synovial tissue obtained by ultrasound-guided needle biopsy of the left wrist (haematoxylin and eosin, x40). Granulation tissue containing small, uniform, oval yeasts with narrow-based budding and eccentric, acorn-like nuclei, clustered within histiocytes (arrows), morphologically compatible with *Histoplasma capsulatum*.

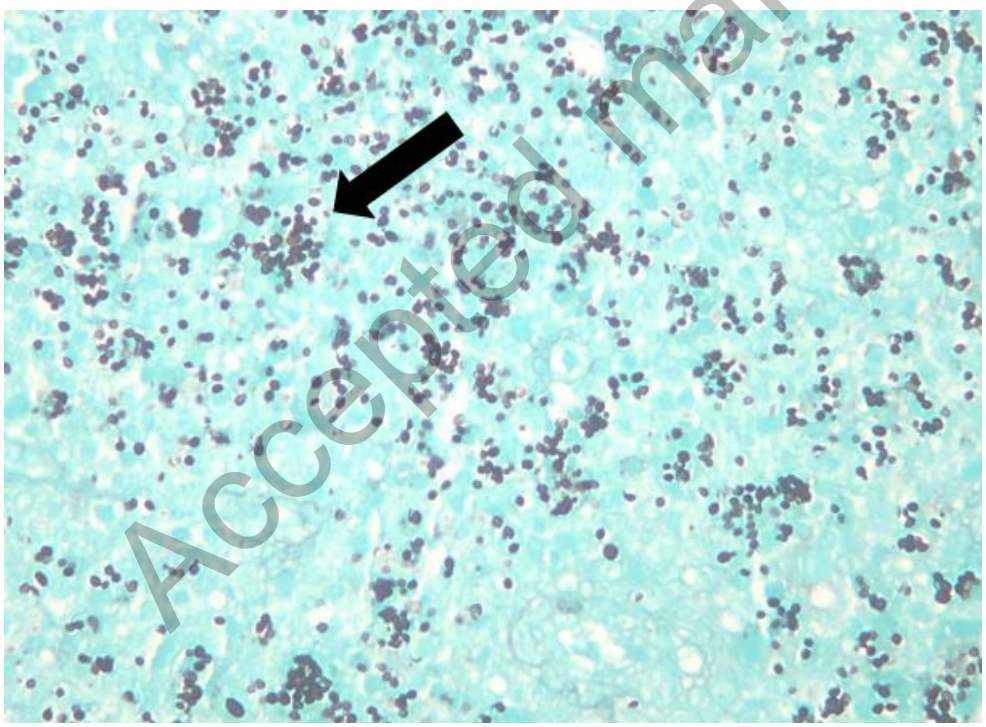


Figure 2. Same specimen (Grocott methenamine silver, x20). Argyrophilic yeast forms within histiocytes (arrows), confirming the morphology of *H. capsulatum*.

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