IDCases 25 (2021) e01243

Contents lists available at ScienceDirect

IDCases

journal homepage: www.elsevier.com/locate/idcr

Case report

Upper extremity Histoplasma capsulatum treatment with isavuconazole

Janet Le[a], David R. Perkins[a], Miguel Sierra-Hoffman[b], Mark L. Stevens[c], Daniel Binz[d], Kimberly Saddler[e], Miriams T. Castro-Lainez[f], Rafael J. Deliz[g,*]

[a] Texas A&M Detar Family Residency Program, Victoria, TX, 77901, USA
[b] Texas A&M affiliated Detar Family Medicine Program, Victoria, TX, 77901, USA
[c] Texas A&M affiliated Detar Family Medicine Program, Victoria, TX, 77901, USA
[d] Department of Orthopedic Surgery, Detar Healthcare System, Victoria, TX, 77901, USA
[e] Detar Healthcare System, Victoria, TX, 77901, USA
[f] Universidad Nacional Autónoma de Honduras, Facultad de Ciencias Médicas, Hospital Escuela Universitario, Boulevard Suyapa, Tegucigalpa, Honduras
[g] UIW School of Osteopathic Medicine, TIGMER Internal Medicine Residency Program, Laredo, TX, 78045, USA

ARTICLE INFO

Article history:
Received 17 March 2021
Received in revised form 1 August 2021
Accepted 1 August 2021

Keywords:
Histoplasma capsulatum
isavuconazole
left wrist infection

ABSTRACT

Extrapulmonary *Histoplasma capsulatum* infections in the immunocompetent population are rare and pose a diagnostic challenge. Upper extremity histoplasmosis without a primary lung infection is uncommon. It is possible to acquire it by inadvertent trauma with direct inoculation.

Our case describes an immunocompetent patient with progressive swelling with minimal pain in the wrist associated with a small puncture wound on the left dorsal forearm. The initial workup failed to identify a specific etiology. For the following six weeks, the patient experienced progressive worsening of symptoms, warranting a referral to an orthopedic

hand surgeon. Left lower extremity magnetic resonance imaging (MRI) findings were non-specific.

The surgeon performed a surgical exploration and debridement with the excision of hypertrophic tissue. Initial stains showed a granulomatous tissue but did not reveal an organism; however, a month later, mold was identified on the growth medium. The patient was initiated in isavuconazole empiric therapy. Four weeks later, a matrix assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) confirmed the diagnosis as *Histoplasma capsulatum*. The patient had clinical remission with isavuconazole used as the United States Food and Drug Administration (FDA) off label use.

Introduction

Histoplasma capsulatum is one of the few endemic mycoses that compose dimorphic fungus (Table 1). Histoplasma capsulatum is endemic in some areas of high humidity, such as river basins or caves. The usual mechanism of acquisition is through inhalation of its mold form in nature. The mold transforms into an invasive yeast in body tissues. Histoplasmosis can present without symptoms, mild self-limited pneumonia, or a disseminated fulminant syndrome.

Conventional regimens for histoplasmosis include amphotericin B or itraconazole, depending on the severity [1]. However, isavuconazole does not have an FDA-approved therapeutic indication for the treatment of histoplasmosis. Isavuconazole's introduction in clinical practice was in 2015.

Case Presentation

A 68-year-old Caucasian male presented persistent, burning pain and swelling in his left wrist for more than a month. He lives in South Texas and works in the library, where he occasionally collects bat guano in the attic as fertilizer. He was hauling firewood logs before the onset of symptoms at the end of October. He had a small puncture wound on his left posterior forearm. The pain exacerbated upon flexion or extension of his hand at the wrist level. The patient denied numbness or tingling involving the fingers of the left hand.

Past medical history is relevant for gout and ankylosing spondylitis. The patient had relief of pain with meloxicam. He was not taking steroids. The physical exam showed an 8.5 cm

* Corresponding author.
E-mail addresses: jle1@sgu.edu (J. Le), daftperk@gmail.com (D.R. Perkins), msh.xatracho@gmail.com (M. Sierra-Hoffman), markmd205@gmail.com (M.L. Stevens), binz.dan@gmail.com (D. Binz), kim.saddler@detar.com (K. Saddler), mtcastrolainez@gmail.com (M.T. Castro-Lainez), rdelizmd@uiwtx.edu (R.J. Deliz).

http://dx.doi.org/10.1016/j.idcr.2021.e01243

Table 1
Fungi Classification.

FUNGI		
Yeast	Mold	Dimorphic
Natural and invasive state	*Ubiquitous in nature*	*Ubiquitous in nature but transforms into invasive pathogenic yeast in humans.*
•*Candida* sp. •*Cryptococcus* sp.	•Aspergillosis •Mucormycosis •Others	•Blastomycosis •Chromoblastomycosis •Coccidioidomycosis •Emergomycosis •Histoplasmosis •Paracoccidioidomycosis •Sporotrichosis •Talaromycosis

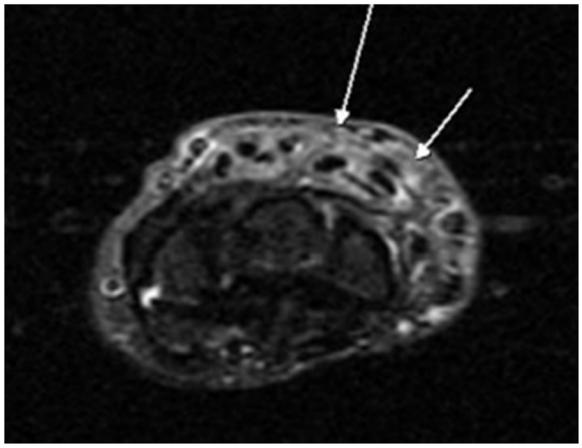

Fig. 1. MRI of Left wrist. Arrows demonstrate the fluid collection to the extensor tendons.

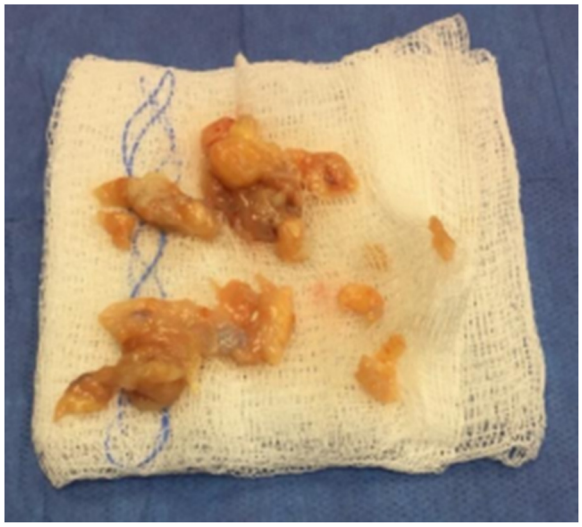

Fig. 2. The specimen consists of multiple fragments of pale-tan tissue with the appearance of synovium and an aggregate measurement estimated to be 4.5 × 4.0 x 2.0 cm.

subcutaneous soft tissue mass vertically and 3.5 cm mass horizontally in the distal left forearm and wrist.

The mass was well-circumscribed, fluctuating, and tender without erythema or warmth. The patient could not flex or extend his wrist beyond 30 degrees from the horizontal plane due to pain. Radial pulses were symmetrical and regular. The skin dermatome sensation was normal.

Fig. 3. Left wrist after extensor tenosynovectomy, irrigated, and removal of tenosynovium. Date of Surgery: February 13, 2018.

The left wrist x-ray did not demonstrate any significant abnormality. Magnetic resonance imaging (MRI) revealed dorsal soft tissue swelling of the hand and wrist with peritendinous edema surrounding the tendons on the second, third, and fourth extensor compartments seen in Fig. 1. The patient underwent tenosynovectomy of the dorsum of the hand and wrist. Findings included thickened brown tenosynovium and rice bodies seen in Fig. 2.

Histologic examination revealed multiple granulomas. There were no microorganisms in the AFB and Grocott's methenamine silver stains of the tenosynovial tissue. Initial cultures were negative, but a month later, the tenosynovial tissue grew a mold. Isavuconazole 327 mg orally was prescribed empirically for 83 days. *MALDI-TOF MS confirmed Histoplasma capsulatum* after a month. The patient had regained a full range of motion in his left wrist without swelling seven months after surgery (Figs. 3 and 4).

Discussion

The acquired immunodeficiency syndrome (AIDS) epidemic in 1981 caused an outbreak of deep fungal infections [2]. The most common opportunistic fungal infections were cryptococcal meningitis, pneumocystis pneumonia, and invasive histoplasmosis. The occurrence of endemic dimorphic fungi became more frequently associated with immunodeficiency. Iatrogenic immunosuppression such as steroids, mTor inhibitors, calcineurin inhibitors and antiproliferative drugs can also be a risk for histoplasmosis.

Understanding invasive mycosis allows us to classify and organize these organisms into an efficient algorithm (Table 1). This knowledge promotes effective therapy with antifungals.

Fig. 4. 1-month post-op at Infectious disease visit.

Dimorphic fungi can "grow in the host as yeast-like forms but grow at room temperature in vitro as molds."

Except for the *Candida* sp., most fungal organisms do not proliferate, even in the appropriate media, and utilizing proper techniques. Therefore, pathology and histological stains surged as an alternative diagnostic method. Since 1981, histoplasmosis was one of the organisms that benefited from new scientific developments. The introduction of improved therapies and diagnostic methods for the immunosuppressed population seems promising. Dr. Wheat and his colleagues developed a new diagnostic method by antigen detection. This method had limitations but was able to identify the sickest patients. Histoplasma urinary antigen test can detect a piece of the histoplasma capsule in the urine which can be used to monitor the treatment response. [1] The matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) is able to detect histoplasmosis without growing it in culture and can be identified within minutes without prior knowledge of the type of organism. The disadvantages for MALDI-TOF MS is that it is not readily available everywhere, databases are exclusive to certain companies and it is limited to the user's technique and instrument's condition to correctly identify the organism [3].

Decades ago the first antifungals were azoles and polyenes. Ketoconazole is no longer used as an antifungal since 2019 due to its risk for adrenal insufficiency, hepatotoxicity, and drug interactions. Amphotericin B was the first compound of the polyene class active against most dimorphic fungi, encompassing histoplasmosis.

The azol class has been the focus of innovation in drug therapy. [1] One example, FDA approved isavuconazole (ISA) in 2015 for invasive aspergillosis and mucormycosis. ISA is the product of hydrolysis of isavuconazonium sulfate. The spectrum of activity resembles that of posaconazole, with activity against *Cryptococcus, Histoplasma, Blastomyces, and Coccidiodes* [4]. The reported minimum inhibitory concentration (MIC) for ISA is 0.12 ug/ml to 2 ug/ml for *Histoplasma capsulatum.* Contrary to posaconazole, ISA has high water solubility. The cyclodextrin vehicle is responsible for the nephrotoxicity of posaconazole [5].

The oral bioavailability of ISA is close to 98%, offering excellent intravenous to oral conversion. ISA also offers an extended terminal half-life of 80 to 130 hours and a large volume of distribution of 450 L [4]. At the moment of this report, we were not aware of clinical trials comparing the efficacy of newer azole agents for histoplasmosis. At this time, itraconazole is the azole of choice for histoplasmosis [6]. In vitro evaluation of MICs found ISA to have a higher barrier to resistance than voriconazole, a structurally similar agent [6]. Despite the new innovations in the azole class, the treatment paradigm has not changed due to lack of randomized controlled studies for histoplasmosis as described in 2007 IDSA guidelines [1].

Histoplasmosis can evolve into a severe systemic fungal disease caused by the dimorphic fungus *Histoplasma capsulatum*. It exists as yeast in tissues at 37 ° C and as a mold in its native environment. The organism grows in soil rich in bat droppings, typically found in river basins, high humidity soil, old abandoned buildings, and caves.

Histoplasma capsulatum is an intracellular pathogen that can remain in a quiescent state for years and only rarely reactivates to produce clinical disease in the immunocompetent population. Reactivation years after initial exposure makes the diagnosis a significant challenge.

Without proper diagnosis, the individual in the case reported could have suffered from a re-emergence of infection with considerable morbidity. The clinical syndrome was suggestive of noninfectious tenosynovitis involving the wrist and the forearm. Surgical exploration, debridement, and extensive workup were required to alleviate the symptoms and identify the underlying cause.

Empirical antifungal therapy was initially chosen based on suspicion of invasive mold infection due to their close relationship to trauma-induced infections. Later in the course of the treatment, MALDI-TOF MS revealed the diagnosis as *Histoplasma capsulatum*.

After confirmation of the causative organism, retrospective review of history, the patient confirmed that he had a superficial abrasion from hauling the firewood. The source of the histoplasmosis was the exposure of bat guano collection used as a fertilizer.

Granuloma formation, as seen in Fig. 2, played a critical role in our case. Granulomas were considered a form of host protection and, overall, benefit in eradicating foreign microorganisms. Recent concepts suggest that granulomas can serve as a potential threat for re-emergence from the latent phase as the host's immunity weakens over time [7]. In our case, surgical debridement and rapidly advanced technology, like MALDI-TOF, made diagnoses possible. Antifungal therapy with isavuconazole resulted in complete remission.

RESULTS

We found twelve similar cases after a review of the literature. Nine of them were immunosuppressed, and three immunocompetent (Table 2). Outdoor activity or occupation was the most common factor among the latter group. The majority of

patients were men, and the most common method of isolation was by fungal culture. The most common treatment used was amphotericin B, and all cases had a significant delay in the final diagnosis from the initial clinical presentation ranging from a few weeks to ten years.

Our case was the only one isolated with MALDI-TOF MS and treated with isavuconazole. None of the cases required amputation, but 8 of them reoccurred and required additional antifungal treatments.

CONCLUSION

Upper extremity histoplasmosis without the presence of a primary pulmonary source is rare. Immunosuppression as a risk factor was present in 69% of reviewed cases. Among the

Table 2
Cases of Histoplasmosis in Extremities.

First Author	Year	Age /Sex	Comorbidities	Location	Immunosuppressed	Presenting Symptoms	Trauma	Occupation	Recurrence	Treatment	Diagnostic method	Outcome: Survival and Bodily part outcome
D. S. Strayer [8]	1981	43/F	None	Missouri	No	Bilateral Hand paresthesia for 7 years	No	school teacher	Yes, right wrist pain in 1 month	Steroid injection, Surgery debridement, Amphotericin B (no recurrence after receiving 1 gram)	Fungal Culture	Survived, small comminuted fracture of the distal radius
G. Randall [9]	1982	43/F	Carcinoma of the right breast	NA	Yes, Chemotherapy: 5-fluorouracil, cyclophosphamide, methotrexate	Tingling sensation in the thumb, index, and middle fingers. Oral lesions	No	NA	Yes, white plaque on the tongue in 2 months after surgery	Cortisone injection, Surgery: carpal tunnel release and debridement, Amphotericin B (no recurrence after receiving 1 gram for about 7 weeks)	Silver staining	Survived, oral lesions resolved.
J. R. Mascola [10]	1991	28/ M	None	Kentucky/ Pennsylvania	No	Left-sided carpal tunnel syndrome for 18 months	No	flight mechanic	Yes, 3 left-sided CTS in 18 months	Nonsteroidal anti-inflammatory agents, steroid injection, surgical debridement, ketoconazole 400 mg daily for 6 months.	Fungal Culture	Survived, full function of left hand
S. B Care [11]	1998	35/ M	None	NA	No	Night awakening, numbness, and tingling in radial digits for 1 month	No	landscaper	Yes, 10 years later pain in the wrist	Surgical debridement, Carpal tunnel release, ketoconazole for 4 months, repeat surgery debridement, itraconazole for 6 months	Histoplasmin complement fixation testing demonstrated mycelial and yeast phase antibody titers of 1:8 and 1:16, respectively. Culture of the proliferative tenosynovial tissue grew *Histoplasma capsulatum*, and skin testing demonstrated a positive histoplasmin reac-tion.	Survived, full range of motion, no pain or tender-ness, and no swelling or soft tissue thickening. X- rays revealed no evidence of new osteolysis and apparent healing of the capitate cyst.
G. D. Smith [12]	2005	43/ M	HIV, Hep C	NA	Yes, CD4 count 20 cells/ml	Right wrist swelling for several weeks (was a mass)	No	NA	Yes, 6 weeks after aspiration, 6 months after 2nd aspiration.	Aspiration, then he was started on Amphotericin B (unable to tolerate), itraconazole-he was not compliant with treatment	Fungal Culture	Deceased due to progression of HIV
G. D. Smith [12]	2005	70/ M	Insulin dependent Diabetic, Asthma	NA	No, took oral steroids intermittently	Left wrist swelling for several months, numbness in the middle, ring and little finger and weakness of the left hand	No	retired	Yes had pulmonary histoplasmosis 9 years ago	Cortisone injection, Surgical debridement, itraconazole (he stopped it after several days due to rash)	PAS and Grocott stains demonstrated oval-shaped yeasts, some budding, consistent with histoplas-ma. Cultures grew *Histoplasma capsulatum* var capsula-tum.	Survived, The wound subsequently required evacuation of a haematoma and the surgical site became secondarily infected, was slow to heal, and required flap coverage.
E. Cucurull [13]	2005	42/F	Systemic lupus erythematosus	New Orleans, Lousiana	Yes, corticosteroids, hydroxychloroquine, and azathioprine	Pain and swelling in the left hand	No	works at an immunology laboratory	No	Valdecoxib, Triamcinolone injection, itraconazole 200 mg daily x 12 months	Fungal Culture	Survived, repeat MRI of the hand showed marked improvement of the edematous signal
S.M. Filali [14]	2006	43/F	Rheumatoid Arthritis, Scleroderma, non-Hodgkin's malignant	NA	Yes, chemotherapy, radiation, prednisone, penicillamine	Swelling in hands and knees	No	NA	No	Aspiration, Amphotericin B (no effect after 6 months), itraconazole (improved after 1 year)	Periodic Acid Schiff	Survived, the peroneus brevis and tibialis anterior tendons were normal and the peroneus

			lymphoma of the parotid gland									longus tendon was improved.
S.Y. Lim [15]	2013	32/F	Systemic lupus erythematosus	NA	Yes, mycophenolate mofetil, prednisone	Redness and swelling and pain in right wrist and forearm for 3 days	No	NA	Yes (7 days after only piperacillin/ tazobactam), and again after pip/tazo/vanc in 7 days, 3rd time was about 1 month later	Piperacillin/Tazobactam, Surgery with right carpal tunnel release, restarted on Piperacillin/ Tazobactam, Vancomycin, and 3rd time surgery on the left wrist with carpal tunnel release, Piperacillin/Tazobactam, Vancomycin, Itraconazole 200 mg BID for 12 months	Fungal culture	Survived, clinically improved
M.A. Vitale [16]	2015	48/F	Sjorgen's syndrome with interstitial lung disease	NA	Yes, mycophenolate mofetil, oral prednisone	Progressive numbness in right hand for 5 months	No	legal transcriptionist	No	Prednisone, nighttime splinting, Corticosteroid Injection, carpal tunnel release, Cefazolin, liposomal amphotericin B, Itraconazole for 1 year	Fungal culture and a serum Histoplasma antibody screen	Survived, At 6 months postoperatively, the patient was asymptomatic with a well-healed surgical wound and no swelling
R.J. Woods [17]	2018	50/F	Takayasu arteritis, Ulcerative Colitis	NA	Yes, infliximab, methotrexate and low dose prednisone	Pain and swelling in right hand and wrist for 4weeks	no	NA	no	Glucocorticoid injection, itraconazole, infliximab	Fungal culture	Survived
J. Compton [18]	2018	86/F	Rheumatoid Arthritis	NA	Yes, methotrexate	Shoulder pain, fevers, and malaise	yes-fall	NA	Yes, 2 months later with fever and worsening right shoulder pain and swelling	Surgical debridement, Vancomycin, Ceftriaxone, Liposomal Amphotericin B 3 mg/kg for 7 days, itraconazole 200 mg BID for 2 onths, Repeat irrigation and debridement, Cement Beads with vancomycin, amphotericin B, itraconazole for another 11 months. methotrexate was held indefinitely	fungal cultures, DNA probe. Histoplasma antigen was elevated at 1.85 ng/ml (normal <0.4 ng/ml) and urine antigen level was elevated at 1.00 ng/ml (normal <0.4 ng/ml).	Survived, full function of right shoulder
Our case	2019	68/ M	Ankylosing Spondylitis	Texas	No	Left wrist pain and swelling for more than a month	Yes- small puncture wound from possibly hauling firewood	editor	No	Nonsteroidal anti-inflammatory agents, Surgery debridement, isavuconazole 327 mg daily x 83 days	Fungal Culture and MALDI TOF	Survived, Full range of motion in left wrist

immunocompetent group, outdoor activity or inadvertent trauma seemed to be a common factor. This disease process is difficult to confirm, as culture base confirmation requires obtaining quality cultures, appropriate media for growth, and a high degree of clinical suspicion.

Although the initiation of isavuconazole was in anticipation of an invasive mold, once histoplasmosis was confirmed, the patient had already experienced significant improvement, and in our opinion, warranted continued treatment with isavuconazole. The patient completed three months of treatment without recurrence after two years of follow-up. In this case, MALDI-TOF provided a diagnosis. Isavuconazole and MALDI TOF are considered new therapeutic and diagnostic tools that would benefit future studies in cases like the one presented here.

Author Statement

We thank the reviewer of *IDCases* for their careful review of the manuscript and the opportunity to improve it.

Funding

None

Ethical approval

Not a clinical study of human subjects

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-In-Chief of this journal on request.

Authors Contributions

All authors wrote and edited the paper.

Declaration of Competing Interest

There are no competing interests by the authors related to this manuscript. Human Subjects Declaration

The patient was briefed and signed an informed consent form for publication.

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