



Epididymo-orchitis caused by *Histoplasma capsulatum*

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ABSTRACT

A 66-year-old man presented with asymptomatic right testicular swelling. He was known to be infected with HIV and was non-adherent to treatment. He was recently treated for nasal leishmaniasis. Surgical drainage was performed and eventually, an orchiectomy was required. A post-mortem diagnosis was made of disseminated histoplasmosis. Testicular infection due to *H. capsulatum* is rare, with only a few cases being reported. Here we present a case of testicular histoplasmosis, followed by a literature review.

1. Introduction

Histoplasma capsulatum is a dimorphic and endemic fungus. Humans get in contact with *Histoplasma* by inhaling fungal conidia from bird droppings, as well as exposure to bat guano in caves, attics, and hollow trees. Most cases of histoplasmosis remain asymptomatic without clinical manifestations, with only less than 1% of infected individuals manifesting overt disease [1]. The lungs are usually affected in acute histoplasmosis most commonly occurring as a self-limited disease. Chronic cavitary pulmonary histoplasmosis, granulomatous mediastinitis, and mediastinal fibrosis are other clinical forms of histoplasmosis, although less common when compared to acute self-limited pulmonary histoplasmosis [1–3]. More importantly, histoplasmosis can disseminate in immunosuppressed patients, particularly those with defective cell-mediated immunity such as individuals with AIDS, transplant recipients, patients on corticosteroids, and those with haematological malignancies and other causes of immunosuppression [4–6]. Genitourinary histoplasmosis, a form of disseminated infection is rare with only a few cases reported in the literature. In this article, we present a case of epididymo-orchitis caused by *H. capsulatum* in an immunosuppressed patient aiming to alert physicians about the importance of this clinical presentation.

2. Case presentation

A 66-year-old white man was transferred to our service due to

intense abdominal pain (day 0). He presented with acute renal failure (urea 178 mg/dL, serum creatinin 7.92 mg/dL) due to the erroneous receipt of a high dose (estimated at 3 mg/kg) of amphotericin B deoxycholate for nasal leishmaniasis (diagnosis was suggested by histopathology). He had been previously diagnosed with HIV infection for more than a decade and he was non-adherent to the treatment. His past medical history was marked gastroesophageal reflux disease. He was a former smoker. His most recent HIV viral load was 92,494 copies/ml (4.96 log), CD4 count was 5 cells/mm³, and the CD4/CD8 ratio was 0.08. At the time he was admitted to the hospital, the patient was pancytopenic: haemoglobin was 6.0 g/dL, leucocytes 1,620 cells/μL, lymphocytes 142 cells/μL, and platelets 64,000 cells/μL. Despite being afebrile, he was emaciated and had a severe nasal lesion, with an ulcer in the hard palate, and an extensive necrotic lesion involving left nasal ala and septum, and dysphonic. A chest computed tomography scan revealed consolidative lesions in both lungs, and small bilateral pleural effusions, no treatment was started then for the lungs lesions. Haemodialysis was required during hospitalization due to worsening renal failure after receiving treatment for nasal leishmaniasis. During hospitalization, he received 16 days of amphotericin B treatment. In the first 3 days of treatment in the hospital, he unfortunately received 5 mg/kg/day of d-AmB (as for amphotericin B lipid complex), which was then switched to L-AmB 4 mg/kg/day for the rest of the course until suspension on (day +16).

He remained stable until an episode of acute respiratory distress related to pulmonary sepsis by *P. aeruginosa* right after finishing his

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Table 1
Previously reported cases of epididymo-orchitis caused by *Histoplasma capsulatum*.

Reference	Country	Age	Clinical manifestation	Underlying condition	Pathology	culture/serology	Treatment	Outcome
Schuster et al., 2000 [12]	USA	70	Left testicular swelling for 2 weeks	Not informed	3.5 x 2.5 x 4.5 cm mass, caseating granulomas in microscopy, GMS stain positive for budding yeast suggestive of <i>Histoplasma</i>	Negative culture from testicular tissue; serology 1:8 by complement fixation (CF) (positive)	Left radical orchiectomy followed by oral Itraconazole 200 mg daily for 6 months	Improved
Kauffman et al., 1980 [13]	USA	42	Right scrotal swelling for 2 weeks; fever, chills, pleuritic chest pain, nonproductive cough	Not informed	Epididymis replaced by a granulomatous mass showing caseating granulomas containing budding yeasts	Serology by CF 1:32	Surgical treatment	Improved
Kauffman et al., 1980 [13]	USA	27	Left scrotal swelling for several weeks	Not informed	Epididymis filled with purulent material; caseating granulomas on GMS staining, testicle not involved	Serology by CF 1:16. Cultures of urine and abscess material negative	Incision and drainage of abscess	Lost from follow-up
Monroe et al., 1974 [14]	USA	69	Swollen left testis	Not informed	Left testicular abscess and granuloma. GMS stain of testicular tissue positive for <i>Histoplasma</i>	Postmortem adrenal culture positive for <i>Histoplasma</i>	Left radical orchiectomy	Deceased
Tichindelean et al., 2009 [15]	USA	46	Scrotal swelling and pain for 9 months, then weight loss, fatigue, fever	AIDS	Testicle 6.5 x 4.5 x 3.2 cm, epididymis 3 x 1.8 x 1 cm, GMS stain of testes showed granuloma with intracellular yeasts	Urine histoplasma antigen 9.9 units by EIA (positive), BAL culture grew <i>H. capsulatum</i>	Left radical orchiectomy, intravenous amphotericin B 0.7 mg/kg for 2 weeks + itraconazole 200 mg twice daily	Improved
Randhawa et al., 1995 [16]	India	55	Intermittent low-grade fever, cough with expectoration and weight-loss. Testicular lump for 2 years.	Pulmonary tuberculosis	Epididymitis, non-caseating granulomas, typical budding yeast forms in giant cells or interstitially.	<i>H. capsulatum</i> isolated from semen culture. Negative serology	Epidymectomy and 1.5 yrs of amphotericin B therapy	Improved
Boone et al., 1969 [17]	USA	50	Right lower quadrant pain; testicular pain and swelling associated with some haematuria, fever, anorexia and weight-loss.	History of mild essential HTN	Biopsy from epididymis showed intercellular yeast forms compatible with <i>H. capsulatum</i>	sputum and urine culture yielded <i>H. capsulatum</i>	Amphotericin B treatment for 30 months	Improved
Baig et al., 2011 [18]	India	37	Scrotal pain and swelling; high-grade fever of 1 week duration, and diarrhoea	Renal transplant recipient	Histopathological examination of epididymal and prostate tissues showed the presence of histoplasmosis	Pus culture from retrotrigonal abscess was positive for <i>H. capsulatum</i> . Urine antigen - negative	Treated with itraconazole for 6 months	Deceased due to unknown cause of massive upper genitourinary bleeding 6 months later
Kahn et al.*, 1992 (presented at VIII international conference on aids/iii std world congress, amsterdam, july 19–24, 1992; 8: 93) [11]	USA	35	Swelling of left testis and left cheek ulcer	Not informed	Biopsy specimen from orchiectomy positive for <i>H. capsulatum</i>	Not informed	Not informed	Not informed
Plazola-Hernández et al., 2020 [19]	Mexico	22	Solid adherent mass in posterosuperior region of the left testis	Not informed	5 x 5 x 2.5 cm left testis and a 3.5 x 2 x 2 cm nodule, with a dark brown, irregular surface of rubbery consistency. Histopathology: fungal structures suggestive of <i>H. capsulatum</i>	Not performed	Left testis simple orchiectomy	Not informed
Botero-García et al., 2017 [20]	Colombia	38	Left testicular pain, swelling, erythema and fever for 1 month	Previously healthy	histopathological analysis: Hematoxylin & eosin and PAS staining showed necrotizing granulomatous epididymo-orchitis with small (2–4 µm) oval buds	Positive sperm culture for <i>H. capsulatum</i> ; positive molecular characterization	Left orchiectomy +200 mg itraconazole every 12 h for 6 months	Improved

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Table 1 (continued)

Reference	Country	Age	Clinical manifestation	Underlying condition	Pathology	culture/serology	Treatment	Outcome
Sanha et al., 2022 [present paper]	Brazil	66	Enlarged and hardened right testis	AIDS	Histopathological examination of testicular liquid under GMS stain: Presence of budding yeasts compatible with <i>Histoplasma</i> sp.	Not performed	Right orchiectomy	Deceased

Legend: BAL, Bronchoalveolar Lavage; CF, Complement Fixation; EIA; Enzyme immunoassay; GMS, Grocott-Gomori methenamine silver; PAS, Periodic Acid-Schiff.

treatment for leishmaniasis, requiring admission to the intensive care unit (ICU) (day + 16). This was associated with melena and severe blood dyscrasia. He had only partial response to his nasal lesion following treatment. At the ICU, a testicular mass was discovered, with local swelling and hyperemia, by ultrasound it was possible to diagnose on the right scrotal testicle, a multiseptate fluid collection, with thick walls measuring 3.2×2.5 cm, in contact with the epididymis on the same side. A diagnostic orchiectomy was required and showed a swollen testicle, with areas of necrosis and fluid accumulation. The patient had an unfavourable clinical outcome a few days after being admitted to the ICU and eventually died (on day +25). Genitourinary histoplasmosis was lately diagnosed by histology and culture of testicular sample analysis (day +27), but unfortunately, this was only done post-mortem.

3. Discussion

Here we report a tragic case of a patient who died of disseminated histoplasmosis due to lack of awareness of this condition. Histoplasmosis has a worldwide distribution with higher frequency in the North America, Central America and Latin America regions. Mississippi and Ohio valley Rivers are the endemic region in the United State of America [7]. In Brazil, histoplasmosis is endemic in many regions of the country, particularly affecting individuals with HIV infection [8]. The presentation may range from asymptomatic, self-limited illness to severe disseminated disease. In immunocompetent individuals, most cases remain asymptomatic and only less than 1% will present clinically [1] – however, in immunosuppressed patients, disseminated disease is a common form of presentation. Although less common if compared to other forms of histoplasmosis, disseminated infections have an increased frequency in patients with defected cellular immunity [4] like the patient presented in this report.

The genitourinary tract is uncommonly involved in disseminated histoplasmosis. Testicular involvement is infrequent, however, the incidence of the genitourinary diseases might be underdiagnosed due to some cases may remain asymptomatic and given the fact that this system is less frequently to be examined - as occurred for our patient, only examined in the ICU due to absence of symptoms [9]. Up to this date there are few cases of orchitis and/or epididymitis caused by *H. capsulatum* reported in the literature. We summarize the main clinical presentation, underlying conditions, diagnostic method, and management of the cases reported [Table 1]. Seven patients were reported from the USA, two from India, one from Mexico, and the other one from Colombia. The age ranged from 22 to 70 years-old, in six of these reports the underlying conditions was not provided, two patients were immunosuppressed (AIDS and renal transplant recipient), one had pulmonary tuberculosis, one had mild hypertension and one was previously healthy. In all cases, *H. capsulatum* was confirmed by the presence of budding yeast in histopathological examination, culture and serology were also positive in most of the cases. Testicular involvement was unilateral in all the cases, and the most common clinical manifestation was testicular swelling and pain that ranged from 2 weeks to several months of evolution. Almost all the reported cases were treated surgically, orchiectomy was the most common procedure, and only one case was treated clinically with itraconazole for 6 months.

Testicular histoplasmosis occurs in the context of disseminated

disease. Even though not properly investigated, we suspect that nasal lesions presented in our patient were actually due to histoplasmosis, and not leishmaniasis. The supposed diagnosis of mucocutaneous leishmaniasis was a result of a nasal biopsy performed in another service before admission to our institution. Moreover, investigations for *H. capsulatum* through antigen detection, serology and/or culture were not performed in order to exclude histoplasmosis. Amastigotes and yeast structures can be easily mistaken when using Giemsa stain therefore the distinction between histoplasmosis and leishmaniasis can be challenging especially in the context of endemic areas for both diseases, and it may require considerable expertise to make the proper diagnosis [15]. It seems evident that the testicular lesion eventually discovered in ICU might occurred concomitantly or followed the nasal lesion which was probably related to histoplasmosis. The diagnosis of disseminated histoplasmosis may be challenging and require a high index of suspicion, especially in high-risk groups living in endemic areas. Recognizing the common presentation of the disease and familiarity with appropriate diagnostic tests will help in early suspicion and diagnosis. Moreover, pauses in antifungal therapy due to drug toxicity may have predispose to disseminated infection and death, as seen in this patient.

Epididymo-orchitis caused by histoplasmosis is a rare entity, nevertheless, needs to be always considered in AIDS patients. Presentation of the testicular histoplasmosis can mimic testicular tuberculosis (TB) and other granulomatous diseases, either case must be considered a differential diagnosis. *Randhawa* et al. [16] describe a patient who was first misdiagnosed as testicular TB and later the workup for histoplasmosis confirmed *H. capsulatum* in microscopic examination and the culture. Testicular TB and histoplasmosis may present with granulomatous inflammation of the testis, although histoplasmosis tends to present unilaterally like all the reported cases. Testicular TB on the other hand can be unilateral and/or bilateral. In a series of 47 patients histologically diagnosed with epididymal TB, 21.3% of patients presented bilateral disease whereas 78.7% were unilateral [10]. Of note, patients with granulomatous testicular lesions should raise suspicion of histoplasmosis, particularly in endemic areas and individuals with defective cell-mediated immunity, appropriate workup should be conducted to establish the proper diagnosis. Patients under investigation for testicular TB should also undergo histoplasmosis investigation, especially in endemic areas for both diseases due to similarities in clinical presentation.

Our patient did not complain of testicular pain or swelling during the initial time of hospitalization which differs from the usual presentation seen in most of the previously reported cases. Although immunosuppressed and living in an endemic region, the lack of the common clinical presentation of testicular histoplasmosis makes the suspicion and diagnosis of our case more difficult. However the fact of living in an endemic area and being an AIDS patient should have raised the suspicion for disseminated histoplasmosis. The diagnosis of histoplasmosis was only confirmed after the patient's death. Testicular histoplasmosis is a rare entity and its diagnosis can be challenging, however high risk patients living in endemic regions should be questioned and given special attention for the possibility of disseminated diseases.

Ethical form

We obtained written and signed consent to publish the case report from the patient legal representative/guardian.

Declaration of competing interest

Dr Pasqualotto has received research grants, speaker honoraria or consulted on behalf of Gilead, Teva, United Medical, Pfizer, IMMY, MSD, and Astellas. Other authors: none to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.mmcr.2022.05.006>.

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