



Published in final edited form as:

Transpl Infect Dis. 2013 April ; 15(2): E64–E69. doi:10.1111/tid.12059.

Cutaneous presentation of progressive disseminated histoplasmosis nine years after renal transplantation

Vera M. Rosado-Odom¹, Jacques Daoud^{1,**}, Raymond Johnson¹, Stephen D. Allen¹, Shawn R. Lockhart², Naureen Iqbal², Wun-Ju Shieh³, Sherif Zaki³, Asif Sharfuddin¹

¹Indiana University School of Medicine, Indianapolis, IN

²Mycotic Diseases Branch, Centers for Disease Control and Prevention

³Infectious Disease Pathology Branch, Centers for Disease Control and Prevention

Abstract

Initial presentation of invasive fungal infections such as histoplasmosis can include non-specific clinical manifestations, especially in immunocompromised patients. A high index of suspicion is required to identify atypical manifestations of these diseases, which carry a high risk of mortality, if the diagnosis is delayed or missed. We describe a case of a kidney transplant recipient with cutaneous lesions as initial manifestation of progressive disseminated histoplasmosis where a skin biopsy was crucial to an early diagnosis.

Initial presentation of invasive fungal infections (IFIs) such as histoplasmosis can include non-specific clinical manifestations, especially in immunocompromised patients. A high index of suspicion is required to identify atypical manifestations of these diseases, which carry a high risk of mortality, if the diagnosis is delayed or missed. We describe a case of a kidney transplant recipient with cutaneous lesions as initial manifestation of progressive disseminated histoplasmosis where a skin biopsy was crucial to an early diagnosis.

Case report

A 42-year-old Caucasian woman from Ohio was evaluated for fevers and a nodular deep dermal skin rash, 9 years after deceased-donor kidney transplantation. Two weeks before presentation, she noticed a tender, warm, and erythematous lesion on the extensor surface of her left thigh, associated with night sweats and a mild dry cough. Additional similar lesions appeared surrounding the original nodule, as well as in the posterior aspects of the knees, right thigh, and right arm.

The patient denied recent travel outside the Ohio area, any new sexual partners, or contact with animals or sick individuals. Of interest, the farm fields adjacent to her property are fertilized with chicken manure from a nearby commercial poultry farm.

Author contributions: V.M.R.-O. and J.D.: Concept, case data collection, and drafting article. R.J.: Concept, case data analysis, and critical revision of article. S.D.A.: Critical revision of article and case histological analysis. S.R.L., N.I., W.J.S., and S.Z.: PCR amplification and identification of organism. A.A.S.: Concept, drafting article, and critical revision.

**First two authors contributed equally to this article.

Her past medical history was remarkable for congenital dysmorphic kidneys and bronchial asthma. Her transplantation induction therapy included anti-thymocyte globulin, and her post-transplant course was significant for 2 mild rejection episodes, the most recent occurring 7 years earlier. Her chronic immunosuppression included mycophenolate mofetil 1000 mg by mouth twice daily (PO BID), cyclosporine 50 mg PO BID (trough level maintained between 50 and 75 ng/mL), and prednisone 2.5 mg PO daily. The initial physical exam revealed a fever (38.7°C), clear breath sounds, a soft ejection murmur along the left sternal border, mild tenderness to deep palpation in the right lower quadrant over the transplanted kidney, and multiple erythematous, non-coalescing, flat macules in the antero-medial aspect of the left thigh, which were nodular and tender to palpation, without epidermal breakdown. Similar, but individual lesions were noted on the postero-medial left thigh, anterior right thigh, posterior aspect of both knees, and extensor surface of the right forearm (Fig. 1A). No lesions were seen on the trunk, back, face, or oral mucosa.

Initial laboratory evaluation revealed pre-renal acute kidney injury (AKI) with a serum creatinine (SCR) of 2.20 mg/dL, higher than her baseline of 1.4 mg/dL, normal liver function tests, and a normal plain chest radiograph. The result of an ImmuKnow[®] assay (Cylex, Inc., Columbia, Maryland, USA) performed after lowering the dose of her immunosuppressants was 188 ng/mL (suggested normal range 226–524 ng/mL adenosine triphosphate). A skin punch biopsy revealed Gomori-methenamine silver stain-positive yeast forms in the deep dermis with a diffuse histiocytic infiltrate and focal granuloma formation, consistent with a deep-seated fungal infection (Fig. 1B). The initial antifungal therapy administered was voriconazole 6 mg/kg intravenously every 12 h (limited to 2 doses because of decreased glomerular filtration rate) owing to concern over possible worsening of AKI with liposomal amphotericin B (LAmB) therapy. The patient subsequently developed dyspnea at rest with oxygen saturation of 88% at room air, requiring oxygen supplementation via nasal cannula and bronchodilators. High-resolution computed tomography scan of the chest revealed numerous subcentimeter mediastinal nodes as well as a supraclavicular node. Urinary *Histoplasma* antigen (MVista[®] *Histoplasma* Quantitative EIA, MiraVista Diagnostics, Indianapolis, Indiana, USA) was positive (result: 4.15 ng/mL; positive, moderate). Antifungal therapy was changed to itraconazole 200 mg oral suspension 3 times per day for 6 doses, continued with 200 mg of oral suspension twice daily. A repeat ImmuKnow[®] assay performed 6 days after initial testing showed an increased value of 389 ng/mL. At time of discharge, the patient's kidney allograft function had returned to baseline after volume repletion and holding cyclosporine for several days, and control of the *Histoplasma* infection was demonstrated by resolution of fevers and improvement in the skin lesions.

Before discharge, the mycophenolate mofetil dose was increased back to 500 mg PO BID and the cyclosporine continued at a reduced dose of 25 mg PO BID, along with 2.5 mg PO of prednisone. Three weeks after discharge from the hospital, the patient was re-hospitalized with AKI, SCR 2.8, including biopsy findings of acute cellular rejection (Banff IB) and acute tubular necrosis. Given the recent diagnosis of disseminated histoplasmosis, no steroid pulse therapy or antibody therapy was administered. Her SCR improved to 2.2 mg/dL at time of discharge, and 1.9 mg/dL 1 month later. The itraconazole level was 2.3 and

maintained at that range. The *Histoplasma* antigenuria, 1 month into itraconazole therapy, had decreased to 2.12 ng/mL from an initial value of 4.15 ng/mL.

After 3 months of itraconazole therapy, all cutaneous lesions had disappeared, her cough had resolved, and follow-up imaging of the chest revealed resolution of lymphadenopathy. At 6 months, the urine *Histoplasma* antigen had dropped to detectable <0.6 ng/mL (weak positive). Itraconazole was discontinued after 12 months of therapy when the urine antigen was no longer detectable. The patient has not had a recurrence 9 months after discontinuation of itraconazole; unfortunately her SCR slowly increased with chronic allograft nephropathy to 3.36 mg/dL.

In collaboration with the Mycotic Diseases Branch of the Centers for Disease Control and Prevention, the remaining skin paraffin block was sectioned for immunohistochemical staining, and its DNA extracted for diagnostic polymerase chain reaction (PCR) amplification. An immunohistochemical assay was performed using a polymer-based colorimetric indirect immunoperoxidase method as previously described 1. The primary antibody used in the assay was a rabbit polyclonal anti-*Histoplasma capsulatum* antibody. The antibody/polymer conjugate was visualized by applying UltraVision LP system with naphthol phosphate substrate (Thermo Scientific/Lab Vision, Fremont, California, USA) to tissue sections. Appropriate positive and negative controls were run in parallel. Negative controls consisted of sequential tissue sections incubated with normal rabbit serum. Yeast-like forms, stained with anti-*H. capsulatum* antibody, were present in areas of granulomatous inflammation (Fig. 1C). Amplification of fungal DNA from paraffin-embedded formalin-fixed tissue was performed as previously described 2. Primers *ArfF* and *ArfR*, which amplify a short region of the *H. capsulatum* ADP-ribosylation factor 3, 4, were used for amplification. A single 246 base pair product was amplified and sequenced in both directions using the amplification primers. As expected, a BLAST search using GenBank gave a 100% match to multiple isolates of *H. capsulatum* including ATCC strain 10886 (GenBank #AF072344). There were no acceptable matches to other species, confirming *H. capsulatum* as the causative agent.

Discussion

Histoplasma capsulatum is a ubiquitous dimorphic fungus endemic to the midwestern United States, Latin America, Africa, India, and Asia. In immunocompetent patients, inhalation of fungal conidia can result in acute pulmonary histoplasmosis 5. The infection can range from subclinical to a mild pulmonary infection, depending on both inoculum size and immune status of the human host. Most patients will develop dissemination via the lymphohematogenous route, but usually only those unable to mount an effective cell-mediated immune response to the organism will develop disseminated infection. Progressive disseminated histoplasmosis is diagnosed by the presence of radiographic, histologic, or microbiological evidence of involvement of at least 2 organs (liver, spleen, bone marrow, lymph nodes, gastrointestinal tract, kidneys, central nervous system, and/or skin), or a positive blood or bone marrow culture or smear, and it is known to be potentially fatal if untreated 6. Although the diagnosis of disseminated disease requires demonstration of *Histoplasma* organisms in culture or a positive result in a urine or serum antigen test,

findings of hepatosplenomegaly, extrapulmonary lymphadenopathy, mucosal or skin lesions, anemia, leukopenia, thrombocytopenia, or hepatic enzyme elevation, are suggestive of disseminated infection 5.

Histoplasmosis affects solid organ transplant (SOT) recipients, a group of patients at risk for endemic and opportunistic infections because of the lifelong requirement for immunosuppression. Although a retrospective analysis in a hyper-endemic area revealed between 0 and 0.092% cases of histoplasmosis in 449 SOT recipients (including 279 kidney allografts) 7, other large centers also in endemic areas have reported attack rates up to 4.1 (2.2–6.8 cases) cases per 1000 solid organ transplantations 8, 9. Surveillance data from 15 US SOT transplant centers identified 48 cases of histoplasmosis among 16,808 SOT recipients 10. Renal allograft recipients from the endemic centers were reported to be affected at a rate of 2.5 (95% confidence interval, 0.5–7.2 cases) cases per 1000 transplantations, with dissemination occurring in 100% of cases 8, 9. Transmission of *H. capsulatum* by organ transplantation has also been reported 11.

H. capsulatum has at least 7 clades, distributed geographically around the world 4. Skin manifestations of disseminated histoplasmosis are rare in the US, with nearly all reported cases in human immunodeficiency-positive (HIV⁺) individuals 12-15. It has been estimated that 11% of HIV⁺ patients with disseminated disease will have skin lesions that are typically ulcerative erythematous papules, or verrucous or nodular in presentation. Conversely, skin manifestations of disseminated histoplasmosis in HIV⁺ patients are relatively common in Latin America 13, 15 and Africa 16, likely reflecting unique pathogenesis of *H. capsulatum* Latin clades A & B and *H. capsulatum var. duboisii*, respectively. Since the advent of calcineurin inhibitor therapies only 1 case of cutaneous *H. capsulatum* presenting as a cellulitis has previously been reported in a SOT recipient in the US 17. A retrospective analysis of 1046 kidney and 708 liver transplant recipients from a large transplant center in Brazil had only 3 cases of histoplasmosis diagnosed in kidney transplant recipients (0.2%), none of which presented skin manifestations 18. A case series from 1979 by Davies et al. 19 reported 5 patients who had skin manifestations of disseminated histoplasmosis, and another case of cutaneous histoplasmosis presenting as an ulcerating cellulitis was reported in a renal transplant patient in Brazil 20. It is possible that globalization in agriculture may expand the distribution of *Histoplasma* clades and alter clinical presentations. In our case, the fungal culture from the skin biopsy sample did not eventually grow the organism.

Our present case illustrates the importance of skin biopsies in SOT recipients who present with unusual skin lesions or cellulitis. The differential diagnosis for our patient's cutaneous lesions included non-infectious causes including panniculitis, contact dermatitis, erythema migrans, as well as infectious etiologies like unconventional bacteria (e.g., *Bartonella*), tuberculosis, atypical mycobacteria, fungi, or parasites 21. In our case, results of the skin biopsy were available before the results of the urine *Histoplasma* antigen test. Serum or urine *Histoplasma* testing can occasionally take longer, depending on different microbiology laboratories set up schedules. Our case is further strengthened by the fact that we had confirmatory findings of *H. capsulatum* based on PCR amplification, rather than only light microscopic histologic confirmation of cutaneous fungal involvement, as other fungi can appear similar in pathology or other endemic fungi can cross react with testing assays.

Our patient had moderate to severe disseminated histoplasmosis with hypoxia. Per Infectious Diseases Society of America treatment guidelines 22, severe cases of progressive disseminated disease (shock, respiratory failure, mental status changes) should be treated with an induction regimen comprised of LAmB (3.0 mg/kg daily for 1–2 weeks), followed by consolidation with oral itraconazole (loading dose of 200 mg 3 times daily for 3 days, followed by 200 mg twice daily) for a minimal duration of 12 months. In immunosuppressed patients a longer course of therapy should be considered 22. In our patient, concerns about nephrotoxicity related to LAmB in the setting of AKI led to the use of intravenous voriconazole 23 as initial therapy, followed by step down to itraconazole therapy. In cases of mild-to-moderate disease, initial therapy with oral itraconazole is sufficient if there is no central nervous system involvement. Itraconazole solution is preferred over capsules for initial therapy, because of more reliable absorption 24. Once the patient is clinically stable it is common to step down to less expensive and better tolerated capsules taken with food. Itraconazole serum levels should be checked approximately 2 weeks after starting therapy to document absorption. Based on limited data, discontinuation of antifungal therapy can be considered after 12 months in SOT recipients with negative urine *Histoplasma* antigen testing, with ongoing follow-up for potential relapse 8. Long-term maintenance therapy is recommended for those patients who relapse 22.

Itraconazole, voriconazole, and all other azole antifungals inhibit CYP3A4 and P-glycoprotein, the principal metabolic pathways of the calcineurin inhibitors (cyclosporine and tacrolimus) and sirolimus. To avoid the excessive immunosuppression and toxicity (e.g., nephrotoxicity) that result from elevated serum levels of these drugs, dosage and serum levels should be carefully monitored during concurrent therapy with azole antifungals. Based on the same principle, doses of cyclosporine, tacrolimus, and sirolimus need to be increased again once the CYP3A4 inhibition by the azole medication has been discontinued. Kramer et al. 25, found that lung transplant recipients required a mean increase in the total daily dose of tacrolimus of 76% and 64% after itraconazole and voriconazole withdrawal, respectively. Careful monitoring of immunosuppressant dosing and serum levels is important to avoid renal allograft compromise by either rejection or toxicity. Routine surveillance immune monitoring by Immuknow[®] assay has been reported in liver transplant recipients as having the potential to identify patients at risk of developing IFIs 26. However, no data report if this assay can predict the risk of rejection in the setting of an active or recent fungal infection by post-infection monitoring follow-up and repeat measurements of the assay. Further studies using this assay are needed in transplant recipients with IFIs to help define the role of this assay as a monitoring tool to prevent under-immunosuppression and subsequent rejection. Hence, while it is standard practice to reduce immunosuppression based on theoretical principles, the data are extremely limited 8 as to whether or to what extent and duration, immunosuppression should be reduced in SOT transplant patients with disseminated histoplasmosis.

Conclusion

A primary cutaneous manifestation of fungal infections in kidney transplant recipients is extremely rare. This case illustrates the need for early skin biopsies in such scenarios, and not only demonstrates the challenge of diagnosing patients with atypical

presentations of opportunistic infections like histoplasmosis, but also the difficulty of tapering immunosuppressants in the setting of ongoing infection and the associated risk of rejection. The role of *in vitro* CD4+ T-helper cell function assays in monitoring the balance between true risk of infection and rejection remains to be defined. Meanwhile, the reduction in immunosuppression in the setting of acute infection will continue to be a popular practice, based so far on theoretical principles and limited anecdotal experience. A multicenter investigation of this practice would be a valuable contribution to patient care.

Acknowledgements

Disclaimer: The findings and conclusions of this article are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

References

1. Shieh WJ, Blau DM, Denison AM, et al. 2009 pandemic influenza A (H1N1): pathology and pathogenesis of 100 fatal cases in the United States. *Am J Pathol* 2010; 177 (1): 166–175. [PubMed: 20508031]
2. Munoz-Cadavid C, Rudd S, Zaki SR, et al. Improving molecular detection of fungal DNA in formalin-fixed paraffin-embedded tissues: comparison of five tissue DNA extraction methods using panfungal PCR. *J Clin Microbiol* 2010; 48 (6): 2147–2153. [PubMed: 20392915]
3. Lodge JK, Johnson RL, Weinberg RA, Gordon JI. Comparison of myristoyl-CoA:protein N-myristoyltransferases from three pathogenic fungi: *Cryptococcus neoformans*, *Histoplasma capsulatum*, and *Candida albicans*. *J Biol Chem* 1994; 269 (4): 2996–3009. [PubMed: 8300631]
4. Kasuga T, White TJ, Koenig G, et al. Phylogeography of the fungal pathogen *Histoplasma capsulatum*. *Molec Ecology* 2003; 12 (12): 3383–33401.
5. Wheat LJ, Conces D, Allen SD, Blue-Hnidy D, Loyd J. Pulmonary histoplasmosis syndromes: recognition, diagnosis, and management. *Semin Respir Crit Care Med* 2004; 25 (2): 129. [PubMed: 16088457]
6. Rubin H, Furcolow ML, Yates JL, Brasher CA. The course and prognosis of histoplasmosis. *Am J Med* 1959; 27: 278–288. [PubMed: 14439879]
7. Vail GM YR, Wheat LJ, Filo RS, Cornetta K, Goldman M. Incidence of histoplasmosis following allogeneic bone marrow transplant or solid organ transplant in a hyperendemic area. *Transpl Infect Dis* 2002; 4 (3): 148–151. [PubMed: 12421460]
8. Freifeld AG, Iwen PC, Lesiak BL, Gilroy RK, Stevens RB, Kalil AC. Histoplasmosis in solid organ transplant recipients at a large Midwestern university transplant center. *Transpl Infect Dis* 2005; 4: 109–115.
9. Cuellar-Rodriguez J, Avery RK, Lard M, et al. Histoplasmosis in solid organ transplant recipients: 10 years of experience at a large transplant center in an endemic area. *Clin Infect Dis* 2009; 49 (5): 710–716. [PubMed: 19635026]
10. Pappas PG, Alexander BD, Andes DR, et al. Invasive fungal infections among organ transplant recipients: results of the Transplant-Associated Infection Surveillance Network (TRANSNET). *Clin Infect Dis* 2010; 50 (8): 1101–1111. [PubMed: 20218876]
11. Limaye AP, Connolly PA, Sagar M, et al. Transmission of *Histoplasma capsulatum* by organ transplantation. *N Engl J Med* 2000; 343 (16): 1163–1166. [PubMed: 11036122]
12. Srivastava B, King B, Galan A. An unusual clinical and histologic presentation of disseminated cutaneous histoplasmosis. *J Am Acad Dermatol* 2011; 65 (5): e146–e148. [PubMed: 22000884]
13. Scheinfeld N. Diffuse ulcerations due to disseminated histoplasmosis in a patient with HIV. *J Drugs Dermatol* 2003; 2 (2): 189–191. [PubMed: 12852372]
14. Cohen PR, Bank DE, Silvers DN, Grossman ME. Cutaneous lesions of disseminated histoplasmosis in human immunodeficiency virus-infected patients. *J Am Acad Dermatol* 1990; 1: 422–428.

15. Rosenberg JD, Scheinfeld NS. Cutaneous histoplasmosis in patients with acquired immunodeficiency syndrome. *Cutis* 2003; 72 (6): 439–445. [PubMed: 14700213]
16. Ramdial PK, Mosam A, Dlova NC, Satar NB, Aboobaker J, Singh SM. Disseminated cutaneous histoplasmosis in patients infected with human immunodeficiency virus. *J Cutan Pathol* 2002; 29 (4): 215–225. [PubMed: 12028154]
17. McGuinn ML, Lawrence ME, Proia L, Segreti J. Progressive disseminated histoplasmosis presenting as cellulitis in a renal transplant recipient. *Transplant Proc* 2005; 37 (10): 4313–4314. [PubMed: 16387107]
18. Batista MV PL, Abdala E, Clemente WT, et al. Endemic and opportunistic infections in Brazilian solid organ transplant recipients. *Trop Med Int Health* 2011; 16 (9): 1134–1142. [PubMed: 21692958]
19. Davies SF, Sarosi GA, Peterson PK, et al. Disseminated histoplasmosis in renal transplant recipients. *Am J Surg* 1979; 137 (5): 686–691. [PubMed: 378009]
20. Marques SA, Hozumi S, Camargo RM, Carvalho MF, Marques ME. Histoplasmosis presenting as cellulitis 18 years after renal transplantation. *Med Mycol* 2008; 46 (7): 725–728. [PubMed: 18671166]
21. Bailey E, Kroshinsky D. Cellulitis: diagnosis and management. *Dermatol Ther* 2011; 24 (2): 229–239. [PubMed: 21410612]
22. Wheat LJ, Freifeld AG, Kleiman MB, et al. Clinical practice guidelines for the management of patients with histoplasmosis: 2007 update by the Infectious Diseases Society of America. *Clin Infect Dis* 2007; 45 (7): 807–825. [PubMed: 17806045]
23. Freifeld AG, Wheat LJ, Kaul DR. Histoplasmosis in solid organ transplant recipients: early diagnosis and treatment. *Curr Opin Organ Transplant* 2009; 14 (6): 601–605. [PubMed: 19812496]
24. Freeman J, Heshmati A, Holland D, Ticehurst R, Lang S. Marked increase in steady-state serum levels achieved with itraconazole oral solution compared with capsule formulation. *J Antimicrob Chemother* 2007; 60 (4): 908–909. [PubMed: 17631506]
25. Kramer MR, Amital A, Fuks L, Shitrit D. Voriconazole and itraconazole in lung transplant recipients receiving tacrolimus (FK 506): efficacy and drug interaction. *Clin Transplant* 2011; 25 (2): E163–E167. [PubMed: 21158923]
26. Zhou T, Xue F, Han LZ, et al. Invasive fungal infection after liver transplantation: risk factors and significance of immune cell function monitoring. *J Dig Dis* 2011; 12 (6): 467–475. [PubMed: 22118697]

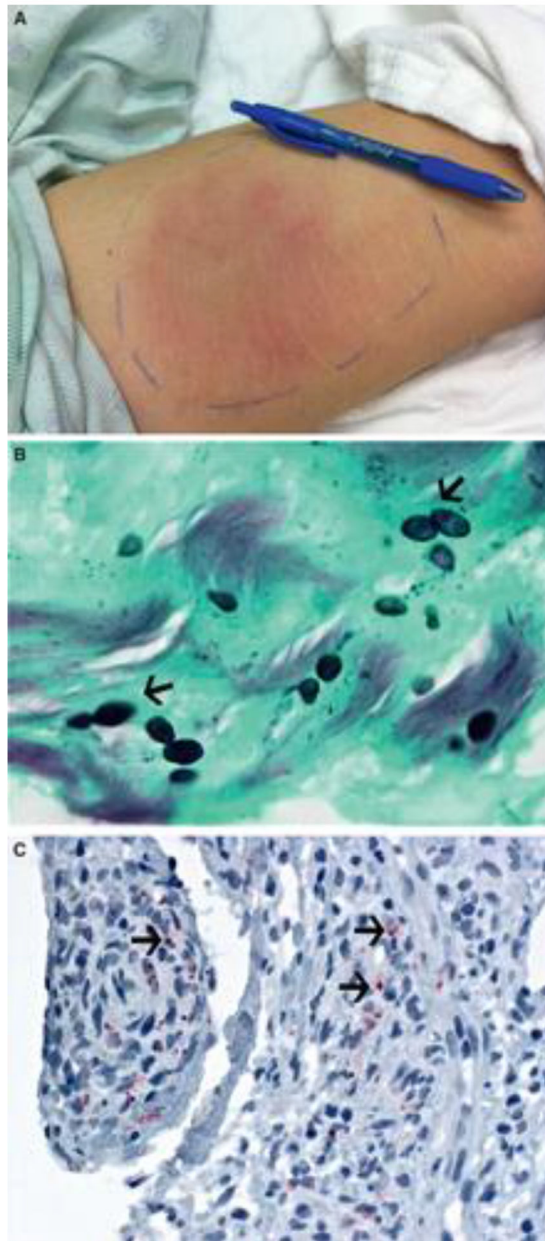


Figure 1. Disseminated cutaneous histoplasmosis. (A) Cutaneous deep dermal skin lesion in the thigh. (B) Skin biopsy of thigh lesion showing isolated, intracellular and extracellular, small (2–4 μm), single, and budding yeast forms morphologically consistent with *Histoplasma capsulatum* dispersed within a diffuse histiocytic infiltrate in the deep dermis and subcutaneous tissue (Gomori-methenamine silver, $\times 100$). (C) Immunohistochemical staining with anti-*H. capsulatum* antibody, confirming that yeast forms were *H. capsulatum* ($\times 40$). Arrows highlight examples of yeast forms in panels B & C.