Case Report: Histoplasmosis in Himachal Pradesh (India): An Emerging Endemic Focus

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Abstract. We describe four cases of histoplasmosis indigenous to Himachal Pradesh (India) that will be of considerable public health interest. A 48-year-old human immunodeficiency virus (HIV)-negative man with cervical and mediastinal lymphadenopathy, hepatosplenomegaly, adrenal mass, and bone marrow involvement was treated as disseminated tuberculosis without benefit. Progressive disseminated histoplasmosis was diagnosed from the fungus in smears from adrenal mass. Another 37-year-old HIV-positive man was on treatment of suspected pulmonary tuberculosis. He developed numerous erythema nodosum leprosum-like mucocutaneous lesions accompanied by fever, generalized lymphadenopathy, and weight loss. Pulmonary histoplasmosis with cutaneous dissemination was diagnosed when skin lesions showed the fungus in smears, histopathology, and mycologic culture. Both were successfully treated with amphotericin B/itraconazole. Third patient, a 46-year-old HIV-negative man, had oropharyngeal lesions, cervical lymphadenopathy, intermittent fever, hepatosplenomegaly, and deteriorating general health. Progressive disseminated oropharyngeal histoplasmosis was diagnosed from the fungus in smears and mycologic cultures from oropharyngeal lesions and cervical lymph node aspirates. He died despite initiating treatment with oral itraconazole. Another 32-year-old man 3 months after roadside trauma developed a large ulcer with exuberant granulation tissue over left thigh without evidence of immunosuppression/systemic involvement. He was treated successfully with surgical excision of ulcer under amphotericin B/itraconazole coverage as primary cutaneous histoplasmosis confirmed pathologically and mycologically. A clinical suspicion remains paramount for early diagnosis of histoplasmosis particularly in a nonendemic area. Most importantly, with such diverse clinical presentation and therapeutic outcome selection of an appropriate and customized treatment schedule is a discretion the treating clinicians need to make.

INTRODUCTION

Histoplasmosis is essentially a systemic mycosis caused by dimorphic fungus *Histoplasma capsulatum* having three varieties; *H. capsulatum* var *duboisii* (large blastoconidia or yeast morphotype form sized 8 to 15 µm) endemic to sub-Saharan Africa (African human pathogen), *H. capsulatum* var *capsulatum* (small blastoconidia or yeast morphotype form sized 2–4 µm) that is more common worldwide (New World human pathogen), and equine *H. capsulatum* var *farciminosum* (Old World horse pathogen) causing epizootic lymphangitis in horses. A phylogenetic analysis of *H. capsulatum* pathogenic to humans has identified at least eight different *H. capsulatum* clades according to geographic distribution and variability of conserved genes.¹ Four of them: 1) North American class 1 clade; 2) North American class 2 clade; 3) Latin American group A clade, and 4) Latin American group B clade are from the Americas whereas others: 5) Australian clade; 6) The Netherlands (Indonesian?) clade; 7) Eurasian clade, and 8) African clade are found in Africa, Europe, Eurasia, and other continents. More recently, six new phylogenetic species, namely, LAm A1, LAm A2, LAm B1, LAm B2, RJ, and BAC-1, have been proposed existing within Latin America.²

The disease is endemic in Ohio and Mississippi river valleys of North America and with reports in all of Central and South America. However, the disease is being reported frequently from nonendemic areas as well especially among immunocompromised individuals and returning travelers.^{3,4} In India, a review of reports published between 1994 and 2017 comprising

144 cases of histoplasmosis recorded after 1954, the year when first report published (Table 1).^{4–24} It revealed their widespread distribution with clustering mostly in small regions of West Bengal and Assam, the Gangetic Plains, western parts of India, and sporadically from southern and few northern Indian states (Figure 1). Himachal Pradesh, a small hill state of India (30°N, 70°E), in the Western Himalayas has high mountain terrain in the Greater Himalayas and semiofoothills/plains in the outer Himalayas with altitudes vary between 350 and 7,000 m above sea. The climatic conditions vary between temperate to semiarctic and near absent rains at higher altitudes in the Greater Himalayas (Chanderbhaba and Kinnaur valleys) and semitemperate to subtropical weather with a good amount of rain year round in semiofoothills or plains. Except for isolated cases, the place is not endemic for histoplasmosis despite the good number of cases with sporotrichosis and other subcutaneous mycoses reported previously.²⁵ In this report, we review two previously reported and present two new cases of histoplasmosis indigenous to Himachal Pradesh (India) with an objective of documenting an emerging focus that will be of considerable public health interest.

CASE REPORTS

Case 1. As reported by Kashyap et al.¹² this 48-year-old human immunodeficiency virus (HIV)-negative man had presented with low-grade fever, weight loss, decreased appetite, and worsening of his breathlessness. He was taking antitubercular treatment of 3 months for disseminated tuberculosis diagnosed after fine needle aspiration cytology (FNAC) of cervical lymph node without benefit. He was febrile (temp. 100°F, pulse rate 94/minutes regular), normotensive (120/80 mm of Hg), had respiratory rate of 16/minutes, pallor, and enlarged cervical lymph nodes

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TABLE 1
Year-wise cases of histoplasmosis reported from various states of India

Year	State wise number of cases of histoplasmosis																		Reference [no.] (type of study)
	HP	UP	WB/Assam	TN	Delhi	Mah	Raj	Bih	Chd	Guj	MP/Chhat	Kerala	AP*	Oris	UK	Megh	Karn	Total	
1954–1994	–	04	14	01	01	07	03	–	02	–	02	01	01	–	–	–	01	37	Randhawa et al. 1994 [5] (review)
1989–1999	–	01	08	01	–	–	–	02	–	–	–	01	04	01	–	–	–	18	Subramaniam et al. 2005 [6] (case series)
2001	–	–	–	–	–	01	–	–	–	–	–	–	–	–	–	–	–	01	Gohar et al. 2001 [17] (case report)
2008	–	–	–	–	–	–	–	–	–	–	–	–	01	–	–	–	–	01	Rao 2008 [7] (case report)
2009	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	02	02	Bhagwat et al. [14] (case report)
2010	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	01	–	01	Vasudevan et al. 2010 [15] (case report)
1995–2011	–	15	11	10	10	05	02	02	02	01	02	01	–	–	–	–	–	61	Kathuria et al. 2013 [4] (review)
2012	–	–	–	–	–	01	–	–	–	–	–	–	–	–	–	–	–	01	Harnalakar et al. 2012 [16] (case report)
2013	–	–	–	–	–	–	–	–	–	–	–	–	02	–	–	–	–	02	Subbalaxmi et al. 2013 [8] (case report)
2014	–	–	–	–	–	–	–	–	–	–	–	–	01	–	–	–	–	01	Komali et al. 2014 [9] (case report)
2014	01	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	01	Kashyap et al. 2014 [12] (case report)
2015	–	–	07	–	–	01	–	–	–	–	–	01	01*	–	–	–	–	10	Jawaid et al. 2015 [10], Ravindran et al. 2015 [11] De and Nath, 2015 [23] Gosavi et al. 2015 [24] (Case series)
2016	01	–	–	01	–	–	–	–	01	–	–	–	–	–	01	–	–	04	Raina et al. 2016 [13] Kotwal et al. 2016 [18] Rastogi et al. 2016 [19] Radhakrishnan et al. 2016 [20] (case report)
2017	–	–	–	–	02	–	–	–	–	–	–	–	–	–	–	–	–	01	Malhotra et al. 2017 [21] Bhattacharya et al. 2017 [22] (case reports)
2017 Total	02	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	02	Current report
Total	04	20	40	13	13	15	05	04	05	01	04	04	10	01	01	01	03	144	–

AP = Andhra Pradesh; Bih = Bihar; Chd = Chandigarh; Guj = Gujarat; HP = Himachal Pradesh; Karn = Karnataka; MP/Chhat = Madhya Pradesh/Chhattisgarh; Mah = Maharashtra; Megh = Meghalaya; Oris = Orissa; Raj = Rajasthan; UK = Uttarakhand; UP = Uttar Pradesh; WB = West Bengal. Numbers in bold depict four cases from Himachal Pradesh described in this report.

* Includes one case from Telengana (a newly constituted state after reorganizing state of Andhra Pradesh).

(1–1.5 cm). He had nontender, firm splenomegaly palpable 6 cm below left costal margin, and just palpable liver of firm consistency. Laboratory investigations showed anemia, leucopenia, erythrocyte sedimentation rate of 30 mm in the first hour (normal value 5–10 mm in the first hour by Westergren method), thrombocytopenia, normal hepatorenal function tests, and urinalysis. Urine and blood cultures were sterile, and chest skiagram showed no significant abnormality. Computed tomography (CT) and ultrasonography scans revealed hepatosplenomegaly, left adrenal mass, and mediastinal lymphadenopathy. Bone marrow examination showed granulomatous pathology. A splenic aspirate showed no evidence of histoplasmosis in smears or in cultures from Sabouraud dextrose agar (SDA). However, a CT guided FNAC of left adrenal mass showed intracellular yeast cells in Giemsa-stained smears. He was treated for progressive disseminated histoplasmosis successfully with liposomal amphotericin B (5 mg/kg/d) for 2 weeks and discharged on itraconazole 200 mg twice daily for 1 year.

Case 2. This 37-year-old HIV-positive man, a farmer by occupation, presented with multiple erythematous

papulonodular lesions all over the body of 3-month duration. The lesions had appeared over face initially and progressively increased in number to involve whole face, neck, trunk, both upper and lower limbs, palms and soles, and oropharynx. He was taking tenofovir (300 mg/d), lamivudine (300 mg/d), efaviranz (600 mg/d), and co-trimoxazole (sulfamethoxazole 800 mg+ trimethoprim 160 mg) for *Pneumocystis* prophylaxis for 3 months, along with rifampicin 450 mg, isoniazid 600 mg, ethambutol 1,200 mg, pyrazinamide 1,500 mg on alternate days for pulmonary tuberculosis under directly observed treatment schedule (World Health Organization-DOTS) for 2 months without benefit. He was thin built (weight 50 kg), ill looking, febrile (temp. 101°C) and had generalized lymphadenopathy. Most of the skin lesions had smooth surfaces, and were globoid papules, and nodules of variable size (Figure 2). Some of the lesions were molluscum contagiosa-like, and few lesions (especially oral) showed ulceration and crusting. Table 2 shows laboratory investigations during hospitalization. Capsulated organisms were visualized in Giemsa-stained slit-skin smears (not in Ziehl-Neelsen staining) from a lesion performed with a provisional

FIGURE 1. Geographic distribution of histoplasmosis cases in India. This figure appears in color at www.ajtmh.org.

diagnosis of erythema nodosum leprosum. The histopathology of a nodular lesion showed unremarkable epidermis, upper dermis had dense infiltrate comprising macrophages, and few lymphocytes extending into lower dermis and blastoconidia within the macrophages (Figure 3). Culture of biopsy sample for fungus on SDA showed growth of *H. capsulatum* identified from characteristic colony characteristics, conversion to yeast form, and characteristic microscopic appearance in lactophenol cotton blue (LCB) mounts (Figures 4 and 5). A diagnosis of progressive disseminated histoplasmosis was made. His fever subsided and general condition improved after treatment with intravenous deoxycholate amphotericin B (1 mg/kg/day) for 14 days. He was discharged on itraconazole (200 mg twice/day) prophylaxis in view of low CD4 cell counts. The treatment cycle was repeated after 3 weeks. He was free of skin lesions and did not follow up after 4 months.

Case 3. A 46-year-old HIV-negative man, a carpenter by occupation, was hospitalized with throat pain and hoarseness for 4 and 2 months, respectively. He had intermittent low-grade fever, 3–4 loose stools daily of 1 month duration, and

weight loss of about 10 kg in last 4 months. He was a smoker and daily consumed small amount of alcohol. He was not a diabetic or hypertensive and had no history of other substance abuse or prolonged drug therapy. Mucocutaneous examination showed multiple well defined, discrete to confluent macerated papuloplaques over oropharynx involving soft and hard palate, anterior pillar, arytenoids, and epiglottis (Figure 6). He had bilateral submandibular lymphadenopathy and nontender mild hepatosplenomegaly. His laboratory investigations during hospitalization are listed in Table 2. FNAC from submandibular lymph node showed capsulated organisms suggestive of histoplasmosis (Figure 7). The histopathology of oral lesion showed features of histoplasmosis confirmed later from culture of *H. capsulatum* on SDA. Treatment was initiated with itraconazole (200 mg BD) pending availability of amphotericin B. However, his general condition deteriorated (BP: 80/50 mm Hg, pulse rate 104/minute), electrolyte abnormalities (serum sodium 128 mEq/L, serum potassium 2.5 mEq/L), and he became delirious in next 3 days; he was shifted to intensive care under internist. On recovery, he left the hospital against medical advice. The patient had succumbed to his illness when contacted after sometime.

FIGURE 2. Case 2. Wide spread papules and nodules over face. Similar lesions were present over trunk and extremities. This figure appears in color at www.ajtmh.org.

Case 4. As reported by Raina et al.¹³ this 32-year-old HIV-negative man, a medical professional, presented with single well-defined punched-out ulcer over left thigh with exuberant granulation tissue, indurated ill-defined borders, and sclerotic hyperpigmented margins (Figure 8). It had started 3 months back as a painless nodular swelling about 3 months after sustaining trauma from a roadside accident. He tried to manipulate this lesion with a hypodermic needle, and other treatment did not benefit. Cutaneous and systemic examination and routine laboratory investigations revealed no abnormality. A skin biopsy performed with a provisional diagnosis of malignant ulcer showed focally ulcerated epidermis, granulation tissue and blood, and acute on chronic inflammation with sheets and groups of macrophages with characteristic intracellular round to oval macroconidia with clear halo in histologic sections. Culture from biopsy tissue in SDA grew *H. capsulatum* confirming the diagnosis of primary cutaneous histoplasmosis. He recovered completely after treatment with

total surgical excision of skin lesion and systemic amphotericin B and itraconazole therapy at another center.

DISCUSSION

Systemic histoplasmosis is typically acquired through inhalation of microconidia or small hyphal elements in soil contaminated with bird and bat droppings leading to primary infection as acute or chronic (cavitary) pulmonary histoplasmosis or as acute, subacute, or chronic progressive disseminated histoplasmosis in most common and classic forms. However, it is frequently mistaken and treated for tuberculosis before the actual diagnosis as in case 1.¹¹ The infection spreads further to lymph nodes, spleen, and other systems via hematogenous spread. However, clinical variations occur from asymptomatic or mild-, self-limiting infections in most patients who are

TABLE 2
Laboratory data of patients

Laboratory investigation (normal values)	Case 2	Case 3
Hemoglobin (11.5–14.5 g/dL)	10.3	8.5
Total leukocyte count (4,000–11,000/mm ³)	3,300	7,000
Differential leukocyte count (N 40–60%, L 30–40%, E 1–4%, M 2–8%, B 0.5–1%)	N 69, L 28, E 1, M 2, B 0	N 72, L 28, E 0, M 0, B 0
Platelet counts (100,000–150,000/mm ³)	173,000	45,000
Erythrocyte sedimentation rate (5–10 mm in 1st hr, Westergren method)	41	40
Random blood sugar (mg/dL)	140	144
Serum proteins total/albumin (6–8.3/3.7–5.3 mg/dL)	9.0/4.2	6.4/2.6
Serum bilirubin total/conjugated (0.2–0.8/0–0.3 mg/dL)	0.3/0.1	1.3/0.4
SGOT/SGPT/Alkaline phosphatase (05–34 IU/06–40 IU/15–112 IU)	32/30/146	51/58/146
Serum sodium/potassium (135–155/3.5–5.5 mEq/L)	140.5/4.5	143.2/4.07
Serum calcium (9–11 mg/dL)	6.6	8.0
Urea/Creatinine (13–45/0.5–1.4 mg/dL)	29/1.2	30/1.0
HIV serology/CD4 counts	Reactive/33 cells/microliter	Nonreactive
Urinalysis	No abnormality	No abnormality
Sputum for acid fast bacilli	Negative	Negative
X-ray chest PA view	Inhomogeneous opacities in mid and lower zones of right lung, perihilar region of left lung	No abnormal findings noted
Mantoux test	Nonreactive	Nonreactive

B = basophils; E = eosinophils; HIV = human immunodeficiency virus; L = lymphocytes; M = monocytes; N = neutrophils; PA = posteroanterior; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase.

Note: Both patients did not consent for bone marrow biopsy.

immunocompetent to progressive, disseminated, and severe infection in the immunocompromised as in acquired immune deficiency syndrome with CD4 counts < 200 cells/microliter causing significant morbidity and mortality.²⁶ The skin lesions of histoplasmosis are nonspecific and arise after dissemination from the primary pulmonary focus. Progressive disseminated histoplasmosis in immunocompromised hosts, a potentially fatal complication, usually presents with mucocutaneous erosions/ulcers, or multiple erythematous papules or nodules with scale or crust. Our case 2 had classic progressive disseminated histoplasmosis presenting with pulmonary histoplasmosis and widespread cutaneous involvement. He was immune compromised, taking treatment for suspected pulmonary tuberculosis without benefit, characteristic skin lesions, and had complete recovery after treatment of histoplasmosis.

In immunocompetent hosts, when chronic disseminated histoplasmosis occurs from pulmonary infection, oral ulcers, nodules, and vegetative plaques are common, and dissemination to liver, spleen, bone marrow, and other organs is frequent.⁴ Gastrointestinal involvement occurs in 70–90% and adrenal gland involvement is not uncommon especially in disseminated form and can be fatal due to adrenal failure.^{9,11,23} Association between involvement of oropharynx and adrenals in immunocompetent individuals noted with a higher incidence of 85% for adrenal insufficiency in an Australian series.²⁷ The disseminated histoplasmosis seen in case 3 was similar in presentation. He had no clinical evidence of immune suppression, had oropharyngeal histoplasmosis with systemic dissemination manifesting with regional lymphadenopathy, hepatosplenomegaly, and diarrhea. His deteriorating clinical condition, hypotension, electrolyte

FIGURE 3. Case 2. Histologic section of skin lesion showing sheets of macrophages with numerous yeast cells of *Histoplasma capsulatum* (A) H&E, $\times 40$; (B) periodic acid Schiff, $\times 40$. This figure appears in color at www.ajtmh.org.

FIGURE 4. Characteristic cottony white colonies with yellowish tinge of *Histoplasma capsulatum* on Sabouraud's dextrose agar at 25–30°C. This figure appears in color at www.ajtmh.org.

imbalance, and altered sensorium ending fatally was perhaps from adrenal insufficiency. However, the reasons for widespread dissemination reportedly remain unknown in 20–70% of such cases as was evident in this case as well.⁹ It is also emphasized that whereas disseminated cutaneous forms are more frequently associated with HIV infection necessitating screening for underlying immune suppression, the oral forms can present with or without HIV infection.

FIGURE 5. Characteristic mycelia and large, rounded, unicellular, tuberculate macroconidia of *Histoplasma capsulatum* on short, hyaline, and undifferentiated conidiophores in lactophenol cotton blue mounts (×40). This figure appears in color at www.ajtmh.org.

FIGURE 6. Case 3. Numerous coalescing macerated papules in the oropharynx, and over palate. This figure appears in color at www.ajtmh.org.

Primary cutaneous histoplasmosis is extremely rare and occurs after accidental direct inoculation of the pathogen. Papules, plaques, punched-out ulcers, purpuric lesions, abscesses, impetigo, local dermatitis, or generalized dermatitis at the site of inoculation may be the presenting features and extensive necrosis and ulceration may occur.^{28,29} However, a history of an injury helps in suspecting the diagnosis of primary cutaneous histoplasmosis and differentiates it from disseminated histoplasmosis as was in case 4. Infectious Diseases Society of America has no guidelines or recommendations specific for treating primary cutaneous histoplasmosis and most localized lesions have been treated with systemic amphotericin B or oral itraconazole.^{30,31} Surgical excision of primary cutaneous histoplasmosis lesion under amphotericin/itraconazole coverage (details are not reported) effectively healed ulcerated lesion without recurrence that is highly desirable treatment outcome.

In practice, diagnosis is usually suspected on visualization of characteristic intracellular yeast (blastoconidia), the pathogenic or tissue form, with a clear rim and granulomatous cellular infiltrate in tissue specimen or lymph node aspirate especially in sections stained with periodic acid Schiff or Gomori methenamine silver whereas culture of pathogen on SDA will be confirmatory. Molecular studies are rarely needed as laboratory culture of *H. capsulatum* on SDA at 25–30°C from clinical samples, with characteristic colony morphology, its conversion to the yeast phase at 37°C in vitro, and spores visualized in LCB mounts are useful diagnostic features in most instances. Demonstration of fungus in cytology smears from skin lesions/lymph node appears useful for rapid diagnosis as was in our patients.

Early treatment with amphotericin B is recommended for acute and chronic cavitary pulmonary histoplasmosis, progressive disseminated histoplasmosis or central nervous system histoplasmosis for a long-term survival.³⁰ Oral itraconazole (200 mg three times daily for 3 days followed by 200 mg twice daily) for 12 weeks is preferred only in patients with mild-to-moderate disease and as step down therapy after initial treatment with amphotericin B.³⁰ However,

FIGURE 7. Case 3. Fine needle aspiration cytology from submandibular lymph node showing intra- and extracellular yeasts of *Histoplasma capsulatum*. This figure appears in color at www.ajtmh.org.

amphotericin B apparently may be preferred as initial treatment pending assessment for disease extent as in case 3 who died despite oral itraconazole therapy. Nevertheless, with such diverse clinical presentation and therapeutic outcome selecting an appropriate and customized treatment schedule is a discretion the treating clinicians need to make. However, immune compromised patients will need itraconazole prophylaxis for life; if immunosuppression cannot be reversed, or when CD4 counts remain < 150 cells/microliter in HIV-affected persons and in patients who relapse despite appropriate therapy.³⁰ Last but not the least, a clinical suspicion remains paramount for an

early diagnosis of histoplasmosis particularly in a non-endemic area.

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FIGURE 8. Case 4. Single punched-out ulcer over left thigh with exuberant granulation tissue, sclerotic, and hyperpigmented margins and indurated ill-defined borders. This figure appears in color at www.ajtmh.org.

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