Available online at www.sciencedirect.com

ScienceDirect

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

Case Report

Solitary pulmonary nodule: An interesting clinical mimicry of pulmonary tuberculosis

Maj Gen Vibha Dutta, SM, (Retd)^a, Lt Col Manu Chopra^b,
Col Uday Bhanu Kovilapu^c, Lt Col G.P.S. Gahlot^{d,*}

^a Former MG (Med), Head Quarters, Delhi Area, Delhi Cantt, India

^b Assistant Professor (Respiratory Medicine), Army Hospital (R&R), New Delhi 110010, India

^c Associate Professor (Radiodiagnosis), Armed Forces Medical College, Pune 411040, India

^d Assistant Professor (Lab Sciences & Molecular Med), Army Hospital (R&R), New Delhi 110010, India

ARTICLE INFO

Article history:

Received 4 March 2018

Accepted 28 July 2018

Available online 15 October 2018

Keywords:

Pulmonary histoplasmosis

Histoplasma capsulatum

Cytology

Immune-compromised

Periodic acid-schiff stain

histopathological examination, these were confirmed as *Histoplasma capsulatum*. Therefore, pulmonary histoplasmosis should be considered as differential while evaluating immunocompetent patients having risk factors of soil exposure and pre-existing lung disease. The index study emphasizes the importance of cytology followed by histopathology to diagnose *Histoplasma* in cases where the clinical suspicion of tuberculosis is very high. The early diagnosis and appropriate timely treatment of the patient are important to improve outcomes.²

Case report

A 59-year-old female patient with a history of postlaparoscopic cholecystectomy (2007), autoimmune hepatitis (2008 treated with azathioprine and prednisolone), solitary lung nodule (2013 acute inflammatory lesion, treated with intravenous ertapenem, later on immunomodulators stopped), invasive ductal breast carcinoma (2014), and cutaneous tuberculosis (2015 anti tubercular treatment [ATT] completed), now presented with complains of fever and dry cough since 2 months. Fever was not associated with rigor/chills/diurnal variation. General and physical examination revealed pallor, left-modified radical mastectomy–healed scar with other normal vital parameters. Systemic examination was unremarkable. The hematological and biochemical parameters including erythrocyte sedimentation rate were within normal limits. Blood and sputum cultures were negative for any pyogenic bacteria. Chest radiograph was

Introduction

Pulmonary histoplasmosis is regarded as an opportunistic/saprophytic respiratory infection caused by a low pathogenic fungus and can be seen in both immunocompetent and immunosuppressed individuals. *Histoplasma* spreads via hematogenous route affecting the reticuloendothelial system.¹ Tissue disease results from host immune response to dispersions of soluble antigen from these focal sources. Cytological imprint smears prepared from resected fresh pulmonary nodule show uniform, round to oval, 2–4 μm sized, budding yeast in intracellular and extracellular sites. On

* Corresponding author.

E-mail address: gpsinghahlot@gmail.com (G.P.S. Gahlot).

<https://doi.org/10.1016/j.mjafi.2018.07.017>

0377-1237/© 2018, Armed Forces Medical Services (AFMS). All rights reserved.

Fig. 1 – NCCT chest (1A; Mediastinal window) shows an ill-defined heterogeneous mass lesion in right breast and 1B; Lung window shows an ill-defined heterogeneous mass lesion in anterior segment of right upper lobe with surrounding haziness. Fludeoxyglucose PETCT scan: 1C; shows diffuse bone marrow uptake in axial and appendicular skeleton (SUV max 8.7), 1D of lung reveals metabolically active soft tissue density nodular lesion with irregular margin in the posterior basal segment of right lower lobe measuring 1.7 AP × 1.4 TR × 2.7 CC cm (SUV max 15.6).

suggestive of right lower zone nonhomogenous opacity with Non-contrast computed tomography (NCCT) chest findings of irregular peribronchial nodule with surrounding haziness seen in the right posterior basal pulmonary segment suggestive of tuberculosis (Fig. 1A and B). Mycobacterium tuberculosis- Polymerase chain reaction (MTB- PCR) test revealed very low positivity with rifampicin resistance. Bone marrow aspirate was hemodiluted; however, biopsy revealed granulomatous inflammatory lesion. In view of previous cutaneous tuberculosis and clinico-radiological correlation, possibility of multidrug-resistant pulmonary tuberculosis was considered. Positron Emission Tomography (PET) computed tomography (CT) scan of whole body showed metabolically active soft tissue density nodular lesion with irregular margins in the posterior basal segment of the right

lower lobe of the lung measuring 1.7 antero-posterior (AP) × 1.4 transverse (TR) × 2.7 cranio-caudal (CC) cm (standardized uptake value [SUV]max of 15.6) with pneumothorax on the right side (Fig. 1C and D). Diffuse bone marrow uptake in the axial and appendicular skeleton was observed. A 4.4 × 2.5 × 1.0 cm resected pulmonary nodule with a gray white lesion of 2.0 × 1.2 × 0.5 cm on the cut surface was observed. Imprint smears prepared from the nodule revealed small, round, intracellular, extracellular microorganisms with an eccentric nucleus and perinuclear halo (Fig. 2A). Further histopathological examination showed sheets of foamy histiocytes, lymphocytes, and multinucleate giant cells in the pulmonary parenchyma (Fig. 2B and C). Numerous small, 2–4 μm, intracellular/extracellular capsulated microorganism with an eccentric nucleus surrounded by a halo were

Fig. 2 – May Gurnwald Giemsa stain (2A; 200×) An imprint smear of pulmonary nodule shows intracellular dimorphic microorganism as foamy vacuolated structures (star). Haematoxylin & Eosin (2B; 100×, 2C; 400×), (2D; 400× PAS stain) sections from pulmonary nodule show ill defined granuloma (arrow) and clusters of foamy histiocytes (arrow head) with multinucleate giant cells. Numerous small 2–4 μm intracellular and extracellular capsulated organisms seen (star).

Table 1 – Differential diagnosis of histoplasmosis.

Features	Fungal infections				Bacterial infections		Protozoal infection	Malignancy
	Histoplasmosis	Pulmonary cryptococcosis	Blastomycosis	Coccidioidomycosis	Pneumonia	Pulmonary tuberculosis	Leishmaniasis	
Clinical presentations	Patients may present with fever, productive cough, weight loss, malaise	May mimic acute or chronic histoplasmosis pneumonia	Fever, cough, fatigue, night sweats, muscle pain, dyspnea	May mimic acute or chronic histoplasmosis pneumonia	Cough, fever, pleuritic chest pain of shorter duration	May mimic acute or chronic histoplasmosis pneumonia	Fever, loss of appetite, splenomegaly	Loss of appetite, weight loss, and other symptoms depending on the organ system affected
Chest X-ray	Solitary nodule or multiple, diffuse, tiny, discrete nodules	Reticulonodular infiltrate or solitary pulmonary nodule	Focal patchy opacity	Single/multiple air spaces consolidation or nodules/cavities	Lobar consolidation. No hilar lymphadenopathy	Focal opacity, patchy consolidation with or without pleural effusion	Mediastinal widening and hilar prominence	Findings depend on the organ system affected or metastatic with pulmonary involvement
Size	2–4 μm	15–20 μm	8–15 μm	2–5 μm	0.2–10 μm	2–4 μm length, 0.2–0.5 μm width	3–5 μm	Malignant cells present on cytology or biopsy
Shape	Oval	Round	Round/crescent	Globular endospores	Cocci/bacilli	Rod	Oval to round	Exact characterization requires ancillary techniques in some cases
Morphology	Small, uniform, thin based budding with intracellular and extracellular forms	Non-uniform, narrow based, tear dropped, budding and halo around, show extracellular forms	Thick-walled spores with double-contoured cell wall	Thick-walled spores with granular cytoplasm	Gram stain positive/negative depending on causative microorganism	Curved, rod-shaped bacilli that wrapped together, i.e., cording	Both intracellular and extracellular forms, kinetoplast and nucleus present	
Capsule	Pseudocapsule	True capsule	No capsule	True capsule	No capsule	No capsule	No capsule	–
Budding	Present	Present	Broad based	Broad based	Absent	Absent	Absent	–
Special stains	Gomori methenamine silver (GMS), periodic acid–Schiff (PAS)	GMS, PAS, capsule stained with mucicarmine	GMS, PAS	Capsule negative for mucicarmine stain	Gram, periodic acid–Schiff	Ziehl–Neelsen, auramine–rhodamine	–	–

also observed on periodic acid–Schiff (Fig. 2D) and Gomori methenamine silver stains; therefore, a diagnosis of *H. capsulatum* was concluded. No granuloma/necrosis/atypia/acid-fast bacilli were seen on Ziehl–Neelsen stain.

Discussion

Histoplasma is a dimorphic fungus of ascomycetes family and was first described by Samuel Darling.³ Initially, it was thought to be endemic in the eastern United States (Ohio, Mississippi, and St. Lawrence River valleys) and most of Latin America,¹ but recently several cases have been reported in Asian countries, mainly in China (across Yangtze River), India (across Ganges and Brahmaputra), and Thailand.⁴ The maximum concentrations of *H. capsulatum* organism are present in soil and nitrogen-rich environments such as decaying trees, old chicken coops, and river banks.² Isolated microfoci of infection in non-endemic region could be due to aerosol aspiration of spore spreaded from the demolished buildings.⁵

Infectious forms of *Histoplasma*, that is, macroconidia (8–15 μ m with slender protrusions on the surface, i.e., tuberculate) and microconidia (2–5 μ m with smooth oval bodies) grow outside the body. Pulmonary involvement of *Histoplasma* is primarily by the small microconidia which within the body are associated with upregulation in transcription of putative calcium-binding protein messenger RNA and get transformed into 2–4 μ m budding yeast forms.⁶ After transformation, yeasts migrate to local draining lymph nodes and macrophage-rich organs, that is, liver and spleen. The decrease in cell-mediated immunity because of the fall in CD4 counts results in reduced macrophage activation. The host is no longer able to control the infection, thus leading to dissemination through hematogenous route involving the reticulo-endothelial system.⁶ The tissue reaction can be categorized into three types: (a) an intra-alveolar lymphohistiocytic infiltrate with microgranulomas and necrosis noted in acute pulmonary histoplasmosis; (b) distinguished necrotizing granulomatous inflammation; and (c) sheets of histiocytes filled with numerous organisms, as observed in disseminated histoplasmosis (Fig. 2). *Histoplasma*-related lung disease classically presents as a large nodule with abundant central necrosis surrounded by a thin rim of epithelioid histiocytes and a fibrotic capsule of variable thickness.

Cytological diagnosis of *Histoplasma* possesses challenges, and sometimes, it may be difficult to differentiate from *Cryptococcus*.⁷ Histopathology using stains for fungi, cultures, antigen detection, and serologic tests for *Histoplasma*-specific antibodies confirm the diagnosis of pulmonary histoplasmosis.⁸ The clinicopathological features with differential diagnosis of *Histoplasma* have been described (Table 1).

Fungal cultures of multiple sputum or bronchoalveolar lavage are most useful in chronic pulmonary histoplasmosis cases. *Histoplasma* antigen detection using enzyme immunoassay in the blood or bronchoalveolar lavage fluid of infected patients provides rapid diagnostic information

mainly in severely ill patients. However, serologic tests are often negative in immunosuppressed and chronic pulmonary cases.

Pulmonary histoplasmosis should be considered while evaluating immunocompetent or immunocompromised patients with risk factors of heavy soil exposure and pre-existing lung disease. The present case had a history of cutaneous tuberculosis, without any symptomatic relief by ATT. Radiological possibilities of multidrug resistance (MDR) tuberculosis was considered; however, the imprint smear followed by histopathology changed the management. Histoplasmosis is a mild and self-limiting disease in most of the healthy individuals; however, antifungal therapy may be indicated in chronic pulmonary, acute pulmonary infection, and progressive cases. Itraconazole should be given as a loading dose (200 mg orally three times daily for the first 3 days) followed by a maintenance dose (200 mg orally once or twice daily) for at least 1 year. Radiographic abnormalities improve during the first year of treatment in at least two-thirds of cases; therefore, the treatment should not be discontinued until radiographic findings have stabilized. As 10–20% of patients with chronic pulmonary histoplasmosis may get relapse mostly within 2 years of stopping therapy, follow-up should be continued for at least 5 years. Here, we are reporting this case because of its rarity in a non-endemic zone; so as to encourage vigilant observation among pathologists to suspect histoplasma in immunosuppressed patients where the clinical suspicion of tuberculosis is very high.

Conflict of interest

The authors have none to declare.

REFERENCES

1. Wheat LJ, Freifeld AG, Kleiman MB, et al. Clinical practice guidelines for the management of patients with histoplasmosis: update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2007;45:807–825.
2. McKinsey DS, McKinsey JP. Pulmonary histoplasmosis. *Semin Respir Crit Care Med*. 2011;32:735–744.
3. Kahi CJ, Joseph Wheat L, Allen SD, et al. Gastrointestinal histoplasmosis. *Am J Gastroenterol*. 2005;100:220–231.
4. Antinori S. *Histoplasma capsulatum*: more widespread than previously thought. *Am J Trop Med Hyg*. 2014;90:982–983.
5. Wheat LJ. Histoplasmosis: a review for clinicians from non-endemic areas. *Mycoses*. 2006;49:274–282.
6. Kauffman CA. Histoplasmosis: a clinical and laboratory update. *Clin Microbiol Rev*. 2007;20:115–132.
7. Ranjan R, Jain D, Singh L, Iyer VK, Sharma MC, Mathur SR. Differentiation of histoplasma and cryptococcus in cytology smears: a diagnostic dilemma in severely necrotic cases. *Cytopathology*. 2015;26:244–249.
8. Jung EJ, Park DW, Choi JW, Choi WS. Yonsei. Chronic cavitary pulmonary histoplasmosis in a non-HIV and immunocompromised patient without overseas travel history. *Med J*. 2015;56:871–874.