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CASE STUDY

ISOLATED IMMUNOGLOBULIN M DEFICIENCY PRESENTING AS PROGRESSIVE DISSEMINATED HISTOPLASMOSIS

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ABSTRACT

Disseminated histoplasmosis is a very severe and often fatal opportunistic infection mostly seen in immunocompromised hosts and rarely in immunocompetent individuals. We report here a rare case of 13 year old male misdiagnosed as pulmonary tuberculosis and hodgkin's lymphoma before eventually being diagnosed as histoplasmosis with an underlying isolated IgM deficiency to increase awareness of the clinical spectrum of disseminated histoplasmosis and its similarity to other infections and malignancies to encourage early diagnosis so that diagnostic and therapeutic pitfalls can be avoided to improve eventual outcome of the disease.

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INTRODUCTION

Histoplasmosis also known as Cave disease, Darling's disease, Ohio valley disease, reticuloendotheliosis, spelunker's lung and caver's disease is a disease caused by the fungus Histoplasma capsulatum. Although life-threatening histoplasmosis is reported more commonly among immunocompromised and very elderly patients, up to 20% of severe illnesses may result from heavy inoculums in immunocompetent people (McAdams *et al*., 1995; Kurowski *et al*., 2002; Wheat *et al*., **?**). In addition, patients with underlying lung disease are specially susceptible and can develop the disease with clinical and radiographic findings that resemble tuberculosis (TB) [(4)]. We report here the presentation, misdiagnosis, and eventual diagnosis of a 13-year-old boy who presented to our hospital with fever and generalized lymphadenopathy with a background of recurrent infections from birth.

Case report

A 13-year-old boy was referred to our hospital with pyrexia and generalized lymphadenopathy and a clinical diagnosis of Hodgkin's Lymphoma. On detailed history and physical examination, the patient was found to have a history of recurrent infections from birth. Pt. had high grade fever since one week prior to presentation. His physical examination revealed hepatosplenomegaly along with lymphadenopathy at multiple sites however examination of respiratory, cardio-vascular and central nervous systems was normal.CXR was suggestive of multiple B/L nodular pulmonary infiltrates. Six months prior to his presentation to our hospital, he had presented to a peripheral hospital with similar symptoms and was started on ATT on the basis of chest radiography. During the course of ATT his symptoms did not improve much and there was no resolution of lymphadenopathy. A tissue diagnosis was then sought and biopsy of axillary lymphnode was done which was suggestive of lympho-proliferative disorder – ? Hodgkin's Lymphoma and immuneohistochemical markers were advised. CECT of chest along with abdomen was done with multiple enlarged discrete and conglomerate heterogeneously enhancing cervical, supraclavicular, axillary, mediastinal & abdominal lymphnodes along with nodular opacities in both lungs with hepatosplenomegaly and mild ascites s/o TB or lympho-proliferative disorder (Lymphoma). Further marker studies were carried out along with review of lymph node biopsy block which showed scattered small yeast like organisms 2-4 micron in diameter highlighted by GMS and PAS stain and acid fast on Z-N stain.

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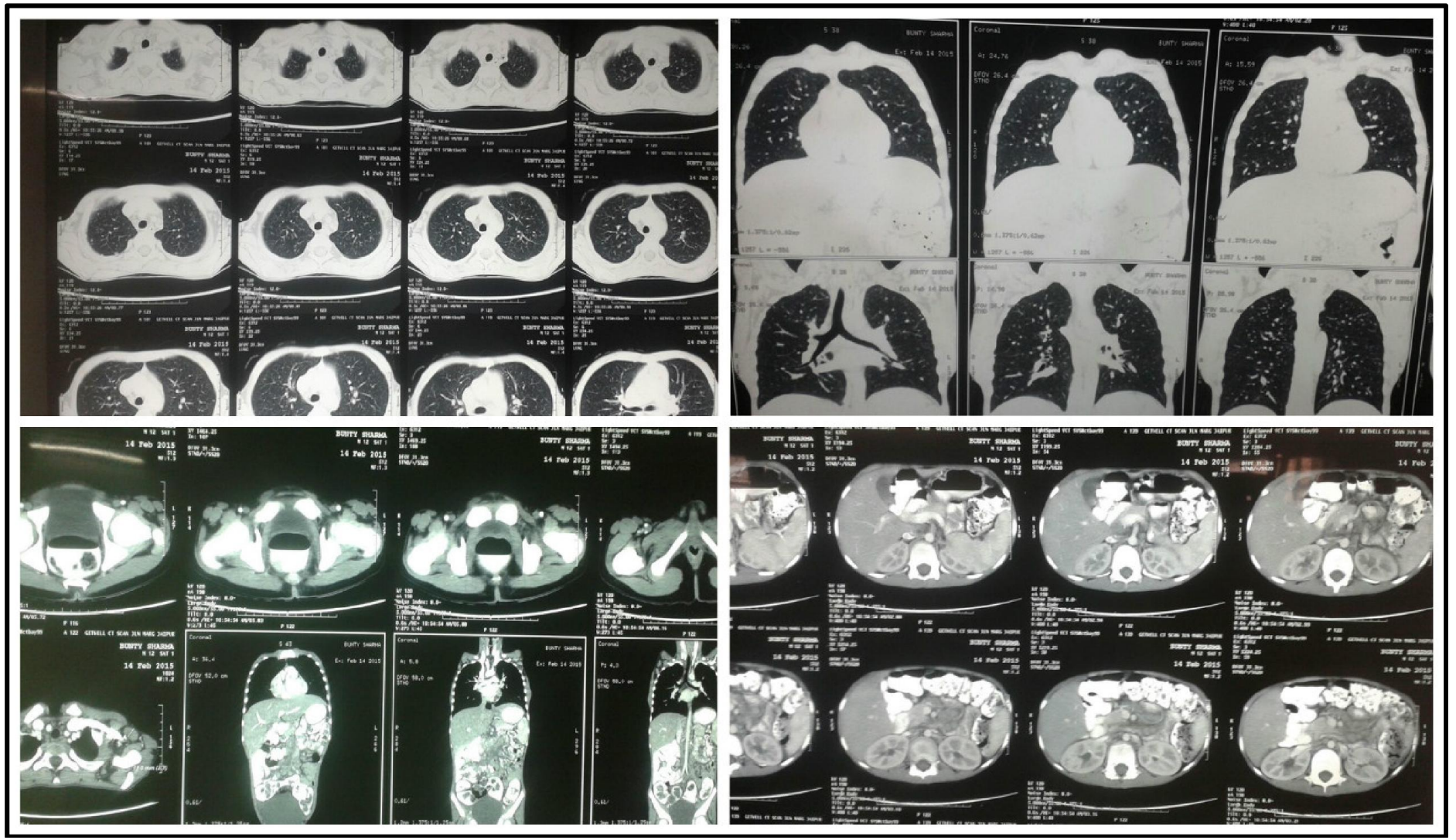

Figure 1. (clockwise from top left) CECT Chest (image 1&2) showing bilateral hilar enlargement with multiple nodular opacities and CECT Abdomen (image 3&4) showing multiple lymphodenopathy with spleen and liver enlargement

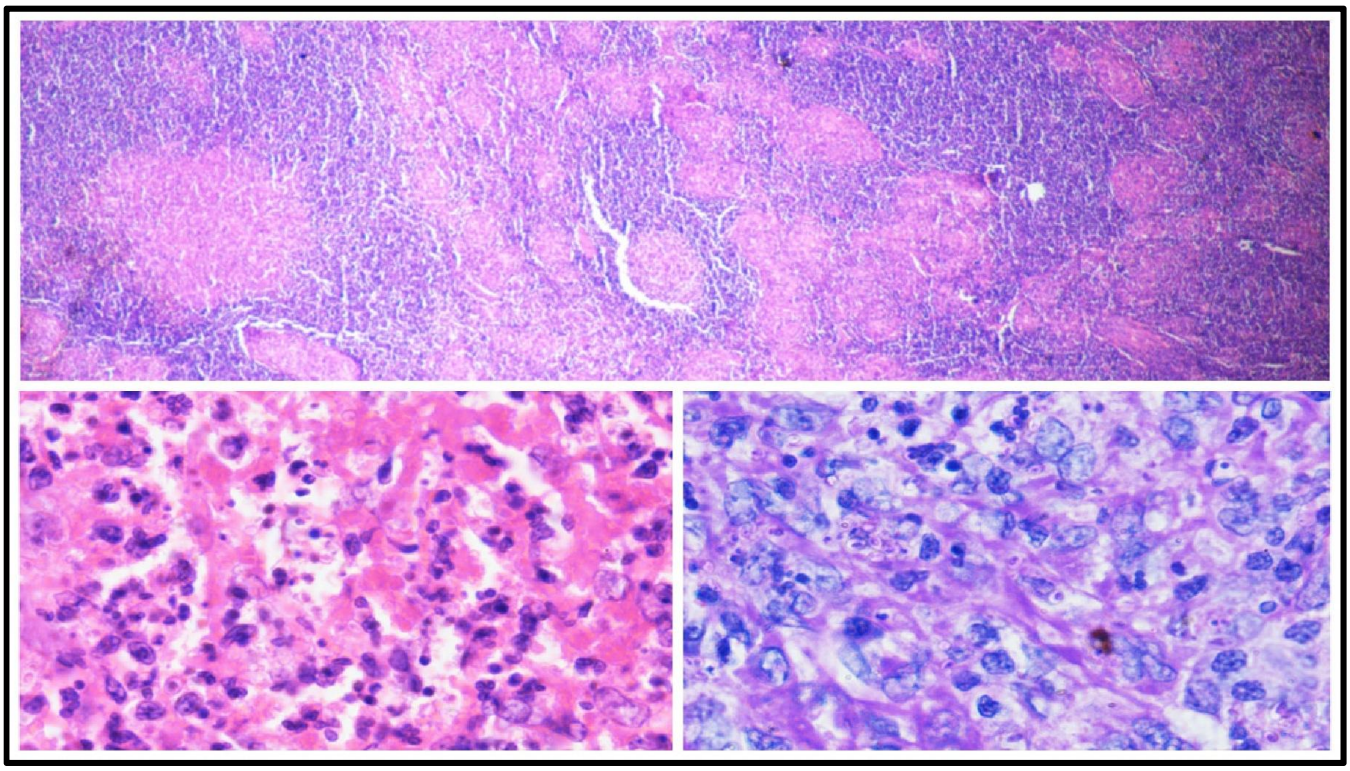

Figure 2. (clockwise from top left) Image 1 showing scanner view 10× showing lymph node tissue with granuloma ; image 2 showing 100× oil immersion view with histoplasma fungus and presence of capsule around it ; image 3 showing PAS staining of fungus with PAS positivity

CD-20 marked the 'B' and CD-3 marked the 'T' zone respectively and CD-30 marked the scattered immunoblasts. The final impression on review was of histoplasmosis of lymph node. His HIV status was negative. Serum IgE levels were 147 (H), IgA : 132.52 (H), IgG : 2644 (H) , IgM 21.89 (L) . Rest all blood investigations were normal. Pt. was started on anti fungals and has responded well.

DISCUSSION

In India, the Gangetic West Bengal is the site of most frequent infections with 9.4 percent of the population testing positive. (Sanyal and Thammayya, 1975) Histoplasma capsulatum was isolated from the local soil proving endemicity of histoplasmosis in West Bengal. (Sanyal and Thammayya, 1980) Symptoms of histoplasmosis infection occur within 3 to 17 days after exposure; the average is 12–14 days. Most affected individuals have clinically silent manifestations and show no apparent ill effects. (Silberberg, 2007) The acute phase of histoplasmosis is characterized by non-specific respiratory symptoms, often cough or flu-like. Chest X-ray findings are normal in 40–70% of cases. (Silberberg, 2007) Chronic histoplasmosis cases can resemble tuberculosis; (Kurowski *et al*., 2002; Wheat *et al*., **?**) disseminated histoplasmosis affects multiple organ systems and is fatal unless treated. (Kauffman, 2007) Severe infections can cause hepatosplenomegaly, lymphadenopathy and adrenal enlargement. (Ryan and Ray, 2004) Our patient too presented with hepatosplenomegaly, multiple lymphadenopathy and chest infiltrates. H. capsulatum grows in soil and material contaminated with bird or bat droppings. If the patient has strong cellular immunity, macrophages, epithelial cells and lymphocytes surround the organisms and contain them and eventually calcify. In immunocompromised individuals, the organisms disseminate to different organs such as bone, spleen, liver, adrenal glands and mucocutaneous membranes, resulting in progressive disseminated histoplasmosis as in our patient with an isolated immunoglobulin M deficiency. Histoplasmosis can be diagnosed by samples containing the fungus taken from sputum (via bronchoalveolar lavage), blood, or infected organs. It can also be diagnosed by detection of antigens in blood or urine samples by ELISA or PCR. Histoplasmosis can also be diagnosed by a test for antibodies against Histoplasma in the blood. Histoplasma skin tests indicate whether a person has been exposed, but do not indicate whether they have the disease. (Ryan and Ray, 2004) Formal histoplasmosis diagnoses are often confirmed only by culturing the fungus directly. (Cotran *et al*., 2005) Diagnosis can also be established on the basis of histopathology as we did in our patient. In the majority of immunocompetent individuals, histoplasmosis resolves without any treatment. Antifungal medications are used to treat severe cases of acute histoplasmosis and all cases of chronic and disseminated disease. Typical treatment of severe disease first involves treatment with amphotericin B, followed by oral itraconazole. (Wheat *et al*., 2007; Histoplasmosis: Fungal Infections at Merck Manual of Diagnosis and Therapy Home Edition) We too treated our patient with liposomal amphotericin-B and initially with voriconazole but eventually shifted him to itraconazole on follow up visit due to economic constraints. Our patient has improved on follow up with substantial weight gain. Treatment with itraconazole will need to continue for at least a year in

severe cases, (Barron and Madinger, 2008) while in acute pulmonary histoplasmosis, 6 to 12 weeks treatment is sufficient. Alternatives to itraconazole are posaconazole, voriconazole and fluconazole. Individuals taking itraconazole are monitored for hepatic function.

Conclusion

We report our experience to increase awareness of the clinical spectrum of disseminated histoplasmosis and its similarity to other infections specially tuberculosis and malignancies to encourage early diagnosis and to avoid diagnostic and therapeutic pitfalls.

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