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CUTANEOUS HISTOPLASMOSIS IN CHILD WITH HYPER IG M SYNDROME

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ABSTRACT

Histoplasmosis is a disease caused by dimorphic fungus histoplasma capsulatum, commonly found in soil contaminated with bird or bat droppings or decay wood. Its route of transmission is through inhalation of aerosolized mycelial form. The organism remains in the mold (mycelial) form at soil temperatures and converts to the yeast form at human body temperature (37°C), where it resides within macrophages. The fungus is rapidly phagocytosed by macrophages and neutrophils but resists intracellular destruction. Intracellular yeast can disseminate through the lymphatics and bloodstream. Infected macrophages release cytokines to recruit additional macrophages and monocytes, which aggregate to form granulomas. A failure of the immune response results in the progressive spread of the infection to other organs. A 7-year-old female with history of intermittent fever for 8 months, multiple joint pain and weight loss for 2 months. On examination, she had pallor, erythematous plaque on face and hepatosplenomegaly. The patient had high levels of immunoglobulins and reduced CD4, CD8 count. cutaneous histoplasmosis was diagnosed on microscopic examination of bone marrow and skin biopsy and was confirmed by fungal culture of bone marrow & blood. histoplasmosis commonly affect immunocompromised individual, presentation varies from primary pulmonary histoplasmosis, disseminated histoplasmosis. Our case represents a unique as histoplasmosis is rarely seen in paediatric age group and Indian population

INTRODUCTION

Histoplasmosis was first identified in 1906 by Samuel Taylor Darling among workers on the Panama Canal. Endemic regions for histoplasmosis include the Ohio and Mississippi River Valleys in the United States, Central and South America, Africa, and Southeast Asia. The etiologic agent responsible for histoplasmosis is Histoplasma capsulatum, a dimorphic fungus with global distribution. This fungus is found in soil, where it exists in a mycelial form. The primary route of entry for H. capsulatum is through the inhalation of aerosolized microconidia. Upon infection, the mycelia transform into the yeast form. The organism remains in the mold (mycelial) form at soil temperatures and converts to the yeast form at human body temperature (37°C), where it resides within macrophages. The fungus is rapidly phagocytosed by macrophages and neutrophils but resists intracellular destruction. Intracellular yeast can disseminate through the lymphatics and bloodstream. Infected macrophages release cytokines to recruit additional macrophages and monocytes, which aggregate to form granulomas. A failure of the immune response results in the progressive spread of the infection to other organs.[1,2]

Clinically, histoplasmosis can present in various forms: asymptomatic infection, acute or chronic pulmonary infection, mediastinal fibrosis or granulomas, and disseminated histoplasmosis (DH). The development of progressive DH indicates compromised cell-mediated immune responses. The acute form of disseminated histoplasmosis predominantly occurs in immunocompromised individuals and is characterized by an abrupt onset of symptoms such as fever, malaise, hepatosplenomegaly, lymphadenopathy, anemia, leukopenia, and thrombocytopenia[3]; absence of a granulomatous inflammatory response; and high case-fatality rates. The chronic form of DH exhibits a more indolent course with focal lesions and an effective cell-mediated immune response. Subacute DH follows a persistent but slower course with focal lesions in various visceral organs.[4]

Clinical History

We report a case of an 11-year-old male child, born of a non-consanguineous marriage, diagnosed with Hyper IgM syndrome at the age of four. The patient had a history of gangrenous BCG mark adenitis treated with antitubercular therapy. The patient experienced recurrent episodes of pyogenic infections, prompting an immunology workup that revealed autosomal recessive Hyper IgM Syndrome. Symptomatic treatment was provided along with monthly intravenous immunoglobulin.

Recently, the patient presented with high-grade fever and was observed to be apathetic with multiple well-defined, firm, mobile, and nontender cervical, axillary, and inguinal lymphadenopathy. Hepatosplenomegaly was noted, with a liver span of 10 cm and grade 2 splenomegaly confirmed by abdominal ultrasonography. Workup for pyrexia, including serum Widal, dengue antigen test, and urine routine microscopy, was negative. The patient exhibited moderate anemia and elevated total leukocyte count with relative eosinophilia. Antibiotics were initiated, but the patient's condition worsened, prompting a high-resolution CT scan (HRCT). HRCT revealed multiple centrilobular and subpleural soft tissue nodules and varying size paratracheal, prevascular, bilateral hilar, and subcarinal lymph nodes, some with calcifications, suggestive of granulomatous lesions such as tuberculosis, histoplasmosis, sarcoidosis, or lymphoproliferative disorders.

Lymph node biopsy revealed epithelioid cells with multinucleated Langerhans giant cells. The patient was started on antitubercular therapy (ATT), but due to ATT-induced hepatitis, the regimen was changed to isoniazid, levofloxacin, and ethambutol, along with cotrimoxazole prophylaxis. Despite ATT, the patient continued to exhibit high-grade fever, lethargy, abdominal distension, weight loss,

lymph node swelling, and developed multiple skin lesions (hyperpigmented nodules with central umbilication) involving the scalp, nape of the neck, angle of the nose, and chin with nodular erosive lesions discharging pus.

Figure 1: hyperpigmented nodules with central umbilication

Non-contrast CT (NCCT) of the neck and abdomen showed persistent multiple enlarged lymph nodes. Fine-needle aspiration cytology (FNAC) and punch biopsy of the lymph nodes revealed cohesive groups and microgranuloma formations by histiocytes containing small organisms surrounded by clear spaces in their cytoplasm, with eosinophils in the hemorrhagic background, suggestive of tubercular lymphadenitis and highly suspicious for histoplasmosis. Skin punch biopsy of a nodular lesion showed chronic inflammatory infiltrate in the superficial dermis, including foaming histiocytes with budding yeast forms, indicative of Histoplasma capsulatum.

Based on these findings, the patient was started on the antifungal drug amphotericin B for four weeks, alongside continuing ATT. The patient gradually improved and was discharged with a recommendation to continue oral itraconazole.

DISCUSSION

In India, histoplasmosis is not considered endemic, but areas of high prevalence exist along the Gangetic plains, particularly in West Bengal and Uttar Pradesh. Histoplasmosis is a rare disease in Indian pediatric patients.

In our patient, Hyper IgM syndrome presents with functional B cells but defective T cells. The CD40 ligand (CD40L), which binds to CD40 on B cells and monocytes, is upregulated on T cells upon activation. Mutations in this pathway disrupt signaling required for B cell isotype switching, resulting in the exclusive production of IgM. This impairment occurs due to defective interaction between T cells and B cells through the CD40-CD40L receptor-ligand pair. The causative mutations involve the CD40 ligand gene on the X chromosome and three autosomal genes: activation-induced cytidine deaminase (AID), uracil DNA glycosylase (UNG), and CD40 on chromosome 20. X-linked Hyper IgM syndrome results from mutations in the CD40 ligand gene (CD154, CD40L), which is expressed on activated T-helper (Th) cells. Children with immune deficiencies, especially those affecting cell-mediated immunity, are at a heightened risk for disseminated histoplasmosis. Mutations in the IL-12/IFN- pathway, such as IL-12R 1 deficiency and IFN- R1 deficiency, have been associated with disseminated histoplasmosis in children. These patients often experience recurrent pyogenic infections, including otitis media, sinusitis, pneumonia, and tonsillitis, and are highly susceptible to Pneumocystis jiroveci pneumonia and Cryptosporidium enteritis.

Our patient exhibits similar symptoms, including recurrent pyogenic infections and receiving regular IVIG treatment. Histoplasmosis primarily affects the respiratory system, causing pulmonary histoplasmosis, but it can also disseminate to other organs. Mosam et al., 2006 reported a case of disseminated histoplasmosis in an 11-year-old female African child who initially received anti-Koch's regimen for two weeks despite negative Mantoux test and negative AFB[5].

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