Case report

Disseminated histoplasmosis in a patient with common variable immunodeficiency: A coincidence or the result of T cell defects?

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ABSTRACT

Background: In endemic regions, histoplasmosis is often seen in hosts with defective cell mediated immunity. We report a case of disseminated histoplasmosis in a patient with common variable immunodeficiency (CVID), a disorder mainly characterized by B cell defects. Case: A 35 year old male with CVID developed fever, headache, dyspnea and pancytopenia within few weeks of swimming in the Tennessee River. After a non-revealing initial evaluation he was transferred to a tertiary facility for fever of unknown origin, where massive splenomegaly was noted. Clinical course was complicated by hypoxia from extensive bilateral lung infiltrates requiring non-invasive ventilation. Urine and serum Histoplasma antigens were positive. He was treated with liposomal amphotericin B followed by itraconazole after clinical improvement within 48 h and discharged home by day 6. Fungal blood cultures sent on day 1 grew Histoplasma capsulatum on day 19. After 5 months splenomegaly completely resolved and he successfully completed one year of treatment with itraconazole.

Conclusions: Our case highlights the significance of T cell defects in CVID. More research focusing on T cell defects in CVID is required to understand the extent of vulnerability to such intracellular pathogens in CVID.

Background

Disseminated histoplasmosis is often seen in immunocompromised hosts [1]. Sporadic and inherited forms of Common variable immunodeficiency (CVID), is classically described as hypogammaglobulinemia from B cell defects predisposing to recurrent bacterial sino-pulmonary infections. Abnormalities in T cells and antigen presenting cells have also been rarely reported [2–4]. Literature on disseminated histoplasmosis in patients with CVID is sparse [3,5–9]. We describe a patient with CVID who presented with disseminated histoplasmosis. We reviewed the literature on T cell defects in CVID that predispose to disseminated histoplasmosis.

Case presentation

A 35 year old man with common variable immune deficiency (CVID) on monthly maintenance intravenous immunoglobulin (IVIG) infusions, was admitted to an outside hospital during the summer with fever, headache, and progressive shortness of breath over a month. He was compliant with monthly IVIG infusions with the most recent dose administered a week prior to the onset of symptoms. Past medical history included asthma, hypertension and depression. He lived in Missouri, never travelled outside of United States. Six weeks before presentation he swam in the Tennessee River. He smoked 1.5 packs of cigarettes per day for 20 years, occasionally consumed alcohol and smoked marijuana. His son also had CVID, but no other family members had known immune-deficiencies. Long ago, he was a construction worker, but he is presently disabled. On exam, he was febrile, tachycardic and had left maxillary sinus tenderness, but otherwise exam was reported as normal. White blood cell (WBC) count was 1.0 × 10³/μL (neutrophils [N] 36%, lymphocytes [L] 50% and monocytes [M] 14%), hemoglobin (Hb) 9.4 g/dL and platelets 53 × 10³/μL. Serum
vealed bilateral crackles in lower lung fields. Chest exam revealed bilateral crackles in lower lung fields. There was no rash, lymphadenopathy, meningeal signs or focal neurologic deficits. WBC 1.94 × 10^3/µL (N 48%, L 36.6%, M 14.4%, basophils [B] 0.5%), Hb 9.8 g/dL, platelets 51 × 10^3/µL, prothrombin time 18.4 s, serum electrolytes and renal function tests were normal, serum aspartate aminotransferase (AST) 60 U/L, total protein 5.0 g/dL, albumin 2.5 g/dL and rest of liver function tests were normal. C-reactive protein was elevated (12.4 mg/dL) and plasma procalcitonin (bioMerieux VIDAS B.R.A.H.M.S PCT) was 1.46 ng/mL. Lactate dehydrogenase (LDH) was 476 U/L and serum ferritin 3016 ng/mL. Blood smear showed atypical lymphocytes and pancytopenia with toxic granulation of neutrophils.

Histoplasma capsulatum is a dimorphic fungus, existing as a mold in the environment at 25–30 °C and yeast at 37 °C in tissues (intracellular in macrophages). Histoplasmosis is endemic in Mississippi and Ohio river valleys, with moist soil containing large amounts of bird or bat guano containing large amounts of the organism [10]. Exposure often occurs during occupational and recreational activities in endemic areas that involve inhalation of dust laden with spores [11–13]. Most infections in the immunocompetent hosts are asymptomatic or result in mild pulmonary disease [14]. Cell mediated immunity is required to control infection [10]. Patients with primary or acquired defects in cell-mediated immunity are at risk for disseminated histoplasmosis with severe manifestations such as septic shock, acute respiratory distress syndrome and multi organ failure [1,10]. Other manifestations of disseminated histoplasmosis include hepatosplenomegaly, mucosal ulcers, cutaneous lesions, gastrointestinal involvement, pancytopenia and elevated AST, ALT, LDH and serum ferritin levels [10,14]. Our patient had elevated LDH, ferritin, pancytopenia and massive splenomegaly. Radin studied CT findings in 16 patients with disseminated histoplasmosis (14 infected with HIV), six (37.5%) had splenomegaly, of which 3(18.8%) had massive splenomegaly ranging from 22 to 26 cm [15].

CVID is the most common primary immunodeficiency with primary defect in B-cell maturation leading to hypogammaglobulinemia [4]. In addition, defects in T cells and antigen presenting cells have been reported [4]. Varying combination of these defects result in different immunological and clinical phenotypes [4]. For both inherited and sporadic forms, diagnosis is based on set criteria: hypogammaglobulinemia plus any one of: decreased IgM or IgA isotypes, onset > 2 years (7.42 ng/mL) returned positive. He became afebrile within the next 48 h and hypoxemia improved. By day 6, he was switched to oral itraconazole 200 mg three times daily and discharged home with a plan to treat for at least one year. Fungal blood cultures sent on day 1 grew Histoplasma capsulatum on day 19. After 2 months, he had improved clinically, blood cell counts had improved to baseline and itraconazole levels were adequate. After 5 months, splenomegaly resolved; after 10 months he had gained weight (from 81 kg to 93 kg) and was symptom free. After 12 months urine Histoplasma antigen was negative and itraconazole was stopped.

**Discussion**

**Histoplasma capsulatum** is a dimorphic fungus, existing as a mold in the environment at 25–30 °C and yeast at 37 °C in tissues (intracellular in macrophages). Histoplasmosis is endemic in Mississippi and Ohio river valleys, with moist soil containing large amounts of bird or bat guano containing large amounts of the organism [10]. Exposure often occurs during occupational and recreational activities in endemic areas that involve inhalation of dust laden with spores [11–13]. Most infections in the immunocompetent hosts are asymptomatic or result in mild pulmonary disease [14]. Cell mediated immunity is required to control infection [10]. Patients with primary or acquired defects in cell-mediated immunity are at risk for disseminated histoplasmosis with severe manifestations such as septic shock, acute respiratory distress syndrome and multi organ failure [1,10]. Other manifestations of disseminated histoplasmosis include hepatosplenomegaly, mucosal ulcers, cutaneous lesions, gastrointestinal involvement, pancytopenia and elevated AST, ALT, LDH and serum ferritin levels [10,14]. Our patient had elevated LDH, ferritin, pancytopenia and massive splenomegaly. Radin studied CT findings in 16 patients with disseminated histoplasmosis (14 infected with HIV), six (37.5%) had splenomegaly, of which 3(18.8%) had massive splenomegaly ranging from 22 to 26 cm [15].

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of age, absent iso-hemagglutinins and/or poor response to vaccines; and exclusion of other causes of hypogammaglobulinemia [4,16]. While replacing IgG confers immunity towards bacterial infections, defects in cell mediated immunity may predispose CVID patients to granulomatous inflammation and autoimmunity [17]. Splenomegaly in CVID has been attributed to the lower number of T regulatory cells resulting in chronic and ineffective/nonselective activation of T cells with inverse CD4/CD8 ratios and polyclonal expansion of large granular lymphocytes [18–20]. This abnormal T cell activation has been linked to the risk of disseminated histoplasmosis in this population [3]. In our case, as splenomegaly improved with antifungal therapy, it is likely a manifestation of disseminated histoplasmosis as a result of such abnormal T cell regulation in CVID. The case presented here adds to the evidence and discussion about the existence of T cell defects in CVID, predisposing hosts to pathogens that require cell mediated immunity to contain or prevent disease, such as histoplasmosis.

Conclusion

Disseminated histoplasmosis can occur in CVID due to cell mediated immune defects that result in abnormal T cell activation. Further research is needed to conclusively add disseminated histoplasmosis to the list of infections that can occur in CVID.

Declarations

Ethics approval and consent to participate

University of Missouri – Health Sciences Review Board approved this case report for submission for publication. IRB # 2006604 HS.

Consent for publication

Not applicable as there are no personally identifiable data in this case report.

Availability of data and material

Not applicable.

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Authors’ contributions

MJ prepared the first draft. HR edited first draft and further expanded the manuscript with significant additions to all sections of manuscript including references. HR added the images. WS and CR provided further critical edits and after several rounds of editing, final manuscript was completed by HR, and then reviewed and approved by all authors before submission.

Conflict of interests

None among the authors.

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