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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 sinopulmonary 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 1.0×10^{-3}/μL (neutrophils [N] 36%, lymphocytes [L] 50% and monocytes [M] 14%), hemoglobin (Hb) 9.4 g/dL and platelets 53×10^{-3}/μL. Serum

Abbreviations: CVID, common variable immuno deficiency; IVIG, intravenous immuno globulin; WBC, white blood cell; N, neutrophils; L, lymphocytes; M, monocytes; B, basophils; Hb, hemoglobin; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; PCT, procalcitonin; HIV, human immuno deficiency virus; CT, computed tomography

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electrolytes, renal and liver function tests were normal. Chest X-ray reported chronic blunting of right costo-phrenic angle, clear lung fields and normal cardiac silhouette. Computed tomography (CT) of the paranasal sinuses showed pan sinus mucosal thickening. Intravenous vancomycin, ceftazidime and levofloxacin were initiated. Blood cultures were negative, urinalysis was normal. A tick-borne panel (*Ehrlichia* PCR, Rocky Mountain spotted fever IgG/IgM, tularemia serology, Lyme IgG/IgM and *Babesia* serology), Cytomegalovirus polymerase chain reaction (CMV-PCR) and monospot were negative. Bone marrow biopsy showed pancytopenia, but no blasts or organisms (acid fast and Giemsa stains). After 5 days, pancytopenia and fever persisted, micafungin was added and patient was transferred to our facility.

At admission to our facility, he was dyspneic, temperature 39.4 °C, heart rate 118/min and oxygen saturation (SpO_2) 93% on nasal oxygen at 11 L/min. Abdominal exam revealed a firm non-tender massive splenomegaly (left upper quadrant to right iliac fossa); 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. Chest x-ray (Fig. 1) showed linear reticular opacities extending from hila to periphery. A subsequent CT chest, abdomen and pelvis (Fig. 2) revealed extensive bilateral confluent alveolar opacities with sub pleural sparing, moderate left and small right pleural effusions, multiple pre- and para-tracheal lymph nodes and massive splenomegaly (27.5 cm craniocaudal). Blood cultures(bacterial, acid fast bacilli and fungal) were sent. Human Immunodeficiency Virus (HIV) 1,2 antigen-antibody and urine *Legionella* antigen were negative. Urinalysis was normal. Serum beta-D-glucan, cryptococcal antigen, and serum and urine for *Histoplasma* and *Blastomyces* antigens were sent. He was treated empirically with intravenous vancomycin, piperacillin-tazobactam and doxycycline (tick season). The next day (day 2), he required transfer to the intensive care unit for worsening hypoxemia and was started on empiric liposomal amphotericin B. Lumbar puncture was performed and cerebrospinal fluid analysis was essentially normal. A nasal endoscopic exam did not show findings consistent with invasive fungal disease. On day 3, serum beta-D glucan returned elevated (493 pg/mL), and *Histoplasma* antigen in serum (2.68 ng/mL) and urine

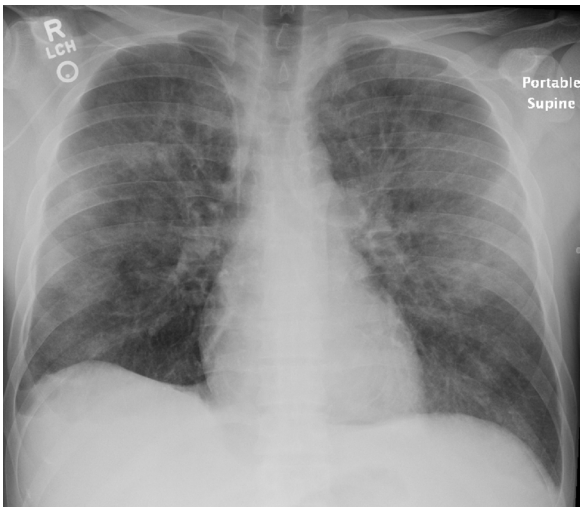

Fig. 1. Chest x-ray at admission.

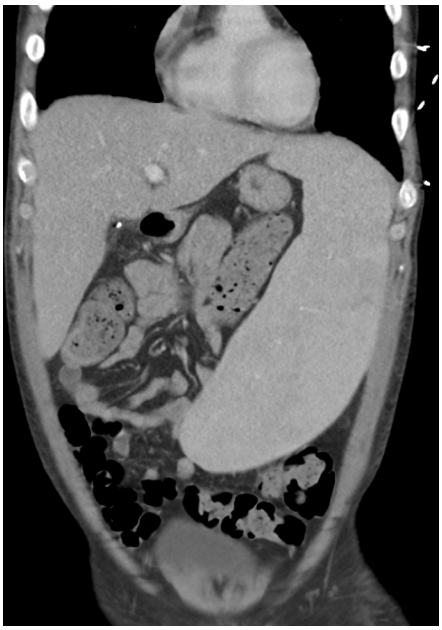

Fig. 2. Contrast enhanced computed tomography of abdomen showing massive splenomegaly.

(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].

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

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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References

[1] Kauffman CA. Diagnosis of histoplasmosis in immunosuppressed patients. Curr Opin Infect Dis 2008;21(4):421–5.
[2] Bonilla FA, Bernstein IL, Khan DA, Ballas ZK, Chinen J, Frank MM, et al. Practice parameter for the diagnosis and management of primary immunodeficiency. Ann. Allergy Asthma Immunol 2005;94(5):S1–63.
[3] Rachid A, Rezende LS, de Moura SF, Loffy PC, Magalhaes FL. A case study of disseminated histoplasmosis linked to common variable immunodeficiency. Braz J Infect Dis 2003;7(4):268–72.
[4] Salzer U, Warnatz K, Peter HH. Common variable immunodeficiency – an update. Arthritis Res Ther 2012;14(5):223.
[5] Couch JR, Abdou NI, Sagawa A. Histoplasma meningitis with hyperactive suppressor T cells in cerebrospinal fluid. Neurology 1978;28(2):119–23.
[6] Dang AT, Schwartz G, Jones L, Absalon MJ, McMasters RL, Assa'ad A. An unusual cause of fever in a patient with common variable immunodeficiency. Ann Allergy Asthma Immunol 2017;119(3):210–3.
[7] Hodgkins PR, Lane AC, Chisholm IH, Absolon MJ, Elkington AR, Smith JL. Immunophenotyping in presumed ocular histoplasmosis like retinopathy. Eye (Lond, Engl) 1995;9(Pt 1):56–63.
[8] Kane S, Brasitus T. Histoplasmosis capsulatum as a cause of lower gastrointestinal bleeding in common variable immunodeficiency. Dig Dis Sci 2000;45(11):2133–5.
[9] Shukla A, Shah C, Hardik P, Gupte P. A probable case of histoplasmosis presenting as portal hypertension and bone lesion in a case of common variable immunodeficiency syndrome. J Postgraduate Med 2015;61(1):49–50.
[10] Kauffman CA. Histoplasmosis: a clinical and laboratory update. Clin Microbiol Rev 2007;20(1):115–32.
[11] Brodsky AL, Gregg MB, Loewenstein MS, Kaufman L, Mallison GF. Outbreak of histoplasmosis associated withthe 1970 earth day activities. Am J Med 1973;54(3):333–42.
[12] Jones TF, Swinger GL, Craig AS, McNeil MM, Kaufman L, Schaffner W. Acute pulmonary histoplasmosis in bridge workers: a persistent problem. Am J Med 1999;106(4):480–2.
[13] Wheat J. Histoplasmosis. Experience during outbreaks in Indianapolis and review of the literature. Medicine 1997;76(5):339–54.
[14] Wheat LJ, Freifeld AG, Kleiman MB, Baddley JW, McKinsey DS, Loyd JE, et al. Clinical practice guidelines for the management of patients with histoplasmosis: 2007 update by the infectious diseases society of America. Clin Infect Dis 2007;45(7):807–25.
[15] Radin DR. Disseminated histoplasmosis: abdominal CT findings in 16 patients. Am J Roentgenol 1991;157(5):955–8.
[16] Conley ME. Diagnostic guidelines—an international consensus document. Clin Immunol 1999;93(3):189.
[17] Cunningham-Rundles C, Bodian C. Common variable immunodeficiency: clinical and immunological features of 248 patients. Clin Immunol 1999;92(1):34–48.
[18] Fevang B, Yndestad A, Sandberg WJ, Holm AM, Müller F, Aukrust P, et al. Low numbers of regulatory T cells in common variable immunodeficiency: association with chronic inflammation in vivo. Clin Exp Immunol 2007;147(3):521–5.
[19] Holm A, Tjønnfjord G, Yndestad A, Beiske K, Müller F, Aukrust P, et al. Polyclonal expansion of large granular lymphocytes in common variable immunodeficiency-association with neutropenia. Clin Exp Immunol 2006;144(3):418–24.
[20] Yu GP, Chiang D, Song SJ, Hoyte EG, Huang J, Vanishsarn C, et al. Regulatory T cell dysfunction in subjects with common variable immunodeficiency complicated by autoimmune disease. Clin Immunol 2009;131(2):240–53.