Disseminated Cryptococcosis in a Deceptively Immunocompetent Adolescent

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Abstract

Cryptococcosis particularly if disseminated or extrapulmonary, in an otherwise immune-competent individual, especially if young, requires thorough evaluation for underlying primary immunodeficiency including Mendelian susceptibility to mycobacterial disease (MSMD). In this context, we describe an adolescent diagnosed with disseminated cryptococcosis involving skin, lymph nodes, spleen and hepato-biliary involvement with reduced IL-12β1 receptor expression suggesting underlying MSMD. Following initial management with conventional amphotericin and fluconazole, along with antibiotics for cholangitis and later suppressive prophylaxis with fluconazole our patient showed good response with resolution of jaundice, normalization of liver function tests by second month of follow-up and had significant regression of lymph nodes as well as skin lesions by six months.

Keywords
MSMD, Disseminated cryptococcosis

Introduction

Disseminated cryptococcosis is most commonly associated with HIV infection. However, cryptococcal infection in an apparently immunocompetent individual, requires exclusion of underlying primary immunodeficiency. Mendelian susceptibility to mycobacterial disease (MSMD) is a rare innate immune defect characterized by predisposition to infections by less virulent mycobacteria, non-typhoidal salmonellosis and more rarely with other intra-macrophagic fungi or parasites [1]. In this context, we describe an adolescent diagnosed with disseminated cryptococcosis involving skin, lymph nodes, spleen and hepato-biliary involvement with reduced IL-12β1 receptor expression.

Case Summary

A sixteen-years-old laborer, with non-contributory past history, presented with fever, jaundice and unintentional weight loss of eight kilograms over two months. The patient had also noticed development of new lesions over his face and trunk. Clinically patient was thin build (BMI-16.4 kg/m²), febrile (39 °C), had non-tender, generalised lymphadenopathy (cervical, axillary and inguinal), warty plaques over face and trunk (Figure 1) with hepato-splenomegaly. Investigations revealed haemoglobin-6.4 g/L, leukocytosis (11.4 × 10⁹/L- 94% neutrophils) and normal platelets. Viral markers including HIV-1 and 2 were negative with CD4 count of 564 cells/mm³. Tuberculin sensitivity test was non-reactive (0 mm). Lymph node biopsies (cervical and inguinal) showed granulomatous reaction and Alcian blue stain revealed blue coloured capsule consistent with cryptococcosis. Further Ziehl Neelsen stain for acid-fast bacilli, mycobacterial PCR and gene Xpert were negative from the specimen. Biopsy from skin lesion also revealed cryptococcal infection and blood was incubated in BACTEC aerobic and anaerobic culture bot-
tion by peri-portal lymphadenopathy, however endo-
soscopic ultrasound and MRCP suggested sclerosing chol-
angitis and consequent autoimmune hepatitis workup
(including ANA, AMA and ASMA) was negative. Further
immunodeficiency work-up including immunoglobulin
profile, Nitro Blue tetrazolium test, T and B lymphocyte
counts and NK cell counts were normal for age. Flow
cytometry for expression of IL12Rβ1 was performed on
peripheral blood mononuclear cells following stimula-
tion with phytohemagglutinin and culture for 72 hours.
Expression of IL12Rβ1 on gated CD3+ T lymphocytes
was reduced compared to control (Figure 3).

Patient also had obstructive jaundice (total and conjugated bilirubin of
10 mg/dL and 7.8 mg/dL respectively) with raised ALP
(1954 IU/L) and GGT (358 U/L). Contrast enhanced CT
showed generalized (mediastinal, abdominal, inguinal)
lymphadenopathy, intrahepatic biliary duct dilatation,
hepato-splenomegaly with multiple hypoechoic lesions
(Figure 2). Initially jaundice was attributed to obstruc-
tion by peri-portal lymphadenopathy, however endo-
scopic ultrasound and MRCP suggested sclerosing chol-
angitis and consequent autoimmune hepatitis workup
(including ANA, AMA and ASMA) was negative. Further
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tion with phytohemagglutinin and culture for 72 hours. 
Expression of IL12Rβ1 on gated CD3+ T lymphocytes
was reduced compared to control (Figure 3). Targeted
next-generation sequencing was performed using a
custom designed gene panel comprising of 44 common
primary immunodeficiency disease genes which include
four genes (IFNGR1, IFNGR2, IL12RB1 and STAT1) asso-
ciated with MSMD phenotype on the IONS5 platform
from Thermo Fisher Scientific. No pathogenic variants
were found in IL12RB1 or other genes associated with
MSMD. All exons of the IL12Rβ1 were well covered and no deletion (homozygous or heterozygous) were noted. Patient was initially managed with conventional amphotericin (1 mg/Kg; cumulative 4.5 g over 6 weeks) and flucytosine (25 mg/Kg), along with antibiotics for cholangitis and later switched over to suppressive prophylaxis with fluconazole. His jaundice improved following anti-fungal therapy and liver function tests normalized by second month of follow-up and lymph nodes as well as skin lesions (Figure 4) also had regressed significantly by six months.

**Discussion**

IL-12-IFN-γ pathway \[2\], required for activation of T cells and NK cells, is defective in MSMD, making the individual susceptible for infection from intracellular pathogens. Fungal infections in MSMD include candidiasis, histoplasmosis, coccidioidomycosis and Paracoccidioidomycosis.

Cryptococcosis is infrequently reported \[3,4\] and
even if there is tangible isolated organ involvement by cryptococcus, thorough evaluation for possible dissemination requires consideration as in index case who had metastatic dissemination to lymph nodes, skin, hepatobiliary system and spleen (without brain or bone marrow involvement) which has never been described in MSMD.

Liver involvement include focal granulomas, regenerative nodules, sclerosing cholangitis [5]; all were present in index patient.

Virulence of C. neoformans is consequent to polysaccharide capsule [6] which can be visualized with light microscopy using India ink, mucicarmine or Periodic acid Schiff (PAS) stain with high specificity (97%) but poor sensitivity (73%) [7]. Etiology of Cryptococcus neoformans in index case was established on the basis of phenotypic and biochemical characteristics alone and techniques such as PCR and MALDI-TOF couldn’t be done due to financial constraints.

The in vitro activity of antifungal agents was determined by the Etest (AB Biodisk, Solna, Sweden) in accordance with the manufacturer’s instructions. MICs for the isolate were: Amphotericin B - 0.250 µg/mL, Fluconazole - 2 µg/mL, Itraconazole - 0.250 µg/mL, voriconazole - 0.1250 µg/mL.

Target next generation sequencing did not reveal any pathogenic variants. However, deeper intronic variants which may be pathogenic are not detected by this method and require a whole genome sequencing (WGS) of the patient along with parents. Other family members of the index patient were not affected, nevertheless WGS could not be performed due to financial constraints. Likewise phenocopies of genetic defects in IFNGR1, IFNGR2, IL12RB1, IL12RB2, IL12A (p35 subunit), IL12B (p40 subunit) due to autoantibodies to IFNγ, IL12p35 or IL12p40 have also been reported to be associated with MSMD however, could not be tested owing to financial constraints. The IL12RB1 gene is enriched for alu repeat sequences (44.7% compared to 25.8% for Chromosome 19 and 10.5% of the entire human genome). Enrichment for these alu repeats in the IL12RB1 gene predisposes to genomic instability leading to significant increase in copy number variations [8].

Conclusion

MSMD is a rare entity signifying an apparent late presentation of congenital immunodeficiency. It predisposes to infections by less virulent intramacrophagic organisms; treatment guidelines for which are still lacking; though good response has been observed following long term appropriate anti-microbial therapy; duration of which is still debatable.

References