CASE REPORT

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Invasive Candidiasis in a Case of Late onset Combined Immunodeficiency

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ABSTRACT

Late onset combined immunodeficiency (LOCID) is a recently described variant of common variable immunodeficiency (CVID), involving adult patients presenting with opportunistic infections and/or low CD4+ lymphocyte counts. We present a case of a 38-year, male, unmarried, who presented with history of abdominal pain and distension, jaundice and altered sleep- wake cycle suggestive of Decompensated liver disease. Patient developed multiple opportunistic infections in ward course which on further work up turned out to be Late onset combined immunodeficiency. Clinicians should be aware of LOCID, which could be confused with HIV infection/AIDS or idiopathic CD4 lymphocytopenia.

Keywords: Late onset combined Immunodeficiency, Opportunistic Infection

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INTRODUCTION

Opportunistic infections are a common occurrence in immunosuppressed cohort including neonates and elderly, solid malignancies, HIV infection, prolonged ICU stay, use broad spectrum antibiotics and immunosuppression. It's often challenging to suspect primary immunodeficiency in clinical practice being rare occurrence.[1] Diagnosis and treatment of Common variable immunodeficiency (CVID) still poses a clinical challenge with a bleak prognosis. A subgroup of CVID patients enrolled in the DEFI cohort study, characterized by the occurrence of opportunistic infections (OIs) and/or a CD4+ T cell count of <200 cells/μL, and showed significant differences from classic CVID patients in terms of clinical and immunologic characteristics. The authors introduced the term "late onset combined immunodeficiency" (LOCID) to describe this distinct CVID patient subgroup.[2]

CASE HISTORY

38-year, Indian male, unmarried, who presented to a tertiary care centre with history of abdominal pain and distension, jaundice and altered sleep- wake cycle. He had history of alcohol abuse amounting to 150 gm per day for 2 years. Clinical examination was revealed pallor and asterixis. On per abdomen examination there was flank fullness with dullness on percussion with no evidence of organomegaly. USG abdomen was suggestive of liver parenchymal disease with moderate splenomegaly and ascites. He was treated as Chronic liver disease with decompensation in the form of hepatic encephalopathy, ascites and portal hypertension. Patient was initiated on broad spectrum antibiotics and anti-encephalopathy measures.

In view of unexplained decompensated liver disease, patient was worked up for the same. Serology of HIV, Hepatitis B and Hepatitis C were negative. Autoimmune panel was unrevealing. 24-hour urinary copper levels were elevated 100 microgram (normal 0 to 30 microgram over 24 hours) with normal serum ceruloplasmin. UGI scopy revealed Gastric Antral Vascular Ectasia. A liver biopsy was planned due to inconclusive investigations.

On second day of hospitalisation patient developed new onset generalised tonic clonic seizure with the episode lasting for around 2 minutes and worsening of sensorium. Patient had post-ictal confusion lasting for 15-20 minutes, followed

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Table 1. Measurements of lymphocyte subpopulations and immunoglobulin levels via flow cytometry during hospital stay

WBC count	Result	Normal range
Total WBC count	1700	5000-10000
Lymphocytes	22.4%	
Absolute lymphocyte count	381 cells/mm3	1400-3300
B lymphocytes	0%	7.8-15.1%
Absolute B lymphocytes (CD3-/CD19+)	0 cells/mm3	110-570
T lymphocytes	91%	
Absolute T lymphocytes (CD3+/CD19-)	347 cells/mm3	1000-2200
Th lymphocytes (CD3+/CD4+)	54%	
Absolute Th lymphocytes (CD3+/CD4+)	206 cells/mm3	530-1300
Tc lymphocytes (CD3+/CD8+)	33%	
Absolute Tc lymphocytes (CD3+/CD8+)	126	330-920
NK cell (CD3-/CD16+/CD56+)	7%	
Absolute NK cell (CD3-/CD16+/CD56+)	27 cells/mm3	70-480
Nitroblue Tetrazolium test		
NBT burst cells	98%	95-100%
Serum Immunoglobulin levels		
IgG	3.53g/L	7.67-15.9
IgA	0.42 g/L	0.61-3.56
IgM	0.19g/L	0.37-2.86
IgE	39.7 IU/ml	0-214

by which patient continued to remain drowsy. On further evaluation, MRI brain revealed multiple ring enhancing lesions in right temporal, left frontal and right cerebellum likely to be tuberculomas. Lumbar puncture indicated CSF with elevated protein 294 mg/dL with 15 lymphocytes. CSG GeneXpert for Tuberculosis disclosed a drug sensitive isolate. Gram stain on CSF displayed budding yeast cells, further confirmed on culture as Candida auris resistant to Fluconazole, Caspofungin, Voriconazole, Amphotericin and Flucytosine.

Patient was started on hepato-safe antitubercular therapy and antifungal therapy with Liposomal Amphotericin. A week after initiation of the aforementioned therapy patient developed dyspnoea and fever along with pancytopenia. Bone marrow examination showed a trilineage haematopoiesis with erythroid hyperplasia. Antibiotics were stepped up. A chest X ray indicated fresh bilateral reticular opacities **(Figure 1, C).** HRCT performed for the same showed evidence of tree in bud appearance with endobronchial spread likely to be Tuberculosis. Sputum studies were negative for Tuberculosis and positive for Klebsiella pneumoniae and E. coli.

In context of widespread opportunistic infections, a Lymphocyte subset analysis was sought which disclosed complete absence of B cells and hypogammaglobulinemia with decreased total leucocyte count and a generalised decrease in all T cell subtypes **(Table1).** Immunophenotyping of the patient revealed Leucopenia (TLC- 1700) with generalised decrease in T cell count 381/mm^3 (T lymphocyte (CD3+/CD19- 91%, CD4 T cells- 54%, CD8 T cells- 33% and NK cells- 7%) and complete absence of B lymphocytes on analysis **(Table 1).** Serum Immunoglobulin levels revealed generalised decrease in serum IgG- 3.53 g/L (7.67- 15.9g/L), IgA- 0.42g/L (0.61-3.56g/L), IgM- 0.19g/L (0.37-2.86g/L) and Normal IgE levels- 39.7 IU/ml (0 to 214 IU/ml). Immunological assays for post-test immunisation, RBC ADA activity and HLA expression wasn't available to us. However the NBT (Nitro blue tetrazolium test) was normal indicating normal neutrophil function. Despite all efforts the patient succumbed to septicaemia and shock. Based on the diagnostic criteria proposed by the European Society for Immunodeficiencies and Pan-American Group for Immunodeficiency, the patient's immune deficiency was labelled as CVID, while, according to the criteria proposed by Malphettes et al.[2] he was placed at the LOCID category/ variant.

DISCUSSION

Late Onset Combined Immunodeficiency (LOCID) is a variant of Common Variable Immunodeficiency (CVID) which encompasses opportunistic infections with low CD4 counts and variable B cell quantitative and/or qualitative dysfunction.[1] It is characterized by a higher prevalence of splenomegaly, granuloma, gastrointestinal disease, and lymphoma and, even on immunoglobulin substitution, they may require more frequent antibiotics administration and hospitalization. The natural course was in accordance with the observations by Malphettes et al. who noted that the sub group of LOCID patients are more likely to have a severe clinical phenotype[3]

Another hallmark feature of LOCID is poor post immunisation response which couldn't be documented. LOCID is associated with normal lymphocyte proliferation in response to Candida species but may be associated with impaired response in 20 to 40% patients which could explain the central nervous system involvement in our case.[2]

The most common liver pathology in LOCID appears to be nodular hyperplasia which further progresses to cirrhosis

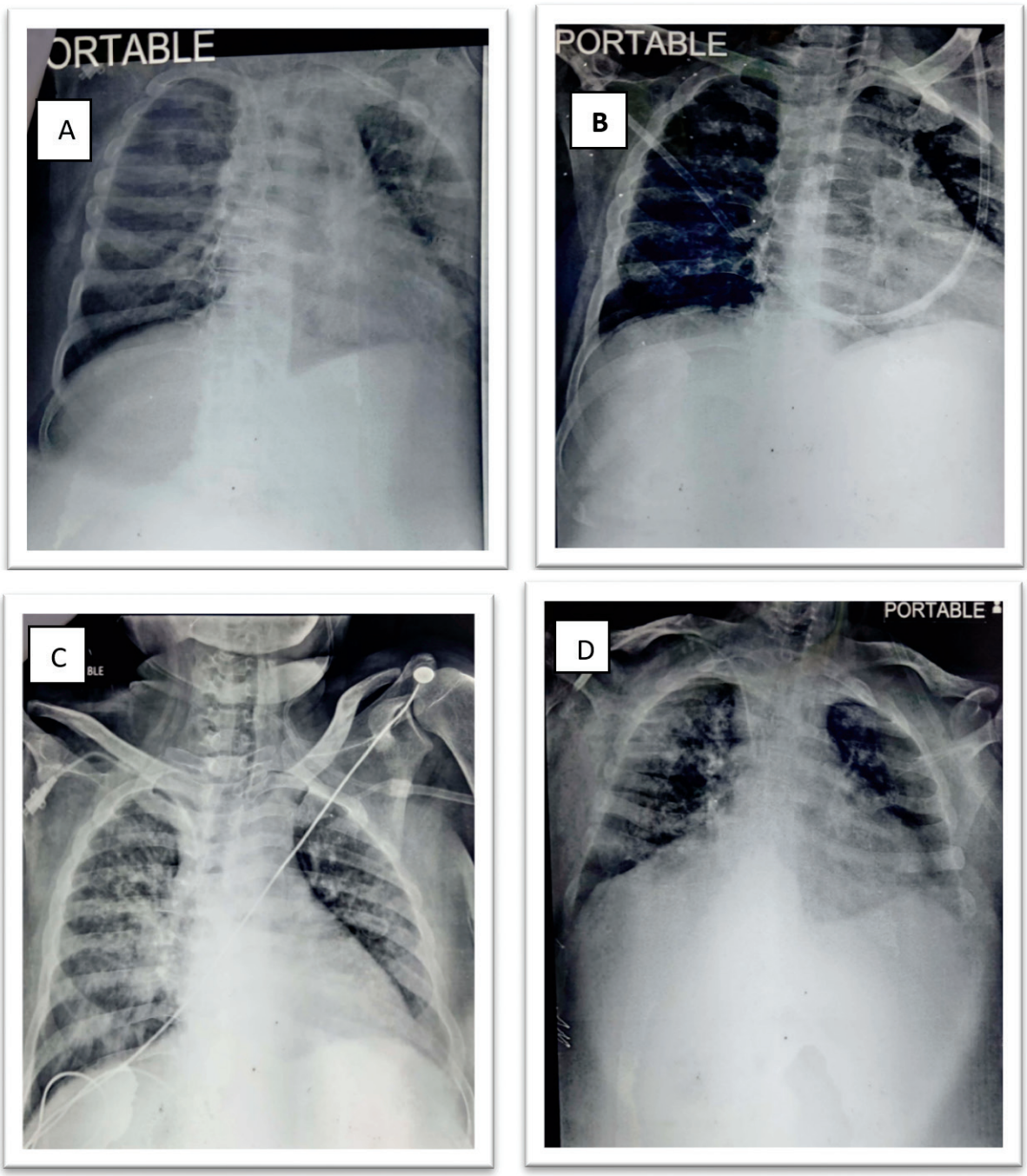

Figure 1 A,B,C,D.

(Images: A and B - Day 1 and Day 11 respectively moderate cardiomegaly and no respiratory parenchymal abnormality.

C- Day 24- Extensive bilateral diffuse reticular opacities suggestive of infective etiology

D- Day 45- Partial resolution of opacities)

and/or portal hypertension[3] and could justify the findings in our case. Hemophagocytic Lymphohistiocytosis was ruled out on the basis of normal serum triglyceride level, mildly elevated serum ferritin levels 685 micro gm/ml and normal serum fibrinogen level. Although splenomegaly was present it could be attributed to Chronic liver disease. Bone marrow examination was in conjunction with absence of haemophagocytosis.

Cirrhosis Associated Immune Dysfunction has two variants namely, Proinflammatory and Immunodeficiency.[4] The immunodeficiency variant is characterised by cellular deficit more than humoral which is not in tandem with our case. Although HIV testing by ELISA was negative, possibility of the same still remains imminent and wasn't ruled out.

CONCLUSION

HIV infection/AIDS or idiopathic CD4 lymphocytopenia are common causes for various opportunistic infections. Clinicians should be aware of LOCID, which could be confused with these entities.

END NOTE

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