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Case Report

Disseminated histoplasmosis in a patient with NADPH oxidase deficiency: a case report

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ABSTRACT

Neutrophil nicotinamide adenine dinucleotide phosphate (NADPH) Oxidase plays a pivotal role in the production of reactive oxygen species and defect of its different subunit leads to the development of chronic granulomatous diseases. The defect of different sub-units of neutrophil NADPH oxidase affects different organs1.In endemic region, histoplasmosis is often seen in host with defective cell mediated immunity. Host with primary immunodeficiency with disseminated histoplasmosis is rare. Host with primary immunodeficiency due to Neutrophil NADPH Oxidase is even rarer2.One such presentation was seen in a 49 years old man who presented to us with recurrent attacks of histoplasmosis involving different organs which was treatment refractory. We report this case so that physicians can consider correlation between primary immunodeficiency and treatment refractory disseminated histoplasmosis in a seemingly immunocompetent patient.

Keywords: Neutrophil nicotinamide adenine dinucleotide phosphate, Oxidase, Chronic granulomatous diseases

INTRODUCTION

The enzymes that make up the multimeric complex known as nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX) belong to the NOX family. It is present in dendritic, neutrophil, eosinophil, and microphase cells. It significantly affects inflammation and host defence against antimicrobials. Chronic granulomatous illnesses develop when there is a shortage of neutrophil NADPH oxidase.[1-3] a primary immunodeficiency that causes potentially fatal fungal and bacterial infections.

Frequency estimates range from 1/200,000 to 1/250,000 babies.[4] Histoplasma capsulatum is the causative agent of histoplasmosis, a lung and hematogenous disease that is frequently chronic and typically develops after an asymptomatic original infection. Pneumonia symptoms or those of an unidentified chronic illness are present. The organism is identified in tissue or sputum, or certain serum and urine antigen tests are used to make the diagnosis.[5]

CASE REPORT

A 49 years old man, non-diabetic, normotensive, married, child of unrelated parent native to Gopalganj, Bangladesh, admitted to National ENT hospital with recurrent sore throat, fever, nodular swelling at cervical region. Fever was high grade with maximum recorded temperature of 103F°, used to come daily and subsided by taking anti-pyretic.

General examination was unremarkable except resistant pyrexia. On oral examination bilateral tonsilitis was diagnosed and due to recurrence of tonsilitis, bilateral tonsillectomy was done. Histoplasma capsulatum was found on histopathological examination of excised tonsil.

Chest radiograph was normal. Result of purified protein derivative skin test was also negative. He was prescribed oral itraconazole 400 mg daily for 6 months & responded well after 5 days.

On November 2021, patient was admitted for progressive weight loss, generalized darkening of whole body. Weight was undocumented, unintentional, significant evidenced by loosening of clothes.

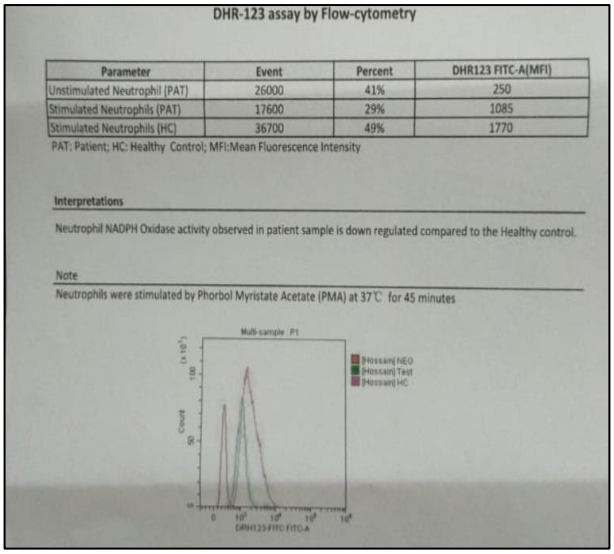
On general examination patient was pigmented including gum, other parts of general examination revealed left anterior chain cervical lymphadenopathy (2×2 cm) in size, firm in consistency, non-tender, free from underlying structure and overlaying skin and there was no scar mark, discharging sinus. Other systemic examination revealed no abnormality. Serum electrolyte showed Sodium was 124 mmol/l, potassium was 4.7 mmol/l. CT scan of whole abdomen showed bilateral adrenal mass, Right side (6×3.5×5 mm) and Left side (5×3×5 mm).

Histopathological examination of core biopsy specimen, obtained from adrenal mass were again positive for histoplasma capsulatum. FNAC of cervical lymph node were also positive for same organism. Patient was treated with antibiotics, steroid and liposomal amphotericin-B (150 mg/day) for 14 days. As patient was responsive, he was discharged with 12 months course of oral itraconazole 400 mg/day.

On April 2023, he was again admitted to BSMMU with painful enlarged scrotum and acute urinary retention. Urine examination revealed urinary tract infection. Ultra sonogram of whole abdomen showed bilateral adrenal mass, gall bladder sludge, prostatic enlargement (PVR-31 ml). Ultrasonogram of testis showed bilateral epididymitis.

Culture of sample taken from ultrasonogram guided FNAC of testis also revealed one histiocyte with intracytoplasmic round to oval yeast organism morphologically consistent with Histoplasma capsulatum. On evaluation of urinary retention, he was diagnosed as bladder neck hypertrophy for which he underwent bladder neck resection via urethroscopy. Histoplasma capsulatum was found on histopathological examination of the resected material. Patient was screened for all classical causes of acquired immunodeficiency, all of which were negative.

On July 2023, he was again admitted to BSMMU due to severely painful scrotal swelling, odynophagia. On ENT examination he had classical papules of Histoplasma capsulatum on posterior soft palate. As disease course is long and treatment refractory and acquired immunodeficiency was not found, Primary immunodeficiency was screened. On Figure 1 shows DHR-123 assay by flow cytometry showed that "Neutrophil NADPH oxidase activity is down-regulated in patient sample".


DHR-123 assay by Flow-cytometry

Parameter	Event	Percent	DHR123 FITC-A(MFI)
Unstimulated Neutrophil (PAT)	26000	41%	250
Stimulated Neutrophils (PAT)	17600	29%	1085
Stimulated Neutrophils (HC)	36700	49%	1770

PAT: Patient; HC: Healthy Control; MFI:Mean Fluorescence Intensity

Interpretations

Neutrophil NADPH Oxidase activity observed in patient sample is down regulated compared to the Healthy control.

Note

Neutrophils were stimulated by Phorbol Myristate Acetate (PMA) at 37℃ for 45 minutes

Figure 1: Neutrophil NADPH Oxidase activity is down-regulated in patient sample by flow cytometry.

DISCUSSION

Numerous characteristics suggested that the patient's development of disseminated histoplasmosis was caused by a lack of neutrophil NADPH oxidase. His infection was initially confined, but it spread over time and was resistant to treatment even after multiple episodes of effective medication. These characteristics are all inconsistent with a patient who is immunocompetent.[6] Defects in phagocytic cell microbicidal activity and white blood cells incapable of producing activated oxygen molecules are hallmarks of chronic granulomatous illness.

Recurrent infections, many granulomatous lesions of the liver, lungs, lymph nodes, and genitourinary tracts, abscesses, and lymphadenitis are among the symptoms. The diagnosis is made by using a flow cytometric oxidative burst assay to measure the generation of oxygen radicals in white blood cells.[5] Rare, primary immunodeficiencies typically appear for the first time in childhood. The primary cause of death in chronic granulomatous disease (CGD) is invasive aspergillosis, which highlights the critical function of phagocyte NADPH oxidase in host defense against opportunistic fungi.[7] Both autosomal recessive and X-linked inheritance patterns are possible for the condition.

The X-linked recessive pattern is the most prevalent type. Both innate and adaptive immunity are involved in the immune response to fungus. Macrophages, neutrophils, and dendritic cells are examples of innate immunological players that offer antifungal defense, whereas Th17 cells play a crucial antifungal role in the adaptive immune compartment.[8] Depending on various immunological illnesses, patients may exhibit variations in the spectrum of fungal pathogens, as well as in the incidence and clinical presentation of the infections. In these patients, fungal infections can occasionally be the initial clinical indicator

of a primary immunodeficiency. If misdiagnosed or managed, they can result in serious morbidity and even death. A high level of suspicion is required, and suitable imaging, mycological, and histological tests should be aggressively used to establish a diagnosis.[9]

Histoplasma infections in immunocompromised hosts can spread or present extrapulmonary. This implies that other patients with undetected neutrophil NADPH oxidase deficiency may have presented with disseminated histoplasmosis.[10] Isolating the patient in a hygienic setting is part of the management strategy for this patient. Liposomal amphotericin-B course length (4-6 weeks). Another option is to employ interferon gamma, which enhances the host's phagocytosis function without affecting neutrophil NADPH oxidase activity.[11]

CONCLUSION

Consequently, we recommend evaluating patients with severe treatment-refractory extra-pulmonary or disseminated histoplasma capsulatum infections for neutrophil NADPH oxidase deficiency.

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