CASE REPORT
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Delayed Severe Presentation of Chronic Granulomatous Disease in Adulthood: A Case Report

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ABSTRACT

Chronic granulomatous disease (CGD) is the most common inherited phagocytic disorder with an increased susceptibility to recurrent infections and inflammatory manifestations due to a defect in any of the 5 NADPH oxidase subunits. Although CGD may manifest at different ages based on the defects of NADPH oxidase proteins, it is usually diagnosed in childhood with an overall median age of 2.7 to 3 years at the onset.

Infections and inflammatory manifestations are known to be two major clinical presentations of CGD, with the infections occurring much earlier in life than the inflammatory manifestations. Despite the patients' clinical history and their noticeable manifestations, sometimes the diagnosis is delayed until adulthood, which could be attributed to physicians' low awareness of the disease. Another reason for such delayed diagnosis could be the fact that some CGD mutations may remain asymptomatic up to a certain age.

The current study is a report of a healthy woman without any history of recurrent infections or inflammation until she was forty. In her early forties, she contracted a mycobacterial infection that was unresponsive to treatment, and was then diagnosed with abnormal reactive oxygen species released by neutrophils, suggesting a case of CGD.

This suggests that primary immunodeficiencies are not solely childhood disorders and should be considered in all refractory or therapy resistant conditions, even in adults.

Keywords: Chronic granulomatous disease; Delayed diagnosis; NADPH Oxidases; Reactive oxygen species

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INTRODUCTION

Chronic granulomatous disease (CGD) is the mostcommon inherited phagocytic disorder with an

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increased susceptibility to recurrent infections and inflammatory manifestations due to a defect in any of the 5 NADPH oxidase subunits.[1-3] Normally, stimulation of phagocytic cells results in oxidase activation and electron transfer from NADPH to molecular oxygen in an oxidative burst. This generates superoxide, which can then be converted to microbicidal reactive oxygen species. Mutations in any of the 5 genes (including *CYBB*, *CYBA*, *NCF1*, *NCF2*, and *NCF4*), that encode NADPH oxidase components lead to different inherited patterns of CGD. These mutations result in impaired production of the microbicidal reactive oxidant superoxide anion and its metabolites.[4-6]

CGD is usually diagnosed in childhood with an overall median age onset between 2.7 and 3 years.[7] Infections and inflammatory manifestations are the two major clinical presentations of CGD, with infections occurring much earlier than the inflammatory manifestations.[8] Despite the patients' clinical history and their noticeable manifestations, diagnosis is sometimes delayed until adulthood. CGD clinical presentation is quite variable as it is currently estimated that nearly 50% of newly diagnosed cases occur in adults over the age of 25.[7]

The CGD phenotype is extremely heterogeneous and can manifest in different organs, such as skin and subcutaneous tissues, gastrointestinal, pulmonary, and central nervous systems, though infectious or inflammatory presentations may occur at virtually any anatomical site.

Therefore, CGD should be considered in patients with refractory or recurrent infections along with granulomatous inflammation, even in adulthood.[9]

While the qualitative assay of nitroblue tetrazolium (NBT), which is more subjective and can be misleading, is still clinically used, the quantitative dihydrorhodamine (DHR) 123 flow cytometry assay for detecting hydrogen peroxide (H_2O_2) is a quite accurate CGD diagnostic test.[10-12]

We report the case of a previously healthy woman without any history of recurrent infections or inflammation who developed a refractory mycobacterial infection in her early forties. Subsequent testing revealed an abnormal release of reactive oxygen species (ROS), leading to a diagnosis of CGD. Consequently, CGD should no longer be considered exclusively a pediatric disorder.[13]

CASE REPORT

A 41-year-old married woman, without any previous history of underlying diseases, was admitted to Masih Daneshvari Hospital in Tehran, Iran, in 2024 with malaise and weakness, while the symptoms had started 3 years before admission. She did not initially report any fever, cough, or weight loss. Due to her constitutional symptoms, comprehensive blood work was performed, revealing pancytopenia on complete blood count (CBC). However, bone marrow analysis showed normal results at the time. There was no similar problem in her family history, and she had no brothers or sons, and her daughters were healthy. The patient's laboratory results are summarized in Table 1. Approximately two weeks later, she developed new symptoms, including night sweats, along with fever and respiratory problems. A chest X-ray revealed pleural effusion, necessitating further evaluation with CT scan, showing pulmonary nodules as well. Subsequently, a bronchoalveolar lavage was performed. The results are presented in Table 2.

Histological assessments of lung tissue showed non-caseating granuloma with foci of foreign body -type giant cell reaction. Concurrently, very slow-growing nodules appeared on her face, hands, and buttocks, which insidiously developed to ulcers and fistulous tracts with persistent purulent discharge (Figure 1).

Table 1. A summary of the patient's laboratory results

LAB Data	Results	Normal range
WBC	1500/µL	3.90–11.10
Neutrophils%	75%	NA
Lymphocytes%	18.9%	NA
Monocytes%	2.3%	NA
Eosinophils%	3.4%	NA
Basophils%	0.4%	NA
RBC	3 080 000/µL	3.90–5.10
Hgb	9 g/dL	11.8–15.5
HCT	27.1%	35–46
MCV	88 fl	80–98
MCH	29.2 pg	27–33
MCHC	33.2 g/dL	31–36
Platelets	159 000/µL	155–440
ESR	15 mm/h	Up to 20
CRP	80 mg/L	Up to 6
IGRA	Negative	NA
Urea	17 mg/dL	15–40
Creatinine	0.8 mg/dL	0.6–1.3
AST	25 U/L	Up to 31
ALT	18 U/L	Up to 31
Ferritin	2013 ng/mL	13–232
25-OH-Vitamin D	16.1 ng/mL	Deficient: <10, Insufficient: 10–29
LDH	440 U/L	Up to 480
ACE	26 U/L	8–65
Anti MPO (p-ANCA)	2.2 Au/mL	Up to 20
Anti PR-3 (c-ANCA)	6.1 Au/mL	Negative <16
Tuberculin test	4 mm	Positive >15
HIV Ab/Ag	0.27	Non-Reactive <1
Wound discharge smear	Gram negative coccobacilli	NA
Wound discharge culture	*Morganella morganii*	NA
Leishmaniosis PCR	Negative	NA
NBT	50% & 40% in two separate times	>90
IgG	4000 mg/dL	700–1600
IgM	50	NA

Table 1. Continued...

LAB Data	Results	Normal range
IgA	185	NA
Anti B titer	1/32	NA
C3	166	NA
C4	31	NA
CD3	55.3%	NA
CD4	33.4%	NA
CD19	9.2%	NA
CD20	8.6%	NA

ACE: angiotensin-converting enzyme; ALT: alanine aminotransferase; ANCA: antineutrophil cytoplasmic antibody; AST: aspartate aminotransferase; CD: cluster of differentiation; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; HCT: hematocrit; Hgb: hemoglobin; HIV: human immunodeficiency virus; Ig: immunoglobulin; IGRA: interferon-gamma release assay; LDH: lactate dehydrogenase; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; MCV: mean corpuscular volume; MPO: myeloperoxidase; NBT: nitroblue tetrazolium; PCR: polymerase chain reaction; PR-3: proteinase 3; RBC: red blood cell; WBC: white blood cell.

Table 2. The results of bronchoalveolar lavage

Test	Results	Normal range
Galactomannan	0.45	<0.5: Negative
Aspergillus	Not detected	NA
Tumor cells	Not detected	NA
Gram stain	Gram negative bacilli	NA
Culture	*Klebsiella* and *Pseudomonas aeruginosa*	NA
Nocardia smear and culture	Negative	NA
Fungi culture	No growth	NA

(A) (B)

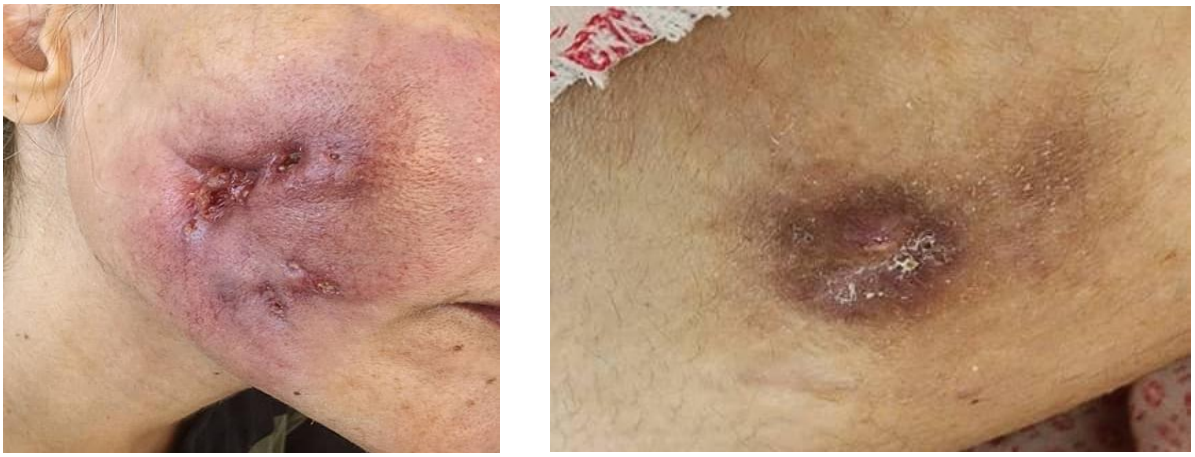


Figure 1. The patient's skin lesions on her face (A) and hand (B).

The initial clinical findings in addition to secondary cutaneous involvements suggesting enough to consider the lesion to be tuberculous scrofuloderma. Consequently, the patient was started on a standard four antitubercular medications (rifampin, isoniazid, pyrazinamide, and ethambutol). The lesions initially responded to treatment. However, upon de-escalation to a two-drug maintenance phase, they recurred—this time localized solely to the face and resistant to the previous therapy. therapy. Prior to starting treatment, secretions were sent for microbiological culture, including specific testing for acid-fast bacilli and non-specific micro-organisms. The results of the cultures obtained before the initiation of treatment showed *Mycobacterium simiae* and beta-lactam negative *Escherichia coli*. Following the detection of these two unusual organisms, primary immunodeficiency was strongly suggested.

Whole blood was examined with specific laboratory tests for neutrophil NADPH oxidase activity, i.e., NBT and DHR tests as well as a complete immunodeficiency screening. Low, subnormal levels of ROS were produced following the simulation of purified peripheral blood neutrophils (PMN) with phorbol 12-myristate 13-acetate (PMA). The patient's DHR is shown in Figure 2 alongside that of a healthy control.

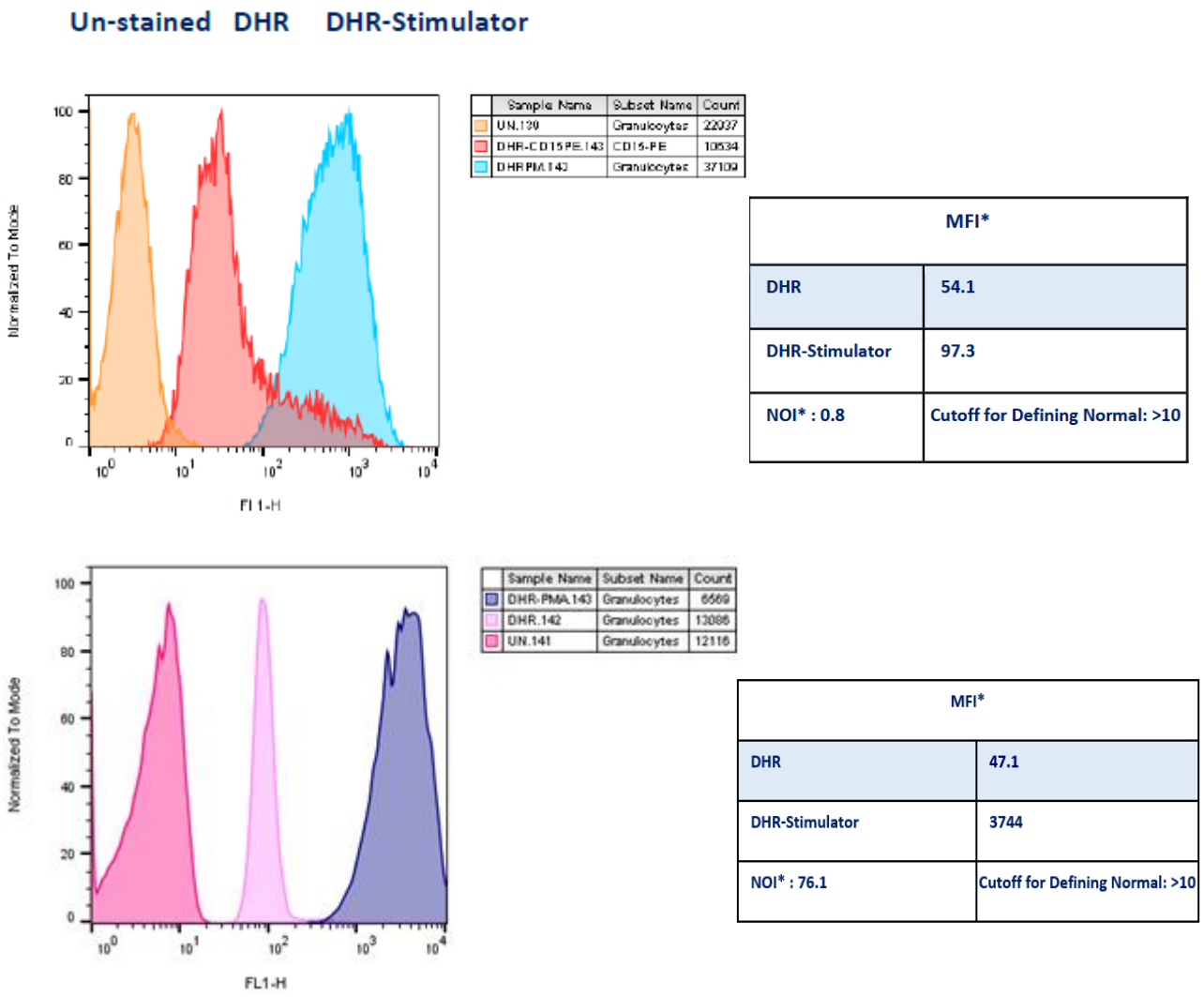


Figure 2. DHR test of the patient compared to a healthy control.

DISCUSSION

The current study is a report of a healthy woman without any history of recurrent infections or inflammation until she was forty. In her early forties, she contracted a mycobacterial infection that was unresponsive to treatment, and was then diagnosed with abnormal results of NBT (Sigma-Alderich, USA) and DHR (FACScalibour, USA) tests, suggesting a case of CGD.

The late diagnosis of CGD could be primarily attributed to physicians' unawareness of CGD as the underlying cause in adults. In many cases, blind administration of wide-spectrum antimicrobial medicines is applied at first encounters to address refractory infections. Although such treatments may temporarily suppress the symptoms, recurrence is common unless the underlying immune defect is identified and specifically managed. The patient in the current study initially presented with severe pulmonary symptoms that prompted a lung biopsy. Histopathological analysis showed non-caseating granuloma in tissue samples. Unfortunately, DHR test was not performed at that time and was significantly delayed until after the onset of cutaneous manifestations. Therefore, in severe conditions necessitating biopsy for further analysis, discovering granulomatous inflammation in tissue samples should prompt physicians to perform DHR testing to evaluate CGD. Furthermore, to confirm the diagnosis, a DHR test should be followed by genetic testing. However, the patient of the present study refused to do any further evaluations due to financial constraints.

The isolation of *M simiae* and beta-lactam negative *E coli* from this patient's skin lesions is a notable finding that should raise suspicion for an undiagnosed primary immunodeficiency. *M simiae* is a slow-growing nontuberculous mycobacterium (NTM), which resides in environmental sources like soil and water, causing pulmonary and disseminated infections. It is an opportunistic pathogen, particularly affecting individuals with pre-existing lung conditions or compromised immunity. Likewise, it is reported that the severe clinical course of any infectious disease with refractory, atypical, or fulminant presentations associated with unusual or environmental pathogens may be an important finding leading to an underlying immunodeficiency.[9]

Therefore, primary immunodeficiencies should no longer considered exclusively pediatric disorder.[13]

In conclusion, high index of suspicion is warranted in adults presenting with refractory, therapy-resistant infections, particularly those with severe or atypical complications.

STATEMENT OF ETHICS

The research protocol received approval from the Ethics Committee of National Research Institute of Tuberculosis and Lung Diseases, according to Declaration of Helsinki. Informed consent was taken from the patient for the pictures shown in this report.

FUNDING

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ACKNOWLEDGMENTS

Not applicable.

DATA AVAILABILITY

Data availability is with the first author, Dr. Mahsa Rekabi, and will be provided upon request from her.

AI ASSISTANCE DISCLOSURE

We, hereby confirm that no AI tools was used in the writing of this manuscript.

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