

## Case Report

# A case of chronic granulomatous disease masquerading as leukemia: Unraveled by flow cytometric and molecular studies

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Received: 06 November 2025  
Accepted: 29 December 2025  
Epub Ahead of print: 04 March 2026  
Published:

DOI  
10.25259/JLP\_343\_2025

### Quick Response Code:



## ABSTRACT

Primary immunodeficiency diseases (PIDs)/inborn errors of immunity (IEI) are inheritable genetic disorders that disrupt immune cells either qualitatively or quantitatively in the performance of their functions. The case report is about a case of chronic granulomatous disease (CGD). A 10-month-old male child presented with a history of on-and-off fever, hepatomegaly (6 cm), splenomegaly (6 cm), and submandibular lymphadenopathy. On the peripheral smear, 12% of atypical cells/blasts were seen; a differential diagnosis, such as leukemoid reaction and juvenile leukemia, was considered. PIDs workup, including nitroblue tetrazolium/dihydrochloride (DHR) test, serum immunoglobulin assay, and lymphocyte subset analysis, was carried out as the mother gave a history of the child being unwell since 6 weeks of age. Bone marrow examination and serial peripheral smears after treatment with antibiotics ruled out leukemia. Chronic infantile leukemias like juvenile myelomonocytic leukemias should be differentiated from septic leukemoid reaction that can occur in the context of CGD. Furthermore, the authors conclude that infections can lead to normal progenitors being released into the periphery, and one should refrain from overdiagnosing these as leukemia cases.

**Keywords:** Leukemoid reaction, Lymphocyte subsets, Nitroblue tetrazolium, Primary immunodeficiency diseases, Respiratory burst

## INTRODUCTION

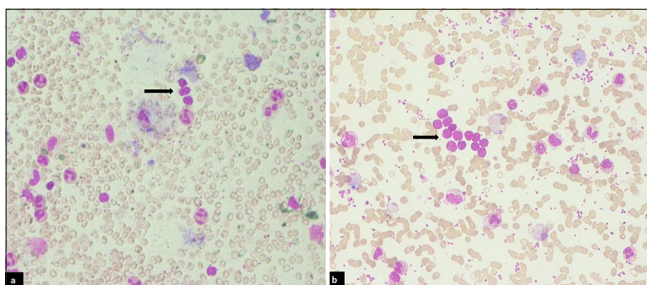
Primary immunodeficiency diseases (PIDs)/inborn errors of immunity (IEI) are inheritable genetic disorders that disrupt immune cells either qualitatively or quantitatively in the performance of their functions.<sup>[1,2]</sup> These constitute a group of more than 485 disorders characterized by an impaired immune system. IEI presents clinically as increased susceptibility to infections, autoimmunity, autoinflammatory diseases, allergy, bone marrow failure, and/or malignancy. There are 10 categories of IEI, and category 5 is of congenital defects in phagocytic number and/or functions. Phagocytic function disorders are a group of inherited or acquired rare diseases that can lead to increased vulnerability to infections. Chronic granulomatous disease (CGD) is the most common phagocytic disorder characterized by pneumonia, abscess, recurrent pyogenic infections, suppurative adenitis, and gastrointestinal infections.<sup>[3,4]</sup> The common hematological findings in disease include anemia, neutrophilic leukocytosis, monocytosis, thrombocytosis, and rouleaux formation.

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## CASE REPORT

A 10-month-old male child presented with a history of on-and-off fever, hepatomegaly (6 cm), splenomegaly (6 cm), and submandibular lymphadenopathy. Mother gave the history of the child being unwell since 6 weeks of age. At admission, he had anemia (8.8 g/dL), leukocytosis (47,390/ $\mu$ L), neutrophilia, lymphocytosis, monocytosis, and marked thrombocytosis (7.83 lacs). On the peripheral smear, 12% atypical cells/blasts were seen [Figure 1a]. A repeat sample was requested after 1 day to look for the blasts. This time, there was a similar picture with peripheral blood showing atypical-looking cells at places forming small aggregates (34% atypical cells/blasts) [Figure 1b]. Differential diagnosis, such as leukemoid reaction and juvenile leukemia, was considered. A nitroblue tetrazolium (NBT) test carried out on the patient's sample showed 0% oxidative burst activity (1/200 neutrophils) [Figure 2]. The dihydrorhodamine (DHR) test carried out showed no significant increase in mean fluorescence intensity difference between the unstimulated [Figure 3a] and stimulated patient samples [Figure 3b]. A provisional diagnosis of CGD was established based on functional assays, pending definitive molecular confirmation. The child was given antibiotics and was being continuously monitored, and a repeat sample was taken after 2 days, whereby the peripheral blood counts dropped to 25,000/ $\mu$ L, and the peripheral blood did not show any significant atypical cells. Furthermore, a bone marrow aspirate and trephine biopsy showed no evidence of leukemia and showed myeloid preponderance [Figure 4a and b]. There were vague histiocytic collections; however, no well-formed granulomas were seen. Simultaneously, blood samples and bone marrow samples were submitted for Lowenstein-Jensen culture and cartridge binding nucleic acid amplification test (CBNAAT) testing, which tested negative for *Mycobacterium tuberculosis*. Serum immunoglobulin profile showed



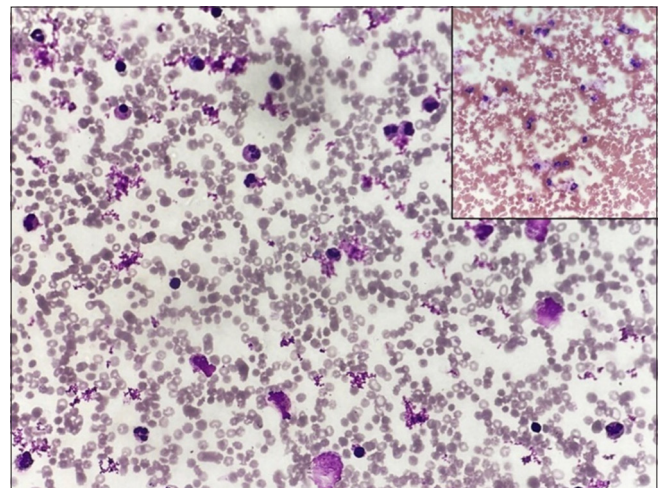
**Figure 1:** (a) Peripheral smear day 1 shows red blood cell series showing mild anisopoikilocytosis and mild hypochromia showing normocytes, microcytes, elliptocytes (Leishman stain,  $\times 400$ ). There is leukocytosis showing neutrophilia, monocytosis with the presence of a few clusters of 12% atypical cells/blasts (Marked by arrow). Platelets are increased on the smear. (b) Peripheral smear from day 2 shows anemia, leukocytosis, thrombocytosis, and 33% of atypical cells/blasts (Marked by arrow) (Leishman stain,  $\times 400$ ).

7.65 g/L, 1.24 g/L, and 1.45 g/L of immunoglobulin G, immunoglobulin A, and immunoglobulin M, respectively. Lymphocyte subset analysis showed T+, B+, and NK+ profiles with an increase in cytotoxic T cells. Serological tests for human immunodeficiency virus, hepatitis B, and C viruses were negative. However, no other viral serologies were tested. Abdominal ultrasonography (USG) revealed hepatosplenomegaly (HSM) and a well-defined splenic cyst.

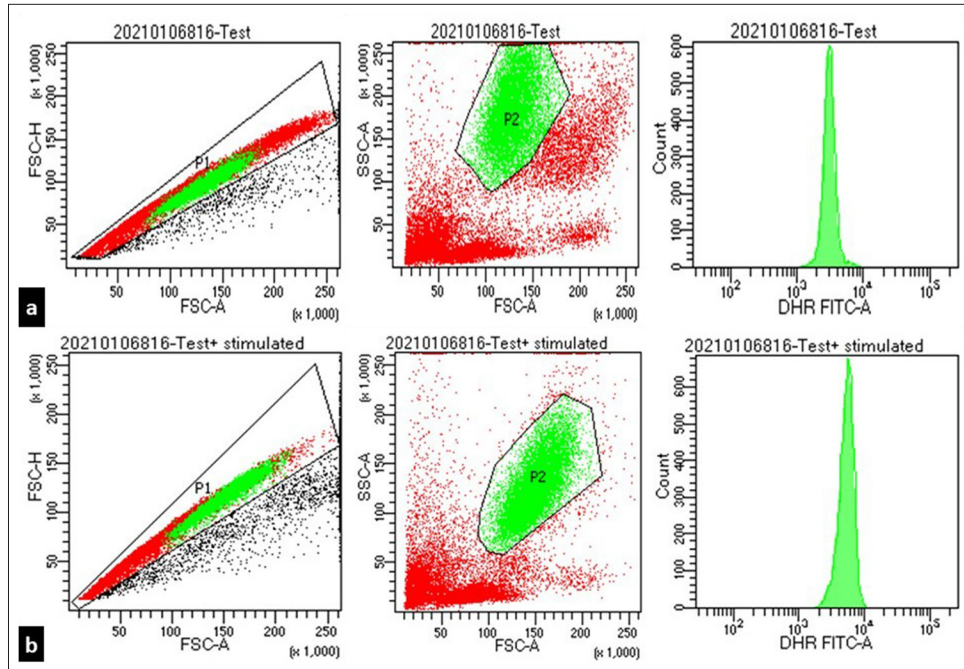
On further advanced flow cytometric analysis for nicotinamide adenine dinucleotide phosphate (NADPH) oxidase components, the p22 component was defective. On molecular diagnosis, A hemizygous 2-base pair insertion in exon 9 of the *CYBB* gene (chrX: g.37804096\_37804097dup; Depth:  $\times 83$ ) that results in a frameshift and premature truncation of the protein 13 amino acids downstream to codon 374 (p.Gln374SerfsTer13; ENST00000378588.5) was detected. Thus, molecular diagnostic workup detected the pathogenic variant in the *CYBB* gene, thus confirming the diagnosis of CGD (X-linked recessive type). The boy was referred to a higher tertiary care center for a bone marrow transplant. The patient's family left against medical advice, and the boy succumbed to infections. The case report highlights a case of CGD masquerading as leukemia, which was unraveled by flow cytometric and molecular studies.

## DISCUSSION

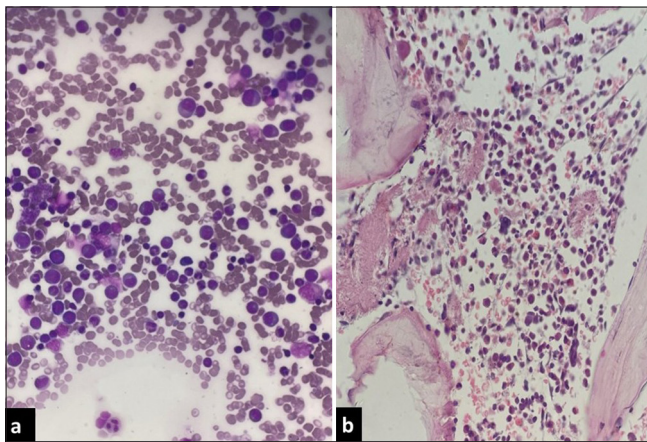
Leukocyte function disorders are a group of inherited or acquired rare diseases that can lead to increased vulnerability to infections.<sup>[1-3]</sup> The inherited defects encompass defects in leukocyte rolling (LAD2), adhesion (LAD1), chemotaxis,



**Figure 2:** Nitroblue tetrazolium (NBT) dye preparation test. The patient's sample does not show any presence of blue black formazan compound in the neutrophils (NBT;  $\times 400$ ). The inset control sample shows the presence of blue black formazan compound in the neutrophils (NBT,  $\times 400$ ).



**Figure 3:** Flow cytometric Dihydrorhodamine test (a) Representing the plots of unstimulated patient sample (P1 plot: Singlets, P2 gate: Neutrophils and DHR plot) (b) Representing the plots of phorbol myristate acetate (PMA) stimulated patient sample. (P1 plot: Singlets, P2 gate: Neutrophils and DHR plot) There is no significant increase in mean fluorescence intensity on stimulation signifying neutrophils having no significant oxidative burst.



**Figure 4:** (a) Bone marrow aspirate showed a normocellular bone marrow with trilineage hematopoiesis with no excess of blasts (Wright Giemsa,  $\times 1,000$ ). (b) Corresponding bone marrow biopsy showed trilineage hematopoiesis with no excess of blasts (Hematoxylin & eosin,  $\times 400$ ).

defects in microbicidal activity (CGD, myeloperoxidase [MPO] deficiency), and defects in phagolysosome formation (Chediak-Higashi). Defect in microbicidal activity is seen in CGD and MPO deficiency. CGD is a phagocytic disorder characterized by normal ingestion and normal phagosome formation but a defect in the respiratory burst

oxidase. These patients are particularly prone to infections by catalase-positive organisms such as *Staphylococcus aureus*, *Pseudomonas* spp., *Burkholderia cepacia*, *Aspergillus*, *Nocardia*, and atypical mycobacteria. The risk of viral infections is not significantly higher than that of the general population.

CGD derives its name from the presence of histiocytic granulomas in the tissues.<sup>[5,6]</sup> It results from inherited defects in the genes encoding phagocytic oxidase (NADPH oxidase). Defective leukocyte function, i.e., absent to decreased microbicidal activity/respiratory burst, is seen due to defective NADPH oxidase in CGD. There is a lack of superoxide production, which is used to kill phagocytosed micro-organisms in neutrophils, eosinophils, monocytes, and macrophages. The NADPH oxidase is composed of 5 components located on different chromosomes. The defect in these components accounts for 5 different types of CGDs. These are gp91phox (X-linked), p47phox, p22phox, p67phox (autosomal recessive), p40phox. The enzymatic component gp91phox, also called Nox2, is encoded by the gene *CYBB* located on the X chromosome. Mutations in this gene are found in about 60-70% of all CGD patients, as was found in the indexed case. p47phox, encoded by the *NCF1* gene, is the most common autosomal recessive form of CGD, which is often clinically milder. Children with X-linked CGD

present earlier and also have a greater number of infections as compared to the autosomal recessive type of CGD. The DHR test by flow cytometry can diagnose the disease, as in these patients, there will not be a considerable change in mean fluorescent intensity in unstimulated and stimulated samples, and the stain index will be low.<sup>[2,7,8]</sup> Furthermore, the age-old technique of the NBT dye test is diagnostic, as children with a CGD defect will not show the formation of formazan compound.<sup>[2,9]</sup> Further typing of the defect can be done by flow cytometry-based tests, gene scan, Sanger sequencing, and next-generation sequencing.<sup>[2,5,6]</sup> In flow cytometric analysis, specific antibodies to gp91phox, p47phox, p67phox, etc., are used. On immunophenotyping, gp91phox (X-linked) and p22phox are generally detected together, which is why the patient showed a p22 component defect.<sup>[2]</sup> Prenatal diagnosis can be done on fetal blood by measuring NADPH oxidase activity, or chorionic villus and amniotic fluid sampling can be taken for DNA analysis.

CGD is pathologically characterized by histiocytic granulomas in the reticuloendothelial system (lymph nodes, liver, spleen, bone marrow), gastrointestinal tract, genitourinary tract, lungs, skin, etc.<sup>[3-6,10]</sup> The patient had HSM and a splenic cyst on USG. The trephine biopsy showed a vague histiocytic collection; however, no well-formed granulomas were seen. Although a fine-needle aspiration cytology of the submandibular lymphadenopathy was initially planned, the procedure was deferred as the provisional diagnosis of CGD sufficiently accounted for the granulomatous lymphadenitis and visceral involvement. More than 90% of CGD patients are afflicted with HSM, and abscesses in the liver and spleen are found in 25–50% of CGD patients. On imaging, splenic cyst formation is seen in 10% of CGD patients. The pathophysiology behind cyst formation is due to splenic abscess, liquefied granulomas, and splenic pseudocyst formation. CGD patients are treated with prophylactic antimicrobials, interferon  $\gamma$ , gene therapy, and bone marrow transplantation.<sup>[11]</sup> The patient responded to antibiotics temporarily and was advised a bone marrow transplant, but succumbed to his illness.

The most common types of malignancies among IEI patients are NHL and Hodgkin lymphoma, and leukemia, and cancers of the skin, genitourinary tract, and gastrointestinal tract have also been described.<sup>[1,12,13]</sup> A case each of T cell acute lymphoblastic leukemia and a case of myelodysplastic syndrome in the context of CGD has also been described in the literature; in this case, however, leukemia was ruled out by doing bone marrow aspiration and follow-up peripheral smear examination. These patients should be closely followed not only for susceptibility to infections but also for propensity for malignancies. Chronic infantile leukemias, such as juvenile myelomonocytic leukemias, juvenile chronic myeloid leukemia, and acute leukemia, should

be differentiated from septic leukemoid reaction with the presence of progenitors that can occur in the context of CGD.

## CONCLUSIONS

We present a rare case of CGD with septic leukemoid reaction with blast-like cells appearing in peripheral blood. Acute leukemias and chronic infantile leukemias, such as juvenile myelomonocytic leukemias, juvenile chronic myeloid leukemia, can come in the differential diagnosis in such cases, and authors advocate that one should refrain from overdiagnosing these as leukemia cases. A holistic approach by clinical, hematological, flow cytometric, and molecular analysis will help in accurate diagnosis.

**Author's Contributions:** UK: Peripheral smear reporting, NBT testing, DHR testing, capacity building for Lab diagnostic services for PID. BD: Treating clinician, capacity building for lab diagnostic services for PID. AK: Treating clinician. DJ: Capacity building for lab diagnostic services for PID. TS: Clinical correlation and bone marrow reporting. EJ: Clinical correlation and peripheral smear interpretation. RMY: Coordinating for reporting PID investigations from referring lab (NIIH). MM: Capacity building and referring lab (NIIH) reporting consultant, molecular diagnosis support.

**Ethical approval:** The case was investigated as a part of research study approved by the Institutional Review Board at AIIMS Bhopal, approval number IHEC-LOP/2019/EF0142, dated 5th November 2019.

**Declaration of patient consent:** The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

**Financial support and sponsorship:** Nil.

**Conflicts of interest:** There are no conflicts of interest.

**Use of artificial intelligence (AI)-assisted technology for manuscript preparation:** The authors confirm that there was no use of Artificial Intelligence (AI)-Assisted Technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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**How to cite this article:** Khurana U, Dhingra B, Kumar A, Joshi D, Sharma T, Jayashankar E, *et al.* A case of chronic granulomatous disease masquerading as leukemia: Unraveled by flow cytometric and molecular studies. *J Lab Physicians*. doi: 10.25259/JLP\_343\_2025