

**Clinical Case Seminar**

**A1(1-5)**

# Atypical Presentation of Chronic Granulomatous Disease in a Child

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## Abstract

Chronic granulomatous disease is a rare, inherited immunodeficiency caused by deletions or mutations in genes that encode subunits of the NADPH oxidase complex. The pattern of chronic granulomatous disease inheritance can be X-linked (about 70% of cases) or autosomal recessive. The basic defect lies in phagocytic cells (neutrophils and monocytes) which fail to effectively destroy invading bacteria and fungi. Also, a dysregulated immune response, characterized by extensive granulomatous inflammation of visceral organs, develops in patients. This immunodeficiency is characterized by repeated suppurative infections mainly located in the lungs, skin, and lymph nodes, but also affecting other organs. The major agents involved in the infections are catalase positive bacteria, mycobacteria, fungi, and other opportunistic germs. Diagnosis is based on clinical suspicion and confirmed by nitroblue tetrazolium test or flow cytometry that demonstrate the inability of phagocytes from affected individuals to produce superoxides. The treatment of chronic granulomatous disease involves, in addition to general care such as the prevention of infections and vaccinations, the use of sulfamethoxazole–trimethoprim in combination with itraconazole for prophylaxis. We report the case of a 3-year-old boy with medical history of recurrent respiratory infections, anemia, growth failure, elevated inflammatory markers and occasional rectal bleeding. He was admitted to our department for a suspected chronic bowel inflammatory disease. Clinical history, lymph nodes involvement and the discovery of intestinal granulomas on biopsies confirmed the diagnosis of chronic granulomatous disease.

**KEYWORDS:** chronic granulomatous disease, anemia, immunodeficiency, granulomatous inflammation

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## Introduction

Chronic granulomatous disease (CGD) is an uncommon inherited (X-linked or autosomal recessive) immunodeficiency, occurring in about one in 250,000 individuals. CGD is caused by defects in the NADPH oxidase, the enzyme complex responsible for generation of superoxide and other reactive oxygen species (ROS) in phagocytic cells. Phagocytes are unable to effectively kill catalase-positive organisms, leading to recurrent, life-threatening bacterial and fungal infections (1,2). The most commonly described infectious complications are pneumonia, lymphadenitis, subcutaneous abscess, liver abscess, osteomyelitis and sepsis. The responsible pathogens for the majority of infections in CGD are *S. aureus*, *Burkholderia cepacia* complex, *Serratia marcescens*,

*Nocardia* species, *Aspergillus* species; but *Salmonella*, *Pseudomonas* spp. and *Bacillus Calmette Guerin* are also identified in some cases (3). CGD patients not only suffer from recurrent infections, but also present with inflammatory, non-infectious conditions (4). There are extreme differences in presentation between patients, varying from a relatively mild presentation late in life to fatal septicemia in infancy (1). Granulomatous inflammation can affect any hollow organ, but morbidity and mortality is caused by damage to the gastrointestinal and genitourinary tracts. Diagnosis of CGD can be made by demonstrating the inability of phagocytes to produce a normal respiratory burst through nitroblue tetrazolium (NBT) test. In this test, activated neutrophils are incubated with the yellow dye NBT. Normal activated neutrophils produce a dark blue pigment while abnormal neutrophils remain yellow (5). Early diagnosis, antimicrobial prophylaxis with Co-trimoxazole and Itraconazole and aggressive management of infectious complications are the cornerstones of CGD management (3).

### **Case report**

A 3-year-old boy came to our attention for occasional hematochezia/rectal bleeding, persistent elevated inflammatory markers and chronic anemia.

Family history was negative for gastrointestinal diseases. He suffered from recurrent respiratory infections (rhinitis, bronchiolitis, pneumonia) since birth. He showed a progressive deflection of the stature growth curve and presented isolated episodes of hematochezia at the ages of one and four months, and two episodes of rectal bleeding at the age of 2 years without vomit, diarrhoea or fever.

On several occasions hematochemical examinations showed microcytic anemia and noticeable/clean-cut increase in inflammatory markers.

At the age of 2 years he underwent blood transfusion for severe anemia during the fever episode.

He continued to follow-up as an outpatient with pediatric gastroenterology management.

At the age of 3 years he was admitted to our department in order to exclude inflammatory bowel disease.

On admission, physical examination revealed a pale child, with eczematous lesions in the nostrils and the right ear, purulent nasal discharge, rales at chest and swollen abdomen, failure to thrive (height inferior to 3<sup>th</sup> percentile).

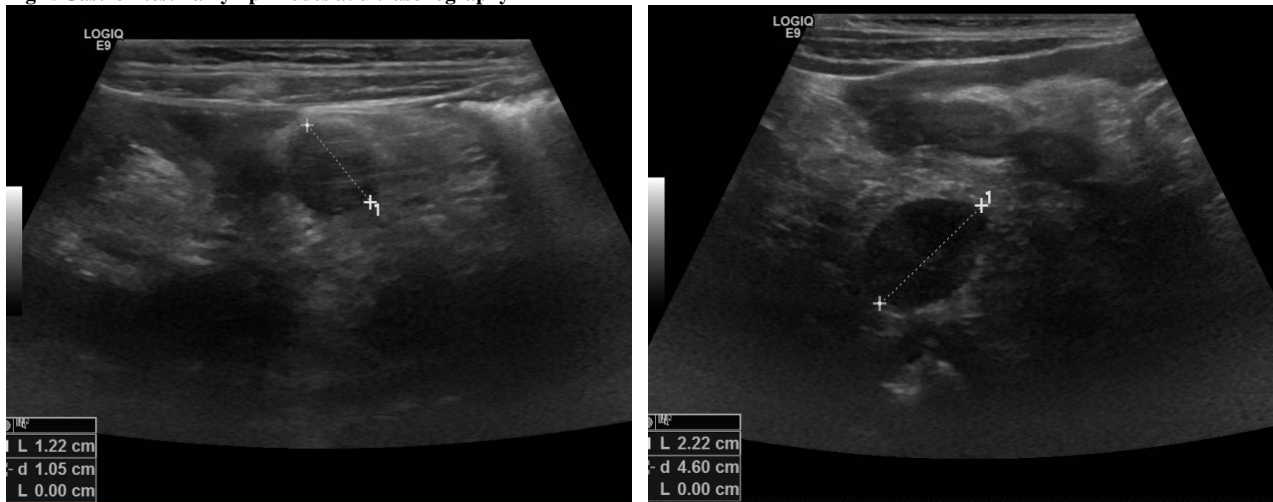
Laboratory tests confirmed remarkable microcytic hypochromic anemia (haemoglobin 9.2 g/dL), elevated inflammatory markers (erythrocyte sedimentation rate of 79 mm/h, C-reactive protein N x 8,5 and thrombocytosis) and increased stool calprotectin (Tab 1).

**Tab 1. Laboratory Findings in Our Patient**

	RBC count (x 10 <sup>3</sup> /uL)	MCV (fl)	Hemoglobin, (g/dL)	Platelet count, (x 10 <sup>3</sup> /uL)	C-reactive Protein( 0-0.5 mg/dl)	Erythrocyte sedimentation rate, (mm/h)	Ferritin (ng/ml)	Treatment
<b>December '15</b>	4.700	63	7,8	513			13	
<b>March '16</b>	3.540	56	5,4	580	9	101		<b>blood transfusion</b>
<b>January '17</b>	4.870	63	8,9	444	5	119		
<b>February '17</b>	4.820	65	9,2	517	4	79	16,9	<b>antibiotic</b>
<b>March '17</b>	4.980	65	9,7	478	1.5	53		

White blood cell count showed hyper eosinophilia. Normal levels of ferritin suggested anemia caused by chronic disease. The immunological work-up revealed Immunoglobulin (Ig) G, IgA, IgM, IgE within his age-matched reference ranges; analysis of subgroups of lymphocytes showed an increase in B cells (CD19). Stool cultures, Clostridium difficile stool antigen, microscopy for parasites did not reveal any abnormalities. Beta thalassemic trait, cystic fibrosis and celiac disease have been excluded. Abdominal ultrasound highlighted splenomegaly, marked hypertrophy and hyperrecogenicity of the mesentere, an intestinal segment, probably ileal, with thickened walls and multiple lymphadenopathies with globular morphology and inhomogeneous structure (Fig. 1).

**Fig 1. Gastrointestinal lymph nodes at ultrasonography**



He underwent esophagogastroduodenoscopy and colonoscopy in sedation, which showed lymphonodular hyperplasia of the duodenal, terminal ileum, cecum and colon mucosal. An aspirated bone marrow excluded lymphoproliferative diseases. During admission, according to hematochemical examinations and clinical presentation, amoxicillin was started, bringing to a significant reduction in inflammatory index and a rise in hemoglobin of 0,5 g/dl in five days. Colonic biopsies showed extensive granulomatous inflammation. In order to confirm a CGD, laboratory evaluation for neutrophil oxidative burst was performed and diagnosis was made through NBT test.

## Discussion

Gastrointestinal tract involvement was reported in 32% to 48% of patients with CGD. GI disease is thought to be a direct result of the inflammatory dysregulation in CGD. GI involvement may appear as colitis, abscess, dysmotility, stenoses of the gastric antrum and delayed gastric emptying, intestinal obstruction, constipation, slit, and oral ulcers (6). The prevalence of GI disease has been found to be higher in patients with X-linked disease than with autosomal recessive disease. Colitis, however, is an uncommon initial presentation of CGD (7). The literature describes a single case of a previously healthy 3-year-old boy whose initial clinical presentation mimicked classic features of Crohn disease (CD), but who was diagnosed with CGD after histopathologic assessment raised suspicion of the rare disorder (8). In fact, clinical data, radiologist and endoscopic examinations of colitis in patients with CGD can be indistinguishable from those of CD, leading to erroneous diagnosis in these patients (6); but careful histopathologic assessment can distinguish the two. Unlike the granulomas of CD, non-caseating granulomas present in the colitis CGDs appear as aggregate of epithelioid histiocytes surrounded by a cuff of dense lymphocytic inflammation (7,8). Although acute treatment for CGD and CD is similar (intravenous glucocorticoids), the differential diagnosis between CGD and CD is important for both infection prevention and why some immunomodulatory drugs commonly used as CD maintenance therapy may be actually dangerous for patients with CGD (7,8).

In our case there were several suggestive immunodeficiency elements (recurrent respiratory infections, chronic anemia, growth failure, elevated inflammatory markers, occasional rectal bleeding, lymphadenopathy) but the histological report of granulomas on intestinal biopsies has allowed us to confirm the diagnosis. At the time of diagnosis there was a very common manifestation of lymph node involvement, and less frequent at the onset of disease, that is, the diffuse granulomatous. The latter was the alarm bell for definitive diagnosis.

**Conflicts of Interest:** There is no potential conflict of interest, and the authors have nothing to disclose. This work was not supported by any grant.

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