



Chronic granulomatous disease with an initial presentation of arthritis and oral ulcers

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ABSTRACT

Chronic granulomatous disease (CGD) is an inherited defect of leukocyte phagocytic function leading to recurrent infections. Autoimmune manifestations are reported in up to 6% of patients with CGD. We report a case of CGD presenting with arthritis as the first manifestation of disease. A 12-year-old Pakistani male of consanguineous parents presented with migratory arthritis and painless oral ulcerations of 6 months duration that were minimally responsive to nonsteroidal anti-inflammatory treatment. Initial assessment demonstrated elevated inflammatory markers (ESR 62), weakly positive ANA (titer 1:40), negative anti-DsDNA, and negative RF. He presented to the emergency department with fevers and arthritis. Repeat work-up suggested early Macrophage Activation Syndrome: normocytic anemia (Hgb 95 g/L), thrombocytopenia (Plt $141 \times 10^9/L$), elevated LDH 1603, ferritin 1230 mcg/L, ESR 127, CRP 9.3, hypertiglycerdemia (3.2 mmol/L) and mild transaminitis (ALT 63, AST 87), normal bone marrow (no hemophagocytosis), but mildly elevated Soluble CD 136 (1086 ng/mL) and Soluble IL-2 receptor (CD25) (1698 U/mL). He was treated with oral prednisone with symptom resolution. The arthritis relapsed after 1 month and the patient developed fever, productive cough, and pleuritic chest pain. Chest imaging revealed multiple nodular opacities and enlarged mediastinal lymph nodes. *Aspergillus fumigatus* complex was isolated from induced sputum prompting screening for primary immunodeficiency. Neutrophil oxidative burst function, as assessed by a dihydrorhodamine flow cytometry based assay, was low at 1.26 and 1.48 (normal range 32–300). Genetic analysis showed a previously described mutation in the *NCF1* gene confirming the diagnosis of autosomal-recessive CGD. CGD can present with an exclusively rheumatologic presentation including arthritis and oral ulceration.

Statement of Novelty: This case demonstrates that CGD can present with rheumatological symptoms prior to any infectious features.

Introduction

Chronic Granulomatous Disease (CGD) is a rare, inherited defect of leukocyte phagocytic function with an inability to produce superoxide radicals. It is the result of a mutation in at least 1 of 5 genes that encode nicotinamide adenine dinucleotide phosphate (NADPH) oxidase complex enzyme. Two of the protein subunits are membrane-bound glycoprotein gp91^{phox} (phagocyte oxidase) and p22^{phox}; the remaining subunits

are cytosolic p47^{phox}, p67^{phox}, and p40^{phox} (Segal et al. 2000).

The disease is characterized by recurrent fungal and bacterial infections, with a predilection to catalase-producing organisms. Other recognized disease manifestations include granulomata causing resultant gastrointestinal or urinary obstruction, inflammatory bowel disease, and rarely, autoimmune disease (Kang et al. 2011).

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Autoimmune manifestations reported in CGD include Lupus Syndromes (Discoid Lupus Erythematosus and Systemic Lupus erythematosus), idiopathic/immune thrombocytopenia, myasthenia gravis, sarcoidosis, IgA nephropathy, steroid responsive pericardial effusion, anti-phospholipids syndrome and autoimmune hepatitis (Schmitt et al. 1995; Macedo et al. 1999; Winkelstein et al. 2000; De Ravin et al. 2006, 2008; van den Berg 2009; Koker et al. 2013).

The prevalence of CGD differs by country with estimated prevalence up to 1:111 000 to 1:1 330 000 in Israeli Arabs and the United Kingdom to as low as 1:1 000 000 in a recent Italian cohort (Jones et al. 2008; Martire et al. 2008; Wolach et al. 2008). In North America, the reported disease prevalence is 1:200 000–250 000 with 70% of patients having the mutation in the X-linked *CYBB* gene encoding gp91^{phox}. Other gene mutations are autosomal recessive (AR); the most common AR gene affected is neutrophil cytosolic factor 1 (*NCF1*), encoding p47^{phox} (Winkelstein et al. 2000). In the Middle East, most patients have autosomal recessive mutations as opposed to the X-linked *CYBB* gene (Fattahi et al. 2011; Al-Muhsen and Alsum 2012; Koker et al. 2013).

Functional and clinical presentation

A 12-year-old Pakistani male of consanguineous parents presented with migratory arthritis and painless oral ulcerations of 6 months duration. The arthritis involved metacarpopharyngeal (MCP), metatarsopharyngeal (MTP), and proximal interphalangeal (PIP) joints at various time points. However, within a week, the patient had diffuse arthritis in most MCP, MTP, and PIP joints of the hands and feet. He had accompanying arthralgias in his neck, shoulder, elbows, wrists, and knees. Painless oral ulcerations were swabbed with negative results for viruses. The arthritis resolved within a week with a nonsteroidal anti-inflammatory (ibuprofen) and without the use of antimicrobial drugs.

Four months later, his arthritis relapsed and he developed daily fevers, anorexia, fatigue, and weight loss. Blood work showed anemia (Hgb 110 g/L), platelets (172×10^9 /L), white blood cells (5.2×10^9 /L), and differential (neutrophils 2.5×10^9 /L, lymphocytes 2.2×10^9 /L). Inflammatory markers were elevated (ESR 62, CRP 29). Rheumatological work-up included a weakly positive antinuclear antibody (ANA) (titer 1:40), negative staining for anti-DsDNA, anti-RNP, anti-Smith, anti-cardiolipin, anti-SS-A, anti-SS-B, and rheumatoid factor. He had

transient response to naproxen. His fever persisted and he was found to have angular stomatitis, cervical lymphadenopathy, hepatomegaly, and arthritis in the left PIP joints of the hand and in the right ankle. Repeated blood work was significant for a normocytic anemia (Hgb 95 g/L), thrombocytopenia (Plt 141×10^9 /L), elevated LDH 1603 U/L, ferritin 1230 mcg/L, ESR 127, CRP 9.3, hypertiglycerdemia (3.2 mmol/L), and mild transaminitis (ALT 63, AST 87). Bone marrow aspirate was not suggestive of hemophagocytosis. Mildly elevated soluble CD 136 (1086 ng/mL) and soluble IL-2 receptor (CD25) (1698 U/mL) were noted. The patient was treated for presumptive Macrophage Activation Syndrome given his arthritis history and blood work. He received 60 mg of oral prednisone with complete symptom resolution, and he was discharged on a tapering schedule. Again, no antimicrobial agents were used.

After 1 month, the arthritis and fever relapsed, and the patient developed a new productive cough and pleuritic chest pain. Chest imaging illustrated multiple nodular opacities and enlarged mediastinal lymph nodes (Figure 1). Induced sputum demonstrated the presence of yeast and pseudohyphae. A follow-up bronchoalveolar lavage confirmed *Aspergillus fumigatus* complex. The identification of this unusual infection prompted a request for an Immunology consultation.

Immunological assessment found that his past medical history was positive for uncomplicated varicella disease at 5 years of age. There was no previous history of pneumonia, lymphadenitis, deep-seated abscess, or osteomyelitis and no prior history of recurrent abdominal pain, vomiting, diarrhea, or blood in the stool. His immunization record was up to date including Bacillus Calmette–Guerin vaccine with no adverse reactions or complications. He had unremarkable lymphocytes subsets (CD3+: 2511 (normal range 800–3500), CD4+: 1250 (normal range 400–2100), CD8+: 1123 (normal range 200–1200), CD19+: 1014 (normal range 200–600), and NK cells: 36 (normal range 70–1200), all in cells/ μ L), high IgG 19.2 g/L (normal range 6.60–15.30 g/L), high IgE 294 IU/mL (normal range < 200 IU/mL), and normal IgM 1.5 g/L (normal range 0.40–1.5 g/L) and IgA 2.9 g/L (normal range 0.50–2.2 g/L). Specific antibody responses were positive for measles, mumps, rubella and varicella, and protective tetanus titers (0.55 IU/mL). Owing to the finding of *Aspergillus fumigatus*, neutrophil oxidative burst function as assessed by dihydrorhodamine flow cytometry based assay (Figure 2) was abnormally low at 1.26 and 1.48 (normal range 32–300). Genetic testing confirmed a homozygous

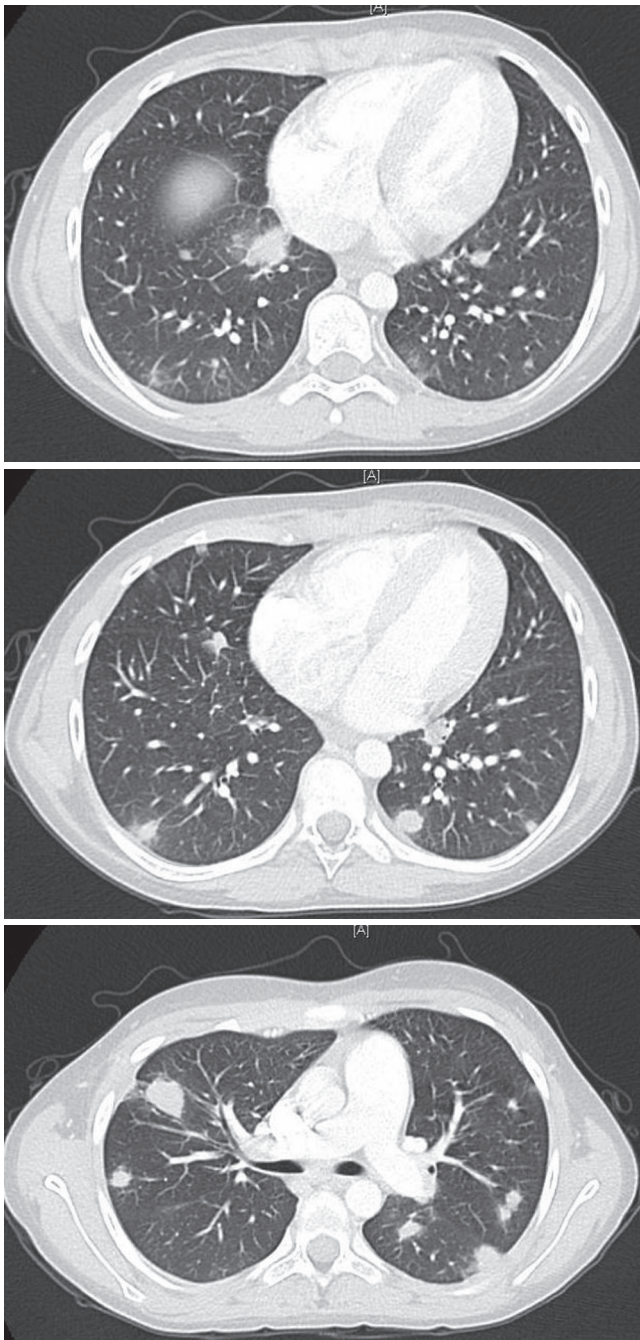


Figure 1: Chest CT illustrating multiple lung nodular opacities and enlarged mediastinal lymph nodes.

mutation in the *NCF1* gene (encoding for p47^{phox}) at c.75_76delGT. The patient received treatment for lung aspergillosis with voriconazole and was placed on cotrimoxazole bacterial prophylaxis. On follow-up, he has continued these treatments and has shown signs of improvement in the size of the lung lesions. He developed intermittent abdominal pain without diarrhea. Enterography MRI and upper and lower endoscopies including biopsies were all normal.

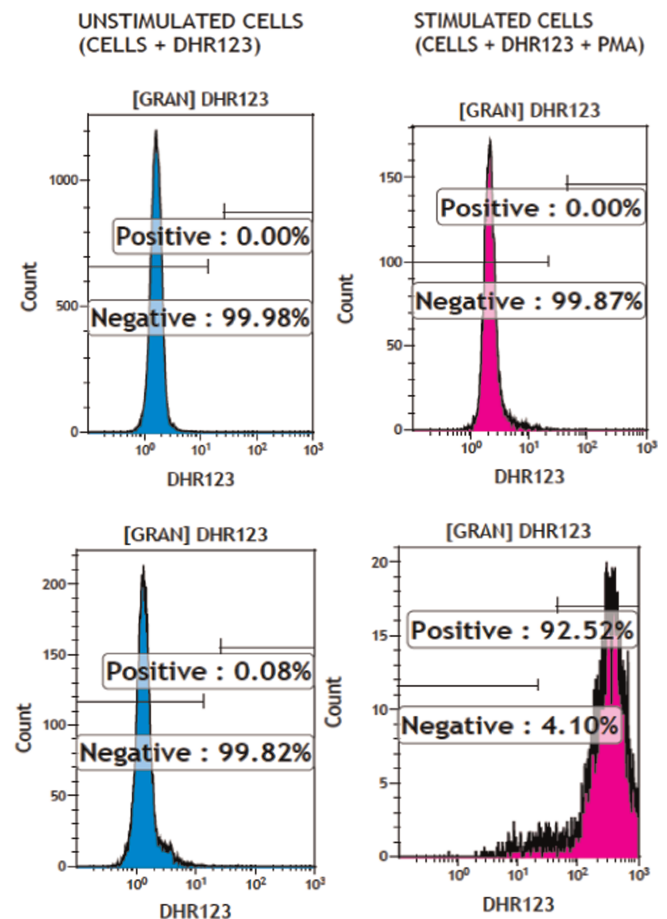


Figure 2: Neutrophil oxidative burst function as assessed by dihydrorhodamine (DHR) flow cytometry demonstrating the patient shows almost no oxidation of DHR. Upper graphs are the patient (unstimulated and stimulated with phorbol myristate acetate (PMA)). Lower graph is the control (unstimulated and stimulated with PMA).

Discussion

The NADPH oxidase complex enzyme is critical in microbial killing, but it also serves a protective role in inflammation and autoimmunity (Brown et al. 2003; Hultqvist et al. 2009). CGD patients are at an increased risk of colitis and discoid lupus, in addition to arthritis, although the latter is rarely reported (Winkelstein et al. 2000; De Ravin et al. 2008; van den Berg et al. 2009). There are case reports as well as entries in large registries that have previously reported arthritis developing after the diagnosis of CGD (Lee and Yap 1994; De Ravin et al. 2008; van den Berg et al. 2009; Koker et al. 2013; Magnani et al. 2014). There are 7 patients reported with arthritis, and only 3 with systemic lupus erythematosus (SLE), found in various large registries of CGD patients. Gene defects are however not reported in these patients and the phenotype of the arthritis is not described (Table 1).

Table 1: Summary of available CGD registries reported in the past 15 years with reported cases of arthritis and available phenotype characterization, systemic lupus erythematosus (SLE) and discoid lupus erythematosus (DLE).

Country	No.	Reference	No. of patients		
			Arthritis	SLE	DLE
Europe	429	van den Berg et al. (2009)	2 (rheumatoid arthritis)	1	18
Turkey	89	Koker et al. (2013)	3 (reactive arthritis)	NR	NR
France	98	Magnani et al. (2014)	2 (arthritis)	NR	2
USA	368	Winkelstein et al. (2000)	NR	2	10
UK/Ireland	98	Jones et al. (2008)	NR	NR	NR
Greece	24	Raptaki et al. (2013)	NR	NR	NR
Israel	38	Wolach et al. (2008)	NR	NR	NR
Spain	13	Soler-Palacin et al. (2007)	NR	NR	NR

NR, not reported.

Our patient’s mutation (c.75_76delGT) accounts for greater than 95% of mutations in the *NCF1* gene (Noack et al. 2001). The *NCF1* gene encodes for the p47^{phox} subunit of the NADPH oxidase complex. Deficiency in the p47^{phox} subunit has been reported in 2 case reports of CGD patients with arthritis. Both of these patients developed arthritis after the diagnosis of CGD. The first case was diagnosed with p47^{phox} deficiency at 2 years of age after presenting with *Aspergillus* pneumonia (Lee and Yap 1994). She developed a diffuse polyarthritis at 4 years of age. Rheumatological evaluation was significant for an elevated rheumatoid factor 395 IU/mL (normal 0–30), weakly positive ANA (1:40, homogenous patter), and positive anti-dsDNA (11 mg/mL). There was also radiographic evidence of progressive bony erosions.

The second case was diagnosed with p47^{phox} deficiency at birth (De Ravin et al. 2008). Her early course was remarkable for recurrent sinusitis, otitis media, and pulmonary infections. She developed a polyarthritis at the 15 years of age with multiple rheumatoid nodules. Rheumatological work-up demonstrated rheumatoid factor in the synovial fluid, and biopsy showed perivascular synovitis without lymphoid aggregates. Imaging illustrated mild subchondreal lucency. The patient required Etanercept for full symptom resolution.

Animal models support the importance of the oxidative burst pathway and the *NCF1* gene in particular in the pathogenesis of arthritis. Rodents with a homogenous mutation in the *NCF1* gene develop severe autoimmune arthritis (Hultqvist et al. 2004, 2009).

There are various proposed mechanisms for the development of hyperinflammation and autoimmunity

in patients with CGD. Animal and human cells exhibit reduced NADPH oxidase activity required for the induction of T regulatory cells (Magnani et al. 2014). Other proposed mechanisms have recently been reviewed (Rieber et al. 2012). These mechanisms include a reduction in neutrophil apoptosis, an imbalance of innate immune receptors (toll-like and complement receptors), alterations in T-cell activation and proliferation due to altered reduction of thiol groups on the T-cell membrane, induction of Th17 cells, impaired Nrf2 activity (a key redox-sensitive anti-inflammatory regulator), and increased inflammasome activation. However, the clinical importance of many of these mechanisms requires further investigation.

Our patient is rare because not only did he have arthritis, which is rare in CGD, but he also had this presentation prior to any other manifestations of the disease. Clinically, the course of arthritis in our patient was likely of autoimmune origin and very unlikely to be of infectious etiology given the intermittent nature of his arthritis, the prompt response to anti-inflammatory drugs, and the complete resolution prior to introducing antimicrobial treatment.

His arthritis was nondestructive; it was diffuse with symmetrical involvement of the small joints of the hands and feet (PIPs, MCPs, and MTPs). Large joints were less affected. The patient was evaluated for SLE. There were neither symptoms nor signs suggestive of photosensitivity, malar or discoid rash, serositis, renal or neurological involvement, as well as negative autoantibodies with the exception of a weakly positive ANA (1:40). He did have anemia with intermittent reticulocytosis and oral ulcers. Therefore, he had only 4 possible criteria of SLE including a borderline ANA. Given that

some of his features, such as the oral ulcers (van den Berg et al. 2009), can be explained by his CGD, he does not currently carry a diagnosis of SLE.

Steroid use is a known risk factor for invasive *Aspergillus* infections, which is positively correlated to the dose and duration (Baddley 2011). In this case, the duration of steroids was short and was not likely to be sufficient to render him prone to this infectious complication. In patients with rheumatological disease and unusual infectious organisms the possibility of a primary immunodeficiency disorder (PID) is plausible (Todoric et al. 2013).

Aspergillus is a common infectious complication of CGD. A detailed discussion of the management of CGD is beyond the scope of this article and has been reviewed recently by Kang et al. (2011). In brief, the management includes prophylactic antifungal medications against *Aspergillus*, antibacterial prophylaxis against *Staphylococcus Aureus*, and consideration of hematopoietic stem cell transplantation.

Conclusions

This case illustrates that rheumatological features can be the presenting feature of a PID and not just an associated feature. It also emphasizes the need to consider a PID in patients with rheumatologic diseases who develop unusual or opportunistic infections. Increased physician awareness may lead to more recognition of the autoimmune manifestations of CGD.

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