

## CASE SERIES

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# Lupus Erythematosus and Chronic Granulomatous Disease: Report of Four Iranian Patients with AR-CGD and One XL-CGD

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## ABSTRACT

Chronic granulomatous disease (CGD) is a rare genetic disorder of neutrophil activity, resulting in increased rate of recurrent infections with catalase-positive bacteria and fungi, as well as various autoimmune diseases such as sarcoidosis, rheumatoid arthritis, and discoid and/or systemic lupus erythematosus. Few reports have reported lupus erythematosus (LE) in patients with X-linked CGD (XL-CGD) and carriers, and very few in autosomal recessive CGD (AR-CGD). Here, we present 5 patients with CGD developing LE at different ages to emphasize on the importance of appropriate follow-up and treatment in patients with CGD with clinical signs and symptoms of autoimmune diseases and even in those with negative serologic results.

**Keywords:** Chronic; Cutaneous; Granulomatous disease; Iran; Lupus erythematosus; Rare diseases

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## INTRODUCTION

Chronic granulomatous disease (CGD) is a rare inherited disease with a defect in oxidative metabolism

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of phagocyte cells.<sup>1</sup> The incidence of CGD is about 1 in 200,000–1,000,000 individuals with varying reported frequencies in different countries.<sup>2</sup> Superoxide production in polymorphonuclear cells (PMNs) is inactive in patients with CGD and has reduced activity in X-linked carriers.<sup>1</sup> This defect results in a tendency for recurrent infections with catalase-positive bacteria and fungi. Therefore, the main clinical presentation of CGD is recurrent life-threatening bacterial and fungal infections with abscesses and granuloma formation.<sup>1-3</sup> There are two types of CGD: X-linked (XL-CGD) and autosomal recessive (AR-CGD). Mutations in *gp91phox* as the XL-CGD is about 65%; while mutations in *p47phox*, and *p67phox/p22phox* as AR-CGD have been reported in approximately 25% and 10% of patients, respectively. Additionally, *p40phox* deficiency as AR-CGD has been reported in 2009.<sup>3</sup> However, these results are very different in Iran and only 15% of cases are diagnosed with XL-CGD.<sup>4,5</sup>

About 10% of patients with CGD have some autoimmune manifestations in their clinical findings.<sup>6</sup> Moreover, according to registry reports from United States, 10% and 3% of patients with XL-CGD and AR-CGD had at least one family member with discoid lupus erythematosus (DLE), respectively,<sup>7</sup> which highlights the necessity to pay greater attention to this issue. Various autoimmune conditions, such as sarcoidosis,<sup>8</sup> rheumatoid arthritis,<sup>9</sup> inflammatory bowel disease,<sup>10</sup> and DLE and systemic lupus erythematosus (SLE)<sup>11-14</sup> have been reported in CGD population, suggesting that these patients are at elevated risk for development of autoimmune disorders.<sup>9</sup> There are some reports indicating the presence of SLE and DLE in patients with XL-CGD and carriers.<sup>11-15</sup>

Herein, we aimed to report four patients with AR-CGD and one with XL-CGD with systemic and cutaneous lupus erythematosus (CLE) who were referred to Immunology, Asthma, and Allergy Research Institute (IAARI), Tehran University of Medical Sciences, Iran. The protocol of the study was approved by IAARI ethics committee (No: 412/P/204). An informed consent was signed by the patients or their parents

### CASE PRESENTATION

#### Patient #1

A 24-year-old woman was diagnosed with AR-CGD (*p47phox*-deficient) at the age of 10 by recurrent

cystic acne and furunculosis. She was treated with Trimethoprim sulfamethoxazole (TMP-SMX) and developed thrombocytopenia at the age of 18. She had a negative family history of CGD or lupus erythematosus. Her medical history and physical examination was unremarkable and laboratory evaluations revealed negative antibodies to cardiolipin, double strand Deoxyribonucleic acid (ds DNA), antinuclear antibody (ANA), and lupus anticoagulant. After 5 years, erythematous lesions appeared over the cheeks and nasal bridge that was compatible with malar rash. Laboratory tests were repeated and resulted in positive Fluorescent antinuclear antibody (FANA) and ds DNA. Thus, she fulfilled the American College of Rheumatology criteria<sup>16</sup> for diagnosis of SLE which was confirmed by a rheumatologist and specific treatment including prednisolone and hydroxychloroquine was started for her. Hip MRI showed avascular necrosis (AVN) of the femoral head that could have been related to corticosteroid usage. After being negotiated in Bone Marrow Transplantation (BMT) Committee, it was decided to perform BMT after finding the completely matched donor.

#### Patient #2

A 9-year-old boy with XL-CGD (*gp91phox*-deficient), was diagnosed at 11 months of age with BCG-osis (cervical and auxiliary lymphadenopathy, hepatosplenomegaly, osteomyelitis), being complicated with pulmonary aspergillosis and cerebellum abscess in the following years. The patient had received TMP-SMX, itraconazole, and interferon- $\gamma$ . At the age of 8, he was diagnosed with CLE by punch biopsy following the development of a plaque-like reddish rash on his face. He received oral hydroxychloroquine.

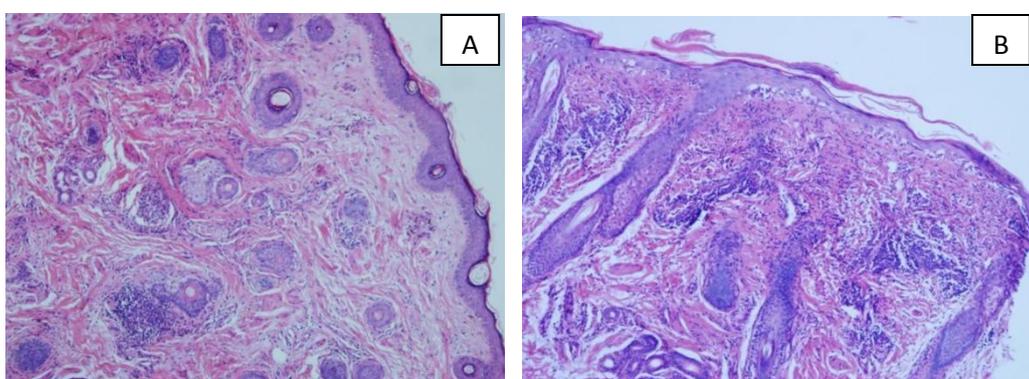
Figure 1 and 2 (A) show the schematic and histopathology findings of skin lesion, compatible with lupus erythematosus. FANA, ds DNA, and other laboratory tests for SLE were negative and other organs were not involved. He suffered from severe complications of CGD and died because of fungal infection of central nervous system (CNS) at the age of 11.

#### Patient #3

A 7-year-old girl diagnosed with AR-CGD (*p67phox*-deficient) during birth screening that was performed because of a positive family history of CGD (her sister), was referred. Her parents had second-degree cousins. She received TMP-SMX, itraconazole,



**Figure 1.** A 9-year-old boy with X-Linked Chronic granulomatous disease (XL-CGD) was diagnosed at 11 months of age with BCG-osis. There is a skin lesion compatible with lupus erythematosus (Patient #2)



**Figure 2.** Pathological findings of face lesion with Hematoxylin & Eosin stain, 20X: (A) A 9-year-old boy with X-Linked Chronic granulomatous disease (XL-CGD): sections show dyskeratosis, perivascular and perifollicular lymphocytic infiltration (Patient #2), (B) A 7-year-old girl diagnosed with autosomal recessive CGD (AR-CGD): sections show parakeratosis, epidermal atrophy, basal layer damage, and dense perivascular infiltration (Patient #3).

and interferon- $\gamma$  after diagnosis and was candidate for Hematopoietic stem cell transplantation (HSCT). She developed a reddish lesion on her face the biopsy of which revealed CLE. The laboratory findings and clinical manifestations were not suggestive of SLE. Figure 2(B) shows the histopathological findings of her face lesions. She received hydroxychloroquine for treatment of LE.

#### **Patient #4**

A 14-year-old boy with AR-CGD (p22*phox*-deficient), diagnosed at age 7 with recurrent abscesses, TB, and aspergillus infections was referred. He received TMP-SMX, itraconazole, and interferon- $\gamma$  and underwent HSCT at 13 years old with satisfactory post transplantation conditions. He developed plaque-like reddish rash on his face which was diagnosed as

CLE by punch biopsy. Laboratory findings and other clinical manifestations of SLE were negative. He received hydroxychloroquine for management of CLE and was followed by a rheumatologist in another center.

#### **Patient #5**

A 13-year-old girl with AR-CGD (p22*phox*-deficient), diagnosed at the age of 4 following TB and recurrent fever was referred. Further investigations revealed multifocal spleen granulomatosis. At 12 years old, malar rash, photosensitivity, and splenomegaly were observed in her physical examination and laboratory results showed pancytopenia, high level of FANA, anti-ds DNA, and decrease C3 and C4 levels, resulting in definite diagnosis of SLE according to American College of Rheumatology criteria. She

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received prednisolone and hydroxychloroquine and followed by pediatric rheumatologist. She was treated with TMP–SMX, itraconazole, and interferon- $\gamma$  and had successful HSCT at 12 years old.

The demographic characteristics, clinical manifestation and laboratory findings of these patients are summarized in Table 1. All of the patients received

oral trimethoprim sulfamethoxazole as prophylaxis. Itraconazole and interferon  $\gamma$  were prescribed with appropriate dose based on age and sex, if necessary. They were referred to rheumatology department for further specific treatment such as prescription of prednisolone and hydroxychloroquine.

**Table 1. Demographic characteristics, clinical manifestation, and treatment of the 5 patients with chronic granulomatous disease with lupus erythematosus**

Patient number	Age (year)	Age at diagnosis of CGD	NBT%	Consanguinity	Clinical presentation of CGD	Type of CGD	Genetic results <sup>19</sup>	Lupus Onset age (year)	Lupus findings	Type of lupus	Autoimmune laboratory tests *	Outcome
1	24	10 years	5	First-cousin	Recurrent cystic acne and frunculosis	AR p47 <sup>017</sup>	<i>NCF1</i> gene, Exon 2, c.75_76 delGT	23	Malar rash, thrombocytopenia	SLE	P**	Alive and under treatment
2	9	11 months	0	Non-relative	BCG–osis, pulmonary aspergillus, cerebellum abscess	XL gp91 <sup>0</sup>	<i>CYBB</i> gene, Exon 9, c.1011G>A	8	Rash on his face	CLE	N***	Died due to CGD complication : CNS fungal infection
3	7	At birth	0	Second degree-cousin	———— Fever, TB	AR p67 <sup>0(18)</sup>	Not performed	7	reddish lesion on her face	CLE	N	Alive
4	14	7 years	0	Far-cousin	Recurrent abscesses, TB, and aspergillus infection	AR p22 <sup>019</sup>	<i>CYBA</i> Gene, Exon 6, c.385_388 delGAGC	13	plaque-like reddish rash on his face	CLE	N	Alive Hematopoietic stem cell transplantation
5	13	4 years	2	First-cousin	TB, recurrent fever, spleen granulomatous is	AR p22 <sup>0</sup>	Not performed	13	Malar rash photosensitivity	SLE	P	Alive Hematopoietic stem cell transplantation

\*ANA, anti–ds DNA assays

\*\*Positive

\*\*\* Negative

### DISCUSSION

Chronic granulomatous disease (CGD) is a rare primary immunodeficiency disorder in which the microbicidal capacity of the phagocytic cells is reduced and this leads to recurrent life-threatening bacterial and fungal infections with abscesses and granuloma

formation.<sup>1</sup> About 10% of patients with CGD have some autoimmune manifestations in their clinical findings.<sup>6</sup> We aimed to report four patients with AR-CGD and one with XL-CGD with systemic and cutaneous lupus erythematosus (SLE and CLE). The novel point of this case series is that the coincidence of lupus erythematosus and AR-CGD as the dominant

form of CGD in Iran, has not been previously discussed. However, considering the limited number of patients in this report, more evaluations are required to draw more firm conclusions.

CGD is a rare inherited disease with phagocytic granulocyte dysfunction, caused by defects in oxidative metabolism of phagocytic cell.<sup>1</sup> Longer follow-up of patients with CGD indicated that various pathological conditions; especially auto-immune disorders, frequently occur in XL-CGD carriers and patients.<sup>9</sup> The diminished or delayed apoptosis of neutrophils and release of apoptotic immunogenic chromatin have been proposed to stimulate autoantibody production through T-helper and B-cell activation and reduce anti-inflammatory mediators secreted by neutrophils and macrophages in patients with CGD. Moreover, deficiencies in producing transforming growth factor  $\beta$  are the possible mechanisms explained for the increased risk of immune deficiency in patients with CGD.<sup>20</sup>

As XL-CGD is the most common type, the most frequently reported autoimmune conditions are among patients with XL-CGD and carriers.<sup>2</sup> Several case reports have reported patients with XL-CGD and DLE lesions<sup>14,21</sup> and few studies have reported AR-CGD and DLE.<sup>22,23</sup> DLE is the most common manifestation of CLE. In the present report, as well, 3 out of 5 patients with CGD had developed CLE, 2 of whom with AR- and one with XL-CGD. Another study on 98 CGD patients reported 0.18-folds increased risk of inflammatory episodes in XL-CGD and 0.08-folds increased risk in AR-CGD.<sup>24</sup>

The underlying mechanism for the association between CGD and lupus is still unclear. Sanford et al. observed that abnormal neutrophil apoptosis in patients with CGD is characterized by diminished or delayed phosphatidyl serine exposure. Moreover, injection of apoptotic neutrophils from gp91 knockout mice into gp91 knockout mice led to the increase of characteristic autoantibodies of lupus. Therefore, it is possible that the apoptotic neutrophils can act as an immunogenic and pathogenic factors underlying lupus-like features in patients with XL-CGD and carriers with defective neutrophil apoptosis.<sup>25</sup>

Inability to efficiently clear phagocytized pathogens and continuous foreign antigen (bacteria, viral) stimulation was considered as the main pathogenic mechanism for autoimmunity in immunodeficient patients.<sup>26</sup> Other explanations for the association

between CGD and lupus are provided by new evidence, suggesting that genes located on the X chromosome may play a role in autoimmunity and immune deregulations as a justification for frequent association of autoimmune phenomena in patients with XL-CGD and other primary immune deficiencies. It is possible that autoimmune manifestations in female carriers of XL-CGD are due to the presence of mutant cells in the periphery due to lyonization.<sup>13,26</sup> A recent study hypothesized that the most logical mechanism for the association of CGD and LE is the release of neutrophil extracellular traps (NETs) as immunological triggers of LE from neutrophils of patients with CGD.<sup>27</sup> Although few cases of CGD and LE are reported worldwide, understanding the underlying mechanisms can help us in treating CGD and prevent the development of LE and its further complications.

In Iran, the most common type of CGD is reported to be the AR form, which is suggested to be due to the high rate of consanguineous marriage.<sup>4,28</sup> Similarly, in the present report, consanguineous marriage occurred in the parents of 4 out of 5 patients. Considering the fact that 4 out of 5 patients had AR-CGD, it seems that CGD might itself be considered as a genetic cofactor which can diminish the threshold of autoimmunity development regardless of type of disease (AR- or XL-CGD). However, mechanisms underlying the association of AR-CGD and LE have to be further investigated.

Considering the fact that the number of patients was limited, it was not possible to evaluate the possible relationship between age/sex and autoimmune presentations as described by previous studies.<sup>13,21</sup> Researchers also suggest that CGD carriers are at greater risk of lupus-like symptoms such as photosensitive skin rashes, mouth ulcers, and joint pains, although serologic tests were negative; suggesting that patients with lupus-like symptoms may benefit from receiving appropriate treatment and negative lupus serology should not exclude these patients from treatment.<sup>29</sup>

Having in mind the death of one case due to infection despite receiving treatment, management of patients with CGD requires meticulous attention. The adverse effects of therapies used for patients with CGD is also of great importance, as studies suggest that combination of voriconazole and SMX-TMP can exacerbate photosensitivity and predispose these patients to higher risk of LE.<sup>30,31</sup> Therefore, despite

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being rare, patients with CGD and carriers need further investigations and routine follow-up.

It seems that LE is an important comorbidity of CGD that should be appropriately managed to prevent complications, especially in countries with a high rate of consanguineous marriages leading to higher rates of AR-CGD. To avoid potential complications of neglected patients, cases with CGD or carriers who are referred with significant clinical signs and symptoms of autoimmune diseases such as mucocutaneous lesions or arthritis, should be investigated and receive appropriate treatment even with negative serology.

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