



Noninfectious Manifestations and Complications of Chronic Granulomatous Disease

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Chronic granulomatous disease (CGD), a primary immunodeficiency characterized by a deficient neutrophil oxidative burst and the inadequate killing of microbes, is well known to cause a significantly increased risk of invasive infection. However, infectious complications are not the sole manifestations of CGD; substantial additional morbidity is driven by noninfectious complications also. These complications can include, for example, a wide range of inflammatory diseases that affect the gastrointestinal tract, lung, skin, and genitourinary tract and overt autoimmune disease. These diseases can occur at any age and are especially problematic in adolescents and adults with CGD. Many of these noninfectious complications present a highly challenging therapeutic conundrum, wherein immunosuppression must be balanced against an already markedly increased risk of invasive fungal and bacterial infections. In this review, the myriad noninfectious complications of CGD are discussed, as are important gaps in our understanding of these processes, which warrant further investigation.

The seemingly contradictory association between primary immunodeficiencies and autoimmune disease is well known [1], and many of the noninfectious complications of chronic granulomatous disease (CGD) exemplify this paradox [2]. In this review, we discuss the remarkable variety of inflammatory conditions that are associated with the CGD phenotype. Many of these disease manifestations result in conundrums for treating physicians, and we discuss the challenges in diagnosis and optimal management of such conditions.

GASTROINTESTINAL MANIFESTATIONS OF CGD

Granulomatous colitis seems to be the most common inflammatory complication of CGD in children, and more than 40% of patients with X-linked CGD ultimately develop some form of inflammatory bowel disease (IBD) [3]. In a series of children with CGD followed at the National Institutes of Health (NIH), gastrointestinal (GI) involvement was identified in 46 (32.8%) of 140

[4]. The median age of GI symptom presentation was 5 years, and most symptoms present in the first decade of life. In a contemporary cohort maintained by the US Immunodeficiency Network (USIDNET), 38% of patients experienced inflammatory GI complications (Supplementary Table 1). GI manifestations of CGD can precede the onset of infectious symptoms and can mimic symptoms of IBD, particularly Crohn disease [4]. Misdiagnosis of CGD colitis as ulcerative colitis or Crohn disease can delay the diagnosis of CGD significantly and can be life-threatening, because the treatment for IBD often involves immunosuppressant agents, which confer significant risk for infectious complications in patients with CGD. In addition, GI complications in patients with a known CGD diagnosis can cause significant morbidity, including detrimental effects on growth, nutritional status, and wound healing [4].

The spectrum of GI symptoms in patients with CGD can be broad and nonspecific, including abdominal pain, diarrhea, weight loss, fever, and nausea. Other features can include rectal bleeding, weight loss, perianal abscesses, bowel obstructions, fistulae, and strictures [5]. Any portion of the GI tract can be involved, although the colon is affected most often; distal disease that involves the rectum and anus (eg, perianal fistulae, rectal strictures) are particularly common [5]. In addition, large granulomas in the gut can lead to obstruction (including gastric outlet obstruction), which can occur anywhere throughout the GI tract, from the rectum to the esophagus [6]. Severe GI involvement occurs more commonly in patients with X-linked CGD [4, 7] than in those with autosomal recessive (AR) disease.

Endoscopic evaluation and tissue biopsy are of critical importance in characterizing GI findings in patients with

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Journal of the Pediatric Infectious Diseases Society 2018;7(S1):S18–24

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DOI: 10.1093/jpids/piy014

CGD. Colitis that involves the rectum and anus is seen most commonly with endoscopic evaluation, although the upper GI tract is often involved, and skip lesions can be found throughout the GI tract [8]. Histopathologic changes found in GI biopsy specimens from patients with CGD include the presence of local inflammation and granulomas, which sometimes are indistinguishable from findings in patients with Crohn disease. However, characteristic findings that can distinguish CGD enteritis from Crohn disease do exist. Pigment-laden macrophages within the lamina propria, tissue eosinophilia, and sharply defined histiocyte aggregates in granulomata have been associated with CGD [5, 9]. Staining for CD68, a monocyte and macrophage marker, revealed significantly fewer CD68+ cells in biopsy specimens from patients with CGD than in those from patients with Crohn disease [9] and might be useful in the diagnosis of CGD-associated enteral disease.

IBD is often classified according to age at disease onset. Patients diagnosed with IBD before they are 6 years of age are classified as having very-early-onset IBD and might represent a subset of patients with a particularly severe IBD disease course and decreased responsiveness to the anti-inflammatory and immunomodulatory therapies conventionally used for the treatment of IBD. These patients, especially those diagnosed before 2 years of age, represent a population of patients with a relatively higher incidence of underlying immune deficiency. Evaluation for CGD and other immune deficiencies should be considered in this population, which might represent an opportunity for the early diagnosis of CGD, because GI symptoms can be the initial presenting symptoms of CGD.

The treatment of CGD-associated colitis and other GI manifestations in patients with CGD represents a therapeutic dilemma. The mainstay of therapy for IBD includes immunosuppressive regimens, which often include corticosteroids and tumor necrosis factor (TNF) inhibition. Such regimens pose a serious potential risk in patients with CGD, particularly for those with an invasive fungal disease such as *Aspergillus* infection. CGD-associated enteritis or colitis management often requires a combination of luminal anti-inflammatory therapy (eg, mesalamine) and low-dose corticosteroids. Antimetabolites, such as methotrexate or azathioprine (while the patient remains on optimal antimicrobial prophylaxis), are also helpful for recurrent cases. TNF-blocking biologic agents have been associated with severe infections and death and are generally contraindicated [10]. Prolonged corticosteroid use in patients with CGD colitis can be associated also with invasive superinfection [11]. In patients with CGD that is complicated by severe GI inflammation, hematopoietic stem cell transplantation is often considered, because it is curative for CGD and related GI manifestations [12] (see also Connelly et al, this supplement).

INFLAMMATORY LUNG DISEASE IN PATIENTS WITH CGD

With optimal preventive care and management of infectious complications, patients with CGD now routinely live to adulthood. Increasing evidence now exists to suggest that certain inflammatory complications of CGD can become more prominent as patients age, and pulmonary disease drives much of the morbidity in this population. Current estimates indicate that at least half of all patients with CGD will develop pulmonary manifestations of CGD in their lifetime, particularly during adulthood [7, 13–17]. Although infectious pulmonary diseases such as pneumonia and lung abscesses are more common than noninfectious pulmonary lesions in patients with CGD, inflammatory complications can have profound effects on CGD-associated morbidity and treatment [15]. These noninfectious respiratory processes seem to be inflammatory in nature, which is consistent with the known chronic dysregulated inflammation associated with CGD [16, 18, 19]. These inflammatory respiratory events can occur independently from or concomitantly with or be triggered by an infection [16, 17, 20, 21].

The epidemiology and prevalence of noninfectious pulmonary manifestations in patients with CGD are unclear. Patients with X-linked CGD seem to have a higher risk of developing inflammatory episodes than do their counterparts with AR CGD [17, 22]. In a retrospective single-center French study of 98 patients with CGD (median age, 13.5 years), the prevalence of respiratory disease was reported to be 26.4%, and it accounted for 8.6% of all inflammatory events recorded [22]. A more recent retrospective study, which drew from the same cohort, found that noninfectious pulmonary events occurred in 28% of the 67 adult patients included in the study [17]. Data from USIDNET indicate that a wide variety of potential sinopulmonary complications of CGD can occur (Supplementary Table 2), including interstitial lung disease, pulmonary nodules, pleural effusions, and chronic obstructive pulmonary disease.

A common presentation for noninfectious events in patients with CGD is granuloma formation, with or without concurrent lymphocytic infiltrate [16, 17]. Lung granulomas can present with obstructive symptoms, depending on their location in the pulmonary tree [23]. These masses have been termed “autoimmune granulomas,” because they typically resolve with immunomodulatory therapy [2]. Granulomas are often sterile, although it can be difficult to exclude the presence of an infectious agent despite negative laboratory evaluation results [16].

Radiologic pulmonary findings are often nonspecific and can reveal consolidation, ground-glass or tree-in-bud opacities, scattered nodules, and bronchiectasis [17, 24, 25]. The radiographic appearance of CGD-associated pulmonary lesions can mimic neoplasm of the lung. CGD, therefore, should be included in the differential diagnosis when abnormal radiologic findings, such as granulomas or masses, are found on

chest imaging to minimize diagnostic delay and/or inappropriate therapy [26–28]. Pathologic findings of CGD-associated inflammatory lung disease are also variable. In the French adult cohort described previously, circumscribed nodules or parenchymal consolidation occurred after a respiratory infection in 7 of 11 patients (6 of 7 after *Aspergillus* infection), which might indicate a dysregulated response to infection. Biopsy results often reveal granulomas, with or without neutrophilic or eosinophilic microabscesses. Other biopsy findings can include increased reticular or ground-glass opacities without previous evidence of infection [17].

The diagnosis and treatment of inflammatory pulmonary disease in patients with CGD are unique challenges. Bronchoscopy with endobronchial biopsy, percutaneous needle biopsy, or open lung biopsy are often indicated to secure a microbiologic diagnosis, although the failure to isolate an organism does not prove the lack of an infectious etiology. When inflammatory disease is strongly suspected, the use of immunomodulators, such as corticosteroids, thalidomide, hydroxychloroquine, and methotrexate, has been found to resolve consolidation but not interstitial lung disease [17]. Some experts recommend short pulses of corticosteroid therapy escalating to additional agents such as methotrexate if a patient's response to steroids is poor, and the patient should remain on optimal CGD prophylaxis throughout that time. The optimal management of these pulmonary complications, however, remains unknown.

Mulch pneumonitis is a specific concern for patients with CGD and has even been reported as the sentinel manifestation of CGD [29]. This syndrome presents with acute-onset hypoxia, dyspnea, fever, and bilateral infiltrates 1 to 10 days after inhalation of fungal spores and hyphae (typically *Aspergillus* spp), such as those that can be found in mulch, hay, peat moss, or dirt [21]. The clinical and radiographic findings can overlap with other hypersensitivity pneumonitis syndromes (eg, farmer's lung). Appropriate treatment for mulch pneumonitis with both glucocorticoids and antifungal agents must be initiated in a timely manner to minimize morbidity and risk of death [21, 29].

AUTOIMMUNE/RHEUMATOLOGIC DISEASE IN PATIENTS WITH CGD

Although a clear association between X-linked CGD carrier status and increased risk of autoimmunity exists (see “Inflammatory Disease in Carriers of X-Linked CGD”), so too does a burden of autoimmune disease in patients with CGD. Study of a national registry of more than 350 patients found that patients with CGD might meet diagnostic criteria for systemic lupus erythematosus (SLE) (0.5% of patients) or discoid lupus erythematosus (DLE) (2.7% of patients) [7]. These rates are substantially higher than those reported for the general US population (2.9 per 100 000 with SLE, 4.2 per 100 000 with DLE) [30]. The increased risk of autoimmunity can be seen across geographies and age ranges,

with a focus on syndromes that resemble lupus, rheumatoid arthritis, and immunoglobulin A (IgA) nephropathy [6]. In a Turkish cohort [31], approximately half of the patients had an autoimmune or autoinflammatory disease (including IBD, stomatitis/gingivitis, reactive arthritis, idiopathic thrombocytopenia [ITP], pericardial effusion, and autoimmune hepatitis). In a French cohort of patients with CGD who reached adulthood, 17% reported at least one autoimmune condition, although the range of autoimmune processes noted was wide and included cold agglutinin disease, IgA nephropathy, acute demyelinating encephalitis, and antiphospholipid syndrome [32]. In a cohort of European patients, 6% were noted to have autoimmune complications; the most common was discoid lupus (18 [4%] of 429), followed by 2 cases of rheumatoid arthritis and 1 case each of SLE, dermatomyositis, sacroiliitis, ITP, and autoimmune hepatitis [15]. In the CGD registry maintained by the NIH, 10% of the patients had an autoimmune complication beyond IBD [33]. Additional reported rheumatologic conditions in patients with CGD include Raynaud phenomenon [34], lymphadenopathy, stomatitis [35], and aphthous ulcers with cutaneous lesions that mimic Behçet disease [36]. Patients with CGD also seem to be at increased risk of developing hemophagocytic lymphohistiocytosis [37]. In the USIDNET registry (summarized in [Supplementary Table 3](#)), 25 patients (4.9%) carried at least 1 autoimmune diagnosis, and the most common were SLE (21.2% of those with an autoimmune diagnosis) and DLE (15.2% of those with an autoimmune diagnosis). With regard to therapy, it has been noted that fully treating an autoimmune condition when identified in a patient with CGD is important. Although patients with CGD ideally will not require more than low-dose prednisone for their autoimmune disease, and immunosuppression clearly should be minimized as much as possible, it is important to treat these complications fully, which includes considering the use of high-dose steroids or immunosuppressing steroid-sparing regimens, should they be necessary [2]. Of course, in such scenarios, it is important also to clinically monitor patients closely.

NONINFECTIOUS AND INFLAMMATORY COMPLICATIONS OF CGD IN OTHER SYSTEMS (GENITOURINARY, OCULAR, AND CUTANEOUS)

Genitourinary Complications

Inflammatory complications of CGD can lead to complications in the genitourinary (GU) tract by the formation of large granulomas that lead to obstruction or stricture at various locations [7, 38], and these complications occur much more commonly in patients with CGD than in the general population [39]. An analysis of the USIDNET cohort performed for this review indicated that GU complications occurred in 16.1% of the patients ([Supplementary Table 4](#)), and of them, 16.8% of such complications were obstructive. In a European cohort of more than

400 patients with CGD, 6% were noted to have an obstruction in their GU system [15]. In a French cohort, 12 (12%) of 98 patients experienced inflammatory GU symptoms [22]. In addition, an increased incidence of eosinophilic cystitis has been noted in patients with CGD, perhaps more frequently in those with X-linked disease [31, 40–43]. Although this condition is often treated with a prolonged course of steroids, some experts recommend using oral antihistamines and intravesical steroids [31].

Ocular Complications

Inflammatory complications of CGD can be seen in the eye, although less commonly than in other organ systems. In a US registry, 8 (2%) of 368 patients had chorioretinitis [6], and in a European registry, 8 of 429 patients had chorioretinitis [15]. In a French cohort, 6 (6%) of 98 patients had ocular complications that ranged from chorioretinitis and ocular granuloma to uveitis [22].

Dermatologic Complications

In a large cohort of patients with CGD who reached adulthood, 13.4% reported cutaneous inflammatory events [32], more commonly after 16 years of age. A similar French cohort had an ~10% prevalence of skin complications, including granulomatous acne, inflammatory nodular lesions, and photosensitivity [22]. In addition, aphthous stomatitis and cutaneous lymphocytic infiltration [44] have been noted in association with CGD [34]. The contemporary USIDNET cohort includes 120 (23%) patients with a dermatologic inflammatory diagnosis (Supplementary Table 5), most commonly acne and eczema. Treatment with topical immunosuppressive therapy, and systemic therapy only when needed, is indicated [32].

CGD also has been associated with increased risks of wound dehiscence, poor wound healing [45], and pyoderma gangrenosum in patients after surgery [46]. A small ($n = 10$) pediatric study found a 30% rate of impaired wound healing [47], and in a separate cohort of patients who required colonic surgery, a 13% dehiscence rate was found [48]. In the cohort of patients with CGD maintained by the NIH, patients with X-linked CGD were more likely to require surgery, and wound complications occurred in 10% of the patients [46]. It should be noted that wound dehiscence in the setting of CGD seems to be atypical in that corticosteroids might speed healing [46].

INFLAMMATORY DISEASE IN CARRIERS OF X-LINKED CGD

X-chromosome inactivation (XCI) is thought to occur early in embryogenesis and leads to random epigenetic silencing of either the maternal or paternal X chromosome and expression of a single X chromosome (ie, lyonization) in females [49]. Female carriers of mutations in *CYBB*, which encodes $gp91^{\text{phox}}$,

are usually clinically unaffected because they have sufficient numbers of phagocytes expressing wild-type *CYBB* and thus have adequate superoxide production to protect against typical CGD infections. Some carriers, however, have nonrandom XCI, in which wild-type *CYBB* is silenced, which leads to markedly reduced oxidase activity. They can develop mild to severe infectious or inflammatory manifestations, including severe IBD [50–53]. In addition, females might have progressive XCI skewing with aging, and previously healthy carriers can develop manifestations of CGD later in life [54]. Interesting to note is that the risk of autoimmune or inflammatory disease in carriers is not clearly correlated with baseline oxidative burst function, unlike the risk of infection [55].

Dysregulated inflammation partly underlies the various degrees of pathology in different organs that X-linked carriers of *CYBB* mutations can exhibit [55–57]. Chorioretinitis was observed in 10% of carrier females in 1 small series of patients and their female carrier relatives [58]. Dermatologic manifestations in carriers include DLE, eczema, folliculitis, and photosensitivity [59–62]. GI manifestations include abdominal pain, intermittent diarrhea, IBD, and colon polyposis [62–64]. Autoimmune manifestations, including polyarthritis, recurrent aphthous ulcers, and Reynaud phenomenon, have been reported to be more prevalent in carriers than in a healthy control population [59–62]. The presence of symptoms consistent with SLE in CGD carriers is correlated with lower neutrophil oxidative burst function than in carriers without SLE symptoms [55].

FRONTIERS AND FUTURE DIRECTIONS

The origin of dysregulated and poorly controlled inflammation in patients with CGD remains somewhat mysterious [65–68]. Many factors can play a role, and a number of theories have been proposed, including the presence of persistent antigen (including smoldering infection [22]) leading to attempted immunologic control via granuloma formation, alterations in key inflammatory pathways (including the inflammasome), alterations in the balance of $CD4^+$ T-helper cell subsets [31, 69], and impaired clearance of chemotactic factors [45]. More recently, there has been a focus on the effect of CGD on apoptosis [33]. Evidence exists to indicate that neutrophils with a defective nicotinamide adenine dinucleotide phosphate oxidase complex (NOX2) are resistant to apoptosis in vitro and produce fewer anti-inflammatory mediators after phagocytosing apoptotic targets [70]. In addition, in mouse models of X-linked CGD, injection of apoptotic *gp91*-knockout neutrophils can lead to autoantibody formation [71]. Also, a role for altered production of neutrophil extracellular traps, wherein absent or altered NOX2 can alter inflammatory pathways [72], has been proposed. In addition, it has been noted that neutrophils from patients with CGD are less able to engage the DNA

damage-repair process properly when they are stimulated using strategies that generate reactive oxygen species and generate more inflammatory cytokines [73].

With a focus on novel therapeutics, both monocytes and macrophages from patients with CGD have revealed decreases in efferocytosis [74, 75]. Pioglitazone, a peroxisome proliferator-activated receptor gamma agonist, restored efferocytosis in vitro, and 2 patients who received the drug for other clinical reasons experienced improved monocyte efferocytosis and improved reactive oxygen species production [75]. It is interesting to note also that a number of candidate genes are associated with disease severity in patients with CGD [33], and recent work has linked variants in myeloperoxidase and FcγRIIIb genes with GI complications and autoimmune disease with mannose-binding lectin and FcγRIIa polymorphisms [76]; additional studies of the genotype–phenotype link in patients with CGD might be illuminating for inflammatory and infectious phenotypes and for therapeutic options (ie, prophylaxis and response to hematopoietic stem cell transplantation conditioning strategies).

Despite advances in medical management of CGD, these important gaps in our understanding of CGD immunopathogenesis remain obstacles to maximizing outcomes for patients. For example, pulmonary involvement remains an important cause of death in this patient population [20]. As patients survive longer, the short- and long-term cumulative effects of repetitive infectious and noninfectious respiratory disorders gain importance [16]. Baseline respiratory burst function correlates with risk of infection, but whether the development of autoimmune or inflammatory complications are similarly correlated remains unclear. In addition, because most noninfectious pulmonary complications occur in adulthood, it would be highly beneficial to identify biomarkers and/or predictors that help us to risk-stratify patients before the development of overt pulmonary signs and symptoms. The development of large clinical registries of patients with a primary immunodeficiency might prove useful in this regard.

No specific evidence-based guidelines regarding the monitoring and management of noninfectious complications of patients with CGD currently exist, which underscores an important knowledge gap that requires future research. With respect to pulmonary complications, 1 group proposed computed tomography of the chest every 2 years with specific pulmonary evaluation once per year and chest radiography and pulmonary function tests performed more frequently as part of routine monitoring; the risk/benefit ratio of this monitoring scheme is uncertain [17]. One important question that remains unanswered is whether aggressive antimicrobial prophylaxis and treatment affect the development of noninfectious respiratory manifestations, especially because infections can serve as triggers or occur concomitantly.

The growing body of evidence suggests that carriers of X-linked CGD indeed have an increased risk of clinically significant disease, and further investigation is warranted to better characterize and address such findings. It is notable that the risk of inflammatory disease in carriers does not seem to correlate with oxidative burst function. It also remains unclear if carriers of CGD might be protected from the development of atherosclerotic disease as patients with CGD seem to be [77]. An additional challenge is how to identify asymptomatic carriers, especially if no affected males are in the family. A prospective study screened 120 pediatric patients with IBD using a dihydrorhodamine flow cytometry assay but failed to identify any patients or carriers [78]. This relatively small study highlights the inherent challenges of detecting a relative rare disease even when a test with good sensitivity and specificity is available and the target population is selected appropriately. Last, no evidence-based guidelines are currently available for the short- and long-term management of carriers. Some authors have proposed that trimethoprim-sulfamethoxazole prophylaxis be initiated in carriers when respiratory burst function falls to $\leq 20\%$, regardless of the presence of symptoms [57]. The optimal management of carriers with autoimmune or inflammatory manifestations remains to be elucidated, and a better understanding of outcomes in these patients in research studies and clinical trials of those with IBD, SLE, and other relevant diseases is needed.

CONCLUSIONS

Noninfectious complications of CGD are clearly associated with all mutations leading to a defective nicotinamide adenine dinucleotide phosphate oxidase complex, and even the X-linked carrier state of CGD. Inflammatory complications are seen more often in patients with X-linked CGD than in those with AR CGD [22], and the patterns and frequencies of these complications vary across body systems. Overall, inflammatory events begin later in life in patients with CGD than do infections [32], and they create a particular challenge for the management of CGD, particularly in adolescent and adult patients.

The treatment of inflammatory disease in patients with CGD requires a difficult balance between therapeutic immunosuppression and the augmented risk of severe infection. Collaboration with subspecialists relevant to the organ systems affected is a critical component of management. Further significant work in the field is needed to decipher the mechanisms that drive this increased risk of inflammatory disease and to guide the optimal management of these challenging conditions.

Supplementary Data

Supplementary materials are available at *Journal of the Pediatric Infectious Diseases Society* online.

Notes

Acknowledgments. We are grateful for data shared by the USIDNET [78], a program of the Immune Deficiency Foundation, supported in part by grant funding from the National Institute of Allergy and Infectious Diseases.

Supplement sponsorship. This article appears as part of the supplement “Chronic Granulomatous Disease,” sponsored by Horizon Pharma USA, Inc.

Potential conflicts of interest. I. P. T. serves as an investigator on studies funded by GlaxoSmithKline and serves on advisory boards for Horizon Pharma and Achaogen, Inc; A. M. J. serves as an investigator on studies funded by Mylan and the Immune Deficiency Foundation and is a consultant for ADMA Biologics; and S. E. H. has served on an advisory board for Horizon Pharma. All other authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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