

# Inflammatory Bowel Disease in CGD Reproduces the Clinicopathological Features of Crohn's Disease

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**OBJECTIVES:** Patients with chronic granulomatous disease (CGD), a rare congenital disorder characterized by defective neutrophil function, frequently develop an inflammatory bowel disease similar to Crohn's disease. The clinical presentations and concordance between the features of the bowel disease in these two conditions have never been formally evaluated.

**METHODS:** Retrospective case note analysis of all adult patients with CGD treated at a tertiary care hospital.

**RESULTS:** A total of 25 eligible patients were identified. Of these, 14 (56%) had experienced gastrointestinal symptoms in the preceding 3 years; and 11 (44%) had documented gastrointestinal inflammation not secondary to infection, manifesting throughout the alimentary canal including the upper gastrointestinal tract (45%), small intestine (27%), colon (73%), and rectum (73%). All had discontinuous inflammation and perianal involvement, and approximately half (55%) demonstrated epithelioid granulomata on histology. All patients fulfilled the Lennard-Jones criteria for the diagnosis of Crohn's disease. Therapeutic responses were observed in five patients to 5-aminosalicylates, and in individual patients to thalidomide, interferon- $\gamma$ , azathioprine, infliximab, and intestinal resection.

**CONCLUSIONS:** There are striking clinical and pathological resemblances between the bowel diseases observed in CGD and Crohn's disease, supporting the possibility of mechanistic similarities in their pathogenesis. Patients with CGD appear particularly prone to developing perianal disease.

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## INTRODUCTION

Crohn's disease is a chronic inflammatory disorder primarily affecting the gastrointestinal tract. The cause remains unknown, although a number of genetic (1) and environmental (2) risk factors have been identified. A variety of hypotheses concerning the underlying pathogenesis have been propounded, ranging from infections with atypical microorganisms (3) to autoimmune (4) processes. An alternative theory, based on the frequent observation of granuloma formation in Crohn's disease, is that the underlying abnormality may be an acute inflammatory response that is too weak. Studies in Crohn's patients have revealed that both the recruitment of neutrophils to sites of experimentally induced new acute inflammatory responses in the skin (5,6) or bowel (5), and the local inflammatory response elicited by introduction of killed bacteria

into the tissues (5), are markedly diminished. This appears to be related to defective production of chemotactic cytokines (5,7), whose secretion from mononuclear phagocytes is attenuated (5,8,9), even in patients with quiescent disease taking no immunosuppressive medication. The hypothesis is that an impaired acute inflammatory response, with decreased recruitment of neutrophils, predisposes to ineffective clearance of bacterial and other organic debris that breaches the bowel wall. Consequent persistence of such material within the intestinal mucosa could then provoke a granulomatous reaction, leading secondarily to the chronic inflammation characteristic of active Crohn's disease. This view is supported by the recent discovery of genetic polymorphisms in a variety of genes that impair the normal functioning of the innate immune response (10). These include those involved in the recognition of

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bacteria by phagocytes, principally *CARD15* (11,12), cytokine signaling (13), and digestive processes such as autophagy (14).

Neutrophils provide the first line of cellular defense in the innate immune response (15). Their primary role is to phagocytose microbes and effect killing and degradation of potential pathogens before their removal from the body. This is accomplished via the respiratory burst, a process in which the NADPH oxidase enzyme system transfers electrons onto molecular oxygen within the phagocytic vacuole. The resulting charge gradient leads to the activation of microbicidal and digestive enzymes discharged into the vacuole from cytoplasmic granules (16).

Chronic granulomatous disease (CGD) is a rare congenital immunodeficiency, affecting approximately 1 in every 250,000 people, in whom genetic mutations in components of the NADPH oxidase complex either abrogate or grossly attenuate the respiratory burst (17). Mutations occur in one of four genes: *CYBB* (encoding gp91<sup>phox</sup>/NOX2), *NCF1* (p47<sup>phox</sup>/NOXO2), *NCF2* (p67<sup>phox</sup>/NOXA2), or *CYBA* (p22<sup>phox</sup>). The *CYBB* gene is located on the X chromosome and these mutations account for approximately 65% of cases; the remainder are autosomal recessive. Failure of the respiratory burst impairs killing of live bacteria and fungi, resulting in a clinical phenotype of severe and recurrent infections, but in addition there is concomitant attenuation of digestion of other exogenous material. As a consequence, these patients frequently develop granulomatous inflammation in the absence of any demonstrable infection, most commonly involving the bowel (18). A number of case reports (19–24) and case series (25–28) have commented on the resemblance between this inflammatory bowel disease and that seen in Crohn's disease. Similar reports exist for other congenital disorders of neutrophil function, including glycogen storage disease-Ib (29), leukocyte adhesion deficiency (30), Chediak-Higashi syndrome (31) and various neutropenias (32,33). Although some of these studies have examined immunological changes in affected bowel (26–28), none have formally compared how closely the clinical features of CGD and Crohn's disease correspond. Here, we set out to examine the clinical behavior of the bowel disease in adult patients with CGD, and determine how frequently the features fulfill accepted diagnostic criteria for Crohn's disease.

## METHODS

### Patients

Adult patients with CGD currently treated at University College London Hospital were identified through clinical and laboratory databases by searching for diagnoses of their neutrophil defect. Patients are primarily referred to this center for management of their immunodeficiency, and linked in to gastroenterology services should such symptoms develop. All CGD patients were included in this study, and a retrospective analysis of their medical notes conducted. Demographic data (including patient's age, sex, and ethnicity) were recorded, as were details of their immunodeficiency (including genetic

subtype, residual oxidase activity, age at diagnosis of immunodeficiency, prevalence and site of infections over a 3-year period from 2003 to 2006, and current antimicrobial prophylaxis). The diagnosis of CGD was confirmed by the nitroblue tetrazolium reaction (34) and/or cytochrome c reduction (35), and activity of the oxidase quantified by the latter in comparison to a panel of healthy controls. The underlying genetic lesion was determined by examining for absence of the specific proteins by immunoblotting, and by DNA sequencing.

### Clinical and pathological disease behavior

In all patients, medical records were searched for prevalence of gastrointestinal symptoms in the 3-year period 2003–2006, clinical investigation of the gastrointestinal tract (including radiological or endoscopic studies) at any time, family history of idiopathic inflammatory bowel disease, and most recent body mass indices.

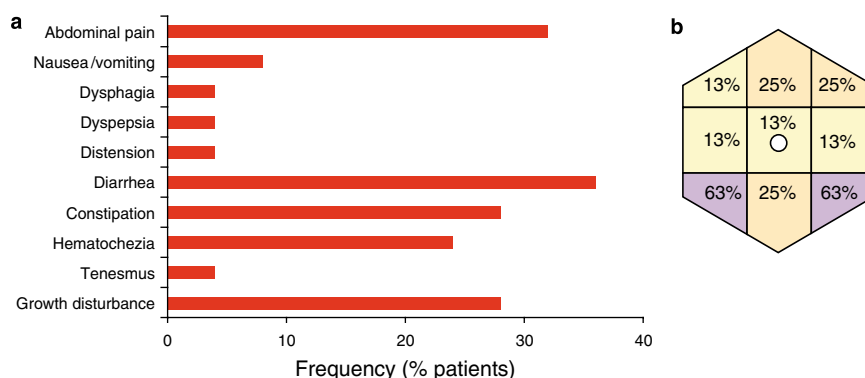
In those with a documented personal history of inflammatory bowel disease, mode of diagnosis was confirmed, as was exclusion of common infective pathogens. The sites of gastrointestinal involvement were recorded, as were levels of blood and serum inflammatory markers at the time of clinical activity, and any original misdiagnosis of CGD as Crohn's disease. The pathological features of their disease were then assessed against the Lennard-Jones criteria for the diagnosis of Crohn's disease (36). The number of patients meeting these criteria was defined as in the original description as the presence of three or more individual features, or of granulomata and one or more additional features, with the exclusion of infective etiologies.

There is no activity score for CGD inflammatory bowel disease comparable to those available for Crohn's disease (37). The effects of medical and surgical treatments on inflammatory bowel disease activity were determined by examining their effects on clinical, biochemical, and endoscopic indices. Clinical response was classified as a sustained reduction (partial) or normalization (complete) in the number of daily bowel openings or pain ratings compared to baseline over the course of treatment, verified by objective improvement on assessment by a gastroenterologist on physical examination. Biochemical remission was classified as a reduction of more than 50% (partial) or normalization (complete) of peripheral blood white cell counts and serum C-reactive protein concentrations from baseline levels above the normal range. Endoscopic remission was classified as improvement (partial) or normalization (complete) of macroscopic and microscopic appearances of previously affected mucosa as determined by a gastroenterologist and histopathologist.

### Statistical analysis

Statistics were calculated using GraphPad Prism v4.01. Data are expressed as median (range) and analyzed using the two-tailed Mann-Whitney *U*-test unless otherwise specified. Frequencies of events or characteristics between different groups were compared using the two-tailed Fisher's exact test or  $\chi^2$ -test. A *P* value of 0.05 was taken as the threshold for significance.



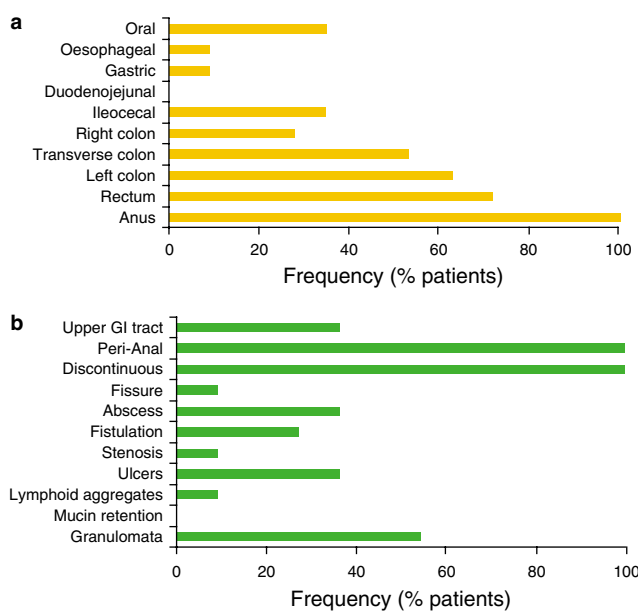


**Figure 2.** Gastrointestinal symptoms in CGD patients. (a) Frequency of symptoms in the preceding 3 years. (b) Location of abdominal pain.

at onset that prompted investigation of the gastrointestinal tract were either recalcitrant abdominal pain and/or diarrhea (nine patients) or perianal disease (two patients). None were reported to have a gastrointestinal infection immediately before the onset of their bowel inflammation, and no patients had a documented family history of inflammatory bowel disease. Mean body mass indices were similar between patients with and without gastrointestinal involvement (20.6 kg/m<sup>2</sup> and 23.1 kg/m<sup>2</sup> respectively). No individuals were recorded to have any of the extra-intestinal features associated with Crohn's disease (38).

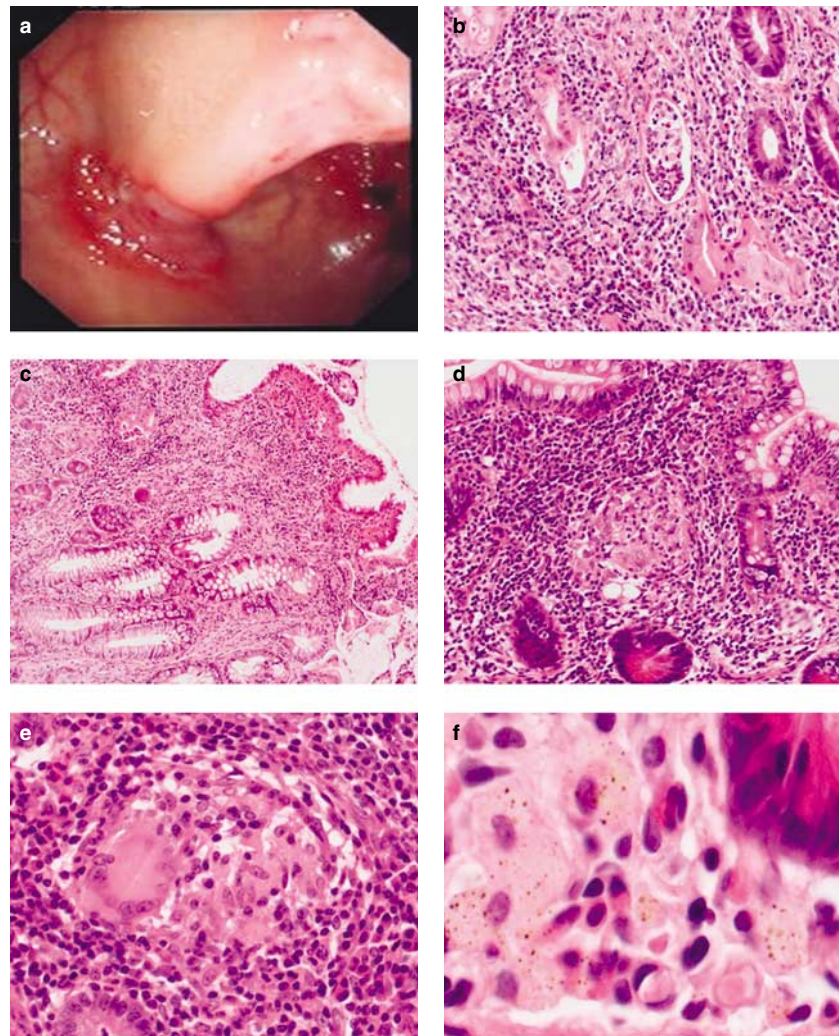
In the patients with inflammatory bowel disease, blood tests were taken at the time of active disease. Complete blood counts showed a mean hemoglobin concentration of 11.8±2.3 g/dl, mean corpuscular volume of 79.4±9.3 fl, peripheral white cell count of 7.9±4.1×10<sup>9</sup> per liter, peripheral blood neutrophils of 6.1±3.8×10<sup>9</sup> per liter, and platelet count of 454±196×10<sup>9</sup> per liter. The mean serum C-reactive protein concentration was 61.4±50.6 mg per liter and serum albumin was 3.9±0.6 g/dl.

Macroscopic inflammation was observed throughout the alimentary canal (**Figure 3a**). A substantial number of patients developed oral aphthous ulceration (36.4%). Upper gastrointestinal inflammation was apparent in one patient, on the basis of endoscopic studies. Although this individual complained of symptomatic dysphagia, no obvious stricture or obstructing lesion was visualized. In the bowel, the frequency of involvement increased along a proximal-distal gradient, rising from 36.4% in the ileocecal region to 63.6% in the left colon, 72.7% in the rectum and 100.0% in the perianal region. The endoscopic features were nondiagnostic and essentially indistinguishable from those of Crohn's disease, ranging from erythematous and friable mucosa, to discrete aphthous, snail track or serpiginous ulceration, through to frank cobblestoning. A typical endoscopic appearance is shown in **Figure 4a**. In each patient, the inflammation was of a discontinuous nature, creating skip lesions. Radiologic studies supported these findings by showing nonspecific discrete areas of ulceration. Three patients (27.3%) developed enterocutaneous fistulae, and one (9.1%) developed an intestinal stricture.



**Figure 3.** Clinical and pathological characteristics of inflammatory bowel disease in CGD patients. (a) Location of inflammation. (b) Concordance with Lennard-Jones criteria for the diagnosis of Crohn's disease.

In terms of the histopathology, the findings were characteristically of a transmural chronic inflammatory infiltrate, with a range of morphological changes almost indistinguishable from Crohn's disease. Biopsies from the upper gastrointestinal tract showed only sporadic nonspecific chronic inflammatory cellular infiltrates. Terminal ileal biopsies demonstrated patchy active chronic inflammation with associated crypt architectural distortion, ulcer-associated cell lineage formation, and occasional granulomata. Colorectal biopsies showed patchy active chronic colitis associated with significant distortion of crypt architecture, with associated cryptitis and crypt abscess formation (**Figure 4b** and **c**). In two cases, marked vascular ectasia was noted, as was colonic Paneth cell metaplasia in one patient. Goblet cell populations were preserved.



**Figure 4.** Endoscopic and histologic appearances of inflammatory bowel disease in CGD. (a) Colonoscopic view revealing a well-demarcated area of inflammation and ulceration with preserved surrounding mucosa. This was associated with synchronous lesions elsewhere in the colon. (b) Colonic mucosa showing patchy active inflammation with withered crypts. (c) Active chronic colitis with crypt architectural distortion, fibrosis, cryptitis, and crypt abscess formation. (d,e) Well-formed epithelioid granuloma with Langhans-type giant cells. (f) Pigment-laden macrophages were prominent in noninflamed regions of bowel.

At all sites of inflammation, the cellular infiltrate contained scattered eosinophils, but their numbers were variable and no more numerous than those typically seen in adult Crohn's disease. Noncaseating epithelioid granulomata (**Figure 4d and e**) were found in intestinal biopsies in 6 (54.5%) patients. Granulomata ranged from small aggregates of epithelioid macrophages (microgranulomata) to classical Crohn's-type well-formed epithelioid granulomata.

The single feature that best distinguished CGD-associated enterocolitis from Crohn's disease was the presence of pigment-laden macrophages within the lamina propria (**Figure 4f**). These macrophages were most easily identified in noninflamed areas, had a yellow-brown hue and were typically clustered in the lower third of the mucosa around crypt bases. They

were present in the majority of terminal ileal and colorectal biopsies, but were much more numerous in the colorectum. These macrophages were unlike those seen in melanosis coli, which contain more granular and darker brown pigment, and are generally more widely dispersed throughout the lamina propria.

All 11 patients (100.0%) with proven inflammatory bowel disease fulfilled the Lennard-Jones criteria for the diagnosis of Crohn's disease (**Figure 3b**); in fact, 3 of the patients were originally misdiagnosed as such.

#### Inflammatory bowel disease therapeutics

All patients were receiving antibacterial prophylaxis. This included co-trimoxazole (72.0%), ciprofloxacin (20.0%),

flucloxacillin (12.0%), co-amoxiclav (8.0%), metronidazole (8.0%), trimethoprim (8.0%), cephalexin (4.0%), erythromycin (4.0%), and penicillin V (4.0%). There were no significant differences in antimicrobial chemoprophylaxis between patients who did and did not develop bowel inflammation. This was accompanied by antifungal prophylaxis with itraconazole in 84% of the patients. Of the patients with inflammatory bowel disease, eight (72.7%) were treated with a 5-aminosalicylate, five (45.5%) with corticosteroids, three with azathioprine, one with methotrexate, two with thalidomide, two with infliximab, one with granulocyte colony-stimulating factor, and two with interferon- $\gamma$ . One patient underwent granulocyte infusion, and two patients required a surgical resection. Partial responses to therapy, as assessed by clinical and biochemical criteria, were observed in five patients on 5-aminosalicylates, one patient on thalidomide, and one patient on interferon- $\gamma$ . Complete and sustained remission was achieved in one patient by azathioprine, in another patient by infliximab, and in a third following surgical intervention (subtotal colectomy). No significant responses were observed following the introduction of corticosteroids.

## DISCUSSION

The observation of a chronic granulomatous, noninfective inflammatory bowel disease in CGD links in with recent developments from studies of Crohn's disease. Genetic analyses have identified polymorphisms in genes involved in phagocyte function, of which the best characterized are *CARD15* (11,12), *ATG16L1* and *IRGM* (14). Polymorphisms in *CARD15* result in impaired recognition of bacterial peptidoglycan (present in both gram-positive and gram-negative bacterial cell walls), leading to attenuated cell signaling responses and secretion of cytokines important in establishing inflammatory reactions (8,9). Those in *ATG16L1* and *IRGM* impede autophagy, an intracellular process that contributes to the digestion of pathogens, antigen processing, and intercellular signaling (14). These are accompanied by clinical studies that demonstrate defective recruitment of neutrophils to sites of acute tissue insult (5–7). The concept that could therefore connect Crohn's disease and CGD enteritis might relate to a primary abnormality in the phagocytic response ultimately resulting in inadequate intracellular processing and digestion of bacteria. This phenomenon would be partial in Crohn's disease, but complete in CGD.

Previous studies of noninfective gastrointestinal involvement in CGD have largely focused on the pediatric or adolescent population. Although many sites of bowel involvement have been documented, these have not been systematically reviewed in adult patients. This is important as, in our cohort of, the median age of onset of bowel disease was in early adolescence. We found evidence of noninfectious inflammatory bowel disease in 44% of the patients, which may be an underestimate as case finding was retrospective and the incidence of endoscopic subclinical disease is unknown. This is greater than in some other series; (18,25) which may represent the fact that we

studied an older population, that our center has a special interest in the gastroenterological complications of CGD and thus have greater ascertainment of such manifestations, or genuine geographical variation in the frequency of bowel involvement. In our patients, inflammation was demonstrated throughout the gastrointestinal tract, but with peak frequencies in the oral cavity, and small and large bowels increasing along a proximal-distal gradient from the terminal ileum to rectum. This mirrors the bacterial loads at these sites.

Gastrointestinal manifestations in CGD have been reported to occur at greater rates in patients with X-linked disease (39), a finding we were not able to replicate here. In fact, we were not able to identify any baseline features that predicted which patients developed gastrointestinal inflammation. Previous reports have suggested that the primary clinical complaint is abdominal pain, most frequently periumbilical; that approximately one-third of patients have evidence of gastrointestinal obstruction, and that the majority present with hypoalbuminemia. Histopathological findings have been summarized in various case series, as typically showing foci of active inflammation with cryptitis in the large bowel in two-thirds of patients. Comparable to our series, and the histopathological features of Crohn's disease, granulomata are reported in approximately 50% of patients, in whom they have been described as sharply defined aggregates of epithelioid histiocytes surrounded by a cuff of dense lymphocytic infiltrations without accompanying necrosis. Inflammatory lesions are also rich in neutrophils and eosinophils, at least in the pediatric population (26,28). One study has examined the influence of potential disease-modifying genes, and found that coincident carriage of polymorphisms in the genes for Fc $\gamma$  receptor IIIb and myeloperoxidase predispose to gastrointestinal involvement, the latter in particular to perirectal disease (40).

Although other reports have remarked upon the apparent similarity between inflammatory bowel disease in CGD and Crohn's disease, the degree of clinical correspondence has never been formally evaluated. Strikingly, in our study of adult patients with CGD, clinicopathological features in all individuals with intestinal involvement fulfilled the Lennard-Jones diagnostic criteria for Crohn's disease. In the absence of knowledge of the concomitant infectious phenotype, the latter diagnosis would undoubtedly have been made, as was the case in just over a quarter of these patients. The principal features common to both conditions were the discontinuous nature of the inflammation forming characteristic "skip lesions", transmural infiltration of inflammatory cells predisposing to stenosis and fistulation, and demonstration of granuloma in approximately 50% of the patients on routine clinical biopsy series. These granulomata were not morphologically distinguishable from those characteristics of Crohn's disease.

Unlike the findings reported in the pediatric literature, we did not observe a disproportionate number of eosinophils within the inflammatory infiltrates beyond those seen in adult Crohn's disease (26,28). This might reflect a difference between the pediatric and adult immune responses. We did, however,

confirm the finding of abnormal pigment-laden macrophages within the biopsies; these were most evident in noninflamed areas of bowel. The biochemical nature of this pigment has never been determined, but presence of such cells should alert the histopathologist to the possibility of CGD as part of the differential of inflammatory bowel disease.

An interesting finding was the high frequency of perianal disease in the CGD patients, documented in every individual with inflammatory bowel disease. Although a universal finding in patients at the time of study, it was the presenting gastrointestinal feature in only two patients, suggesting it develops and becomes more common as a function of either increasing age or disease duration. Fistulae-in-ano are not uncommon in the general population, and evidence of perianal disease has been reported in up to 38% of patients with Crohn's disease (41), in which dependence upon contents of the fecal stream has been demonstrated (42). Lesions are thought to arise from inflammation or infection of perianal glands, or occasionally from penetration of ulcers or fissures originating from the rectum (43). Their unusually high prevalence in CGD may reflect an inability to clear debris from a region already prone to its deposition and collection, high rates of proctitis, and/or liability of this area to minor trauma related to the passage of harder fecal contents.

Due to rarity of the condition, there have been no randomized controlled trials of the treatment of inflammatory bowel disease in CGD. There are previous reports that steroids ameliorate symptoms and induce clinical remission, and that sulphasalazine may have a modest effect (44). There are single reports of efficacy of cyclosporine (45), infliximab (39), and granulocyte colony-stimulating factor (46), as well as evidence of remission following bowel diversion (47), bowel resection, or bone marrow transplantation (39). Interpretation of treatment efficacy from our cohort is also limited by small numbers, lack of a validated disease activity score, and the retrospective nature of the analysis. Nonetheless, there was evidence of partial therapeutic response in individual patients to 5-aminosalicylates, thalidomide, and interferon- $\gamma$ , and much more potent responses following azathioprine, infliximab, or surgical resection of affected bowel. We did not find any patient who responded well to corticosteroids. We were unable to assess the efficacy of any agents in maintaining disease remission. Although acknowledging the shortcomings of these findings, they may act as a guide to clinicians treating inflammatory bowel disease in CGD whilst a prospective controlled trial can be undertaken. Additionally, in our personal experience with these patients, we find that whereas immunosuppressive agents may reduce inflammation in the short term, there are very real concerns about exacerbating the underlying immunodeficiency and precipitating infections. All patients should receive prophylactic antibacterial and antifungal agents. We have a relatively low threshold for employing immunostimulatory approaches with either granulocyte colony-stimulating factor or interferon- $\gamma$  in patients with recalcitrant inflammation, as these can also be highly efficacious at reducing the

frequency of infections (48). Finally, although intestinal diversion can be associated with amelioration of distal inflammation, we have experienced difficulties with parastomal cutaneous infection and stoma breakdown.

The principal limitation of this study is its retrospective nature, and the susceptibility of such investigations to ascertainment bias and other confounding influences. We attempted to minimize the impact of these factors by including all patients with CGD, and employing strict and identical criteria to all subjects. It would be highly informative to now study these patients in detail in a prospective manner, particularly in regard to their response to therapeutics.

Nonetheless, the importance of these current data is threefold. Firstly, they add to the at present sparse literature base on the clinical presentation and therapeutic options for this disease, and will hopefully stimulate collection of prospective data and clinical therapeutic trials. Secondly, they emphasize the importance of considering CGD or another congenital immunodeficiency in the differential diagnosis of inflammatory bowel disease. A high index of suspicion is required in the pediatric population (in whom Crohn's disease is less common) and adults who have recalcitrant disease, particularly those with perianal involvement. The histopathological finding of pigment-laden macrophages should also raise the question of the diagnosis. In such individuals, a history of recurrent episodes of infection should be specifically sought, as it may not have previously been recognized and will provide a strong clue to alert clinicians to the underlying diagnosis.

Finally, it may shed further light on the pathogenetic mechanisms underlying Crohn's disease. The fact that patients with defective neutrophil function develop a chronic granulomatous inflammatory bowel disease validates the concept that impaired innate immunity can elicit an apparently proinflammatory picture as seen in active Crohn's disease (5). Furthermore, it suggests that a subgroup of patients with Crohn's disease may possess subtle aberrations in neutrophil function that contribute to such a phenotype, with an associated panel of possible candidate disease susceptibility genes. Given the high prevalence of perianal involvement observed in CGD patients with inflammatory bowel disease, patients with perianal Crohn's disease might be the most informative group in whom to search for such an abnormality.

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#### CONFLICT OF INTEREST

**Guarantor of the article:** Daniel J.B. Marks, PhD.

**Specific author contribution:** Daniel J.B. Marks, Kana Miyagi, and Farooq Z. Rahman designed the study and collected and analyzed the data, with the assistance of Marco Novelli (histopathology), Stuart L. Bloom (clinical and endoscopic findings), and Anthony W. Segal (immunodeficiency phenotype). All authors had access to the raw data, and were

involved in writing the article and the decision to submit for publication.

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**Potential competing interests:** There are no competing interests.

## Study Highlights

### WHAT IS CURRENT KNOWLEDGE

- ✓ CGD is a congenital neutrophil immunodeficiency.
- ✓ Innate immune responses are diminished in Crohn's disease.
- ✓ Anecdotal reports suggest CGD bowel disease resembles Crohn's disease.

### WHAT IS NEW HERE

- ✓ CGD bowel disease fulfills diagnostic criteria for Crohn's disease.
- ✓ These patients are highly predisposed to perianal disease.
- ✓ Several therapies are associated with disease suppression.

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