Inflammatory manifestations in a single-center cohort of patients with chronic granulomatous disease

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Background: Chronic granulomatous disease (CGD) is a rare phagocytic disorder that results in not only infections but also potentially severe inflammatory manifestations that can be difficult to diagnose and treat.

Objective: To describe inflammatory manifestations in a single-center cohort of patients with CGD.

Methods: Medical records of patients treated at Necker-Enfants Malades Hospital (Paris, France) between 1968 and 2009 and registered at the French National Reference Center for Primary Immunodeficiencies (CEREDIH) were retrospectively reviewed.

Results: In a study population of 98 patients, a total of 221 inflammatory episodes were recorded in 68 individuals (69.4%). The incidence rate of inflammatory episodes was 0.15 per person-year (0.18 in patients with X-linked [XL] CGD and 0.08 in patients with autosomal-recessive [AR] CGD). The most commonly affected organs were the gastrointestinal tract (in 88.2% of the patients), lungs (26.4%), the urogenital tract (17.6%), and eyes (8.8%). Inflammation at other sites (the skin, central nervous system, and tympanum) and autoimmune manifestations (lupus, arthritis, etc) were recorded in 19.1% and 10.3% of the patients, respectively. Granuloma was found in 50% of the 44 histological analyses reviewed. The risk of inflammatory episodes was 2-fold higher in patients with XL-CGD than in patients with AR-CGD (relative risk, 2.22; 95% CI, 1.43-3.46).

Conclusions: Patients with XL-CGD have a higher risk of developing inflammatory episodes than do patients with AR-CGD. Although the most commonly affected organ is the gastrointestinal tract, other sites can be involved, making the management of patients with CGD a complex, multidisciplinary task. (J Allergy Clin Immunol 2014;■■■:■■■-■■■.)

Key words: *Chronic granulomatous disease, inflammation, primary immunodeficiency, granuloma, inflammatory bowel diseases, macrophage, granulomatous, interstitial lung disease*

Chronic granulomatous disease (CGD) is a rare primary immunodeficiency of innate immunity leading to increased susceptibility to recurrent infections and to dysregulated inflammatory responses.[1] CGD is caused by a defect in the nicotinamide adenine dinucleotide phosphate oxidase complex in phagocytes. The mode of inheritance can be either X-linked (XL-CGD with a deficiency in $gp91^{phox}$, in approximately 70% of the patients) or autosomal recessive (AR-CGD with deficiencies in $p47^{phox}$, in 25% of the patients, or, more rarely, in $p22^{phox}$, $p67^{phox}$, or $p40^{phox}$).[1]

Ever since the disease was first described in 1959,[2] the associated infections have been studied more extensively than inflammation. Thanks to progress in diagnosis and the management, the patients' life expectancy has increased considerably.[3] Accordingly, inflammatory manifestations have become an increasingly relevant issue in CGD. Patients develop granulomatous obstructive disorders as a result of a dysregulated inflammatory response, the mechanism of which is still subject to debate.[4,5] The gastrointestinal (GI) tract is the most frequently affected organ. Similarities with Crohn disease may lead to misdiagnosis, especially in the absence of a suggestive history of infections.[6,7] Although the histopathology of these inflammatory manifestations is not fully delineated, some specific features have been reported.[8-12] The urogenital tract is the second most commonly affected organ,[13] followed by the lungs[14] and eyes.[15] Autoimmune events are more frequent in patients with XL-CGD and female carriers than in healthy individuals.[16-18] The concurrent predisposition to both infections and inflammatory disorders may lead to diagnostic and management issues. The relationship between infectious and inflammatory manifestations is yet to be studied in detail and is probably complex.

The treatment of inflammatory episodes is still primarily based on the use of corticosteroids.[19-21] Although the use of other drugs[21-25] as second-line treatments for refractory granulomatous complications has been reported, there are no published data on the latter's efficacy and associated risk of infections in a large series of patients. It has been suggested that surgical procedures could be helpful in the management of inflammatory conditions.[26] Hematopoietic stem cell transplantation (HSCT) is the only available curative therapy for CGD.[27-29]

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Abbreviations used
AR: Autosomal recessive
CGD: Chronic granulomatous disease
GI: Gastrointestinal
HSCT: Hematopoietic stem cell transplantation
NBT: Nitroblue tetrazolium
NSAID: Nonsteroidal anti-inflammatory drug
QOL: Quality of life
RR: Relative risk
XL: X-linked

Despite the increasing focus on inflammatory manifestations in CGD, these aspects have not always been analyzed.[18,30-37] With a view to providing a comprehensive overview of noninfectious inflammatory manifestations in CGD, we performed a retrospective study of a large cohort of patients referred to Necker-Enfants Malades Hospital (Paris, France).

METHODS

In accordance with French regulatory requirements, informed consent was obtained from patients and/or parents on registration in the French National Center for Primary Immunodeficiencies registry (CEREDIH).[38] In this context, we carried out a retrospective analysis of the medical records of patients with CGD referred to Necker-Enfants Malades Hospital, Paris, between April 1968 and June 2009. *CGD* was defined as the presence of a characteristic mutation and/or the absence of (or a strong decrease in) the production of reactive oxygen species by neutrophils. Inheritance was ascertained by determination of the genetic defect or defined as unambiguous XL inheritance when a detailed family history was available. In other cases, the inheritance was classified as "unknown."

A total of 106 eligible patients were identified. Data were missing for 8 patients. All medical records were reviewed retrospectively. Data were collected and analyzed against a predefined checklist. Auxological parameters (weight and height expressed as the SD as a function of chronological age and sex, and body mass index) were retrieved at last follow-up or at the time of the HSCT. Inflammatory manifestations in female carriers of XL-CGD were also retrieved.

For the purposes of this study, inflammatory episodes were characterized according to their histological and endoscopic characteristics, the presence or absence of ongoing infections at the inflammation site (ie, the presence or absence of pathogens in tissue/fluid specimens), and responsiveness to anti-inflammatory treatments (when available). On the basis of the literature data, we checked for the following histological features: a paucity of neutrophils, an eosinophil-rich infiltrate causing typical crypt abscesses, large pigment-containing macrophages in the lamina propria, and noncaseating granulomata. In contrast to the histological parameters, the checklist for endoscopic signs was nonspecific and included the presence of acute inflammation at any level (gastritis, duodenitis, colitis, rectitis, anitis, ulcers, aphthous and cobblestone aspect) and obstructive features (pseudocysts and narrowing of the lumen). These data were available for the GI tract and a few other body sites that could be accessed for tissue sampling. In line with routine clinical practice, the workups were performed most comprehensively during the first 2 episodes and less extensively during the subsequent follow-up. When available, imaging provided additional data on classification of the inflammation (eg, in the lungs or the urogenital tract). For ocular and autoimmune manifestations, the specific diagnostic criteria for each condition were checked. The presence of single versus multiple inflammation sites was defined according to the number of organs affected during the episode. Given the difficulty in characterizing inflammatory episodes in routine clinical practice and episodes that possibly overlapped with atypical infectious episodes, all doubtful cases were discussed with a multidisciplinary panel of specialists. If a consensus could not be reached, the episode in question was excluded from the analysis.

Anti-inflammatory treatments included corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs; including 5-aminosalicylic acid, sulfasalazine, mesalazine, and hydroxychloroquine), anti-TNF drugs (including etanercept, infliximab, adalimumab, and thalidomide), immunosuppressive agents (including azathioprine, cyclosporine, cyclophosphamide, and methotrexate), and other miscellaneous treatments (including immunoglobulin replacement therapy and isotretinoin). Long-term treatment with corticosteroids was defined as more than 12 months of administration. When assessing the correlation between infections and episodes, we excluded patients requiring long-term corticosteroid treatment or immunosuppressive therapy because of the known associated increase in the risk of infections.

A *complete response* was defined as a total absence of symptoms and morphologic signs (ie, endoscopy or computed tomographic scan). A *partial response* was defined as an incomplete improvement in symptoms, which might have required the maintenance of another immunomodulatory agent without increasing the dose.

Statistical analyses were performed using SAS software (version 9.1, SAS Institute, Inc, Cary, NC), and all survival analyses were carried out using the *survival* (version 2.37-4) and *PackHV* (version 1.7) packages in the R software (Version 2.15.0; www.R-project.org). Continuous variables were presented with their median or mean and minimum/maximum values. Patients were divided into 3 groups according to the year of birth (group 1, 1966-1983; group 2, 1984-1994; and group 3, 1995 and later) to compare age at disease onset, at diagnosis, at first infection, and at first episode. The Kaplan-Meier nonparametric model was used to estimate time to episode. The log-rank test of equality was used to compare subgroups. To take account of differences in the durations of follow-up, a Poisson regression was used to estimate the relative risk (RR) of episodes as a function of genotype.[39] The episodes incidence rates in five 5-year age classes were compared in a mixed model including the genotype. The XL and AR subgroups were compared, whereas cases of unknown inheritance were not included in the analyses. The threshold for statistical significance was set to $P < .05$ in all analyses.

RESULTS

Characteristics of the study population

The final study population comprised 98 patients (from 85 kindreds). Of these, 70 (71.4%) had XL-CGD, 20 (20.4%) had AR-CGD, and 8 (8.1%) had CGD of unknown inheritance (see Table I). Within the AR-CGD group, defects in $p47^{phox}$ were the most prevalent (50%), followed by defects in $p22^{phox}$ (30%) and $p67^{phox}$ (20%). There were no significant differences between the XL and AR subgroups in terms of age at diagnosis, at disease onset, and at first episode and the duration of follow-up. In contrast, age at first infection was significantly lower in the XL-CGD group. Seventeen patients had died by the time the study was performed (see the Online Repository at www.jacionline.org).

The course of inflammatory disease

Sixty-eight patients (69.4% of the whole cohort and 76% of the XL-CGD subgroup) presented at least 1 inflammatory episode (see Table II). A total of 221 episodes were recorded: 185 in the XL-CGD, 22 in the AR-CGD, and 14 in the "unknown inheritance" subgroups (see Table III). The incidence rate of inflammatory episodes/person-year was 0.15 for the population as a whole (0.18 in the XL group and 0.08 in the AR group; $P = .07$). There was a significant difference in the incidence of inflammatory episodes between the 3 age groups: 0.13 flares/person-years in group 1, 0.26 in group 2 (group 1 vs group 2; $P = .002$), and 0.11 in group 3 (group 2 vs group 3; $P = .004$). This observation might be due to a better management of the inflammatory episodes in the recent years, while the low incidence found in group 1 could be due to the underestimation of these complications.

TABLE I. Characteristics of the study population

Characteristic	Total (n = 98)	XL (n = 70)	AR (n = 20)	Unknown (n = 8)	*P* value*
Genetic patterns					
CYBB (gp91^{phox})		70			
NCF1 (p47^{phox})			10		
CYBA (p22^{phox})			6		
NCF2 (p67^{phox})			4		
Males, n (%)	88 (89.8)	70 (100)	13 (65)	5 (62.5)	
Age at disease onset (y), median (min-max)	0.3 (0-9.2)	0.3 (0-9.2)	0.3 (0-7.6)	1.3 (0-6.9)	NS
Age at diagnosis (y), median (min-max)	1.4 (0-12.8)	1.3 (0-12.3)	1.6 (0-12.2)	2.8 (0.2-12.8)	NS
Age at first infection (y), median (min-max)	0.4 (0-23.4)	0.3 (0-19.4)	3.4 (0-11.0)	1.6 (0-23.4)	.01
Age at last follow-up (y), median (min-max)	13.5 (0.1-35.4)	14.3 (0.1-35.4)	12.6 (0.8-29.6)	15.5 (4.4-26.1)	NS
Deceased, n (%)	17 (17.3)	12 (17.1)	2 (10)	3 (37.5)	NS
Age at death (y), median (min-max)	8.5 (0.9-24.8)	11.7 (1.2-24.8)	6.4 (0.9-11.8)	5.9 (4.4-8.1)	NS
NBT test, n (%)	n = 67	n = 47	n = 15	n = 5	
0%	53 (79.1)	36 (76.6)	15 (100.0)	2 (40)	.04
>0%	14 (20.9)	11 (23.4)	0	3 (60)	

NS, Not significant.
*For the XL-CGD subgroup compared with the AR-CGD subgroup.

TABLE II. Inflammatory episodes and inheritance mode

Characteristic	Total (n = 98)	XL (n = 70)	AR (n = 20)	Unknown (n = 8)
≥1 Inflammatory episode, n (%)	68 (69.4)	53 (76)	11 (55)	4 (50)
1-2 Episodes, n (%)	32 (32.6)	22 (31.4)	8 (40)	2 (25)
≥3 Episodes, n (%)*	36 (36.7)	31 (44.3)	3 (15)	2 (25)
No inflammatory episodes, n (%)	30 (30.6)	17 (24.6)	9 (45)	4 (50)
Age at first inflammatory episode (y), median (min-max)				
All sites	3.2 (0.14-22.2)	3.2 (0.14-22.2)	5.4 (0.3-14.9)	2.0 (0.2-6.9)
Gastrointestinal	2.2 (0.1-22.2)	2.0 (0.1-22.2)	2.9 (0.3-14.9)	2.0 (0.2-6.9)
Pulmonary	6.9 (2.0-19.8)	6.9 (2.0-19.8)	8.3 (6.9-9.7)	—
Urogenital	4.8 (0.6-6.9)	4.8 (0.6-6.9)	—	—
Ocular	11.3 (0.6-12.8)	5.9 (0.6-11.3)	12.8	—
Autoimmune	4.1 (1.1-8.0)	4.9 (1.1-8.0)	3.3	—
Other	15.9 (0.2-19.8)	15.9 (0.2-19.8)	—	—

*P = .095 (Fisher exact test).

The number of episodes per patient ranged between 1 and 12, with a median of 2 in the XL subgroup and 1 in the AR subgroup (P = .0006). Eighty-one percent of the patients presented up to 4 episodes. The mean duration of an episode was 7.5 months (range, 0.8-85.2; data available for 72% of the patients). By age 20 years, 85% of the patients had experienced their first inflammatory episode (see Fig 1). Episodes occurred regularly over time, and there were no signs of attenuation with age.

There was no statistically significant difference between the XL and AR subgroups in terms of time to first episode (see Fig 1). Age at first episode was lower in the youngest patients (ie, born in 1995 or later) than in adults (1.2 vs 6.3 years, respectively; P = .047). When considering every single patient's follow-up, the RR of developing inflammation was significantly greater in the XL subgroup than in the AR subgroup (RR, 2.22; 95% CI, 1.43-3.46). Similarly, at any age, the episode incidence rate was higher in patients with XL-CGD. Furthermore, the episode incidence rates differed significantly (P = .0001) from one age group to another (see Fig 2).

Thirty patients had not developed inflammatory episodes by the time of data collection (see Table II). It is noteworthy that the median age at last follow-up was significantly lower in this subgroup than in patients having inflammatory manifestations (7.6 and 17.1 years, respectively; P = .002). There were no significant differences between these 2 subgroups in terms of age at diagnosis, the death rate, and the frequency of HSCT. Although not statistically significant, the age at first infection was higher in patients without inflammatory manifestations (1.40 vs 0.33 year in patients with episodes; P = .05). No statistically significant correlations were found between nitroblue tetrazolium (NBT) test results and the number of inflammatory episodes (RR, 1.02; 95% CI, 0.68-1.51; P = .93). It would be useful in the future to repeat this analysis based on a more sensitive assessment of the residual oxidase activity using the dihydrorhodamine test as recently shown for the infectious risk.[40]

Inflammatory episode sites

Six main sites were observed: gastrointestinal, urogenital, pulmonary, ocular, autoimmune, and other sporadic sites (see Table III). Single-site episodes were more common (87%) than double-site and triple-site episodes (11.8% and 0.9%, respectively).

The GI tract was the most commonly involved organ (60 patients). There were 156 episodes in the GI tract alone or concurrently with other sites. The most frequent symptom was noninfectious diarrhea, followed by oral aphthae, anal fistulae, vomiting, anorexia, and

TABLE III. Inflammatory episode sites

	No. of episodes, all CGD, n	No. of patients with ≥1 episode			
		All CGD, n(%)	XL, n	AR, n	Unknown, n
No. of sites					
Single site	193	49 (72)	36	9	4
Two or more sites*	28	19 (28)	17	2	0
Total	221	68 (100)	53	11	4
Localization					
Gastrointestinal	156	60 (88.2)	46	10	4
Pulmonary	19	18 (26.4)	15	3	0
Genitourinary	20	12 (17.6)	9	2	1
Ocular	6	6 (8.8)	4	2	0
Autoimmune	7	7 (10.3)	6	1	0
Other†	16	13 (19.1)	10	2	1

*Twenty-six double sites (including 9 gastrointestinal + pulmonary episodes and 6 gastrointestinal + genitourinary episodes) and 2 triple sites (gastrointestinal + pulmonary + ocular and gastrointestinal + pulmonary + other episodes).
†Other sites: skin, central nervous system, and tympanum.

abdominal pain. At the first inflammatory episode, the prevailing features were noninfectious diarrhea (including bloody diarrhea), aphthae, and anal fistulae, followed by anorexia, vomiting, abdominal pain, and gastritis. In 2 cases, gastric outlet obstruction was the revealing symptom. In subsequent episodes, anorexia, vomiting, diarrhea, and aphthae were the predominant manifestations followed by anal fistulae and abdominal pain. Sixty percent of the patients had undergone at least 1 endoscopic examination. A total of 52 endoscopic investigations were analyzed. Eighty percent of these had been performed by the fourth episode (see Table E1 in this article's Online Repository at www.jacionline.org). In 71% of the cases, only 1 examination was performed (mostly at the second episode) (see Table E2 in this article's Online Repository at www.jacionline.org). Acute and chronic inflammatory features were found in 70% and 5.7% of the examinations, respectively. Four endoscopic macroscopic examination results were normal in 4 different patients (at first episode in 2 cases). A total of 44 histological analyses were available. Acute and chronic inflammatory features were found in 56.8% and 47.7% of the samples, respectively, and mainly corresponded to an eosinophil-rich infiltrate, crypt abscesses, large pigment-containing macrophages in the lamina propria, and noncaseating granulomata (see Table E3 in this article's Online Repository at www.jacionline.org). Ninety-three percent of the analyses did not reveal any signs of causative or concomitant infections. In 3 histological analyses in 3 different patients, pathogens were detected concomitantly with inflammatory features (*Cytomegalovirus*, *Microsporidium*, and an unidentified bacterium) but not considered to be causative of the inflammatory symptoms. Interestingly, abnormal histological features (lymphoid nodules and granuloma) were found in 2 of the 4 patients with normal endoscopic results (see above).

Lungs were the second most commonly involved organs (18 patients). The most common symptom was dyspnea. The number of episodes per patient ranged between 1 and 7. One patient was monitored via lung function tests alone, but each of the other 17 patients had undergone an average of 1.5 imagings (x-ray or computed tomography scans)—mostly at the first episode (4 x-rays and 6 computed tomography scans). Pathological features were found in 14 of these 17 cases (including granulomata, micronodules, pleural thickening, lymphadenopathy, interstitial lung disease, and lung fibrosis).

Urogenital tract episodes were recorded in 12 patients. The most common features were hydronephrosis, inflammatory cystitis, and granulomatous orchitis. Imaging was performed in 8 patients, with a mean of 1.7 per patient (mostly ultrasound scans but cystography in 2 cases). Imaging was performed at the first episode for 3 patients, at the second for 3 patients, and by the fifth for the remaining. Imaging revealed pathological features in 5 of these 8 cases (including bladder wall thickening and granulomata).

Ocular involvement was recorded in 6 patients. Chorioretinitis, uveitis, and ocular granuloma were the most frequent manifestations. Autoimmune manifestations were recorded in 7 patients, including arthritis (n = 2), discoid lupus (n = 2), leukocytoclastic vasculitis (n = 2), and dermatomyositis (n = 1). Thirteen patients presented with granulomatous inflammation at other body sites, including the skin (n = 10), the central nervous system (n = 2), and tympanum (n = 1). The most common noninfectious skin manifestations were granulomatous acne, inflammatory nodular lesions, and photosensitivity (not related to drug exposure); 2 of these cases required treatment (isotretinoin and corticosteroids). Data regarding XL-CGD female carriers are reported in this article's Online Repository at www.jacionline.org.

Infectious episodes

At the time of data collection, all patients experienced at least 1 medically confirmed infectious episode (range, 1-15), except 3 patients (2 with XL-CGD and 1 with AR-CGD; 2 with follow-up <1 year) diagnosed thanks to a family screening and receiving anti-infective prophylaxis since birth.

The total number of infectious episodes was 528 (399 in the XL, 81 in the AR, and 48 in the unknown CGD subgroups; see Table E4 in this article's Online Repository at www.jacionline.org). The overall incidence rate for infections per person-year was 0.36 (0.38 in the XL subgroup and 0.29 in the AR subgroup: RR, 1.13; 95% CI, 0.86-1.49).

We next analyzed the RR of developing infectious episodes as a function of the number of inflammatory episodes (0, 1-2, and ≥3) and the genotype. We found a statistically significant correlation when considering all patients with CGD (RR, 1.04; 95% CI, 1.01-1.08; $P = .007$) but not within the XL or AR subgroups (see Table E5 in this article's Online Repository at www.jacionline.org). The RRs in those younger than 16 years (RR, 1.10; 95% CI, 1.04-1.17) and adults (RR, 1.08; 95% CI, 1.04-1.12) were similar. No significant correlations were found between NBT test results and the number of infectious episodes (RR, 1.05; 95% CI, 0.83-1.33; $P = .66$).

Conversely, we found a significantly higher RR of developing an inflammatory episode as the number of infectious episodes increased (considered as a continuous variable), with 1.10 (95% CI, 1.07-1.13) for all patients with CGD ($P < .0001$); 1.09 (95% CI, 1.05-1.12) for patients with XL-CGD ($P < .0001$); and 1.33 (95% CI, 1.15-1.54) for patients with AR-CGD ($P = .009$).

Treatments and outcome

Overall, 52 (76.4%) patients with inflammatory manifestations had received anti-inflammatory treatments (see Table E6 in this article's Online Repository at www.jacionline.org). At first episode, 37% of the patients had received corticosteroids or NSAIDs. Relapses occurred in 86% of the patients treated with corticosteroids at the first episode, in 74% at the second episode, and in 63% at the third episode. Relapses occurred in 100% of the

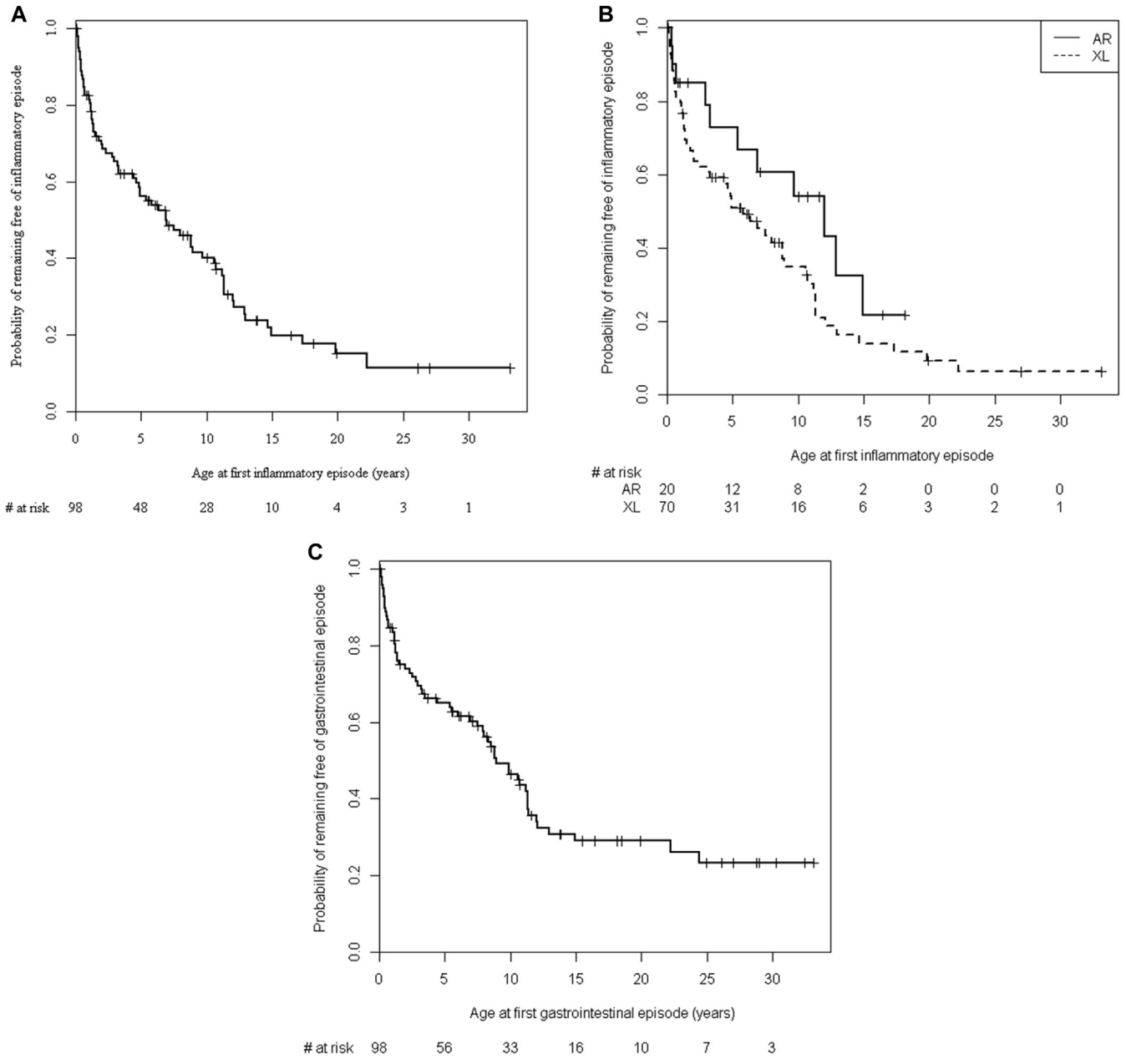

FIG 1. A, Probability of being free of inflammatory episodes (Kaplan-Meier analysis) in the overall cohort of patients with CGD. Median age for episode-free survival is 6.9 years (95% CI, 4.9-10.7). **B,** Probability of being free of inflammatory episodes (Kaplan-Meier analysis) as a function of inheritance mode (XL vs AR-CGD; $P = .115$). Median age for episode-free survival in AR-CGD and in XL-CGD is 12.0 (95% CI, 5.4-13.3) and 5.8 years (95% CI, 3.3-8.9), respectively. **C,** Probability of being free of inflammatory episodes (Kaplan-Meier analysis) for digestive episodes in the overall cohort of patients with CGD. Median age for gastrointestinal episode-free survival is 8.9 years (95% CI, 7.5-11.3).

patients treated with NSAIDs at the first episode, 66% at the second episode, and 50% at the third episode. Twenty-nine percent of the patients had received corticosteroids at least once during the course of the disease. Ten patients with XL-CGD required long-term corticosteroid therapy. There were no significant differences between patients who were treated with long-term corticosteroids and those who were not in terms of age at diagnosis or at disease onset, the number of episodes, and the death rate. The incidence of infectious complications was higher in patients on long-term corticosteroid treatment ($P = .04$). Four patients with XL-CGD with gastrointestinal inflammation required anti-TNF therapy. Efficacy was observed for 2 of them who did not relapse after treatment completion, but 2 of these switched to thalidomide because of lack of efficacy. Two other patients with XL-CGD were treated with thalidomide because of gastrointestinal inflammation (combined with lung disease in 1 case). Complete responses were observed in 2 of them and partial responses in the remaining. Although no adverse events were recorded, definitive conclusions cannot be drawn on the efficacy and tolerance of these treatments. Eight patients with inflammatory manifestations

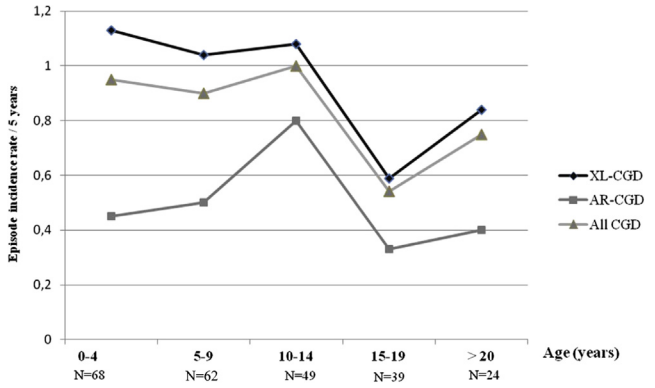

FIG 2. Incidence rate of inflammatory episodes as a function of age and inheritance mode.

underwent HSCT. None of them presented inflammatory episodes after HSCT. Description of the subcohort of patients who underwent HSCT and auxological parameters at last follow-up of the whole cohort are reported in the Online Repository (see text and Table E7 at www.jacionline.org, respectively).

DISCUSSION

Although infections in CGD have been studied in depth over the last few decades, data on inflammatory complications are less abundant. Our retrospective study of a large, single-center cohort of patients provides an overview of these manifestations. We found a higher prevalence of inflammatory manifestations (69.4%) than reported in the literature.[7,34,36] Moreover, 85% of our patients had experienced their first inflammatory episode by the age of 20 years. Our cohort is similar to other large series in terms of the demographic characteristics and distribution of inheritance patterns.[18,30-37] The fact that our retrospective study covered a 30-year period of follow-up in a tertiary care center probably accounts for the observed higher frequency of inflammatory manifestations. In our cohort, residual oxidase activity was measured only with the NBT test. As a result, considering the significant lack of sensitivity of NBT compared with the dihydrorhodamine test, available data unfortunately do not allow us to further address correlation with the ultimate outcome. Changes in treatment strategies over time were unlikely to have biased our analysis because the occurrence of inflammatory manifestations did not appear to be influenced by the introduction of newly available anti-infectives.[7] Furthermore, selection bias was unlikely because our cohort was similar to previously reported cohorts in terms of disease severity (as assessed by the age at onset of inflammatory manifestations,[7] death rate, median age at death,[7,18,34] and the frequency of infections per person-year[7,19,34]). As a result, it can be argued that the higher frequency of inflammatory complications we observe suggests better diagnosis of underestimated complications. The concurrent predispositions to infectious and inflammatory complications may lead to diagnostic and management issues. Indeed, differentiating between inflammation and atypical infectious episodes is a frequent challenge in clinical practice. All inflammatory episodes were considered in our study, so significant bias in the selection of episodes (over-representation of minor episodes, for example) was unlikely.

Gastrointestinal manifestations were most prevalent in terms of both the number of patients affected (60 of 68) and the proportion of all episodes (156 of 221). Characteristic histological features were found in 95% of gut samples. Interestingly, inflammatory features were found in pathology samples in 2 cases that had yielded normal endoscopy results. This is noteworthy because it may suggest that virtually all patients with CGD may have subclinical colitis. This phenomenon needs to be investigated further and might require systematic screening. Growth retardation is a common feature in patients with CGD and inflammatory manifestations.[7] We found impaired growth parameters in patients with earlier-onset and more severe inflammatory disease and a significantly lower mean body mass index in younger patients. The overall parameters at follow-up were not significantly impaired, suggesting that growth may improve during adolescence and patients may finally achieve acceptable growth. It has been shown that quality of life (QOL) is better in patients with CGD having undergone HSCT than in nontransplanted patients.[41] Furthermore, it has been shown that markers of disease activity (relapses and hospitalization), work disability, and psychological distress consistently determine health-related QOL in patients with inflammatory bowel diseases.[42] Studying health-related QOL in patients with CGD and inflammatory complications would be of value.

Another crucial aspect is the link between infection and inflammation. Whether inflammation is linked to infection or is even antigen-driven is still unclear. Although data suggest that the mechanism is not antigen-driven, current methods of detecting infectious agents may not be sufficiently accurate. Alternatively, other as-yet unidentified infectious agents could be involved. Analysis of gut microbiota in patients with CGD with and without inflammatory complications is thus warranted. Accordingly, bacterial DNA was recently detected in eye tissue samples from patients with CGD-associated chorioretinopathy, suggesting that infection may have a role in its pathogenesis.[43]

Despite major improvements in anti-inflammatory therapies over the last decade, treatment of the inflammatory complications of CGD remains challenging. Although treatment is still mainly based on corticosteroids, patients with CGD may benefit from novel therapeutics (such as anti-TNF mAbs). Strikingly, only one third of the patients received anti-inflammatory therapies for the first episode. Corticosteroids and NSAIDs were used as first- or second-line monotherapies. For subsequent episodes, the time to initiation of anti-inflammatory therapy was shorter and other therapeutics, such as immunosuppressants and anti-TNF agents, were used. However, the latter are still not used as first-line therapies because corticosteroids and NSAIDs can be effective.[4,19] Furthermore, anti-TNF agents are associated with an increased risk of infections and/or malignancies; this is a particular concern in patients with primary immunodeficiencies, who are prone to these complications.[11,23,44,45] Although our study was not designed to fully assess treatment efficacy and safety, it is noteworthy that we did not find any evidence of infectious adverse events during immunosuppressive therapy (unlike in patients receiving anti-TNF agents for rheumatic diseases, for example).[46,47] Interestingly, recent research suggests that thalidomide has no effect on antimicrobial immunity.[48] At present, HSCT is the only curative option for patients with severe CGD (including severe inflammatory complications). Because it could be argued that an inflammatory background increases the risk of graft-versus-host disease, this question must be addressed in the future. Nevertheless, the use of appropriate conditioning regimens has significantly improved survival and QOL.[41,49]

In conclusion, inflammatory complications in patients with CGD (with a greater risk in those with XL-CGD) are of increasing importance and deserve better screening and prevention. Management of these complications is often complex and requires a multidisciplinary approach.

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Clinical implications: In our cohort, the prevalence of inflammatory episodes was higher (69.4%) than generally reported. Patients with XL-CGD have twice the risk of developing inflammatory episodes than do patients with AR-CGD.

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CAUSES OF DEATH IN OUR COHORT

Seventeen patients had died before the study was performed, including 12 with XL-CGD, 2 with AR-CGD, and 3 of unknown genetic basis. Twelve patients had a history of inflammatory episodes, with a median of 2 inflammatory (range, 1-6) and 8 infectious episodes (range, 2-14). One patient died of a documented inflammatory complication (cerebral vasculitis). The causes of death were infectious in 9 cases: disseminated *Aspergillus* species (n = 3), *Aspergillus nidulans* (n = 1), *Serratia marcescens* pneumonia (n = 2), *Burkholderia cepacia* pneumonia (n = 1), *Salmonella bovis* sepsis (n = 1), and *Staphylococcus* infection (n = 1). Two of the patients with *Aspergillus* infections had received corticosteroids (long-term treatment in 1 case). Two patients died after HSCT: 1 patient with XL-CGD died 16 months after HSCT of a multiorgan failure in the context of disseminated cytomegalovirus infection while receiving immunosuppression for severe extended graft-versus-host disease (GVHD), and 1 patient with AR-CGD who needed a second HSCT for bone marrow failure due to bone marrow GVHD died 10 days later of varicella-zoster virus meningo-encephalitis and pneumonia in the context of liver and bone marrow GVHD. One patient died of a brain hemorrhage of undetermined etiology. The cause of death was not known in the remaining 4 cases.

DESCRIPTION OF OUR SUBCOHORT OF PATIENTS WHO UNDERWENT HSCT

A total of 12 patients with CGD received HSCT: 8 with XL-CGD, 2 with AR-CGD, and 2 of unknown genetic basis.

For all patients, major indication for HSCT was significant infections even in patients who experienced some inflammation. Ten patients were alive at the time of data collection (9 patients were alive and well and 1 experienced a graft rejection and was awaiting a second HSCT). There were 2 deaths (1 patient with XL-CGD died 16 months after HSCT of a multiorgan failure in the context of disseminated cytomegalovirus infection while receiving immunosuppression for severe extended GVHD and 1 patient with AR-CGD who needed a second HSCT for bone marrow failure due to bone marrow GVHD died 10 days later of varicella-zoster virus meningo-encephalitis and pneumonia in the context of liver and bone marrow GVHD).

Eight patients presented at least 1 inflammatory episode before HSCT (range, 1-3). No patients presented inflammatory manifestations after HSCT. Seven patients presented acute GVHD. Of these, 4 patients had inflammatory flares before HSCT. These 4 patients presented, respectively, acute gut GVHD grade 2, acute skin and liver GVHD grade 4 then chronic GVHD, acute liver GVHD grade 3, and acute GVHD (gut grade 3 associated with cytomegalovirus infection evolving in gut chronic GVHD and skin grade 2) and chronic ocular GVHD. The 3 patients presenting with GVHD without previous inflammatory manifestations had, respectively, acute skin GVHD grade 1 in 2 cases and acute grade IV GVHD (skin, gut) evolving in chronic GVHD in 1 case.

AUXOLOGICAL PARAMETERS

At last follow-up, the overall mean weight, height, and body mass index were −0.95 SD, −1.28 SD, and 18.1, respectively (see Table E7). There were no significant differences as a function of the mode of inheritance or the requirement for long-term corticosteroid therapy. Significantly lower weight and body mass index values at last follow-up were observed in patients with early-onset CGD (<0.3 years; $P = .01$) and early-onset inflammatory episode (<3.2 years; $P = .03$), respectively. The youngest patients had a lower mean body mass index than did the adults.

XL-CGD CARRIERS

Data regarding 18 female carriers of XL-CGD were retrospectively available. Inflammatory manifestations were recorded in 14 (78%), including systemic lupus erythematosus (4), discoid lupus (7, in 3 cases associated with recurrent oral aphthae and infections of unspecified etiology), arthritis and autoimmune hepatitis (1), photosensitivity and recurrent oral aphthae (1), and minor retinitis pigmentosa (1).

TABLE E1. Endoscopic description of gastrointestinal episodes

Total no. of endoscopic examinations	52
Endoscopic results*	
Normal	4
Acute inflammatory features	40
Nodules	8
Pancolitis	3
Colitis	14
Rectitis, anitis, or segmental colitis	3
Gastritis or duodenitis	10
Crohn-like or hemorrhagic rectocolitis-like features	2
Obstructive features	3
Pseudocysts	1
Colic narrowing	2
Endoscopic site	
Upper tract	13
Lower tract	17
Upper and lower tracts	22

*Missing data for 5 examinations.

TABLE E2. Digestive endoscopy and inheritance mode

Characteristic	Total (n = 98)	XL (n = 70)	AR (n = 20)	Unknown (n = 8)
No. of patients with ≥1 endoscopic examination/no. of patients with ≥1 digestive episode	34/60 (56.7%)	28/46 (60.8%)	4/10 (40.0%)	2/4 (50.0%)
No. of patients with:				
1 endoscopic examination	25	19	4	2
2 endoscopic examinations	6	6	0	0
>2 endoscopic examinations	3	3	0	0
No. of patients with endoscopic examinations/no. of patients with digestive episodes				
First episode	12/48 (25.0%)	10/37	2/7	0/4
Second episode	13/29 (44.8%)	10/24	2/2	1/3
Third episode	8/25 (32.0%)	8/14	0	1/1
Total no. of endoscopic examinations	52	46	4	2

TABLE E3. Histologic description of gastrointestinal episodes

Total no. of histologic examinations	44
Histologic description	
Normal	2
Acute inflammatory features	25
Thickened mucosa	1
Lymphoid infiltrate	3
Lymphoid nodule	1
Neutrophil-rich infiltrate	2
Eosinophil-rich infiltrate	9
Crypt abscess	5
Rectitis and ulcerations	2
Necrosis	2
Chronic inflammatory features	21
Granuloma	21
Infectious features*	3

*Microsporidium, an unidentified bacterium and cytomegalovirus.

TABLE E4. Details of infectious episodes among our cohort of 98 patients

Type of infections	No. of episodes
Pneumonia	123
Lymphadenitis	102
Sepsis	34
Liver abscess	30
Osteoarticular infections	26
Perianal abscess	23
BCGitis	16
Cutaneous abscess	11
Pulmonary abscess	9
Brain abscess	3
Other	151
Total	528

TABLE E5. Correlation between infectious episodes and inflammatory episodes

No. of infectious episodes, incidence rate per person-year: mean (min-max)	No. of inflammatory episodes			RR (95% CI)*	*P* value
	0	1-2	≥3		
All patients with CGD (n = 98)	n = 30 0.28 (0-2.06)	n = 32 0.30 (0.06-3.06)	n = 36 0.40 (0.05-1.96)	1.04 (1.01-1.08)	.007
Patients with XL-CGD (n = 70)	n = 17 0.33 (0-1.8)	n = 22 0.31 (0.07-3.06)	n = 31 0.39 (0.14-1.9)	1.03 (0.99-1.06)	.11
Patients with AR-CGD (n = 20)	n = 9 0.19 (0-2.06)	n = 8 0.28 (0.06-1.7)	n = 3 0.42 (0.05-0.47)	1.03 (0.95-1.13)	.44

*Poisson univariate regression analysis: number of infections and episodes during the follow-up period.

TABLE E6. Treatment of inflammatory episodes

Characteristic	First episode (n = 68)	Second episode (n = 52)	Third episode (n = 36)	Fourth episode (n = 22)
Inheritance mode				
CGD XL	53	42	31	20
CGD AR	11	6	3	2
CGD unknown	4	4	2	0
Patients treated, n (%)	25 (37)	29 (56)	18 (50)	14 (64)
No. of treatments				
1	22	21	17	11
2	1	5	1	3
3	2	2		
4		1		
First-line therapy*				
Corticosteroids	17	19	11	7
NSAIDs	8	10	4	5
Immunosuppressive agents			2	
Anti-TNF agents			1	1
Miscellaneous				1
Second-line therapy*				
Corticosteroids	1	4		1
NSAIDs	2	1		2
Immunosuppressive			1	

*NSAIDs: 5-aminosalicylic acid/sulfasalazine/mesalazine/hydroxychloroquine; immunosuppressive agents: azathioprine/cyclosporine/cyclophosphamide/methotrexate; anti-TNF agents: thalidomide/etanercept/infliximab/adalimumab; miscellaneous: immunoglobulin/isotretinoin; NB: Additional treatments are not shown.

TABLE E7. Auxological parameters at last follow-up

Parameter	Weight (SD) (n = 56)	Height (SD) (n = 52)	BMI (n = 60)	*P* value
Total				
Mean (min; max)	−0.95 (−3.46; 1.94)	−1.28 (−4.60; 1.70)	18.1 (13.9; 25.5)	
CGD inheritance mode				
CGD XL	−0.94 (−3.46; 1.94)	−1.16 (−4.60; 1.70)	17.7 (13.9; 25.5)	NS
CGD AR	−0.80 (−2.40; 1.90)	−1.55 (−3.80; 1.60)	18.9 (14.4; 24.2)	
CGD unknown	−2.02 (−2.60; −1.45)	−2.06 (−3.0; −1.13)	19.4 (17.0; 21.9)	
Age at last follow-up (y)				
≤16	−0.83 (−3.10; 1.94)	−1.39 (−4.60; 1.20)	16.9 (13.9; 25.5)	NS
>16	−1.27 (−3.46; 1.90)	−0.93 (−3.33; 1.70)	20.2 (16.9; 22.8)	
Age at disease onset (y)*				
≤0.3	−1.36 (−3.46; 1.94)	−1.64 (−4.60; 0.60)	17.8 (13.9; 25.5)	.01 (weight)
>0.3	−0.60 (−2.40; 1.90)	−1.02 (−4.00; 1.70)	18.1 (14.5; 24.2)	
Age at first episode (y)*				
≤3.2	−0.98 (−3.10; 1.90)	−1.30 (−4.60; 1.70)	17.5 (13.9; 24.2)	.03 (BMI)
>3.2	−0.87 (−3.46; 1.94)	−1.22 (−3.50; 0.27)	19.2 (14.6; 25.5)	
No. of inflammatory episodes				
No episode	−0.89 (−3.10; 1.90)	−1.54 (−4.60; 1.60)	17.8 (13.9; 24.2)	NS
≥1 episode	−0.98 (−3.46; 1.94)	−1.13 (−4.0; 1.70)	18.0 (14.4; 25.5)	

BMI, Body mass index; *NS*, not significant.
*Overall median values.