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Gastrointestinal Histopathology in Chronic Granulomatous Disease – a Study of 87 Patients

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Abstract

Gastrointestinal (GI) involvement in chronic granulomatous disease (CGD), a rare genetic immunodeficiency, mimics other inflammatory bowel diseases. We report GI pathology from 87 CGD patients seen at the NIH Clinical Center, with vague – severe clinical symptoms, who had biopsies (313) evaluated {esophagus (23), stomach (71), small bowel (52) including duodenum (39), ileum (12) and jejunum (1), colon (167)}. Additionally reviewed was GI tissue from 15 autopsies. In our patient cohort, mean age was 22years, age range 3 – 44 years (2:1 male to female ratio). There were pathologic changes in 83/87 (95%) patients; with colon being the most commonly involved site and esophagus the least. There were microgranulomas in 53/87 (61%), pigmented macrophages in 64/87 (74%), tissue eosinophilia in 31/87 (36%), chronic and/or acute inflammation in 57/87 (66%) patients. Subset of patients had villous shortening in the duodenum (8/39) and ileum (5/12). We identify microgranulomas in 76/167 (46%) colon, 12/52 (23%) small bowel and 4/71 (6%) gastric biopsies; pigmented macrophages in 109/167 (65%) colon and 7/52 (13%) small bowel biopsies and 14/15 autopsies; chronic and/or acute inflammation in 97/167 (58%) colon, 13/52 (25%) small bowel, 42/71 (59%) gastric and 5/23 (22%) esophageal biopsies; tissue eosinophilia in 43/167 (26%) colon, 7/52 (13%) small bowel and 2/71 (3%) gastric biopsies. Only 4/87 (5%) patients had normal histology. No infectious etiology was identified in majority of inflammatory lesions. We found that mild to severe GI pathology was common in CGD. Additionally, microgranulomas, pigmented macrophages and eosinophilia are not associated with acute (neutrophilic) inflammation.

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Keywords

Chronic Granulomatous Disease; granulomas; colitis; pigmented macrophages; eosinophilia; inflammatory bowel disease; gastrointestinal tract

INTRODUCTION

Chronic granulomatous disease (CGD) is a rare genetic immunodeficiency, with an incidence of 1 in 200,000 live births in the United States (15). CGD was first described in the 1950s, and since then great strides have been made to elucidate its genetically heterogeneous nature and pathogenesis. CGD is a single disease with different genetic etiologies that cause defects in the subunits of nicotinamide dinucleotide phosphate (NADPH) oxidase enzyme complex in phagocytes. Inheritance of CGD is either X-linked or autosomal recessive. The X-linked mutation causes a defect in the gp91^{phox} subunit of NADPH; the autosomal recessive mutations cause defects in p47^{phox}, p67^{phox}, p22^{phox} or p40^{phox} subunits of NADPH.

The defective NADPH complex impairs superoxide generation, and phagocytes are unable to effectively kill intracellular and some extracellular micro-organisms. There is also dysregulated immune response with extensive granulomatous inflammation but ineffective killing of pathogens. Therefore, patients with CGD suffer from recurrent life-threatening bacterial and fungal infections (1–3, 15). The X-linked form of CGD is most common and found in 65% of North American cases and is associated with more severe infections and worse prognosis (15). Once suspected, the diagnosis of CGD is confirmed by tests of phagocyte function (dihydrorhodamine oxidation) and by genetic testing to identify the specific mutation.

CGD usually presents in early childhood with unusual, severe or recurrent infections. Gastrointestinal (GI) problems are common in immune deficiencies and it is estimated that up to 50% of CGD patients present with non-specific clinical symptoms such as diarrhea, abdominal pain, constipation, weight loss, and failure to thrive (2–4). The GI tract is often involved by inflammatory lesions, with or without an identified infectious etiology. GI tract involvement was reported in 32% to 48% of patients with CGD (2,4). The spectrum of GI manifestations in CGD includes colitis, abscesses, dysmotility, gastric antral narrowing and delayed gastric emptying, intestinal obstruction, strictures, fissures and oral ulcers (4, 14).

In a previous study conducted at the National Institutes of Health (NIH), GI involvement was recorded in 32.8% of 140 CGD patients, although pathologic evaluation of GI tissue was available for only 15 of the 140 patients (4). Any portion of the GI tract may be involved - from the mouth to the anus (5,6) - and displays a spectrum of non-specific histopathology that may mimic other inflammatory bowel disease (IBD) entities such as Crohn's disease, ulcerative colitis, sarcoidosis or mycobacterial infection.

Not only is GI involvement a common feature of CGD but it may well be the first presentation of disease. From their registry of 368 CGD patients, Winkelstein et al reported that GI manifestations preceded the diagnosis of CGD in up to 17% of patients (3). The pathologic features of GI involvement may even suggest further testing in a previously undiagnosed patient. To further characterize the histopathology of GI involvement, we evaluated 313 GI biopsies from 87 CGD patients with non-specific GI clinical symptoms, as well as GI tract tissue from 15 autopsies of patients with CGD. Despite its overlapping histopathology with other forms of IBD, we identified salient features that help distinguish GI involvement in CGD.

METHODS

We identified 87 patients diagnosed with CGD, confirmed either by nitroblue tetrazolium reduction, dihydrorhodamine oxidation or molecular sequencing, at the NIH Clinical Center from 1987 to 2011. The available archival material of 313 GI biopsies included biopsies of esophagus (23), stomach (71), small bowel (52), colon (167). All patients had mild to severe non-specific clinical GI symptoms. We also reviewed GI tissue from 15 autopsies of patients with CGD (autopsies were performed at the NIH from 2000 to 2011).

A systematic retrospective review of histopathology was performed by three pathologists (JL, PA, MQ) on paraffin-embedded, hematoxylin and eosin stained sections of GI tract tissue from the previously described 313 biopsies and 15 autopsies. All sections were evaluated for the type of inflammation using the following definitions. *Acute* inflammation in the colon (acute/active colitis) was defined as the presence of neutrophils in the lamina propria, in crypts (cryptitis), or crypt lumens (crypt abscess); ulceration or erosion with fibrinopurulent debris/granulation tissue were also noted in this setting. *Chronic* inflammation in the colon (“chronic colitis”) was defined as expansion of lamina propria by lymphoplasmacytic infiltrate or basal cell plasmacytosis; additional features of architectural distortion and intraepithelial lymphocytosis were also assessed and noted as possible accompanying features. In the small bowel, acute and chronic inflammation in the terminal ileum was defined as above. Acute inflammation in the duodenum/jejunum was described by the presence of neutrophils in the lamina propria or glands, with or without surface ulceration/erosion. In the duodenum, chronic inflammation (“chronic duodenitis”) was defined as expanded lamina propria by increased mononuclear infiltrate, intraepithelial lymphocytosis, and lymphoid aggregates with or without germinal centers; villous architectural blunting/shortening, foveolar metaplasia and Brunner’s gland hyperplasia were also noted as possible additional features. *Acute* or active gastritis was defined by presence of neutrophils in the lamina propria, glands with or without surface ulceration/erosion. In the stomach, *chronic* gastritis was defined as mucosal lymphoplasmacytic infiltrate, prominent in the lamina propria of superficial region or within the deeper glandular component. Atrophy, foveolar hyperplasia and/or intestinal metaplasia were possible additional components. We assessed for the presence/absence of *H. pylori* only on H&E evaluation. Acute inflammation was assessed in the esophagus and characterized by the presence of neutrophils within the squamous epithelium or subepithelium tissues, intercellular edema, ballooning degeneration of squamous cells and/or surface ulceration/erosion. Presence of increased intraepithelial or subepithelial lymphocytes characterized chronic inflammation in the esophagus.

Granulomas, pigmented macrophages and eosinophilia were separately evaluated as follows: pigmented macrophages (0: none; 1: mild; 2: moderate; 3: numerous), granuloma formation (0: none; 1: poorly formed/few; 2: poorly formed/multiple; 3: well formed/few; 4: well formed/multiple), microscopic eosinophilic abscess and tissue eosinophilia - defined as more than 30 eosinophils per high power field. We also assessed the presence/absence of dysplasia. On selected sections, special stains for PAS, GMS and AFB-Fite were also reviewed.

RESULTS

In our patient cohort, the mean age was 22 years, age range 3 – 44 years and we had an approximately 2:1 male to female ratio. 83 of 87 (95%) patients had evidence of histopathology and the colon was the most commonly involved site. Normal histology was found in the GI biopsies of the remaining 4 patients (5%). Of note, there was no dysplasia identified in any of the 87 patients.

Colon

167 colon biopsies included the ascending/right colon (35 biopsies); transverse (17 biopsies), left colon - including descending, sigmoid and rectum (78 biopsies) and unspecified (37 biopsies). Varying degrees of inflammation were present in 58% (97/167) of colon biopsies (35 of 53 patients), making the colon the most commonly involved GI site. The left colon appeared to be more affected than the right colon; however since we had many more biopsies of the left as compared to the right colon, this may represent a sampling bias. In 20 of 53 patients, acute colitis was present in 25% (41/167) of biopsies with acute cryptitis (24 biopsies) and/or crypt abscess (25 biopsies) (Figure 1A). Ten percent (17/167) of colon biopsies showed ulceration. In 29 of 53 patients, 38% (63/167) of biopsies showed chronic colitis with or without active inflammation (Figure 1B). Changes of chronic colitis included lymphoplasmacytic infiltrates in the lamina propria and basal cell plasmacytosis (47 biopsies), architectural distortion (20 biopsies). Paneth cell metaplasia was noted in 12 biopsies. Increased numbers of eosinophils or eosinophilic microabscesses were found in 26% (43/167) of colon biopsies (19 of 53 patients) (Figure 1C). Poorly to well-formed microgranulomas (figure 2A–D) were present in 46% (76/167) of colon biopsies (32 of 53 patients) involving superficial and deep mucosa and submucosa. Pigmented macrophages were present singly or in ill-defined clusters in the lamina propria in 65% (109/167) of colon biopsies (39 of 53 patients) (Figure 3A). When evaluating colonic tissue from autopsy specimens, pigmented macrophages were identified in the superficial and deep mucosa and submucosa, as well as muscularis propria, and surrounding the Auerbach' plexus.

Small bowel

52 biopsies from the small bowel included biopsies from the duodenum with or without Brunner's glands (39), ileum (12) and jejunum (1). Chronic or acute inflammation was present in 25% (13/52) of biopsies (9 of 41 patients). Increased numbers of eosinophils were identified in 13% (7/52) of biopsies. Poorly to well-formed microgranulomas were identified in 23% (12/52) of biopsies (12 of 41 patients). Pigmented macrophages were present in the lamina propria in 13% (7/52) of biopsies (5 of 41 patients) (Table 1). Acute neutrophilic inflammation was present in 6/39 duodenal biopsies and 3/12 ileal biopsies. In 15 of 41 patients, villous shortening was seen in 25% (13/52) of small bowel biopsies involving 8 duodenal biopsies and 5 ileal biopsies (Figure 1D). Mild chronic inflammation was present in 2 duodenal biopsies and 1 ileal biopsy. Similar to the findings in the colon, pigmented macrophages were seen in the superficial lamina propria in duodenal biopsies. In duodenal tissue from autopsy specimens, pigmented macrophages were identified in the superficial and deep mucosa, submucosa, and muscularis propria and surrounding the Auerbach' plexus (Figure 3B). Intraepithelial lymphocytosis was not encountered in the small bowel biopsies.

Stomach

71 gastric biopsies reviewed included biopsies from the antrum (26), fundus (3), body (9), cardia (1), pylorus (1), lesser curvature (1) and unspecified (30). Inflammation was present in 59% (42/71) of gastric biopsies, most commonly as mild chronic focal gastritis (38 biopsies) and occasional focal acute gastritis (3 biopsies) and 1 case of chronic active diffuse gastritis. Increased numbers of eosinophils were seen in 3% (2/71) of gastric biopsies. Microgranulomas were found in 6% (4/71) of gastric biopsies (4 of 47 patients). Pigmented macrophages were not identified (Table 1).

Esophagus

23 esophageal biopsies were reviewed from 23 patients. The esophagus was the least commonly involved site of the GI tract with inflammation involving only 22% (5/23) of esophageal biopsies with 3 biopsies showing acute esophagitis and 2 biopsies showing mild

increase in intraepithelial lymphocytes. Granulomas or pigmented macrophages were not identified in any of the esophageal biopsies (Table 1). Significant tissue eosinophilia was likewise absent in the esophageal biopsies reviewed.

Evidence of Infectious organisms

Special stains (PAS, GMS and AFB-Fite) performed on specimens from stomach, duodenum and colon with evidence of chronic, acute or active inflammation, and/or granulomas and/or pigmented macrophages, were negative for fungal organisms and mycobacteria. Special stains (PAS, GMS and AFB-Fite) performed on specimens from esophagus revealed GMS positive fungal organisms (yeast and hyphae) in four esophageal biopsies; the fungal organisms were detached and were not associated with tissue invasion or acute inflammation. There were no invasive fungal organisms seen within the viable squamous epithelium.

Tissue from autopsies

Sections of esophagus, stomach, small bowel and colon were reviewed from 15 autopsies of patients with CGD; the causes of death in all cases were unrelated to GI disease. Tissue autolysis precluded a detailed pathologic evaluation. Scattered pigmented macrophages were identified in the lamina propria, submucosa, muscularis propria and surrounding the Auerbach' plexus in colonic sections from 14 cases (14/15) (Figure 3B) and in small bowel sections from 8 cases (8/15), but absent in sections from stomach and esophagus. Dysplasia was not identified in these cases.

DISCUSSION

Chronic granulomatous disease (CGD) is the prototype of phagocyte immunodeficiency diseases. CGD is caused by mutations in genes encoding subunits of the NADPH oxidase enzyme complex, which leads to impaired superoxide production and ineffective destruction of phagocytosed intracellular and some extracellular micro-organisms. Patients with CGD are susceptible to recurrent serious bacterial and fungal infections. In addition to infections, CGD patients are subjected to various inflammatory manifestations, such as granuloma formation in the gastrointestinal tract mimicking Crohn's colitis (1). In recent years, GI disease is believed to be a primary manifestation of the inflammatory process/immune dysregulation in CGD (19, 20). A recent study found high levels of serum antibodies to GI-tract associated microbes in CGD patients suggesting an underlying defect in innate immunity (20). However, unlike the situation in Crohn's, there was no difference in antibody positivity in those with or without GI disease, indicating that immune exposure to GI flora was universal in CGD but did not discriminate between those with and without GI involvement. Therefore, the etiology of the GI lesions in CGD remains unclear and may be of infectious or inflammatory (non-infectious) etiology, or both.

IBD affects more than 1 million people in the United States; 10% of them are children (17). IBD encompasses not only common entities such as Crohn's disease (CD) and ulcerative colitis (UC), but also rare entities such as CGD, Hermansky Pudlak syndrome, sarcoidosis, and Behcet's disease. The clinical manifestations of IBD are varied and non-specific and range from diarrhea, abdominal pain, failure to thrive, and weight loss to life-threatening bowel obstruction, strictures, colitis and abscess. Added to the challenge of determining a diagnosis in the face of such varied clinical presentations and a wide differential, is the overlapping histopathology in IBD. Studies have reported GI disease in 32% to 48% of patients with CGD (2,4). Though certain aspects of GI histopathology have been previously described (7–13), many of them are limited to colonic pathology and are drawn from small patient cohorts. The inflammatory process, pathogenesis and etiology of GI lesions in CGD

remain unclear. This is the largest histopathologic study to date, providing a comprehensive documentation of GI histopathology of the entire GI tract in CGD. We have systematically evaluated pathologic features of 313 GI biopsies from 87 CGD patients with clinical GI symptoms. We have also reviewed GI tissue from 15 autopsies. Our findings demonstrate that:

1. mild to severe pathologic changes affect the majority (83/87) of CGD patients with clinical GI symptoms (Figure 4);
2. the colon is the most commonly affected site and the esophagus is the least commonly affected site;
3. microgranulomas, pigmented macrophages, tissue eosinophilia and chronic and/or acute inflammation are commonly encountered histopathologic findings;
4. presence or absence of granulomas, pigmented macrophages and tissue eosinophilia may occur independent of neutrophilic inflammation and are not directly associated with acute inflammation
5. villous shortening occurs in the duodenum (8/39 biopsies) and ileum (5/12 biopsies)
6. majority of inflammatory lesions do not have an identifiable infectious etiology

Our cohort of 87 CGD patients was drawn from those with mild to severe clinical GI symptoms who underwent upper or lower GI endoscopy. In our study, we found that 95% of patients (83 of 87 patients) with clinical GI symptoms had mild to severe findings on pathologic evaluation (Figure 4) - confirming a high prevalence of GI disease in CGD. GI lesions in CGD are discontinuous and may involve any part of the GI tract. (Table 1).

Microgranulomas were found in 61% of patients (53 of 87 patients). The histology of granulomas varied from poorly-formed to well-formed with foreign body giant cells (Figure 1A–1D, Table 1). The granulomas were often microgranulomas composed of clusters of 5 to 15 epithelioid histiocytes. Confluent epithelioid granulomas or necrotizing granulomas were not present. Well-formed microgranulomas were occasionally surrounded with a sharply defined lymphoid cuff and foreign body-like giant cells or Langhans-like giant cells. Microgranulomas were present in 46% of colon biopsies from 60% of patients, involving superficial and deep mucosa and submucosa. Microgranulomas were present in fewer biopsies from the small bowel (23%) and stomach (6%) and absent in the esophageal biopsies. Microgranulomas were not encountered on the tissue sections from the 15 autopsies, presumably because of the autolysis of the GI tract in autopsy specimens. Granuloma formation is a characteristic feature of CGD and has been reported in the GI tract, liver, urinary tract and skin (1). In the pathogenesis of this disease, ineffective phagocytosis is thought to be associated with abnormally intense inflammatory responses leading to granuloma formation in multiple organs. Granulomas are postulated to be a function of immune dysregulation and may represent a primary phagocyte dysfunction/ inflammatory response or abnormal phagocyte response to an infectious agent. Therefore, special stains are required to rule out fungal and mycobacterial organisms. With the exception of four esophageal biopsies with fungal organisms in superficial mucosa, all other specimens in our study were negative for infectious organisms, arguing in favor of a dysregulated pathogenesis. Microgranulomas in CGD resemble those of sarcoidosis since they are not necrotizing and do not show an infectious etiology. In a previous study of 25 CGD patients, Marks et al reported that 56% patients had gastrointestinal symptoms and 44% patients had documented gastrointestinal inflammation not secondary to infection, involving upper and/or lower GI tract (7). That study demonstrated epithelioid granulomata in 55% of patients (7).

Along with granulomas, pigmented macrophages are a hallmark of CGD. The pigment is hypothesized to be a by-product of ineffective digestion of organisms, membranes, and lipids. Cytoplasmic brown granular pigmented inclusions in macrophages were easily identified in GI biopsies from 74% (64/87) patients and in both small and large bowel tissue from 14 of 15 autopsies. In some cases, there were a few scattered pigmented macrophages while in others large collections of pigmented macrophages were seen infiltrating the parenchyma at all levels – lamina propria, superficial and deep mucosa and submucosa, as well as muscularis propria, and occasionally surrounding Auerbach's plexus. The presence of pigmented macrophages in the deep layers is especially useful as it is distinctive from melanosis coli in which the distribution of pigmented macrophages is mainly restricted to the lamina propria. Another rare inherited disease, Hermansky Pudlak syndrome, can also present with GI manifestations and macrophages with brown inclusions from ceroid pigment accumulation (14).

We found increased numbers of eosinophils with more than 30 eosinophils per high power field or eosinophilic microabscesses in 36% (31/87) patients – involving 26% (43/167) colon, 13% (7/52) small bowel and 3% (2/71) gastric biopsies. Tissue eosinophilia with increased numbers of eosinophils around crypts in colonic biopsies from 8 CGD patients was previously described by Schappi et al (19). Schappi et al also suggest that certain endothelial adhesion molecules may be expressed that facilitate the transendothelial migration of eosinophils and granulocytes during inflammatory processes in CGD (19).

66% (57/87) patients had evidence of chronic and/or acute inflammation. Chronic and/or acute inflammation was present in 58% (97/167) colon, 25% (13/52) small bowel, 59% (42/71) gastric (Figure 3C) and 22% (5/23) esophageal biopsies. As has been previously established, colon is the most commonly involved site in CGD and colitis was seen in 66% of our patient cohort (35 of 53 patients). Colitis been reported in the literature as a common cause of clinical symptoms (8). A spectrum of chronic and/or active colitis is encountered in our study including active neutrophilic colitis in 25% biopsies with acute neutrophilic cryptitis (24 biopsies) and crypt abscess (25 biopsies), ulceration (10% colon biopsies). There was evidence of chronicity in 38% biopsies with architectural distortion, Paneth cell metaplasia and/or basal cell plasmacytosis.

Chronic (lymphocytic) or acute (neutrophilic) inflammation and granulomata are non-specific findings in any IBD or mycobacterial infection. However, in our experience, the histologic pattern of microgranulomas, disseminated pigmented macrophages and tissue eosinophilia with paucity of neutrophils and lymphoid aggregates and lack of fibrosis is more typical of GI disease in CGD. Additionally, in CGD, microgranulomas, pigmented macrophages and tissue eosinophilia are not associated with neutrophilic inflammation and often occur without accompanying acute inflammation.

One of the major limitations of our present study is the lack of detailed clinical correlation. Clinical data together with histopathologic evidence of GI involvement in CGD will further our understanding of the disease pathogenesis and help to direct patient tailored therapy. Additional work is needed to correlate our findings with clinical characteristics such as history of infections, genotype, clinical presentation and therapeutic interventions. Additionally, histopathology needs to be correlated with endoscopic findings for each patient. Bowel strictures and fistula have been described in colonoscopy of CGD patients (22) but little is known about upper GI endoscopic findings in this disease. While we had limited endoscopic information for our patient's cohort, we are aware that endoscopic changes involved both upper and lower GI tract, with the lower part being more commonly involved, and with predominant rectal/anal involvement. In a prior study at NIH, the X-linked form of CGD was associated with more severe GI involvement (4). The mainstays of

therapy in CGD are antimicrobial agents and interferon gamma. In a previous study, it was reported that the rate of colitis in CGD did not correlate with prophylactic antimicrobials or interferon gamma use (4). It is a challenge to treat GI disease in CGD using a combination of immunosuppressive therapy and antimicrobials (21). Clinical trials show that bone marrow transplantation is potentially curative and restores normal immune function of phagocytes leading to immune recovery and better survival in CGD patients with stable remission (16). It would be important to analyze histopathologic data in the context of the different therapeutic modalities as GI lesions may occur as the primary pathogenesis of CGD or due to post-transplantation sequelae (such as Graft versus Host Disease and opportunistic infections due to immunosuppression). It is also important to know if any of the CGD patients in our study were diagnosed with other autoimmune/immunologic diseases, as reported previously (3).

In summary, our review of GI specimens from 87 patients validates some previously described features of GI histopathology while supporting an inflammatory/immune dysregulated pathogenesis of GI disease in CGD. We found mild to severe pathologic changes of GI tract in the majority of CGD patients with clinical GI symptoms. Due to the high prevalence of GI disease in CGD patients, non-specific clinical symptoms may require GI investigation and pathologic evaluation. Colon is the most commonly affected site in the GI tract. Microgranulomas, pigmented macrophages and tissue eosinophilia are commonly encountered in the GI tract and not associated with acute inflammation. Better recognition of the characteristic histopathologic findings of CGD should be helpful in alerting the pathologist to include CGD in the differential diagnosis of various GI conditions.

Abbreviations

GI	gastrointestinal
CGD	chronic granulomatous disease
IBD	inflammatory bowel disease

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Figure 1.

Acute (A, x200) and/or chronic colitis (B, x100) was present in 58% (97/167) of colon. A: Acute colitis with gland destruction and crypt abscesses. B: Chronic colitis with expanded lamina propria by lymphoplasmacytic infiltrates and mild architectural distortion. Tissue eosinophilia was present in 26% of colon (C, x400). Villous shortening was seen in 30% of duodenum (D, x200).

Figure 2.

A–D, Granuloma formation was present in 46% (76/167) of colon involving mucosa and submucosa without (A and B, x200) or with (C and D, x200) surrounding lymphoid cuff and Langhan or foreign body-like giant cells.

Figure 3.

A–B, Pigmented macrophages were present in 65% (109/167) of colon (A, x200), and 13% (7/52) of duodenum (B, x200).

Figure 4.
Spectrum of GI histopathologic findings in cohort of 87 CGD patients

Table 1

Summary of the pathologic changes in 313 GI tract biopsies from 87 CGD patients with GI symptoms

	Esophagus	Stomach	Small bowel	Colon
Biopsies performed	23	71	52	167
Granuloma formation	0 (0%)	4 (6%)	12 (23%)	76 (46%)
Well-formed	0	2	2	41
Poorly-formed	0	2	10	35
Pigmented macrophages	0 (0%)	0 (0%)	7 (13%)	109 (65%)
Tissue eosinophilia	0 (0%)	2 (3%)	7 (13%)	43 (26%)
Acute (neutrophilic) and/or chronic inflammation (LP) **	5 (22%)	42 (59%)	13 (25%)	97 (58%)
Ulceration	0 (0%)	4 (5%)	7 (13%)	17 (10%)
Other (site-specific) features			shortened villi: 13	cryptitis/abscess: 49 crypt distortion: 20 Paneth cell metaplasia: 12 basal cell plasmacytosis: 47

** Please refer to text for additional details. (LP: Lymphoplasmacytic inflammation).