Data S1. Detailed patient clinical features, related to Figure 4.

Patient 1:

Patient 1 is a 10-year-old male, the second of three children born to Turkish consanguineous parents, with a birthweight of 3500 g and an uneventful perinatal period. Symptoms presented at 18 months with failure to thrive, mucous diarrhea, bronchial hyperreactivity, and tenesmus. Diarrhea was initially intermittent at 6–10-day intervals until the age of 2.5 years when it became persistent. Remission was achieved with antibiotics for a suspected infectious etiology. At the time, he received vitamin and formula supplementation. He experienced several episodes of wheezing, and skin testing revealed house dust mite allergy. When he was 3.5 years old, gastrointestinal endoscopy revealed aphthous ulcers at the terminal ileum and nodularity in the caecum (see report below). The sigmoid colon and rectum showed prominent vascular appearance and hyperemia. Histopathology of biopsies showed non-specific colonic inflammation. Celiac antibody testing and microbiologic investigation of the stool were negative. He was placed on 5-aminosalicylic acid treatment and over the following months, his symptoms were ameliorated with the successful withdrawal of the medication. Currently, the patient is doing well with no symptoms.

Because of the early onset of disease, he underwent immunological evaluation. A complete blood count testing and immunoglobulin quantification were normal. Lymphocyte immunophenotyping revealed that $CD3^{+}CD4^{+}$ T cell proportions were reduced for age at 6 years of age; a repeat examination at 10 years of age was within normal limits.

G.I. biopsy report (12.11.2013):

1. Terminal ileum: increased abundance of lymphoplasmocytic cells, slightly increased eosinophil leukocytes
2. Caecum: Edema, focal lymphoplasmocytic cell abundance
3. Ascending colon: increased abundance of lymphoplasmocytic cells, lymphoid aggregates, focal eosinophilic pericryptitis
4. Transverse colon: Edema, abundant lymphoplasmocytic cells, lymphoid aggregates
5. Sigmoid colon: abundant lymphoplasmocytic cells
6. Descending colon: abundant lymphoplasmocytic cells lymphoid aggregates
7. Rectum: increased abundance of lymphoplasmocytic cells, lymphoid aggregates, focal cryptitis
8. Esophagus: Superficial esophageal mucosa
9. Antrum, corpus: edematous oxynthic mucosa
10. Duodenum: edematous duodenal mucosa

Patient 2:

Patient 2 is a 9-year-old male born to non-consanguineous parents and the youngest of six children. He presented at the age of 18 months with failure to thrive and chronic diarrhea. Endoscopic evaluation demonstrated inflammation in the stomach, duodenum, and ileum, with granulomas seen in the biopsies. The patient was treated with antibiotics and placed on a lactose- and gluten-free diet with a generally good response, though episodes of abdominal pain recurred at the age of 4 years. Repeated endoscopic evaluation showed the normal macroscopic appearance of the upper and lower GI tract. However, biopsies showed tissue eosinophilia in the ileum, colon, and esophagus. Basal cell hyperplasia was demonstrated in the lower esophagus together with more than 50 eosinophils per high-powered field (HPF) and lymphocytic infiltration of the duodenum. The patient was given omeprazole for eosinophilic esophagitis and instructed to avoid milk products. Endoscopy after treatment showed a significant decrease in eosinophils in the esophagus.

At 5 years old, the patient developed bilateral arthritis of ankles and knees. Calprotectin was elevated in stool (1,725 mg/g stool). Colonoscopy demonstrated moderate-severe inflammation of the ileocecal region characterized by ulcers, edema, and fibrin. Ileal biopsies showed distorted architecture, focal goblet cell depletion, focal acute and chronic inflammation, and cryptitis. Colonic biopsies were normal. Steroid therapy achieved a good clinical response, but subsequently he started 6-mercaptopurine. At 7.5 years of age, the patient had a repeat upper endoscopy due to failure to gain weight and a period of exposure to milk (mistaken by the family doctor as a fortifying formula). Macroscopically, the esophagus, stomach and duodenum were normal; however, esophageal biopsies demonstrated basal cell hyperplasia with increased intraepithelial eosinophils and 21, 15, and 4 eosinophils per HPF in the lower, middle, and upper esophagus, respectively. A repeat endoscopy two months after a complete avoidance of milk showed a reduction in eosinophil infiltration at all levels. Proton pump inhibitor (PPI) treatment was added. At 9 years of age, the patient is feeling well and thriving while avoiding all milk products. He receives PPI and 6-mercaptopurine therapy. His latest calprotectin analysis was 60 mg/g stool.

As part of his work-up:
IgE was elevated – 1,490 KU/L
Food allergy testing – negative
Eye examination – no signs of uveitis; posterior polymorphous dystrophy was demonstrated in the right eye

Patient 3:

Patient 3 is a 14-year-old male born to Pakistani parents who presented at 3 months of age with mouth and lip inflammation and fever. The patient experienced 2 months of perianal symptoms, ulcerations, and found blood in formed stool together with decreased energy and weight loss of 2 kilograms. At 5 years old, endoscopy showed a friable white linear superficial ulcer in the distal esophagus as well as mild erythema throughout the stomach. Microscopically, focal clusters of mononuclear cells and eosinophils were found in the gastric antrum. In the distal esophagus, moderate basal hyperplasia, marked spongiosis, and prominent numbers of intraepithelial lymphocytes were found. Colonoscopy revealed a perianal skin tag and 4 fissures. The lower GI tract was normal macroscopically and microscopically. Lip and buccal mucosa biopsies showed chronic non-necrotizing granulomatous inflammation.

At 5 years old, the patient was diagnosed with Crohn's Disease. A primary presenting feature was significant orofacial granulomatosis. His mouth and cheeks were visibly swollen. He did not have colitis or terminal ileum (TI) involvement but was found to have macroscopic disease in the mouth, esophagus and jejunum/ileum, microscopic disease in stomach, and a perianal fistula. At 6 years old, imaging showed mild thickening and enhancement of the TI and ileocecal valve and prominent peri-cecal lymph nodes. Additionally, perianal inflammatory changes (at the anal verge) and mild left sacroiliitis were observed. The patient responded well to oral prednisone and oral metronidazole. He is currently 14 years old and has stopped all medications. The most recent labs showed normal inflammatory markers and mild iron deficiency anemia (Hemoglobin 108). There is no family history for IBD or consanguinity between parents.

Labs:

- Neutrophil Oxidative Burst Index (NOBI) 303 (normal being 32-300, Nov 2010)
- Normal albumin, c-reactive protein, erythrocyte sedimentation rate, platelets
- ASCA negative (IgA 1, IgG 10)
- ANCA negative
- Mild eosinophilia
- Normal ferritin
- Normal immunoglobulins
- Normal complement levels