The clinical significance of focal enhanced gastritis in adults with isolated ileitis of the terminal ileum

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Background. Isolated chronic ileitis in the terminal ileum, without accompanying chronic colitis, is not an uncommon finding present in biopsy specimens from patients being evaluated for chronic diarrhea. Among the many entities that should be included in the differential diagnosis are Crohn’s disease and nonsteroidal antiinflammatory drugs (NSAIDs)-induced enterocolitis. In high-prevalence Crohn’s disease populations, focal enhanced or active gastritis (FEG) may be a good predictor of Crohn’s disease; however, this criterion may not apply in a general clinical setting. Our goal was to determine if FEG is a pathological marker of Crohn’s disease in patients with isolated chronic ileitis in the terminal ileum.

Methods. We examined 46 consecutive cases of isolated chronic ileitis with concurrent stomach biopsies. These patients did not have evidence or previous history of inflammatory bowel disease. The diagnostic criteria of chronic ileitis included crypt distortion and inflammation, plasmacytosis in the lamina propria, ulceration, and/or pyloric gland metaplasia.

Results. Of the 46 cases reviewed, 25 (54%) cases were diagnosed with Crohn’s disease later, confirmed by clinical manifestations and/or biopsies with a follow-up of up to 4 years. The stomach biopsies of these patients were either normal or demonstrated a spectrum of histological findings, including FEG, chronic gastritis with or without Helicobacter pylori organisms, chemical gastropathy, and normal tissues. FEG was more commonly present in Crohn’s disease patients (36%) than in non-Crohn’s disease patients (5%) (P < 0.01).

Conclusions. The presence of FEG is a good indicator for the diagnosis of Crohn’s disease in adult patients with isolated chronic ileitis.

Key words: focally enhanced gastritis, chronic ileitis, Crohn’s disease, NSAID, inflammatory bowel disease

Introduction

The term “regional ileitis” was first introduced in 1932. Afterward, “Crohn’s disease” was used to describe an entity in which patients exhibited both regional ileitis and concurrent colitis. Over the next several decades, Crohn’s disease was recognized as the etiology of chronic ileitis. However, it is clear that not all patients with chronic ileitis have Crohn’s disease. Several other entities, including infectious agents, seronegative spondylarthropathy, and commonly used over-the-counter nonsteroidal antiinflammatory drugs (NSAIDs), have been shown to cause terminal chronic ileitis.

In patients being evaluated for both bloody and nonbloody diarrhea, biopsy specimens with isolated chronic ileitis without accompanying colitis are not uncommon findings. The histological features diagnostic of chronic ileitis include crypt distortion, plasmacytosis in the lamina propria, and pyloric gland metaplasia. The most common cause for these findings is early or mild Crohn’s disease; however, recent research has shown that spondylarthropathy and NSAIDs can induce similar histological changes in the terminal ileum. Thus, it may be difficult to determine the etiology of a patient’s clinical findings based on histological features alone. Currently, a gold standard test to definitively diagnose Crohn’s disease does not exist, and clinicians rely on a combination of clinical, endoscopic, histological, serological, and radiologic criteria to arrive at such a diagnosis. The early diagnosis of Crohn’s disease among patients with isolated terminal ileitis may be particularly challenging, as these patients may not have the classical features of the fully developed illness.
In addition to a lower gastrointestinal tract workup, many patients undergoing evaluation for symptoms of abdominal pain and diarrhea will undergo assessment of the stomach as part of an upper gastrointestinal tract workup. Our aim was to determine whether the histological findings in stomach biopsies could help further elucidate the etiology of a patient’s concurrently identified isolated chronic ileitis.

The histological presentation of gastric Crohn’s disease includes a wide spectrum of nonspecific changes, including Helicobacter pylori-negative gastritis and focal active or enhanced gastritis (FEG), which is typified by small collections of neutrophils, lymphocytes, and histiocytes surrounding a small group of foveolae or gastric glands.9–15 FEG may be a good marker of Crohn’s disease in high-prevalence populations, although in the general population it may be a nonspecific finding.16 We propose that the concurrent existence of FEG and chronic ileitis is highly suggestive of Crohn’s disease. To study this further, we reviewed all cases with concurrent terminal ileum and stomach biopsy specimens performed in 3 calendar years to determine the relationship among isolated chronic ileitis, FEG, and Crohn’s disease in a general patient population.

Methods

In this retrospective study, we retrieved all terminal ileum biopsies with chronic inflammation obtained during 2002–2006 at University Hospitals of Cleveland/Case Medical Center. Biopsies were identified using a SNOMED (Systematized Nomenclature of Medicine) free text search of “ileitis” and “ileum, chronic inflammation.” All cases in our surgical pathology archive since 1993 have been SNOMED coded and can easily be searched. After further reviewing the SNOMED search results, we selected only the cases in which the patients also underwent stomach biopsy within 3 months of the initial terminal ileum biopsy. Any cases in which the patient had a prior history of inflammatory bowel disease, documented rheumatoid diseases, or history of gastrointestinal tract surgery or malignancies were excluded. Patients with terminal ileum biopsies without simultaneous colon biopsies were also excluded. The stomach biopsy specimens not containing at least one fragment of body- and one fragment of antral-type mucosa were also excluded after light microscopic examination. The hematoxylin and eosin-stained slides of terminal ileum, colon, and stomach, which typically contained a minimum of ten serial sections, were reviewed by two authors (W.X. and A.A.P.). In total, 382 cases were reviewed. Consensus cases of chronic ileitis (n = 46) were identified in adult patients and reviewed with both authors (W.X. and A.A.P.) conjointly at a double headed microscope.

The histological criteria used to define ileitis were the presence of variable degree of chronic inflammation including crypt distortion, increased plasma cells in the lamina propria, blunting of villi, fibrosis, and pyloric gland metaplasia. The cases with presence of epithelioid granuloma were excluded. The criterion for the diagnosis of focal enhanced gastritis (FEG), as described earlier,17 is the presence of a single focus or multiple foci of foveolae, pit, or gland inflammation in the absence of other specific pathological changes. The histological diagnostic features for chemical (reactive) gastropathy included superficial edema, smooth muscle proliferation in lamina propria, foveolar hyperplasia, and foveolar cell mucin depletion, as well as no accompanying active or chronic inflammation, or intestinal metaplasia, or Helicobacter pylori organisms.18

All simultaneous colon biopsies from patients with chronic ileitis showed no significant pathological abnormalities. Follow-up data on all cases were obtained by review of pertinent medical records as well as subsequent or prior pathology specimens. The follow-up time ranged from 18 months up to 4 years, with a mean follow-up of 2.5 years. The cases with follow-up diagnosis of Crohn’s disease were confirmed by a combination of clinical and tissue histological diagnosis. This study was approved by the Institutional Review Board of University Hospitals Case Medical Center.

Unstained 5-μm sections were cut from the paraffin blocks selected for each case by routine techniques. Slides were treated with 1× sodium citrate buffer (diluted from 10× heat-induced epitope retrieval buffer; Ventana-Bio Tek Solutions, Tucson, AZ, USA) before steaming for 20 min at 80°C. Slides were then cooled 5 min before incubating with anti-Helicobacter pylori polyclonal antibody (1:40 dilution; DakoUSA, Carpinteria, CA, USA) using a Dako automated stainer. Finally, Helicobacter pylori primary antibody was detected by adding secondary antibody followed by avidin-biotin complex and 3,3′-diaminobenzidine chromagens. Sections were counterstained with hematoxylin. Immunohistochemical labeling of Helicobacter was evaluated by two of the authors (W.X. and A.A.P.) with agreement in all cases examined.

Results

Of 382 cases reviewed, 46 adult patients with isolated terminal ileitis (Fig. 1A,B) and concurrent stomach biopsies were identified. The demographic features and stomach histological findings are summarized in Table 1. Of the 46 cases reviewed, 25 (54%) cases that adhered to our criteria for inclusion in this analysis