Clinical Immunology (2009) **132**, 1–9

available at www.sciencedirect.com

Clinical Immunology

www.elsevier.com/locate/yclim

The FOCIS Centers of Excellence were established in 2004 to advance interdisciplinary clinical immunology. This network provides multiple opportunities for trainee and faculty education and interaction. For more information please visit www.focisnet.org

FOCIS Centers of Excellence Review

Advances in the pathogenesis and treatment of IBD

Nicholas A. Braus [a], **David E. Elliott** [b,c,*]

[a] *Doris Duke Clinical Research Fellowship Program Carver College of Medicine, University of Iowa, Iowa City, IA, USA*
[b] *Division of Gastroenterology and Hepatology, Department of Internal Medicine, University of Iowa, Roy J. and Lucille A. Carver College of Medicine, Iowa City, IA, USA*
[c] *Department of Veterans Affairs Medical Center, Iowa City, IA, USA*

Received 22 November 2008; accepted with revision 17 February 2009
Available online 24 March 2009

KEYWORDS
Inflammatory bowel disease;
Crohn's disease;
Ulcerative colitis;
Helminths;
T lymphocytes;
Interleukin 10;
Interleukin 17;
Interleukin 4;
TGF-beta;
IFN-gamma

Abstract Crohn's disease and ulcerative colitis are chronic remitting and relapsing inflammatory bowel diseases. We present a typical case of Crohn's disease in a young woman and discuss potential treatment options. Crohn's disease and ulcerative colitis likely result from interaction of multiple genetic and environmental risk and protective factors. Both are diseases ultimately caused by immune dysregulation. Medical therapy is with mesalamine compounds, corticosteroids, immunomodulators and/or biologics that target TNFα signaling or α4-integrin-mediated trafficking. Investigational agents include those targeted against other cytokines and costimulatory molecules or designed to promote immune regulation such as exposure to helminths which is a focus of this review.
Published by Elsevier Inc.

* Corresponding author. Division of Gastroenterology (4611 JCP), University of Iowa College of Medicine, 200 Hawkins Drive, Iowa City, IA 52242-1009, USA. Fax: +1 319 353 6399.
E-mail address: david-elliott@uiowa.edu (D.E. Elliott).

1521-6616/$ – see front matter. Published by Elsevier Inc.
doi:10.1016/j.clim.2009.02.006

Introduction

Case presentation

A 30-year-old woman with a history of Crohn's disease (CD) was admitted to the hospital with fever, severe crampy abdominal pain, and diarrhea. The patient was first diagnosed with CD at the age of 26, when she developed intermittent bouts of sharp abdominal pain, accompanied by fevers and diarrhea. Initial colonoscopic examination revealed apthous ulceration at the terminal ileum and around the ileocecal junction. The patient was treated initially with oral prednisone (0.5 mg/kg/day) to good effect. She remained in remission on azathioprine (2.5 mg/kg/day) maintenance therapy for approximately four years, at which point she experienced a recurrence of symptoms, including frequent episodes of abdominal pain, severe diarrhea, dehydration and weight loss. Colonoscopy studies revealed discrete patchy segments of ulceration and inflamed mucosa throughout the colon (Fig. 1). A biopsy revealed ulceration and mixed (lymphocytic and neutrophilic) infiltration, and deep inflammation of the intestinal mucosa. Her symptoms showed moderate improvement with administration of high dose corticosteroids (solumedrol 60 mg/day IV), however she failed attempts at tapering the dose. The patient underwent an induction course of infliximab (5 mg/kg at 0, 2, and 6 weeks) without significant improvement. Azathioprine was discontinued and she is currently on a trial of weekly low-dose methotrexate. She may be a candidate for alternative biologics, surgery, or investigational therapies.

Discussion

Idiopathic Inflammatory Bowel Disease

Idiopathic Inflammatory Bowel Disease (IBD) is a chronic inflammatory disorder of the gastrointestinal tract that presents as either ulcerative colitis (UC) or Crohn's disease (CD). UC and CD are both characterized by chronic remitting/relapsing inflammation of the intestinal mucosa, often resulting in intermittent abdominal pain, fever, and diarrhea. Each disease also possesses distinguishing clinical, pathological, and endoscopic features [1]. Inflammation in UC typically involves the rectum, and extends continuously in a retrograde fashion. In severe cases, it can involve the entire colon. Endoscopic features include edema that obscures the normal vascular appearance, granular erythema and mucopurulent exudate, areas of extensive superficial ulceration, and the presence of inflammatory pseudopolyps. As illustrated in the case above, CD is characterized by sharply demarcated, non-contiguous inflammatory lesions that can become transmural (Fig. 1). Non-caseating granulomas are occasionally present. While CD lesions may involve any segment of the gastrointestinal tract, they occur most commonly in the terminal ileum.

Genetics and immunopathogenesis

Current evidence strongly suggests that IBD arises from a disruption of mucosal immune homeostasis in genetically susceptible individuals, resulting in altered processing of enteric antigens, pathogenic T cell activation, and chronic inflammation. The essential role of enteric microflora is supported by studies showing responsiveness of UC and CD to antibiotics and CD to fecal stream diversion, as well as experiments with induced mutant germ-free mice in which spontaneous colitis is dependent on reconstitution with normal luminal microflora [2,3]. Various innate, adaptive, and regulatory immune mechanisms have been implicated in IBD. These include dysregulated cellular stress responses, microbial recognition, autophagy, and processing of antigens by innate immune effector cells, pro-inflammatory CD4+ T cell polarization, and blunting of cytokine or T cell-driven tolerance [4]. Genetic factors contribute significantly to IBD pathogenesis. Approximately 5–10% of patients have at least one affected first degree relative and twin studies demonstrate a 50% concordance rate of CD among monozygotic twins, with lower rates (~18%) for UC [5–7]. In addition, specific genetic correlates have recently been identified in IBD, shedding new light on the underlying mechanisms

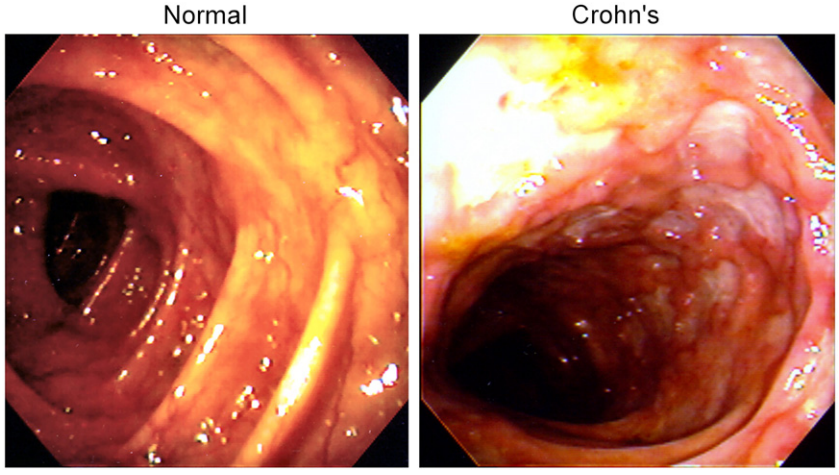

Figure 1 Colonoscopic view of the transverse colon in health (Normal) and disease (Crohn's). The normal colon shows regular haustra and a transparent intact mucosa. The colon from the patient with Crohn's disease shows numerous deep ulcerations and areas of more normal appearing mucosa.