EDITORIAL

Gastrointestinal endoscopy biopsy derived proteomic patterns predict indeterminate colitis into ulcerative colitis and Crohn’s colitis

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Abstract

Patients with indeterminate colitis (IC) are significantly younger at diagnosis with onset of symptoms before the age of 18 years with significant morbidity in the interim. The successful care of IC is based on microscopic visual predict precision of eventual ulcerative colitis (UC) or Crohn’s colitis (CC) which is not offered in 15%-30% of inflammatory bowel disease (IBD) patients even after a combined state-of-the-art classification system of clinical, visual endoscopic, radiologic and histologic examination. These figures have not changed over the past 3 decades despite the introduction of newer diagnostic modalities. The patient outcomes after restorative proctocolectomy and ileal pouch-anal anastomosis may be painstaking if IC turns into CC. Our approach is aiming at developing a single sensitive and absolute accurate diagnostic test tool during the first clinic visit through endoscopic biopsy derived proteomic patterns. Matrix-assisted-laser desorption/ionization mass spectrometry (MS) and/or imaging MS technologies permit a histology-directed cellular test of endoscopy biopsy which identifies phenotype specific proteins, as biomarker that would assist clinicians more accurately delineate IC as being...
either a UC or CC or a non-IBD condition. These novel studies are underway on larger cohorts and are highly innovative with significances in differentiating a UC from CC in patients with IC and could lend mechanistic insights into IBD pathogenesis.

Key words: Indeterminate; Ulcerative; Crohn’s colitis; The colitides; Proteomics; Diagnostic accuracy

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Core tip: This Editorial is introductory, dedicated to a novel and innovative study with clinical relevance regarding precision of indeterminate colitis (IC) into accurate diagnosis of either ulcerative colitis (UC) or Crohn’s colitis (CC). To date, it is very difficult to predict the clinical course of IC, whether it will evolve into UC or CC. About 90% of IC is diagnosed at the time of colectomy for fulminant colitis and subsequent management critically depends on the correct eventual diagnosis. The outcome after colectomy and pouch anastomosis may be painstaking if IC turns into CC. The underlying studies of proteomic analysis on colon biopsy specimens, if successful will permit delineate IC into UC or CC precision which could be of great help in decision making regarding treatment indication. Although the present data is convincing and support differentiated between UC and CC, this data requires validation and confirmation on a large scale by clinical studies. Hopefully, this editorial will stimulate research into this field to trying to overcome the diagnostic accuracy challenges in inflammatory bowel diseases.

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INTRODUCTION

In endoscopic medicine, predicting the phenotypic outcomes of “indeterminate colitis (IC)”, given its unpredictable clinical presentation and disease course, is challenging[2,3]. Inadequate differentiated diagnoses of the two predominantly colonic inflammatory bowel diseases (IBD), ulcerative colitis (UC) and Crohn’s colitis (CC), may lead to the inconclusive IC diagnosis even when a state-of-the-art classification system of combined clinical, endoscopic, radiologic and histologic tools[1,2] are used. Unless there is a unique and yet unclassified class of colitis, the field needs to develop supplemental molecular biomarker tools for precise and rapid distinction between UC and CC for patients that will otherwise be diagnosed with IC. Previous studies using mucosal biopsy[3,4] have been successful as prognostic indicators for IBD whether the colitis is in a quiescent or active state, but have not been able to distinguish UC from CC[3,4]. Patients with IC are significantly younger at diagnosis (M ± SEM, 9.53 ± 4.8 years)[5-8] with onset of symptoms before the age of 18 years[9-13]. IC shows an equal gender distribution[8,14,15]. In contrast, UC is predominant among males and the mean age at onset is 36-39 years[14-18]. These figures have not changed over the past 3 decades despite the introduction of newer diagnostic modalities[19]. Even after long-term surveillance, a substantial number of patients with IC still have an unchanged diagnosis[15,19,20] with significant patient suffering in the interim[15,19,20]. The continued presence of an IC diagnosis over a long period of time supports part of our hypothesis that IBD may represent a spectrum of diseases rather than just two entities, Crohn’s disease (CD) and UC[21].

The need for IC classification into either UC or CC is important for proper care in patients suffering from IBD, with obvious therapeutic and prognostic implications[22]. Early and accurate diagnosis and sub-classification of UC and CC is therefore the cornerstone for personalized and evidence-based interventional care[23-25]. These two pathologies have differing therapeutic strategies and prognoses. Most patients with UC, or IC likely to develop UC[22], will require pouch surgery for resolution[26-30]. Pouch surgery is well-established[22] and restores gut continuity, defecation, deferral, and discrimination, but is only successful if the UC and/or IC likely to develop UC diagnosis is correct[21,32]. However, IC and UC are mistakenly diagnosed in patients with CC[1,33]. Current data show that 15% of IBD patients who undergo pouch surgery for presumed definitive UC (or IC likely to develop UC) subsequently are diagnosed with de novo CD in the ileal pouch[34,35]. Identifying patients with CC and positive outcomes after pouch surgery is a painstaking clinical experience[34,35]. Ileal pouch anal anastomosis is acceptable standard care for UC patients, and restorative proctocolectomy should be contraindicated for CC patients[4,36,37].

Pouch complications are significantly higher in patients with CC (± 64%) and IC (± 43%) vs patients having UC (± 22%) (P < 0.05)[23,38,39]. This diagnostic dilemma holds potential morbidity from unnecessary and/or inappropriate surgery, and underscores the need for a research strategy focused on developing molecular biometrics to improve diagnosis of colitides at initial endoscopic biopsy[40-46]. De novo CD in the ileal pouch is the diagnosis most feared by IBD patients and doctors due to its intractable nature and associated complications which often necessitate excision of the pouch with a permanent end-ileostomy[45-49].

ADVANCES

Mass spectrometry (MS) and imaging mass spectrometry (IMS)[21] are non-invasive technologies that can measure individual molecules in complex endoscopic and surgical clinical specimens[40,41]. These analyses
provide quantitative and qualitative data about cellular systems, and can differentiate diseases from normal tissue, and can identify diseases within the same organ\(^ {40,41,50}\). These characteristics offer significant diagnostic and prognostic potential for clinical medicine and could supplement known clinicopathologic variables for delineating IC into UC or CC at a patient’s first clinical visit. Due to the current alarming epidemiologic studies indicate that the incidence and prevalence of IBD is widening worldwide, especially in developing nations\(^ {59,21,51-60}\), established techniques like MS and IMS, which are affordable, non-invasive, easier, accurate and faster at screening for potential delineation of IBD, ought to be considered for clinical applications in IBD laboratories. The basic steps of the MS/IMS methodology of histology-directed proteomic patterns profiling are outlined in Figure 1.

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