Clinical Diagnosis and Manifestation of Inflammatory Bowel Disease

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Colonic inflammatory bowel disease (IBD), or the colitides, encompasses Crohn's colitis (CC) and ulcerative colitis (UC), the two highly heterogeneous, debilitating, incurable, persistent, relapsing/worsening, immune-arbitrated inflammatory pathologies of the digestive system canal.

inflammatory bowel disease | ulcerative colitis | Crohn's colitis | indeterminate colitis | clinical diagnosis guideline | diagnostic challenges | molecular diagnostics advances | global emergent disease | socioeconomic strata

1. Background

Colonic inflammatory bowel disease (IBD), or the colitides, encompasses Crohn's colitis (CC) and ulcerative colitis (UC), the two highly heterogeneous, debilitating, incurable, persistent, relapsing/worsening, immune-arbitrated inflammatory pathologies of the digestive system canal [1]. UC causes inflammation and ulceration of the epithelial layer and, to a lesser degree, the submucosae layer of the larger intestine (colon and rectum) only [2]. CC varies from UC in location, in that it is segmental and causes inflammation impacting the whole digestive system from the mouth to the anus and can further cause inflammation deeper within all the intestinal layers (transmural and skip lesions) that may affect other organs through fistulation [3][4]. IBD has significant impacts on patient health quality of life (QoL), mental health, work productivity, and healthcare resources [5][6].

There are established guidelines for the diagnosis of IBD [7][8], which include international clinical practice tool recommendations that incorporate various best practices, and other evidence has widely been issued [9][10]. Thirty percent of IBD patients with colonic IBD present with ambiguous diagnosis [11]. In the past two decades, there have been vast advances in research, i.e., molecular diagnostics and surgical technical evolution for IBD management [12][13]. The aim of this overview is to provide disease guidance consensus for healthcare professionals managing IBD, to ensure that investigation, diagnosis, surgical treatment, and monitoring decisions are based on the best available common consent evidence, and to promote and ameliorate the best accepted practice.

Effectuates of IBD are not yet fully understood, but are believed to be multifactorial [1][14][15], i.e., a susceptible host (e.g., genetic, gut barrier and the exaggerated innate/adaptive immune response) and external/exogenous factors (e.g., normal indigenous intestinal luminal flora) are important basic associates that probably induce and

perpetuate the pathogenesis of IBD [16]. The mechanistic trigger processes are mediated through components of the autoimmune response to self-antigens [17][18]. Recently, research has paid attention to the role of antibodies in downstream events and mechanisms of autoimmunity and inflammation [19][20]. Whether the fabrication of antibodies is a serologic product of IBD or if it is a consequence of barrier dysfunction caused by inflammation remains a significant knowledge gap.

While the Western world including US, Canada and Europe continues to advance and improve ambulatory regimens care delivery [21][22] to meet high-quality, safety, efficacy, coordination of care, and recommended precision evidenced-based care in IBD patients [23][24], developing nations at large have healthcare service constraints and limitations to meet the required standard of care [25] due to limited resources and healthcare personnel not being trained and having no knowledge about treating these diseases [26]. Furthermore, regarding cost-effectiveness considerations and recommendations by the World Health Organization (WHO) and the World Gastroenterology Organization (WGO) [27][28], developing countries struggle the most. The economic implications of IBD are enormous [29]. Hospital admission rates and costs for IBD show an increasing trend [30][31]. In the US alone, the estimated annual direct treatment costs are greater than USD 6.8 billion, and indirect costs amount to an additional USD 5.5 billion [32][33].

2. Clinical Diagnosis and Manifestation

Currently, there is no standardized diagnostic test tool for IBD [34][35]. The standard state-of-the-art diagnosis of IBD relies on amassing of clinical, radiologic, endoscopic, and histopathologic clarification [36][37]. This inexact compilation technique is not always accurate, and about 15% of colonic IBD patients cannot be delineated as UC or CC and are labeled as having ‘‘indeterminate colitis’’ (IC). This is because the clarification criteria for UC and CC are indefinite [38][39]. In addition, another 15% of the colonic IBD cases that undergo pouch surgery, i.e., restorative proctocolectomy with ileal pouch-anal anastomosis (RPC-IPAA) for their definitive UC diagnosis based on the pathologist’s final designation of endoscopic biopsies, will have their initial UC diagnosis reciprocated to ileal Crohn’s disease (CD) based on the postoperative follow-up when clinical and histopathology changes indicate the evolution of CD in the ileal reservoir and/or because authentic CC was not evident prior to colectomy [40][41]. Half of these patients with pouch ileal CD will require reservoir/pouch excision or diversion [42][43].

2.1. Ulcerative Colitis

Ulcerative colitis’ (UC) peak onset is mostly in early adulthood [44]. A consequence of untreated UC is chronic inflammation and ulcerations in the mucosal and to a lesser degree submucosal linings confined to the large intestine (colon and rectum) [37][44]. Approximately 15% of patients may encounter hostile development, and these patients may require hospital admission for fulminant disease [44][45]. To establish the diagnosis and disease state of a patient sample, gastrointestinal pathologists depend most on nanoscopic visual examination and the elucidation of marked and/or colored tissue sections [46][47]. These procedures are endowed with a significant degree of discourse [48], and are surfeited with expostulations [48][49]. Careful professional tutoring in pathology subspecialties has helped to achieve the benchmark of care and abolish exorbitant oversights [50][51].

Notwithstanding these eminently thorough benchmarks, ineludible scenes arise in which impartiality cannot be formally assured and where significant variance of opinion occurs amongst consultant specialists [52]. Further to the fundamental guidelines and associated specialized reviews, moderate to severe UC is circumscribed based on the Truelove and Witts criteria and Mayo Clinic score [53][54][55] [55-57]. Mayo Clinic scores of 6–12 with an endoscopic subscore of 2 or 3 are viewed as moderate to severe disease. These guidelines are explicated as hospital-admitted patients with the following Truelove and Witts criteria: six or more hematochezia (bloody diarrhea) movements/day with at least one marker of inseparable toxicity, including heartbeat/rate > 90 beats/min, body temperature > 37.8 °C, blood hemoglobin < 10.5 g/dL, and/or an erythrocyte sedimentation rate (ESR) of −30 mm/h [54].

2.2. Crohn's Disease

Predominantly colonic Crohn's disease, or Crohn's colitis, is an IBD diagnosed in at least four patients per 100,000 live births in the United States and Canada, and the incidence and prevalence are rising internationally [56][57][58] [58-59], specifically in developing nations [26][56]. Clinically, CC differs from UC in that it may result in inflammation deeper within the entire colonic walls (mucosa, submucosa, muscularis and serosa, (transmural) (colon, and rectum) [37]. Furthermore, CC may also affect other systemic organs outside the colon tract through fistulation [3][4] [59]. The conciliate features for diagnosing CC comprise an inexact combination of classification systems discussed above for IBD clinical diagnosis, and histopathological findings demonstrating focal, asymmetric, transmural, or granulomatous features [60][61]. Abdominal computed tomography (CT) colonography is the most widely recommended and preferred first-line radiologic study used in the evaluation/assessment of CC. The diagnostic accuracy of magnetic resonance colonography is equivalent to that of CT scans and prevents liability exposure to ionizing radiation. Endoscopic score metrics are the gold standard tool used to estimate the activity of CC, and they are used more often in clinical trials to compute proof of the efficacy and safety of various drugs inducing and maintaining remission and mucosal healing. There are several multipronged scoring systems, but the most used to measure clinical disease severity include the CC Activity Index (CDAI), the Harvey–Bradshaw index (HBI), the short IBD questionnaire (SIBDQ) and the Lehmann score [60][61].

2.3. Indeterminate Colitis

In colonic IBD, delineation between CC from UC is often inconclusive [11][38][39][62], thereby confounding effective and appropriate surgeries [37]. Approximately 30% of patients with colonic IBD are indistinguishable, especially during the prodromal stage, and are therefore labeled as "indeterminate colitis" (IC) due to the non-definitive establishment of criteria for CC and UC [38][63][64]. Therefore, understanding the biomolecules and different cellular mechanisms driving IBD heterogeneity is vital to the development of future drug inhibitors to improve patient care [65][66][67][68] [67-70]. The distinction between UC and CC in otherwise IC is of utmost importance when determining a patient's candidacy for RPC-IPAA, the standard curative surgical procedure in the treatment for UC. The success of RPC-IPAA surgery and convalescence largely depend on correct diagnosis. To address the IBD diagnosis dilemma in clinical settings, there are published data that have shown robust evidence supporting the presence of human alpha defensin 5 (*DEFA5*, alias HD5) in the colon crypt mucosa with aberrant expression of Paneth cell-like cells (PCLCs) and/or apparent crypt-cell-like cells (CCLCs) in areas identified with an ectopic colonic ileal

metaplasia that is consistent with the diagnosis of CC [11][69]. This conceptual innovation relies on the expression of *DEFA5* and the CCLCs in the colonic mucosal crypt of CC patients and its definitive discriminatory use as a biomarker to facilitate the unambiguous diagnosis of CC with a positive predictive value (PPV) of 96 percent [11][69].

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