Minerva Gastroenterologica e Dietologica
EDIZIONI MINERVA MEDICA

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Journal: Minerva Gastroenterologica e Dietologica
Paper code: Minerva Gastroenterol Dietol-2577
Submission date: March 17, 2019
Article type: Review Article

Files:

1. Manuscript
   Version: 1
   Description: text
   File format: application/vnd.openxmlformats-officedocument.wordprocessingml.document

2. Figures 1
   Version: 2
   Description: Patient with pyoderma and inflammatory bowel disease
   File format: image/tiff

The gut and the Inflammatory Bowel Diseases inside-out:

The extra-intestinal manifestations

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Conflicts of interest: none to declare.

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Abstract

An increasing deal of attention is being conveyed on the extra-intestinal manifestations of inflammatory bowel diseases (IBD). We compiled the present review in an attempt to upgrade the accuracy of the classification of such polymorphic entities. We focused on three patterns. First, the conventional extra-intestinal manifestations localized to bone and joints, to the eye, to the biliary tree and to the skin. Second, the so-called IBD-like syndromes accompanied by bone marrow-derived anomalies of innate or acquired immunity. Third, specific disorders of the skin and of the lungs. The extra-intestinal manifestations are thought to derive from an altered gut permeability, the release of cross-reacting antigens, and subsequent peripheral inflammation; T helper 17 cells boosted by a polymorphic interleukin 23 circuitry would be the main effectors of this chain. Inflammatory bowel disease-like pictures would derive from inborn errors of the immune response causing undue inflammation home to the gut. Monogenic IBD belong to this subset, and are of specific pediatric interest. Psoriasis, chronic obstructive pulmonary disease, and IBD are all inflammatory disorders of the barrier organs: skin, lungs, and gut. The demonstration that specific antigen hyper- or hyporesponsiveness raised at any of the three districts can modulate the response of the other two sites, has led to the innovative concept of a system-wide mucosal immunological organ. An improved knowledge of these entities has not only a speculative importance, but can also bear a clinical impact, insofar as the extra-intestinal manifestations prove often more disabling than the underlying IBD itself.

Key words: Arthritis – Cholangitis – Microbiota - Erythema nodosum - Pyoderma - Uveitis

Introduction

The inflammatory bowel diseases (IBD) (ulcerative colitis and Crohn's disease) present in Italy and in the rest of the Western World with a prevalence reported between 180 and 300 cases/10^5 and are on the rise in emerging countries.[1] Pharmacological disease control is still far from perfect,[2-5] partly reflecting our limited understanding of the pathogenesis of the disease, and its complex phenotypic presentation.[6] A few years ago, we delineated the concept that, despite an inflammatory core centered on the gut, the IBDs include a crucial intertwining of circuits and relevant organ damage that can take place beyond the bowel boundaries.[7] More recently, we have elaborated on the concept of IBD-like syndrome, and examined the factors, either accompanying or causative, that may play a role.[8]

The envisaging of IBD as a systemic disease has now been fostered by a group examining the extra-intestinal manifestations (EIM) of IBD.[9] We based on the contents of this review, and those of a previous one,[10] to reappraise such challenging matters.

Materials and Methods

Data Acquisition

To identify all appropriate publications, a PUBMED search of all studies published from 1965 to 2019 was conducted. The final date was March 16, 2019. The following medical subject headings were used and combined: Inflammatory bowel disease, IBD, Crohn's disease, ulcerative colitis, arthritis, cholangitis, microbiota, psoriasis, erythema nodosum, pyoderma, uveitis, chronic obstructive pulmonary disease (COPD), amyotropic neuralgia, hidradenitis suppurativa, innate immunity, adaptive immunity, Signal Transduction and Activation of Transcription (STATs), X-linked apoptosis inhibitor (XIAP), Protease a disintegrin and metalloproteinase (ADAM) 17.

The search was also performed using reference lists from published articles. The titles of these publications and their abstracts were scanned in order to eliminate duplicates and irrelevant articles.

We evaluated literature data on the basis of the classification of the IBD-associated EIM, as exemplified below.

1) *Classically named EIM*

a) Rheumatologic phenomena (grossly divided in axial *versus* peripheral);

b) eye phenomena (e.g., uveitis);

c) liver/biliary tree pathology (e.g., cholangitis);

d) skin manifestation: erythema nodosum, pyoderma;

e) rare phenomena: e.g., hidradenitis suppurativa, amyotrophic neuralgia and others.

2) Major accompanying pathologies

a) Pathology inscribing an IBD-like phenomenon:

- innate immunity;

- adaptive immunity;

- key molecule clusters: STATs, XIAP, ADAM 17.

b) Contiguous pathology (affecting functionally related systems):

- psoriasis (skin dysfunction);
- COPD.

Results

The classically defined phenomena enumerated in (1) (conventional EIM) are often tentatively understood under a common comprehensive hypothesis. It is envisaged that the gastrointestinal

mucosa can initiate immune responses at extra-intestinal sites because of the existence of shared epitopes between luminal and extra-luminal antigens in the presence of a favoring genetic tendency.[11-13] The emphasis recently placed on gut microbiota and their role in homeostasis has further enriched this mind frame: indeed, Toll-like receptors (TLR) are known to correctly effect innate immune responses in the presence of correctly working microbiota; disturbing microbiota composition or function can lead to wrong TLR signaling, undue inflammation, and, among others, arising of any EIM.[14] We now proceed by examining the updated theories on the pathogenesis of the conventional EIM as listed in 1).

1) Classically named EIM

The rheumatologic phenomena

Occurring in approximately 20 to 30% of patients with no gender differences,[15] joint manifestations are the most common EIMs in IBD patients. Peripheral arthropathy and axial arthropathy are included in this category. The former is further divided in type 1 or type 2 according as to whether less or more than 5 joints are respectively involved.[10] Recent attempts to clarify the pathogenesis of these entities have led to the conceptualization of a "gut-synovium axis"[16] for which some notions on the physiologic and pathophysiologic working of T helper (Th)17 cells is essential.

Similarly to Th1, Th2, and FoxP3+, also Th17 cells[17] derive from naïve T-cells in secondary lymphoid tissues in response to antigen presentation. Characteristically expressing interleukin (IL)-17A, IL-17F, IL-21, and IL-22, Th17 lymphocytes have long been thought to exert a primary line of defense against various invaders, including viruses and fungi; in the absence of any infection, their primary migration site is the intestine.[18] However, it has become evident that Th17 cells do express certain trafficking receptors to migrate specifically to target tissue sites, including the synovial structures that are our topic at this point. The story began with the observation that Th17 cells can induce bone destruction in autoimmune arthritis by acting as an osteoclastogenic helper T-cell subset.[19] The presence of the chemokine receptor 6 (CCR6) receptor has proven central to this Th17 cell

function. Indeed, CCR6 has shown preponderant affinity for the chemokine (C-C motif) ligand 20 (CCL20).[20] Highly expressed on the synovial cells of arthritic joints, CCL20 can thus be interpreted as the receptor substrate underlying the osteoclastogenic potential of Th17 cells: injection of anti-CCR6 abolished experimental autoimmune arthritis in animal models.[20] The Th17 loops are under the strong influence of IL-23 and its polymorphism.[21]

Besides this general template, several working hypotheses have been proposed.

a) A leaky intestinal barrier may initiate a response against luminal bacteria with release of inflammatory mediators.[22]

b) Pathology is triggered by adhesion of intestinal lymphocytes to synovial blood vessels, mediated by the action of vascular adhesion protein (VAP)-1, a cell-surface expressed oxidase.[23,24] This hypothesis centers on the facilitating roles of abnormal human leukocyte antigen (HLA) loci (B35 and/or B44).[25]

c) Role of polymorphisms. Polymorphic caspase activation and recruitment domains (CARD) and nucleotide-binding oligomerization domain (NOD) could affect wrong responses to bacterial agents and systemic repercussion;[26] a Th17 mediated inflammation fueled by polymorphism of IL-23 has been indicated as relevant in the genesis of ankylosing spondylitis.[27,28] These data are supported by the efficacy of an anti-IL23 drug (ustekinumab) both in IBD and in psoriatic arthritis.[29]

Eye phenomena

Their reported prevalence has varied between 1.1 and 10%.[30] It is thought that HLA specifity variants may play a major role in the pathogenesis: the genetic propensity could then overlap with a diminished intestinal barrier for an environmental trigger to induce T-cell activation and clinical disease. Most investigators' attention has focused on the role of HLA B27. [31] Its association with uveitis and entero-hepatic arthropathy could interestingly justify the frequent finding of associated ocular manifestations and joint involvement in many IBD cases.[32]

Liver/biliary tree

The epidemiological importance of this association is underscored by the finding of abnormal liver function tests in up to 1/3 of IBD patients.[10] Primary sclerosing cholangitis (PSC) is the most feared manifestation of this dangerous gut/liver axis.[33] It is characterized by chronic inflammation, strictures in intra- and more often extra-hepatic ducts; unfortunately, there is not yet a medical treatment able to prevent or modify the natural history towards liver cirrhosis and failure, so orthotopic liver transplantation is the only viable solution for patients presenting with advanced disease.[34] Autoimmune factors are commonly invoked, including the well-known serologic markers p-antineutrophil cytoplasmic antibodies (ANCA), antinuclear antibodies (ANA), anti-smooth muscle antibody (ASMA).[35] A genetic predisposition to PSC is highlighted by the frequent detection of HLA-B8 and HLA-DRB1 specificities.[36] Pathogenetic theories do not fail to emphasize the hypothetic role of a response to a bacterial contamination of biliary tree.[37] Patients with Crohn's disease and abnormal liver function tests but without PSC or autoimmune hepatitis do not have higher risks of liver disease progression (hence, significant fibrosis[38]) than the general population.[39,40]

Skin manifestations

This category traditionally includes erythema nodosum and pyoderma (Figure 1), and may affect 1-15% of all IBD patients.[41] A very popular hypothesis holds that a cross response may take place to antigens that are shared between the gut flora and the skin. This would evolve into a hypersensitivity reaction with immune complexes forming in blood vessels adjacent to subcutaneous fat.[42] In the case of pyoderma investigators stress a heightened expression of pro-inflammatory cytokines: IL8, IL16, IL17, tumor necrosis factor (TNF)-alpha.[43] As usual, the influence of a permissive HLA expression is invoked: B15 has been associated to development of erythema nodosum;[44] TRAF3IP2 an intermediate of the inflammatory response and possibly a driver of IL17, has been summoned for both erythema and pyoderma.[45] Unfortunately, a drug acting specifically against IL17 resulted

efficacious against rheumatic and cutaneous inflammatory disorders, but a trigger for IBD reaction and new-onset.[46]

Rare phenomena

Rarely, IBD may be accompanied by unusual manifestations involving various organs. We hereby include an arbitrary selection of these events.

a) Hidradenitis suppurativa

This co-morbidity has recently been exhaustively reviewed. Publication of the first case series dates back to 1993. Pooled analysis of four studies indicates a prevalence of 12.8%; Crohn's diseases, female gender, and tobacco addiction seem to be risk factors. Anomalies of the TLR and NOD innate immune responses are suspected to play a favoring role. The frequent finding of *Staphylococcus aureus* in the lesions may be a witness of these hints. Hidradenitis suppurativa seems to respond to the same immune modulatory drugs (including anti-TNF molecules) as the underlying IBD.[47]

b) Parsonage-Turner (PT) syndrome (amyotrophic neuralgia)

PT patients experience sudden violent pain of girdle muscles, followed by profound motor weakness, and muscle atrophy.[48] A hereditary (often bilateral) form and an idiopathic presentation have both been described.[49] Interestingly, the literature lists only two cases of PT as a comorbidity of IBD. The first one dates back to 2014.[50] The second one, included in our out-patient series,[30] reports a middle-aged woman presenting with bilateral PT that flared synchronously with a pancolitis. Again, simple coincidence must be excluded; however, this disabling disorder calls for neurologists to be included in the list of IBD caretakers.

c) Posterior segment ophthalmic manifestations

Posterior segment manifestations are not usually described. The recent literature describes a 28-yr old female patient who underwent resection for Crohn-induced bowel stenosis.[51] Owing to significant loss of visual acuity, she underwent complete diagnostic work-up. The results led to diagnose severe ischemic retinopathy secondary to Crohn's disease. In the discussion

the authors emphasized that an ileal or ileo-colonic localization, and presence of another co-morbidity (e.g., arthralgia) may effect a 33% increment of the risk of ocular involvement.

d) Bilateral Achilles tendinitis

The recent literature reports on a single case of bilateral Achilles tendinitis coincidental with active ulcerative colitis. This 26 yr old female, presenting with active disease deserving 9 marks of the Lichtiger score, responded to mesalamine; the bilateral tendinitis followed clinical remission from her IBD. Though simple coincidence could not be excluded, the authors purport that this instance can correctly be added to the list of the IBD dependent EIM.[52]

e) Pancreatitis

Patients with Crohn's disease, specifically if females, are reportedly at a four-fold risk of experiencing acute pancreatitis.[53] Reasonable causative factors include gallstones and drugs. The latter may most often include mesalamines and thiopurines.[54,55] Whether acute pancreatitis has to be classified as a true EIM is a matter for debate. Type 2 autoimmune pancreatitis may be co-morbid of UC; yet the type 1 variant, with its IgG4 excess seems not to associate preferentially with either IBD. Recent evidence from cellular studies would favor the EIM bias: T-cells bearing receptors for mucin-1 (the composition of which is abnormal in IBD) have been documented to migrate to both gut and pancreas.[56]

f) Cogan's syndrome

This syndrome, first described in 4 cases by D. Cogan,[57] is nowadays understood as a vasculitis. In its typical presentation, the patient experiences the abrupt onset of audio-vestibular symptoms including vertigo and tinnitus. Deafness may ensue with any delay. Within any interval, even of years, ocular symptoms may then develop with interstitial keratitis. Lack of the latter justifies identification of a so-called atypical Cogan. Prompt diagnosis of Cogan's syndrome may not be within the reach of any physician; irrespective of the time lag with which the correct diagnosis is made, Cogan's syndrome often takes to

deafness. Most cases are bilateral, though cases of monolateral Cogan's syndrome have been claimed. The literature reports some 200 cases, with less than 20 being associated to an IBD.[58] We have recently followed a young male patient, with a Crohn's history in siblings, who presented with acute vestibular syndrome in 1999 on top of aggressive Crohn's invading esophagus and stomach. He responded to high-dose steroids and then received maintenance with thiopurines. In these days, the patient's Crohn's disease is in remission on thiopurines; monolateral deafness and tinnitus have required an audio-therapeutic device; no keratitis has appeared yet.

2)Major accompanying pathologies

Regarding major accompanying pathologies, in the last decade, we have begun to appreciate that a deal of effector immunologic circuitry is taking place beyond the bowel borders; while gut-generated events may hit locations afar (the EIM above are an example), systems afar, often entailing innate and acquired immunity, may generate inner gut pathology, allowing a sort of bi-directional traffic. The result of the latter events is often an IBD-like pathology that is indistinguishable from genuine IBD,[59] but, specifically if aroused by anomaly of a non-redundant yet vital cell function, may prove life threatening in the pediatric life phase (monogenic IBD).[60,61] We have recently compiled a review of these conditions,[8] here we limit ourselves to an arbitrarily selected presentation.

Pathology inscribing an IBD-like phenomenon

a) X-linked apoptosis inhibitor

Apoptosis is a crucial cell homeostasis regulator, under the opposing influences of pro- and anti-apoptotic signaling molecules.[62] Overexpression of anti-apoptotic signaling may be at the basis of both some cancers and severe inflammatory disorders. All anti-apoptotic molecules share the ability to bind caspases through baculovirus IAP repeat domains (BIR).[63] The family

of the XIAP is the most potent and best studied: it effectively neutralizes caspases 3, 7, and 9. XIAP invariably leads to a key triad of clinically severe manifestations: sensitivity to Epstein-Barr virus induced histiocytosis, recurrent splenomegaly, and IBD.[64] Few pediatric cases of XIAP malfunction have recently been published. Genetic analysis of the first one revealed a G to A substitution at a highly conserved position causing a cysteine to tyrosine switch on the XIAP molecule; this child underwent eventual progenitor cell transplant with immediate response,[65] like another similar case.[66] Differently, another cases[67,68] did not undergo bone marrow cell replacement, ran a rocky course, and at least one is now dealing with unchecked fistulizing Crohn's disease.

b) The signal transduction and activation of transcription

They are a family of mediators of cell signaling during immune responses, with their intact action depending on the protein family Janus kinase (JAK), which can activate specific STATs to downstream signaling.[69] Studies in animal models[70] have shown that loss of STAT function: (a) favors chronic enterocolitis; (b) increases sensitivity to apoptosis, impairs wound healing, increases sensitivity to endotoxin. An intact STAT signaling through the IL10R is necessary to prevent such changes. The consanguineous members of two unrelated families have recently been diagnosed with incurable skin and respiratory infections: documentation of loss-of-function mutation of IL10R disclosed the cause of the life-threatening disorder and indicated successful bone marrow replacement.[71] JAK inhibitors, in the form of oral small molecules, are new drugs recently revenue available in the therapeutic armamentarium for ulcerative colitis.[72]

c) Protease a disintegrin and metalloproteinase-17

It is a disintegrin metalloprotease capable to cleave TNF, L-selectin, and epidermal growth factor receptor (EGFR) ligands from plasma membranes: when up-regulated, ADAM-17 can control cancer and inflammation.[73] The multiplex dysfunctions of three children born to consanguineous parents have recently been described and attributed to failure to activate

STAT3 via a normally shed EGFR (consequence of lacking ADAM-17). The multiple skin, hair, and gut lesions of these subjects responded to treatment and were compatible with a nearly normal life.[74] Incidentally, these findings discourage a strategy of abolishing ADAM-17 to treat inflammatory disease suspected to be due to excess TNF release.

The reader is referred to our review for an exhaustive coverage of this topic.[75]

Contiguous pathology (affecting functionally related systems)

Psoriasis

If psoriasis is a peculiar inflammatory dysfunction of the skin as a barrier organ, it cannot be described without IBD in mind. Clinical, pathogenetic, and genetic observations contribute to pose the two affections in contiguity: 1) Psoriasis is seven times more common in Crohn's disease patients than controls; 2) ten percent of Crohn's disease patients have first-degree relatives with psoriasis; 3) both disorders do respond to the T-lymphocyte modulator drug cyclosporine,[76] to methotrexate,[77] anti-TNF inhibitors,[77] anti-IL-12/23 ustekinumab.[29] Modern theories on the pathogenesis of psoriasis do no longer speculate on autoimmunity, but emphasize the role of a malfunctioning innate immunity combined with variations of skin microbiota. Of the four most studied peptidoglycan recognition proteins, the genes of two of them (peptidoglycan recognition proteins [PGRP]-3 and PGRP-4) on chromosome 1q show polymorphism in psoriasis.[78,79] Such theory could not be viable without stressing the role of skin microbiota.[80] Indeed, it is now appreciated that microbiota species variation can modify the psoriatic phenotype (e.g. guttate psoriasis seems to be connected with presence of *Streptococci* in the throat) and the localization of the plaques.[81] Not only can the microbiota phylum with its specific immune reaction modify local skin conditions, but also remote immunity, e.g. lung immunity can be influenced by skin inflammatory events as driven by resident microbiota.[82] This may serve as an introduction to the next paragraph on gut-lung dialogue.

The dialogue between gut and lung (COPD)

Gut and lung share anatomic and embryonic commonalities. These materialize at various levels, as detailed below.

a) Clinics

The IBDs may exhibit subclinical lung involvement detectable as bronchial hyper-reactivity in 48% and 71% respectively of adult and pediatric patients.[83] IBD patients are at an increased risk for COPD,[84] COPD develops independently from smoking habits;[85] COPD patients have recently been shown to carry a mutated NOD gene, in analogy with the IBDs.[86]

Furthermore, granulomatous and interstitial lung disease are rare respiratory disorders that have been associated with IBD, that require hospitalisation and systemic steroids. In a recent case series half of cases were drug-related but there was no signal of relationship between IBD therapy and the onset of interstitial lung disease.[87] More studies are needed to investigate the pathogenesis and causative association.

b) Immunology (vaccination studies)

Diet fibers in the gut can regulate lung immune responses.[88] Asthmatics may have allergic lung disease with high eosinophil numbers, these cells utilizing the same syalomucin CD34 to enter gut and lung.[89] Gut challenge with a given antigen may protect from future airway disease.[90] Maneuvers of mouth–driven desensitization can downregulate Th2 responses at lung level.[91]

c) Microbiota

A diminished microbiota diversity (such as in inflammatory gut disorder) reduces availability of short chain fatty acids, hence produces poor shaping of lung immune environment.[92] TLR-like responses need normal gut microbiota to respond to ligands.[93] Wrongly gut-initiated TLR signaling induces abnormal inflammatory lung responses.

d) Candidate mediator molecules

The thymic stromal lymphopoietin protein (TSLP)[94] (constitutively expressed by intestinal epithelial cells) can regulate responses at body interface (mucosae-skin-ocular tissues) to Th2-driven allergic responses.[95]

The bulk of this evidence speaks in favor of a system-wide mucosal immunological organ.

Discussion

Current knowledge and understanding holds the gut as the prototype barrier organ wherein the dialogue with the "outside" is finely handled in a swing between inflammation (active defense) and tolerance (preservation of integrity).[96] The data compiled above, though arbitrarily selected and partial, indicate that the gut, and particularly the colon, are constitutively the objects and the drivers of bidirectional dynamics whereby inner phenomena may materialize at the periphery (the EIM are an example), and conditions afar may perturb the inner events and create disease (e.g., genetic variants).

Specifically, the IBD-associated EIM mainly recognize the following mechanisms:

1) an increased colon permeability with massive antigen release to the periphery;
2) maturation of bone-destructive Th17 cells;
3) systemic effects of microbiome;
4) generalized modulation of mucosal response (gut-lung axis).

Correct recognition of these complications may help the internist to suspect IBD disguising under an unusual EIM, and the IBD caretaker to decide to call on a second line other specialists to best help the patient. This is so important, inasmuch as often the EIMs are more threatening or disabling than the underlying IBD itself.

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