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REVIEW ARTICLE

Pathogenesis of Crohn's Disease

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ABSTRACT

There was a time when "pathogenesis" meant the genesis of the pathology, patho plus genesis. Today, however, the word is used to introduce topics such as immunodysregulation, alterations in the microbiome, or an imbalance of the two, some sort of disconnect between the patient's flora and the immune system of the gastrointestinal tract. Pathogenesis, pathophysiology, and etiopathogenesis seem to be buzzwords, introduced to catch the eye of the reader or the editor. Few who use those words have seen any "pathology" since second year medical school, or perhaps they have viewed biopsies of the surface but not cut sections of resection specimens. Dalziel was the first to describe Crohn's disease. Pathologists, or groups of pathologists, elucidated the pathogenesis, often referring to the granulomas, the obstructed lymphatics of the wall and the edema. Dalziel called this disease "chronic interstitial enteritis". Those writing about microflora, immune dysregulation, cytokine cascades, fibrosis, and mouse models would do well to study the early pathology that is the essence of Crohn's disease.

Keywords: Dalziel's Disease, Crohn's disease, Regional enteritis, Lymphatics, Elephantiasis, Early Pathology

Introduction

This paper aims to give insight into how "pathogenesis" should be approached by contemporary clinical scientists and research investigators.

Pathogenesis, pathogenesis, pathogenesis. It seems today that every resident or fellow asked to write a review on Crohn's disease starts with the word "pathogenesis". That'll catch the reader's eye. Then they espouse their line of research, one known to them, i.e., genetics, the microbiome, immunology, cytokines, fibrosis, etc. There was a time when "pathogenesis" meant sequential steps in the anatomic alterations that lead to an end point, i.e., a disease, a disease characterized by symptoms, diagnostic tests or lab values. For example, a foreign body elicits granulocytes, followed by lymphocytes, granuloma cells, fibrosis, and encapsulation or resolution. Now however, "pathogenesis", in the minds of many, equals physiologic or biochemical changes that result in disease.

Pathogenesis in accordance with early researchers

Every scientist who intends to write about "pathogenesis" should be required to understand and appreciate the pathology, i.e., the morphologic alterations that progress over time. Every resident or fellow contemplating writing about microflora, immunodeficiency or dysregulation, or genetic alterations should be required to read the works of individuals who came before them, those who described the disease, starting with Dalziel's description in 1913[1] and including Warren and Sommers' work on the pathology of 120 patients[2] or Van Patter's, who did 34[3,4]. A thorough reading of the works of those who devoted years to understanding "pathogenesis" is warranted[5]. Contemporary scientists are of the opinion that cytokine cascades represent pathogenesis. Or that dysregulated immune responses equal pathogenesis. But opinions represent hypotheses, hypotheses often not correlated with the morphologic alterations. Explain, for example, how the ulcers form, the fistulas, the granulomas, the obstructed lymphatics. How does "dysregulated cross-talk between commensal microflora and the gut mucosal-associated immune system"[6] lead to lymphatic obstruction, to the histopathology?

The essence and pathology of Crohn's disease

We've all been indoctrinated to the fact, or premise, that gastrointestinal pathogens damage the intestinal surface. Think *Escherichia coli*, salmonella, shigella, clostridia, rotavirus, giardia, cryptosporidia, entamoeba, coccidia[7]. One can visualize the damage, either see the attached organisms or recognize the effects of their exo or endotoxins. The surface takes a beating, e.g. sloughed necrotic epithelium, damaged and distorted villi, pseudomembranes, and ulceration. So, it is no wonder that gastroenterologists would look at Crohn's disease for some agent that enters orally and invades and traumatizes the surface. Perhaps no bacteriology or pathology course teaches about an enteritis that is centered in the

tissues deep to the epithelium, the interstitium, the lymphatics. Dalziel called this disease a chronic interstitial enteritis[1], and Warren and Sommers followed suit with cicatrizing enteritis[2]. The latter authors recognized that the essence of the disease was elephantiasis. Edema has been recognized by many. But gastroenterologists remain fixated on the surface—they get to see the surface damage endoscopically. Few gastroenterologists elect to see the pathology of the resections –they never sit with a pathologist to view the interstitial nature of the disease. They may see the biopsies of surface changes, but seldom see the interstitial edema and obstructed lymphatics, certainly not as shown by immunohistochemistry(IHC)[8]. Who does IHC with D2-40 antibody routinely?

Clinical persons have in their mind's eye the healing of the surface but fail to recognize the corruption in the wall –features that don't resolve even when the surface and aphthous ulcers are healed (at least healed temporarily). They know Crohn's disease very well because they see patients every day; however, they lack understanding of the essence of the disease. Irrespective of computed tomography and ultrasound, they don't know the damaged gut of which they speak or write. They need to study the works of early pathologists[9-14], and then, and only then, explain how genetics yields lesions, how immune dysregulation yields lesions; how deranged flora yield lesions. If you believe genetic immune deficiency is responsible for Crohn's disease, why doesn't it occur shortly after birth rather than during late teenage or early adult life? If you believe a compromised or dysregulated immune system is responsible for Crohn's disease, why doesn't the inflammation extend orally, to engulf the entire intestine? How do microbial, immunologic and/or cytokine processes selectively cause damage of a segment of small intestine with sharp demarcations? How do proposed mechanisms single out 10 or 30 cm of ileum and spare all the remainder?

Lymphatic damage is fundamental to Crohn's disease

That the lymphatics are damaged is not speculation, not hypothetical[15,16]. Employing immunohistochemistry, it is clear that the earliest lesion in Crohn's disease is lymphatic obstruction (Figure 1)[16], then edema, then disruption of the mucosa, followed by ulceration or fistulas or both. Of course there are changes in mucosal integrity and cytokine and lymphocyte responses. What else would one expect from a mucosa that is swollen with edema and that cannot eliminate invasive bacteria, bacterial byproducts and the products of tissue necrosis?

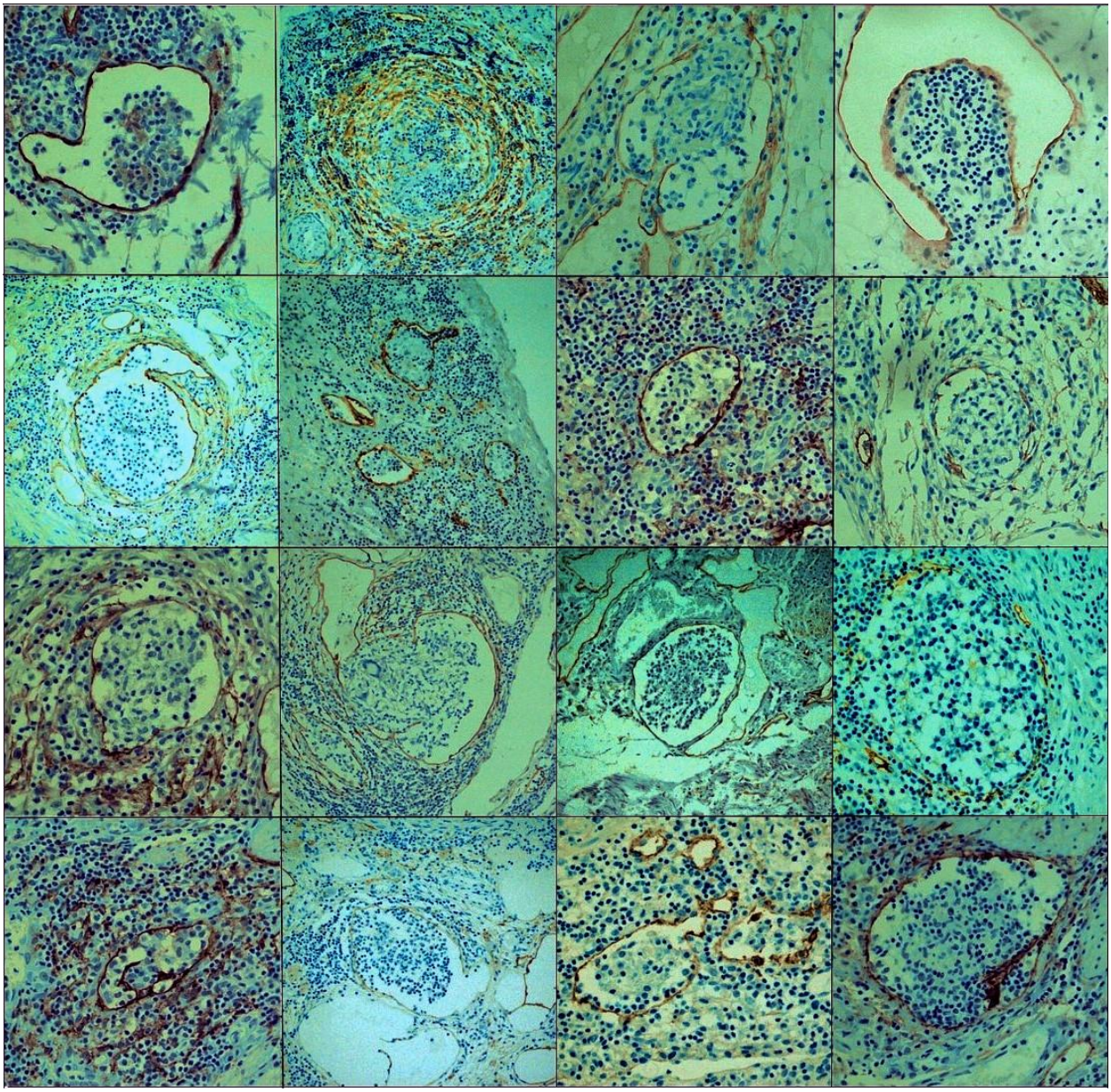

Figure 1. A montage of obstructed lymphatics, from resection specimens of patients with Crohn's disease. Some stained with hematoxylin and eosin, others immunolabeled with D2-40 antibody to demonstrate lymphatic endothelium. Original magnifications 200 or 400X. (First published in reference 16.)

Important features that constitute a pathogenesis worth study in Crohn's disease.

It is admirable that researchers can create mouse models with intestinal inflammation[17], however, there is need for models that have compromised intestinal lymphatics, lymphangiectasia, and compromised lymph removal. There is a chlamydial infection pig model that has damaged intestinal lymphatics, with endolymphatic granulomas and perilymphangitis[18], all features that would provide a pathogenesis worth study.

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Conflict of Interest Statement

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