Crohn’s disease – The pathogenesis of a granulomatous vasculitis: A hypothesis

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Crohn’s disease, considered by many authorities to be a disease primarily of the intestinal mucosa (1,2) is characterized both histologically and immunologically by a cell-mediated immune response to an unidentified antigen(s) (3).

In 1987, based upon macroscopic similarities between rejecting experimental intestinal allografts and Crohn’s disease, the hypothesis was formulated that common pathogenetic factors may be operating in these two otherwise distinct disease entities. In allograft rejection, microvascular activation and injury are early events, initiated by host immune recognition of alloantigen on graft vascular endothelium (4). In Crohn’s disease there are clues to suggest that microvascular injury may be involved in the pathogenesis of intestinal inflammation: in biopsies of patients with inflammatory bowel disease, mucosal capillary thrombi can be seen (5) and vasculitis, including granulomatous vasculitis, is a recognized feature of Crohn’s disease (6,7). Regarded previously as a secondary phenomenon, however, vasculitis was seen only occasionally in routinely processed histological sections and was considered to be of little pathological significance (6,7). Parallel to this apparent dismissal of the potential significance of granu-
Granulomatous vasculitis in Crohn’s disease was a disregard, with notable exceptions (8,9), for the tissue origins of the granuloma, an early and hallmark lesion of this condition. The granuloma represents a localizing reaction to persistent and potentially causative antigen. Therefore, the tissue relationships of this lesion assumed great importance in progressing understanding of Crohn’s disease.

**GRANULOMATOUS VASCULITIS IN CROHN’S DISEASE**

Based on the hypothesis that foci of both granulomatous and lymphocytic vasculitis in Crohn’s disease evolved from blood vessels that contained foreign antigen, clarifying the interrelationship of these two tissue elements was a priority. This was aided by overcoming vascular artefacts produced by routine immersion-fixation of tissues, and immunostaining for specific vascular and granulomatous elements in tissue sections (10,11).

Perfusion-fixation at mean arterial pressure not only produced excellent tissue preservation, but also prevented vascular collapse and blood clots obscuring the relationship of blood vessels to foci of inflammation. Immunostaining for vascular elements and macrophages on serial sections showed that the majority of granulomas in Crohn’s disease arise from blood vessels – predominantly thin-walled veins. This process is associated with thrombosis, vascular occlusion and likely ischemia of the dependent tissues (Figures 1,2). The author and colleagues have since shown that vasculitis and a chronic ischemic injury of the intestine may help to explain many of the idiosyncrasies of this condition, including ‘skip’ lesions and transmural inflammation (12,13), aphthoid ulceration (14), anastomotic recurrence (15) and thrombogenesis (unpublished data,16-18).

Of greater importance, perhaps, was...
the observation that many granulomas were associated intimately with pathologically altered endothelium. In view of the capacity of activated endothelium to present antigen in association with class II determinants (19), the hypothesis that the mesenteric microvascular endothelium is a reservoir for the persistent antigen that induces Crohn's disease seemed increasingly attractive. The hypothesis did not maintain that the vasculature, or indeed the endothelium, was the only site of primary antigen presentation. These elements did, however, provide a target for further detailed studies.

MEASLES VIRUS AND MICROVASCULAR ENDOTHELIUM

The hypothesis proposed that persistent viral infection of the mesenteric endothelium is necessary for the development of Crohn's disease. Certain criteria were considered in the selection of candidate viruses for further study:

REFERENCES