Invited lecture (1):

Pathology of Inflammatory Bowel Disease

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Invitation

In this lecture I will confine any remarks to a summary of the salient features of the microscopic pathology of Crohn's disease, the histology of the earliest lesions and the value of granuloma counts. Some aspects of the differential diagnosis from tuberculous, ulcerative colitis and ischaemic bowel disease will also be considered.

Microscopic diagnosis of Crohn's disease

The most valuable diagnostic feature is the presence of a sarcoid or tuberculoid reaction in the affected tissues and the regional glands. This sarcoid reaction is essentially the same as the tissue response in sarcoidosis, non-caseating tuberculosis and beryllium poisoning, for example, except that the "granulomas", as they are sometimes called, tend to be smaller and fewer in Crohn's disease. In the context of inflammatory bowel conditions in Europe and North America, Crohn's disease is by far the commonest cause of a sarcoid reaction. The latter is present in about 50-70% of all cases. Large numbers of granulomas are found in some specimens while in others they can be so few as to escape detection except by the examination of many microscopic sections.

Early Crohn's disease

The earliest macroscopic sign is probably the type of ulceration described as "aphthoid". The resemblance to aphthoid ulceration of the mouth may not be entirely irrelevant as far as pathogenesis is concerned. Such tiny ulcers can be found in mucous membrane at a distance from more obviously diseased mucosa. They vary in size from tiny, pinpoint lesions with a haemorrhagic appearance, to small, clearly defined, shallow ulcers with a white base. If surgical specimens of Crohn's disease are not carefully prepared for macroscopic observation these small lesions may be missed. They are sometimes detected close to the limit of excision of resected specimens of gut and if left behind by the surgeon they may well be the pathological basis for recurrent disease. Experience suggests that these early lesions take many years to progress to a state of sufficient structural damage to give rise to detectable clinical or radiological signs. Sigmoidoscopists occasionally observe these tiny ulcers in the rectum in patients who have classical disease of the terminal ileum.

Histology of early Crohn's disease

The hyperplasia of lymphadenoid tissue and the obstructive lymphoedema which largely contribute to the widened submucosa have been noted by a number of authors and it has been suggested that the earliest lesions of Crohn's disease are in the lymphoid follicles and Peyer's patches of the gastrointestinal mucous membrane. These undergo hyperplasia followed by ulceration. Moreover,
fissures probably begin in the mucous membrane at the site of lymphoid aggregates. It has been stated that ulceration in Crohn's disease is preceded by a focal accumulation of lymphocytes in the basal part of the mucous membrane and this is followed by degeneration of the tubular epithelium. It is well known that the granulomas of Crohn's disease have a close histological relationship in lymphatic channels in the bowel wall. Moreover, the presence of granulomas in the regional lymph nodes is likely to be significant in the pathogenesis. For all these reasons it has been suggested that Crohn's disease is essentially a disorder of the lymphoid tissue of the gastrointestinal tract. The frequency with which the terminal ileum and anal region are involved could be explained by the fact that both regions are normally rich in lymphoid aggregations.

Microscopic examined of the "aphthoid" ulcers mentioned previously as a macroscopic sign of early Crohn's disease suggests that many of them are enlarged lymphoid follicles with ulceration of the overlying epithelium. Others could just be foci of lymphocytic infiltration arising independently. Sometimes typical granulomas are found in these early lesions which suggests that they can be a feature present during the entire natural history of the disease and are not just the result of a long-standing inflammatory process. It could be argued that the earliest histological lesions of Crohn's disease are, in the first place, small foci of mucosal inflammation which are caused by the passage of particulate matter from the bowel lumen into the lymphoid tissue of a part of the gastrointestinal tract. The nature of this particulate matter could be viral, bacterial or some chemical agent and perhaps this will be first demonstrated in the contents of the intestine rather than within the tissues of the bowel wall.

Healed lesions in Crohn's disease

Evidence suggesting that the inflammatory process of Crohn's disease may undergo spontaneous resolution is occasionally seen. One well-documented case of "burnt-out" disease has been reported. Microscopically, ulceration is absent although evidence of former disease may be apparent from patchy mucosal atrophy and fibrosis of the muscularis mucosae. There is no oedema or inflammatory infiltrate, but an excess of fibrous tissue in all layers of the bowel wall with scattered aggregations of lymphoid tissue. The granulomas undergo hyalinization and atrophy similar to that seen in tuberculosis and sarcoidosis, but without calcification.

Granuloma counts

The number of granulomas in sections of bowel involved by Crohn's disease has been counted and related to length of previous history, treatment with steroids, site of involvement, and the subsequent course of the disease. It was found that a high content of granulomas predicted a good prognosis in the large bowel and anus, but was of no prognostic significance in the small bowel. A large regional variation in granuloma counts was observed from an average of 1 per section in the small bowel to 6 in the colon, 18 in the rectum, and 36 in the anus. Those patients with a long clinical history showed a low granuloma content. The findings are consistent with the view that the granuloma represents an adaptive mechanism for the removal or localisation of the causative agent of Crohn's disease.

Tuberculosis

It has been stated that Crohn's disease can affect any part of the gastrointestinal tract from the stomach to the anus inclusive. The same is true of chronic tuberculosis. Both disorders are most frequently found in the terminal ileum and ileocaecal region. But whereas large bowel Crohn's disease seems to be relatively common, it is rare for tuberculosis to be seen in the colon or rectum. This is also true of those countries, such as India, where the incidence of intestinal tuberculosis is still high.

In those cases of Crohn's disease in which there is a florid "sarcoid" or "tuberculoid" tissue response, it may be impossible to make a distinction from tuberculosis on histological evidence alone. In such cases reliance has to be placed on clinical evidence (including the racial origin of the patient), chest radiographs and attempts to culture the tubercle bacillus. The Mantoux Test can also be useful, particularly if it is negative. In Britain and North America intestinal tuberculosis is rare and is mostly seen in association with a pulmonary lesion. The same applies to tuberculous anal fistula. It seems that acute