Whipple's disease with minimal intestinal involvement

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SUMMARY An uncharacteristic case of Whipple's disease is reported, in which, although overt intestinal involvement was absent, and there was only a patchy histological lesion, the diagnosis was confirmed by electron-microscopic examination of peroral intestinal biopsies.

The small intestine is characteristically involved in Whipple's disease, and biopsy of the intestinal mucosa is the standard method for diagnosis (Maizel et al., 1970; Trier, 1973). However, in some cases signs and symptoms referable to the gastrointestinal tract are either absent or appear late in the course of the disease, and involvement of the central nervous system, joints or lymphatic system, or simply fever, may be the major clinical manifestations (Hargrove et al., 1960; Lampert et al., 1962). We are reporting the gastroenterological aspects of an unusual case of Whipple's disease, in which, despite the absence of overt intestinal involvement, and with only a patchy histological lesion, the diagnosis was confirmed by electron-microscopic examination of peroral intestinal biopsies. The involvement of the central nervous system and the rheumatological aspects of this case are being reported elsewhere (Rubinow et al., 1976).

Case history

A 46 year old white man was admitted to the Boston Veterans Administration Hospital for evaluation of progressive dementia of two years' duration. Neurological evaluation revealed dementia, supranuclear ophthalmoplegia, and focal myoclonic seizures. Additionally, he had fever, lymphadenopathy, panhypopituitarism, and arthritis of both knees. Biopsies of both the synovial membrane of the knee, and an axillary lymph node revealed clusters of macrophages which stained positive with the periodic acid-Schiff technique. Gastroenterological investigations were then initiated in order to confirm the diagnosis of Whipple's disease.

The patient appeared to be undernourished, but had neither diarrhoea nor abdominal pain. Serum electrolytes, albumen, proteins, cholesterol, and prothrombin time were normal. Barium contrast examinations of the upper (Fig. 1) and lower gastrointestinal tract were normal. The stool was well formed and showed no excess fat when stained with Sudan III. Urinary excretion of d-xylose in five hours after a 5 g dose was 1·25 g. Histological findings are reported below. The patient was treated

Fig. 1 Barium contrast examination of upper gastrointestinal tract and small intestine. Neither nodules nor thickened folds are demonstrated in the small intestine.
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with penicillin, 1,200,000 units administered parenterally daily for two weeks, and was continued on orally administered penicillin, 800,000 units, daily. He became afebrile, and his arthritis and general physical condition showed objective improvement. He has demonstrated moderate improvement in his mental status, but no significant changes in his ophthalmoplegia and panhypopituitarism since treatment was instituted.

HISTOLOGICAL FINDINGS

Peroral biopsies of the proximal intestinal mucosa at the ligament of Trietz were obtained using a multipurpose suction biopsy tube (Rubin Tube) with a double-port capsule (Brandborg et al., 1959). Two biopsy procedures, each yielding two specimens, were performed one week apart. Portions of each of the four biopsies were prepared for light- and electron-microscopy. Histological sections for light

Fig. 2 (a) Low power photomicrograph of peroral biopsy of small intestinal mucosa. Architecture is normal and the lamina propria contains no PAS positive staining macrophages. PAS, × 100. (b) Higher power photomicrograph of a portion of the companion biopsy to that shown in (a). This focus of macrophages which stain positive with PAS represents the most severe mucosal lesion seen in the two abnormal biopsies. PAS × 200.

Fig. 3 (a) Electron-micrograph of intestinal macrophage which contains bacilli cut in cross- and longitudinal sections. × 3400. (b) Higher power view of intracellular bacilli showing the bacilli in varying degrees of degeneration. × 10,000.
microscopy were stained with either haematoxylin and eosin or with periodic acid-Schiff reagent with haematoxylin counter stain. Specimens prepared for electron-microscopy were fixed in glutaraldehyde, post-fixed with osmium tetroxide embedded in Spurr low viscosity embedding medium, sectioned at 1 μ and stained with toluidine blue for light microscopy. Thin sections were cut, stained with lead citrate and uranyl acetate and examined with a Phillips EM-300 electron microscope.

Two of the biopsies, obtained at separate biopsy procedures, were histologically normal. Neither showed mucosal architectural abnormalities, nor collections of macrophages within the lamina propria (Fig. 2a). In the two companion biopsies, the mucosal architectures were normal in most sections; however, in one biopsy a focus of macrophages containing PAS-positive staining material occurred in the lamina propria (Fig. 2b), and in the other biopsy scattered PAS-positive staining macrophages were found at the base of the crypts.

With electron microscopy, only in sections from one biopsy were macrophages that contained bacilli identified. Bacilli were seen in various cross- and longitudinal sections (Fig. 3, a and b). No organisms were found free within the lamina propria or within the surface epithelium.

Two peroral intestinal biopsies taken four months after treatment was started were normal.

Discussion

It is not unusual for patients with systemic Whipple's disease either to lack intestinal symptoms or have these as a late manifestation of the disease. In reviewing 114 cases with proven intestinal or mesenteric lymph node involvement, Maizel et al. (1970) determined that 5% lacked weight loss, 22% lacked diarrhoea, and 40% lacked abdominal pain. Seven of 53 patients studied (13%) had normal barium contrast examinations of the small intestine. When Whipple's disease involves the central nervous system, the intestine does not appear to be either unusually spared or particularly severely involved (Sieracki et al., 1960; Smith et al., 1965). Lampert et al. (1962) reported a fatal case of Whipple's encephalopathy in which the patient had no diarrhoea but had typical intestinal and mesenteric nodal lesions at necropsy. In a report by Knox et al. (1968), a positive peroral intestinal biopsy established the diagnosis of Whipple's disease in a patient with ocular inflammation and minimal intestinal involvement, and it is possible that early treatment prevented more serious CNS disease. In our case, it appears that the severe CNS manifestations have, at least, not progressed further since treatment was instituted, and it is unlikely that the patient will succumb to his disease.

It is noteworthy in this case that two of four peroral biopsies were histologically normal, and that the companion biopsies showed only minimal, patchy involvement. Moreover, that macrophages which contained bacilli were identified by electron microscopy in one of the biopsies was indeed fortuitous, as these sections were obtained from small random segments of the original biopsies.

The gastroenterological findings in this case may be useful in future evaluations of patients with suspected Whipple's disease. In such cases, even in the absence of intestinal symptoms, steatorrhoea, or abnormal radiographs of the small bowel, peroral intestinal biopsies and examination of serial sections stained by the PAS technique are indicated to attempt to confirm the diagnosis. However, because the intestinal lesion may be minimal or patchy rather than diffuse, several normal biopsies may not necessarily exclude the diagnosis of Whipple's disease, and multiple biopsies may have to be obtained. Additionally, with a minimal intestinal lesion, follow-up biopsies to assess response to treatment may not be helpful because of the chance of taking biopsies from uninvolved areas of the mucosa.

The authors acknowledge the kind assistance of Dr Jerry Trier, Peter Bent Brigham Hospital, Boston, Mass., in reviewing their histological and electron-microscopic material.

References


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Journal of Neuropathology and Experimental Neurology, 19, 70-75.