Granulomatous Encephalitis in Whipple’s Disease

Electron Microscopic Observations

S. S. Schochet, Jr., and P. W. Lampert

Neuropathology Branch, Armed Forces Institute of Pathology and the Veterans Administration Special Reference Laboratory for Pathology at the AFIP, Washington

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Summary. Among the 21 autopsied cases of Whipple’s disease on file at the Armed Forces Institute of Pathology, 4 had neurological symptoms and prominent involvement of the central nervous system. By light microscopy the lesions were composed of nodular aggregates of macrophages having cytoplasm that stained a distinctive pale blue with hematoxylin-eosin and bright red with the periodic acid-Schiff technique. By electron microscopy the cerebral lesions revealed bacilli morphologically identical to and undergoing the same sequence of degenerative changes as those observed in the intestine. The periodic acid-Schiff reaction stains the walls and the capsular material that persists even after intact organisms disappear. These observations further support the infectious nature of Whipple’s disease.

Key-Words: Whipple’s Disease — Granulomatous Encephalitis — Electron Microscopy.

In 1907 Whipple reported a new condition characterized by accumulations of foamy macrophages and lipid deposits in the submucosa of the small intestine and in mesenteric lymph nodes. He termed this condition intestinal lipodystrophy, focusing attention on the prominence of abnormal lipid deposits. Although he was uncertain about the etiology, he did report the presence of rod-shaped organisms in the mesenteric lymph nodes. Subsequently, many more reports were published, establishing that the disease could be diagnosed by the presence of periodic acid-Schiff-positive glycoprotein particles in the foamy macrophages (Black-Schaffner, 1949) and that the condition involves many organs (Upton, 1952; Farnan, 1958; and Siiracki, 1958), including the brain (Siiracki et al., 1960; Krücke and Stochdorph, 1962; Lampert et al., 1962; Badenoch et al., 1963; and Smith et al., 1965).

Haubrich et al. (1960) were among the first to study Whipple’s disease by electron microscopy. They observed mononuclear cells which they interpreted as being mutant reticular cells that elaborated the PAS-positive material. Cohen
et al. (1960) described macrophages containing sinuous membranous sacs and extracellular dense bodies that they considered to be microorganisms. Yardley and Hendrix (1961) recognized these bodies as bacteria. Chears and Ashworth (1961) concluded that the undigested capsular material of the bacteria gave rise to the typical PAS-positive particles in the macrophages.

The demonstration that a favorable clinical response could be achieved with antibiotic therapy (England et al., 1960; Davis et al., 1963; Trier and Phelps, 1963) provided further evidence that bacteria play a role in the pathogenesis of Whipple's disease. Trier et al. (1965) made the critical observations that the bacteria are absent from the intestine of antibiotic-treated patients during remission but reappear with clinical relapse.

While there are now numerous electron microscopic studies of the intestinal lesions in Whipple's disease (Kurtz et al., 1962; Kent et al., 1963; Trier et al. 1965; Dobin and Ruffin, 1967; Phillips and Finlay, 1967), we are unaware of any such studies of the cerebral lesions. In this report we wish to draw further attention to the encephalitis that may accompany or even precede the other manifestations of Whipple's disease and to demonstrate that the cerebral lesions contain bacilli and their derivatives identical to those described in the intestine.

Material and Methods

In the files of the Armed Forces Institute of Pathology, which include case material from military, Veterans Administration, and civilian sources, there are 21 autopsied cases of Whipple's disease. Fifteen had been previously reported by Enzinger and Helwig (1963). Among the additional cases four showed prominent cerebral involvement and were available for this electron microscopic study. A histochemical study of one of these cases has been reported previously (Lampert, 1962). We are unaware of any such studies of the cerebral lesions. In this report we wish to draw further attention to the encephalitis that may accompany or even precede the other manifestations of Whipple's disease and to demonstrate that the cerebral lesions contain bacilli and their derivatives identical to those described in the intestine.

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For light microscopy, paraffin-embedded sections were stained with hematoxylin-eosin, periodic acid-Schiff, Gomori methenamine-silver, and Gram stains.

For electron microscopy, the formalin-fixed tissue was post-fixed in 1% phosphate-buffered osmium tetroxide, dehydrated, and embedded in Epon. Sections 2 microns thick were stained with paraphenylenediamine, and suitable blocks were selected for further cutting. The thin sections were stained with uranyl acetate and lead citrate and were examined with a Siemens IA electron microscope.

Results

Light Microscopic Findings

Viscera. The small intestine showed accumulations of macrophages in the mucosa and submucosa. The individual villi were widened by the cellular infiltrate and contained cystic spaces, but the overlying epithelium was unremarkable. The macrophages in the mucosa and the submucosa were rounded and possessed amphophilic foamy cytoplasm. These cells were stained intensely by the periodic acid-Schiff (Fig.1a) and the Gomori methenamine silver techniques. In addition, there were scattered lymphocytes, plasma cells, and polymorphonuclear leukocytes.

Mesenteric lymph nodes showed multiple irregular cystic spaces that obscured the usual follicular pattern. These were occasionally lined by multinucleated giant cells. Admixed with the lymphocytes were large foamy macrophages. As in the