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Case Report

Epithelioid Cell Granulomata in the Mucosa of the Small Intestine in Whipple's Disease*

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Summary. This report is the first description of sarcoid-like epithelioid cell granulomata in the mucosa of the small intestine in a case of Whipple's disease. The epithelioid cells do not contain PAS-positive material or products of bacterial degradation. Their ultrastructural features characterize them as histiocytes which have become secretory rather than phagocytic. These sarcoid-like lesions are considered to be a morphological manifestation of an immunological process in Whipple's disease and not to represent evidence of sarcoidosis as a concomitant or associated disorder.

Key words: Whipple's disease – Epithelioid cell granulomata – Sarcoid-like lesions.

Introduction

The morphological features of Whipple's disease seem to be well defined. Its characteristic feature is PAS-positive inclusions within the macrophages of the mucosa of the small intestines (Black-Schaffer, 1949; Sieracki, 1958), in mesenteric lymph nodes and in many other organs (Sieracki and Fine, 1959; Enzinger and Helwig, 1963). Ultrastructural studies show bacilliform bodies in the intestinal mucosa and these are considered to be an important aetiological factor (Miksche et al., 1974; Otto, 1975).

Epithelioid cell granulomata, which have been found in some organs of this systemic illness are not a feature of most descriptions of the disease and have not yet been described in the intestines. To our knowledge this report is the first to describe sarcoid-like epithelioid cell granulomata in the mucosa of the small bowel in a case of intestinal lipodystrophy. An attempt is made to provide an interpretation of these findings.

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Case Report

A 50-year-old male was admitted to the Städt. Krankenhaus München-Schwabing[1] complaining of tiredness, weakness, fever, weight loss, epigastric pain and painful joints. From time to time he had been treated with antibiotics. The type of antibiotics and the duration of the treatment are unknown. He had normal values for serum immunoglobulins and cutaneous anergy for tuberculin. On lymphography and computer tomography enlarged mesenteric lymph nodes were found. At exploratory laparotomy a mesenteric lymph node and a lymph node from the hepatoduodenal ligament were removed, endoscopic biopsies of the jejunum were taken. After diagnosis, the patient was successfully treated with tetracyclines.

Materials and Methods

The lymph nodes and biopsies of the small bowel were fixed in 4% formalin and examined by light microscopy. Frozen and paraffin sections of the lymph nodes were treated with the following stains: haemalum-eosin, haematoxylin-van Gieson elastic, Goldner's trichrome, periodic-acid Schiff, Ladewig's stain, Ziehl-Neelsen's stain and Sudan III. The biopsies of the jejunum were stained with haemalum-eosin, periodic-acid Schiff and Ziehl-Neelsen's stain. Mucosa biopsies were also fixed in glutaraldehyde, postfixed in osmium tetroxide solution, embedded in Epon 812 and used for transmission electron microscopic studies (Zeiss "EM 10").

Results

Jejunum

Light Microscopy. The jejunal surface is composed of a regular columnar epithelium with normal brush borders. The villi are broadened, the oedematous lamina propria contains dilated lymphatic vessels, a few plasma-cells, lymphocytes and many mononuclear macrophages with granules and rods of PAS-positive material in their cytoplasm (Fig. 1). In the deeper layer of the mucosa, towards the lamina muscularis mucosae, some epithelioid cell granulomata are found (Fig. 2). They consist of closely packed epithelioid cells with ill-defined boundaries. Their cytoplasm is lightly staining, the nuclei are ovoid with medium chromatin density. There are no PAS-positive inclusions or acid-fast bacilli. Some multinucleated giant cells are present. No central necrosis is observed. The granulomata are surrounded by a thin margin of lymphocytes, which are sometimes found between the epithelioid cells.

Electron Microscopy. The PAS-positive macrophages in the mucosa show lamellar, granular or amorphous membrane-bound bodies (Fig. 3). Bacillary forms are never seen. The resorptive cells are normal and have regular microvilli.

The epithelioid cells manifest great variations in their cellular detail (Figs. 4 and 5). The plasmalemma shows many protrusions and an intertwinning of these delicate peripheral cell processes with neighbouring cells is observed. The

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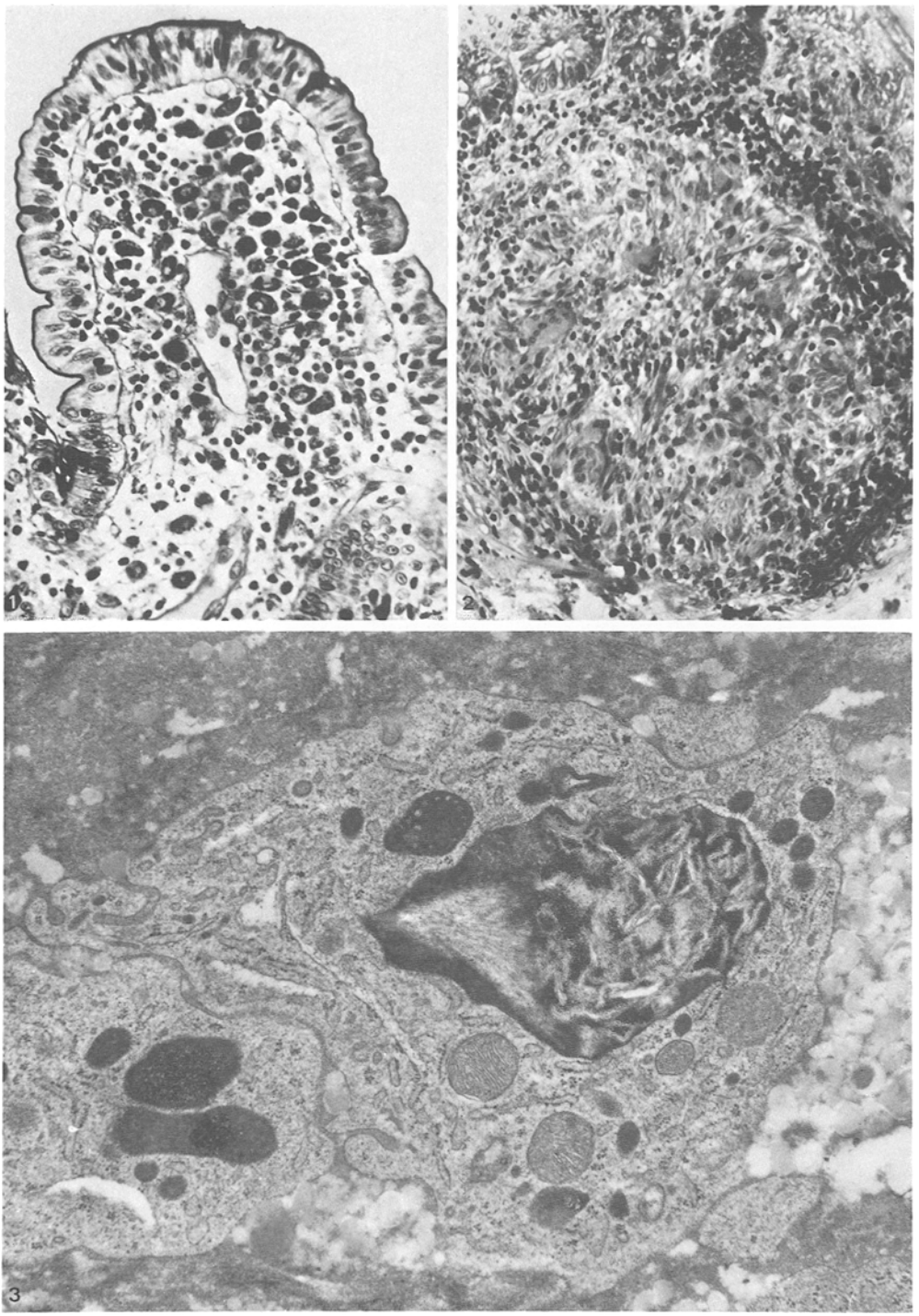

Fig. 1. Typical PAS-positive macrophages in the lamina propria of the intestinal mucosa, so-called SPC-cells, PAS. ×325

Fig. 2. Sarcoid-like epithelioid cell granuloma in the deeper layer of the intestinal mucosa. HE. ×190

Fig. 3. Phagolysosome with lamellar and granular structures of bacterial degradation surrounded by a single membrane in the lamina propria of the intestinal mucosa. Uranylacetate – lead citrate. ×30,000

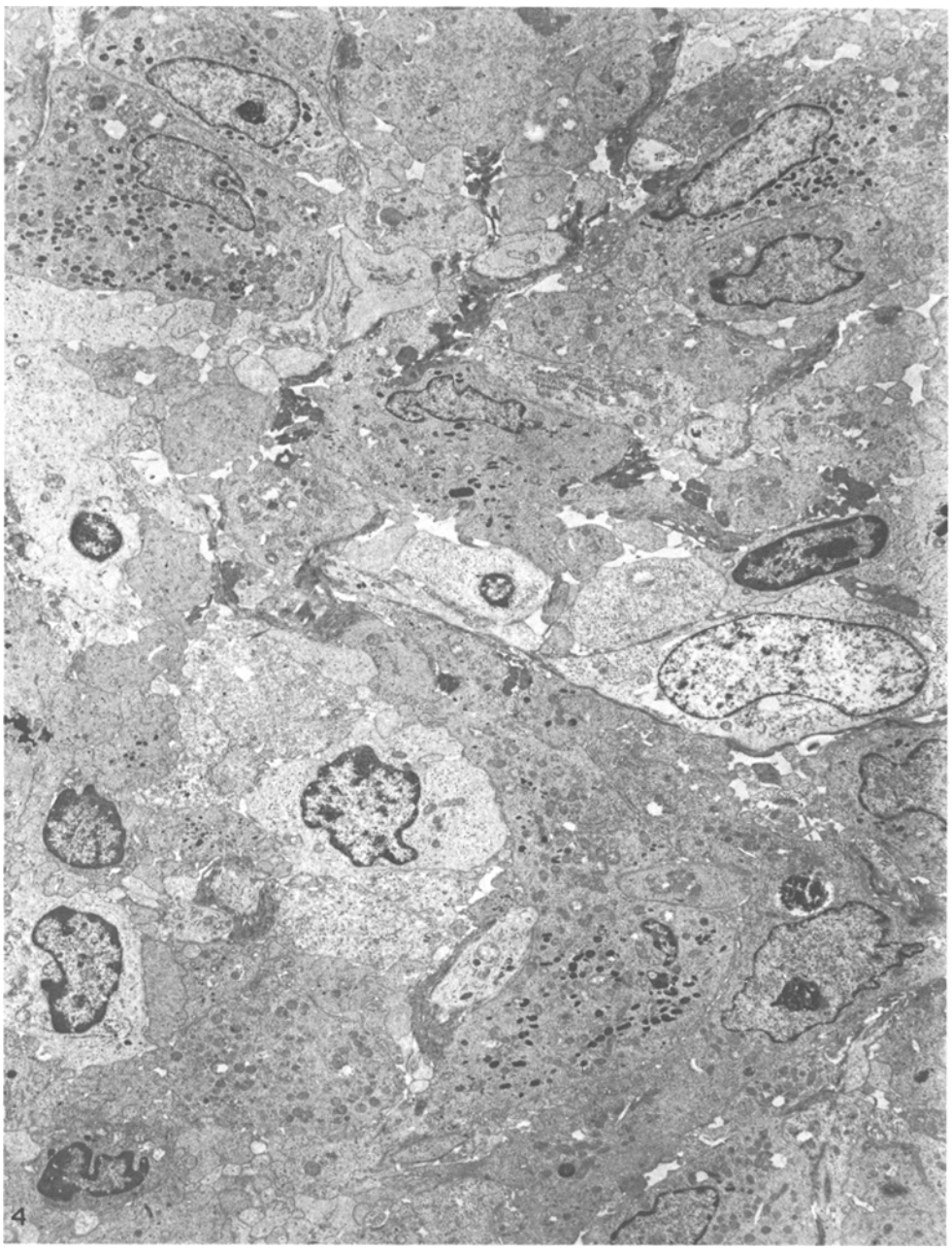

Fig. 4. Epithelioid cells of sarcoid-like granuloma in the lamina propria of the intestinal mucosa. Uranylacetate – lead citrate. ×3,200

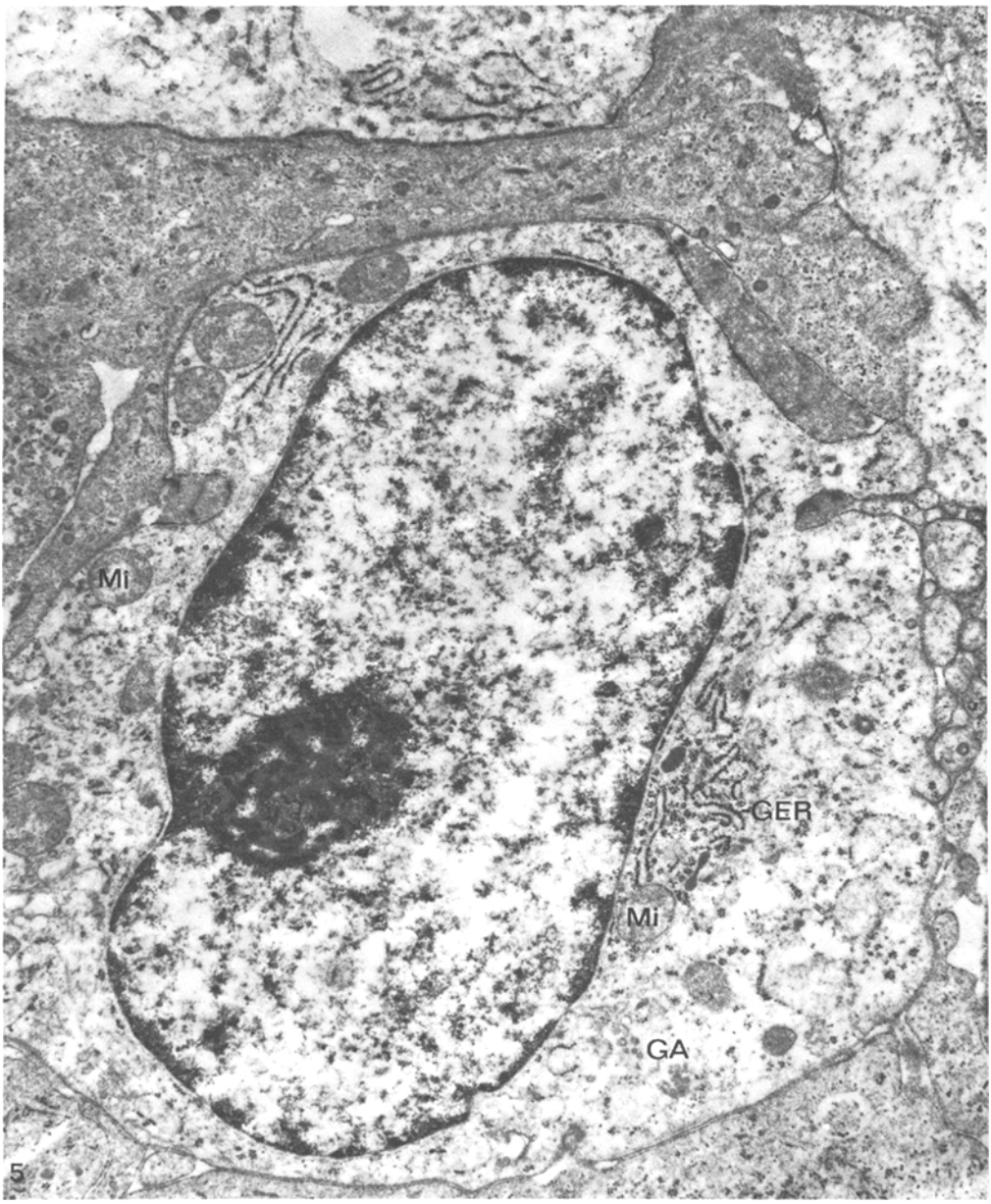

Fig. 5. An epithelioid cell containing a Golgi apparatus (*GA*), granular endoplasmic reticulum (*GER*) and crista type mitochondria (*Mi*) in the lamina propria of the intestinal mucosa. Uranylacetate – lead citrate. ×20,000

content of cell organelles is variable, in general the cells contain a Golgi apparatus and granular endoplasmic reticulum of varying extent, free ribosomes, a large number of crista type mitochondria, but only few lysosomes. There is a lack of bacteria or residues of micro-organisms.

Lymph Nodes

The apricot sized mesenteric lymph node (approximately 25 mm in diameter) contains cystic spaces, filled with Sudan III staining material, and surrounded by foamy macrophages and lipid containing multinucleated giant cells. Many macrophages also include PAS-positive material in their cytoplasm. Epithelioid cell granulomata are not seen. In comparison with this, the apple pip sized lymph node (approximate dimensions 5:3:2 mm) of the lesser omentum does not show dilated spaces, foamy or PAS-positive macrophages, but contains some epithelioid cell granulomata similar to those in the jejunal mucosa. In the periphery of these nodules there is fibrosis and hyalinosis.

Discussion

In our case the diagnosis of Whipple's disease has been established by the finding of numerous PAS-positive macrophages, the so-called SPC-cells, in the small intestine. At the ultrastructural level the SPC-cells contain rod-like inclusions consisting of lamellar, granular or amorphous structures with a limiting membrane; they are products of bacterial degradation. Intact bacteria are not demonstrated, probably due to the treatment with antibiotics. The lipid-containing cystic spaces and lipophage granulomata in the mesenteric lymph node represent typical changes of intestinal lipodystrophy.

Of particular importance is our observation of sarcoid-like epithelioid cell granulomata in the lamina propria of jejunal mucosa and in the small lymph node of the lesser omentum. Such granulomata have not been previously reported in the intestinal mucosa in Whipple's disease. Oliva et al. (1972) reported on the presence of lymphohistiocytic granulomata near the lamina muscularis mucosae of the small bowel, these were PAS-negative. The granulomata shown in the photographic illustrations of that paper are not identical with the granulomata we found in the intestinal mucosa. Oliva and his colleagues illustrate lymphohistiocytic granulomata which do not look like epithelioid cell nodules and are characterized by central coagulative necroses surrounded by a crown of lymphocytes. Incidentally, these morphological changes were not described as sarcoid-like lesions by the authors. We are not able to determine whether or not they represent an earlier or later phase of the granulomata that we have seen.

In a few cases of Whipple's disease sarcoid-like epithelioid cell granulomata have been observed in the lymph nodes (Apperly and Copley, 1943; Oliver-

Pascual et al., 1947; Newman and Pope, 1948; Rutishauser et al., 1948; Porter, 1951; Russo, 1952; Upton, 1952; Ammann, 1957; Gross et al., 1959; Sugarman et al., 1960; Enzinger and Helwig, 1963; Müller and Schlotterhoß, 1966; Gold and Margolin, 1971; Otto et al., 1972; Rodarte et al., 1972), in the liver (Apperly and Copley, 1943; Cornet et al., 1976; Pequignot et al., 1976), in the spleen (Ammann, 1957; Müller and Schlotterhoß, 1966), in the kidney (Ammann, 1957), and in the lung (Rodarte et al., 1972). Ammann (1957) assumed that one of his two patients had suffered from sarcoidosis in addition to Whipple's disease and that sarcoidosis might be the cause of intestinal lipodystrophy following obstruction of lymphatic vessels. He suggested a differentiation between Whipple's syndrome with a well-known pathogenesis and idiopathic Whipple's disease. Moreover, Otto et al. (1972) who found lung involvement and hilar lymphadenopathy with epithelioid cell granulomata in a patient with intestinal lipodystrophy accepted the coincidence of both diseases. Apperly and Copley (1943) considered "tuberculous-like" lesions in mesenteric lymph nodes to be a reaction caused by the presence of free fatty acids. Rutishauser et al. (1948) interpreted these changes as a phenomenon of resorption. Other authors (Newman and Pope, 1948; Müller and Schlotterhoß, 1966; Rodarte et al., 1972) suggested the uncommon epithelioid cell granulomata to be an earlier stage of intestinal lipodystrophy. In 1966 Müller and Schlotterhoß injected formol-fixed homogenized intestinal mucosa of a man suffering from Whipple's disease into mice, producing epithelioid cell granulomata, described as an early phase of Whipple's disease.

In our case tuberculosis was excluded. From the clinical data, X-ray investigations and the course of illness of our patient, we are not able to find any criterion for concomitant disease like sarcoidosis. Whipple's disease (Enzinger and Helwig, 1963) and intestinal involvement in sarcoidosis (Longcope and Freiman, 1952; Scadding, 1967; Miyamoto et al., 1972; Nissen, 1977) are very rare, so that the coincidence of both disorders seems extremely unlikely. We assume that the sarcoid-like epithelioid cell granulomata found in the mucosa of the small bowel and in the excised lymph node from the lesser omentum, are a morphological manifestation of an immunological process in Whipple's disease. In light microscopy the epithelioid cells lack PAS-positive material; electron microscopy does not show any bacillary forms or membrane-bound structures in these cells that might be explained away as bacterial degradation products. On the contrary these epithelioid cells contain only a few lysosomes but are rich in granular endoplasmic reticulum, free ribosomes, Golgi apparatus and crista type mitochondria. The morphological peculiarities of the cells are similar to those of the epithelioid cells in the granulomata of sarcoidosis (Azar et al., 1973; James and Jones Williams, 1974; Spector, 1976). It is possible that the epithelioid cells in Whipple's disease may produce active substances such as lymphokines in a fashion comparable to the epithelioid cells in sarcoidosis, as has been considered by Jones Williams (1977). The immunological mechanisms of Whipple's disease may have some similarity to those suggested for sarcoidosis, and the antigen may be derived from the undigested bacterial material in SPC-cells.

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