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Diagnosis of Cerebral Whipple's Disease by Cerebrospinal Fluid Cytology

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Summary. In a case of Whipple's disease the diagnosis was made by careful cytologic evaluation of the cerebrospinal fluid (CSF), identifying "Sieracki cells". A basal granuloma invaded the hypothalamus, diencephalon, and rostral parts of the brainstem. An exploration in the initial stage led to misdiagnosis as a granular cell tumor. Diagnosis was then confirmed by intestinal biopsy.

Key words: Whipple's disease – Basal granuloma – Granular cell tumor – CSF cytology

Zusammenfassung. Es wird über einen Fall mit Morbus Whipple berichtet, der bei sorgfältiger Untersuchung des Liquor cerebrospinalis durch den Nachweis von Sieracki-Zellen diagnostiziert wurde. Die Exploration eines basalen Granuloms, das in den Hypothalamus, das Diencephalon und die rostralen Anteile des Hirnstamms eingewachsen war, hatte im Frühstadium zur Fehlinterpretation eines Granularzelltumors geführt. Die Diagnose wurde schließlich durch Dünndarmbiopsie bestätigt.

Introduction

Intestinal lipodystrophy or Whipple's disease is a chronic disease that primarily affects the mucosa of the small intestine. The principal clinical features are loss of weight, steatorrhea, abdominal pain, and recurrent arthralgia. Other symptoms include myalgia (cervical muscles in particular), cough, recurrent attacks of fever, and dirty gray skin pigmentation, which may appear years before the intestinal symptoms [8].

Histological demonstration of "sickleform particle-containing" (SPC) cells, particularly in the mucosa of the small intestine, is specific for the diagnosis. These macrophages contain inclusions that stain intensely with the periodic acid-Schiff

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(PAS) reagent and consist of lysosomal-bound bacterial membranes [2]. Morphologically intact bacteria may be detected extracellularly, but attempts to isolate or cultivate organisms from biopsies have failed to identify a specific agent, responsible for the disease beyond reasonable doubt [12]. Approximately 10% of affected patients have symptoms of an ambiguous encephalitis, sometimes this is the first manifestation [9]. In most of these cases the diagnosis was established after death.

We now report that Whipple's disease with primary cerebral symptoms can be diagnosed by demonstrating Sieracki cells [10] in the CSF.

Case Report

For five years a 36-year-old paramedic had been treated repeatedly for recurrent arthralgia of the hands, fingers, and hips, with increased sedimentation rate and leukocytosis, up to 30,000 WBC per mm^3. Despite normal joint radiograms and tests for antistreptolysin, rheumatoid factor, and LE-cells he was treated with chloroquine and gold salts for 4 years. Night sweats and chronic cough were other symptoms. In 1978 he became dizzy due to the lack of saccadic eye movements with preservation of slow movements. Gaze was usually shifted by head movements and refixation occurred when the eyes slowly drifted back to the midline position. Although this suggested a pontomesencephalic lesion, the CT showed a clearly delineated enhancing mass about 1 cm in diameter in the suprasellar cistern (Fig. 5). Angiography, however, was normal. CSF contained approximately 180 cells/mm^3 with an initial slightly elevated protein content, and cytologically there was a mixed cell reaction with lymphocytes, plasma cells, activated monocytes, as well as neutrophilic and eosinophilic granulocytes, indicating the presence of an inflammatory granuloma. Liver biopsy and repeated tests of CSF for fungi, parasites, and acid-fast bacilli were negative. There was rapid deterioration of visual acuity, severe pulsating headache, altered sleeping and wakeing rhythms, and a complete gaze palsy with paralysis of vestibulo-ocular reflexes. At craniotomy, there was a tumor-like distension of the tuber cinereum with extensive basal adhesions.

Histologically, the tissue was thought to be a granular cell tumor because of abundant, large, foam-like cells with PAS-positive granules and occasional inflammatory cells. CSF taken before surgery was reevaluated. Macrophages contained material that stained with PAS and gave faint columbine-blue with May-Grünwald/Giemsa stain (Fig. 2). The PAS appearance was an accumulation of intensely stained sickle-like particles (Fig. 1). These so called Sieracki or SPC-cells were considered to be pathognomic for Whipple's disease. The diagnosis was confirmed by microscopic examination of biopsies from brain and jejunum (Figs. 3 and 4).

Serum IgA concentration (500–600 mg%) was moderately elevated during the entire observation period. The initially elevated IgG (2,800 mg%) became normal before antibiotic treatment and serum IgM concentration was normal throughout.

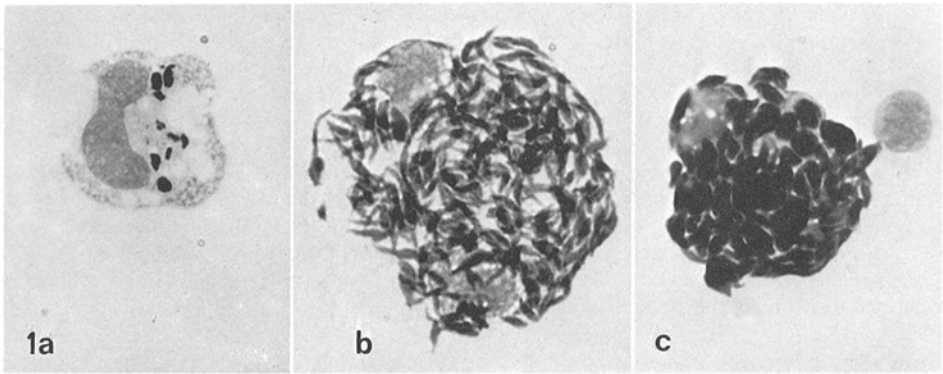
Fig. 1a–c. PAS reaction of typical Sieracki cells in CSF (sedimentation technique, magnification: ×1,200). **a** Macrophage with a few sickle-form particles. **b** Binucleated macrophage filled with sickleform particles. **c** Macrophage filled with globular particles

Fig. 2. Sieracki cell in CSF (May-Grünwald/Giemsa stain, magnification: ×1,200)

Fig. 3. Sieracki cell in jejunal biopsy specimen as seen with electron microscopy. Lysosomal bound membranes *(open arrow)* and microorganisms in the extracellular space *(arrow)* (magnification: ×10,500). (Dept. of Submicroscopic Pathology and Neuropathology, Tübingen)

Fig. 4. PAS reaction in granulomatous tissue in biopsy specimen from infundibular region (magnification: ×300)

Fig. 5. CAT scan after administration of contrast medium; enhancing mass can be seen within the basal cistern. (Dept. of Neuroradiology, Tübingen)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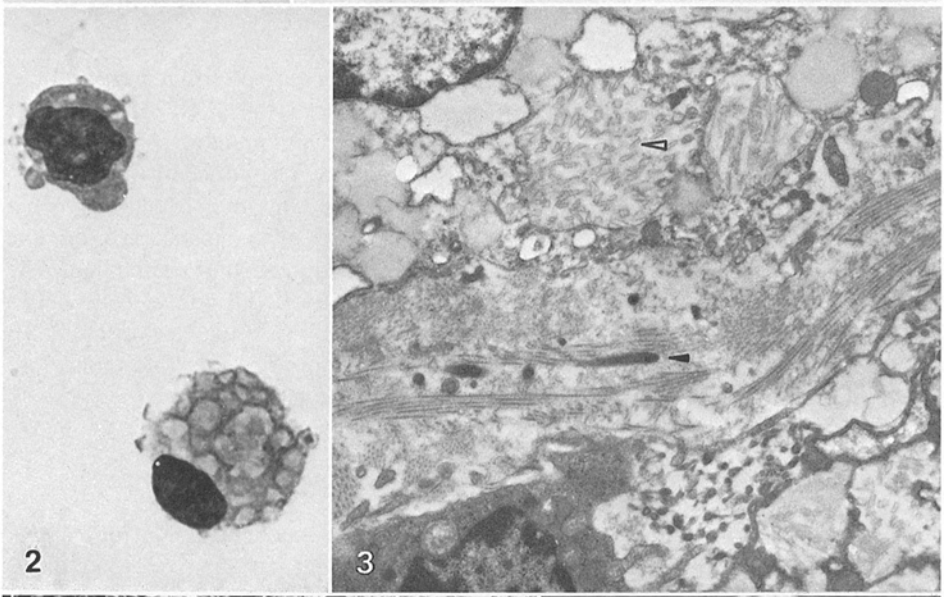
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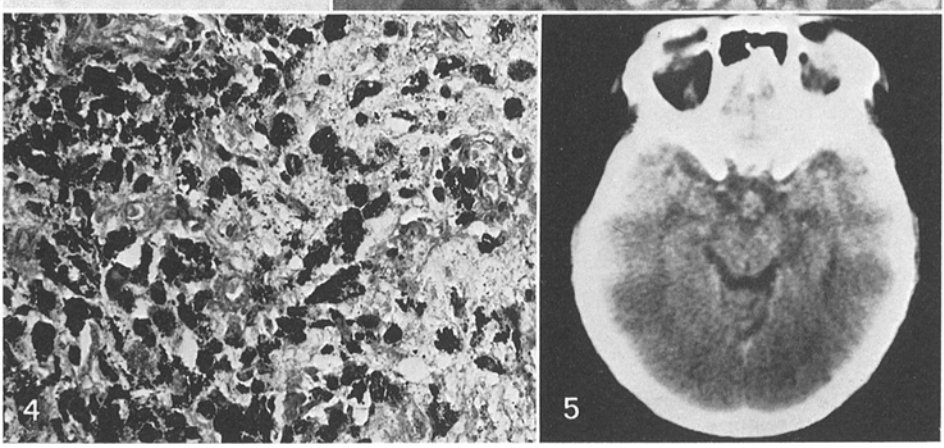
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Mitogen responses of blood lymphocytes with PWM, PHA, and Con A were normal. Only the activation of suppressor cells was markedly depressed in the presence of the patient's serum.

All the tested lysosomal enzymes in the granulocytes were normal. Adherence response, chemotaxis, phagocytosis, NBT dye reduction, and intracellular killing of S. aureus were within the normal range. The capacity for killing Candida albicans in the presence of autologous, as well as pooled serum, however, was pathologically reduced on repeated tests.

Soon after surgery a severe diencephalic crisis was manifest by a fall in blood pressure, dysregulation, and electrolyte imbalance. There was retraction and convergence nystagmus with complete gaze palsy in all directions. Bilateral myoclonus of the facial and limb muscles was synchronous with the nystagmus. There were episodes of abnormal sleeping states during which the patient could not even be awakened by pain stimuli. The patient also showed signs of mental alterations with periods of confusion.

Therapy

Fever attacks (occurring regularly once a month), increased sedimendation rate, and leukocytosis subsided after treatment with rolitetracycline (2×275 mg per day) for two months. His condition, however, deteriorated and malabsorption increased and there was evidence of secondary osteomalacia. The concentration of rolitetracycline in CSF was found to be too low for bactericidal action (1 µg/ml); a combination of minocycline and metronidazole was given unsuccessfully. The clinical picture did not improve even after administration of chloramphenicol. The only success was a certain degree of normalization in the CSF findings, especially a decrease in the number of Sieracki-cells and a drop in the initial elevation of CSF IgG. The clinical condition has not changed for approximately one and a half years, although antibiotic therapy has been discontinued.

Discussion

The diagnosis of Whipple's disease is usually not considered when the gastrointestinal key symptoms and malabsorption are absent. In our case, the clinical signs—recurrent arthralgia, chronic cough, recurrent fever, increased sedimentation rate, leukocytosis, hypoalbuminemia, hyperchromatic anemia, and mesencephalic, as well as hypothalamic symptoms, were not sufficient to stimulate consideration of Whipple's disease. A CT with clearly delineated enhancing mass approximately 1 cm in diameter suggested a basal granuloma. In another case CT showed only diffuse atrophy [12], and a CT in a further case demonstrated areas in the temporal region and the tegmentum of the right pons with decreased attenuation values without mass effect and enhancement after the administration of contrast medium [4]. Basal granulomas of the size demonstrated in our case have not been described previously, but smaller granulomas of no more than 5 mm in size have been seen [9]. One exception may be the report of Badenoch [1], who found a tumor-like cell proliferation in the infundibular region. In the biopsy the large number of closely-packed foam cells containing PAS-positive granular material resembled a granular cell tumor (choristoma). Unlike tumor cells they, however, were clearly identified as macrophages. They were much more clustered and the inclusions were less regularly shaped and more intensely PAS-positive than tumor cells (Fig. 4).

Cytological evaluation of CSF was crucial in this case. The mixed cell reaction with moderate pleocytosis, as well as slightly elevated total protein content and IgG concentration tended to indicate initially a granulomatous process. The pathognomic Sieracki cells were demonstrated by PAS staining (Fig. 1). This test was suggested by Smith et al. [11] and was used successfully in two cases following confirmation of Whipple's disease by jejunum biopsy [3, 6]. The proportion of Sieracki cells in our patient ranged in different specimens from 1% to 18%. Sieracki cells with 1 or 2 granules were found adjacent to cells filled with PAS-positive, filamentous or globular material (Fig. 1). These cells were undoubtedly phagolysosomes that contained membranous bacterial remnants. They were also seen on electron micrographs of biopsies of jejunum and brain (Fig. 3). There are other reports in which bacterial remnants were visible in brain biopsies [4, 5, 7]. The possibility of an early diagnosis is important because the disease usually responds to tetracycline therapy, this failed in our case, although apparent arrest may have indicated a partial effect. It remains an open question whether the serious cerebral defects might have been prevented if antibiotic therapy had been instituted earlier. All diagnostic possibilities therefore should be exhausted, when granulomatous encephalitis is suspected, particularly if arthritic episodes are mentioned in the case history. Cytologic evaluation of CSF is particularly important in establishing the diagnosis.

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