Arch. Dermatol. Res. 266, 187–196 (1979)

Archives of
Dermatological
Research

A Specific Ultrastructural Marker for Disseminated Lipogranulomatosis (Farber)* **

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Summary. An ultrastructural investigation of two cutaneous lesions in a two-year-old Turkish boy with disseminated lipogranulomatosis (Farber) revealed curvilinear bodies in fibroblasts, histiocytes, and endothelial cells; "elongated membranes" in fibroblasts and endothelial cells; "zebra bodies" in endothelial cells; and spindle-shaped bodies in Schwann cells. In peripheral lymphocytes only alterations of mitochondria (swelling and ruptured cristae) but no inclusion bodies were found. Curvilinear bodies were numerous and easily identifiable; they appear to be characteristic of Farber's disease, and naming them "Farber bodies" is proposed. The diagnosis of this ceramide storage disease, in which the histological examination is relatively unspecific, can therefore be confirmed ultrastructurally.

Key words: Disseminated lipogranulomatosis – Farber's disease – Sphingolipidoses – Ceramide – Ultrastructure

Zusammenfassung. Eine elektronenmikroskopische Untersuchung von 2 Hautläsionen bei einem aus der Türkei stammenden 2jährigen Jungen mit disseminierter Lipogranulomatosis (Farber) zeigte curvilineare Körper in Fibroblasten, Histiocyten und Endothelzellen, flache Membrananordnungen in Fibroblasten und Endothelzellen und spindelartige Körper in Schwann-Zellen. In peripheren Lymphocyten fanden sich nur Veränderungen der Mitochondrien (Schwellung und aufgebrochene Cristae), jedoch keine Einschlußkörper. Die intracytoplasmatischen curvilinearen Körper waren zahlreich und leicht nachweisbar. Sie scheinen für den M. Farber spezifisch zu sein, und es wird vorgeschlagen, sie "Farber Körper" zu nennen. Die Diagnose dieser Ceramidspeicherkrankheit, in der das histologische Bild weitgehend unspezifisch ist, kann daher ultrastrukturell bestätigt werden.

Schlüsselwörter: Disseminierte Lipogranulomatose – M. Farber – Sphingolipidosen – Ceramid – Ultrastruktur

* Dedicated to Prof. Dr. Klingmüller on his 60th birthday
** Supported by the Deutsche Forschungsgemeinschaft

0340-3696/79/0266/0187/$2.00

Table 1. The sphingolipidoses and their principal storage products

ceramide →			FARBER'S DISEASE
→	+ phosphorylcholine	= sphingomyelin	NIEMANN-PICK DISEASE
→	+ glucose	= cerebroside	GAUCHER'S DISEASE
→	+ galactose-6-sulfate	= sulfatide	METACHROMATIC LEUCODYSTROPHY
→	+ oligosaccharide	= ganglioside	AMAUROTIC FAMILY IDIOCY
→	+ glucose + galactose galactose	= trihexosyl ceramide	FABRY'S DISEASE

Disseminated lipogranulomatosis (Farber, 1952) is a rare autosomal recessive storage disease [2] of which at least 20 cases have been reported. It should be listed among the sphingolipidoses (Table 1), since ceramide, the ground substance of various lipids, is found in an excessive concentration in different organs including the skin [11, 14]. The origin of this disorder is probably a genetically determined low activity of ceramidase, as shown in four cases [6, 16]. This enzyme defect results in death of the patient in either very early [10] or occasionally later childhood [19]. Its principal clinical symptoms are hoarseness of voice, progressive arthropathia, and subcutaneous nodules slowly increasing in size and number. Later, particularly in the rapidly progressing variant, the nervous system is affected.

Among the sphingolipidoses, Farber's disease as well as Fabry's disease are most interesting for the dermatologist because of the specific skin lesions, which allow the diagnosis to be established (Table 1). The diagnosis of disseminated lipogranulomatosis must be confirmed biochemically through detection of a high accumulation of ceramide. This study focuses on the ultrastructural examination, which in this disease seems to be as important for confirmation of the diagnosis.

Case Report

A physical examination of a two-year-old Turkish boy showed yellow-brown nodules in the dorsal surface of joints (fingers, elbows, knees), as well as on the ears and in the supraglottic part of the larynx (Fig. 1). These nodules were seen to slowly increase in size and number. His voice was hoarse, and he had never been able to stand up or crawl; even minor movements seemed to be painful for him. This polyarthropathy was slowly worsening in spite of physiotherapy. An older brother with similar symptoms had died at the age of 7 years.

Laboratory Studies. Blood chemistry surveys revealed an increased ESR (45/100) and slightly elevated levels of immunoglobulins. Results of histopathologic examination of a biopsy specimen of a cutaneous nodule were unspecific and showed fibrotic tissue with fibrocytes and histiocytes.

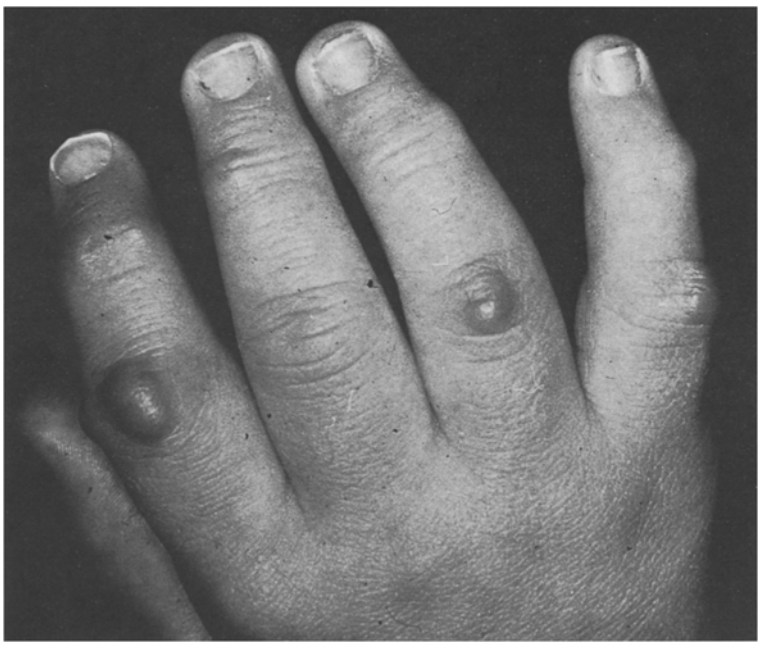

Fig. 1. Farber's disease. A two-year-old boy with subcutaneous nodules on the finger joints

Materials and Methods

Skin biopsies as well as peripheral human lymphocytes (isolated through Ficoll Isopaque solution and centrifuged at 500 g for 10 min) were fixed in 1 % OsO_4, embedded in Epon, and cut with diamond knives on a Reichert ultramicrotome OMU2. Thin sections were post-stained with uranyl acetate and lead citrate, and examined with a Phillips electron microscope EM 300.

Biochemical Analysis

High levels of ceramides within a biopsy of a subcutaneous nodule were demonstrated biochemically through gaschromatography (Dr. H. Christomanou, Max-Planck-Institute of Psychiatry, Munich). These biochemical studies will be published elsewhere in more detail.

Results

On semi-thin sections spindle-shaped cells with a foamy cytoplasm containing dark granules were seen between collagen fibers of the subcutaneous tissue; some lymphocytes were also present (Figs. 2 and 3). On the ultrastructural level most of these cells were found to be fibroblasts and fibrocytes, characterized by a prominent nuclear membrane and by a dilated endoplasmic reticulum. Within the cytoplasm lipid vacuoles were observed as well as vacuoles filled with curvilinear bodies, easily seen at low magnification (Figs. 4a, b; 5). Occasionally, these curvilinear bodies appeared to lie freely in the cytoplasm (Fig. 5). Random "elongated membranes"

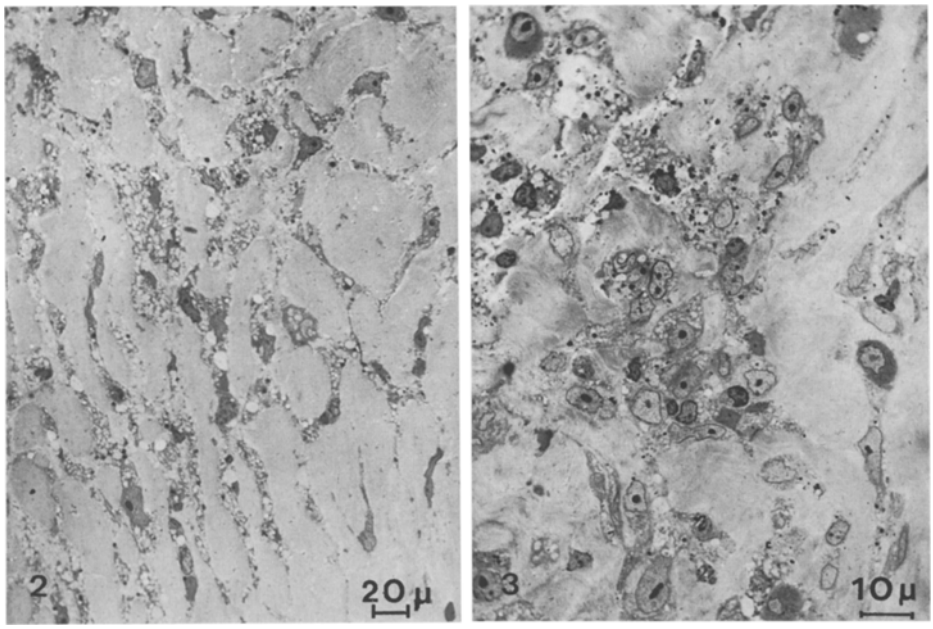

Fig. 2. Farber's disease. Semi-thin section showing fibrotic tissue with fibrocytes and fibroblasts both with foamy cytoplasms. ×580

Fig. 3. Farber's disease. Semi-thin section showing mostly fibroblasts with a foamy cytoplasm containing dark granules (phagosomes). ×240

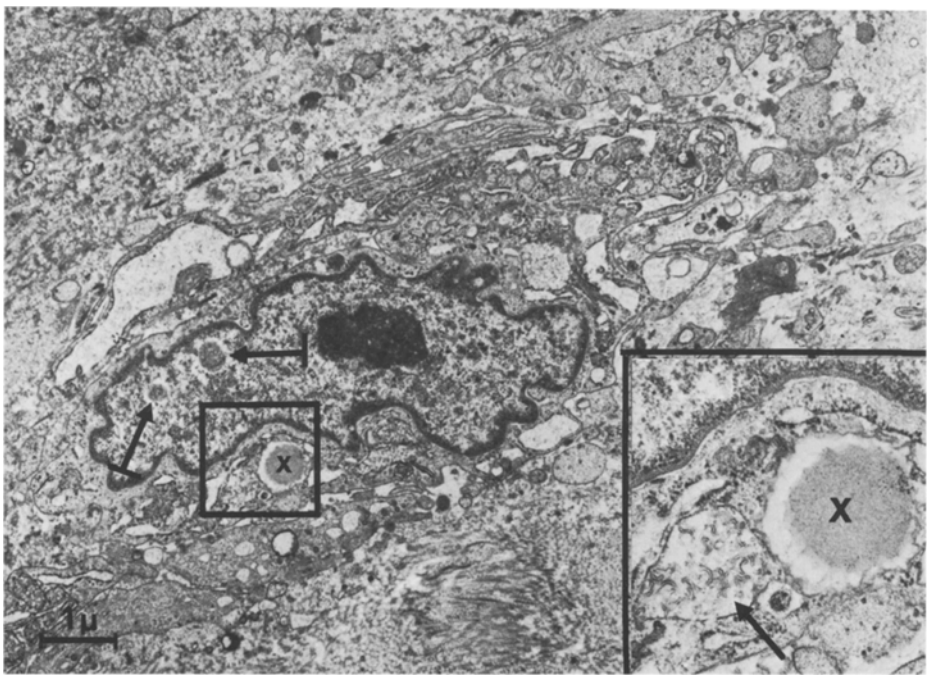

Fig. 4. Farber's disease, thin section. Fibroblast with a dilated endoplasmic reticulum and a thickened nuclear membrane (*inset*), within the nucleus two sphaeridia (↦). Next to the liposome (*X*) a vacuole with Farber bodies (→) is seen. ×8,600, inset ×24,300

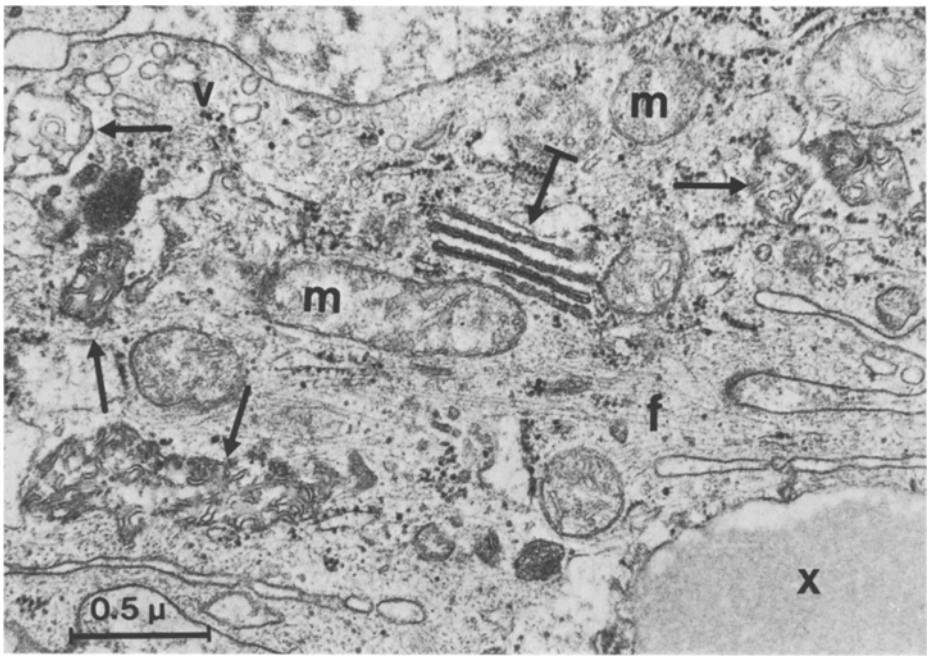

Fig. 5. Farber's disease, thin section. Cytoplasm of a fibroblast showing normal mitochondria (*m*), vesicles (*v*), filaments (*f*), ribosomes, a liposome (*X*), Farber bodies (→) contained in vacuoles, and elongated membranes (↦). × 38,400

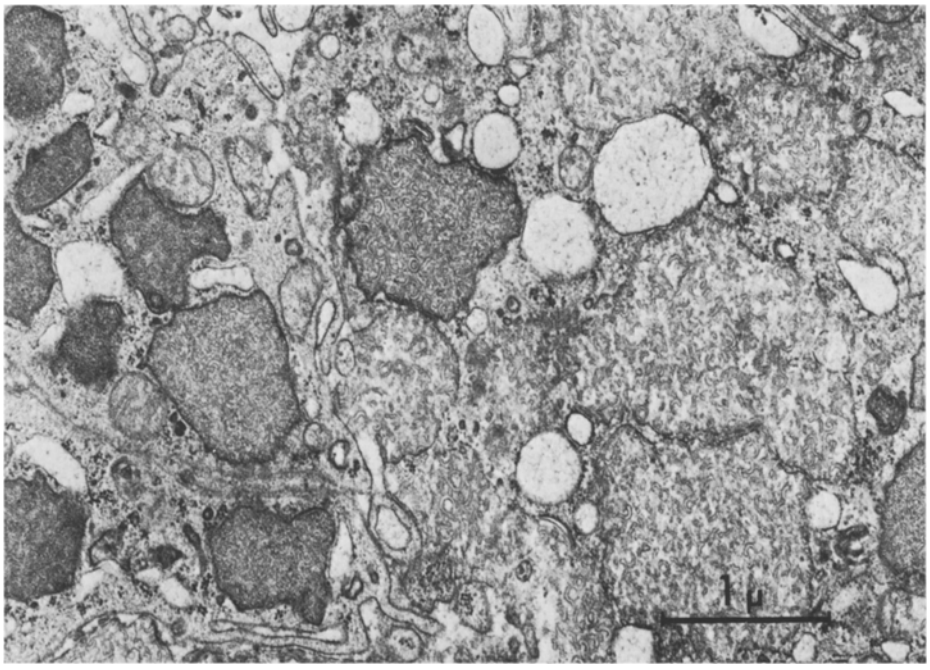

Fig. 6. Farber's disease, thin section. Portions of two histiocytes, the cytoplasm of which are nearly filled with vacuoles containing Farber bodies with varying degrees of density. × 22,300

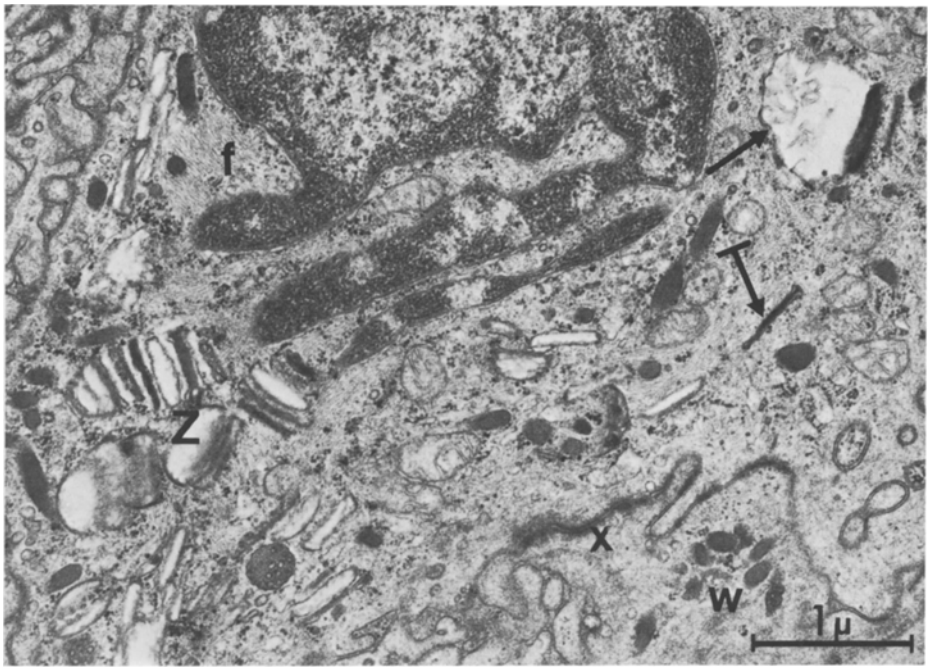

Fig. 7. Farber's disease, thin section. Endothelial cell characterized by Weibel-Palade bodies (*w*), tight junctions (*X*), and filaments (*f*), also showing "zebra bodies" (*z*), elongated membranes (↦), and Farber bodies (→). ×22,300

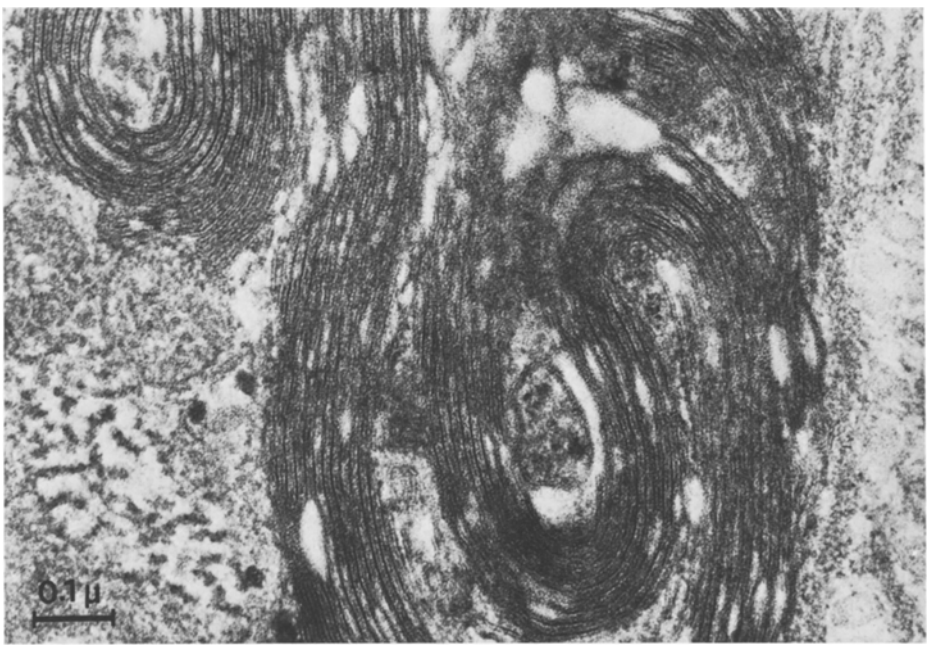

Fig. 8. Farber's disease, thin section. Peripheral cutaneous nerve showing gaps in the myelin probably due to lipid storage material dissolved during the embedding procedures. ×93,500

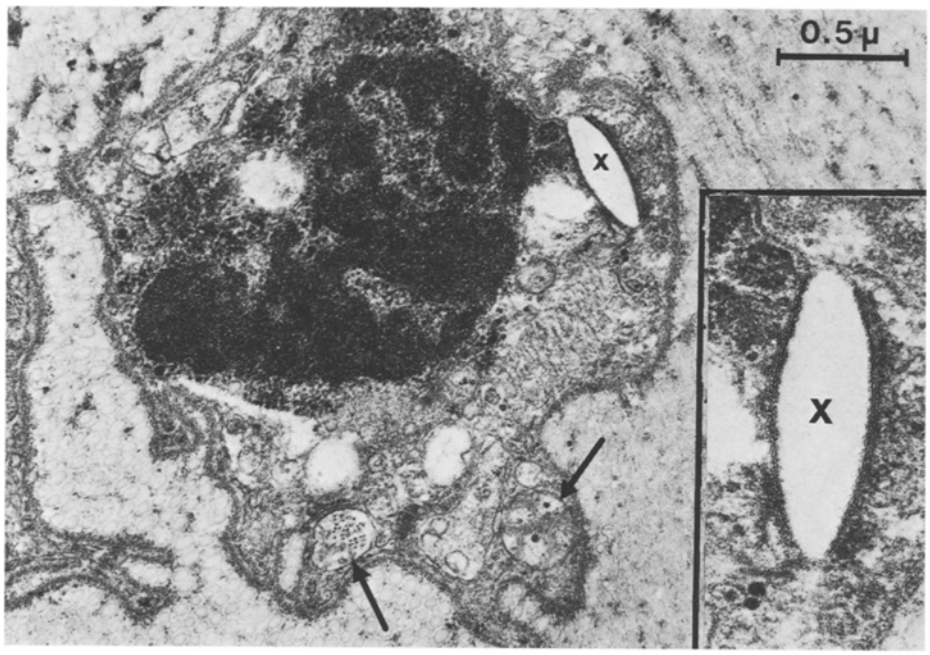

Fig. 9. Farber's disease, thin section. Cutaneous Schwann cell showing unusual lysosomes (→) and a white spindle-shaped body (*X*) with several membranes at its outer surface (inset). ×34,000, inset ×82,500

were also present (Fig. 5). Mitochondria showed various degrees of damage to such an extent that a relationship to vacuoles with vermiform structures can be inferred. Vermiform structures were also seen in histiocytes as being more densely packed and condensed than in fibroblasts (Fig. 6).

In endothelial cells "zebra bodies", "elongated membranes", and occasionally curvilinear bodies were observed (Fig. 7). Examination of cutaneous nerves revealed focal alterations in the myelin, i.e., white areas possibly due to lipid storage (Fig. 8); and a spindle-shaped body was seen within the cytoplasm of a Schwann cell (Fig. 9a, b). In peripheral lymphocytes mitochondria occasionally showed swelling, disruption of cristae, and granular deposits (Fig. 10) but no curvilinear bodies or other inclusions were found. In monocytes and neutrophils lysosomes were noted to be unusually large.

Discussion

This is a further case report of disseminated lipogranulomatosis (Farber). The clinical symptoms were typical (hoarseness of voice, progressive arthropathia, development of subcutaneous nodules), and the diagnosis was confirmed biochemically by a high concentration of ceramide in a cutaneous lesion. Electron

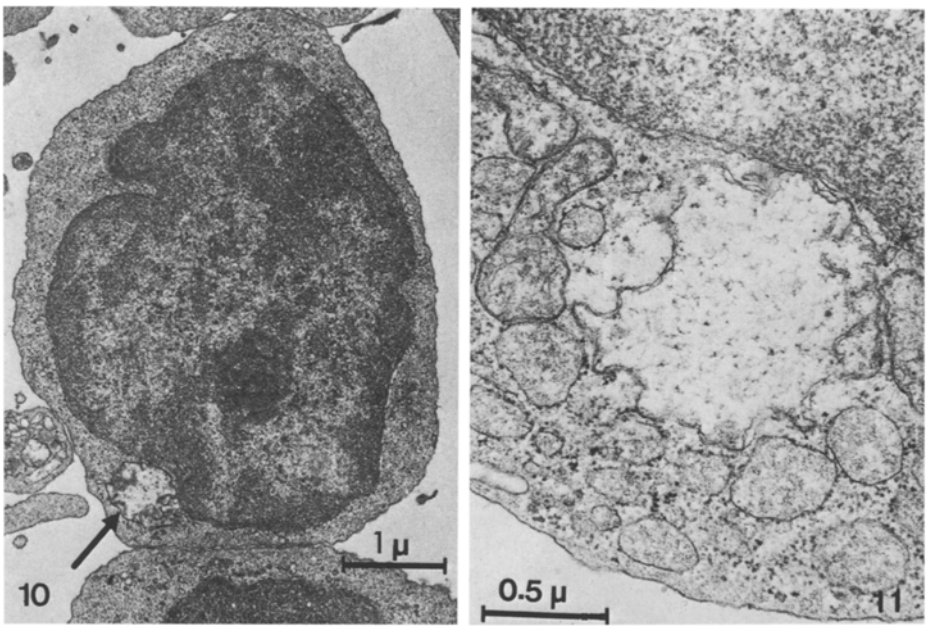

Fig. 10. Farber's disease, peripheral blood, thin section. Lymphocyte showing an abnormal mitochondrion (→). ×14,200

Fig. 11. Farber's disease, peripheral blood, thin section. Swollen mitochondria with ruptured cristae within the cytoplasm of a lymphocyte. ×34,000

microscopy was found to be an important method for establishing the diagnosis of this disease by the demonstration of a specific ultrastructural marker. Five cases of Farber's disease with submicroscopical investigations and consistent findings have been reported [3–5, 8, 13]. Curvilinear bodies were found in the skin [4, 5, 8], as well as in the lung and in the thymus [5]. They were also present in fibroblast cultures of a patient with disseminated lipogranulomatosis exposed to a high concentration of ceramide [14]. These structures seem to be unique, as they have not been observed in other diseases, but they were easily detected in various cell types, particularly in fibroblasts, histiocytes, and to a lesser degree in endothelial cells in this case. Therefore, calling them "Farber bodies" appears to be justified. Furthermore, the term "curvilinear body" is probably not totally consistent with the three-dimensional aspect of these structures. Similar but morphologically different curvilinear bodies were found in the frontal cortex of a child with juvenile amaurotic idiocy [18]. On the other hand, "Farber bodies" were not observed in the central nervous system in Farber's disease [3, 4]. Other intracytoplasmic organelles demonstrated in disseminated lipogranulomatosis are less specific; "zebra bodies" (vacuoles with transverse membranes) were seen in cutaneous endothelial cells [4] and in the central nervous system [3, 4], but they were also found in other diseases, such as metachromatic leucodystrophy [16] and gargoylism [1]. Spindle-shaped bodies within the cytoplasm of Schwann cells were also observed in disseminated

lipogranulomatosis [4], whereas "elongated membranes" to our knowledge have not yet been described in this disease. In this context it is interesting that ceramide and ceramide containing compounds are membrane-forming lipids. The biochemical significance of these various structures remains unknown, although "Farber bodies" seem to be related to ceramide [14].

Morphological alterations in peripheral lymphocytes, as reported in other diseases, such as mucopolysaccharidoses [12] and Niemann-Pick disease [9], were also observed in this case. They consisted mainly of swelling and disrupted cristae in mitochondria, whereas no inclusions were found within the cytoplasm.

In conclusion, the detection of "Farber bodies" by electron microscopy appears to confirm the diagnosis of disseminated lipogranulomatosis in suspected cases, particularly when a biochemical analysis cannot readily be carried out.

Acknowledgement. We are grateful to Ms. V. Kügler for her skilled technical assistance.

References

1. Aleu, F. P., Terry, R. D., Zellweger, H.: Cerebral biopsies in gargoylism. J. Neuropathol. Exp. Neurol. **24**, 304–317 (1965)
2. Amirhakimi, G. H., Haghighi, P., Ghalambor, M. A., Honari, S.: Familial lipogranulomatosis (Farber's disease). Clin. Genet. **9**, 625–630 (1976)
3. Battin, J., Vital, C., Azanza, X.: Une neuro-lipidose rare avec lésions nodulaires sous-cutanées et articulaires: La lipogranulomatose disséminée de Farber. Ann. Dermatol. Syphiligr. (Paris) **97**, 241–248 (1970)
4. Becker, H., Auböck, L., Haidvogl, M., Bernheimer, H.: Disseminierte Lipogranulomatose (Farber) – Kasuistischer Beitrag des 16. Falles einer Ceramidose. Verh. Dtsch. Ges. Pathol. **60**, 254–258 (1976)
5. Dustin, P., Tondeur, P. M., Jonniaux, G., Vamos-Hurwitz, E., Pelc, S.: La maladie de Farber. Etude anatomo-clinique et ultrastructurale. Bull. Acad. Med. Belg. **128**, 733–762 (1973)
6. Dulaney, J. T., Milemsky, A., Sidbury, J. B., Hobolth, N., Moser, H. W.: Diagnosis of lipogranulomatosis (Farber disease) by use of cultured fibroblasts. J. Pediatr. **89**, 59–61 (1976)
7. Farber, S.: A lipid metabolic disorder – disseminated "lipogranulomatosis". A syndrome with similarity to, and important difference from, Niemann-Pick and Hand-Schüller-Christian disease. Am. J. Diss. Child. **84**, 499–500 (1952)
8. Hers, H. G., van Hoof, F.: Genetic abnormalities of lysosomes. In: Lysosomes in biology and pathology, Dingle, J. T., Fell, H. B., (ed.) Vol. 2. Amsterdam, London: North-Holland Publ. Co.
9. Lazarus, S. S., Vethamany, V. G., Volk, B.: Fine structure of PHA-transformed lymphocytes from patients with Niemann-Pick disease. Arch. Pathol. (Chic.) **86**, 176–183 (1968)
10. Molz, G.: Farbersche Krankheit. Pathologisch-anatomische Befunde. Virchows Arch. Pathol. Anat. **344**, 86–99 (1968)
11. Moser, H. W., Prensky, A. L., Wolfe, H. J., Rosman, N. P.: Farber's lipogranulomatosis (report of a case and demonstration of an excess of free ceramide and ganglioside). Am. J. Med. **47**, 869–890 (1969)
12. Murata, F., Wohltman, H., Spicer, S. S., Nagata, T.: Fine structural and ultrachemical studies on the lymphocytes in three types of genetic mucopolysaccharidoses. Virchows Arch. Cell Pathol. **25**, 61–73 (1977)
13. Ozaki, H., Mizutani, M., Hayashi, H., Oka, E., Ohtahara, S., Kimoto, H., Tanaka, T., Hakozaki, H., Takahashi, K., Suzuki, Y.: Farber's disease (disseminated lipogranulomatosis): The first case reported in Japan. Acta Med. Okayama **32**(1), 69–79 (1978)
14. Rutsaert, J., Tondeur, M., Vamos-Hurwitz, E., Dustin, P.: The cellular lesions of Farber's disease and their experimental reproduction in tissue culture. Lab. Invest. **36**, 474–480 (1977)

15. Samuelsson, Zetterström, R.: Ceramides in a patient with lipogranulomatosis (Farber's disease) with chronic course. J. Scand. J. Clin. Lab. Invest. **27**, 393–403 (1971)
16. Sugita, M., Dulaney, J. T., Moser, H. W.: Ceramidase deficiency in Farber's disease (lipogranulomatosis). Science **178**, 1100–1102 (1972)
17. Toga, M., Berard-Badier, M., Pinsard, N., Gambarelli, D., Hassoun, J., Tripier, M. F.: Etude clinique, histologique et eltrastructurale de quatre cas de leucodystrophie métachromatique infantile et juvenile. Acta Neuropathol. **21**, 23–38 (172)
18. Zeman, W., Donahue, S.: Fine structure of the lipid bodies in juvenile amaurotic idiocy. Acta Neuropathol. **3**, 144–149 (1963)
19. Zetterström, R.: Disseminated lipogranulomatosis (Farber's disease). Acta Paediatr. (Uppsala) **47**, 501–510 (1958)

Received August 6, 1979