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Case report

Farber disease: an ultrastructural study

Report of a case and review of the literature

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Summary. A case of Farber disease is reported and the ultrastructural pathology of the disease is reviewed. The present case showed the typical clinical picture of Farber disease. Acid ceramidase deficiency was demonstrated biochemically. Ultrastructural features of one subcutaneous nodule and a skin biopsy are described. Three lysosomal inclusions characterize Farber disease: curvilinear tubular bodies observed mainly in the reticuloendothelial system, "banana bodies" recorded only in the peripheral nervous system and zebra-like bodies which are essentially a neuronal storage. The nature of each is discussed and the skin biopsy is emphasized for its important diagnostic interest.

Key words: Farber disease – Ultrastructural pathology – Ceramides – Skin biopsy

Introduction

Farber (1952) was first to describe disseminated lipogranulomatosis, regarding this disease as intermediate between an intracellular lipid metabolic disorder and Hand-Schüller-Christian histiocytosis. It has since been shown that it is in fact a neurolipidosis with autosomal recessive transmission (Farber 1952; Azanza 1969; Battin et al. 1970; Gellis and Feingold 1971; Amirhakimi et al. 1976; Pavone et al. 1980; Antonarakis et al. 1984; Burck et al. 1985; Zarbin et al. 1985). The enzymatic defect concerned is a lack of an acid ceramidase (EC 3.5.1.23) (Sugita et al. 1972) which carries out hydrolysis of ceramide into sphingosine and fatty acids. This enzyme has been shown to be completely or partly absent in leucocytes, viscera, cultured fibroblasts of patients and of their heterozygote carriers (Dulaney et al. 1976; Chen and Decker 1982; Momoi et al. 1982) and in cultured amniotic cells (Fensom et al. 1979). This defect brings about the accumulation of ceramides in the tissues (Prensky et al. 1967; Sugita et al. 1973; Chen and Decker 1982; Zarbin et al. 1988) in lysosomes (Chen et al. 1981).

Outstanding clinical features are articular symptoms (stiffness, pain and swelling, with amyotrophy) and mucocutaneous lesions consisting of nodules under periarticular skin, in the larynx (with hoarse or faint voice), less often in the occipital and lumbosacral regions, on the scalp, and on thoracic or abdominal walls. Psychomotor and staturoponderal retardation is present, as well as progressive cachexia and interstitial lung lesions (miliary, perihilar in distribution). In decreasing order adenomegaly, hepatosplenomegaly, macular cherry-red spot, conjunctival nodules, macroglossia, peripheral nervous symptoms (hypo- or areflexia) and central nervous system (CNS) disorders (axial hypotonia, limb paresis, myoclonus, fits) are noted. CNS disorders suggest a more severe prognosis (Moser et al. 1969). Coexistence with congenital hypothyroidism (Dustin et al. 1973; Toppet et al. 1978), Sandhoff disease (Fusch et al. 1989) or hydrocephalus (Rampini and Clausen 1967; Becker et al. 1976) may be found. Death usually occurs during the first 3 years of life, due to malnutrition and respiratory failure.

In connection with the ultrastructural changes found in periarticular subcutaneous nodules and a skin biopsy in one case, our study focuses on those ultrastructural features described in the literature. They seem to us to be important for confirmation of the diagnosis and have not yet been reviewed. The real value of skin biopsy in this disease will be emphasized.

Case report

The patient was the son of Tunisian first-cousin parents. From the age of 10 months, he displayed a psychomotor retardation and claw-like painful articular retraction of the fingers. When 14 months old, examination at Hôpital Debrousse (Lyon) revealed a mental age of 6 months, staturoponderal retardation (1.5 SD below the mean), small subcutaneous periarticular nodules of a few

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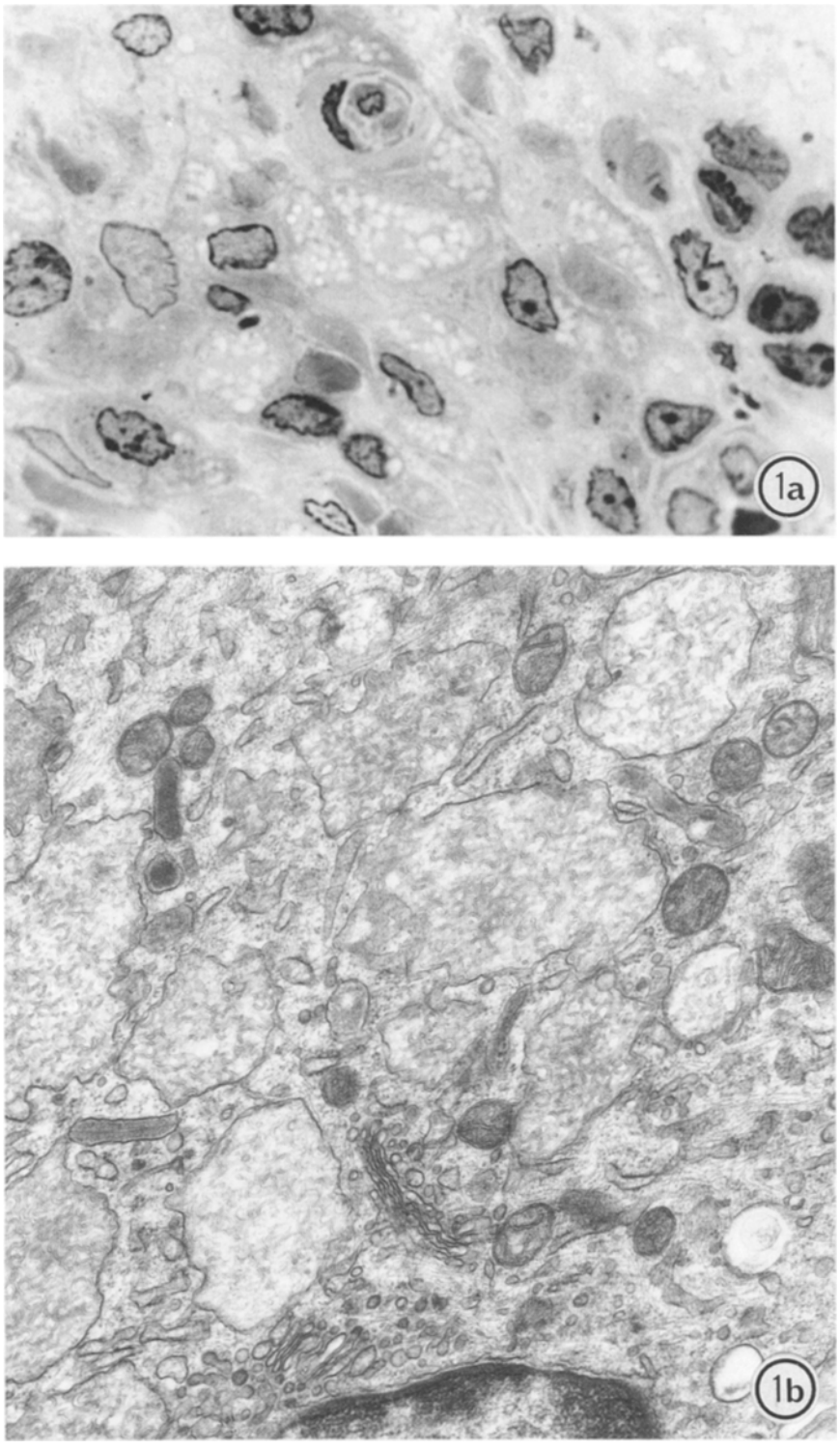

Fig. 1. Subcutaneous nodule biopsy: **a** semithin sections of the infiltrate showing spumous cells, ×600; **b** a histiocyte containing numerous lysosomal inclusions with curvilinear tubular bodies, ×24000

millimetres in size on the third, fourth and fifth fingers of the right hand, stiffness, pain and swelling of phalanges (mostly on the right hand), and of the knees and elbows. The voice was hoarse. The facies was peculiar with some lengthening and anteversion of the upper lip, and a mongoloid obliquity of the eyes. A macular cherry-red spot was found in the fundus. There was no hepatosplenomegaly.

The main biological investigations showed a major defect of the patient's leucocyte lysosomal acid ceramidase (Dr. Fensom, London) (0.003 mmol/h per mg protein). This defect was less marked in both parents (0.084 and 0.0107 mmol/h per mg protein). The normal values of two check samples were 0.260 and 0.280 mmol/h per mg protein. In his healthy sister no defect was found (0.224 mmol/h per mg protein). No biochemical analysis of the tissues, especially ceramides accumulation, has been performed.

Assays of hexosaminidase, cerebroside beta-galactosidase, galactosylceramidase, arylsulfatase A and beta-galactosidase in leucocytes yielded normal values. No storage cells were found in blood and bone marrow.

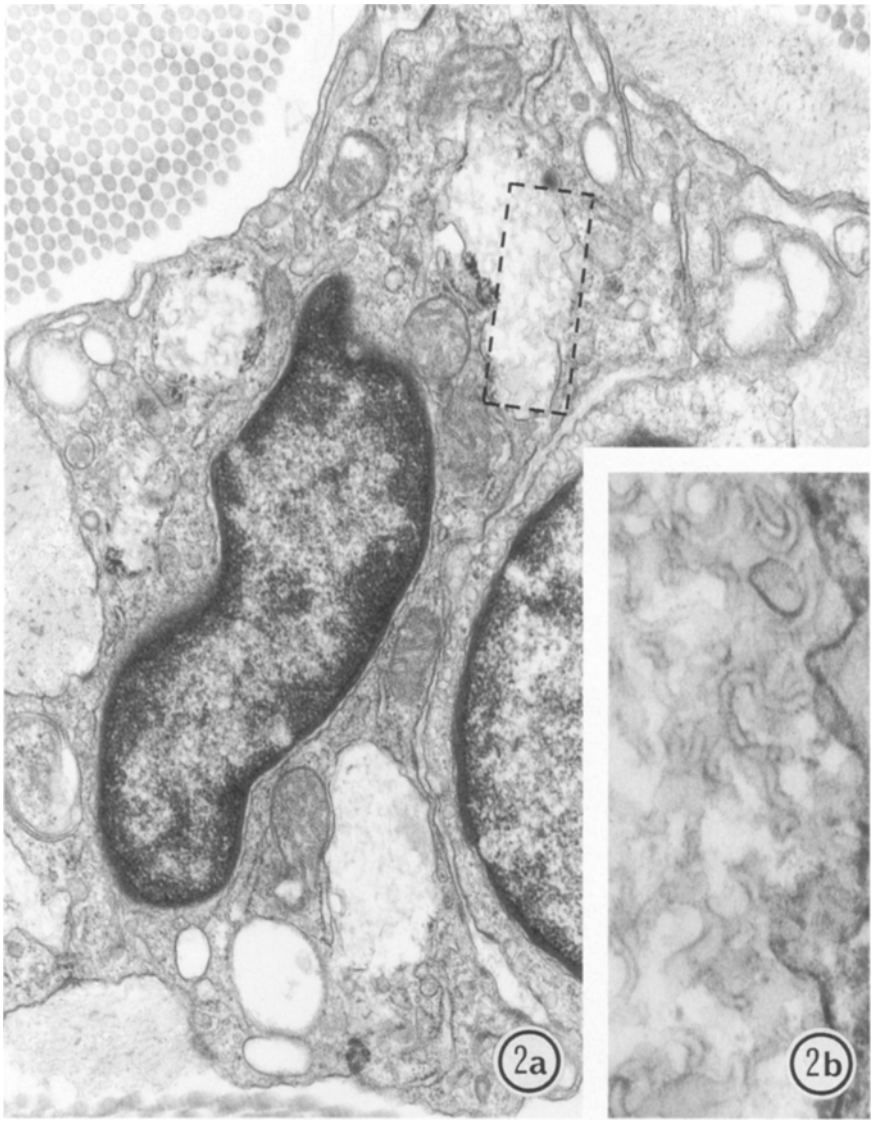

Fig. 2. Skin biopsy: **a** a fibroblast with membrane-bound inclusions, ×24000; **b** curvilinear tubular bodies with low dense matrix, ×95000

Other findings were a high level of proteins in the cerebrospinal fluid (1.03 g/l), a slight decrease of sensitive and motor conduction speeds in the sural nerve and mild cortical brain atrophy on CT scan. The karyotype was normal.

In view of the progressive worsening of articular symptoms and the psychomotor state, and of supervening bronchial obstruction phenomena with radiological perihilar miliary changes, a bone marrow graft was carried out (Dr. Souillet, Lyon). Rapidly, the subcutaneous finger nodules and articular complaints disappeared, the voice became less hoarse, radiological lung changes lessened and the amount of lysosomal acid ceramidase increased. However, psychomotor retardation worsened and the child died in Tunisia when 23 months old. No necropsy was performed.

Three specimens were obtained: two subcutaneous nodules, and one skin biopsy with hypodermis. One specimen of subcutaneous nodule was fixed in 10% formalin, embedded in paraffin and stained by haemalum-phloxine-saffron and periodic acid-Schiff (PAS) methods. Another specimen of subcutaneous nodule and the skin biopsy were fixed separately in 4% glutaraldehyde (Ladd 70%), and 2% formalin buffered with cacodylate 0.3 m/l (pH 7.4), post-fixed in 2% osmium tetroxyde buffered at pH 7.4 and stained "en bloc" with 2% aqueous uranyl acetate. After washing, tissues were dehydrated in graded ethanols and embedded in araldite. Semithin and ultrathin sections were prepared with a Reichert OMU 3 ultramicrotome. Semithin sections were stained with methylene blue-azur 2; ultrathin ones were contrasted with lead citrate and examined on a Jeol JEM 1200 EX electron microscope.

On light microscopy of the subcutaneous nodules it was evident that the lesions were situated in the deep dermis, and consisted of an accumulation of histiocytes with a finely granular or even foamy cytoplasm. The granulations were PAS-positive. There were no granulomas or fibrosis. Lymphoplasmocytic infiltration and capillaries with swollen endothelial cells were found in papillary dermis (Dr. Hermier, Lyon).

On semithin sections, the nodule was mainly formed by large mononucleated cells resembling histiocytes, some of which were foamy with some fibroblasts and histiocytes. Between these cells, the connective fibrillar frame was rich. Some dilated capillaries were found with swollen endothelial cells (Fig. 1a).

On electron microscopy, foamy cells contained numerous inclusions with variable sizes (0.5–2 μm), more or less rounded shapes, always membrane-bound. In these inclusions, curvilinear microtubular profiles accumulated (curvilinear tubular bodies, CTBs) from 15–17 nm in diameter (Fig. 1b). Most of these cells were histiocytes. Some were macrophages as attested by the presence of secondary lysosomes. Similar inclusions were observed, but in lesser number, in fairly numerous connective cells of the infiltrate.

The skin biopsy showed microvacuolization in some Schwann

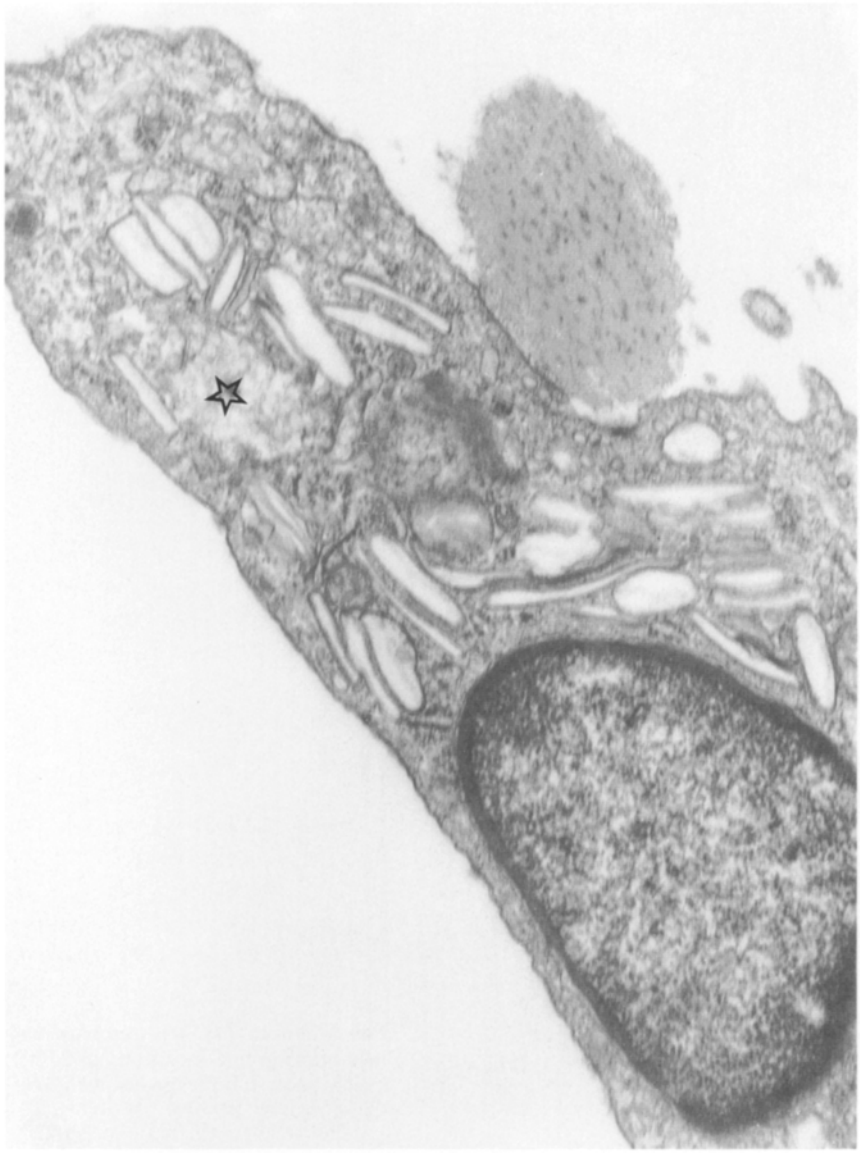

Fig. 3. Skin biopsy. A fibroblast showing clear lysosomal inclusions, ×24000. ☆ Inclusion with curvilinear tubular bodies

cells of small cutaneous nerves and, above all, a conspicuous vacuolization of sudoral gland cells which does not affect excretory ducts.

On electron microscopy, the storage involved fibroblasts, myelinated fibres in Schwann cell cytoplasm and secretory sweat cells. No pathological inclusions were found in endothelial and epidermal cells. The fibroblasts involved were mainly located around hair follicles and in the deep dermis, which appeared hypertrophied and hyperactive, with numerous figures of elastogenesis. They enclosed two types of lysosomes: some with curvilinear double-contour profiles in a low electron-dense amorphous material similar to those found in histiocytes of the cutaneous nodule (Fig. 2a, b), others oval or rhombohedric (500 nm/100–350 nm) with lucent material or with one or two arrays of osmiophilic material (Fig. 3). One zebra body was observed.

The cytoplasm of some Schwann cells in myelinated nerve fibres was packed with oval or spindle-shaped bodies (1–3 μm length) whose material, always with relatively low density, seemed to have been dissolved. These structures were evocative of "banana bodies" (Fig. 4). However, some of them enclosed one or two osmiophilic striations.

Many secretory sweat cells stored some typical zebra bodies, but mainly with more or less geometrical striations but no lamellar organelles (zebra-like bodies, Fig. 5). Always membrane-bound, these lysosomes were mainly located at the apical pole of the cell.

Some concentric lamellar bodies were encountered in histiocytes. Neural lesions are inconspicuous, consisting of disorganization in rare myelin sheaths.

Discussion

Fifty cases of Farber disease have been reported. Both males (23 cases) and females (22 cases) seem to be equally affected. Ten families (Farber 1952; Azanza 1969; Amirhakimi et al. 1976; Vital et al. 1976; Schmoeckel and Hohlfed 1979; Pavone et al. 1980; Antonarakis et al. 1984; Cartigny et al. 1985; Zarbin et al. 1985; Vaidya et al. 1987; Zarbin et al. 1988; Chanoki et al. 1989) have been recognized since 1952 with 23 siblings (including 2 twins) and one cousin. Consanguinity of parents, which is obvious in our case, was disclosed in 6 cases (Dustin et al. 1973; Amirhakimi et al. 1976; Ozaki et al.

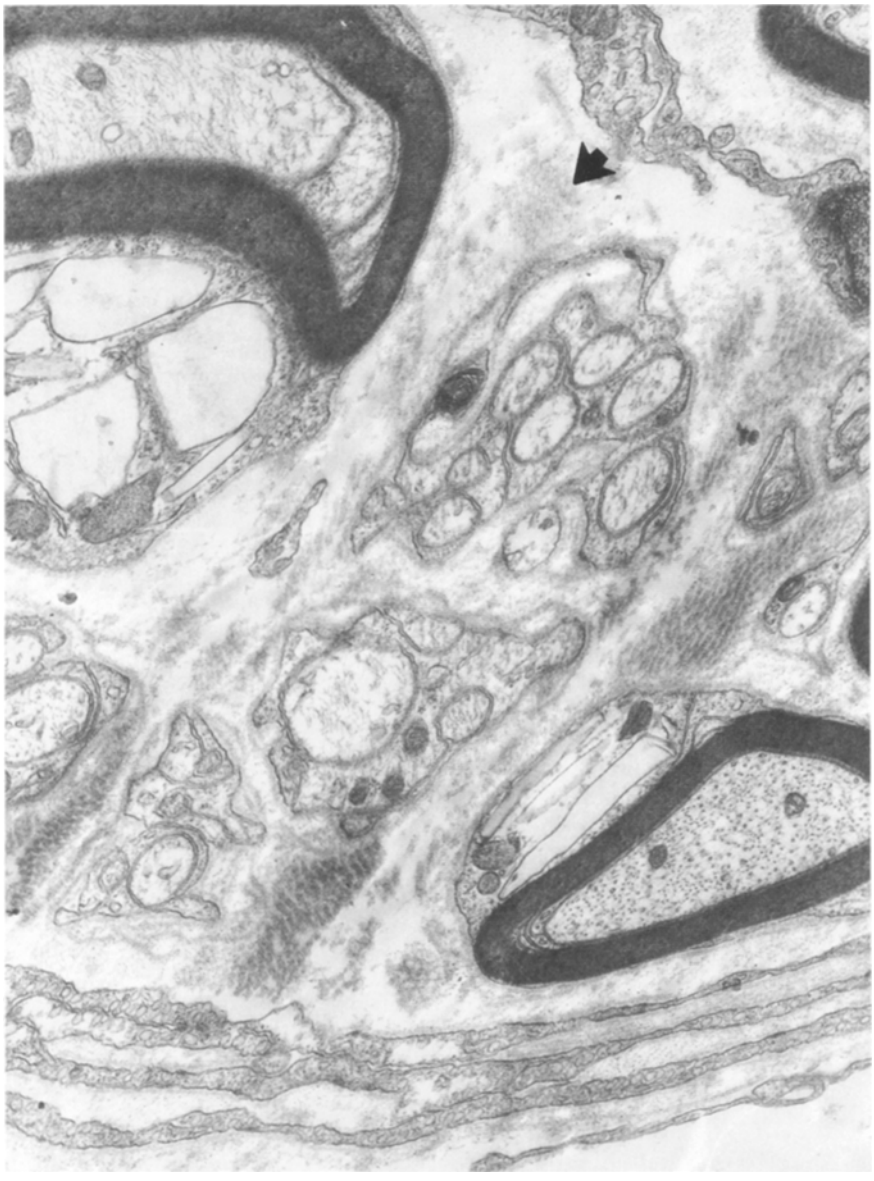

Fig. 4. Skin biopsy. Various shaped "banana bodies" of myelinated fibres in Schwann cell cytoplasm, ×20000. ➧ Connective tissue

1978; Pavone et al. 1980; Pellissier et al. 1986; Fusch et al. 1989). The enzyme deficiency was confirmed biochemically in only 20 of the 50 patients described. The onset of the disease occurs between birth and 4.5 years of age, with a mean age of 9 months.

Subcutaneous periarticular nodules are generally present, from some millimetres (as in our case) to several centimetres in diameter (Azanza 1969). They are sometimes absent (Antonarakis et al. 1984; Abenoza and Sibley 1987) or become apparent shortly before death (Pellissier et al. 1986). However, these 3 cases did not display the typical symptomatology of Farber disease.

The macular cherry-red spot, present in our patient, was found in 5 cases (Cogan et al. 1966; Ozaki et al. 1978; Zarbin et al. 1985; Pellissier et al. 1986; Fusch et al. 1989). The ocular lesions present in 3 other cases affected the conjunctiva (Zetterström 1958; Cartigny et al. 1985; Palcoux et al. 1985).

Death usually occurs before the age of 40 months (25 cases), as in our case. Some patients never presenting with visceral lesions had a more protracted course (Crocker et al. 1967; Samuelsson et al. 1972; Barrière and Gillot 1973; Schönenberg and Lindenfelser 1974; Amirhakimi et al. 1976; Differt 1977; Pachman et al. 1978; Pavone et al. 1980; Jameson et al. 1987). The disease may have different phenotypes: an early infantile form, to which our patient belonged, usually with a rapid course, and a late infantile one (Moser and Chen 1983; Burck et al. 1985).

With regard to the pathological changes, Moser et al. (1969) have shown in the rat that subcutaneous injection of ceramides obtained from a patient with Farber disease induced the formation of granulomas characteristic of this disease. At an early stage, nodules are made of foamy PAS-positive histiocytes, later infiltrated with lymphoplasmocytes and evolving towards fibrosis (Azanza 1969; Battin et al. 1970; Gellis and Feingold 1971; Barrière and Gillot 1973; Tanaka et al. 1979;

Table 1. Correlation between biochemical and morphological findings in cases studied ultrastructurally in the literature

Cases	Authors	Biochemical findings		Ultrastructural findings			
	(Ultrastructural study)	CD	Glycolipids accumulation	Nature of samples	Inclusions with CTBs	Banana bodies	Zebra-like bodies
1	Azanza (1969)		Acid glycolipids (spinal cord)	Spinal cord (a)			Anterior horn cells (+++)
2	Van Hoof and Hers (1973)		Ceramides (liver and subcutaneous nodule)	Liver (a)	Kupffer cells (+) Macrophages (+)		
				Subcutaneous nodule (a)	Histiocytes (+++)		
3	Dustin et al. (1973)	+	Ceramides with non-hydroxylated fatty acids (subcutaneous nodule)	Nodules (a) or (b) (subcutaneous, thymus, synovia, lung)	Histiocytes (+++)		
4	Becker et al. (1976)			Skin (b)	Fibroblasts (++)		Endothelial cells (++)
				Sural nerve (b)		Myelinated fibres in Schwann cells cytoplasm (++)	
				Cerebellum (a)			Endothelial cells (++)
5	Vital et al. (1976) Rivel et al. (1977)			Musculo-cutaneous nerve (b)		Myelinated fibres in Schwann cells cytoplasm (++)	
				Subcutaneous nodule (b)			Endothelial cells (++)
				Spinal cord (a)			Anterior horn cells (+++), pericytes (+++) endothelial cells (+++)
6	Tanaka et al. (1979)		Ceramides (subcutaneous nodule)	Subcutaneous nodule (b) Abdominal skin (a)	Fibroblasts Fibrocytes (+++)		Fibroblasts (rare) Fibrocytes (rare) Epidermal cells and pericytes (++)
7	Schmoeckel and Hohlfed (1979) Schmoeckel (1980)		Ceramides (subcutaneous nodule)	Subcutaneous nodule (b)	Fibroblasts (++) Fibrocytes (++) Histiocytes (++) Endothelial cells (++)	Myelinated fibres in Schwann cells cytoplasm (rare)	Endothelial cells (+)
8	Rauch and Auböck (1983)			Subcutaneous nodule (b)	Fibroblasts (++) Fibrocytes (++) Histiocytes (++) Endothelial cells (++)		
				Sural nerve (b)		Myelinated fibres in Schwann cells cytoplasm (+)	
				Cerebellum (a)			Endothelial cells and neurons
9	Antonarakis et al. (1984)	+	Ceramides (liver)	Spinal cord (a)			Anterior horn cells
10	Cartigny et al. (1985)	+		Subcutaneous nodule (b)	Histiocytes (+++)		
11	Burck et al. (1985)	+		Subcutaneous nodule (b)	Histiocytes (+++)		
				Skin (b)		Myelinated fibres in Schwann cell cytoplasm (+) Epidermal cells (+)	Epidermal cells (++)

Table 1 (continued)

Cases	Authors (Ultrastructural study)	Biochemical findings		Ultrastructural findings			
		CD	Glycolipids accumulation	Nature of samples	Inclusions with CTBs	Banana bodies	Zebra-like bodies
12	Zarbin et al. (1985)	+	Ceramides (+ + +) and cerebrosides (+) (retina)	Eye (a)			Ganglion, glial, endothelial cells of retina (+ + +) Glial cells of optic nerve (+ + +) Scleral fibrocytes Ganglion cells and inner plexiform layer of retina (zebra-like bodies with CTBs)
13 14	Pellissier et al. (1986)	+ +		Sural nerve (b) (cases 13 and 14)		Myelinated (+ +) and unmyelinated (rare) fibres in Schwann cell cytoplasm	
				Subcutaneous nodule (b) (case 13)	Histiocytes and macrophages (+ + +)		
15	Abenoza and Sibley (1987)	+		Skin (b)	Histiocytes (+)	Myelinated fibres in Schwann cell cytoplasm (+ +)	Histiocytes (+) Sweat gland duct cells (+)
				Liver (a)	Hepatocytes (+ +) Kupffer cells (+ + +)		Endothelial cells (+) Kupffer cells (+) Hepatocytes (+)
16	Fusch et al. (1989)	+ and HEX A and B	Ceramides (subcutaneous nodule)	Subcutaneous nodule (b)	Histiocytes (+ + +), macrophages (+ + +) endothelial cells and pericytes (+ + +)		Endothelial cells and pericytes (rare) Axons of unmyelinated fibres (rare)
17	Chanoki et al. (1989)			Subcutaneous nodule (b)	Fibroblasts (+ + +)		
18	Our case	+		Subcutaneous nodule (b) Skin (b)	Histiocytes (+ + +) Macrophages (+ +) Fibroblasts (+ +)	Myelinated fibres in Schwann cell cytoplasm (+ +)	Sweat secretory cells (+ +)

(a), Autopsy; (b), biopsy; CD, ceramidase deficiency; CTBs, curvilinear tubular bodies; HEX A and B, hexosaminidase A and B deficiency; (+), few; (+ +), abundant; (+ + +), very abundant or spumous cells

Schmoeckel 1980; Lake 1984). At postmortem examination such nodules are found in many viscera: larynx, tongue, lung, heart, liver, spleen, lymph nodes, digestive tract, intestinal lymphoid tissue, urinary system, less often articular synovia (Dustin et al. 1973; Vaidya et al. 1987), thyroid gland (Farber 1952), adrenals (Abenoza and Sibley 1987), striated muscle (Schönenberg and Lindenfelser 1974) or thymus (Molz 1968; Dustin et al. 1973; Schönenberg and Lindenfelser 1974).

Lipid storage has been recorded in swollen neurons of cerebral cortex, cerebellum, brain stem and anterior horns of spinal cord (13 out of 18 autopsied cases) and in peripheral nerve Schwann cells (10 cases). When PAS stain is used (Azanza 1969; Rivel et al. 1977), the stored material is PAS-positive. Similarly, a PAS, luxol oil red 0- and Sudan black-positive storage has been noted in neuronal cells of the retina (Zarbin et al. 1985).

These light microscopic changes have been explained by electron microscopy. Seventeen cases have been studied in the literature, as shown in Table 1. Three types of inclusions are characteristic of Farber disease: inclusions with CTBs, "banana bodies" and zebra-like bodies.

Inclusions with CTBs, first described by Van Hoof and Hers (1973), so-called Farber bodies (Schmoeckel 1980) or comma-shaped tubules (Abenoza and Sibley 1987) are observed mainly in the reticuloendothelial system (Table 1). Their size is variable (6–17 nm in diameter). We also found them in the same type of cells with comparable size.

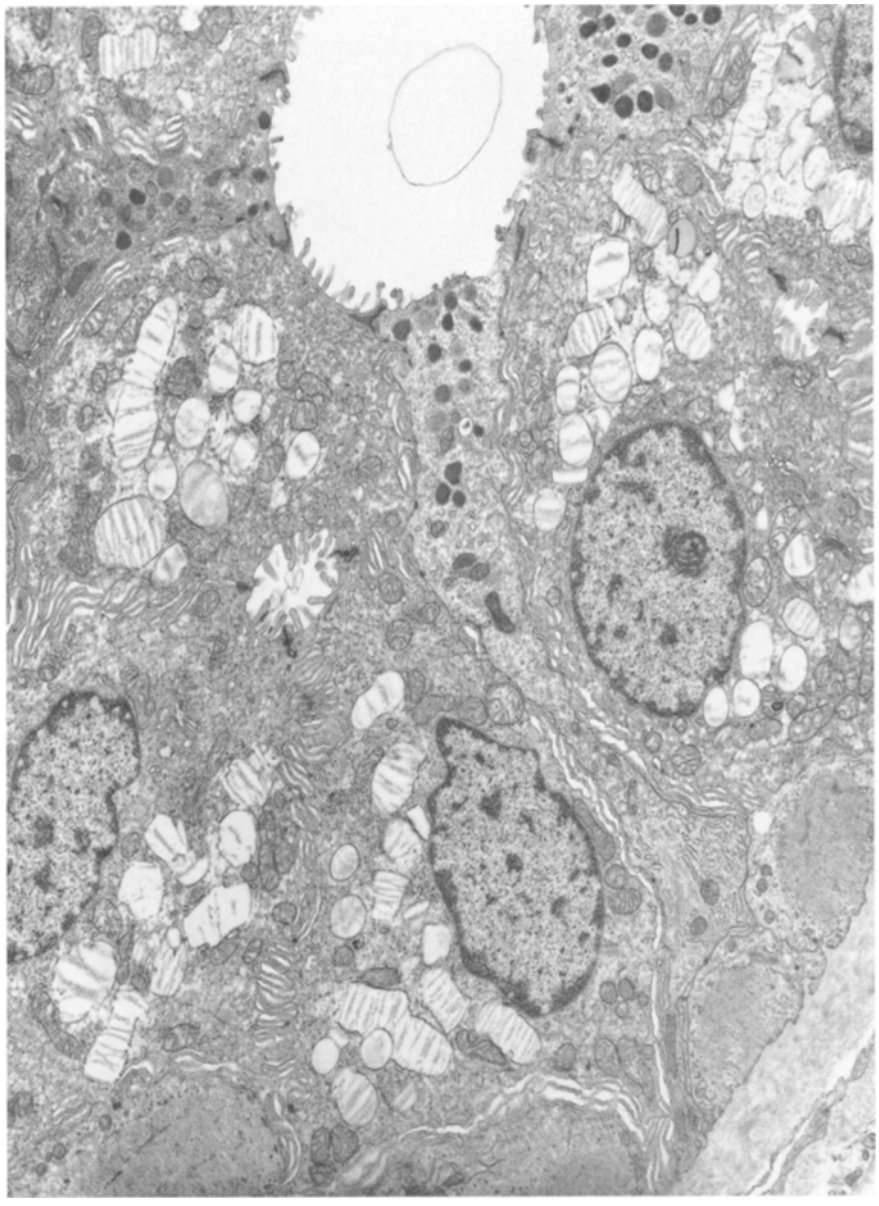

Fig. 5. Skin biopsy. Zebra-like bodies in sweat secretory cells, ×6000

Rutsaert et al. (1977) have reproduced them experimentally by culture of a patient's fibroblasts in a medium containing ceramide with non-hydroxylated fatty acids. Schmoeckel and Hohlfed (1979) were first to point out their specificity and they are still today regarded as very characteristic of the disease. Table 1 shows a good correlation between their presence and ceramide accumulation in subcutaneous nodules. It has been demonstrated that, in these nodules, stored ceramides contain non-hydroxylated fatty acids (Samuelsson et al. 1972).

Such CTBs cannot be mistaken for single profiled curvilinear bodies of ceroid lipofuscinosis (Carpenter et al. 1977; Goebel 1977) or twisted tubules found in fusiform or elongated lysosomes of Gaucher disease (Lee and Ellis 1968; Naito et al. 1988). CTBs are often found in an osmiophilic or low electron-dense finely granular material (Van Hoof and Hers 1973; Tanaka et al. 1979; Burck et al. 1985; Cartigny et al. 1985). With respect to these aspects, Dustin et al. (1973) suggest a transition between this matrix and tubular bodies.

"Banana bodies" (first described by Becker et al. 1976) are large (1.5–5 μm in length) membrane-bound, spindle-shaped vacuoles which often appear empty, sometimes with one or two osmiophilic arrays. They were also called needle-like inclusions by Burck et al. (1985). They have been recorded only in the peripheral nervous system and never found in the CNS, especially in the white matter. A certain analogy with characteristic inclusions of Krabbe leucodystrophy may be found. The latter, however, are much more angular (Yunis and Lee 1972) or cleft-like (Schlaepfer and Prensky 1972).

The neuronal lipid storage mainly consists of zebra or zebra-like bodies localized in restricted parts of the CNS (Table 1). The numerous lamellar bodies noted in retinal ganglion cells (case 12), corresponding to zebra-like bodies, are principally correlated with ceramide ac-

cumulation (Zarbin et al. 1988). Several biochemical forms of free ceramide are stored in Farber disease according to the nature of fatty acids (Sugita et al. 1972; Zarbin et al. 1988). The form with non-hydroxylated fatty acids seems to correspond to CTB inclusions (Rutsaert et al. 1977). Therefore the zebra-like bodies in this disease could represent the accumulation of different types of ceramide, especially hydroxylated fatty acid ceramides associated with other complex lipids. Coexistence of CTBs in zebra-like bodies (case 12) shows that non-hydroxylated fatty acid ceramides may also be present.

However, zebra bodies are in no way specific to Farber disease. They are usually found in the CNS neurons of types 1 and 2 mucopolysaccharidosis (Aleu et al. 1965; Johannessen 1978) and GM1 gangliosidosis (Goebel 1984), where they also represent complex lipids, mainly gangliosides.

Banana bodies may also represent heterogenous accumulations of ceramides and complex lipids in a particular site, the Schwann cell. In Farber disease heterogeneity of the fatty acids suggests that ceramides come from locally produced lipids (Samuelsson et al. 1972). It may be that the fatty acids in Schwann cells come from myelin.

Other non-specific inclusions are often present, beside these characteristic ones. The most frequent are vacuoles (empty or with lipids or with granular material) described in hepatocytes, fibroblasts or histiocytes by several authors, and dense bodies or concentric lamellar bodies. "Angulate lysosomes" were noted by Dustin et al. (1973) in histiocytes of nodules. They may represent secondary storage as found in any neurolipidosis. Chanoki et al. (1989) showed, with ruthenium red, that mucopolysaccharides accumulate in histiocytes of subcutaneous nodules. Some of them are perhaps related to ceramide storage and could represent transition material in the formation of ceramides. In our case rhomboidal inclusions noted in fibroblasts of the skin biopsy have never been described. We saw no transitional forms between them and CTBs.

Polymorphism of storage is found in skin biopsies. Four cases (Becker et al. 1976; Burck et al. 1985; Abenoza and Sibley 1987) and our own case report have described them. In three cases, CTB inclusions, the most characteristic, were found in connective cells. They were absent in case 11 (Burck et al. 1985), but banana bodies are very suggestive of the disease. Indeed, they represent the morphological substratum of the storage in a peripheral nerve biopsy (Vital et al. 1976; Rauch and Auböck 1983; Pellissier et al. 1986). Zebra-like bodies which, in our case, are numerous in sweat secretory cells, have only been found by Abenoza and Sibley (1987) in sweat excretory cells. The homogeneity and the localization of this storage have never been documented in other sphingolipidosis, and we think that such inclusions in this situation may be highly suggestive of the disease.

The ultrastructural study of skin biopsy, which is easy to obtain, seems to be especially valuable and to have a major diagnostic interest in clinically atypical forms of the disease, such as the case of Antonarakis et al. (1984), which appeared as a malignant histiocytosis, the patient of Pellissier et al. (1986), who had central and peripheral nervous symptoms, and the patient of Abenoza and Sibley (1987), who exhibited articular stiffness, hepatosplenomegaly and facial erythematous lesions. In each case, subcutaneous nodules were absent or appeared only shortly before death.

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