

ANGIOKERATOMA CORPORIS DIFFUSUM (FABRY DISEASE): ULTRASTRUCTURAL STUDIES OF THE SKIN

Takehiko Nakamura,¹ Hiroshi Kaneko² and Isao Nishino³

¹Joetsushi, ²Department of Pathology, Nagaoka Red Cross Hospital, Nagaokashi and ³Department of Internal Medicine, Niigata, Rosai Hospital, Joetsushi, Japan

Abstract. A case of Fabry disease in a 34-year-old male who had typical exanthemas and familial occurrence is reported. Biochemical examinations revealed a decreased level of serum α -galactosidase (0.04 n mol/h/cc). On electronmicroscopy the granules specific for Fabry disease were observed in the skin lesions. By the excessive accumulation of specific granules in the vascular wall, the endothelial cells were replaced by thrombi and the muscle cells were disarrayed. This process might be followed by the appearance of teleangiectatic eruptions.

Key words: X-linked recessive disease; α -galactosidase; glyco-sphingo-lipidosis; Ceramide trihexoside; Angiokeratoma corporis diffusum

Fabry disease was first reported in 1898 by Fabry & Anderson (3, 1). It is an X-linked recessive disease. Its familial occurrence is frequent. Sweeley & Kliensky (9) defined the disease biochemically as sphingo-lipidosis, showing an accumulation of trihexosyl-ceramide by deficiency of α -galactosidase. There are many generalized small exanthemas, which coincide with an involution of the kidney, as well as of other visceral organs. A 34-year-old male with typical manifestations of Fabry disease was encountered and examined ultrastructurally and biochemically. There was a patient suffering from this disease in his family line.

CASE REPORT

History

The patient, a 34-year-old male, had had episodes of fever over 38°C, general myalgia, arthralgia, and fatigue several times a year over a period from about 5 to 13 years of age. In his family anamnesis, a 27-year-old male cousin is suffering from similar symptoms.

He first noticed dark-red punctate eruptions scattered in the lower abdominal region at about 20 years of age. The lesions gradually spread to the chest, back, inguinal region, scrotum and parts of the extremities. At 23 years of age, he was found to have proteinuria and edema of the lower extremities and was hospitalized on the diagnosis of

nephritis. Thereafter, he had continuous proteinuria and edema of the feet. At 31 years of age, he felt residual urine and was suspected to have prostatic illness. At 32 years of age (2 years ago), he noticed general malaise and felt oppression in the chest when he moved. Fever, vomiting and edema were not seen. On January 25, 1977, he was hospitalized with the chief complaints of pain in the right latus, proteinuria and malaise.

Physical examination

Stature and nutrition were moderate. Blood pressure was 129/90. Pulse, 72. Body temperature, 36.6°C. Pain in the right latus on pressure. Clusters of dark-red, punctate teleangiectasias were seen on the lower abdomen, the anterior surface of the chest, inguinal region, scrotum, and some parts of the extremities. They were almost symmetric, about pin-head in size, partly elevated and symptomless (Fig. 1). Joints were not swollen, though erythematous and hot to the touch.

Laboratory findings

Hb, 14.6 g/dl. WBC, 9600 with normal differential and platelet counts. Urinalysis showed 1.5% of protein. PSP, 32%/15 min and 67%/120 min. Fishberg concentration test, below 1.015. Creatinine clearance, 102 l/day. Bleeding time, 2½ min. Coagulation time, 7 min. Urea N, 12 mg/dl. Creatinine, 1.4 mg/dl. Uric acid, 5.6 mg/dl. Na, 142 mEq/l. K, 4.5 mEq/l. Cl, 103 mEq/l. CRP, (-). ASLO, 320. ASK, 640. Serum protein, 7.3 g/dl. A/G ratio, 1.5. Al, 60.0%. α_1 , 2.4. α_2 , 7.0. β , 10.7. γ , 19.9. GOT, 13. GPT, 14. Alkaline phosphatase, 5.6 mU/ml. Total cholesterol, 162 mg/dl. LDH, 322. LAP, 201. Serologic test for syphilis, negative. The electrocardiogram and chest X-ray were normal. Activity of serum α -galactosidase, 0.04 n mol/h/cc. Renal biopsy showed the findings of proliferative glomerulonephritis.

HISTOPATHOLOGICAL FINDINGS

Light microscopy

Specimens were obtained from two different lesions by punch biopsy. Microscopically, dilatation of blood capillaries was seen in the papillae of the dermis and within fibrinous thrombi in some places showing organization. In the areas surrounding the

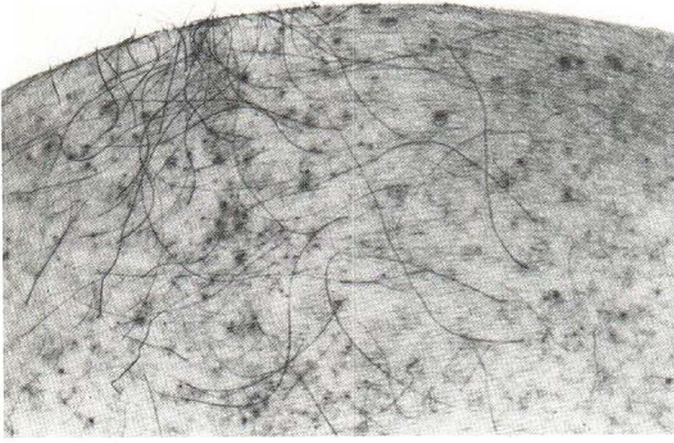


Fig. 1. Many punctate, teleangiectatic eruptions of the lower abdominal region.

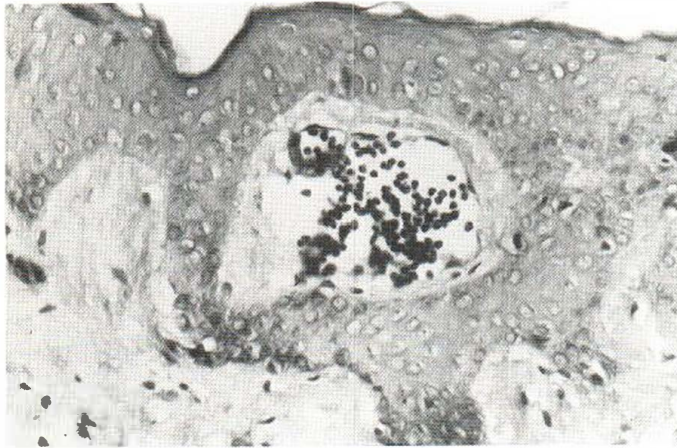


Fig. 2. Capillary dilatation in the papillary region of the dermis. H.E. $\times 160$.

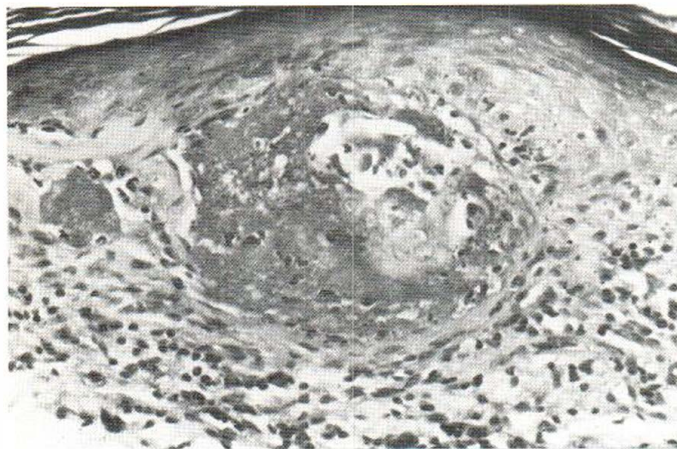


Fig. 3. Thrombus with organization is seen in the dilated capillary. H.E. $\times 160$.

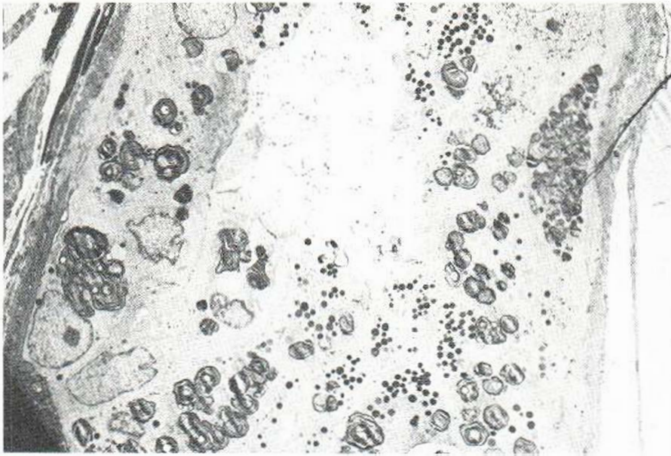


Fig. 4. A large amount of granules specific for Fabry disease in the eccrine gland. 800 \times .

capillaries, lymphocytes, histiocytes and others infiltrated and fibroblasts increased (Figs. 2 and 3).

PAS staining showed, although rarely, the presence of fine PAS-positive granules in the cytoplasm of the sweat glands. In some regions of subcutaneous fatty tissue, fine yellowish-brown granules were noticed in the wall of the capillaries.

Electronmicroscopy

Specimens were fixed in glutaraldehyde following osmium tetroxide in phosphate buffer at pH 7.4. They were embedded in Epon 812. Sections were stained with uranyl acetate and lead acetate and examined in the Hitachi HS-9 electronmicroscope. Numerous granules characteristic of Fabry disease were observed in many cells, such as endothelial cells of capillaries and veins, muscle cells of the

media, glandular, ductal, and myoepithelial cells of the sweat gland, and fibroblasts. They showed electron density ranging from low to high and a myelin-like, concentric, lamellar structure. They were very small, massive, confluent granules and so numerous as to occupy almost all the cytoplasm. A few of the granules were delimited by limiting membrane (Figs. 4 and 5).

Endothelial cells might be replaced by thrombi in places because they destroyed due to an excessive accumulation of granules (Fig. 6). Granules were largely deposited in the smooth muscle cells of the venous media. They were frequently seen near both sides of the nucleus on the line of apsides. From the overhead view of the media, there was seen a disarray in the structure of the venous wall (Fig. 7).

Nothing particular was seen in mitochondria, Golgi plexus, or any other organelle.

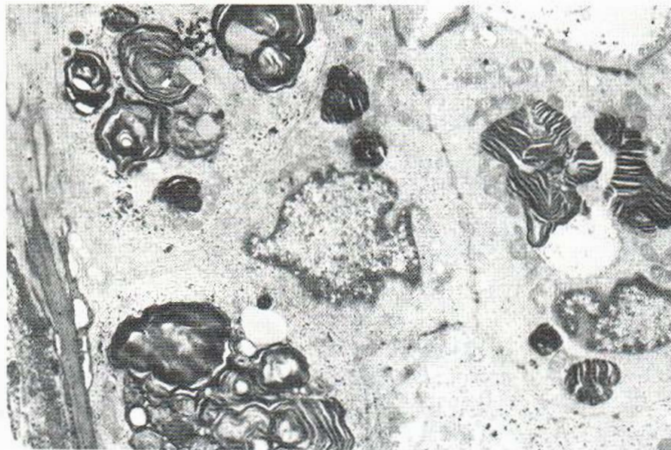


Fig. 5. Higher magnification of Fig. 4. 2400 \times .



Fig. 6. Endothelial cells are injured and replaced by thrombus. 4000 \times .



Fig. 7. The media, showing the accumulation of the specific granules and disarrangement of the muscle cells. The intima is replaced by thrombus.

DISCUSSION

It is evident from the many findings that this is a case of Fabry disease. It was characterized by familial occurrence, a marked decrease in serum α -galactosidase and characteristic electronmicroscopic changes. This disease was first reported as purpura hemorrhagica nodularis by Fabry (3) in 1898. Later, it was called angiokeratoma corporis diffusum. In addition to cardiomegaly, hypertension, renal lesions and nervous symptoms, the deposition of a substance in the blood vessels of visceral organs all over the body was found by Ruiter (8) at autopsy. He reported the disease to be a systemic one involving visceral organs. Sweeley et al. (9) extracted high concentrations of ceramide trihexoside and ceramide dihexoside, both of which are glycolipids, from the kidney. Brady et al. (2) demonstrated the deficiency of ceramide trihexosidase in the intestinal mucosa. In 1970, the deficiency of α -galactosidase was found in the leukocytes by Kint (6). It is said that the deficiency of α -galactosidase activity in the serum and leukocytes is of the greatest of value for the diagnosis of Fabry disease.

At all events, Fabry disease is considered to be one of the representative diseases caused by glycosphingolipidosis and is at present characterized by the accumulation of trihexosyl ceramide due to α -galactosidase deficiency (7).

On electronmicroscopy, granules specific for Fabry disease are observed in various organs and tissues, such as kidney, liver, spleen, digestive canal, lung, skin, eye, bone marrow, nerve, and muscle. In the skin, the specific granules were found in the endothelial cells and pericytes of blood vessels, the sweat gland, fibroblast, connective tissue cells of the perineurium, and Schwann's cells. Hashimoto et al. (4, 5) have proposed the following theory with reference to the formation of specific granules. Lysosomal inclusion might start as small acid-phosphatase-positive vesicles. As they gradually grow by accumulation of a laminated substance, they may lose acid phosphatase activity. Primary lysosomes containing acid phosphatase may fuse with lipid substances in the cytoplasm, but they may be unable to digest these substances because of an inherited defect of the enzyme required. This might result in the formation of huge secondary lysosomes: these are specific granules. However, because acid phosphatase can be detected in various organelles other than lysosomes, Hashimoto's theory is not accepted completely.

In the case presented, specific granules were distributed in the same cells and tissues as mentioned in references. In particular, large numbers of granules were detected in the eccrine glands. Vascular changes were worthy of mention. By the excessive accumulation of specific granules the endothelial cells were injured and replaced by thrombi. A disarrangement of cells in the media of blood vessels was also explained by the accumulation of granules in muscle cells. It is reasonable to

presume that this might be followed by the appearance of the telangiectatic lesions.

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H. Kaneko, M.D.
Department of Pathology
Nagaoka Red Cross Hospital
Nagaokashi, 940
Japan