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A Case of Farber Lipogranulomatosis

A 35 month old girl had suffered from painful joint contractures of the whole body since a few months after birth, and she gradually developed numerous periarticular and subcutaneous nodules, hoarseness, swallowing difficulty with recurrent respiratory infections, nystagmus, and mental and developmental retardation. She was misdiagnosed as having juvenile rheumatoid arthritis at several university hospitals. Serologic studies for rheumatoid arthritis were all negative. Radiologic findings of the whole body showed osteoporosis and bony erosions; on brain CT the brain was diffusely atrophied. On cine-esophagography barium refluxed into the nasopharynx. Light microscopically, the reticular dermis and subcutis were markedly thickened with hyalinized sclerotic collagen bundles. There were interstitial and perivascular aggregates of foamy histiocytes which were positive for CD-68 immunostaining. On electron microscopy, foamy histiocytes were packed with numerous membrane-bound inclusions having C-shaped or worm-like profiles in addition to many myelin figures, occasional lipid droplets and rare banana-like bodies.

Key Words : *Farber lipogranulomatosis, Ultrastructural finding*

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INTRODUCTION

Farber lipogranulomatosis, first described by Farber et al. in 1957, is an extremely rare disease and is thought to be inherited as an autosomal recessive trait. Its manifestations are present at or shortly after birth and rapidly progress and the baby usually dies before 2 years of age (1). Its clinical manifestations are painful joint swelling and contracture, nodules in periarticular skin and larynx, psychomotor and mental retardation, intermittent lung infection, central nervous system (CNS) symptoms (paresis, axial hypotonia, myoclonus, nystagmus) and cachexia (2). The enzymatic defect is a lack of acid ceramidase (3), and a marked decrease or absence of ceramidase activity in leukocyte, viscera, and cultured fibroblast was confirmed (4). Two-thirds of the reported cases were diagnosed with this disease by pathognomonic ultrastructural findings, lysosomal inclusion bodies; zebra-like inclusions in neuronal storage, curvilinear inclusions in reticuloendothelial systems, and banana-like inclusions in peripheral nervous systems (5, 6). In our case, there were numerous membrane-bound inclusions having curvilinear tubular structures and rare banana-like bodies in foamy histiocytes of the skin nodule.

CASE REPORT

A 35-month-old girl showed weak sucking power and a hoarse cry shortly after birth; painful joint contractures of most joints developed after she was 5 months old followed by hoarseness, nystagmus, swallowing difficulty, developmental retardation, and periarticular subcutaneous nodules (Fig. 1). She had been diagnosed as a juvenile rheumatoid arthritis at several university hospitals.

Her body weight was below 3 percentiles, she looked cachectic. Her eyes showed very rapid spontaneous pendular nystagmus which aggravated by vertical gaze. Most joints, especially small ones, were contractured, nearly fixed and she felt much pain on motion. She could not sit, stand, walk and could not speak even a word. She could swallow only small granules and frequently regurgitated. Many subcutaneous nodules were scattered on the periarticular skin of the whole body. The size of the nodules was variable from 3 mm to 1 cm. Intercostal and subcostal retractions were noted, and the breathing sound was coarse. The heart beat was fast (140/min) but no murmur was heard. The lymph node enlargement was not noted. The size of the tongue was not enlarged. The liver edge was palpable and but the spleen was not

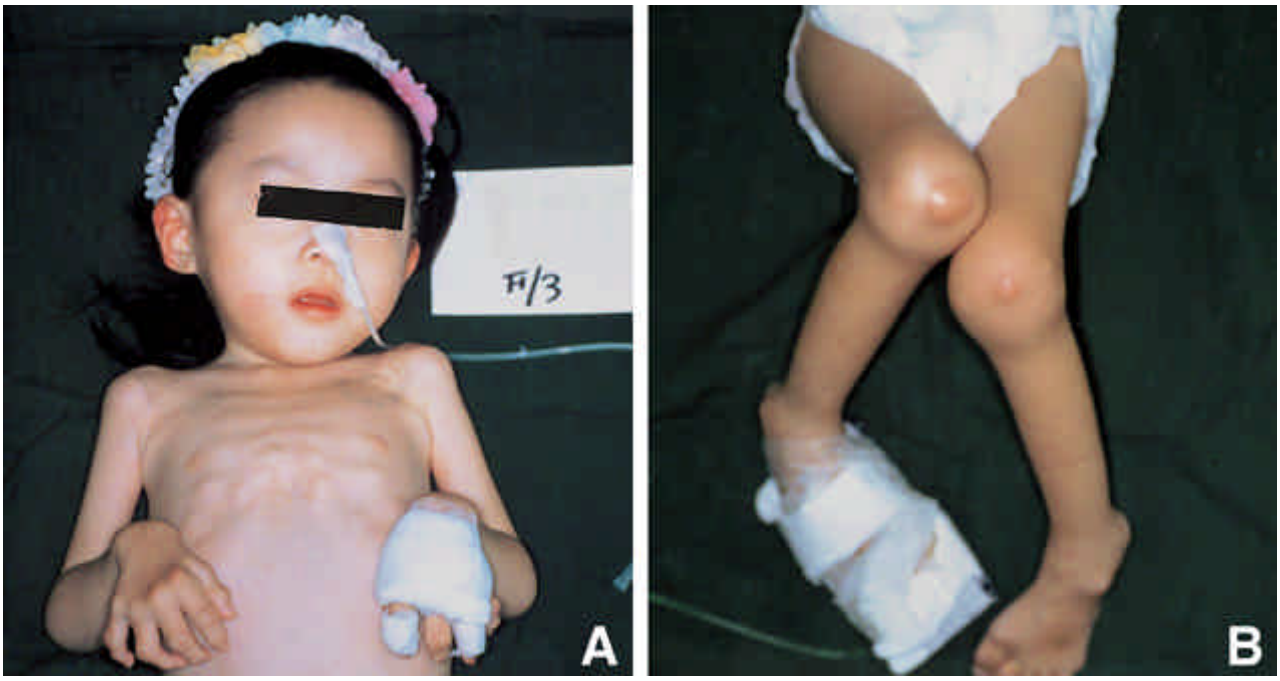

Fig. 1. Severely cachectic patient with Farber disease showing periarticular swelling, flexion contractures of most joints, and multiple periarticular subcutaneous nodules.

palpable. The neck was very stiff and deep tendon reflexes were normal. Farber disease was suggested clinically on account of the typical findings including painful, swollen and contractured joints, skin nodules, hoarseness, neurologic abnormalities such as developmental retardation, swallowing difficulty and nystagmus (Fig. 1).

Serologic tests for rheumatoid arthritis (antinuclear antibody, lupus erythematosus cell, antiperinuclear factor, and complements) were all within normal limits. CBC, urinalysis, liver transaminases, and muscle enzyme tests

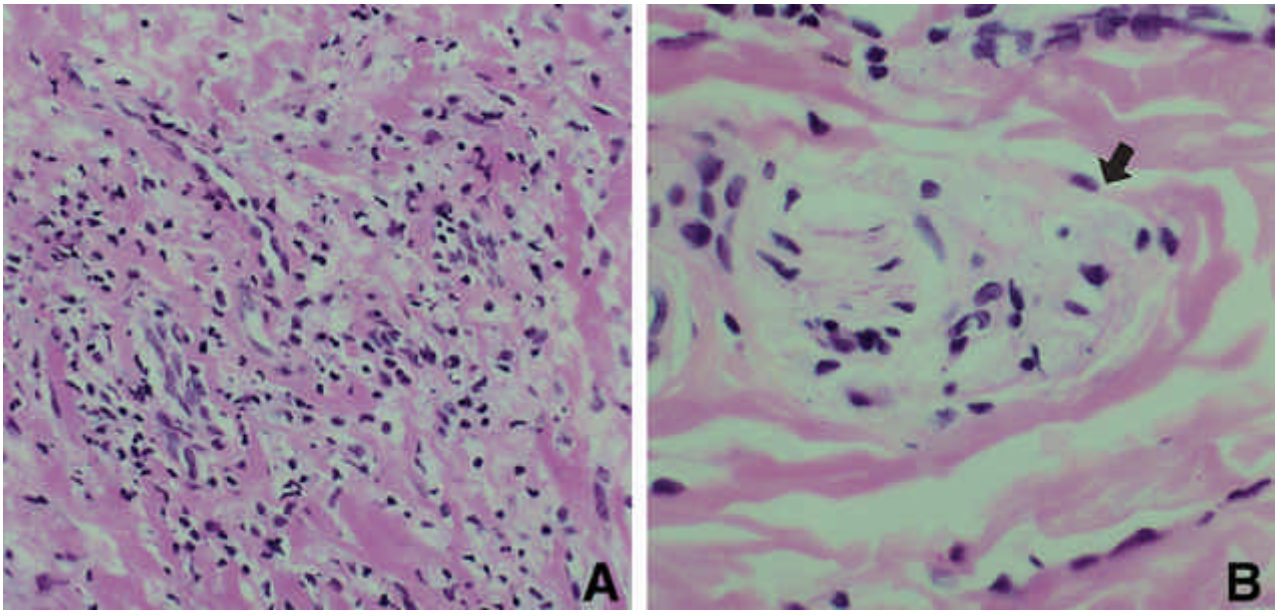

Fig. 2. Skin biopsy of a subcutaneous nodule showing sclerotic dermis and subcutis with interstitial and perivascular aggregates of foamy histiocytes (A). Microvacuolization in some Schwann's cells of cutaneous nerves was present (B, arrow) (Hematoxylin-eosin stain, A×400, B×200).

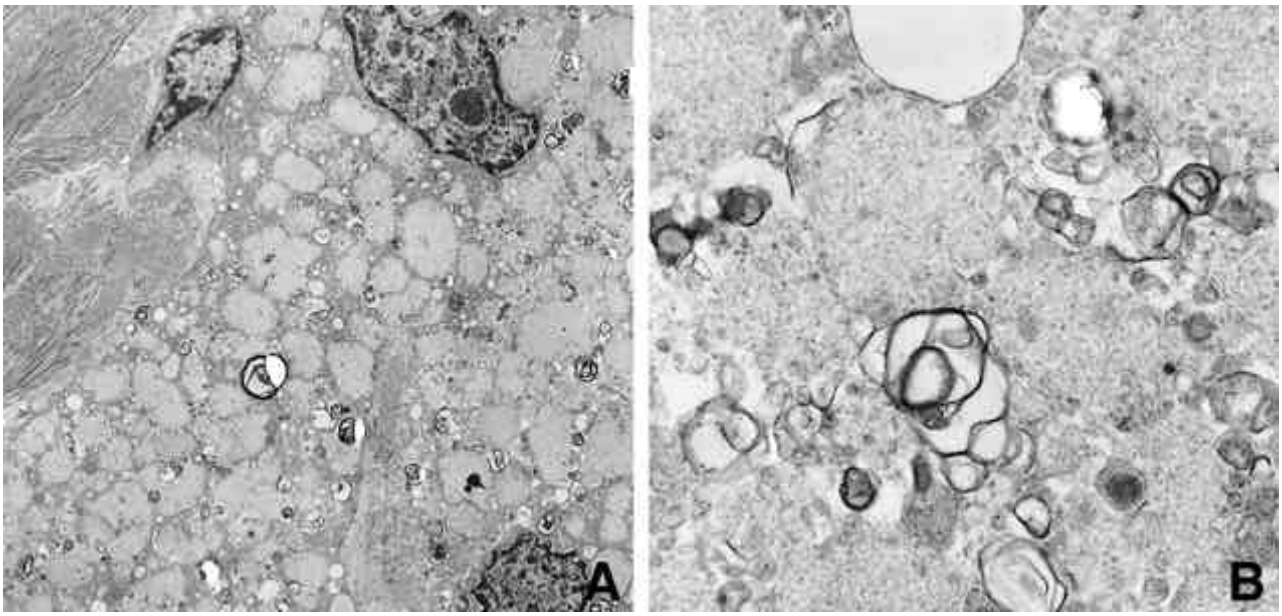

Fig. 3. On electron microscopy, foamy histiocytes were packed with numerous membrane-bound inclusions (A×3,000) having c-shaped or worm-like profiles in addition to many myelin figures, and occasional lipid droplets (B×27,000).

were all unremarkable. Radiologic findings were multiple consolidation in both lungs on chest PA film, barium reflux into the nasopharynx on cine-esophagography, profound osteoporosis, epiphyseal enlargement, bony erosion and soft tissue swelling on bone x-ray films, and diffuse brain atrophy on brain CT.

An excisional biopsy was performed from a periarticular nodule of the left index finger. Light microscopically, the epidermis was unremarkable except for mild hyperkeratosis. The reticular dermis and subcutis were markedly thickened with hyalinized sclerotic collagen bundles. There were interstitial and perivascular aggregates of foamy histiocytes (Fig. 2A). Most of the foamy histiocytes were PAS-negative although some histiocytes contained PAS-positive and D-PAS-positive granules in the cytoplasm. Foamy histiocytes were positive for CD-68 immunostaining. Some increase of mast cells, elongated small blood vessels with plump endothelial cells and mild perivascular infiltration of lymphocytes and a few plasma cells were also seen in the superficial and deep reticular dermis. Microvacuolization in some Schwann's cells of cutaneous nerve was present (Fig. 2B). However no granuloma was found. Elastic van-Gieson stain revealed decrease of elastic fibers in the sclerotic dermis. Alcian blue and colloidal iron stain failed to reveal mucin deposits. On electron microscopy, foamy histiocytes were packed with numerous membrane-bound inclusions (Fig. 3A) in addition to many myelin figures, occasional lipid droplets, and rare banana-like bodies. These membrane-bound inclusions were also found in fibroblasts and endothelial cells, and had c-shaped or worm-like profiles (about 31.7 to 47.6 nm thick) (Fig. 3B). Zebra-like bodies were not found.

The authors performed a skin biopsy from the nodule on the patients hand to take fibroblast in which the acid ceramidase deficiency could be confirmed. The fibroblasts were contaminated with bacteria during culture, but the parent would not allow the second biopsy of the nodule. So the authors could not confirm acid ceramidase deficiency. The patient was discharged with no clinical improvement except for pneumonia. The patient died one year later at home due to severe pneumonia and respiratory failure.

DISCUSSION

Farber disease is a very rare disorder of the lipid metabolism that is inherited as an autosomal recessive trait and the primary biochemical defect is a deficiency of lysosomal acid ceramidase (N-acylsphingosine deacyase), which results in tissue accumulation of ceramide. In most cases the clinical manifestations are present shortly after birth; hyperesthesia of the joints followed by painful joint swelling and periarticular subcutaneous nodules, hoarse cry, swallowing disturbance, respiratory distress, joint rigidity with flexion contractures, progressive course with recurrent infections, neurologic deterioration, failure to thrive and severe inanition (1).

The types of Farber disease are severe, intermediate,

and mild according to the involvement of visceral organ and the length of life (7). Subcutaneous nodules and vocal cord thickening are present in all types. The patients of severe type die before 4 years of age, mentally retarded, and show one or more visceral organ involvement. Those of intermediate type live more than 4 years old, are mentally retarded, but show no visceral organ involvement. Those of mild type usually live longer than 10 years of life, do not present visceral organ involvement, but some of them show mental retardation. This case showed lung and CNS lesion, died before 4 years old, so belongs to the severe type of Farber disease.

Pathogenesis of these clinical manifestations results from accumulated ceramide which causes proliferation of histiocytes, lymphocytes and fibroblasts in skin, subcutaneous tissues, tendons, synovium, viscera and nervous system (1, 3).

Clinical manifestation, biochemical study of acid ceramidase deficiency, and ultrastructural findings are required to confirm Farber disease. In this case fibroblasts taken from the skin nodule were contaminated with bacteria during culture, so acid ceramidase deficiency could not be confirmed. But clinical and ultrastructural findings definitely helped us to diagnose Farber disease. Ultrastructurally, three lysosomal inclusions characterize Farber disease: inclusions with curvilinear tubular bodies (CTBs), banana-like bodies and zebra-like bodies (6). Inclusions with CTBs, first described in 1973 (8), so-called Farber bodies (9), are observed mainly in the reticuloendothelial system. These curvilinear profiles were also seen in neuronal lipofuscinosis and their fine structural defects were different (10). Banana-like bodies, first described in 1976 (11), also called needle-like inclusions (5) are large membrane-bound, spindle-shaped vacuoles which often appear empty, sometimes with one or two osmiophilic arrays and are noted only in the peripheral nervous system, never in the central nervous system (6). Zebra or zebra-like bodies, numerous lamellar bodies, are noted in the central nervous system and are correlated with ceramide accumulation.

In this case membrane-bound inclusions having CTBs, rare banana-like bodies and many myelin figures were noted in histiocytes, fibroblasts and endothelial cells of the skin nodule. These findings are the hallmark of Farber disease. Even though we have not proven enzymatic deficiency, this case is typical of Farber disease on account of ultrastructural and clinical findings and is the first reported case in Korea.

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