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Histological characterisation of visceral changes in a patient with type 2 Gaucher disease treated with enzyme replacement therapy

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ABSTRACT

Gaucher disease is a lysosomal storage disease caused by deficiency of glucocerebrosidase and accumulation of glucocerebroside. Three major sub-types have been described, type 2 is an acute neurological form that exhibits serious general symptoms and poor prognosis, compared with the other types. This case was a girl diagnosed with type 2 Gaucher disease at 12 months of age who presented with poor weight gain from infancy, stridor, hypertonia, hepatosplenomegaly, trismus and an eye movement disorder. Enzyme replacement therapy (ERT) was administered, but she had frequent myoclonus and developmental regression. She needed artificial ventilation because of respiratory failure. She died at 11 years of age. An autopsy demonstrated infiltrating CD68-positive large cells containing abundant lipids in alveoli, while in the liver, kidney and bone marrow CD68-positive cells were small and round. In the bone marrow, myelodysplastic changes were present without Gaucher cells. The infiltration of Gaucher cells in alveoli was marked, suggesting that ERT was relatively ineffective in pulmonary involvement, particularly intra-alveolar. Additional treatments are necessary to improve the neurological and pulmonary prognosis of type 2Gaucher disease.

1. Introduction

Gaucher disease is an autosomal recessive lysosomal storage disease caused by deficiency of the enzyme glucocerebrosidase which leads to the accumulation of glucocerebroside in macrophages and the reticuloendothelial system. Three major sub-types have been described, based on the absence (type 1) or presence (type 2 and 3) of a neurological component in addition to the visceral findings [1]. Type 2 is an acute neuronopathic disease, which exhibits serious general symptoms compared with the other types, with a poor prognosis.

Pulmonary involvement is not uncommon in type 2 and 3 Gaucher disease, while distinctly rare in type 1 [1,2]. Pulmonary symptoms are observed in 67% of Gaucher disease type 2 (GD2) cases [3]. The mean survival age of GD2 is 11.7 months (range 2–25 months), and pulmonary symptoms (GD-pneumopathy) and aspiration caused by Gaucher disease or the aggravation of respiratory conditions such as central apnea are the cause of 50% of fatal cases [3].

The number of patients with neuronopathic Gaucher disease is lower than patients with type 1 in the world, and there have been few pathological reports of this subtype. A female case with neuronopathic Gaucher disease presented at our hospital and underwent enzyme replacement therapy (ERT) with respiratory care. She survived until 11 years of age despite severe progressive neurologic and respiratory symptoms. Here, we report her clinical course and pathological findings based on a postmortem examination.

2. Case report

2.1. Clinical course

The case was a girl who was 12 months of age at her first visit. Her gestation period was 38 weeks and birth weight was 2524 g. The patient was born by normal delivery without asphyxia. Her weight gain was poor from 6 months of age. She choked easily during lactation and stridor was observed. Her parents noticed that she frequently stretched out her lower limbs and threw her head back. She was referred to our

Abbreviations: ERT, enzyme replacement therapy; ACP, acid phosphatase; ACE, angiotensin converting enzyme; GC, Gaucher cells; GD2, Gaucher disease Type 2.

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hospital at 12 months of age. There was no family medical history of note, and no consanguineous marriage.

At the first visit, her weight was 6780 g (−2.2 SD) and she had remarkable inspiratory stridor when crying but no hoarseness. There was no murmur or cardiac arrhythmia. Her upper abdomen was swollen and hard. The liver was palpable 6 cm and the spleen 8 cm below the costal margin. There was no redness of the pharynx or enlarged lymph nodes. Neurologically there was an increase in muscle tone, trismus, and strabismus. Her patella tendon reflex was slightly enhanced but parachute reflex was not induced. A sitting position was possible, but balancing was difficult. The developmental quotient (DQ) using the Enjoji Developmental Scale was 80 [4].

Laboratory findings at the first visit are shown in Table 1. A decrease in platelets and an increase in acid phosphatase (ACP) and angiotensin converting enzyme (ACE) were observed. Chest X-ray showed an infiltrative shadow and granular shadow in both lung fields with poor permeability. A head CT scan was normal. The abdominal CT confirmed remarkable hepatosplenomegaly but masses or enlarged lymph nodes were absent. Bone marrow examination showed large cells with wide pale-stained cytoplasm, eccentrically located nuclei and wrinkled cytoplasm (Fig. 1) considered to be Gaucher cells. The leukocyte β-glucosidase activity of the bone marrow culture was 2.8% of normal values (1.5 nmol/mg protein/h). The F213I/R463C mutation was identified by genetic testing.

The patient was diagnosed with Gaucher disease type 2 because the patient had stridor, hypertonia, eye movement disorder, delayed development from infancy, marked convulsions, myoclonus, and developmental regression which progressed rapidly immediately after her first visit.

Enzyme replacement therapy with imiglucerase (ERT, 60 units/kg/2 weeks intravenously) was administered from 12 months of age. Hepatosplenomegaly resolved, along with improvement in the platelet count. The neurologic symptoms such as opisthotonus and convulsions however, deteriorated and required the administration of anticonvulsants, valproic acid and zonisamide. The patient developed intractable convulsion and was bed-ridden. Airway obstruction caused by a lower respiratory tract infection and viscous respiratory secretion occurred and resulted in repeated hospitalizations. Respiratory failure progressed and a tracheostomy was performed for artificial ventilation when she was 2.5 years of age, after informed consent from her parents.

Table 1
Blood examination at first visit.

Factor	Measurement
WBC	8700/μl
RBC	394×10^4/μl
Hemoglobin	11.3 g/dl
Platelet	6.0×10^4/μl
C-reactive protein	0.2 mg/dl
Blood sugar	91 mg/dl
AST	66 IU/l
ALT	26 IU/l
LDH	350 IU/l
ALP	249 IU/l
Creatinine kinase	44 IU/l
Ammonia	31 μg/dl
Urea	11.3 mg/dl
Creatinine	0.2 mg/dl
Blood gas analysis	Normal
Thyroid hormone	Normal
ACE	76.7 U/l
ACP	97.5 U/l
CMV-IgM	(−)
CMV-IgG	(+)
EBV-VCA-IgM	(−)
EBV-VCA-IgG	(−)
EBNA	(−)
HAV-IgM	(−)
HBs-Antigen/antibody	(−)/(−)
HCV	(−)

ACE: Angiotensin converting enzyme, ACP: acid phosphatase, AST: aspartate aminotransferase, ALT: Alanine aminotransferase, CMV: Cytomegalovirus, EBV: Epstein-Barr virus, HAV: Hepatitis A virus, HBs: Hepatitis B surface, HCV: Hepatitis C virus.

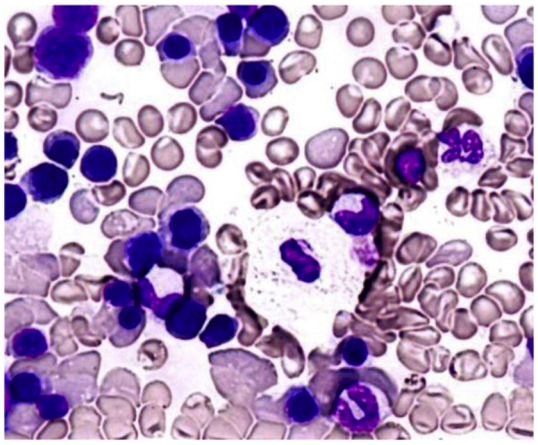

Fig. 1. Bone marrow examination at first visit. Large cell with clear and large cytoplasm, and with the nucleus pushed off to the side. Nucleated cell count: 10.4×10^4/μl, Megakaryocytes: 18.8/μl. (May-Giemsa stain ×400).

She had no cough reflex during suction and less frequent convulsion from 11 years of age. A decrease in platelet counts and anemia with anisocytosis and dyskaryosis of neutrophils became severe from 11.5 years of age and she became transfusion dependent.

At the time of the final hospitalization (11.9 years old), she had lower limb edema with petechiae and purpura. The abdomen was slightly distended and soft and 1 cm of the liver was palpated, although the spleen was not palpated. She had lost some hair and thick eschar was attached to the scalp. Gingival bleeding was observed. Laboratory examinations showed increased inflammatory response, hypoproteinemia, renal impairment and respiratory acidosis. The biomarkers angiotensin converting enzyme and acid phosphatase were not elevated. Her general condition gradually worsened and the patient died at 11 years and 10 months. We obtained consent from her family to perform an autopsy.

We performed autopsy imaging and percutaneous needle biopsy 1 h postmortem, and obtained bone marrow, liver, lung, and kidney tissues. We used May-Giemsa stain for bone marrow, hematoxylin and eosin (HE) stain for the liver, lung and kidney, and PAS stain and Masson-Trichrome stain for the kidney. We performed CD68 immunostaining to identify Gaucher cells.

2.2. Findings at autopsy

The findings of autopsy imaging are shown in Fig. 2. The CT findings of the lung showed bilateral infiltrative shadow with air-bronchogram and atelectasis. The head MRI indicated significant atrophy of the cerebral parenchyma, lateral ventricle expansion and subcutaneous edema. Abdominal CT (3D imaging) showed that scoliosis was evident, hepatomegaly was not remarkable and splenomegaly was not seen.

The findings of histological examinations were follows.

Lung (Fig. 3): Significant fibrous hypertrophic stroma of the visceral pleura was seen with inflammatory cell infiltrate and interstitial fibrosis. High numbers of large macrophages that phagocytized lipids were observed in alveoli.

Liver: Inflammation of the bile canaliculi and phagocytosis of bile pigments by phagocytes were observed.

Kidney (Fig. 4): A total of 24 glomeruli were obtained and two sclerotic glomeruli and one fibrous crescent were seen along with interstitial edema, fibrosis and tubular atrophy. Exfoliation of renal tubular epithelial cells from the basement membrane was present, while

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