

A very rare cause of protein losing enteropathy: Gaucher disease

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ABSTRACT

Background. Mesenteric lymphadenopathy is a rare manifestation of Gaucher disease (GD) in children and can be accompanied by protein losing enteropathy (PLE). PLE is a difficult-to-treat complication of GD. To date, only a few pediatric GD cases with PLE and massive mesenteric lymphadenopathies have been reported.

Case. Here, we report a girl with chronic neuronopathic GD, whose disease course was complicated by massive mesenteric lymphadenopathies with resultant protein losing enteropathy despite a regular and appropriate enzyme replacement therapy of 60 IU/kg/biweekly until the development of mesenteric lymphadenopathies and 120 IU/kg/biweekly thereafter.

Conclusions. PLE is a devastating and life threatening complication of GD developing despite long term use of high dose ERT. Clinicians should be alert for this complication particularly in GD patients presenting with progressive abdominal distension, edema, ascites and diarrhea or in patients who have already developed mesenteric lymphadenopathies. Timely diagnosis may allow early intervention with previously suggested surgical or medical treatment options. Although there is no specific and effective treatment, surgical and aggressive medical interventions in addition to ERT were reported to relieve diarrhea and halt progression of mesenteric lymphadenopathies.

Key words: enzyme replacement therapy; lymphadenopathy; lysosomal storage disorder; Gaucher disease.

Gaucher disease (GD) is a rare, autosomal recessive genetic disorder caused by deficiency of lysosomal enzyme, glucocerebrosidase, which results in the accumulation of glucocerebrosidase-laden macrophages (Gaucher cells) in the reticuloendothelial system.¹ Mesenteric lymphadenopathy is a rare manifestation of GD in children and can be accompanied

by protein losing enteropathy (PLE). PLE is a difficult-to-treat complication of GD. To date, only a few pediatric GD cases with PLE and massive mesenteric lymphadenopathies have been reported.¹⁻⁴ Here, we report a girl with chronic neuronopathic GD whose disease course was complicated by massive mesenteric lymphadenopathies with resultant protein losing enteropathy despite a regular and appropriate enzyme replacement therapy (ERT).

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Case Report

The patient was the first child of non-consanguineous parents and the diagnosis of GD was made at the age of 18 months. At the time of diagnosis, she had severe hepatosplenomegaly

and pancytopenia (Table I). Her neurological examination was completely normal initially. Gaucher cells were seen on bone marrow aspirate and leukocyte enzyme assay showed decreased beta glucocerebrosidase activity. Diagnosis was confirmed with genetic testing showing a compound heterozygosity (L393V and L444P mutations) in the *GBA* gene. ERT with imiglucerase at an intravenous dose of 60 IU/kg/biweekly was started immediately. A splenectomy was performed because of hypersplenism and intractable pancytopenia at the age of 3.5 years (Table I). On routine follow-up visit at the age of 5 years, physical examination revealed an ill-defined abdominal mass. Ultrasound and computed tomography (CT) of abdomen demonstrated a lobulated, heterogeneous mass reaching a diameter of 8 cm and consisting of multiple conglomerated mesenteric lymphadenopathies with cystic degeneration and calcification (Fig. 1). A simultaneously performed CT of the chest also revealed accompanying axillary, supraclavicular, paratracheal, and hilar lymphadenopathies. A tru-cut biopsy from abdominal mass was performed with a high suspicion of lymphoma. Histopathology of biopsy specimens revealed a completely effaced lymph node structure by diffuse infiltration of Gaucher cells with no evidence of malignancy.⁵ Treatment dose of imiglucerase was escalated to 120 IU/kg/biweekly. The patient remained

clinically stable without any change in the size of lymph nodes for 7 years following dose escalation. Imiglucerase-specific antibodies were not detected at routine controls. At 10 years of age oculomotor apraxia and hearing loss developed and she was diagnosed as type 3 Gaucher disease.

The patient was hospitalized with the symptoms of chronic watery diarrhea and progressive abdominal distention at the age of 12 years. Physical examination showed ascites and generalized edema in addition to a palpable abdominal mass. Laboratory examinations revealed hypoalbuminemia and hypoproteinemia with electrolyte imbalance and alkalosis. Hepatic synthetic function tests and urine evaluation for albuminuria were normal. Acute phase reactants were negative. There was no evidence of pathogenic bacteria, viruses and parasites in stool examinations. Echocardiographic evaluation was normal. Fecal alpha-1 antitrypsin level was elevated suggesting an excessive protein loss from the intestinal system. Abdominal ultrasound confirmed the presence of moderate ascites and persisting giant conglomerated mesenteric lymphadenopathies (Table I). Gastrointestinal symptoms were relieved partially with supportive treatment including intermittent albumin infusions, fluid and electrolyte replacement, medium chain triglyceride (MCT)-enriched oil supplementation and parenteral



Fig. 1. Ultrasound imaging (A) and CT scan of the abdomen (B) showing a large, lobulated and heterogeneous abdominal mass consisting of conglomerated mesenteric lymphadenopathies some of which exhibiting cystic degeneration and calcification (5 years of age). Follow-up CT scan of the abdomen (C) showing similar radiological findings with areas of cystic breakdown and more extensive calcification in enlarged lymph nodes (7 years of age). No regression in radiological findings was observed despite high dose ERT (120 IU/kg/biweekly).

Table I. Laboratory and imaging parameters of the patient at critical time points.

Parameters	Time point (age of the patient)		
	Diagnosis (18 months)	Splenectomy (3.5 years)	Development of mesenteric lymphadenopathies (5 years)
Complete blood count			
Hemoglobin (g/dl)	5	5.3	12.9
White cell/lymphocyte count (/mm ³)	5,900/2,900	5,700/3,600	15,900/7,100
Platelet count (/mm ³)	17,000	23,000	487,000
Serum biochemical profile			
ALT/AST (U/L)	8/37	5/33	19/49
GGT/ALP (U/L)	17/117	27/85	21/154
Total / conjugated bilirubin (mg/dl)	0.83/0.39	0.46/0.18	0.12/0.01
Albumin / total protein (g/dl)	3.42/5.97	3.5/6.7	4.32/7.19
BUN / creatinine (mg/dl)	7.1/0.19	13/0.27	15.1/0.18
Sodium / potassium / chloride (mEq/L)	135/3.2/106	139/4.5/101	134/5/100
Triglyceride / cholesterol (mg/dl)	163/37	-	134/196
Further evaluation	Increased ACE level Gaucher cells in BMA Decreased glucocerebrosidase activity Compound heterozygosity of L393V and L444P in the GBA gene	Histopathology of the splenectomy specimen: Compatible with Gaucher disease	Slight neutrophil predominance on the peripheral smear. Normocellular BMA with no evidence of blastic infiltration Histopathology of the tru-cut biopsy specimen: Completely effaced lymph node structure by diffuse infiltration of Gaucher cells
Abdominal imaging	Hepatomegaly, massive splenomegaly, splenic parenchymal heterogeneity, peripheral hypodense splenic lesions suggesting areas of splenic infarction Insufficient response to ERT in terms of spleen volume		Chemical and microbiological stool examinations: Normal Urinalysis: Normal Serum APR levels: Normal Echocardiography: Normal Increased fecal alpha-1 antitrypsin level

ALT: alanine aminotransferase, ALP: alkaline phosphatase, APR: acute phase reactants, AST: aspartate aminotransferase, BMA: bone marrow aspiration, BUN: blood urea nitrogen, ERT: enzyme replacement therapy, GGT: gamma-glutamyl transpeptidase.

nutrition while continuing high dose ERT. However, the patient died of complications of PLE during outpatient follow-up.

Informed consent was received from the family.

Discussion

Including the present case, only five pediatric cases with GD whose disease course were complicated with PLE have been reported to date (Table II).¹⁻⁴ Parallel with our observations, all previously reported cases were on ERT before presenting with this life threatening complication. ERT is a safe and effective option for the treatment of visceral and hematological manifestations of GD; however, central nervous system, lymph nodes and lungs have been reported to show insufficient response to this treatment or even unresponsive to ERT compared to other tissues.⁶ It is postulated that these organs are relatively inaccessible to intravenously administered enzyme. The mechanistic basis for poor permeability of enzyme to lungs and lymph nodes is still a matter of debate. Effacement of normal lymph node architecture with Gaucher cells and resultant histological changes such as fibrosis and calcification may reduce drug access to lymph nodes.

Calcified mesenteric lymphadenopathy seems to be a common finding in GD complicated by PLE. Autopsy of a boy with GD who developed progressive mesenteric lymphadenopathies and PLE showed an acellular material with areas of calcification in place of normal lymphoid tissue.⁷ Lymph node calcification was also reported previously in a 16-year-old boy and in a 4.6-year-old boy both of whom had neuronopathic GD and PLE.^{2,3} We also observed progressive calcification of mesenteric lymph nodes in our patient (Fig. 1).

Another contributing factor might be the development of antibodies against the enzyme. Neutralizing antibodies might possibly lead to a reduction in treatment efficacy. Lee et al.² reported a patient who was tested positive

for antibodies to enzyme and developed progressive mesenteric lymphadenopathy with resultant PLE.

Splenectomy might also be considered as a contributing factor in the development of lymphadenopathies as it may lead to deposition of substrates in other reticuloendothelial organs.⁸ It is recommended to spare splenectomy for cases of splenic rupture or cases not responding to well conducted ERT with persistent severe cytopenia related to massive splenomegaly, as was the case in the present patient. To our knowledge none of the previously reported patients had a history of splenectomy. Removal of the spleen might have contributed to the enlarged mesenteric lymph nodes in our patient and played an indirect role in the development of PLE.

Lymph node involvement in GD is not restricted to intraabdominal region. Abdelwahab et al.⁴ reported eight children with GD type 1 and 3 developing mediastinal lymphadenopathy in addition to mesenteric lymph node enlargement and underscored the importance of awareness of this complication as it can easily be confused with malignancy both clinically and radiologically. Despite being less prominent, mediastinal, axillary and supraclavicular lymphadenopathies were also present in our patient and we had to perform a biopsy to rule out lymphoma.⁵

All patients in the literature including the present case were chronic neuronopathic GD patients carrying L444P mutation in *GBA* gene (Table II). However, it is impossible to make a definitive conclusion regarding phenotype-genotype relationship as there is very limited data. Although PLE has not been reported with non-neuronopathic phenotype, mesenteric lymphadenopathies were also reported to develop in children with type 1 GD.⁴

PLE in a GD patient most likely results from secondary lymphatic obstruction. Enlarged mesenteric lymph nodes block mesenteric lymphatic outflow resulting in

Table II. Clinical characteristics of the present case and previously reported pediatric patients with Gaucher disease and protein losing enteropathy.

	Case 1	Case 2	Case 3	Case 4	Present case
Age (years)	5	4.6	16	5	12
Gender	Male	Male	Male	Male	Female
Genotype	D409H/L444P/A456P/ K79N	L444P/L444P	L444P/L444P	L444P/L444P	L393V/L444P
Phenotype	Chronic neuronopathic	Chronic neuronopathic	Chronic neuronopathic	Chronic neuronopathic	Chronic neuronopathic
Preceding ERT	(+)	(+)	(+)	(+)	(+)
Preceding splenectomy (indication)	(-)	(-)	(-)	(-)	(+)
ERT/SRT (Dose at last follow-up)	(+)/(-) 60 IU/kg/weekly	(+)/(-) 120 IU/kg/biweekly	(+)/(-) 100 IU/kg/biweekly / 400 mg/day	(+)/(-) 60 IU/kg/biweekly	(+)/(-) 120 IU/kg/biweekly
Accompanying manifestations	Thrombophilia, ascites, peripheral edema, mediastinal lymphadenopathy, parenchymal and interstitial lung disease, <i>A. israelii</i> and <i>C. difficile</i> infections	Retropertoneal, inguinal and paraesophageal lymphadenopathies, abdominal distention and respiratory difficulty	Weight loss, abdominal pain	Pelvic abdominal masses with cystic breakdown and multiple flecks of calcification, hilar and mediastinal lymphadenopathies, ascites	Axillary, supraclavicular, paratracheal and hilar lymphadenopathies, progressive abdominal distention, ascites, peripheral edema

ERT: enzyme replacement therapy, MCT: medium chain triglyceride, PLE: protein losing enteropathy, SRT: substrate reduction therapy.

Table II. Continued.

	Case 1	Case 2	Case 3	Case 4	Present case
Mesenteric lymphadenopathy	(+)	(+)	(+)	(+)	(+)
Treatment for PLE	-ERT: Increase in dosing frequency -Symptomatic management with MCT containing diet, fluid and electrolyte replacement, albumin supplementation, total parenteral nutrition was needed later in disease course	-ERT: Dose escalation -Intermittent albumin infusions, high-protein diet with supplementation of MCT	-ERT: Dose escalation -SRT: Continued as it was -Low fat diet supplemented with 30 ml of MCT oil 3 times a day, along with 9 mg daily oral budesonide and total parenteral nutrition (overnight, 6 nights a week)	-ERT: No change -Albumin infusions	-ERT: Dose escalation -Intermittent albumin infusions, fluid and electrolyte replacement and daily MCT-enriched oil supplementation
Lymphadenectomy	(-)	(+) Serial partial excisions of lymph nodes with adhesiolysis	(-)	(-)	(-)
Treatment response	No reduction in lymphadenopathies, there is progression of sequelae of PLE, succumbed to death at 12.5 years due to continued progression of his many comorbidities	Diarrhea was resolved	Decrease in number and density of lymph nodes, diarrhea and abdominal pain were resolved, patient gained weight and serum albumin normalized	Died of an unexplained cause	No reduction in lymphadenopathies, stable with supportive care but died of an unexplained cause during outpatient follow-up
Reference	Burrow et al. (2, 8)	Lee et al. (3)	Mhammi et al. (4)	Abdelwahab et al. (5)	Present report

ERT: enzyme replacement therapy, MCT: medium chain triglyceride, PLE: protein losing enteropathy, SRT: substrate reduction therapy.

increased lymphatic pressure and intestinal lymphangiectasia which eventually leads to PLE. Development of PLE seems to deteriorate disease course by causing further complications. Difficult-to-control thrombophilia with multiple venous thromboses, need for recurrent hospitalizations due to the severe diarrhea complicating with abdominal distention and respiratory difficulty, and growth retardation with significant weight loss were reported previously in these patients.¹⁻³ Our patient was clinically stable until development of PLE even in the time period between detection of giant lymph nodes and initiation of PLE associated diarrhea. After that, she was hospitalized several times for supportive treatment before she succumbed to death.

There is no specific and effective treatment for mesenteric lymphadenopathies and PLE in GD. Neither increasing intensity of ERT nor switching to a combination therapy with substrate reduction therapy seems to be effective.³ Surgical excision of lymph nodes was recommended by Lee et al.² They reported that diarrhea was resolved with serial partial excision of lymph nodes with adhesiolysis and concluded that surgical intervention might help control the serious complication of PLE.² However, it should be considered if removal of enlarged lymph nodes will result in deposition of Gaucher cells in other organs as it does in splenectomy.

Another successful treatment approach was reported by Mhanni et al.³ In addition to increasing ERT dose in combination therapy, they provided a low fat diet supplemented with MCT oil, along with oral budesonide and total parenteral nutrition. They achieved clinical, laboratory and even radiological improvement with this treatment regimen.³ Although we followed a similar management approach except corticosteroid use, our patient failed to respond to supportive treatment and showed an intractable disease course. The patient Mhanni et al. reported might have benefited from budesonide therapy. Budesonide has been

used in PLE developing after Fontan procedure as a common and devastating complication. A recent meta-analysis showed that it is effective in ameliorating serum albumin levels in this setting.⁹

Long-term complications of GD which were not observed before the availability of ERT are becoming more apparent with increased life expectancy due to ERT. All five reported GD cases with PLE belong to post-ERT era. Mesenteric lymphadenopathy is not always accompanied by PLE highlighting non-predictability of the development of this complication. As we still do not know in whom and when these complications will develop, clinicians should be alert to this life threatening complication particularly in GD patients presenting with progressive abdominal distension, edema, ascites, and diarrhea or in patients who have already developed mesenteric lymphadenopathies. Timely diagnosis may allow early intervention with previously suggested surgical or medical treatment options. Further studies are warranted to understand why lymphadenopathy and PLE develop despite ERT in some patients. Alternative treatment modalities should be investigated for treatment of poorly accessible organs including central nervous system, lungs and lymph nodes which are involved in GD.

Author contribution

The authors confirm contribution to the paper as follows: Conception and design, data collection, interpretation of data, draft manuscript preparation: MAG, EG, HHG; preparation of tables and figures: EG, HHG; drafting and revising the article: HD, HO, INST, SG, AY; critical revision: AY. All authors reviewed the results and approved the final version of the manuscript.

Conflict of interest

The authors declare no conflict of interest.

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