EJR European Journal of Rheumatology

DOI: 10.5152/eurjrheum.2022.21156

Case-based Review

A challenging etiology of myopathy: The late-onset Pompe disease

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Abstract

Pompe disease is a rare metabolic disorder that is characterized by the deficiency of the acid α-glucosidase. As a result, glycogen accumulates in several tissues including motor neurons, skeletal, cardiac, and smooth muscles. The course of the disease varies according to the type of mutations, and the clinical phenotype can be affected by the enzyme levels. Late-onset Pompe disease (LOPD) is a challenging issue for clinicians as it has a milder phenotype with later onset of symptoms and slower disease progression. One of the most important differentials in the diagnosis of LOPD is inflammatory myositis as both diseases have some common clinical and laboratory features. Herein, we presented a 30-year-old female patient initially diagnosed as polymyositis and treated with immunosuppressive therapy without a benefit on her symptoms and later diagnosed as LOPD.

Keywords: Late-onset Pompe disease, polymyositis, inflammatory myopathy

Introduction

Pompe disease is a rare metabolic disorder that is characterized by the deficiency of the acid α-glucosidase (GAA). The mutations in the GAA gene lead to the accumulation of lysosomal glycogen in the tissues, particularly in skeletal, smooth, and cardiac muscles resulting in muscle weakness, organ failure, and/or death.[1] The phenotype of Pompe disease is heterogeneous. The infantile-onset form is rapidly progressive, characterized by cardiomyopathy, respiratory failure, and death in the first year of life; the late-onset Pompe disease (LOPD) has a relatively mild phenotype, may occur until the sixth decade of life, and typically present with musculoskeletal (MSK) symptoms or respiratory involvement.[2] Because of its milder phenotype with later onset of symptoms and slower disease progression, the diagnosis of LOPD is challenging. One of the most important differentials in the diagnosis of LOPD is idiopathic inflammatory myositis as both diseases have some common clinical and laboratory features.[3,4] Herein, we presented a 30-year-old female patient initially diagnosed as polymyositis and treated with immunosuppressive (IS) therapy without a benefit on her symptoms and later diagnosed as LOPD.

Case Presentation

A 30-year-old woman was referred for a second opinion regarding refractory polymyositis. She was diagnosed with polymyositis 2 years earlier on the basis of increased creatine kinase (CK) levels, positive electromyography (EMG) findings suggestive of myositis, and mild lymphocytic infiltration on muscle biopsy suggestive of myositis. Despite the usage of several IS agents including varying doses of corticosteroids, methotrexate, and azathioprine, her symptoms did not improve. Her medical inquiry was suggestive of symptoms related to proximal muscle weakness such as fatigue, and difficulty climbing stairs and rising from a seated position. For the last 2 months, she started having dyspnea on exertion. Her physical examination showed a positive Gowers sign and decreased muscle strength on her proximal lower extremities (bilateral 3-4/5). She had no deformity or contracture. Deep tendon reflexes and tone were normal. There were no other comorbidities in her past medical history, and the family history was unremarkable.

Laboratory showed increased muscle enzymes (CK:854 U/L, LDH:395 U/L, and AST:57 U/L). CRP and ESR were normal. Antinuclear antibody testing along with myositis-specific and myositis-associated antibodies was negative. Some key manifestations of the patient are shown in Table 1. Repeated EMG revealed electrophysiological findings compatible with myopathy at the proximal muscles accompanied by positive sharp waves. Extremity MRI revealed fatty atrophic changes and muscle edema in bilateral thigh muscles (Figure 1). Repeated muscle biopsy from the rectus femoris showed cytoplasmic vacuolization consistent with vacuolar myopathy (Figure 2). Periodic Acid Schiff (PAS) staining revealed no glycogen deposition, whereas Oil red O revealed lipid droplets. The α-glucosidase enzyme level was 0.2 nmol/mL/hr (normal

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Cite this article as: Yüce İnel T, Köken Avşar A, Teke Kısa P, Özer E, Sarı İ. A chal-lenging etiology of myopathy: The late-onset Pompe disease. *Eur J Rheumatol.* 2023;10(1): 26-28.

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Received: August 8, 2021
Accepted: November 1, 2021
Publication Date: April 5, 2022

Table 1. Some Key Manifestations of the Patient

Tests	1. Evaluation*	2. Evaluation†
CK (0-145 U/L)	1182 U/L	849 U/L
AST (0-35 U/L)	55 U/L	63 U/L
ALT (0-35 U/L)	92 U/L	92 U/L
LDH (125-220 U/L)	395 U/L	431 U/L
CRP (0.2-5 mg/L)	4.6 mg/L	8 mg/L
ESR (0-20 mm/hr)	15 mm/hr	13 mm/hr
EMG	Short-term low-amplitude MUP activity	Compatible with myopathy, positive sharp waves
MRI	Unavailable	Fatty atrophic areas, muscle edema in the bilateral thigh muscles
Muscle biopsy	Atrophic myofibrils, perimysial and perivascular mild inflammatory infiltrate	Cytoplasmic vacuolization of some of the muscle fibers, no lymphocytic infiltration

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; CRP, C reactive protein; EMG, electromyography; ESR, erythrocyte sedimentation rate; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging.
*At the beginning of polymyositis diagnosis.
†Refractory to immunosuppressive therapy and when the diagnosis is reevaluated.

level > 2.3 nmol/mL/hr). She eventually underwent targeted genetic sequencing, which showed that the patient is a compound heterozygote for two variants in *GAA* gene: the most common variant in Caucasian individuals with late-onset GSD2, c.-32-13T>G, and a nonsense mutation c.1061delA (p.Tyr354Serfs). The patient was diagnosed as LOPD and was started on enzyme replacement therapy. There was no other systemic organ involvement. After 15 months of follow-up, she had a significant clinical improvement with a decrease in her muscle enzyme levels.

Discussion

Pompe disease is a rare metabolic disorder with an incidence of approximately 1/40,000. The adult-onset form may present with MSK, respiratory, cardiac, and neuromuscular symptoms. Progressive myopathy is a common feature, and the proximal muscles of the lower extremities are usually more affected.[5,6] Muscle involvement can be asymmetrical or symmetrical. The muscle groups most likely to be affected are the trunk, thigh, and pelvic girdle muscles.[7] Patients may have difficulty walking, climbing stairs, getting up from a chair or lying position, and may complain of back pain, fatigue, and muscle cramps.[8–10]

Main Points

- LOPD should be considered in the differential diagnosis of idiopathic inflammatory myositis.
- Mild phenotype and slower disease progression make the diagnosis of LOPD difficult.
- Dried blood spot assay, which is a cheap and easy method to measure enzymatic activity, should be sent.

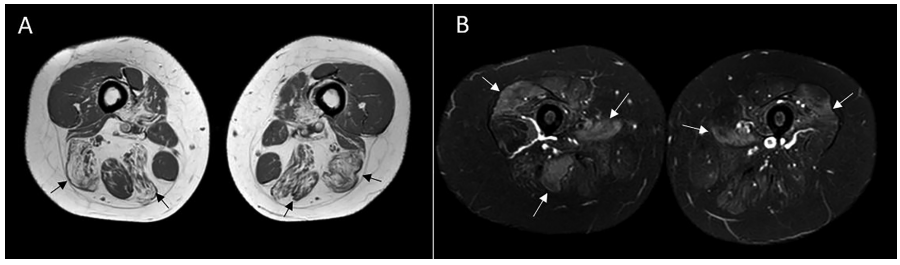

Figure 1. A, B. (A) Fatty atrophic changes in T1-weighted image; (B) muscle edema areas in T2-weighted SPectral Attenuated Inversion Recovery sequences.

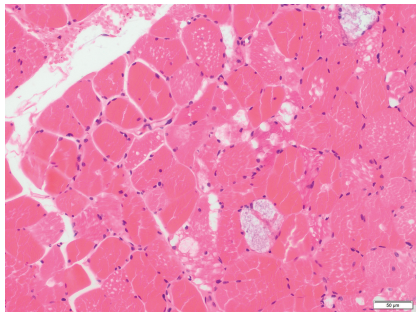

Figure 2. Muscle biopsy from the rectus femoris showed cytoplasmic vacuolization.

The differentiation of LOPD and inflammatory myopathies, particularly polymyositis, maybe a challenging diagnostic issue as both conditions are rare, and their signs and symptoms may overlap. In this respect, proximal muscle weakness, abnormal gait, dyspnea on exertion, difficulty swallowing, and elevated muscle enzymes can be seen in both conditions.[11] Whereas diaphragm involvement and decreased forced vital capacity, myotonic discharges in EMG may suggest LOPD; the presence of connective tissue disease-related findings such as arthritis, photosensitivity, Raynaud's phenomenon, and autoantibodies may favor polymyositis.[12] However, muscle biopsy interpretation is one of the most important clues in differentiating both disease conditions. PAS-positive vacuoles without inflammatory infiltrates strongly suggest metabolic myopathy and guide the clinician in further diagnostic steps.[12] However, there may be false-negative results in the muscle biopsy examination in LOPD because PAS-positive material can be lost due to tissue fixation, and muscle histopathology can show high variability in the extent of vacuoles.[13,14]

Our patient initially diagnosed as polymyositis and had been treated with several IS therapies without clinical or laboratory improvement. Currently, symmetrical proximal muscle weakness and elevation of muscle enzymes are sufficient to classify patients in the possible polymyositis category.[15] Taken together with the low specificity of EMG and MRI findings along with the experience of the pathologist are the possible factors for misdiagnosis in our patient. Therefore, it is important to consider metabolic myopathies in patients who are negative for connective tissue disease (CTD)

findings and resistant to IS therapies. On the other hand, biopsies should be referred to the dedicated centers, and sufficient clinical information should be provided to the experts reviewing muscle biopsies. Physicians should have a suspicion for LOPD, and in the light of treatment and in any possible case, they must send a dried blood spot assay which is cheap and easy for the measurement of the enzymatic activity.

In conclusion, LOPD and inflammatory myopathies share similar clinical and laboratory findings, and it could be hard to differentiate. Patients who are negative for CTD-related findings and resistant to IS therapies should lead to suspicion of adult-onset Pompe disease.

Informed Consent: Written informed consent was obtained from the patient who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - T.Y.İ.; Design - T.Y.İ., İ.S.; Supervision - T.Y.İ., İ.S.; Resources - T.Y.İ., İ.S.; Materials - T.Y.İ., A.K.A., P.T.K., İ.S.; Data Collection and/or Processing - T.Y.İ., İ.S., P.T.K., A.K.A.; Analysis and/or Interpretation - T.Y.İ., İ.S., E.Ö.; Literature Review - T.Y.İ., A.K.A., P.T.K., İ.S.; Writing - T.Y.İ., İ.S.; Critical Review - T.Y.İ., İ.S., E.Ö.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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