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Autopsy findings in late-onset Pompe disease: A case report and systematic review of the literature

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ABSTRACT

Background: Late-onset Pompe disease (LOPD) is a rare cause of declining proximal muscle strength and respiratory function that can also affect other organ systems. The development of enzyme replacement therapy has made it one of the few inherited muscle disorders with treatment, but clinical response is difficult to assess due to the variable and often slow progression of illness. A better understanding of the disease's systemic effects can be gleaned through autopsy findings.
Purpose: The purpose of this study was to: (1) describe the histological findings observed in LOPD, (2) provide correlations between reported histological and clinical findings, and (3) review the literature on autopsy findings in LOPD.
Methods: Histological evaluation of autopsy tissues from a 62-year-old woman with LOPD was conducted. A clinical history was obtained by review of the medical records. The literature was reviewed for previously reported histological and clinical findings in LOPD. Based on this case report and information from prior publications, histological and clinical findings for the disease were correlated.
Results: Histologic examination revealed mostly mild vacuolar myopathy typical of glycogen accumulation within skeletal and smooth muscle cells. The most prominent vacuolar myopathy was in quadriceps muscle, which also exhibited chronic myositis with degenerating and regenerating muscle fibers. Transmission electron microscopy disclosed lysosomal glycogen accumulation within skeletal, cardiac, and vascular smooth muscle cells, correlating with published case reports of basilar artery and ascending aortic aneurysms and carotid artery dissection. Organs containing smooth muscle cells (the bladder, intestine, and esophagus) were also affected, explaining reports of symptoms such as urinary incontinence and dysphagia. In addition to glycogen accumulation, there was obvious damage to the contraction apparatus of myofibrils within cardiac and skeletal muscle cells. These histological and ultrastructural findings correlate with the clinical manifestations of LOPD.
Conclusions: This study is the first to describe histological findings of LOPD utilizing both traditional paraffin-processed tissues and epoxy resin embedded tissues for high-resolution light microscopy. The findings are similar to those seen in previous studies, but with improved morphological detail and glycogen preservation. This patient exhibited histological involvement of multiple organs, correlating with the clinical features of LOPD. With the advent of definitive therapy for Pompe disease, it is important to be aware of these findings and use them to develop methods for tracking therapeutic response.

Abbreviations: cm, Centimeters; CNS, Central nervous system; EM, Electron microscopy; FDA, Food and drug administration; FEV1, Forced expiratory volume in one second; FVC, Forced vital capacity; g, Grams; GAA, Acid α-glucosidase; HRLM, High resolution light microscopy; kg, Kilograms; L, Liter; LOPD, Late-onset Pompe disease; PAS, Periodic acid–Schiff; U, Units.

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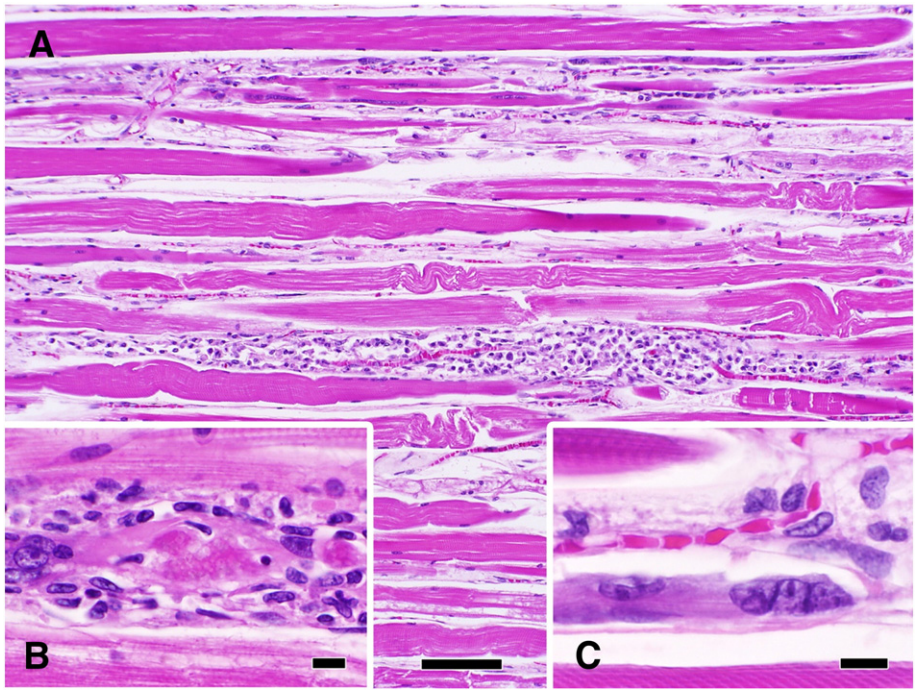

Fig. 1. Inflammatory changes were observed in skeletal muscle. Chronic myositis (A) with both degenerating (B) and regenerating muscle fibers (C) was identified on paraffin-embedded, H&E stained sections of the quadriceps. (The magnification bar for A = 10 μm and for B and C the magnification bar = 1 μm.)

1. Introduction

Pompe disease (also known as glycogen storage disease type II, glycogenosis type II, acid alpha-glucosidase deficiency, acid maltase deficiency) is an autosomal recessive disorder resulting from deficiency of the lysosomal enzyme acid α-glucosidase (GAA). This enzyme is essential for the degradation of lysosomal glycogen, and a deficiency of this enzyme results in excessive glycogen accumulation, most notably in cardiac and skeletal muscle [1].

Pompe disease is classified into two broad categories based upon age of disease onset and extent of organ involvement. The infantile form is a rapidly progressive subcategory that is characterized by prominent cardiomegaly, muscle weakness and hypotonia, with death in the first year of life secondary to cardio-respiratory failure. Infantile-onset Pompe disease, represents the most severe end of the disease spectrum [2].

Late-onset Pompe disease (LOPD), with childhood, juvenile, and adult variants, presents beyond infancy. Age of onset can be anywhere between 1 year of age to as late as the seventh decade. The overall disease course is slowly progressive, most frequently involving skeletal and respiratory muscles. The vast majority of LOPD patients do not develop cardiomyopathy [3–5], but cardiac conduction abnormalities (Wolff Parkinson White syndrome) have been reported in adults [6]. Involvement of other organs and body systems is increasingly recognized.

Autopsy has been a valuable means of characterizing the effects of LOPD on body tissues. There are only 16 published Pompe disease-related autopsy cases, and six of these cases were of late-onset Pompe disease in adults. These reports have been important in understanding the extent of LOPD, with Kretzschmar et al., in 1990 describing mild central nervous system (CNS) involvement [7], with broadened brain gyri, increased numbers of astrocytes and vacuolar changes in cerebral vasculature that were associated with numerous small aneurysmal dilatations. Complete autopsy findings were last published in 1987 by Van der Walt et al. [8]. Previous reports describe glycogen accumulation affecting a multitude of organ systems to various degrees, including striated and smooth muscles, nerves, heart, and even the CNS. In contrast to extensive involvement of cardiac muscle in infantile onset [9], there is minimal, if any, involvement in LOPD [10,11], although involvement of the conduction system might be difficult to evaluate in the absence of special dissection procedures at autopsy.

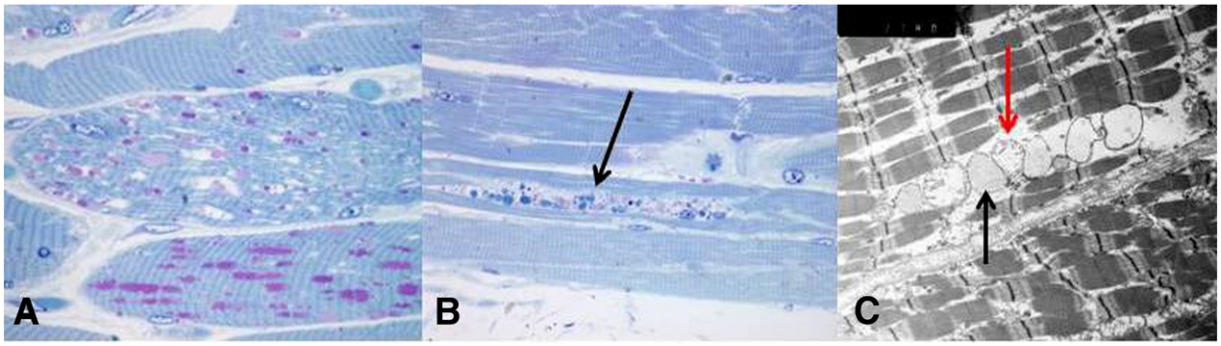

Fig. 2. Multiple skeletal muscles exhibited changes associated with Pompe disease. (A) Numerous PAS-positive membrane-bound vacuoles were visible in most skeletal myocytes of the quadriceps and appear purple by high resolution light microscopy (PAS/Richardson's stain, magnification 1000×). (B) A section of deltoid muscle contains a skeletal myocyte with a central core of autophagic debris and glycogen at arrow (HRLM, PAS/Richardson's stain, magnification 600×). (C) EM images of the deltoid revealed lysosomal glycogen (black arrow) and swollen mitochondria (red arrow) within myocytes (magnification 15,400×).