Cardiac and Muscular Pathology on Autopsy in a Man with Duchenne Muscular Dystrophy

Eugene Choi¹, Joo-Young Na²,³, Kyung Ryoul Kim⁴, Jin-Haeng Heo⁴, Young-Il Park⁴

¹Department of Pathology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea, ²Department of Forensic Medicine, Pusan National University School of Medicine, Yangsan, Korea, ³Department of Pathology, Pusan National University Yangsan Hospital, Yangsan, Korea, ⁴Forensic Medicine Division, National Forensic Service Busan Institute, Yangsan, Korea

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Correspondence to
Joo-Young Na
Department of Forensic Medicine, Pusan National University School of Medicine, 49 Busandaehak-ro, Mulgeum-eup, Yangsan 50612, Korea
Tel: +82-51-510-8051
Fax: +82-55-360-1865
E-mail: pdrdream@gmail.com

Duchenne muscular dystrophy (DMD) is a degenerative muscle disease characterized by a progressive decline in muscular function, with cardiomyopathy in the later stages. We report the autopsy findings of a 29-year-old man with DMD. He had been stable with the assistance of mechanical ventilation until he was found unconscious, without known cause. External examination confirmed generalized muscular atrophy and contracture consistent with his clinical history. Histopathology revealed varying degrees of fibrofatty changes in the muscles, with the calf muscles being the most extensively affected, followed by the diaphragm and heart. The cardiac muscle showed the least involvement and the pathology was confined to the left ventricular wall and the interventricular septum, exhibiting a unique morphology of fibrosis resembling stretched springs. The cause of death was attributed to cardiac failure due to DMD progression. This case highlights the clinical course of DMD, emphasizing the need for thorough examination of both skeletal and non-skeletal muscles, including the cardiac muscles, to obtain a better understanding of the disease.

Key Words: Duchenne muscular dystrophy; Forensic pathology; Autopsy; Heart

Introduction

Muscular dystrophies are diseases of the muscles that are primarily caused by mutations in more than 40 genes, which results in changes to dystrophin in skeletal muscle tissue [1]. Most genes responsible for these diseases have been identified; therefore, an accurate diagnosis can be made through genetic analysis, and muscle biopsy is not essential for the diagnosis of muscular dystrophy. These diseases share the clinical features of progressive muscular weakness and a dystrophic appearance of muscle tissue on histopathology. Duchenne muscular dystrophy (DMD) is the most common muscular dystrophy in children [1]. Patients with DMD become symptomatic in early childhood. Early symptoms include frequent falls
and an inability to climb stairs, as well as combined disabilities such as delayed speech acquisition (50%) and other issues (30%), such as intellectual disability and attention deficit disorder. Loss of the ability to walk independently appears by the age of 12 years, followed by scoliosis, loss of arm function, respiratory insufficiency, and cardiomyopathy [1]. Cardiac death due to progressive dilated cardiomyopathy is currently known as the leading cause of death in older patients. It is assumed that the pathological changes of DMD follow the same sequence as the clinical progression and start in the muscular tissue of the lower legs extending to the respiratory muscles and cardiomyocytes. Herein, we report a case of sudden unexpected death due to DMD in a man with pathological findings in the leg, diaphragm, and heart muscle tissue, to provide insight into the pathophysiology of DMD.

Case Report

An autopsy was conducted on a 29-year-old man with DMD. The deceased had been diagnosed with DMD at the age of 7 years and had been bedridden since early adolescence. Although he was dependent on

Fig. 1. Changes in the calf muscle. (A, B) The calf muscle is entirely replaced by fibrofatty tissue (A, gross image; B, H&E, ×40). (C) Complete substitution of muscle for nonfunctional fibrotic tissue is shown by the blue color using Masson's trichrome (MT) staining (MT stain, ×40). (D) Dystrophin expression is not identified (dystrophin with hematoxylin counterstain, ×100).
mechanical ventilation, he was still able to eat and talk and, according to a report by his sister, had been doing as well as usual on the day of his death. A governmental home-care helper visited the house after his sister left for work, and found him unconscious and cyanotic. He died in the emergency room without recovery of spontaneous circulation, despite cardiopulmonary resuscitation.

External examination revealed generalized muscular atrophy and contractures, consistent with previously diagnosed muscular dystrophy. No other injuries were identified, except for those resulting from previous medical interventions such as tracheostomy and percutaneous nephrostomy. Dissection revealed total fatty replacement of the calf muscle. In contrast, the diaphragm and heart were macroscopically normal. During the internal examination, muscle tissues from the calf, diaphragm, and heart were collected to assess the extent of disease involvement. Histological examination of the sampled tissues revealed varying degrees of fibrofatty change in the muscles. Grossly, the muscles of the legs were totally replaced by fatty

![Image A](image1.png)
![Image B](image2.png)
![Image C](image3.png)
![Image D](image4.png)

**Fig. 2.** Changes in the diaphragm. (A) The diaphragm is macroscopically unremarkable (gross image). (B) Multifocal fibrofatty changes with admixed remnant muscular bundles are observed in the diaphragmatic muscle (H&E, ×100). (C) In the adjacent area, a few myocytes show glassy pink cytoplasmic inclusions, which are stained deep-red by Masson's trichrome (MT) staining (MT stain, ×100). (D) Complete loss of dystrophin expression is observed in remnant myocytes (dystrophin with hematoxylin counterstain, ×100).
tissue (Fig. 1A). Microscopic examination of the calf muscle showed the most extensive replacement, with nearly 100% involvement (Fig. 1B, C); furthermore, dystrophin expression was not identified (Fig. 1D). Although the diaphragm was grossly unremarkable (Fig. 2A), microscopy revealed multifocal, patchy fibrofatty changes in the diaphragmatic tissue that accounted for approximately 50% of the area (Fig. 2B). The myocytes adjacent to the affected area contained glassy cytoplasmic inclusions, which stained a deep-red using Masson's trichrome staining (Fig. 2C). Additionally, loss of dystrophin expression was observed in the remaining myocytes of the diaphragmatic tissue (Fig. 2D). The heart weighed 305 g and had an unremarkable gross appearance (Fig. 3A). The cardiac muscle showed the least involvement, with approximately 10% replacement. The fibrofatty changes observed in the heart were confined to the left ventricular wall and interventricular septum, whereas other regions, including both atria, the right ventricular wall, and the conduction system (sinoatrial and atrioventricular nodes), were preserved. The fibrofatty tissue had a

![Fig. 3. Changes in the heart muscle. (A) The heart is macroscopically unremarkable. (B) Multifocal fibrofatty changes are present exclusively in the myocardium of the left ventricle and interventricular septum, sparing the right ventricle and both atria. Replaced fibers have a wavy, “stretched spring”-like appearance (H&E, ×100). (C) Under higher magnification, the transformation of cardiomyocytes into elastic fibers resembles unravelled knots (H&E, ×400). (D) Complete loss of dystrophin expression is observed in the cardiomyocytes (dystrophin with hematoxylin counterstain, ×100).](image-url)
distinct appearance, characterized by collagenous fibers resembling a stretched spring (Fig. 3B, C). In addition, the complete loss of dystrophin expression in cardiomyocytes further supported the diagnosis of DMD (Fig. 3D). The myofibers in the affected area displayed a mottled pattern of desmin expression, whereas those in the unaffected area displayed a uniform staining pattern. Furthermore, the changes were more extensive on the left side of the interventricular septum than on the right side (Fig. 4). In conclusion, the cause of death was attributed to cardiac failure due to the progression of DMD, and the manner of death was classified as a natural death.

Discussion

DMD is a degenerative disease of muscle. Patients with DMD present with symptoms of gradual deterioration, starting with difficulty in climbing stairs at around 2 to 3 years of age, proceeding to loss of the ability to walk by early adolescence, and reliance on mechanical ventilation during the second decade of life. Eventually,
even with optimal supportive care, most patients die between 20 and 40 years of age due to cardiac and/or respiratory failure [1].

The most plausible hypothesis concerning the pathophysiology of DMD is that erroneous production of dystrophin results in repetitive damage and impaired recovery of striated muscles [2]. Dystrophin is a cytoplasmic protein that mediates the binding of the muscle cytoskeleton to the extracellular matrix [3]. It is also involved in intracellular, extracellular, and transmembrane interactions by forming dystrophin-associated protein complex (DAPC) [4]. Although it is expressed in various tissues of the human body, such as the muscle, brain, and kidney, the function of the muscle-specific isoform (Dp427m) has been primarily investigated because of its contribution to the structural integrity and contraction of muscle [2]. This isoform is encoded by DMD (encoding dystrophin) gene on the X chromosome, which explains the X-linked recessive inheritance of muscular dystrophies, including DMD. Genetic analysis has revealed that patients with DMD have nonsense or frameshift mutations that disrupt the original transcription frame, resulting in a loss of function. In Becker muscular dystrophy (BMD), which has similar but milder clinical presentation, the mutations in DMD do not disrupt the reading frame. Considering the role of dystrophin as a mediator of interactions that bind its both termini to various proteins, patients with BMD may retain the capacity to produce dystrophin, albeit with potentially decreased function, whereas patients with DMD experience more severe symptoms due to the absence of functional dystrophin [2]. For example, in a previously reported autopsy case of a patient with BMD by Kim and Park [5], the deceased experienced his first symptom, gait disturbance, during late adolescence and eventually succumbed to cardiac and respiratory failure at the age of 34 years due to muscular dystrophy. The diagnosis of BMD was made based on the late onset and relatively slow clinical progression.

Although both skeletal and cardiac muscle consist of striated muscle fibers, symptoms associated with cardiac involvement in DMD usually manifest at a later stage of the disease. The degree of change on histological examination of the skeletal and cardiac muscle tissue in this case corresponded with the expected course of DMD, with marked fibrofatty changes observed in the skeletal muscle and a relatively preserved condition observed in the cardiac muscle. A previous study suggested that this temporal discrepancy might arise from tissue-specific functional variations in dystrophin and subsequent differences in the composition of DAPC [4,6].

DMD is diagnosed based on clinical suspicion and an elevated serum creatine kinase level, supported by genetic evaluation for associated mutations. Histological examination using skeletal muscle sampling is an alternative in case in which genetic sequencing does not detect any mutations [7]. Hence, the pathological features of DMD, particularly in the non-skeletal muscles, remain relatively unexplored. In this case, we compared the pathological findings of the calf, diaphragmatic, and cardiac muscles from an autopsy of patient with DMD. The calf was the most severely affected muscle, followed by the diaphragm and heart. This fibrofatty change in muscular tissue aligns with the progression pattern of DMD, which is characterized by a late manifestation of cardiomyopathy. During the early phase of the disease, degenerated muscle is repaired by regeneration. However, in the later phase, dead myocytes are replaced by fatty and fibrotic tissues owing to repressed autophagy and impaired regenerative capacity in chronically inflamed tissue of DMD [2]. Furthermore, the fibrofatty change in the cardiac muscle was most prominent in the left ventricle and left side of the interventricular septum, particularly in the outermost portion of the myocardium, located just beneath the epicardium. Considering the essential role of dystrophin in maintaining structural stability during repetitive damage from contraction, muscles with more vigorous movement may be more susceptible to damage in cases of dystrophin deficiency, as shown in this case. Comprehensive examination of both skeletal and non-skeletal muscle, including cardiac muscle, may improve our understanding of the pathophysiology of DMD.

ORCID: Eugene Choi: https://orcid.org/0000-0002-0457-7785; Joo-Young Na: https://orcid.org/0000-0003-1138-433X; Kyung Ryoul Kim: https://orcid.org/0000-0001-8279-6716; Jin-Haeng Heo: https://orcid.org/0000-0002-3940-8615; Young-II Park: https://orcid.org/0000-0003-2187-5618
Conflicts of Interest
Joo-Young Na, a contributing editor of the Korean Journal of Legal Medicine, was not involved in the editorial evaluation or decision to publish this article. All remaining authors declare that there is no conflict of interest.

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