

A case of dermatomyositis in a patient with central core disease: Unusual association with autoimmunity and genetic muscle disease

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Case Report

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Abstract

Background

Dermatomyositis is an inflammatory muscle disease caused by immune-mediated muscle injury, and central core disease (CCD) is a congenital myopathy associated with disturbed intracellular calcium homeostasis and excitation-contraction coupling. To date, CCD has not been reported to have autoantibodies or coexist with inflammatory myopathy.

Case presentation

Here, we described the case of a 25-year-old woman who had progressive proximal muscle weakness, myalgia, pruritic macular rash, skin ulcers, and calcinosis. Dermatomyositis was initially suspected based on the clinical symptoms accompanied by elevated muscle enzyme levels, electromyography abnormalities, and a positive antinuclear antibody test. However, the patient's muscle biopsy revealed the characteristic findings of both dermatomyositis and CCD, suggesting that dermatomyositis occurred in this patient with previously asymptomatic CCD. The patient did not have any pathogenic gene mutations associated with congenital myopathy, including *RYR1* and *SEPN1* in targeted next-generation sequencing. She received high-dose glucocorticoid therapy and azathioprine with a significant improvement in muscle strength.

Conclusions

We present a case of rare coexistence of dermatomyositis and CCD. Clinicians should be aware that patients with CCD may have inflammatory myopathy that responds well to immunosuppressive therapy.

Background

Dermatomyositis and central core disease (CCD) are well-recognized, distinct muscle diseases. Dermatomyositis is an autoimmune inflammatory myopathy associated with progressive proximal muscle weakness, a characteristic rash and extramuscular manifestations (1). CCD is a congenital myopathy characterized by the early onset of hypotonia, predominantly proximal muscle weakness and histopathological features of focally reduced oxidative enzyme activity seen as the central core. Congenital dislocation of the hips and scoliosis and foot deformities are common in CCD (2). CCD is mainly due to dominant mutations in the ryanodine receptor 1 (*RYR1*) gene, which encodes proteins involved in skeletal muscle calcium homeostasis and excitation-contraction coupling (ECC) (3). Although the severity of muscle weakness varies depending upon the causative mutations, most patients with CCD achieve independent ambulation and have a static or slowly progressive course (4).

There seems to be little relationship between inflammatory myopathy and genetic muscle diseases. However, there have been descriptions of patients with muscular dystrophy and myositis-specific autoantibodies (5). The presence of autoantibodies may exacerbate muscle inflammation due to the high

levels of autoantigens expressed by regenerating muscle cells, leading to overlapping inflammatory myopathy. To date, congenital myopathy has not been reported to have autoantibodies or coexist with inflammatory myopathy.

Here, we report a rare case of dermatomyositis coexisting with CCD presenting as severe progressive proximal muscle weakness and a skin rash with ulcerations and calcinosis.

Case Presentation

A previously healthy 25-year-old Korean woman had a two-month history of progressive proximal muscle weakness. She had myalgia, fever, severe alopecia and a pruritic macular rash over her face, hand dorsum, upper anterior chest and upper back. She had difficulty in sitting up and could only move around using a wheelchair. She had no hypotonia, feeding difficulty, dysarthria, motor developmental delay, or orthopedic abnormalities in infancy or early childhood. Her family history was unremarkable.

On physical examination, her vital signs were stable, and her body mass index was 21.8 kg/m² (height 156 cm, weight 53 kg). Her bilateral muscle strength was grade 4/5 at neck flexion, 4/5 at shoulder abduction, 4/5 in wrist flexion, 4/5 in hand grip, 2/5 in the proximal hips, and 4/5 in ankle dorsiflexion. She had normal reflexes of the biceps brachii, patella, and ankle. Facial erythema involving the nasolabial folds and an erythematous rash on the upper back and anterior chest wall were observed. Skin ulcers were seen on the hand knuckles, right elbow and lateral aspect of the right thigh (Fig. 1). She had diffuse, palpable soft tissue thickening of the bilateral thigh and upper arm with tenderness, which turned out to be calcification. The laboratory results were as follows: white blood cell count, 6440/mm³ with lymphopenia (lymphocyte 322/mm³); haemoglobin, 9.1 g/dL; platelet, 148,000/mm³; erythrocyte sedimentation rate (ESR), 72 mm/hr; C-reactive protein (CRP), 0.44 mg/dL; aspartate aminotransferase (AST), 95 (1–40) IU/L; alanine aminotransferase (ALT), 30 (1–40) IU/L; creatine kinase, 128 (20–270) IU/L; lactate dehydrogenase (LDH), 553 (100–225) g/dL; myoglobin, 47.1 (0–106) ng/mL; aldolase, 10.8 (0–7.6) U/L; C3, 83 (83–193) mg/dL; and C4, 19 (15–57) mg/dL. The antinuclear antibody test was positive and showed a homogeneous pattern at a 1:160 dilution, but the anti-dsDNA, anti-Sm, anti-phospholipid, and anti-Jo-1 antibody tests were all negative. Magnetic resonance imaging (MRI) of her thigh confirmed symmetric diffuse muscle signal changes with an enhanced T2 signal and diffuse patchy contrast enhancement involving both the anterior and posterior compartments of the thigh, consistent with inflammatory myopathy (Fig. 2). Her radiographs showed extensive, plaque-like soft tissue calcification of both hips, thighs and upper arms. Electromyography (EMG) showed an increased amplitude of motor unit potential and reduced interference pattern in the biceps, whereas the nerve conduction study revealed normal responses. A muscle biopsy of the right vastus lateralis demonstrated many degenerating and regenerating muscle fibers and perifascicular atrophy with moderate infiltration of inflammatory cells in the endomysial and perivascular areas, consistent with dermatomyositis. However, enzyme histochemical analysis showed centrally placed cores in the type I myofibers with nicotinamide adenine dinucleotide dehydrogenase (NADH) and succinate dehydrogenase staining, suggesting CCD (Fig. 3A). Electron microscopy showed both tubuloreticular bodies in the endothelial cells

Several muscular dystrophies, such as facioscapulohumeral dystrophy and limb-girdle muscular dystrophy, show muscle regeneration and inflammatory cell infiltrates in muscle fibers, similar to inflammatory myopathy (9). Additionally, myositis-specific autoantibodies such as anti-Jo-1 and anti-Mi2 were found in patients with muscular dystrophy (5). Based on these findings, autoantigens may also be expressed in the regenerating muscle fibers of muscular dystrophy, triggering an autoimmune process and overlapping with inflammatory myopathy (10). In contrast, congenital myopathies rarely show muscle regeneration, and may lead to very low levels of myositis autoantigen expression. Instead, aberrant intracellular calcium homeostasis in congenital myopathy may affect the immune system. For instance, increased T cell receptor-mediated calcium influx in lupus T cells contributes to T cell activation by inducing the activation of calcineurin (11). RYR1, a calcium-release channel protein associated with CCD, is expressed preferentially in skeletal muscle, but is also expressed in B cells and dendritic cells. RYR1-mediated intracellular calcium influx in B cells and dendritic cells may cause their activation and the release of pro-inflammatory cytokines (12–14). Interestingly, dermatomyositis is characterized by abnormal humoral immunity related to B cell activation producing autoantibodies.

The management of congenital myopathies is mainly supportive (15), whereas dermatomyositis responds well to glucocorticoid and immunosuppressive therapy. Immunosuppression was also effective in improving muscle strength in the present case with inflammatory myopathy coexisting with congenital myopathy. Therefore, inflammatory myopathy should be suspected in a patient with congenital myopathy if he or she presents with a sudden deterioration in muscle strength, particularly along with extramuscular symptoms or the presence of autoantibodies. We suggest that a muscle biopsy or MRI should be performed to evaluate for overlapping inflammatory myopathy.

To the best of our knowledge, this was the first report of dermatomyositis coexisting with CCD. Targeted next-generation sequencing did not detect genetic mutations related to CCD, particularly *RYR1*, in our patient. However, the histopathologic features of this patient were consistent with both dermatomyositis and CCD. Furthermore, due to the large size of the *RYR1* and *NEB* genes, variants of uncertain significance are common in congenital myopathies (16). Locus-specific databases for each gene may help clarify the significance of any variant identified (16).

Conclusion

In summary, we reported a rare case of the coexistence of dermatomyositis and CCD. Clinicians should be aware that patients with CCD could have inflammatory myopathy, which responds well to immunosuppressive therapy. Testing for autoantibodies, and muscle MRI or muscle biopsy may help distinguish between inflammatory myopathy and underlying genetic muscle diseases. Further research may be needed to decipher the association between autoimmunity and congenital myopathy-associated intracellular calcium homeostasis.

Abbreviations

ALT, alanine transaminase

AST, aspartate transaminase

ATP, adenosine triphosphate

CCD, central core disease

CRP, C-reactive protein

ECC, excitation-contraction coupling

EMG, electromyography

ESR, erythrocyte sedimentation rate

LDH, lactate dehydrogenase

MRI, magnetic resonance imaging

NADH, nicotinamide adenine dinucleotide dehydrogenase

RYR1, ryanodine receptor 1

SR, sarcoplasmic reticulum

Declarations

Ethics approval and consent to participate: The study complied with the Declaration of Helsinki and was approved by the Institutional Review Board of Seoul National University Hospital. Informed consent was obtained from the patient.

Consent for publication: Informed written consent for patient information and images to be published was obtained from the patient.

Availability of data and materials: The datasets used during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests

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Authors' contributions: YWS contributed to the study conception and design. Material preparation, data collection and analysis were performed by all listed co-authors. The first draft of the manuscript was

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Figures



Figure 1

Skin ulcerations on A) the elbow and B) thigh.

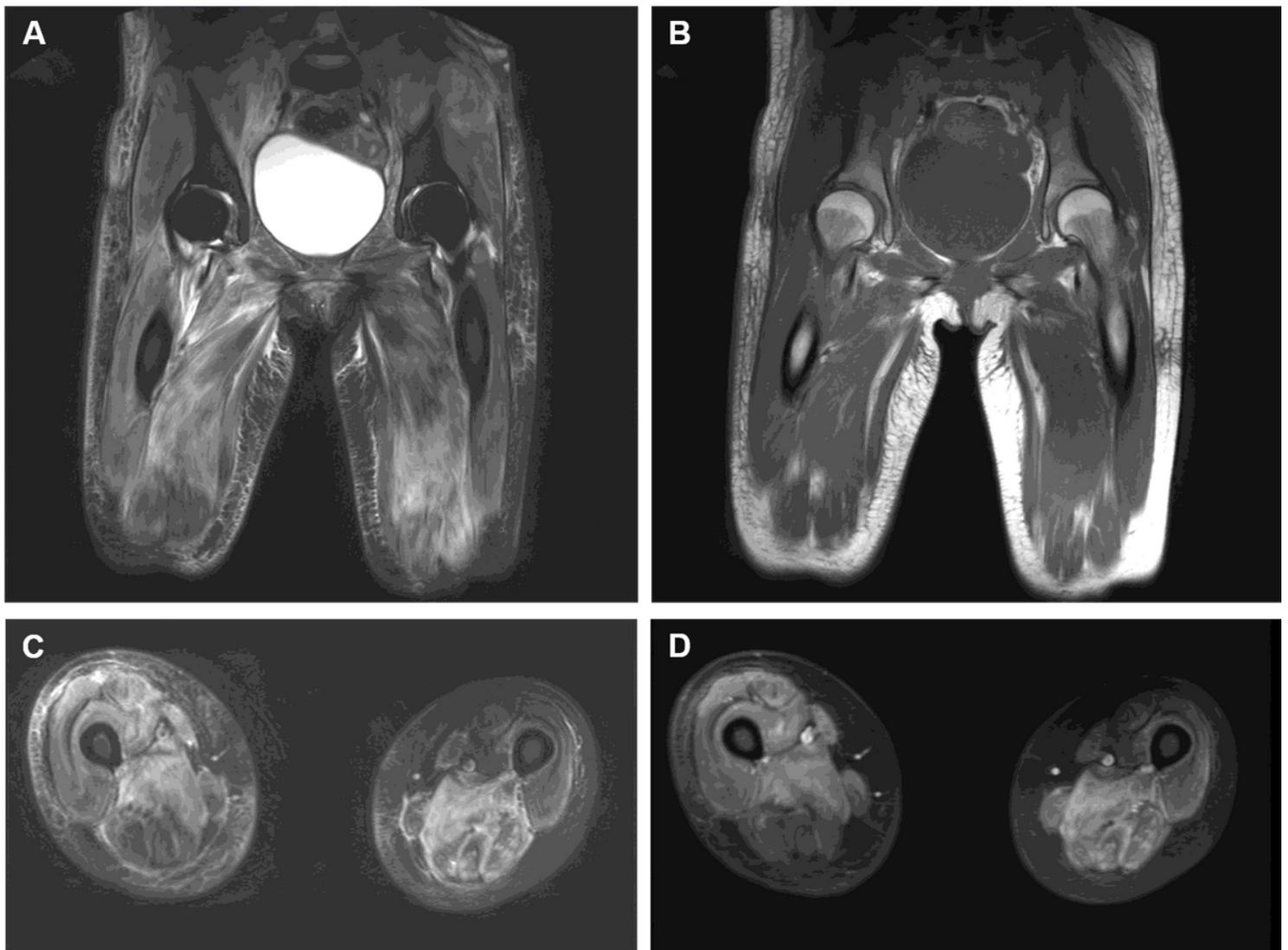


Figure 2

Magnetic resonance imaging of the thigh. Coronal images show A) increased T2 signal intensity and B) normal T1 signal intensity in the pelvis and proximal thigh. C) Axial T2-weighted and D) gadolinium-

enhanced T1-weighted image shows symmetric diffuse muscle edema and inflammation with relative preservation in the left anterior compartment of the thigh.



Figure 3

Histological findings in a muscle biopsy specimen obtained from the vastus lateralis. A) NADH-tetrazolium reductase stain shows irregularly outlined central cores in the type I myofibers (bar: 200 μm). B) ATPase pH 4.3 shows pale central cores in the type I myofibers (bar: 200 μm). Electron microscopy (adenyl acetate and lead citrate stain) shows C) a structured central core composed of randomly scattered short z-bands and fine filaments (arrow) (bar: 5 μm), and D) two tubuloreticular bodies (arrows) in the endothelial cells (bar: 500 nm).