C1-inhibitor Deficiency Induces Myositis-like Symptoms Via the Deposition of the Membrane Attack Complex in the Muscle

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Abstract:
We herein report a 56-year-old Japanese woman who had been diagnosed with hereditary angioedema. She experienced progressing muscle weakness and pain in the upper and lower extremities. Blood tests revealed a marked increase in creatine kinase levels; however, myositis-specific autoantibodies were not detected. Serum C1-inhibitor activity and C4 levels were low. A muscle biopsy showed mild muscle fiber necrosis and C5b-9 deposition in the endomysial capillary vessel walls and sarcolemma, mimicking necrotizing myopathy. These results suggest that C1-inhibitor deficiency induces myositis-like symptoms through the activation of the complement pathway and deposition of the membrane attack complex in the muscles.

Key words: hereditary angioedema, C1-inhibitor, muscle weakness and pain, C4, C5b-9

Introduction
Hereditary angioedema (HAE) is an autosomal dominant disease caused by a non-functioning C1-inhibitor or by C1-inhibitor deficiency due to gene mutations (1, 2). The clinical manifestation of HAE is recurrent episodes of swelling of localized submucosal or subcutaneous tissues in almost any part of the body, including the skin, gastrointestinal tract, or upper airways (1-3). The complement components C4 and C2 are not cleaved in C1-inhibitor deficiency, leading to loss of inhibition of the classical complement pathway and induction of very low levels of C4 (4). HAE is associated with several autoimmune diseases, such as systemic lupus erythematosus (SLE) or lupus-like syndrome (4-7) and juvenile dermatomyositis (DM) (8).

We herein report a patient with HAE who presented with myositis-like symptoms and muscle pathology mimicking necrotizing myopathy. The findings from this case suggest that low C1-inhibitor and C4 levels induce inflammatory reactions in the muscles.

Case Report
A 56-year-old Japanese woman with HAE and psoriasis vulgaris (PV) was admitted to the neurology department. She presented with muscle weakness and muscle pain in both the upper and lower extremities along with elevated serum creatine kinase (CK) levels. She had been diagnosed with PV at 10 years old and been started on treatment with cyclosporine A (150 mg/day) at 48 years old. Her sisters had also been diagnosed with PV. In her mid-40s, she presented with muscle weakness (manual muscle testing: 4/4) and muscle pain, especially in the upper and lower extremities. At 51 years old, she experienced sudden onset of abdominal pain on several occasions.

Abdominal computed tomography (CT) revealed submucosal edema of the small intestine. Her blood tests showed significantly low C1-inhibitor activity (<25%, normal: 70-130%) and C4 (<4 mg/dL, normal: 17-45 mg/dL) and CH50 (13.9 U/mL, normal: 31.6-57.6 U/mL) levels; however, her C3 levels were in the normal range (111 mg/dL, normal: 86-160 mg/dL). The patient’s father had experienced similar
The muscle biopsy showed mild myogenic changes (Fig. 2A) with a few necrotic (Fig. 2B) and regenerative fibers (Fig. 2C). Dysregulation of myofibrillar structures was visible on NADH-TR staining (Fig. 2D). In contrast, MHC class I-positive fibers were not observed (Fig. 2E). Perifascicular atrophy was not visible. Necrotic muscle fibers (Fig. 2B) showed no infiltration of CD4- or CD8-positive lymphocytes (Fig. 2F, G), and only CD68-positive macrophages were present in the necrotic fibers (Fig. 2H). Deposition of C5b-9, the terminal membrane attack complex (MAC), was visible on the endomysial capillary vessel walls (Fig. 2I) as well as the sarcolemma (Fig. 2J).

A skin biopsy showed hyperkeratinization with a micro-abscess and an infiltration of lymphocytes around the vessels of the dermis, findings that were indicative of PV. The patient’s clinical symptoms, including muscle weakness and pain, as well as her elevated serum CK levels significantly improved soon after the oral administration of prednisolone (30 mg/day).

Discussion

In the present study, we reported the case of a patient with C1-inhibitor deficiency presenting with myositis-like symptoms as well as deposition of the MAC, leading to cell injury, in the muscles. To our knowledge, only one case report of HAE with juvenile DM is present in the literature (8); however, there are several reports suggesting that there is an association between HAE and autoimmune disorders, including SLE (4-7). These results suggest that deficiency of the C1-inhibitor and subsequent disturbances of the complement system can induce myositis through inflammatory reactions. Oral steroid therapy immediately improved the patient’s symptoms, as was reported in a similar case (8).

The mechanisms underlying the association of SLE-like autoimmune disorders with HAE remain unclear. However, studies have shown that deficiency in or low levels of complement proteins, such as C4, can lead to autoimmunity disorders (4, 9). Reduced levels of complement proteins and/or receptors lead to the disturbance of the macrophage-mediated uptake and clearance of apoptotic cells as well as the clearance of immune complexes (10-12). The inadequate clearance of apoptotic cells and immune complexes can cause inflammatory responses, including the release of intracellular antigens, which trigger an autoimmune response. Furthermore, deficiency of C4A can be a risk factor for juvenile DM (13). In the present case, long-term low levels of C4 may have triggered an inflammatory reaction in the muscles.

The muscle pathology in the present case was not typical for DM but was somewhat similar to that of immune-mediated necrotizing myopathy. The infiltration of inflammatory cells was very mild, and only necrotic fibers were observed. Neither MHC class I-positive fibers nor perifascicular atrophy was visible. One possible explanation for the
atypical muscle pathology may be that the patient had received an immunosuppressive drug for over eight years, which might have modified her muscle pathology. However, it is noteworthy that the deposition of C5b-9 was visible on the endomysial capillary vessel walls as well as sarcolemma. Although the deposition of C5b-9 on endomysial capillaries is recognized as a diagnostic hallmark of DM (14, 15) even without the infiltration of inflammatory cells (16), the capillary deposition of C5b-9 has been observed in cases of necrotizing myopathy (17) as well as other types of myositis (18). It is of great interest that disturbance of the classical complement pathway can induce MAC deposition through as-yet-undetermined mechanisms, such as the activation of other complement pathways or generation of unknown antibodies.

To our knowledge, this is the first report to describe a case of HAE accompanied by PV. Regarding skin lesions, reports suggest that erythema marginatum (EM) is observed in approximately 28% of patients with HAE (19). In particular, certain HAE patients experience EM as a prodromal symptom, and the administration of plasma-derived C1-inhibitor concentrate during EM is reported to be effective as prophylaxis for HAE attacks (19). Regardless of the presence of skin lesions, four different types of drugs (plasma-derived or recombinant C1-inhibitor concentrates, kallikrein inhibitors, or bradykinin B2 inhibitors) are selected for the treatment of acute attacks (20, 21); the administration of C1-inhibitor concentrate is effective for long-term prophylaxis (21).

Conversely, several reports have suggested that PV may be associated with myopathy. Tanabe et al. reported that PV may induce myopathy with vascular amyloid deposition (22), and Xing et al. demonstrated an association between PV and juvenile DM; however, the muscle pathology was not elucidated (23). PV may have also had a certain impact on the muscle pathology in the present case, via an unknown inflammatory pathway; however, the patient demonstrated myositis-like symptoms during the treatment of PV with cyclosporine A.

In conclusion, this present case indicates that C1-inhibitor deficiency can cause myositis-like symptoms and inflammatory myopathy-like pathology. Steroid therapy was an effective treatment. Further investigation will be necessary to clarify the mechanisms underlying autoimmunity caused by uncontrolled activation of the classical complement pathway.

The authors state that they have no Conflict of Interest (COI).

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