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Inclusion body myositis accompanied with T-cell large granular lymphocyte leukemia

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Inclusion body myositis (IBM) is a late-onset myopathy that manifests as distinct muscle weakness in the quadriceps, finger flexors, and ankle dorsiflexors. T-cell large granular lymphocyte (T-LGL) leukemia is a late-onset clonal disorder of CD8+ cytotoxic T-cells that is often accompanied by autoimmune diseases. To date, the association between IBM and T-LGL leukemia has been infrequently reported. Here, we report a case of a patient with T-LGL leukemia who developed IBM, along with in-depth laboratory, electrophysiological, and pathologic findings.

Key words: Autoimmune diseases; Inclusion body myositis; T-cell large granular lymphocyte leukemia

Inclusion body myositis (IBM) is a late-onset inflammatory myopathy, and the pathogenesis of IBM remains poorly understood. T-cell large granular lymphocyte (T-LGL) leukemia is a late-onset clonal disorder of CD8+ cytotoxic T-cells that is often accompanied by autoimmune diseases. To date, the association between IBM and T-LGL leukemia has been infrequently reported. Here, we report a case of a patient with T-LGL leukemia who developed IBM and discuss the underlying pathogenesis of the treatment refractoriness.

CASE

A 71-year-old female presented with a 1-year history of limb weakness. She had been diagnosed with T-LGL leukemia 5 years prior, at the time she was treated with methotrex-

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ate, cyclophosphamide, cyclosporine, and mycophenolate mofetil. However, owing to recurrent opportunistic infections, she discontinued all medications 2 months prior to her visit. She gradually developed difficulty swallowing food, buttoning clothing, and climbing stairs for 1 year.

Neurological examination revealed an intact mental status and sensory functions. Asymmetric motor weakness in shoulder abduction (Medical Research Council grade: right 5, left 4+), triceps (right 5, left 4), finger flexor (right 4+, left 4), hip flexion (right 5, left 4+), knee extensor (right 4+, left 4), and facial diplegia were noted. Finger flexion and knee extension were weaker than shoulder abduction and hip flexion, respectively, indicating distinctive weakness features of IBM. Deep tendon reflexes were reduced, and pathologic reflexes were absent. Laboratory tests showed increased serum creatinine kinase (1,151 IU/L) levels. A blood smear examination confirmed the presence of LGL with eccentric nuclei and cytotoxic granules (Fig. 1A). The T-cell clonal expansion was confirmed by a T-cell receptor gamma gene rearrangement assay. Flow cytometry revealed a loss of CD5, a molecule typically expressed on all T-cells, on the patient's CD8+ T-cells, which is a specific feature of T-LGL leukemia (Fig. 1B). The findings of motor and sensory nerve conduction studies were unremarkable. Electromyography revealed diffuse positive sharp waves, fibrillations, and polyphasic, low amplitude, and short duration motor unit action potential with early recruitment in the bulbar and limb muscles, suggesting active generalized myopathy. On her thigh magnetic resonance imaging, T2 high signal intensities with enhancement, muscle atrophy, and mild fatty infiltration were found in the bilateral vastus muscle groups with relatively preserved rectus femoris (Fig. 1C, D). A muscle biopsy performed on the left vastus medialis revealed CD8+ and CD57+, which is another specific marker for T-LGL leukemia,

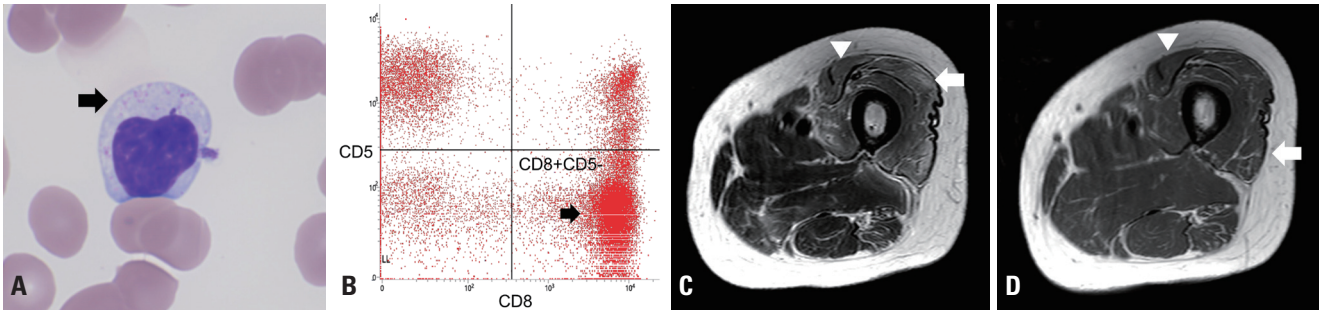

Fig. 1. Peripheral blood smear, flow cytometry, and thigh magnetic resonance imaging findings. (A) Blood smears show large granular lymphocytes (LGL) with eccentric nuclei and large cytotoxic granules (arrow, ×200). (B) Flow cytometry with large CD8+ expansions of T-LGLs with CD5- expression (arrow). (C, D) Thigh magnetic resonance image revealed T2 high signal intensity (C, T2-weighed image) and mild fatty infiltration (D, T1-weighed image) of the vastus lateralis (arrow) with relatively preserved rectus femoris (arrowhead).

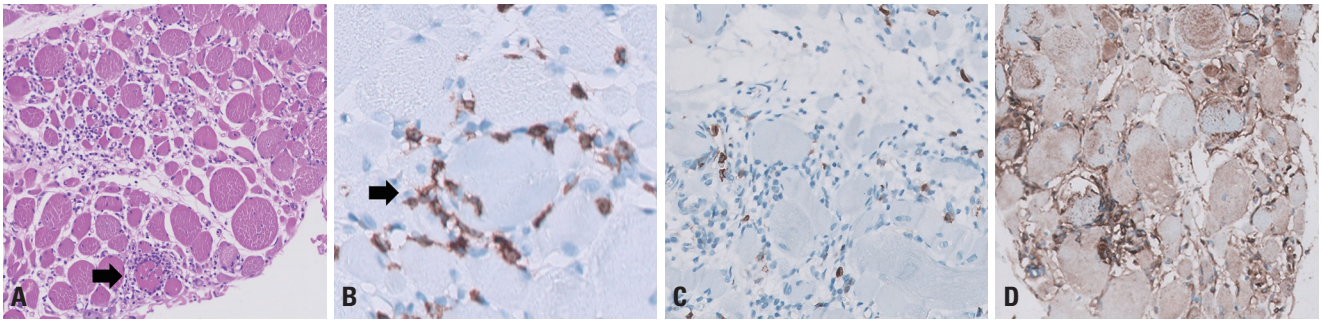

Fig. 2. Muscle pathology findings. (A) Hematoxylin and eosin-stained muscle biopsy shows endomysial inflammation and focally invaded myofiber (arrow, ×40). (B) Immunohistochemistry for CD8 reveals CD8+ T-cell invasion of non-necrotic myofiber (arrow, ×400). (C) Immunohistochemistry for CD57 demonstrates endomysial infiltration of the T-cells (×200). (D) Immunohistochemistry for major histocompatibility complex type I demonstrates widespread upregulation in the myofibers (×200).

T lymphocytes infiltrating the endomysium and invading myofibers (Fig. 2A-C). Upregulation of major histocompatibility complex type 1 (MHC-1) was observed at the sarcolemma and in the cytoplasm of several muscle fibers (Fig. 2D). No rimmed vacuoles were identified, and amyloid Congo red, p62, and TDP43 staining were all negative. In addition, anti-cytosolic 5′-nucleotidase 1A antibody was detected in the serum by enzyme-linked immunosorbent assay.

IBM was diagnosed based on the clinical, laboratory, and muscle biopsy findings. Treatment with concomitant use of prednisolone and methotrexate was initiated. However, when she revisited the outpatient clinic 2 months later, her weakness worsened even though her serum creatine kinase (CK) level had normalized. Cyclophosphamide, doxorubicin, vincristine, and prednisolone chemotherapy was initiated, but she nevertheless experienced a slow progression of motor weakness.

DISCUSSION

According to the European neuromuscular center IBM research diagnostic criteria 2011,[1] our patient was diagnosed with clinically defined IBM, meeting the following criteria: 1) duration >12 months, age at onset >45 years, and serum CK level no greater than 15 × upper limit of normal value; 2) knee extensor weakness ≥hip flexor weakness and finger flexion weakness >shoulder abduction weakness; and 3) one or more of the following pathological features (endomysial inflammatory infiltrate, rimmed vacuoles, protein accumulation or 15 to 18 nm filaments, and/or upregulation of MHC class I). These criteria are reported to have high specificity (>99.0%) but low sensitivity (57.0%); therefore, simple machine learning-based criteria have been proposed with 90.0% sensitivity and 96.0% specificity:[2] 1) finger flexor or quadriceps weakness; 2) endomysial inflammation; and 3) invasion of non-necrotic muscle fibers or rimmed vacuoles. Our patient fully met these new criteria.

IBM is traditionally known as an autoimmune disease. Supporting evidence for this view are its endomysial CD8+ T-cell infiltration on muscle pathology,[3] its association with HLA-DRB1 genes,[4] and the identification of an autoantibody to cytosolic 5′-nucleotidase 1A.[5] Since a patient with IBM and CD8+ chronic lymphocytic leukemia was reported in 2001,[6] the association between T-LGL leukemia and IBM has been reported several times.[7] A total of 58.0% of IBM patients revealed aberrant populations of LGL in the blood, meeting the diagnostic criteria for T-LGL.[7] The extent of clonally expanded CD8+, CD57+ cells in the blood correlated with those in the muscle, suggesting causality.[7] The T-cells found in IBM demonstrate specific characteristics of highly differentiated populations of T-cells, including the loss of CD5, CD28, and gain of CD57 and KLRG1.[8] These T-cells are composed of effector memory T-cells and terminally-differentiated effector memory T-cells, which are known to produce high level of cytokines and cytotoxic molecules.[8] In addition, highly differentiated T-cells have been reported to be resistant to immunomodulating therapy including corticosteroids, immunosuppressants, and alemtuzumab, none of which are able to deplete these cells.[9] Therefore, several researchers have proposed a treatment that targets highly differentiated cytotoxic T-cell markers, such as KLRG1.[8]

The treatment refractoriness of conventional immunosuppressant therapy in IBM suggests that other pathogeneses, such as age-associated degenerative myopathology, play a role. Muscle pathologies, such as rimmed vacuoles, protein aggregates, and mitochondria pathologies, are notable and distinctive characteristics of IBM, supporting a degenerative pathogenic mechanism. Some authors have argued that IBM is not an autoimmune disease but a degenerative muscle disease;[10] in contrast, others have suggested that degenerative abnormalities can stem from endoplasmic reticulum stress through interferon-gamma produced by T-cells.[9]

In summary, clinicians should be aware that IBM has distinctive neurological examination features such as finger flexion, knee extensor weakness, and comorbidity with T-LGL leukemia. In addition, our case indicates that treatment refractoriness of conventional immunosuppressant therapy may be due to the characteristics of a highly differentiated T-cell population resistant to conventional therapy or to the degenerative myo-pathological features of IBM, which remain to be elucidated.

Conflicts of Interest

None.

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