CASE REPORT

Efficacy of immunosuppressive treatment in a systemic lupus erythematosus patient presenting with inclusion body myositis

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SUMMARY

Inclusion body myositis (IBM) is an inflammatory myopathy that is generally unresponsive to immunosuppressive drugs. The coexistence of IBM with other autoimmune connective tissue diseases is rare. We present a case of a 76-year-old woman with systemic lupus erythematosus (SLE) who developed proximal muscle weakness of lower extremities and mild elevation of serum creatine kinase (CK) at 495 U/L. Muscle biopsy showed changes of endomysial inflammation and rimmed vacuoles consistent with IBM. She was treated with prednisone 40 mg daily and methotrexate 12.5 mg weekly. One month later, her physical examination showed minimal proximal weakness of lower extremities. CK levels decreased to 44 U/L. Prednisone dose was gradually decreased to 5.0 mg daily. She remained stable with normal CK levels during a follow-up period of 10 months. This case, together with other reports, suggests that IBM in the setting of SLE represents a different subtype that can benefit from immunosuppressive treatment.

BACKGROUND

Inclusion body myositis (IBM) is a rare presentation of inflammatory myopathy with clinical features that clearly separate it from the other inflammatory myopathies such as polymyositis and dermatomyositis.^{1–2} One of the characteristic features of IBM is the presence of proximal and distal muscle weakness.² The underlying pathology driving the disease is unknown. IBM tends to more frequently affect males over the age of 50 years and carries a poor prognosis.² This form of myopathy is considered to be, in most cases, refractory to treatment with conventional immunosuppressive medications and those who respond, subsequently have a progressive slow decay in function.³ IBM usually presents as an isolated disease but there are some reports of IBM occurring in patients with autoimmune connective diseases, including systemic lupus erythematosus (SLE).^{4–6} We present a case of a 76-year-old woman with SLE who developed IBM and experienced a remarkable clinical response to immunosuppressive therapy.

CASE PRESENTATION

A 76-year-old woman with SLE since September 2003 presented with non-erosive inflammatory polyarthritis, prolonged morning stiffness (>1 h), lymphopenia, leukopenia, mild thrombocytopenia,

elevated erythrocyte sedimentation rate (130 mm/h), elevated C reactive protein (6.0 mg/L), positive antinuclear antibodies (1:320, speckled pattern) and C3 hypocomplementemia. She met the Systemic Lupus International Collaborating Clinics classification criteria for SLE.⁷ She was treated with hydroxychloroquine 400 mg daily and prednisone 20 mg daily. She responded well to this treatment and prednisone dose was gradually decreased until discontinued in July 2004. She remained in complete clinical remission until October 2011, when she developed severe inflammatory polyarthritis. Prednisone 10 mg daily was started and synovitis resolved. However, multiple attempts to decrease prednisone dose below 10 mg daily were unsuccessful due to recurrent polyarthritis.

In December 2013, the patient developed mild difficulty getting up from a chair or bed. On examination, she had mild proximal muscle weakness (4/5) of lower extremities. Electromyography showed a mixed pattern of myopathic and neurogenic changes. Serum creatine kinase (CK) was mildly elevated at 484 U/L (normal range 30–223 U/L) but aldolase levels were normal. The possibility of corticosteroid-induced myopathy was considered, for which prednisone dose was gradually decreased until discontinued in December 2014. After discontinuation of prednisone, she had worsening of muscle weakness requiring assistance while standing up or climbing stairs. She had no other associated symptoms. On examination, she had proximal muscle weakness (3–4/5) of lower extremities, including knee extensors and hip flexors. She had normal strength in the upper extremities and distal lower extremities. The rest of the examination was unremarkable.

INVESTIGATIONS

Laboratory tests showed normal white cell count, haemoglobin, platelet count, urine analysis, liver enzymes, blood urea nitrogen, serum creatinine, thyroid tests and serum protein electrophoresis. Westergren sedimentation rate was normal at 19 mm/h. CK was elevated at 495 U/L. Serum aldolase level was normal. Anti-double stranded DNA, anti-Smith, anti-ribonucleoprotein (RNP), anti-Ro, anti-La and anti-Jo-1 antibodies were not elevated. C3 and C4 levels were normal. Malignancy screening tests including chest X-rays, mammography, pelvic examination and colonoscopy were unremarkable. A muscle biopsy of the left thigh,

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Figure 1 Predominantly endomysial inflammatory infiltrate is present. Rimmed-like vacuoles are observed near the inflammatory area (H&E ×100).

performed in March 2015, revealed endomysial inflammation and rimmed vacuoles with deposits of P62 (figures 1 and 2). The microscopic description and histochemistry and immunohistochemistry analyses of the examined tissue are shown in box 1. The patient met the clinicopathological criteria for defined IBM according to the 2011 European Neuromuscular Centre IBM Research Diagnostic Criteria.⁸

TREATMENT

In April 2015, the patient was treated with prednisone 40 mg daily and methotrexate 12.5 mg orally weekly.

OUTCOME AND FOLLOW-UP

The patient had a remarkable clinical response to this therapy. One month later, she was able to stand up without assistance. Physical examination showed minimal proximal weakness of the lower extremities (4–5/5). CK decreased to normal levels (44 U/L). Muscle strength was fully recovered after 2 months of therapy. Prednisone dose was gradually decreased to 5.0 mg daily. The patient remained stable with normal CK levels during a follow-up period of 10 months.

Figure 2 Rimmed-like vacuoles stain strongly positive for P62 protein (P62 ×200).

Box 1 Microscopic description and histochemistry and immunohistochemistry analyses of muscle biopsy

MICROSCOPIC DESCRIPTION (H&E AND MODIFIED GOMORI TRICHROME STAINS)

- ▶ Focal muscle fibre size variation and atrophy, with some angulated fibres
- ▶ Internal nucleation observed in 15–16% of fibres
- ▶ No fibre splitting observed
- ▶ Mild to moderate endomysial and perimysial fibrosis
- ▶ Fatty penetration/replacement
- ▶ Hyper basophilic regenerating fibres observed
- ▶ Moderate inflammatory infiltrate, predominantly endomysial
- ▶ No perifascicular pattern of atrophy or inflammation
- ▶ Focal fibre necrosis with phagocytosis present
- ▶ No ragged red fibres observed.
- ▶ Rimmed-like vacuoles focally present

HISTOCHEMISTRY

- ▶ Nicotinamide adenine dinucleotide (NADH) and ATPase: type 2 fibre predominance with no fibre type grouping; atrophic fibres are both type 1 and type 2
- ▶ Periodic acid-Schiff stain: no abnormal distribution of glycogen
- ▶ Oil red O stain: no abnormal size nor distribution of lipid droplets
- ▶ Congo red examined with polarised light: negative for amyloid

IMMUNOHISTOCHEMISTRY

- ▶ Myosin heavy chain immunohistochemistry: type 2 fibre predominance with no fibre type grouping
- ▶ Normal pattern of spectrin and dystrophin (1, 2 and 3) stains
- ▶ Human leucocyte antigen-Class 1 overexpression
- ▶ Infiltrate predominantly endomysial consisting of a lymphoid and monocytoid cell population, composed of T-cells, with a prominent expression of CD3, CD4 and CD8. The proportion of CD4:CD8 was 1:2.
- ▶ Numerous CD68 macrophages present, some associated to degenerating fibres and blood vessels.
- ▶ Tau protein positive in rimmed vacuoles
- ▶ P62 deposits present in rimmed vacuoles

DISCUSSION

We present a case of an elderly woman with SLE who developed IBM, and had a rapid and effective clinical response to corticosteroids and methotrexate. The frequency of IBM associated with a connective tissue disease is unknown although it appears to be very rare. There are few reports in the literature of patients developing IBM in association with other connective tissue diseases such as Sjögren's syndrome, scleroderma, rheumatoid arthritis and SLE.^{4–6} In most of these cases, the patients had a favourable response to immunosuppressive treatment.

Previously, five cases of SLE have been reported in association with IBM (table 1).^{9–13} In these cases, the dominant presentation was proximal muscle weakness and all had a modest elevation of CK serum levels, normal or slightly elevated inflammatory markers, absence of myositis-specific antibodies and marked elevation of antinuclear antibody titres. As in sporadic

Table 1 Demographic features, clinical manifestations, serological tests and clinical outcomes of patients with coexistent systemic lupus erythematosus and inclusion body myositis

Authors/ publication year	Age and gender	Time interval between SLE and IBM	Clinical manifestations of lupus	Clinical manifestations of IBM	Autoantibodies	EMG and NCS	Biopsy	Treatment	Clinical outcome
IBM preceding SLE									
Yood and Smith ¹² /1985	60-year-old woman	7 years	Malar rash Arthralgia Myalgia Proteinuria	Symmetric proximal UE and LE weakness Symmetric distal LE weakness ↑CK=270 U/L	Positive Ab: ANA ENA RF Neg Ab: Anti-Pm-1	Positive sharp waves, fibrillation and small polyphasic units	Chronic inflammatory myopathy, presence of rimmed vacuoles	Prednisone 60 mg daily for 3 months, then 40 mg every other day for 3 months	Reverted to pretreatment state
SLE preceding IBM									
Limaye et al ¹¹ /2000	51-year-old man	20 years	Malar rash Arthritis Myalgia Raynaud's SLE myositis (prior to IBM))	Symmetric Proximal LE weakness ↑CK=2192 U/L	Positive Ab: ANA Anti-dsDNA	Not performed	Inflammatory myopathy, presence of rimmed vacuoles	Methotrexate 25 mg IM weekly, azathioprine 50 mg daily and prednisolone	Stabilised
Wenzel et al ¹³ /2001	71-year-old man	2 years	Subacute cutaneous lupus Leukopenia Lymphopenia Thrombocytopenia	Symmetric LE weakness CK=16 U/L	Positive Ab: ANA Anti-SSB Anti-SSA RF Neg Ab: Anti-Ku Anti-Jo1 Anti-Mi-2	Mixed sensorimotor neuropathy, acute denervation	Atrophic muscle fibres, presence of rimmed vacuoles	Methotrexate 25 mg IV weekly and prednisolone (initial dose 100 mg, then 20 mg daily)	Reverted to pretreatment state
Derk et al ⁹ /2003	57-year-old woman	16 years	Oral ulcers Arthritis Sicca symptoms	Symmetric proximal UE and LE weakness ↑CK=529 U/L	Positive Ab: ANA anti-dsDNA Neg Ab: Anti-Jo1 Anti-SRP Anti-Mi-2 Anti PM-Scl anti-Ku	Polyphasic units without fibrillation or positive waves	Variation in muscle fibre diameter, perivascular lymphocytic and interstitial infiltrates, presence of rimmed vacuoles	Methotrexate 25 mg PO weekly and prednisolone 40 mg daily tapered over 4 months	Reverted to pretreatment state
Massawi et al ¹⁰ /2003	73-year-old woman	15 years	Arthralgia Sicca symptoms Leukopenia SLE myositis	Symmetric UE and LE distal muscle weakness ↑CK=190 U/L	Positive Ab: ANA Anti-dsDNA Anti-SSA Anti-SSB Neg Ab: Anti-Jo1	Not done	Chronic myopathic changes, prominent fibrosis, rimmed vacuoles	Intravenous immunoglobulins Failed methotrexate PO 25 mg weekly	Reasonable recovery of muscle strength and functional status
Current case	76-year-old woman	11 years	Arthritis Leukopenia Lymphopenia Thrombocytopenia	Symmetric LE weakness ↑CK=495 U/L	Positive Ab: ANA Neg Ab: Anti-dsDNA Anti-SSA Anti-SSB Anti-Jo1	Mixed myopathic and neurogenic changes	Muscle fibres variations, moderate inflammatory infiltrate, rimmed vacuoles	Methotrexate 12.5 mg PO weekly and prednisone 40 mg daily tapered to 5 mg daily over 5 months	Recovery of muscle strength and functional status

Ab, antibodies; ANA, antinuclear antibodies; CK, creatine kinase; dsDNA, double stranded DNA; ENA, extractable nuclear antigens; IBM, inclusion body myositis; IM, intramuscular; IV, intravenous; Jo1, histidyl tRNA synthetase; LE, lower extremities; Mi-2, chromodomain helicase DNA binding protein; Pm1, antipolymyositis 1; PM-Scl, polymyositis-scleroderma; PO, orally; RF, rheumatoid factor; SLE, systemic lupus erythematosus; SRP, signal recognition particle; SSA Ab, Sjögren's syndrome antigen A; SSB Ab, Sjögren's syndrome antigen B; UE, upper extremities.

IBM, symptoms appeared after the age of 50 years and presented with a slow progressive muscle weakness. Just as reported with patients with other connective tissue diseases, a positive response to therapy was again described. Our patient had onset of symptoms late in the course of disease, proximal muscle weakness, undetected myositis-specific antibodies and excellent response to immunosuppressive treatment. Altogether, these cases suggest that, in the scenario of patients with an underlying connective tissue disease, IBM may present as a different entity with a favourable outcome when treated with immunosuppressive therapy.

The differential diagnosis of a patient with SLE presenting with myopathy should include the possibilities of SLE-associated myositis and drug-induced myopathy. Other important considerations are alcohol or drug abuse, endocrinopathies and an overlap presentation with an inflammatory myopathy. Of particular interest in our case is the history of chronic treatment with hydroxychloroquine and prednisone, both drugs known to be possible culprits of myopathy.^{14 15} Initially in the course of our patient's muscle weakness, the possibility of steroid-induced myopathy was a strong consideration; thus, prednisone was withdrawn. This intervention led to worsening of her muscle weakness, which warned against steroid-induced myopathy. Her positive response to reintroduction of corticosteroids was more consistent with an inflammatory process. Furthermore, no atrophy of type II fibres was observed in the muscle biopsy, as expected for corticosteroid-induced myopathy. With regard to the possibility of hydroxychloroquine as a causative agent, this may induce neuromyotoxicity and, therefore, can produce muscle weakness, such as that described in our patient. However, this toxicity has very specific characteristic ultrastructural changes present in the muscle, which were absent in the biopsy specimen.¹⁶

IBM is considered to be resistant to treatment with corticosteroids and immunosuppressive drugs, as the degeneration of muscle fibres is the main feature promoting slow disease progression.^{3 17} However, this case, together with other reports, serves to support the concept that patients with underlying SLE may have a more prominent immune-mediated inflammatory component in the disease manifestations, thus explaining the response to therapy. It is therefore necessary to keep in mind the unusual presentation of IBM in patients with SLE, particularly in elderly populations. Prompt treatment with immunosuppressive drugs may reverse or halt the progression of the disease. Also, consideration must be given to the importance of timely use of diagnostic procedures such as muscle biopsy and electromyography, to assist with the diagnosis and proper treatment in SLE patients presenting with atypical or recurrent myositis. Perhaps the most important lesson to be drawn from the cases reported, including ours, is that, in the setting of an autoimmune disease, the diagnosis of IBM does not represent a hopeless diagnosis.

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Learning points

- ▶ Inclusion body myositis (IBM) is an inflammatory myopathy that is generally unresponsive to corticosteroids and immunosuppressive drugs.
- ▶ IBM usually presents as an isolated disease but there are reports in the literature of patients developing IBM in association with other connective tissue diseases such as systemic lupus erythematosus (SLE).
- ▶ The case presented here and other reports suggest that, in the scenario of patients with SLE, IBM may present as a different entity with favourable outcome when treated with immunosuppressive therapy.

Competing interests None declared.

Patient consent Obtained.

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