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CASE REPORT

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Inclusion body myositis in connective tissue disorders: case report and review of the literature

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Abstract We report a patient with systemic lupus erythematosus (SLE) and secondary Sjögren's syndrome (SS) who developed inclusion body myositis (IBM) which, contrary to the typical presentation of this disorder, was symmetrical in nature although the diagnosis was only made after electron microscopy was performed. Therapy with increased doses of methotrexate proved to be beneficial, with the patient having full recovery after 8 months of therapy. It appears that a subset of IBM may be related to autoimmune disorders, an issue that was disputed in the past, and these patients may have a better prognosis than typical IBM patients. This is the first case report of IBM in a patient who had the dual diagnosis of SLE and SS.

Keywords Inclusion body myositis · Systemic lupus erythematosus · Sjögren's syndrome

Introduction

The term 'inclusion body myositis' (IBM) was initially proposed by Yunis and Samaha in 1971, to describe a patient with a chronic inflammatory myopathy who had intranuclear and intracytoplasmic tubular filaments within muscle fibres on electron microscopy [1]. In 1978 Carpenter et al. further defined IBM as a distinct nosologic entity with features different from those of polymyositis and dermatomyositis [2]. Subsequent studies revealed a male predominance, an insidious but progressive course, asymmetry of muscle weakness, proximal and distal muscle involvement, mild to minimal elevation of the creatinine phosphokinase and a lack of response to corticosteroids [3]. Myalgias, dysphagia and involvement of facial muscles have also been described. Light microscopy of biopsy specimens typically demonstrates an inflammatory myositis characterised by lymphocytic endomysial infiltrates, fiber degeneration and regeneration, and basophilic rimmed vacuoles on the modified Gomori trichrome stain. The most characteristic feature of IBM, however, is the presence on electron microscopy of intranuclear and cytoplasmic inclusions with tubular filaments that measure 13–18 nm in diameter [4]. Earlier reports noted the similarity of IBM inclusions to myxovirus or paramyxovirus particles and prompted the investigation of a possible viral aetiology that was never proven. More recently the presence of inclusion body myositis was demonstrated in patients with various autoimmune and connective tissue disorders [5–10], and fuelled the hypothesis that IBM may be an autoimmune disease as well. We report a patient with both systemic lupus erythematosus (SLE) and secondary Sjögren's syndrome (SS) who developed biopsy-proven IBM as a late complication in her course, and responded to treatment with methotrexate. The response of this and other similar patients to immunosuppressive therapy is reviewed and may define a subset of IBM patients with a more favourable prognosis and immune-mediated disease.

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Case report

A 57-year-old Caucasian woman with a past medical history of systemic lupus erythematosus, secondary Sjögren's syndrome, vasculitis, gastro-oesophageal reflux disease, steroid-induced osteoporosis, protein S and protein C deficiency, deep venous thrombosis, pulmonary embolus and multiple cerebrovascular accidents presented with new-onset proximal muscle weakness. She was initially diagnosed with SLE 16 years earlier following the development of arthritis, oral ulcers, antinuclear antibodies (ANA) and antidouble-stranded DNA antibodies (dsDNA). A year later she developed sicca symptoms and was diagnosed with secondary SS by labial minor salivary gland biopsy. Three months prior to her most recent presentation she developed gradually progressive symmetric proximal

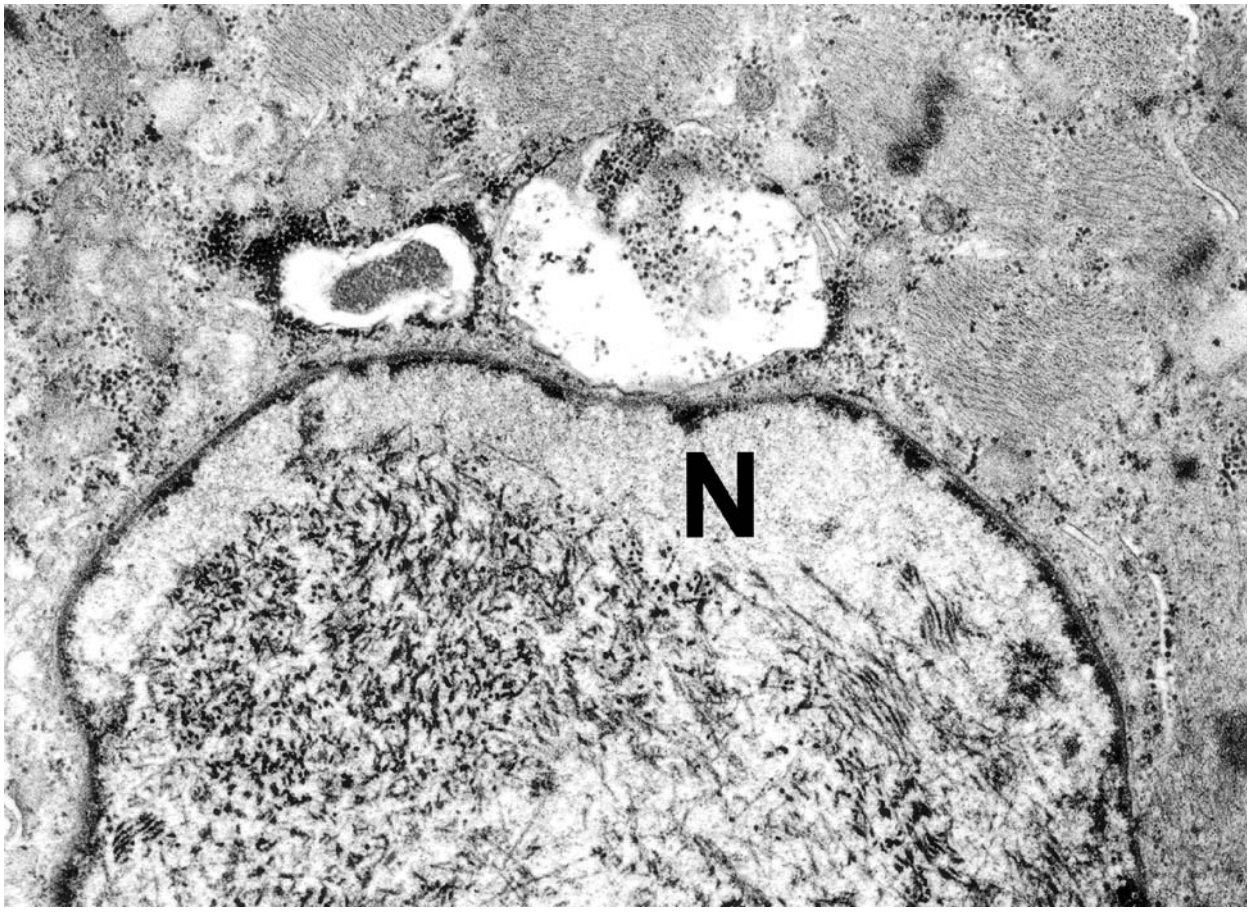
muscle weakness involving both upper and lower extremities. She related that she had felt weak for the past year, though her symptoms had dramatically progressed over the past 3 months. She initially had proximal weakness of her anterior thighs and had noticed difficulty going up steps and getting out of chairs. In the next few months this progressed to involve the posterior thigh muscles as well as the proximal muscles of both arms, making it difficult to reach in overhead cabinets. On presentation she also related left shoulder pain on abduction as well as left upper extremity paresthesias down into her fingers. At the time of presentation the patient was taking celecoxib, cevimeline, omeprazole, atorvastatin, warfarin and methotrexate 10 mg orally every week.

On physical examination she was found to have proximal muscle weakness of all four extremities, the left upper extremity being more affected than the right. Deep tendon reflexes were diminished throughout. A creatinine phosphokinase level was 529 U/l (0–200 U/l) and an aldolase level was 14.6 U/l (0.0–7.0 U/l). Her erythrocyte sedimentation rate (ESR) was 13 mm/h (0–20 mm/h) and C-reactive protein (CRP) was $<$ 5.0 mg/l (0–5.0 mg/l). Complements C3, C4 and anti-dsDNA antibody titre were normal. Atorvastatin was discontinued, but follow-up examination and muscle enzyme elevations were unchanged. An electromyographic study (EMG) showed polyphasic units without fibrillations or positive waves of the proximal upper extremity muscles and similar findings in the lower extremity muscles (proximal $>$ distal). Studies for myositis-specific antibodies, including anti-Jo1, anti-SRP, anti-Mi-2, anti-PM-Scl and anti-Ku, were negative. A muscle biopsy from the left quadriceps was then performed. H &E-stained formalin-fixed and frozen sections demonstrated an increased variation in muscle fibre diameter ranging from 20 to 100 μm, with scattered angular fibres. There was no perifascicular atrophy but several degenerating and regenerating fibres. There were multiple foci of a perivascular lymphocytic and interstitial inflammatory infiltrate which was associated with fiber damage. A modified Gomori trichrome stain of frozen tissue showed no evidence of rimmed vacuoles or ragged red fibres. Additional stains (PAS, oil red orcein, ATPase pH 4.2 and pH 10, acid phosphatase, NADPH Tr and SDH) were unremarkable. Electron microscopy revealed multiple autophagic vacuoles, several of which demonstrated adjacent filamentous inclusions (12–20 nm in diameter), both intranuclear (Fig. 1) and cytoplasmic (Fig. 2), diagnostic of inclusion body myositis. The patient was treated by gradually increasing her methotrexate up to 25 mg weekly and by adding prednisone 40 mg/day, with a slow taper over the next 3 months. Within 6 months the patient's muscle strength had reverted to normal, with normalization of muscle enzymes and suppression of inflammatory indices. Twelve months after the initial diagnosis of inclusion body myositis the patient remains clinically asymptomatic without recurrence of her myositis. The methotrexate dose has been brought back down to the level prior to the myositis diagnosis, and she is currently not receiving corticosteroid therapy.

Fig. 1 Intranuclear (N) filamentous inclusions of IBM. N marks the nucleoplasm. Original magnification × 25 000

Discussion

Rheumatologists are more likely to encounter the sporadic or late adult onset form of IBM than hereditary IBM, which is much less common. Earlier descriptions of sporadic IBM emphasized the absence of collagen vascular disease and lack of response to corticosteroids as important distinguishing features from other forms of myositis [2]. On the contrary, some reports have



suggested that some patients with IBM respond favourably to immunosuppressive therapy and corticosteroids, and in these patients the muscle biopsies have shown evidence of active inflammation, suggesting a possible distinction of IBM into inflammatory and non-inflammatory types [11–13]. The present report, as well as a review of the English-language literature, clearly documents that IBM can coexist with other autoimmune disorders (Table 1). Other differences between sporadic IBM and this unique subset of patients are also apparent.

In contrast to the usual patient with IBM (an elderly male with progressive myositis that is difficult to treat) the male:female ratio of IBM associated with autoimmune disease is approximately 1:1, and the majority of patients respond, at least in part, to immunosuppresive therapy. Our patient was successfully treated by increasing her dose of methotrexate and adding corticosteroid therapy, and was able to do leg curls and quadriceps strengthening exercises with 30 lb weights within 6 months of treatment.

At present there is no clear consensus regarding the immunosuppressive agent of choice for IBM associated with autoimmune disorders. However, as many of these patients were already under care for other medical problems when IBM developed, successful treatment could be attributed in some instances as much to early diagnosis and intervention as to the choice of immunosuppressant.

This subset of IBM patients may present with proximal and distal muscle weakness as seen in sporadic IBM, or as in our case, with classic symmetrical proximal muscle weakness that clinically resembles polymyositis. The definitive diagnosis can therefore only be made by muscle biopsy. Because rimmed vacuoles can frequently be missed as a consequence of tissue processing for paraffin fixation, cryostat sections should always be used. In our patient, however, cryostat sections also failed to reveal rimmed vacuoles and the correct diagnosis was only established after electron microscopy. These observations suggest that the prevalence of IBM, including forms associated with autoimmune disease, may be even greater than previously appreciated. Consequently, routine ultrastructural examination of all biopsy specimens remains the only reliable way to ensure that all cases are identified.

The pathogenesis of IBM has recently been reviewed and the cause remains undefined [14]. An initial report noted the similarity of IBM to myxovirus or paramyxovirus nucleocapsid [15]. Another study by the same investigator subsequently reported immunoreactivity to mumps virus antigens in these inclusions. However, more sensitive polymerase chain reaction assays for the mumps P protein gene and in situ hybridisation with mumps nucleic acid probes failed to confirm a viral aetiology [16]. More recently, immunohistochemical studies of vacuolated muscle fibres have demonstrated

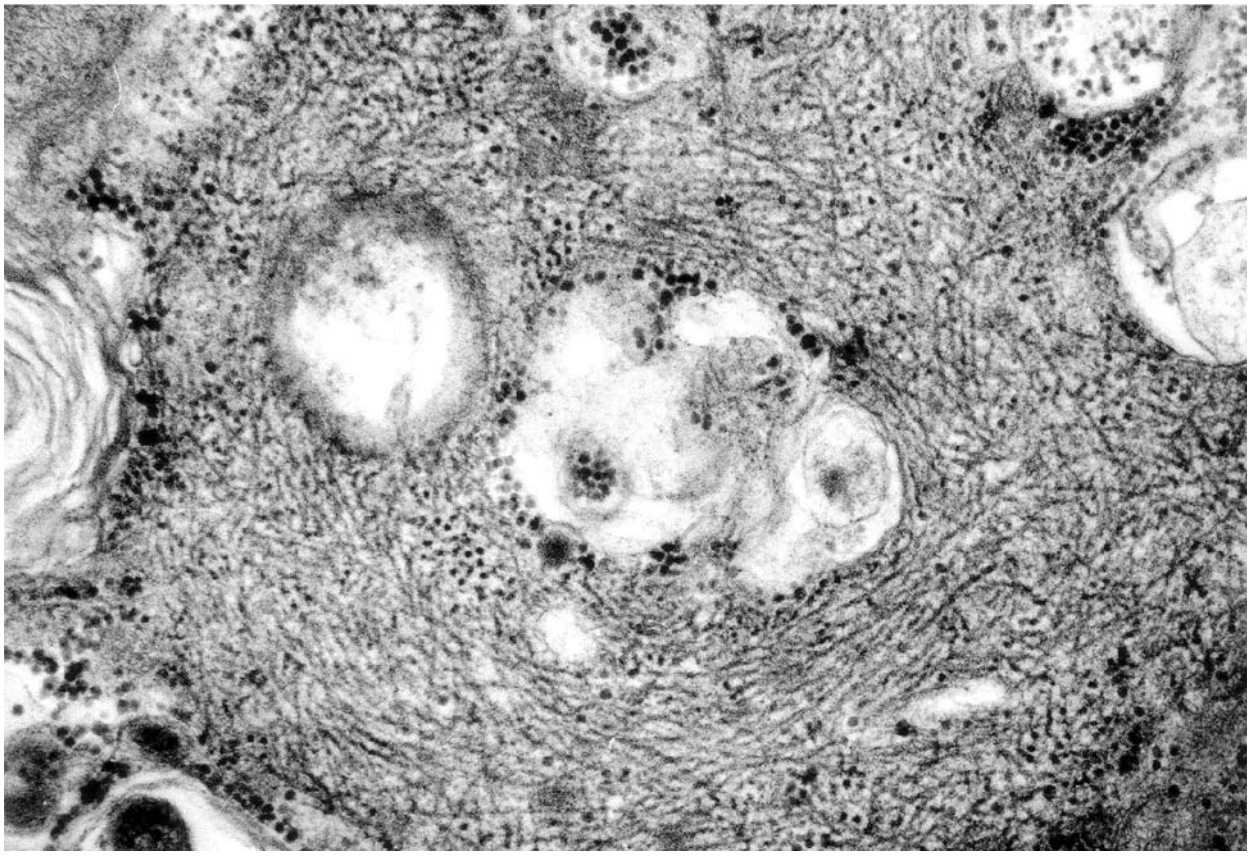


Fig. 2 Cytoplasmic filamentous inclusions of IBM. Original magnification × 72 500

Table 1 Inclusion body myositis related to autoimmune disorders: a comparison of case reports

	Age	Pattern of weakness	CPK (0–270 U/l)	Sex	ANA	RF	Autoimmune disease	Disease chronicity	Pathologic results for IBM	Treatment	Response to therapy
Chad et. al. (5)	49	Symmetric Distal and proximal	nl	F	+	+	Primary SS	18 years	+ LM + EM	Pred. 60 mg/day, Aza. 1.5 mg/kg/day	No
Yood et. al. (6)	53	Symmetric Distal and proximal	270	F	+	+	SLE	10 years	+ LM + EM	Pred. 40 mg/day	Yes
Limaye et. al. (7)	31	Symmetric proximal	2192	M	+	NA	SLE	weeks	+ LM + EM	MTX 25 mg/week, AZA 50 mg/day, Pred. taper	Yes
Lanc et al. (10)	53	Symmetric proximal upper extremity	nl	M	–	–	UCTD	6 months	+ LM + EM	Pred 20 mg/day AZA 50 mg/day	Yes
Riggs et. al. (8)	52	Symmetric Proximal and distal	nl	M	–	+	Chronic immune thromboc-ytopenia	7 years	+ LM + EM	MTX 10 mg/week, AZA 100 mg/day, pred.40 mg/day	No
Current Case	57	Symmetric Proximal	529	F	+	+	SLE Secondary SS	3 months	–LM + EM	MTX 25 mg/week pred. 40 mg/day	Yes

MTX, methotrexate; AZA, azathioprine; F, female; M, male; SLE, systemic lupus erythematosus; SS, Sjögren's syndrome; LM, light microscopy; EM, electron microscopy; pred., prednisone; nl, normal; IBM, inclusion body myositis; UCTD, undifferentiated connective tissue disorder

the presence of β-amyloid and other proteins similar to those seen in the cerebral plaques of Alzheimer's disease [17]. These findings raise the possibility of similar pathogenetic mechanisms. However, it remains unclear whether this aberrant expression of proteins results from or stimulates the inflammatory process.

Inclusion body myositis has been strongly associated with HLA-DR3, and a recent study mapped a candidate IBM susceptibility gene to the region between HLA DR and C4 [18]. Other observations also support the concept of an autoimmune pathogenesis of IBM. Non-necrotic muscle fibres that bear class I MHC antigens are surrounded and invaded by CD8+ cytotoxic T cells, and this phenomenon is found more frequently than the other typical pathologic features of IBM [19, 20]. Selective induction of intracellular adhesion molecule I (ICAM-1) also occurs on most non-necrotic fibres, especially where their surfaces face the invading mononuclear cells [21]. Finally, as in the present report, the coexistence of IBM with other autoimmune diseases, as well as the response to immunosuppressive therapy, suggests that IBM, or at least a subset of IBM patients, is an immune-mediated disease.

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