A rare association of early-onset inclusion body myositis, rheumatoid arthritis and autoimmune thyroiditis: a case report and literature review

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Summary

Sporadic inclusion body myositis (sIBM) is a slowly progressive, red-rimmed vacuolar myopathy leading to muscular atrophy and progressive weakness; it predominantly affects males older than fifty years, and is resistant to immunotherapy. It has been described in association with immuno-mediated thrombocytopenic purpura, multiple sclerosis, connective tissue disorders and, occasionally, rheumatoid arthritis.

A 37-year-old man with longstanding rheumatoid arthritis and autoimmune thyroiditis with hypothyroidism was referred to us with slowly progressive, diffuse muscle weakness and wasting, which had initially involved the volar finger flexors, and subsequently also the ankle dorsiflexors and knee extensors. Needle electromyography showed typical myopathic motor unit potentials, fibrillation and positive sharp waves with normal nerve conduction studies. Quadriceps muscle biopsy was suggestive of sIBM. Considering data published in the literature, this case may be classified as an early-onset form. The patient was treated with long-term intravenous immunoglobulin and obtained a substantial stabilization of his muscle strength.

KEY WORDS: autoimmune thyroiditis, connective tissue disorders, inclusion body myositis, inflammatory myopathy, rheumatoid arthritis

Introduction

The inflammatory myopathies encompass four major categories of muscle disease: polymyositis (PM), dermatomyositis (DM), necrotizing autoimmune myositis (NAM) and inclusion body myositis (IBM) (Dalakas, 2011a). PM, DM and NAM are usually characterized by progressive and subacute proximal muscle weakness, while the development of IBM is slower and more insidious, with five to six years elapsing between symptom onset and diagnosis (Needham and Mastaglia, 2007).

The term IBM was originally introduced by Yunis and Samara (1971) to describe a patient with a chronic inflammatory myopathy characterized by intranuclear and intracytoplasmic tubular filaments within muscle fibers on electron microscopy. Subsequently, Carpenter et al. (1978), on the basis of clinical and histopathological findings, codified IBM as an entity distinct from the other inflammatory myopathies.

From a clinical point of view, IBM is the most common myopathy in patients older than fifty years, occurring only rarely in people younger than fifty (Amato and Barohn, 2009; Hilton-Jones et al., 2010); it is more common in men, having a male/female ratio of approximately 3:1 (Hilton-Jones et al., 2010; Dalakas and Karpati, 2010).

The disease affects and weakens the distal muscles of the arms and legs. Typically, the deep finger and wrist flexors are affected initially, the impairment of these muscles being greater than that of the finger and wrist extensors. In the lower limbs, the muscles affected early on are the knee extensors and ankle dorsiflexors, but also the quadriceps femoris (Hilton-Jones et al., 2010; Dalakas and Karpati, 2010).

Although the disease tends to progress slowly, usually painlessly and often in an asymmetric manner with extension to the proximal muscles, it leads to severe atrophy of the forearm flexors and quadriceps, resulting in progressive and severe disability (Hilton-Jones et al., 2010; Dalakas and Karpati, 2010).

Patients usually experience difficulty getting up from a chair and during walking; they may suffer falls, and may have difficulty in grasping, lifting, and using hand-held tools. Reduced tolerance to exertion and fatigue are very common (Amato and Barohn, 2009; Dalakas and Karpati, 2010). Dysphagia occurs in about 60% of patients, while facial muscle weakness may appear in the middle stages of the disease and, when present, constitutes a major criterion against a diagnosis of PM (Dalakas and Karpati, 2010). Extra-ocular muscles are usually spared, as are tendon reflexes, even though

these may be absent in the advanced stages of the disease (Amato and Barohn, 2009; Dalakas and Karpati, 2010; Dalakas, 2011a).

Inclusion body myositis is classified into two forms: sporadic (sIBM) and hereditary (hIBM). The latter, which is much rarer, is an autosomal recessive, quadriceps-sparing entity associated with a specific mutation in the *GNE* gene which encodes the bifunctional enzyme uridine-diphospho-N-acetylglucosamine (UDP-GlcNAc) 2-epimerase/N-acetyl-mannosamine (Man-NAc) kinase (GNE/MNK) (Huizing and Krasnewich, 2009). sIBM, on the other hand, is an acquired autoimmune disease, characterized by the coexistence of both inflammatory and degenerative features (Greenberg, 2010).

The diagnosis is based primarily on the clinical, neurophysiological and histopathological findings, but, in recent years, an important diagnostic contribution has also come from MRI study of skeletal muscle in patients with sIBM. The particular, asymmetric pattern of muscle involvement, the amount and extent of the fatty infiltration, and the presence of inflammatory infiltrate may effectively contribute to the differential diagnosis between sIBM and other myopathies (Cox et al., 2011a).

Case report

We describe the case of a 37-year-old man with a fifteen-year history of seropositive rheumatoid arthritis (RA) associated with bone scintigraphic hallmarks (enhancement of the small joints of the hands and feet). At diagnosis, rheumatoid factor (RF) was markedly increased (3350 UI/l) with a mild elevation of serum creatine kinase (CK=418 U/l). He was treated with prednisolone (50 mg per day) and hydroxy-chloroquine sulfate (400 mg per day for six weeks,

followed by a maintenance dose of 200 mg per day for eight weeks).

In view of his good clinical response, the patient discontinued steroid treatment after three years, but continued to receive non-steroidal anti-inflammatory drugs to relieve pain: as a consequence of the withdrawal of the steroid treatment, the patient showed scintigraphic disease progression characterized by the presence of several nodular erosions. Laboratory tests (Table I) disclosed active RA and autoimmune thyroiditis with hypothyroidism necessitating thyroxine administration. At the age of 31, the patient resumed treatment with prednisolone (25 mg per day), reporting a significant reduction of both pain and articular involvement.

At the age of 37, he was referred to us with a four-year history of slowly progressive, diffuse muscle weakness and wasting, which had initially involved the volar finger flexors, and subsequently the ankle dorsiflexors and knee extensors.

The neurological examination showed bilateral limb weakness and wasting (Fig. 1A), more pronounced on the left side. Muscle strength was evaluated using the Medical Research Council (MRC) scale and coded as follows: 2/5 for the biceps and deltoids, 2/5 for the left and right wrist and finger flexors, 3/5 for the left and right wrist and finger extensors, 3/5 for the quadriceps and right psoas, 2/5 for the left psoas, 2/5 for the right tibialis anterior, 1/5 for the left tibialis anterior, and 2/5 for the extensor digitorum brevis muscles. Deep tendon reflexes were diffusely decreased with preserved sensory function. The patient complained of moderate myalgia, while swallowing was normal. Laboratory tests documented a slight increase in serum CK (341 U/l) and RF (310 U/l) levels, while polymyositis scleroderma, signal recognition particle, histidyl-tRNA synthetase, anti-

Table I - Results of laboratory tests.

Test	Acronym	Result	Normal range
Rheumatoid factor	RF	384	< 40 UI/ml
Anti-cyclic citrullinated peptide antibodies	ACCP	95	< 25 UI/ml
Anti-nuclear antibodies	ANA	1:320 speckled	< 1:80
Anti-double-stranded DNA antibodies	anti-dsDNA-Ab	Negative	Negative
Complement fragment 3	C3	139	79-152 mg/dl
Complement fragment 4	C4	22	16-38 mg/dl
C-reactive protein	RCP	9.8	< 5 mg/l
Erythrocyte sedimentation rate	ESR	24	< 15 mm/h
Serum creatine kinase	CK	218	< 190 U/l
Serum hepatitis B surface antigen	HBs-Ag	Negative	Negative
Serum hepatitis B surface antibodies	HBs-Ab	Positive (IgG fraction)	> 10 mUI/ml
Serum hepatitis C virus antibodies	HCV-Ab	Negative	Negative
Thyroid peroxidase antibodies	TPO-Ab	307	< 60 U/ml
Human thyroglobulin antibodies	hTG-Ab	118	< 60 U/ml
Thyroid-stimulating hormone	TSH	0.2	0.31-4.5 μUI/ml
Free triiodothyronine	fT3	1.4	2.2-5.3 pg/ml
Free thyroxine	fT4	0.38	0.75-1.9 ng/dl
HLA phenotype	A03-A23-B18-B44-C04-C12-B04-B14-DR4-DRw6-DRw52-DRw53-DQw1-DQw3		

helicase family protein, and anti-double-stranded-DNA antibodies were negative.

Needle electromyography showed typical myopathic motor unit potentials, a variable degree of spontaneous activity (fibrillation and positive sharp waves) and early recruitment at minimal effort. Motor and sensory nerve conduction studies were normal.

Magnetic resonance of the quadriceps femoris disclosed widespread fatty infiltration with marked hyperintensity on T2-weighted sections corresponding to edema, thus suggesting an active inflammatory myopathy (Fig. 1B). Quadriceps muscle biopsy, under light microscopy, revealed rimmed vacuoles and endomysial mononuclear cellular infiltrates (Fig. 1D), Congo-red positivity and up-regulation of class I major histocompatibility complex (MHC-I) (Fig. 1E) without perifascicular atrophy. Electron microscopy showed tubulo-filamentous inclusions of approximately 14 nm in diameter, in both the nuclei and the cytoplasm of muscle cells (Fig. 1C). These findings fulfilled the diagnostic criteria for sIBM.

We treated the patient with hydroxychloroquine sulfate (400 mg per day) and oral steroids (50 mg per day) for five weeks, after which he refused to continue with the treatment. We also adopted an immunosuppressive approach, opting for an immunomodulating treatment with intravenous immunoglobulin (IVIg), according to the following regimen: 0.4 g/kg/day for five consecutive days followed by a free interval of 30 days for the first six months, and then 0.4 g/kg/day every three months thereafter for two consecutive years. He reported not only a subjective clinical benefit, mainly in his ability to walk, but also a substantial stabilization of his muscle strength; a progressive reduction of the electromyographic spontaneous activity was also obtained.

The MRC scale (baseline values: 2/5 for biceps, wrist and finger flexors, 3/5 for deltoids, 3/5 for wrist and finger extensors, 3/5 for quadriceps, 2/5 for left/right psoas and tibialis anterior, 2/5 for extensor digitorum brevis muscles) was administered every three months and showed only minor fluctuations in the scores recorded while, from a clinical point of view, the Barthel Index, showing a mean value of 50±5/100, remained quite stable. Slight positive fluctuations were consistently recorded in the MRC scale values within 8-9 weeks of the end of the IVIg cycle, with subsequent return to the average baseline values. Dimachkie and Barohn (2013) recently described the usefulness and the high sensitivity of the IBM functional rating scale (IBMFRS) in quantifying changes in clinical progression, especially com-
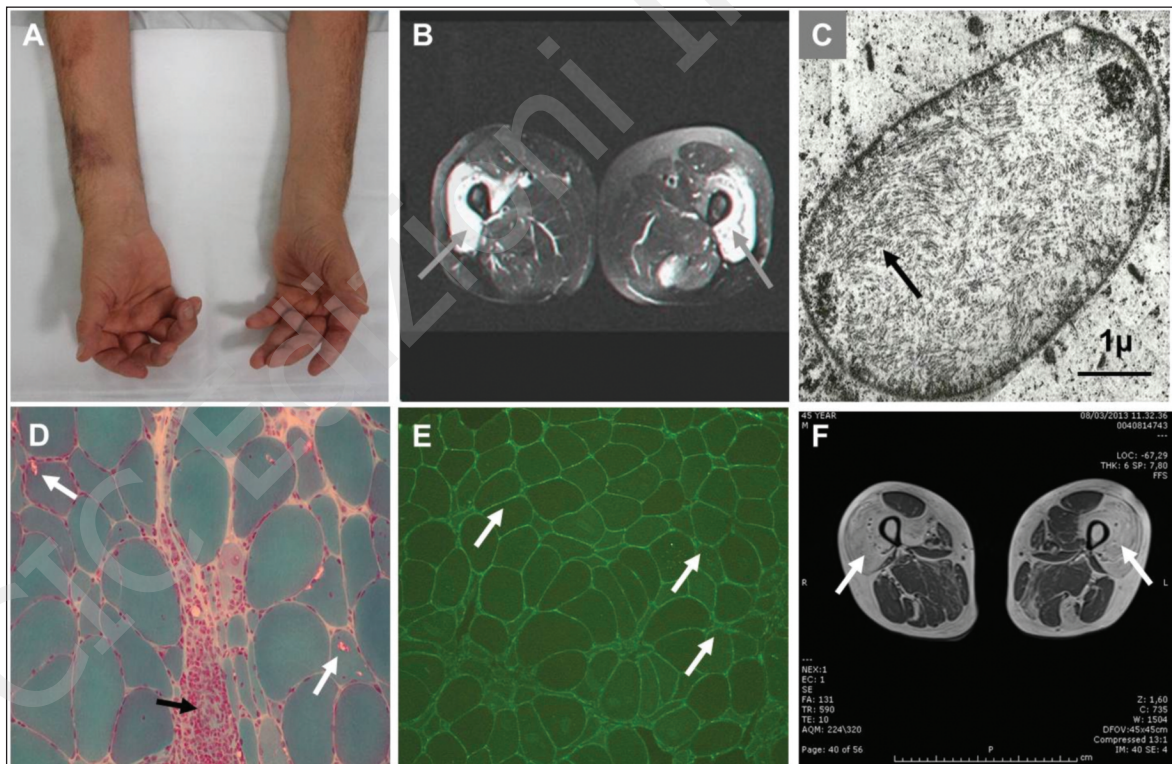

Figure 1 – Clinical, histopathological and imaging findings in inclusion body myositis.
(A) Severe and asymmetrical finger flexor weakness while attempting to close hands and forearm atrophy; axial proton density-weighted magnetic resonance section of the thighs showing severe involvement of the quadriceps femoris with increased signal bilaterally, consistent with inflammatory myositis (gray arrows); C) electron microscopy section showing intranuclear tubular inclusion (14-18 nm in diameter – x 16,000 – original magnification) (black arrow); D) Gomori trichrome stain showing rimmed vacuoles (white arrows) and inflammatory infiltrate (black arrow); E) immunofluorescence section showing muscle fibers with over-expression of class I major histocompatibility complex (white arrows); F) axial T1-weighted (TSE) magnetic resonance section of the thighs showing severe fatty infiltration of the vastus muscles (white arrows) with sparing of the rectus femoris and initial involvement of the hamstrings.

pared with other functional scales: in our patient we recorded an IBMFRS score of 19/40.

Finally, we recently performed a follow-up MRI study of the lower limbs, comparing the results with the baseline data. This examination confirmed the massive fatty infiltration of the vastus muscles (right>left) with sparing of the rectus femoris (Fig. 1F); it also showed a much less severe involvement of the hamstring muscles, minimal at the medial compartment (left>right). Inflammatory infiltrate was absent in the upper legs, but detectable (with edema) in small amounts at the gastrocnemius muscles (medial>lateral part), tibialis anterior, extensor digitorum longus and extensor digitorum hallucis on the left side. The above findings were accompanied by bilateral fatty degeneration, severe in the medial part of the gastrocnemius muscles. Overall, this picture is in line with the most recent MRI findings in skeletal muscle in IBM patients.

Discussion

The reported case is of interest for three main features: i) the rare association between sIBM, RA and autoimmune thyroiditis; ii) the patient's relatively young age at the time of IBM diagnosis, iii) the clinical stabilization after long-term, high-dose IVIg treatment. The association between inflammatory myopathies and connective tissue disorders is a condition still debated. It is described in about 20% of cases (Soden et al., 1994; Dalakas, 2011a), particularly in the course of scleroderma (Derk et al., 2003), systemic lupus erythematosus (SLE) (Soden et al., 1994; Derk et al., 2003), RA (Soden et al., 1994; Vordenbäumen et al., 2010), Sjogren's syndrome (Hama et al., 2004), and mixed connective tissue diseases (Derk et al., 2003).

The detection of an active myositis is uncommon in SLE (<10%), scleroderma (5-17%), and RA (13%), and rare in Sjögren's syndrome (Soden et al., 1994).

In sIBM, however, these associations seem to be even less common: sIMB has been reported, in single patients, in the presence of SLE and Sjögren's syndrome (Derk et al., 2003), systemic sclerosis, autoimmune cholangitis and chronic thyroiditis (Hama et al., 2004), while four sIBM patients with RA have been reported (Soden et al., 1994; Derk et al., 2003; Vordenbäumen et al., 2010).

From a pathogenic point of view, sIBM is interesting mainly because of the possible mechanisms leading to the coexistence of both inflammatory and degenerative features (Dalakas, 2010; Dalakas, 2011a). The progressive involvement of skeletal muscle cells that leads to their shrinkage and weakness is due, in addition to inflammation, to abnormal cytoplasmic deposition of granular eosinophilic material (inclusion bodies). These inclusions contain amyloid proteins similar to those found in the brains of Alzheimer's disease patients (Askanas et al., 2009).

The immunopathology of sIBM reflects an antigen-directed cytotoxicity mediated by CD8+ T cells that invade healthy muscle fibers overexpressing the MHC-I antigen on the sarcolemmal surface (Dalakas, 2011a,b). In normal conditions, muscle fibers do not express detectable amounts of MHC class I or II antigens, while in sIBM the overexpression is widespread (Dalakas, 2011a,b).

The CD8+ T lymphocytes, together with macrophages, send spike-like processes into non-necrotic muscle fibers, thus giving rise to focal displacement and compression. The final necrotic phase is catalyzed by a lytic enzymatic complex released by CD8+ T lymphocytes (Dalakas, 2011a,b). The putative factors able to break the immune tolerance remain unknown. The most widely debated hypothesis is that of a viral etiology leading to activation of macrophages (as antigen presenting cells) and CD8+ T cells (Dalakas, 2011b). The subsequent release of cytokines up-regulates vascular cell adhesion molecule-1 (VCAM-1) and inter-cellular adhesion molecule-1 (ICAM-1) thus allowing the transmigration of T cells from the endothelial cell wall to the muscle fiber. The whole process is facilitated by the simultaneous up-regulation of MHC-I antigens, co-stimulatory molecules and chemokine receptors on the muscle fibers thereby facilitating the invasion of T cells and the maintenance of the inflammatory process (Dalakas, 2011b).

With regard to feature ii, although it is known that muscular symptoms may anticipate, by as many as twenty years, the histopathological diagnosis of sIBM, our case, given his young age at diagnosis, is nevertheless atypical (Dimachkie and Barohn, 2012). We have compared this finding with the data provided by the two major long-term observational studies, namely those of Cox et al. (2011b) and Benveniste et al. (2011) which documented, respectively, a mean age at onset of 57±9 and 61 years, with a male prevalence (67.2% and 74%, respectively). Our patient began to show progressive muscular weakness and wasting at the age of 33 – much earlier than the expected average (Dimachkie and Barohn, 2012). The absence of myalgia and the distribution of the muscle weakness led us to consider unlikely the possibility of simple muscular involvement in the course of RA or due to long-term steroid treatment.

The third point of interest is the patient's moderate clinical response after long-term high-dose IVIg treatment. Indeed, the patient's 24-month follow-up, at which we considered his Barthel Index (Mahoney and Barthel, 1965) and MRC scale scores (Compston, 2010), revealed minimal disease progression with substantial muscle strength stabilization. The relatively positive outcome, in this patient, is confirmed by comparison with the data of Cox et al., who reported a mean MRC decline of muscle strength – per year – of 3.5±1.6% (Cox et al., 2011b). It is interesting to note the recent paper by Dimachkie and Barohn (2013), which reports the high sensitivity of the IBMFRS. Our case recorded a baseline IBMFRS score of 19/40, but we have no data allowing us to define the functional trend. However, we have now added the IBMFRS to our panel of assessment tools.

IVIg treatments are considered in the spectrum of the therapeutic options for sIBM patients, even though evidence about their effectiveness is heterogeneous (Amato et al., 1994; Dalakas et al., 1997; 2001; Dalakas, 2011c; Zschüntzsch et al., 2012). Some controlled studies have shown a clinical response in up to 25% of cases with high-dose IVIg administration (Hughes et al., 2009). Conversely, Recher et al. (2012) described a case responsive to low-dose IVIg. Moreover, the mechanisms underlying the IVIg anti-inflammatory effect in muscle tissue remain unknown. In this regard, it seems interesting to consider some experimental evidence deriving from research studies on the anti-inflammatory property of IVIg in patients with chronic demyelinating polyradiculoneuropathy (CIDP). Indeed, Lehmann and Hartung (2011) recalled that previous investigation of the expression of several cellular determinants of circulating leukocytes in patients with CIDP treated with IVIg showed a significant reduction of ICAM-1-positive lymphocytes, compared with the unchanged expression of ligands for endothelial cell adhesion. It was speculated that ICAM-1 down-regulation may lead to a decrease in leukocyte transmigration into the immune compartment of the peripheral nerve, thus reducing the pro-inflammatory stimulus (Lehmann and Hartung, 2011). As described above, the overexpression and up-regulation of ICAM-1 is crucial for the maintenance of the inflammatory process in IBM patients: in this sense, ICAM-1 may represent a possible pathogenic link between these two very different conditions and, in a sense, could partially account for some of the therapeutic effects of IVIg. This hypothesis was also advanced by Quick and Tandan (2011) in a recent paper on inflammatory myopathy treatments.

Returning to the reported case, it is worth noting a few considerations regarding the follow-up MRI. The most important finding, compared to baseline, was the absence of inflammatory infiltrate at the level of the upper legs. The evolution of the fatty infiltration, on the other hand, reflected the natural history of the disease, confirmed, moreover, by the distribution of the muscular impairment.

It is difficult to quantify the possible cause-effect relationship between IVIg treatment and modulation of the inflammatory process, but the bilateral absence of inflammatory infiltrate at the level of the upper legs does not reflect, in our opinion, the natural evolution of the disease. It is realistic to assume that the high-dose, long-term IVIg treatment may have played an active role in the down-regulation of the inflammatory process, as argued by several authors (Recher et al., 2012; Lehmann and Hartung, 2011; Quick and Tandan, 2011). Support for this assumption, from a clinical point of view, may be provided by the patient's subjective improvement in walking and, more generally, by the relatively diffuse stability of his muscle strength over a period of 24 months. Regarding the lower legs we have no baseline data for comparison.

In conclusion, sIBM is a poorly understood atrophying muscle disease. We have described a young sIBM patient with long-lasting RA and autoimmune thyroidi-

tis, partially responsive to long-term IVIg treatment. It remains to be established whether or not these associations are fortuitous or have etiological significance.

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