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CASE REPORT

Treatment of inclusion body myositis: is low-dose intravenous immunoglobulin the solution?

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Abstract Inclusion body myositis (IBM), the most common inflammatory myopathy in the elderly, is often resistant to various forms of therapy. Placebo-controlled treatment trials with high dose intravenous immunoglobulins (IVIG) have shown disease amelioration in some but not all patients. Here, we present the informative case of a 70-year-old woman with diagnosed inclusion body myositis that showed progressive muscle weakness without treatment and following immuno-suppressive treatment with corticosteroids and azathioprine. A trial with low-dose intravenous immunoglobulins was started at that time. The patient responded rapidly to low dose IVIG treatment with amelioration of muscle strength and normalization of CK serum activities. Our results demonstrate that IBM patients may respond to low-dose IVIG treatment which has important clinical and economic consequences.

Keywords IBM · IVIG · Myositis · Inclusion body myositis · Low-dose IVIG

Abbreviations

IVIG	Intravenous immunoglobulins
IBM	Inclusion body myositis
CK	Creatin-kinase

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Introduction

Inclusion body myositis (IBM) is the most frequent inflammatory myopathy in the elderly [1]. The disease typically progresses slowly and involves mostly the quadriceps muscles, arm flexors and small muscles of the fingers. Spontaneous stabilization of disease activity has been reported in the absence of any therapy [2]. Characteristic microscopic findings are typical intramuscular vacuoles and foci of amyloid as well as immunological features including MHC I up-regulation and oligoclonally proliferated infiltrating $CD8^+$ T cells [3]. In general, response to any treatment of IBM is weak [2]. Placebo-controlled studies showed limited effects of high dose (2 g/kg) IVIG therapy in IBM [4, 5]. It has been noted that at least in some patients progression of disease stopped while others did not respond, resulting in a mild overall effect of IVIG therapy [5]. As a consequence, Pongratz et al. [6] suggested a 3-month trial of high-dose (2 g/kg/month) IVIG to identify IVIG responders among IBM patients.

Case report

A 70-year-old woman was evaluated for progressive muscle weakness and mildly elevated serum creatin-kinase (CK) activity. CK elevation and muscle weakness continued following cessation of treatment with a HMG-Co A reductase inhibitor. Muscle weakness mostly affected strength in the quadriceps muscles. There were enhanced signal intensities in water-sensitive MRI sequences of the adductor magnus muscle in both legs and of the semimembranous muscle in the right leg (not shown). Biopsy of the right M. adductus magnus showed vacuoles in several muscle fibers; some of them appeared as typical ‘rimmed

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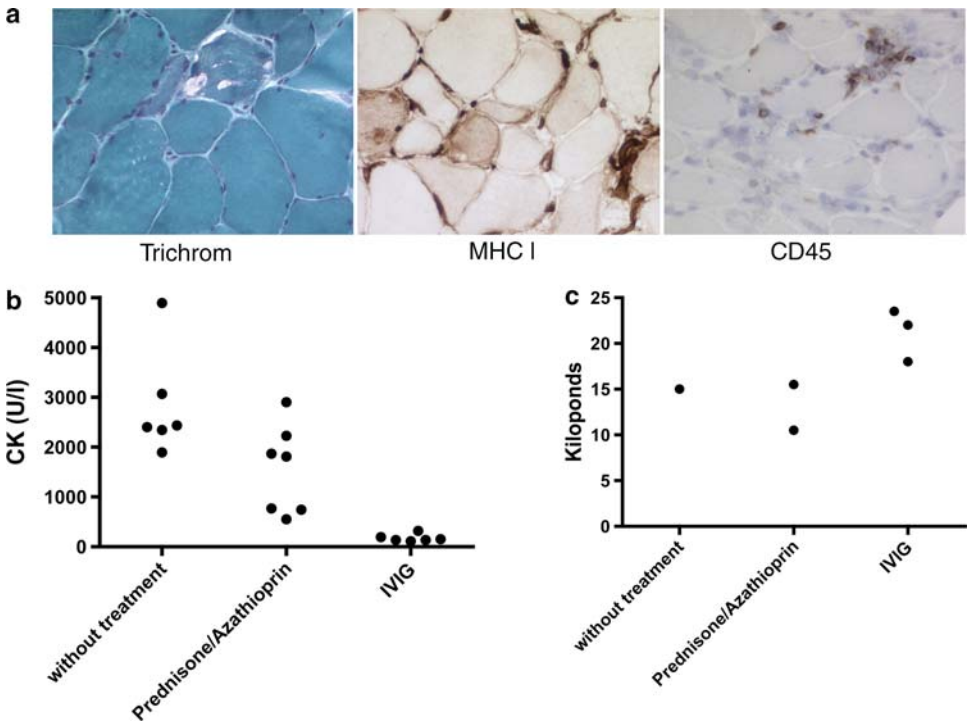

Fig. 1 **a** Histology of the patient's muscle biopsy (M. adductor magnus). Trichrome staining shows a rimmed vacuole. Immunohistochemistry demonstrates upregulation of MHC class I expression on several muscle fibers, and endomysial infiltrates of CD45 (leukocyte common antigen) positive leukocytes. **b** Serum creatin-kinase (CK) activities are shown. **c** Muscle strength of knee extension on the right leg is indicated at individual time-points under different therapies

vacuoles'. MHC class I expression was up-regulated on several muscle fibers (Fig. 1a). Together with infiltrating leukocytes (Fig. 1a), histologic findings were most consistent with inclusion body myositis (IBM). Histological alterations indicative of statin-induced myopathy were not found. Myositis-related serum autoantibodies (Anti Jo-1, Anti-PM SCL, Anti PL-7, Anti PL-12, Anti-Ku, Anti Mi-2) were not detected. There was no clinical evidence of viral- or superimposed systemic autoimmune disease. The diagnosis of IBM was established. Due to the reported very limited efficacy of any immune-modulating therapy and the reported spontaneous stabilization of IBM disease, no medication was started at that time, and the disease followed clinically.

However, muscle weakness progressed. The patient was finally unable to leave the house alone and became increasingly depressed. In the end, hospitalization was required due to intake of a neuroleptic drug with the purpose of suicide.

A therapeutic trial with prednisone/azathioprine (given at usual doses, prednisone initially 1 mg/kg with tapering thereafter, azathioprine 2 mg/kg) was started at that time, but it showed no effect on quality of life and muscle strength, although it was associated with mildly decreased CK serum activity (Fig. 1b). Prednisone/azathioprine treatment was stopped after 6 months due to lack of subjective and objective signs of improvement. A trial of intravenous immunoglobulins (IVIG) was initiated at that time.

In the light of rather disappointing effects of IVIG in recent studies in IBM (see below), we reduced the standard trial dose of IVIG from 2 to 0.3 g/kg/day given on two consecutive days as a monthly cycle (0.6 g/kg IVIG per month). The reason for using a lower than normal IVIG dose was mostly to reduce IVIG-related side effects in light of the low probability of clinical success. Within days after the first infusion, there was an unexpected rapid subjective amelioration of the muscle strength and trend to amelioration at the objective level over the next months (Fig. 1c). Elevated muscle enzymes normalized within 1 month (Fig. 1b) and since then without exception stay within normal range for now 12 months after initiation of IVIG therapy. Control MRI scans of the leg muscles now failed to detect active myositis (not shown). Quality of life improved remarkably, and the patient remains in remission for now 12 months after initiation of IVIG therapy.

Discussion

The rapid response following initiation of low-dose IVIG treatment in this patient was highly unlikely representing spontaneous disease course since the patient was before followed clinically for several months without any medication; however, muscle weakness and general condition progressed. Also, the negative response to a prednisone/azathioprine trial at usual dosage (initially 1 mg/kg Prednisone

and 2 mg/kg azathioprine) further excludes other types of inflammatory muscle disease that would clinically respond to this standard immuno-suppressive regimen. High IVIG doses require long infusion time or a higher infusion rate, which is associated with IVIG-related side effects, such as fever, chills, headache or skin reactions [7]. For patients weighing 80 kg, 2 g/kg IVIG equals 160 g IVIG which would require infusion of 13 large ampoules (12 g each) of a common IVIG product. This reflects an infusion volume of 2.6 l and costs of approximately 10,000 US dollars per month. Thus, reducing the IVIG dose reduces volume load, infusion time, IVIG-related side effects and medication costs.

The immune-suppressive mechanism of high-dose IVIG is best documented in idiopathic thrombocytopenic purpura (ITP), where a transient inability of macrophages to opsonize immune complexes following IVIG treatment has been demonstrated [8, 9]. In recent publications, especially the group of Ravetch [10] has shed new light to the immune-suppressive effects of high dose IVIG. First, IVIG acts by means of the inhibitory IgG receptor. Second, the immune-suppressive activity is restricted to a small proportion of IgG whose Fc fragment is sialylated [11]. Sialylated IgG-Fc can be recombinantly produced and is much more effective on a molar basis than conventional IVIG [12]. Finally, sialylated IVIG mediates its effects by binding to a receptor called DC-Sign in humans [13]. IVIG treatment has been associated with normalization of complement activation in patients with dermatomyositis [14]. How IVIG may improve myositis in IBM patients that respond to the treatment is completely unknown. A study analyzing specifically immune-modulating effects of IVIG on muscle infiltrating cells and their respective cytokines demonstrated very limited effects in inflammatory muscle diseases [15]. Myocytes have been shown to express B7-H3, which might protect myocytes from $CD8^+$ T cell-mediated lysis [16]. In contrast to many autoimmune conditions, TNF blockade was associated with high incidence of disease flares in inflammatory myopathies [17].

In our patient, IVIG treatment was unexpectedly successful in a low-dose regimen which costs approximately fourfold less than high-dose IVIG. The very rapid decrease of CK serum activity following the first IVIG application after a reasonable period of no therapy and a trial with prednisone/azathioprine make it unlikely that the amelioration was reflecting spontaneous disease course. In addition, a similar long lasting and unexpectedly good response to a comparable low-dose IVIG trial has been reported in an IBM patient [18]. It may be asked whether high dose IVIG is counterproductive because of temporarily increased blood viscosity and/or direct toxic effects of immunoglobulins on the already abnormal myocytes in IBM. Alternatively, the few patients that positively respond to IVIG therapy in the high dose IVIG trials would probably also respond to much lower IVIG doses. This would have important implications for economic reasons and would likely help reducing IVIG related side effects. Taken collectively, we propose to conduct a novel prospective controlled clinical trial of the effectiveness of low-dose IVIG therapy in IBM patients.

Conflict of interest statement The authors report no conflicts of interest.

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