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CASE REPORT

Inclusion body myositis in a patient with long standing rheumatoid arthritis treated with anti-TNFα and rituximab

Stefan Vordenbäumen · Eva Neuen-Jacob · Jutta Richter · Matthias Schneider

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Abstract Adult inflammatory myopathies are rare conditions. Amongst them, inclusion body myositis (IBM) is considered to be the most common acquired myopathy in adults above 50 years of age, follows a slowly progressive course, and ultimately leads to severe disability. The case of a 57-year-old patient with long standing rheumatoid arthritis (RA) who developed muscle wasting and weakness of the quadriceps femoris after initiation of anti-TNFα treatment is presented. Further workup including muscle biopsy revealed IBM. Initiation of rituximab for continuing synovial inflammation led to remission of RA, but no amelioration of muscle weakness was noted. Although cases of IBM in patients with autoimmune disorders have occasionally been reported and are believed to more favourably respond to immunosuppressive treatment, our patient was unresponsive to glucocorticoids. Furthermore, deterioration of muscle strength was noted with both adalimumab and etanercept treatment. Rituximab, not previously used in IBM, successfully controlled RA, but showed no effect on muscle strength. The present case underlines the therapeutic difficulties in IBM and suggests that anti-TNFα therapy might even be deleterious. While an early trial of the lymphocyte-depleting antibody alemtuzumab in IBM showed promising results, selective anti-B-cell-therapy remained without effect in our patient.

Keywords Cytochrome-c-oxidase · Immunosuppressive treatment · Mitochondrial dysfunction · Myopathy

S. Vordenbäumen · J. Richter · M. Schneider
Department of Endocrinology, Diabetology, and Rheumatology,
Heinrich Heine University,
Düsseldorf, Germany

E. Neuen-Jacob
Department of Neuropathology, Heinrich Heine University,
Düsseldorf, Germany

S. Vordenbäumen (✉)
Department of Endocrinology, Diabetology, and Rheumatology,
Heinrich Heine University,
Moorenstr. 5,
40225 Düsseldorf, Germany
e-mail: stefan.vordenbaeumen@med.uni-duesseldorf.de

Introduction

Inclusion body myositis (IBM) is considered to be the most common acquired myopathy of adults and is most commonly characterised by a predominant weakness of the quadriceps and the hand flexor muscles [1]. The diagnosis is confirmed by distinct pathological changes in the histological workup of muscle biopsies [2]. The pathogenesis of the illness most likely involves T-cell-mediated autoimmunity [3] and abnormal accumulation of misfolded proteins in an ageing cellular milieu [4], but there is ongoing dispute as to the predominant mechanism [1, 5]. Unlike other inflammatory myopathies, IBM did not show convincing responses in numerous trials concerning immunosuppressive treatments [1, 6–11]. Occasionally, cases of IBM associated to autoimmune disorders like systemic lupus erythematosus, Sjögren's syndrome, and systemic sclerosis have been described and they are generally believed to respond more favourably to immunosuppressive treatment [12–14]. So far, only three concise cases of IBM associated to rheumatoid arthritis (RA) have been described and one was successfully treated by mycophenolate mofetil and prednisolone [15, 16]. We present another case of RA and IBM resistant to various therapeutic interventions and discuss the influence of anti-TNFα and the hitherto unused rituximab on the disease course of IBM.

Case report

We report the case of a female patient who was diagnosed with seropositive RA at the age of 57 in 1993. Symptoms were initially controlled by intramuscular gold until 1998, when—out of concern for gold toxicity—treatment was switched to methotrexate and low-dose glucocorticoids. Because of insufficiently controlled symptoms under the medication with concomitant local glucocorticoid injections and radiosynovioorthesis of MCP-joints and radiographically documented progressive erosions, leflunomide, cyclosporine, and azathioprine were sequentially used for adequate periods of time without symptomatic control of the disease. Finally, adalimumab treatment was initiated in March 2004 with rapid effect on tender and swollen joints. After 3 months of therapy, rapid progression of as yet mild symmetrical weakness of the thighs was noted. The hitherto undetermined creatine kinase (CK) was elevated up to 1,015 U/l (normal <170 U/l). No changes were observed by electromyography at the time. The patient was diagnosed with drug-induced myopathy, adalimumab was discontinued and a course of 50 mg prednisolone tapered over 3 months was initiated. CK values decreased to 325–472 U/l during the following months and the muscle weakness was subjectively felt to progress at a slower rate. Because of uncontrolled RA disease activity, etanercept was initiated in December 2006, but discontinued after 3 months because of progressive weakness of the thighs. Neuromyographic reassessment was unremarkable. The patient declined further treatments of RA out of concern for progressive muscular dysfunction until February 2009, when pain and swelling of her hands, fingers and feet were severe enough to impair most daily tasks, and rituximab was begun with sustained effect on joint complaints. The patient was referred to our clinic for assessment of persistently elevated CK values and muscle weakness in August 2009. At that time, medication consisted of 5 mg prednisolone, 600 mg gabapentin and over-the-counter analgesics. Physical examination showed symmetric weakness of knee- and hip-flexion (3/5), distal symmetric impairment of sensitivity, absence of patellar and Achilles tendon reflex. CK was 371 U/l, CRP 1.1 mg/dl (<0.5), immunofluorescence for antinuclear antibodies was negative, rheumatoid factor was 387 U/ml (<15) and anti-CCP was >200 U/ml (<5). Electromyography of right rectus femoris and iliopsoas muscle revealed pathological spontaneous activity, positive sharp waves and complex repetitive discharge. Open biopsy of the left rectus femoris muscle was performed. Neurohistopathological workup demonstrated typical signs of inclusion body myositis [2]

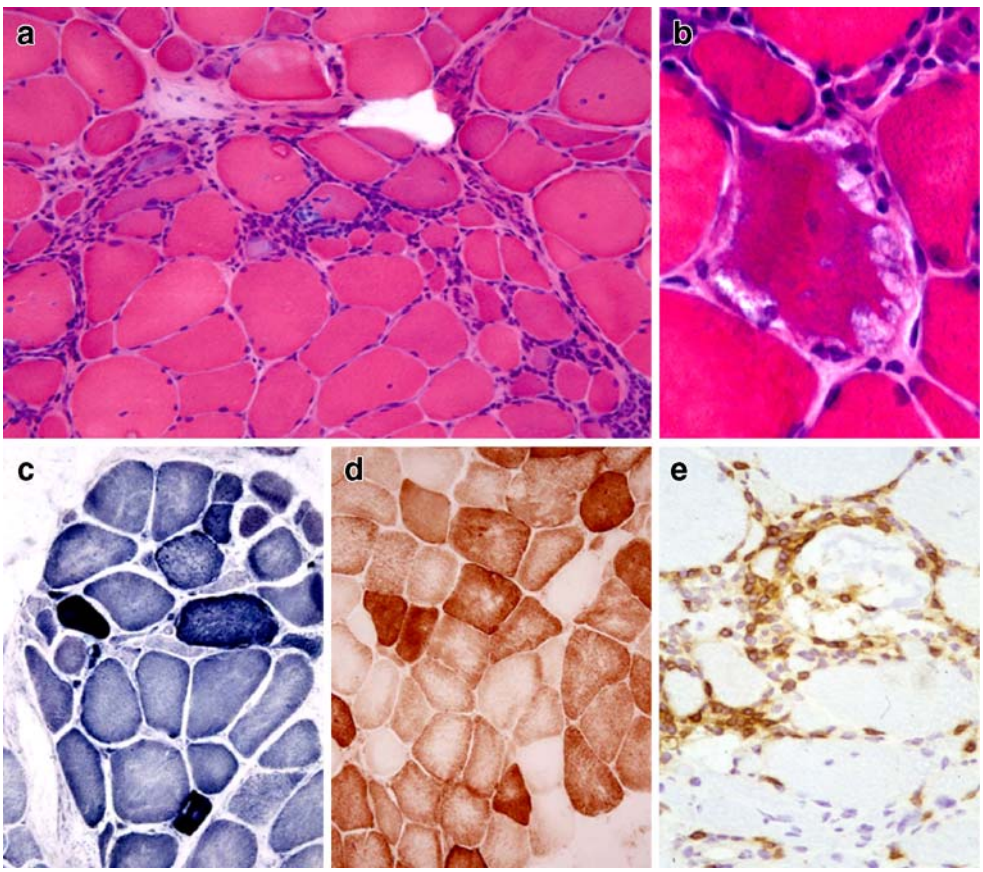

Fig. 1 **a** Muscle biopsy showing inclusion body myositis with necrotizing inflammation combined with signs of chronic neurogenic atrophy. **b** Muscle fibre with multiple rimmed vacuoles. **c** *Ragged-red-fibres* are visible in the SDH-reaction. **d** Cytochrome-c-oxidase revealing COX-negative fibres. **e** CD8-positive cells invading necrotic and non-necrotic fibres

with angular atrophic fibres, hypertrophy, fibre type grouping, rimmed vacuoles, small calibre and hypertrophied muscle fibres, invasion of predominantly CD8-positive lymphocytes into necrotic and non-necrotic muscle fibres, endomysial fibrosis and lipomatosis (Fig. 1a, b, e). Ragged-red fibres and cytochrome-c-oxidase negative fibres were indicative of mitochondrial dysfunction (Fig. 1c, d). Additionally, typical changes of denervation atrophy were identified. The patient was advised to continue physical therapy, prednisolone, and rituxmab for RA.

Discussion

Although cases of IBM associated to various autoimmune disorders are being described occasionally [12, 15, 16], there are only three other concise reports of RA patients developing IBM [15, 16]. Interestingly, Kalla et al. noted the development of IBM after infliximab treatment, while our patient had pre-existing muscle weakness and felt deteriorating strength after both adalimumab and etanercept treatment prior to the biopsy proven diagnosis of IBM. Even though these observations are based on only two patients and no changes in muscle strength were observed in a controlled trial of etanercept in IBM [17], anti-TNF treatment might be deleterious in patients with IBM and concomitant RA concerning progression of the myopathy. Additionally, the development of both IBM and other inflammatory myopathies as well as worsening of diverse symptoms under anti-TNFα treatment have been described in single cases and an open uncontrolled trial, respectively [18, 19].

Although B-cell-mediated inflammation was suggested to contribute to the pathogenesis of IBM [20], we are unaware of any patient previously treated with rituximab. In our case, treatment was successfully administered for ongoing inflammatory polyarthritis. However, no effect on IBM was noted during 7-month follow-up and muscle strength continued to decline slowly. Unlike specific targeting of CD20-positive B-lymphocytes as in our case, administration of the lymphocyte-depleting anti-CD52 antibody alemtuzumab showed promising results in an early phase trial for the treatment of IBM [21]. These observations together with the limited data of our case support the notion that T-helper-cells rather than B-cells might play a pathogenetically important role in IBM.

Even though there generally seems to be a more favourable response to immunosuppressive treatments in patients with concomitant autoimmune disorder and IBM [12–14], various agents including glucocorticoids remained without sustained effect in our patient. Publication bias favouring successful treatments might be responsible for this finding. More randomised controlled trials are clearly needed for this rare yet disabling disorder.

Disclosures None.

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