

Inclusion body myositis: therapeutic approaches. A case report

Wtrętowe zapalenie mięśni: możliwości terapeutyczne. Opis przypadku

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Abstract

Inclusion body myositis (IBM) seems to be the most common acquired myopathy among patients of age 50 or over. The characteristic clinical features of IBM include involvement of the quadriceps as well as distal muscles, mainly foot extensors and deep finger flexors. The course of the disease is slow but steadily progressive and most patients after 5 to 10 years require the aid of an assistive device. What distinguishes IBM from other inflammatory myopathies is its resistance to corticosteroids and other immunotherapies.

We present a case report, the first in the Polish population, of a male patient with a 10-year history of inclusion body myositis responding well to intravenous immunoglobulin (IVIG) therapy. Despite the almost 10 years duration of the disease, its course was slowly progressive and rather stable. Essential aspects of diagnosis and pathogenesis as well as the therapeutic approach adopted are also discussed.

Key words: inclusion body myositis, inflammatory myopathies, immunoglobulin, muscle biopsy.

Introduction

Inclusion body myositis (IBM), dermatomyositis (DM) and polymyositis (PM) constitute a group of inflammatory myopathies. The real incidence of these disorders is difficult to estimate but IBM is thought to

Streszczenie

Wtrętowe zapalenie mięśni (*inclusion body myositis* – IBM) to najczęstsza nabyta miopatia zapalna po 50. roku życia. W obrazie klinicznym najbardziej charakterystyczne jest zajęcie mięśni czworogłowych ud, jak również mięśni dystalnych, zginaczy grzbietowych stopy i zginaczy głębokich palców. Przebieg choroby jest powolny, ale systematycznie postępujący, po kilku latach trwania choroby większość pacjentów przestaje chodzić. W przeciwieństwie do pozostałych miopatii zapalnych, wtrętowe zapalenie mięśni nie odpowiada na leczenie kortykosteroidami i innymi lekami immunosupresyjnymi. Przedstawiana praca to pierwszy w Polsce opis przypadku chorego z dziesięcioletnim wywiadem wtrętowego zapalenia mięśni, u którego leczenie dożylnie podawanymi preparatami immunoglobulin (IVIG) przyniosło dobre efekty. Przebieg choroby w ciągu niemalże 10 lat był powoli postępujący i względnie stabilny. Ponadto omówiono zagadnienia związane z diagnostyką, patogenezą i obecnymi możliwościami leczenia wtrętowego zapalenia mięśni.

Słowa kluczowe: wtrętowe zapalenie mięśni, miopatie zapalne, immunoglobuliny, biopsja mięśnia.

be the most common acquired myopathy above the age of 50 [1]. The common clinical features of IBM include involvement of the quadriceps femoris muscle, and distal muscle weakness, mainly of the foot extensors and deep finger flexors. Unusual clinical presentation may include ‘dropped-head’, camptocormia and scapulope-

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roneal or facioscapulohumeral muscle weakness [2]. Dysphagia in advanced stages of the disease has been reported in almost 60% of patients [1]. IBM is characterized by an insidious beginning and slow but steady progression with around 10% drop in muscle strength in one to two years [1]. In some cases it also progresses more rapidly if the beginning is later in life [3]. Additionally, in contrast to dermatomyositis and polymyositis, IBM patients are in most cases resistant to corticosteroids and other immunosuppressive therapies [4]. Therefore, it is a challenge to find an effective therapeutic option for IBM patients.

Case report

Here we report a case of a male patient aged 63, first referred to the Department of Neurology, Medical University of Warsaw in 2002 with the suspicion of motor neuron disease. He complained of slow, progressive weakness of leg muscles of 2 years duration. The family history was negative. Neurological examination revealed distinct weakness of quadriceps muscles and mild weakness of trunk muscles and distal lower limb muscles. Plantar reflexes were absent. Electromyography presented a myopathic-neurogenic pattern, and a nerve conduction evaluation showed mild axonal neuropathy. Creatine kinase activity was elevated up to 237 IU (laboratory norm up to 34 IU). Additional stud-

ies presented no abnormalities. A skeletal muscle biopsy was performed and revealed necrosis, necrosis with phagocytosis and muscle fibre splitting. There were multiple small vacuoles, some of which contained inclusions (Fig. 1A). Infiltrations composed of mononuclear cells were also noticed (Fig. 1B). Electron microscopy revealed the presence of vacuoles, myelin structures (Fig. 2A), nuclear and cytoplasmic tubulofilamentous inclusions of 16-21 nm diameter (Fig. 2B), some cytoplasmic bodies and 'honeycomb-like' structures. Therefore, the diagnosis of IBM was established. Oral corticosteroid therapy was introduced, but with a rather insignificant effect. After a few months, at the end of 2003, due to gastrointestinal complications – diverticulitis with perforation – the corticosteroid therapy was withdrawn. The disease subsequently progressed more rapidly and the patient complained mainly of leg muscle weakness. He was secondly hospitalized at the Department of Neurology in April 2004. The neurological examination disclosed atrophy and weakness of proximal lower limb muscles without knee reflexes and little deterioration of upper limb strength. As it was not possible to continue the corticosteroid therapy, the patient received a first course of intravenous immunoglobulin (IVIG). A dose of 0.4 g/kg/day in 5 days was administered without any serious side effects. After 6 months, muscle strength was again assessed using the Medical Research Council (MRC) Scale (Table 1). The results

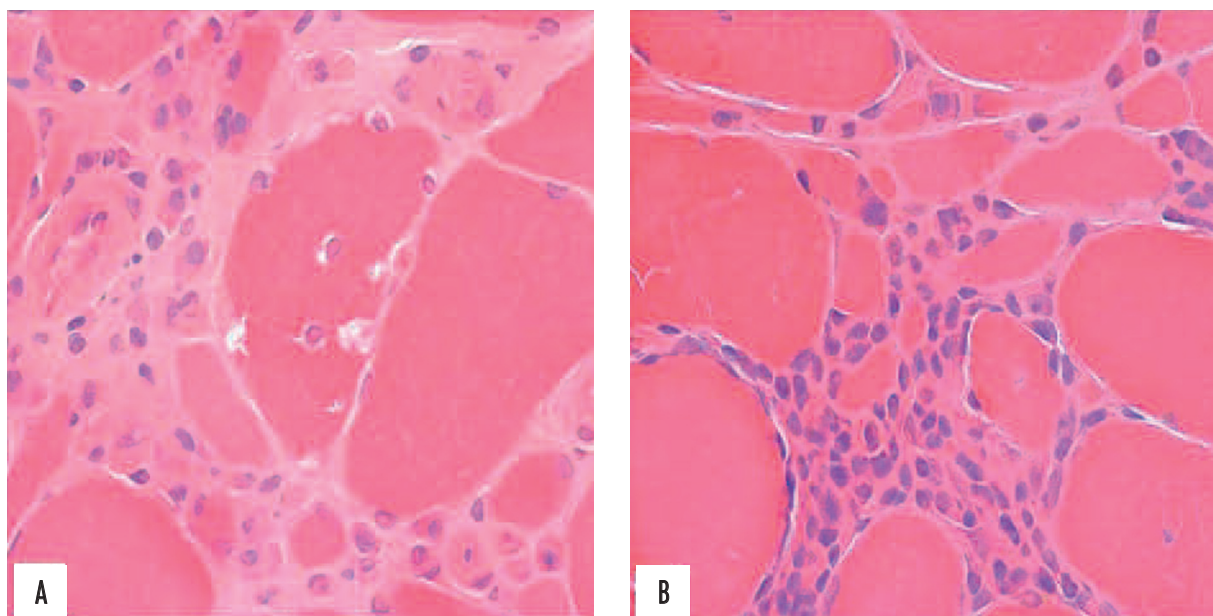


Fig. 1. Inclusion body myositis: A) muscle fibre containing multiple vacuoles, HE \times 100; B) mononuclear inflammation infiltrates present in the endomysial space, HE \times 100

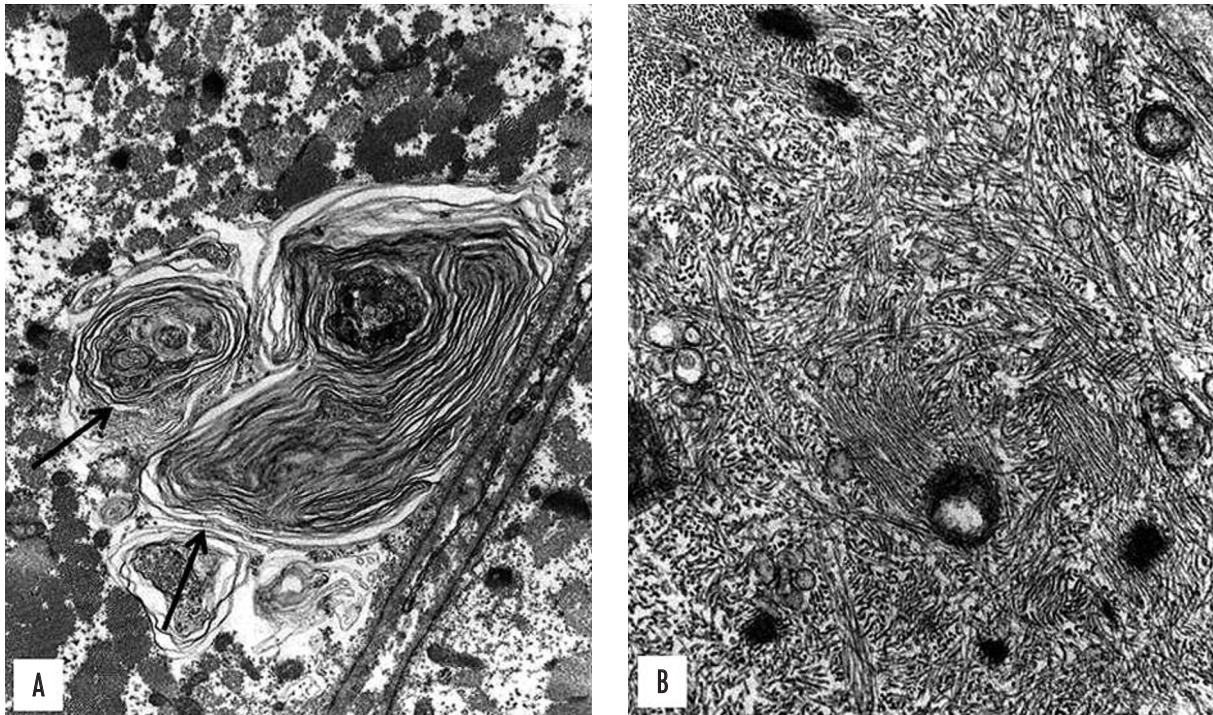


Fig. 2. Inclusion body myositis: A) myelin structures (arrows), EM \times 7500; B) cytoplasmic inclusion composed of tubulofilaments of 16-21 nm diameter, EM \times 30 000

Table 1. Medical Research Council (MRC) Scale at different stages of the disease and intravenous immunoglobulin administration

Muscle group/ Date of examination	XII 2002	III 2004	↓	XI 2004	↓	IV 2005	III 2006	↓	VI 2007	↓	XI 2009
Cervical spine	4-5	4-5		4-5		4-5	4-5		3-5		3-5
Trunk	3-5	1-4		1-4		1-5	1-4		1-4		3-4
Scapula	5	3-5		3-5		3-5	3-5		3-5		4-5
Brachial joint	4-5	4-5		1-5		3-5	3-5		3-5		3-5
Elbow joint	5	3-5		2-5		3-5	3-5		3-5		3-4
Wrist	4-5	4-5		4-5		4-5	4-5		4-5		3-4
Hip joint	3-5	2-5		3-5		3-5	3-5		2-5		3-5
Knee joint	4-5	2-5		2-4		2-5	2-5		1-5		2-3
Ankle joint	3-4	3-5		3-5		3-5	3-5		2-5		2-3

↓ – intravenous immunoglobulin administration

were similar to those of the previous test with worse scores obtained from brachial joint muscles. The patient complained of severe pain of the left shoulder, not connected with the disease.

During this second hospitalization he reported steady progression of the disease over the last few months with only minor progression mainly affecting the gait. The neurological examination showed mild paresis and atro-

phy of upper extremities' proximal muscles and slightly worse strength of proximal lower extremity muscles. The control MRC Scale presented almost the same results in comparison to the previous ones (Table 1). The patient received a second course of intravenous immunoglobulin (0.4 g/kg/day in 5 days). Over the next 2 years his neurological state was quite stable (Table 1), and in 2007 he was given a third course of intravenous

immunoglobulin (0.4 g/kg/day in 4 days). Shortly after he reported slight progression of the disease; however, the MRC Scale showed only minor differences. He was still able to work and walk with only one stick. The patient was again hospitalized in 2009 at the Department of Neurology and received a fourth course of intravenous immunoglobulin (0.4 g/kg/day in 4 days). Additional studies showed elevated creatine kinase activity up to 165 IU (laboratory norm up to 34 IU). Other laboratory tests failed to show any significant results. The neurological examination revealed minor weakness and atrophy of the proximal muscles in the upper limbs and more severe weakness and atrophy predominantly of the proximal muscles in the lower limbs.

During the course of almost 10 years of the disease the patient did not complain of trouble with swallowing, nor was dysphagia detected through any additional studies. Oesophageal scintigraphy was performed but there were no signs of the illness. A computed tomography of leg muscles showed generalized muscle atrophy, the most severe in the quadriceps muscle, but lower leg muscles were also atrophied. In comparison to the clinical presentation at the beginning of the illness, there was obvious deterioration. However, it is noteworthy that the patient was still self-supporting and was able to walk with only a stick. After a few courses of intravenous immunoglobulin he reported significant subjective improvement.

Discussion

Inclusion body myositis is thought to be the most common myopathy acquired at age 50 or above [4]. Its prevalence varies across different populations and the incidence of 2.2 patients per million per year was reported in 1994 in Göteborg in Sweden [5]. In epidemiological studies performed in Western Australia it was estimated to be 9.3×10^{-6} ; however, the age-adjusted prevalence for those over 50 years was 35.5×10^{-6} [6]. It is noteworthy that in the follow-up study in Western Australia performed after a few years the prevalence was reported to be 14.9 per million inhabitants, and 51.3 per million population above 50 years [7]. In the Netherlands, the prevalence was established at 4.9 patients with IBM per million inhabitants, but other data suggested that it might be underestimated [8]. The differences between populations are probably related to the presence of the HLA-DR3 allele, which is strongly correlated with sporadic IBM as well as associated with much more severe course of muscle weakness progression [2].

In populations with lower frequency of HLA-DR3, such as Turkey (1.0 per million) or Thailand, IBM is rare [7]. However, epidemiological data for the Polish population do not exist.

Diagnostic criteria for IBM were summarized by Griggs *et al.* [9]. The diagnosis of IBM should be considered when proximal and distal muscle weakness of the upper and lower extremities has lasted for more than 6 months in patients above 30 years old, when finger flexor weakness is obvious and when the wrist flexor is more affected than the wrist extensors, and finally when the quadriceps muscle weakness is equal to or less than 4 points on the MRC Scale. Additionally, serum creatine kinase activity will be elevated up to 12 times normal, electromyography will present mostly myopathic features and family history is likely to be negative. Moreover, muscle biopsy will reveal very specific abnormalities – vacuolar degeneration and atrophy of muscle fibres with mononuclear cell inflammation. The most characteristic for light microscopy will be the so-called ‘rimmed vacuoles’ [4]. Other distinctive features will be cytoplasmic bodies, necrotic or regenerating fibres as well as signs of inflammatory response. Electron microscopy often presents tubulofilamentous inclusions, which may be seen in both the cytoplasm and the nuclei. Immunohistochemistry shows many various proteins such as β -amyloid, ubiquitin, presenilin-1, apolipoprotein E, α -synuclein, tau protein and TDP-43 [10,11]. TAR DNA-binding protein 43 (TDP-43) is a novel factor involved in transcription regulation, which may alter protein production, modification and accumulation [11]. Although the precise pathological mechanisms are yet not known, recent studies have shown the presence of the extranuclear sarcoplasmic TDP-43 aggregates as highly specific for IBM patients [12]. Moreover, there are close correlations between the stage of the disease and the muscle biopsy results. It has been documented that at the beginning the most characteristic are inflammatory changes. However, biopsies taken from patients affected from many years reveal mostly myodegenerative patterns, including ‘rimmed vacuoles’ and specific inclusions [2].

According to the diagnostic criteria proposed by Griggs *et al.* [9] the definite IBM is based on the presence of all typical features in muscle biopsy. In such a case, none of the other clinical or laboratory symptoms and signs is obligatory. Probable IBM is defined by the presence of only inflammatory features in muscle biopsy. Then, however, other clinical and laboratory symptoms and signs must be present [9]. And finally, when

there are atypical clinical presentations and muscle biopsy is also not characteristic, the diagnosis of possible IBM may be established.

Subacute or long-lasting symptoms, with early falls, and with the involvement of both proximal and distal muscles, may strongly suggest IBM. The course of this myopathy is steadily progressive, and very often after 5 to 10 years it results in the need to use an assistive device and subsequently in severe immobilization [10]. However, in some cases even without any treatment the progression of the disease may be very slow [1]. It was also reported that the earlier the disease starts, the less severe is its course and the slower is muscle strength deterioration [13]. It is believed that together with quadriceps and finger flexor muscle weakness, dysphagia is the key symptom in the diagnosis of IBM [14]. Clinicians should pay careful attention to any symptoms of impaired swallowing, as these may lead to potentially life-threatening complications. Recent observations have shown that dysphagia may be present even in 65% of investigated patients, yet only 46% of them had previously reported such symptoms to their physicians [14].

Even though we are able to provide the precise clinical and morphological characteristic of IBM, its pathogenesis still remains unknown [10]. Among many potential factors, immunogenetic association with certain human leukocyte antigen genes should be mentioned. The correlation between HLA-DR3 and the MHC 8.1 ancestral haplotype has been recently widely discussed in the literature [2]. Some differences in the prevalence of the disease in various populations may be explained by the frequency of specific genotypes [2]. Moreover, in single cases IBM may be associated with autoimmune diseases, for example with paraproteinaemia. The autoimmune hypothesis supports the upregulation of major histocompatibility complex (MHC) class I antigens and costimulatory molecules on muscle fibres, including those not invaded by T cells. High upregulation of cytokines and chemokines makes the muscle fibres active modulators and contributors in the immune response [10]. In addition to these immunological processes, there is strong evidence pointing to the role of degenerative processes in IBM. Various proteins, such as β -amyloid, presenilin-1, apolipoprotein E, α -synuclein, phosphorylated tau and TDP-43, are present in intracellular deposits [10]. Histopathological studies show some similarities between IBM and other neurodegenerative disorders, such as Alzheimer disease (AD) and Parkinson disease (PD). Protein accumulation, like that of β -amyloid and

phosphorylated tau, is present both in the muscle tissue from patients with IBM and in the brain tissues from individuals with AD. Aggregates of α -synuclein and parkin typical for PD-affected brains are likewise in muscle samples from IBM patients [15]. Therefore, this supports the hypothesis of multifactorial and poly-genetic nature of IBM, AD and PD [15].

In contrast to other inflammatory myopathies, inclusion body myositis remains resistant to the most immunosuppressive therapies [10]. Only slight improvement was reported and as for now none of the treatment options may reverse or stop the disease [16]. Some data suggest a potential improvement after corticosteroids but usually it is temporary and cannot be maintained [17]. Even when the creatine kinase activity decreased, there was progression in muscle weakness and repeated muscle biopsies showed more advanced morphological changes [18]. Mofetil mycophenolate gave similar transient and insignificant effects [17]. Among other tested agents are cyclophosphamide, azathioprine, methotrexate, cyclosporin, anti-T-lymphocyte globulin, plasma exchange and leukapheresis, unfortunately so far without any significant effect [19,20].

Recent years have seen many new therapeutic possibilities for the use of IVIG in neuromuscular disorders. In many cases they are not only equally effective as plasma exchange or corticosteroids, but also safe. Among their many possible mechanisms are the neutralization of pathogenic autoantibodies affecting antibody production in autoimmune disorders, modulation of T-cell function, suppression of pathogenic cytokines and adhesion molecules, and inhibition of complement binding and activation [21]. As for IVIG treatment in IBM, there have been only 3 fairly small randomized trials in which despite some improvement in swallowing the general outcome was negative. One trial showed improvement in muscle strength, which mainly affected the bulbar muscles; however, the results were not statistically significant [22]. High-dose IVIG has been tested in another double-blind, placebo-controlled study in 22 patients with IBM and it proved to be a safe therapy with potential to slow the disease progression and to give moderate benefits, with 5% strength improvement in 90% of patients for a limited time [23]. The third study evaluated the effectiveness of combined therapy of IVIG with high-dose prednisone versus placebo and high-dose prednisone, but after 3 months there was no significant improvement [24]. Only some minor benefits were reported in the group treated with IVIG, but they were very subjective and insignificant. How-

ever, it is important that in some cases the differences may be located only in certain groups of muscles [19]. Thus, generally, according to the 'EFNS guidelines for the use of intravenous immunoglobulin in treatment of neurological diseases', IVIG is not recommended for IBM [25]. It has to be remembered, however, that such negative recommendations are based on a relatively small number of controlled clinical trials. Apart from prescribing vitamins and advocating non-fatiguing exercises, there is very little to offer if corticosteroids and other immunotherapies are ineffective. In conclusion, it is believed that in single cases IVIG may have a significant impact on the disease progression [19]. Taking into consideration all aspects of the therapeutic possibilities, it is really challenging to choose the most beneficial strategy in IBM.

Disclosure

Authors report no conflict of interest.

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