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Authors: Agata Sebastian, Piotr Wiland

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Diagnosis and treatment options for inclusion body myositis – a case report

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Agata Sebastian (0000-0001-6332-8714), Piotr Wiland (0000-0001-9999-0267)

Department of Rheumatology and Internal Medicine, Wroclaw University Clinical Hospital, Poland

Corresponding Author: Agata Sebastian, Department of Rheumatology and Internal Medicine, Wroclaw University Clinical Hospital, Poland; e-mail: agatasebastian@vp.pl

Abstract

Inclusion body myositis (IBM) is a progressive inflammatory myopathy. In the article, we describe the diagnosis of myopathy and long-term observation in a patient with IBM. In the discussion, we explore available IBM treatment strategies based on the current literature review.

Key words: inclusion body myositis; IBM treatment

Introduction

Inclusion body myositis (IBM) represents a group of diseases known as idiopathic inflammatory myopathy (IIM).

It is the most common myopathy in patients over 50 [1]. The prevalence of IBM is estimated at 24.8 per 1,000,000 people [1]. The pathogenesis of the disease is not yet fully understood. In addition to an autoimmune component, muscle cell degeneration with muscle cell destruction (protein deposition) is suspected to be prevalent in the later course of IBM [2]. The muscle structure shows muscle fibres of different diameters and shapes, with centrally located nuclei and features of mitochondrial damage (ragged-red and COX-negative fibres). In the perimysium around the vessels and muscle cells, infiltrates composed of mononuclear

cells, mainly CD8+ T-cells and an accumulation of major histocompatibility complex (MHC) class I molecules are found. In addition, degenerative changes such as protein aggregates, rimmed vacuoles and mitochondrial abnormalities are evident. Protein aggregates are composed of amyloid precursor protein, β-amyloid 42, phosphorylated tau protein, alpha-synuclein, αB-crystallin, clusterin, presenilin-1, gelsolin, apolipoprotein E, ɣ-tubulin, p62 protein, among others. Electron microscopy reveals myofibril defects filled with myelin and tubulofilament structures. Similar inclusion bodies are observed in cell nuclei. In addition, paracrystalline inclusion bodies are often found, reflecting damage to the mitochondrial structure [3].

Unlike other idiopathic inflammatory myopathies, IBM is characterised by a slow progression of symptoms, involvement of both proximal and distal muscles and asymmetry of symptoms. The first clinical signs concern the involvement of the finger flexor muscles and the quadriceps [4]. There is progressive weakness and atrophy of the forearm muscles, quadriceps femoris muscles, and weakness of the dorsiflexors of the feet. The disease results in difficulties with walking (weakness of the knee extensors), standing up from a squatting position and problems with manual dexterity (weakness of the flexor digitorum profundus). Half of IBM patients develop facial muscle involvement and swallowing disorders at an advanced stage [5].

The diagnosis of a patient with IBM and a description of the long-term clinical follow-up of the patient are presented below. Based on this, the available treatment options for IBM are discussed. The patient's consent for publication was obtained.

Case presentation

A 59-year-old woman was admitted to the rheumatology clinic for the diagnosis of painless, lower limb muscle weakness with widening of the calf contour, making it difficult to climb stairs or kerbs and stand up from a squatting and sitting position without using her arms. The patient first noticed symptoms of muscle weakness at 55 (in 2008). In addition, a physical examination revealed slight weakness in the upper limb strength and atrophy of the quadriceps femoris muscles. The symptoms were more prominent on the left side of the body. The patient reported no dysphagia, dyspnoea or stenocardial symptoms. For at least a year, the patient had been using a continuous positive airway pressure (CPAP) machine at night due to sleep apnoea. The electromyography (EMG) recordings of the lower limbs showed no primary muscle damage. Laboratory tests revealed increased values of muscle damage

markers (creatine kinase, alanine and aspartate aminotransferase, lactate dehydrogenase). Antinuclear antibodies and rheumatoid factor were not found. Table 1 shows the values of the muscle damage parameters from 2014 until this case report.

In order to diagnose the type of myopathy, a dermomuscular specimen was sampled, which revealed a small infiltrate composed of lymphocytes (70% CD3 cells, 10% CD20, 20% CD68, 0 CD138 cells) whose location was consistent with minor to moderate polymyositis. The diagnosis was then supplemented with an electron microscopy evaluation of the muscle biopsy, which detected inclusion bodies typical of IBM. The IBM diagnosis was made using the 1995 Griggs-Barohn criteria (symptoms lasting over six months, age of onset over 30, asymmetric quadriceps muscle weakness, and intracellular inclusion bodies typical of IBM) [6]. The clinical picture and additional investigations excluded polymyositis, dermatomyositis, drug-induced myopathies, and glycogen storage diseases. Treatment included methylprednisolone (500 mg intravenously continuing for three consecutive days, followed by prednisone at 0.5 mg/kg for three months until discontinuation) and mycophenolate mofetil at a dose of 2 g per day. At the same time, regular rehabilitation and physiotherapy (inpatient and outpatient) were initiated. Due to the progression of the disease (atrophy of the quadriceps femoris muscles, increasing difficulty in standing up from a sitting position, limitations in locomotor function), despite the treatment, the patient was additionally administered at irregular intervals (difficulties in financing the therapy in the rheumatology department), intravenous immunoglobulins between 2018 and 2022 (May 2018 at a dose of 2 g/kg, July 2018 at a dose of 1 g/kg, December 2020 at a dose of 1 g/kg, February 2021 at a dose of 1 g/kg, December 2022 at a dose of 1 g kg). In early 2023, there was no lasting improvement in muscle function, with a steady increase in muscle weakness, particularly in the lower limbs (dorsiflexors of the feet, extensors of the knee joints), which led to the patient having to use knee stabilisers and forearm crutches.

Table 1. Muscle damage parameters and C-reactive protein (CRP) in a patient with inclusion body myositis (IBM) from diagnosis to this case report

Parameter/mo. and year (normal range in IU)	**Jan. 2014**	**May 2017**	**May 2018***	**Jul. 2018***	**Dec. 2020***	**Feb. 2021***	**Dec. 2022***

CK (0–145 IU/L)	2947	2721	2110	1100	360	456	686
ALT (0–35 U/L)	104	86	33	28	13	17	25
AspAT (0–31 U/L)	60	69	22	38	15	21	23
LDH (0–248 U/L)	393	N/A	316	305	205	334	240
CRP (0–5 MG/L)	2.1	3.9	3.6	3.4	5.1	3.5	3.8

IU — international units; mo. — month; CK — creatine kinase; CRP — C-reactive protein; ALT — alanine aminotransferase; ASPAT — aspartate transaminase; LDH — lactate dehydrogenase; *immunoglobulin administration

Discussion

This article presents the diagnostic and therapeutic management of IBM in line with current knowledge. The authors were prompted to expand the diagnosis by electron microscopy due to the following circumstances: asymmetry of symptoms, involvement mainly of the quadriceps muscles, absence of skin lesions typical of dermatomyositis, no interstitial infiltrates in the lungs and lack of antibodies typical of myositis. Electron microscopy showed inclusion bodies typical of IBM [7]. It is important to note that the pattern of histopathological changes in IBM may mimic minor polymyositis at an early stage. Inflammatory infiltrates, mainly intramuscular, are observed, where inflammatory cells surround and focally infiltrate muscle cells. In addition to the inflammation, rimmed vacuoles, atrophic fibres, and congophilic inclusions, which may be inside or outside the vacuoles, are found in IBM. Mitochondrial changes, especially increased cytochrome C oxidase-negative fibres, are observed in most IBM patients [8, 9]. This can be helpful for a differential diagnosis with other myositis, especially at an early stage of IBM, when typical rimmed vacuoles may not yet be evident. Altered vacuolar morphology is evident at the later stages of IBM.

There is still no specific biomarker to confirm the diagnosis of IBM unequivocally. It is possible to determine antibodies against cytosolic 5′-nucleotidase 1A (cN-1A) in IBM patients. The role of these antibodies in the pathogenesis of IBM is unknown. The cN-1A antibodies are proteins involved in nucleic acid metabolism [10]. However, these antibodies are not specific to IBM and may be present in other diseases, such as Sjögren's syndrome,

systemic lupus erythematosus and other myopathies [11]. The specificity of these antibodies in IBM varies between 30–80% [12]. Nevertheless, although the cN-1A antibodies should not be used as a stand-alone test to diagnose IBM, a positive result raises suspicion about the diagnosis, especially in patients with atypical symptoms or at the preclinical stage [13].

Corticosteroids were given to the patient in the first stage of treatment, but there was no clinical or laboratory improvement. Unlike polymyositis and dermatomyositis, IBM treatment with corticosteroids has not produced satisfactory results [14]. However, individual authors recommend their administration early in the development of IBM, considering that such action may slow the transition from the inflammatory to the degenerative stage. This is especially true in younger patients with rapidly progressive IBM, increased inflammatory changes revealed by histopathology, and increased CK activity [15, 16].

Despite IBM's inflammatory component, classic disease-modifying drugs show little efficacy and only temporary improvement is observed during their use [9, 17, 18]. In the patient described here, mycophenolate mofetil was used chronically. However, no clinically significant improvement was achieved at long-term follow-up. There are no established treatment guidelines for IBM due to the lack of effective therapies, including disease-modifying drugs [19, 20]. Positive effects of both immunosuppressive and immunomodulatory drugs, including azathioprine, methotrexate, intravenous immunoglobulin (IVIG), IVIG + prednisone, interferon beta 1a, etanercept, infliximab, anakinra, natalizumab, alemtuzumab, canakinumab, oxandrolone, and simvastatin, have not been demonstrated [13].

IVIG was also attempted in the described patient, and an initial subjective improvement in muscle strength was observed. In long-term follow-up, this treatment modality showed little efficacy. Based on the available literature and the results of clinical trials investigating IVIG *vs* placebo in IBM patients, it appears that IVIG has no beneficial effect on the course of the disease [21–24]. However, it has been suggested to have some efficacy when administered in patients with symptomatic dysphagia [25, 26].

Studies on the treatment of IBM pay particular attention to the benefit of regular physiotherapy and rehabilitation [27–29]. Such management allows the locomotor function to be preserved for as long as possible, which, until the COVID-19 pandemic, was applied to the patient and helped her markedly in daily functioning. Non-pharmacological treatment is one of the therapeutic options for patients with IBM [30–32].

Hope for the future comes from new clinical trials being undertaken with gene therapy using follistatin to inhibit the myostatin pathway [33] and arimoclomol, a drug targeting the so-called heat shock receptor (HSR). In recent years, clinical trials have also been conducted with bimagrumab (a fully human monoclonal antibody that binds to activin receptor IIB (ActRIIB). Ultimately, however, the efficacy of this antibody was not demonstrated at two-year follow-up [34]. A randomised controlled trial in IBM with sirolimus is underway (clinical trial NCT04789070 and ABC008) [13]. Sirolimus inhibits the mammalian target of rapamycin (mTOR) pathway and has pleiotropic effects on cell metabolism, autophagy and mitochondrial function [35]. Another project is evaluating the efficacy and safety of monoclonal antibodies that selectively destroy cytotoxic T cells (clinical trial NCT05721573) [13].

Despite the inflammatory infiltration found in muscle biopsies of IBM patients, the efficacy of immunosuppressive drugs has not been proven. IBM leads to significant disability within a few years, which significantly affects patients' quality of life. This has significant pharmacoeconomic and social implications [36]. Establishing a correct diagnosis early can avoid iatrogenic complications of ineffective steroid therapy (e.g. osteoporosis, steroid myopathy, diabetes) in this group of patients. The authors' description of the IBM patient shows the real limitations in treating this group of patients. The ineffectiveness of the immunosuppressive disease-modifying drugs does not allow the establishment of treatment guidelines for IBM.

Conflict of Interest

The authors declare no conflict of interest.

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