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Inclusion body myositis – a case based clinicopathological update

Research Article

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Abstract: Inclusion body myositis is a slowly progressive myopathy affecting predominantly the middle-aged and older patient population. It is a major form of the idiopathic inflammatory myopathies which are chronic systemic autoimmune diseases characterized by symmetrical proximal muscle weakness. Unfortunately, there is no effective therapy yet; however, the early diagnosis is essential to provide treatment options which may significantly slow the progression of the disease. In our case-based clinicopathological study the importance of the close collaboration between the clinician and the neuropathologist is emphasised.

Keywords: *Idiopathic inflammatory myopathies • Inclusion body myositis (IBM) • Amyloid- • Hyperphosphorylated tau • p62 • TDP-43 • IBMPFD*

Abbreviations

ANF=antinuclear factor;
BACE=Beta-secretase;
CK=creatine kinase;
cTNT=cardiac troponin T;
EMG=electromyography;
ENG=electroneurography;
GOT=glutamate-oxaloacetate-transaminase;
GPT=glutamate-pyruvate-transaminase;
HLA=human leukocyte antigen;
HRCT=high resolution computed tomography;
IBM=inclusion body myositis;
IHC=Immunohistochemistry;
IMACS=International myositis assessment and clinical studies group;
LDH=lactate-dehydrogenase;
MHC=major histocompatibility complex;
MMT=manual muscle testing;
MRI=magnetic resonance imaging;
PAS=periodic acid-Schiff staining;
proBNP=B-type natriuretic peptide;
SIRTUIN1=NAD-dependent deacetylase sirtuin-1;
TDP-43=TAR DNA-binding protein 43;
TGFβ= transforming growth factor beta

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1. Introduction

Idiopathic inflammatory myopathies are systemic, autoimmune diseases characterized by symmetrical proximal muscle weakness. Primary adult polymyositis, primary adult dermatomyositis, juvenile myositis, overlap myositis, tumour-associated myositis, inclusion body myositis and other types of myositis (amyopathic myositis, eosinophilic myositis and giant cell myositis) belong to this category. The aetiology and pathomechanism of these rare, multifactorial diseases are still unclear. Their frequency is 0. 1-1/100000 people/year while the men-women ratio is 1:2. The diagnosis is established according to Bohan and Peter criteria: 1. symmetrical proximal muscle weakness, 2. positive muscle biopsy, 3. elevation of serum skeletal muscle enzymes, 4. myopathic triad on electromyography and 5. characteristic skin symptoms in dermatomyositis [1]. Ethnic differences and the HLA-associations suggest that genetic factors may play a part in the aetiology. Autoimmune origin is supported by the morbid deviation of cellular and humoral immunity. In case of polymyositis, muscular damage is caused by CD8+ cytotoxic T-cells and macrophages are also important cells in the inflammatory process. As for dermatomyositis, cytokines are mediated by helper T-cells, while the humoral mechanisms are carried out by B-cells. Owing to these factors both diseases can be characterised by chronic inflammation, damage and death of muscle fibres and fibrosis.

The aim of this review is to share our experience about our patients who suffer from inclusion body myositis (IBM). Moreover we would like to raise awareness about this rare but important entity. The presented histological figures (Figure 1-4) demonstrate the key features of the disease, and underline the important role of neuropathologists in the diagnosis. The presented cases also support the view that this is a slowly progressing disease with no effective curative therapy [3].

Our knowledge about the inflammatory myopathies has broadened in the last few years. At the same time – our current topic – the IBM, is a less well-known, progressive disease of the middle-aged and older people that can lead to severe disability. Although it has been described more than forty years ago the unexplainable degeneration and loss of muscle fibres, appearing together and the intracytoplasmatic, basophilic-rimmed vacuoles is still a mysterious feature.

The prevalence of inclusion body myositis is diverse among different ethnic groups and populations. Similar to other autoimmune diseases, the sensibility of the Caucasian population is associated with the HLA-DR3 allele and the 8.1 MHC haplotype. The pathomechanism of IBM is a complex process, including many factors. Both the degeneration of the muscle fibres and the presence of many mononuclear cells are part of the pathology, however their relationship is unknown (Figure 1). Several proteins become accumulated as inclusions in the cytoplasm of muscle fibres (Figure 2). Such proteins are amyloid-β_{42} and its different oligomers, as well as hyperphosphorylated tau protein in double helical filaments [4,5]. They are supposed to cause the degeneration of the fibres. Besides amyloid-β and the hyperphosphorylated tau, there are many other potential proteins that can play a part in the muscle fibre destruction [6]. In inclusion body myositis, the non-necrotic fibres are focally surrounded and also invaded by CD8+ T-cells and macrophages (Figure 3). High amount of invaded and non-invaded fibres express HLA-1 molecules that are necessary for antigen presentation towards CD8+ T-cells.

IBM is a chronic, slowly deteriorating disease. The diagnosis of inclusion body myositis is usually established five years after the onset of the symptoms. It has to be emphasized that the Bohan and Peter criteria are mainly applicable to polymyositis and dermatomyositis; therefore the Hilton-Jones MRC criteria has to be used for IBM. Table 1 summarizes the main points of this criteria.

The typical neurological features are muscle weakness and atrophy in the quadriceps femoris muscle and in the flexors of the wrist and fingers. The most frequent concomitant signs are dysphagia and asymmetric weakness. The serum creatine kinase level is usually under 2000 U/L. Muscle biopsy shows endomysial inflammation with the invasion of mononuclear cells into the non-necrotic fibres and round vacuoles. All these suggest that inflammation and degeneration are always together at the onset of the disease. The general cause of inclusion body myositis is unknown, however genetic and ambient factors, aging and lifestyle may play a part in the pathogenesis. Although, the association between dysphagia and IBM is well-known, only a few papers have been published on this symptom. In contrast to polymyositis and dermatomyositis, IBM rarely affects the heart. Inclusion body myositis is a slowly progrediating disease, and there is still no effective therapy [7]. A subset of patients should respond to steroids temporarily, most of them do not. Methotrexate, cyclosporine A, azathioprine or mycophenolate mofetil are ineffective in the the majority of cases. Several experiments with intravenous immunoglobulins proved that these are the most effective agents, but also this kind of therapy seems to be disappointing [8,9]. Physiotherapy may decelerate the progression of IBM and improve the quality of everyday life.

Group of inclusion body myositis	Clinical symptoms, laboratory features	Pathological findings
1. Pathologically defined disease	Consistent with IBM	- endomysial exudate - partial invasion - vacuoles - Congo-red or crystal violet or hyperphosphorylated tau or TDP43 or 15-18 nm filaments
2. Clinically defined disease	-duration more than 6 months - age at onset > 30 years - EMG consistent - m. quadriceps weakness > hip flexion - finger flexor weakness > shoulder abduction	- endomysial exudate OR - ↑MHC1 NO - Congo-red or hyperphosphorylated tau or 15-18 nm filaments
3. Possible disease	-duration more than 6 months - age at onset > 30 years - EMG consistent - m. quadriceps weakness > hip flexion OR - finger flexor weakness > shoulder abduction	- endomysial exudate OR - ↑MHC1 NO - Congo-red or hyperphosphorylated tau or 15-18 nm filaments

Table 1. Revised diagnostic criteria for IBM. (adapted from [2])

2. Methods

In the main part of our publication we demonstrate three case histories of patients suffering from IBM. All patients were, or are treated at our institute. The presented histological pictures represent the characteristic features of inclusion body myositis (Figure 1-4). The biopsy-samples were fresh frozen and stained with haematoxylin and eosin. In every case we used enzyme- and immunohistochemical reactions, too (ATPase, acid phosphatase, cytochrome oxidase, diaphorase, HLA-ABC, Gömöri, PAS, ePAS, Sudan black). The histological sections were digitized with Panoramic Scanner, distributed by 3D Histech, and we made digital pictures using 3D Histech Panoramic Viewer [10,11]. The muscle strength of the patients was defined by the Manual Muscle Testing (MMT) score. MMT of proximal muscle groups has been used as a major end point for idiopathic inflammatory myopathy therapeutic trials and in clinical practice to follow patients longitudinally. Traditionally, MMT has been assessed using 5-point MMT scales, including the Medical Research Council (MRC) Scale [12]. An expanded 0–10-point MMT scale [13] has also been used in recent therapeutic trials and it is postulated to be more sensitive in delineating weakness. Routinely we also examined the following eight muscle groups on a 0-10 scale: neck flexors, musculus deltoideus, musculus biceps brachii, musculus gluteus maximus, musculus gluteus medius, musculus quadriceps femoris, wrist extensors and ankle dorsiflexors. Except for the neck flexors, every group can be tested on both sides, so together we can give 150 points (MMT 150). If we test the muscles unilaterally (generally on the right side), than we can give 80 points (MMT 80).

3. Results, case reports

First of all, we demonstrate a „typical" IBM case. The elderly female patient had her first polymyositis-like symptoms at the age of 76, previously she had no similar symptoms. The strength of her proximal limb muscles (deltoid muscles and quadriceps femoris muscles) decreased gradually and symmetrically, the raising of the limbs became increasingly difficult. She also could hardly catch anything with her hand, she had tendon-weakness. The „sit-up" from lying position became more and more difficult and later it was impossible without help. In the next few months she lost 10 kgs weight without loss of appetite. She also felt the weakening of her lower limbs, she had problems during walking (the MMT80 score was at this time 16/80). Three months after the appearance of the first symptoms, according to the opinion of the vascular surgery, the arterial and venous circulation of her lower limbs were in good condition. Two months later electromyography was made in the deltoid muscle on the right side, in the vastus lateralis muscle on the left side and in the anterior tibial muscle on the right side. In all of the three muscles, acute myositis was found. In the same month, the followings were significant in her laboratory values: CK 3830 U/L (normal range: 24-195 U/L), GOT 147 U/L (normal range: <40 U/L), GPT 181 U/L (normal range: <40 U/L) and LDH 997 U/L (normal range: 135-220 U/L). Based on the clinical symptoms, laboratory values and electromyography we began to treat the patient with the

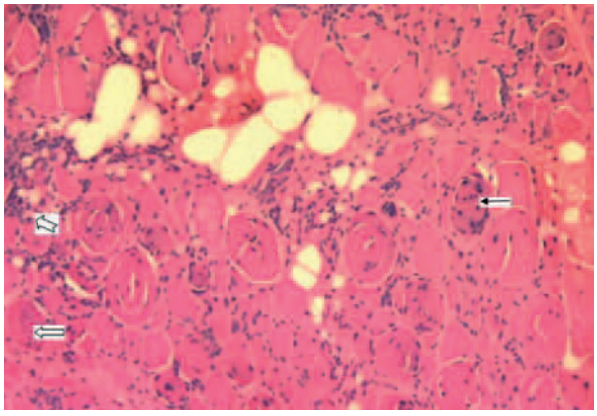

Figure 1. Histological picture of IBM. Increased variation of fiber size, frequent intracytoplasmic nucleus (black arrow), endomysial fibrosis, fiber splitting, whorled fibers (white arrow) and chronic inflammation can be seen (cutted white arrow). (HE; 100x)

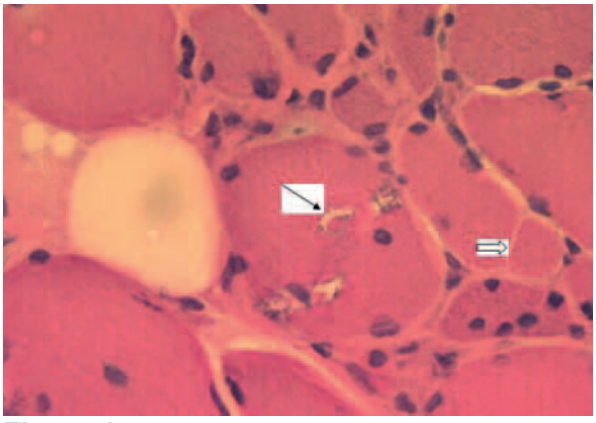

Figure 2. Histological picture of IBM. Characteristic cytoplasmatic basophilic rimmed vacuoles can be observed (black arrow) and fiber splitting (white arrow). (HE; 400x)

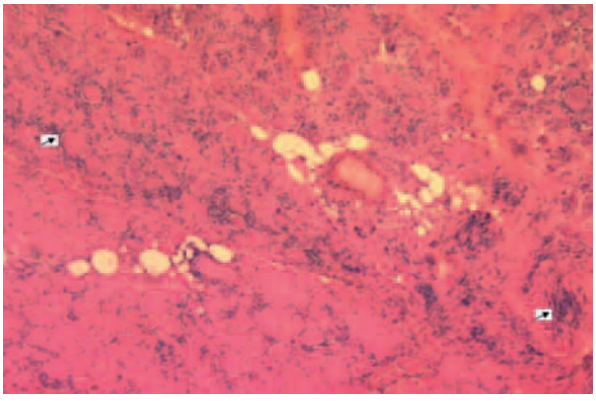

Figure 3. Histological picture of IBM. Severe chronic inflammatory cell infiltrate (arrows). (HE; 50x)

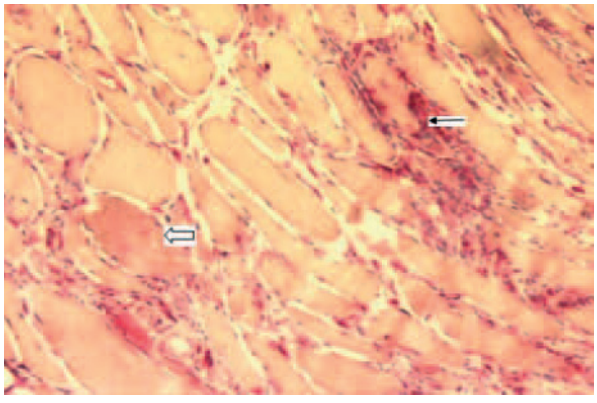

Figure 4. Histological picture of IBM. Overexpression of acid-phosphatase is the sign of intense lysosomal activity associated to inflammation, both in the inflammatory cells (white arrow) and in the muscle fibers (black arrow). (Acid phosphatase; 100x)

suspicion of polymyositis. There was no difference in the autoantibody status, there was no anti-syntethase syndrome. Detailed investigation procedures did not find cancer. During the clinical stay, muscle biopsy was made from the deltoid muscle. We started oral methylprednisolone treatment. In the literature there is no unequivocal evidence of increase in muscle strength after steroid treatment. Due to our steroid treatment protocol and physiotherapy the laboratory values improved (CK 1117 U/L, GOT 79 U/L, GPT 151 U/L, LDH 601 U/L), and the muscle strength of the patient also increased, not significant, but moderately (the muscle strength increased with 20%). We could diagnose a small but perceptible clinically improvement, according to IMACS [14]. After a week of clinical stay, we emitted the patient with methylprednisolone treatment. The result of the histology was typical for inclusion body myositis. The result of acid phosphatase staining shows overexpression of acid-phosphatase, which is the sign of intense lysosomal activity associated with inflammation (both in the inflammatory cells and in the muscle fibres) (Figure 4). Furthermore, sections display increased variation of fibre size, the frequent intracytoplasmic nucleus, endomysial fibrosis, fibre splitting, whorled fibres and chronic inflammation. Characteristic cytoplasmatic basophilic rimmed vacuoles could be observed and fibre splitting. One month later, her muscles were much weaker, we saw atrophied muscles, the patient had broad-based walk, and she could walk only with help. She felt herself much more tired than before. This time the laboratory values were the following: CK 969 U/L, GOT 62 U/L, LDH 814 U/L and GPT 186 U/L. The complaints of the patient persisted, and according to the histological and clinical picture she had a defined inclusion body myositis. It has to be underlined that at the beginning the CK level was nearly 4000 U/L. According to the published observations the CK level usually stays under 2000 U/L, but in this case we could reach this level only with the help of corticosteroids. So we can identify that these high CK

levels are rarely found in IBM. At present, she gets 2x24 mg methylprednisolone treatment and physiotherapy. The weakness of the distal lower limb muscles is also more significant than at the beginning.

The next presented patient was a fifty years old female patient. Since the age of 9 she suffered from chronic idiopathic thrombocytopenic purpura, therefore she had splenectomy at the age of 29. Since the age of 49, she had treatment-resistant lower limb oedemas (cardiac decompensation, thyroid abnormality, venous obstruction, significant proteinura were ruled out), only lymph massage therapy has been effective. Two months later, she had also proximal muscle weakness in the upper and the lower limbs (deltoid muscles, quadriceps muscles). At this time, the laboratory values were appropriate: CK 76 U/L, GOT 16 U/L, GPT 16 U/L and LDH 204 U/L. These are not so unequivocal symptoms, in the background of the complaints could be some possibilities, e.g. inclusion body myositis, eosinophil fasciitis. A few weeks later, the patient felt herself severe weak, and pain in her fingers and in both sides of her tendons. We performed a muscle biopsy and the muscle biopsy showed IBM in this patient, as well. There was no severe chronic inflammatory cell infiltrate, but the increased variation of fibre size and the cytoplasmatic basophilic rimmed vacuoles could be observed in the myopathic muscle, which is characteristic IBM. We started also methylprednisolone treatment of this patient. The MRI examination also did not confirm any inflammation. Here, we refer to the literature [15], especially regarding to the role of MRI examination. Although the MRI can aid the diagnosis, the physical examination, laboratory analysis and muscle biopsy are the three most important diagnostic procedures in inclusion body myositis. According to the last out-patient visit, the patient exercises regularly and she is in relative good condition. The laboratory values are satisfactory (CK 100 U/L, GOT 20 U/L, GPT 20 U/L), ANF (antinuclear factor) granular positivity was confirmed. Her muscle strength on the manual muscle testing (MMT) scale is almost perfect, 142/150. At present, her condition shows only a minimal progression (the distal muscles in the lower limbs are slightly weaker).

Finally, we present the case of an elderly female patient, who unfortunately died during her final hospitalisation. Her proximal muscles became weaker. Here we also can verify the typical experience that inclusion body myositis patients turn to the physician often only months or even years after the first symptoms have appeared. At the end of the disease course, our patient could not hold her neck and back, and got tired very soon. Neurological examination took place, and with a suspicion of myasthenia gravis, Mestinon treatment was started. Three months after this neurological examination, the repetitive stimulation test on electroneuronography was negative. After it, the electromyography showed the picture of chronic polymyositis in the right deltoid muscle, and in the right vastus lateralis muscle. Two months later, when our clinic saw the patient for the first time, an acute admission was necessary. The patient was in a very weak, frail condition. She wore a Schantz collar, and complained about dysphagia. She also had symmetric proximal muscle weakness and high-grade kyphosis, MMT score was 70/150. The creatine kinase value was 285 U/L, elevated cTNT (207,50 ng/L; normal range: <30 ng/L) and proBNP (59,6 pmol/L; normal range: <41,6 pmol/L) indicated possible myocardial involvement. We could also see myocardial involvement on echocardiography. All these suggested polymyositis, so muscle biopsy took place. We started methylprednisolone treatment with 1 mg/kg. Nasogastric tube was also installed, X-ray examination confirmed the oesophagus dismotility. ANF nucleolar positivity was shown, anti-Jo-1 was negative. The steroid treatment was moderately effective as for the clinical signs, and the laboratory values also improved. Swallowing ability also improved, thus, respecting the definitive request of the patient, nasogastric tube was also removed. HRCT did not show any signs of interstitial lung disease or fibrosis. Methylprednisolone treatment was continued. Some days later, she had suddenly dyspnoea and she died of breathing insufficiency. Autopsy of the patient revealed aspiration of gastric content and pneumonia. The patient died suddenly and the result of the histology became known only after her death. The two main pathological findings were the atrophic fibres and the basophilic rimmed vacuoles. According to these findings, two differential diagnosis were possible: IBM and neurogenic muscle-atrophy, but the clinical and pathological findings the patient were consistent with IBM. In this case the disease was recognized in a very advanced stage. Beside the muscle weakness, oesophagus and heart involvement were also confirmed. The involvement of the oesophagus was noticed as an unusually intense component of the systemic manifestation and this contributed to the death of the patient. Furthermore, although it is very rare in IBM, we detected myocardial involvement with echocardiography. This tragic case highlights the importance of the early diagnosis, and treatment in order to slow down the course of the disease.

4. Conclusion

The aim of this case-based update was to emphasize the most typical clinical and pathological features of IBM. We provided an overview of this idiopathic inflammatory myopathy-subgroup. We demonstrated three of our inclusion body myositis cases – two of them were clinically not entirely typical for this disease, however, neuropathological examination of the muscle biopsy confirmed the diagnosis. The pathomechanism of the disease is not clear (for review see [5]) and further studies are warrated. Current therapy including physiotherapy can slow down the progression of the disease and improve quality of life of the patients.

5. Acknowledgements

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