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CASE REPORT

Inclusion Body Myositis

A case report on navigating diagnostic challenges

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abstract: Inclusion body myositis (IBM) is a rare progressive myopathy affecting individuals older than 50 years. It is associated with significant morbidity by restricting the patient's mobility and it has a relatively low mortality risk with respiratory muscles involvement. Muscle biopsy is the gold standard method for diagnosis. We report a 72-year-old female patient who was admitted to a tertiary care hospital in Muscat, Oman, in 2023 with progressive weakness of lower limbs. Various diagnostic tests were performed and the patient was subsequently diagnosed with IBM. The patient was treated with methylprednisolone, immunoglobulins, rituximab and prednisolone; this resulted in moderate clinical improvement. This case highlights the intricate nature of the diagnostic journey, as diagnosing IBM remains a challenge in clinical practice, requiring a high degree of suspicion and precise application of available diagnostic tools with the guidance of a collaborative multidisciplinary approach in investigating and providing patient care. This case report contributes valuable insights to the understanding of this complex myopathy, facilitating more accurate diagnosis and enhancing patient care strategies.

Keywords: Sporadic Inclusion Body Myositis; Idiopathic Inflammatory Myopathy; Case Report; Oman.

Idiopathic inflammatory myopathies are heterogeneous group autoimmune disorders with varying clinical presentation that affect several systems, including the musculoskeletal, cardiopulmonary and gastrointestinal systems, but more prominently skeletal muscles.[1] Inclusion body myositis (IBM) is a subset of the 3 main idiopathic inflammatory myopathies, along with others such as dermatomyositis and polymyositis.[2,3] It has a slow progression with distinct clinical and pathological presentations. The hallmark of these inflammatory disorders is inflammation and necrosis of muscle fibres associated with rising levels of muscle enzymes and presenting primarily as weakness. IBM is either sporadic or hereditary; both types of IBM have similar features with one distinction, the absence of inflammation in the latter.[4,5]

The prevalence of IBM is frequently underestimated due to diagnostic challenges and a high rate of misdiagnosis. A study in the Netherlands estimated a prevalence of 5 cases per million in 2000.[6] More recently, a population-based study in Ireland in 2017 reported a much higher prevalence of 112 cases per million; a recent meta-analysis reported a pooled prevalence of 46 patients per million, reflecting a sharp increase in the last decade, indicating a significant increase which may be attributed to improved diagnostic methods and increased awareness.[6,8]

The importance of accurate classification became apparent with the incorporation of IBM into the International Classification of Diseases (ICD). In 2018, the introduction of the ICD, Ninth Revision, and Clinical Modification code offered a more precise estimation of prevalence and healthcare costs, revealing an annual cost of $35,000 for patients with IBM and Medicare coverage, alongside a prevalence of 84 cases per million in individuals over 65 years of age in the USA.[7,9]

IBM is more common in males than in females and most patients progress to being wheelchair bound 20 years from the first presentation.[5] Classically, there is an asymmetric involvement of finger flexors and knee extensors. However, atypically, dysphagia, weakness in the proximal upper limbs or axial muscles may also occur, particularly in advanced cases. The eventual involvement of respiratory muscles is anticipated, contributing to premature mortality.[5] Bio-chemically, abnormal creatinine kinase levels and the detection of monoclonal immunoglobulin through serum immunofixation may be observed. Additionally, positive results may be noted for other markers, including antinuclear antibodies, anti-RO antibodies, anti-La antibodies, rheumatoid factor and anti-cN1A autoantibody.[7] This report describes a patient with the classical features of IBM. However, the presence of concurrent medical issues posed a diagnostic challenge, necessitating the application of various diagnostic tools for definitive diagnosis.

Case Report

A 72-year-old female patient presented to a tertiary care hospital in Muscat, Oman, in 2023 with a 3-month history of progressive lower limb weakness,

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Table 1: Laboratory results of a 72-year-old female patient with inclusion body myositis.

Test	Finding	Normal range
Total white cell count ×109/L	10.7	2.4–9.5
Neutrophils ×109/L	10	1–4.8
Lymphocytes ×109/L	0.4	1.2–3.8
Haemoglobin in g/dL	10	11–14.5
Serum sodium in mmol/L	126	135–145
Serum calcium in mmol/L	2.68	1.15–2.55
Creatine kinase in U/L	54	26–192
Osmolality in serum in mOsm/kg	248	275–295
Fractional excretion of sodium in mmol/L	124	135–145
Osmolality in urine in mOsm/kg	570	40–1,400
Cortisol in nmol/L	298	Morning cortisol:133–537
Alanine aminotransferase in U/L	Day of admission = 35	
Day 10 of admission = 136		
Last reading before discharge = 46	0–33	
Aspartate aminotransferase in U/L	Day of admission = 20	
Day 10 of admission = 62		
Last reading before discharge = 28	0–32	
Alkaline phosphatase in U/L	Day of admission = 103	
Day 10 of admission = 125		
Last reading before discharge = 97	35–104	
Bilirubin in umol/L	Day of admission = 9	
Day 10 of admission = 10		
Last reading before discharge = 5	0–17	
Limbic encephalitis screen in cerebrospinal fluid	Negative	-
Paraneoplastic syndrome screen in cerebrospinal fluid and serum	Negative	-
Autoimmune myositis screen	Strong positive anti-Ku remaining antibodies are negative	List of tested antibodies: Anti-Mi-2 alpha, anti-Mi-2 beta, anti-TIF1f, anti-MDA5, anti-NXP2, anti-SAE1, anti-Ku, anti-PM-Scl100, anti-PM-Sc175, anti-Jo-1, anti-SRP, anti-PL-7, anti-PL-12, anti-EJ, anti-OJ, anti-Ro52
Anti-nuclear antibody	Negative	
ANCA in U/mL	Weak positive c-ANCA; anti-myeloperoxidase MPO = 1, anti-proteinase 3 antibodies PR3 = 1	
0.00–20.00		
Thyroid antibody in IU/mL	136	0–50
Free thyroxin T4 in pmol/L	20.5	12.3–20.2
Thyroid stimulating hormone in mIU/L	4.59	0.27–4.20
Parathyroid hormone in pmol/L	6.5	1.6–6.9
Syphilis	Negative rapid plasma reagin, non-reactive venereal disease research laboratory. Positive treponema pallidum haemagglutination with a titre of 320	
Anti-Hepatitis B core	Positive	
HCV antibodies	Negative	
Serum protein electrophoresis in g/L	IgG = 41.9, remaining Ig within normal ranges. No abnormal protein bands were detected and confirmed on immunofixation	7–16
Urine protein electrophoresis in g/L	0.70	0.00–0.15
Free light chain profile	Normal	

ANCA = antineutrophil cytoplasmic antibodies.

inability to stand or walk with gradual loss of mobility. Her symptoms were progressive, eventually rendering her bedbound with a decline in performing daily activities. Additionally, occasional episodes of disorientation and visual hallucinations were reported. She had a medical history of type 2 diabetes mellitus, hypertension and dyslipidaemia; she was receiving treatment with metformin for diabetes and valsartan for hypertension. There was no history of fever, convulsions, upper respiratory symptoms, dysuria, or any rashes. There was no significant family history of autoimmune disorders or malignancies and no contributing environmental exposures.

On initial examination, the patient was alert, communicative and following simple commands. While no fasciculations were observed, there was mild muscle wasting in the lower limbs with evident

hypotonia. An assessment of muscle power revealed the following: proximal upper limb power ranged from 1–2 out of 5; elbow flexion was at 2–3 out of 5; and wrist and hand grip was at 3 out of 5. Proximal muscles in the lower limbs exhibited a power of 1 out of 5, with knee flexion at 1 out of 5 and dorsi/plantarflexion of 3 out of 5. Deep tendon reflexes were diminished; the plantar response was normal with no evidence of sensory loss.

The initial laboratory results showed normal inflammatory markers but exhibited elevated liver enzymes. Renal parameters and electrolytes were within normal ranges but the patient had hyponatraemia. Her creatine kinase levels were normal on 2 separate occasions. The autoimmune myositis screening returned a strong positive result for anti-Ku antibodies. Other autoimmune parameters, including antinuclear antibodies (ANA) and antineutrophil cytoplasmic antibodies (ANCA), were negative. She also had a positive latent syphilis profile. Lumbar puncture results including limbic encephalitis screening and screening for paraneoplastic syndrome were unremarkable [Table 1].

Computed tomography and magnetic resonance imaging of the brain showed features consistent with cerebral atrophy and microvacuolar changes.

A nerve conduction study showed mild prolongation of distal latencies, slowing of the conduction velocities and preserved compound muscle action potential amplitude of bilateral ulnar, peroneal and tibial motor neurons. Her electromyography (EMG) showed active denervation of the examined muscles with mixed myopathic and neurogenic units and reduced recruitment. Her electroencephalogram tracings showed global slowing with occasional generalised bursts of high amplitude slow waves consistent with cortical dysfunction.

After performing the EMG and the nerve conduction study, a muscle biopsy of the left quadriceps femoris was taken based on the EMG report. Her muscle biopsy showed numerous regenerating myofibres, dispersed necrotic/degenerate myofibre, and significant numbers of myofibers with striking rimmed vacuoles [Figure 1]. There was type II myofibre atrophy and increased variation in the size of type I myofibres. Foci of mild endomysial and perivascular lymphocytic inflammation were noted and there was mild increased perimysial fat infiltration. Immunohistochemistry showed sarcolemma upregulation of MHC-1 stain. MAC stain (C5b-9) was positive in necrotic myofibres but negative in capillaries. The inflammatory cells consisted mainly of many CD68+ macrophages and occasional endomysial

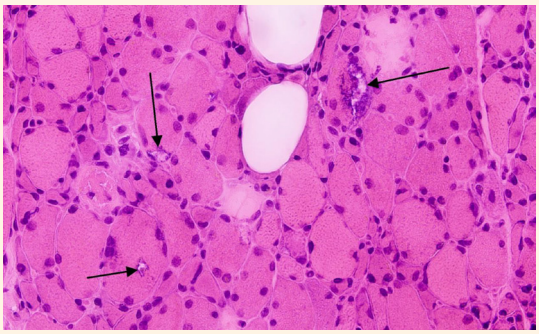

Figure 1: Haematoxylin and eosin stain at ×400 magnification of frozen skeletal muscle tissue showing variation in myofibre size and striking rimmed vacuoles in occasional myofibres (arrows).

CD3+ T-lymphocytes comprised of CD4+ >CD8+ lymphocytes (the latter was also noted in necrotic fibres). There was also strong p62 immunoreactivity in scattered rimmed vacuoles and in small protein aggregates within myofibres [Figure 2].

An 18-fluoro-deoxyglucose positron emission tomography (FDG-PET) scan showed a low-grade homogenous increased FDG uptake involving the muscles and subcutaneous tissue of the left lateral thigh, worse on the *vastus lateralis*; these findings are consistent with myositis [Figure 3].

Considering the initial suspicion of inflammatory myopathy, the patient was commenced on treatment courses of intravenous methylprednisolone and intravenous immunoglobulins, followed by rituximab injections and oral prednisolone. However, in view of the absence of autoimmune symptoms, the negative results for ANA and ANCA, the possibility of false-positive anti-Ku antibodies and the diagnostic findings from the muscle biopsy, a diagnosis IBM was established. The patient's treatment was overseen by a collaborative, multidisciplinary team from general medicine, neurology, infectious diseases, physiotherapy and speech therapy specialists. The

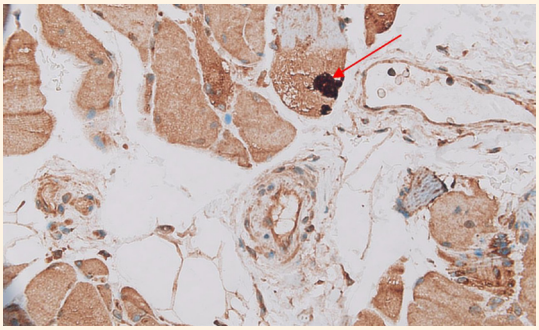

Figure 2: Immunohistochemical stain at ×600 magnification of skeletal muscle tissue showing strong positive immunoreactivity of p62 in a rimmed vacuole (arrow).

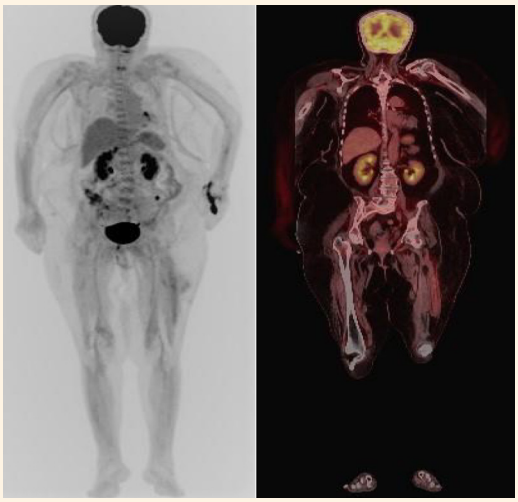

Figure 3: F-18 FDG PET-CT: showing low grade homogenous increased FDG uptake involving the muscles and subcutaneous tissue of the left lateral thigh, worse on the vastus lateralis, these findings are consistent with myositis (see arrow).

treatment plan involved the initiation of tenofovir for chronic hepatitis B and benzylpenicillin for syphilis in view of needing to continue immunosuppressant medications. Continuous physiotherapy was strongly recommended.

Following admission, confirmation of diagnosis and start of the management plan, the patient showed a moderate clinical improvement characterised by enhanced trunk stability and the capacity to maintain evaluated postures. Additionally, there was a significant increase in muscular strength across all limbs. Subsequently, she was discharged to her home with arrangements made for continued treatment at a tertiary care hospital.

Verbal consent was obtained from patient's next of kin for publication purposes as the patient had episodes of disorientation.

Discussion

This case represents exceptional challenges due to the patient's complex medical history, including hyponatraemia, syndrome of inappropriate antidiuretic hormone, a positive syphilis profile, hypercalcaemia, hepatic encephalopathy and initial suspicion of paraneoplastic syndrome. Investigating these concurrent conditions significantly prolonged the diagnostic process, as her symptoms could easily have been misconstrued as manifestations of any of these underlying issues and can influence the disease progression. This report explores the challenges in diagnosing and managing IBM requiring a collaborative effort of a multidisciplinary team approach for diagnosis and management.

Pathogenesis of IBM has been debated due to its unclear nature. Published literature has shown that IBM results from a series of immune and degenerative reactions with no specific trigger. Auto-immunity is believed to have a significant role; however, inflammation is the primary precipitating factor of this cascade.[10] The pathogenesis is thought to revolve around multiple processes namely rimmed vacuoles and myonuclear degeneration, mitochondrial pathogeny and protein aggregation. The immune process is led by the infiltration of CD+8 T cells within muscles triggered by inflammation; the production of differentiated cells results further exerts cytotoxic properties causing the production of autoantibodies such as cN1A which is detected in 60% of patients.[10] Moreover, another non-immune process, that works in parallel, is the production of gamma interferon which results in the accumulation of protein aggregates.[10] Several distinctive molecules were described previously in the pathogenesis of IBM such as amyloid seen by Congo red, ubiquitin, B-amyloid and tau. But more recently, degenerative muscle biomarkers such as p62, LC4 and TDP43 proved to be more valuable and superior in the detection of IBM.[7] Lastly, mitochondrial dysfunction due to inflammatory cytokines also results in mitochondrial damage through oxidative stress, the severity of this damage is correlated to atrophy of muscle fibres.[4,10] Genetic predisposition with the presence of some human leukocyte antigen genes is presumed to have a part in sporadic IBM.[4]

Diagnosis of IBM is highly dependent on histopathological findings which are reflective of the disease process. Commonly, the presence of rimmed vacuoles, protein deposits, CD8+ T cells, and major histocompatibility complex are diagnostic. The latter could also present in polymyositis, dermatomyositis and muscular dystrophies.[10] The decision of which muscle to biopsy should be taken cautiously to avoid false negative results.[11]

Electromyography is done as part of investigations; the results can be used to select the site of biopsy. Both long-duration high amplitude and short-duration and low amplitudes might be present imposing a challenge in result analysis.[11]

Musculoskeletal radiology is now emerging as a non-invasive modality deemed useful in detecting specific radiological patterns associated with IBM. For instance, MRI might demonstrate features such as muscle atrophy, oedema and fatty infiltration which assist in biopsy site selection, monitoring disease progression and differentiating IBM from the other subsets of myositis. In a recent review, the distinct features seen in different imaging modalities were

summarised to help in diagnosing IBM. For example, in PET scans using F-18 FDG, specific tracers are used to detect potential markers such as beta amyloid and tau proteins in affected muscles and to monitor the progression of the disease. Moreover, dual energy X-ray absorptiometry scan can demonstrate muscle mass and quantities of muscle atrophy, which ultimately helps assess disease progression or evaluate therapeutic effects.[12]

Non-pharmacological management of IBM includes measures towards ensuring regular assessment of swallowing and respiratory muscles along with tackling mobility and ambulation through exercise routines. Fall precautions and education should also be emphasised.[7,11]

Swallowing dysfunction, falls and a decline in quality of life are common in patients with IBM and significantly affect morbidity and mortality. Approximately 40% of patients complain of dysphagia at diagnosis and around 80% have dysphagia with the advancement of disease. For evaluation of dysphagia in IBM, the penetration-aspiration scale, video-fluoroscopy and endoscopic evaluation of swallowing along with MRI can quantify swallowing dysfunction. Several measures such as the Mendelsohn manoeuvre and expiratory muscle strength trainer device were proposed to reduce the risk of aspiration, however, their role in improving swallowing function has not been established. Similarly, ankle foot orthosis has been proposed for prevention of recurrent falls which correlate with disease progression, however, its role in the prevention of falls has not been determined yet.[13]

The role of immunosuppression therapy has transient effects with myodegeneration being the main target for therapy, especially in cases where bulbar and proximal muscle presentation are exhibited. Agents such as arimoclomol, bimagrumab, follistatin, oxandrolone and rapamycin were proposed in recent clinical trials.[3]

In a study, follow-up of patients over a period averaging 61.1 months revealed a monthly muscle power deterioration of −0.79%. The natural course without immunosuppressive treatment showed a steeper decline of −1.03% per month, most rapidly at knee extension. Males in the initial 5 years post-onset saw a quicker decline; notably, serum creatine kinase levels, region and age at onset didn't predict prognosis. Inversely, treated patients had a significantly lower decline (−0.76%) than untreated patients (−1.03%); mycophenolate mofetil treatment showed a more favourable prognosis at −0.67%. These findings emphasise the potential benefit of immunosuppressive interventions in slowing muscle power loss in IBM patients.[14]

Conclusion

The diagnosis of IBM necessitates a comprehensive approach that integrates clinical evaluation, biochemical analysis and metabolic imaging such as F-18 FDG PET-CT. The current case not only emphasises the significance of this multimodality approach and clinical acumen but also the vital role of multidisciplinary management. The collaborative efforts of experts from diverse fields, including general medicine, neurology, pathology, radiology and rehabilitation therapy, were instrumental in not only accurately diagnosing the patient but also formulating a holistic management plan tailored to the patient's specific need.

AUTHORS' CONTRIBUTION

Drafting the manuscript was done by MS and SB. SJ provided the details of histopathology slides and description. JZ provided details of imaging and the related description. HF and AA managed the case and AA critically revised the manuscript. All authors approved the final version of the manuscript.

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