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Inclusion Body Myositis

Navigating diagnostic challenges, case report

***Marwa Al Sharji,[1] Salim Al Busaidi,[2] Suad Al Jahdhami,[3] Zabah Jawa,[4] Hatem Farhan,[1,2] Abdullah M. Al Alawi[1,2]**

[1]Internal Medicine Residency Program, Oman Medical Specialty Board, Muscat, Oman; Departments of [2]Medicine, [3]Histopathology and [4]Radiology & Molecular Imaging, Sultan Qaboos University Hospital, Sultan Qaboos University, Muscat, Oman.
**Corresponding Author's e-mail: r2281@resident.omsb.org*

Abstract

Inclusion body myositis (IBM) is a rare progressive myopathy affecting individuals older than 50 years. It is associated with significant morbidity once 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. In this complex scenario, we present a case involving a 72-year-old woman admitted to our hospital with progressive weakness of lower limbs. The diagnostic process was challenging due to the case's complexity necessitating a multidisciplinary team approach. This case highlights the intricate nature of the diagnostic journey, as diagnosing IBM remains a challenge in clinical practice, requiring a high 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; rimmed vacuoles

Introduction

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 three main idiopathic inflammatory myopathies, along with others like dermatomyositis and polymyositis.[2,3] It has a slow progression nature with distinct clinical and pathological presentations. The hallmark of these inflammatory disorders is inflammation and necrosis of muscle fibers associated with rising levels of muscle enzymes and presenting primarily as weakness. IBM is of two types, sporadic and hereditary; both 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] But more recently, a population-based study in Ireland in 2017 reported a much higher prevalence of 112 cases per million, and 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 possibly 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 (ICD9CM) code offered a more precise estimation of prevalence and health care 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 United States.[7,9]

Inclusion body myositis is more common in males than in females and most patients progress to being wheelchair bound by 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] The presentation of our patient mirrored the classical features of IBM. However, the presence of concurrent medical issues posed a diagnostic challenge, necessitating the application of various diagnostic tools to arrive to the final diagnosis.

Case Report

A 72-year-old female patient, with a medical history that includes type 2 diabetes mellitus, hypertension, and dyslipidaemia, is currently receiving treatment with metformin for her diabetes and valsartan for her hypertension. She presented with a 3-month history of progressive lower limb weakness, 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. 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. Assessment of muscle power revealed the following: proximal upper limb power ranged from 1-2/5, elbow flexion at 2-3/5, and wrist and hand grip at 3/5. Proximal muscles in the lower limbs exhibited power of 1/5, with knee flexion at 1/5 and dorsi/plantarflexion of 3/5. Deep tendon reflexes were diminished, and the plantar response was normal, with no evidence of sensory loss.

Her Initial laboratory workup (Table 1) showed normal inflammatory markers but exhibited elevated liver enzymes. Renal parameters and electrolytes were within normal apart from

hyponatremia. Her creatine kinase levels were normal on two 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.

Neuroimaging, namely computed tomography, and magnetic resonance imaging of the brain showed features consistent with cerebral atrophy and microvacuolar changes.

Patient 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 generalized bursts of high amplitude slow waves consistent with cortical dysfunction.

After performing EMG and the nerve conduction study, a muscle biopsy of the left quadriceps femoris was performed, based on the EMG report. Her muscle biopsy showed numerous regenerating myofibers, dispersed necrotic/degenerate myofibers, and significant numbers of myofibers with striking rimmed vacuoles (Figure 1.). There was Type II myofiber atrophy and increased variation in the size of Type I myofibers. 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 myofibers but negative in capillaries. The inflammatory cells consisted mainly of many CD68+ macrophages and occasional endomysial CD3+ T-lymphocytes comprised of CD4+ > CD8+ lymphocytes (the latter also noted in necrotic fibers). There was also strong p62 immunoreactivity in scattered rimmed vacuoles (Fiure2.) and in small protein aggregates within myofibers.

As part of work up, 18-Fluoro-deoxyglucose positron emission tomography (FDG-PET), (FIGURE 3.) was performed. The images 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.

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, along with the possibility of false-positive anti-Ku antibodies and the diagnostic findings from the muscle biopsy, a diagnosis IBM was established. Additionally, and following the confirmation of the diagnosis, the patient's treatment was overseen by a collaborative, multidisciplinary team, from general medicine, neurology, infectious diseases, physiotherapy, and speech therapy. The 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 emphasized.

During her hospital stay, the patient showed a moderate clinical improvement, characterized 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. A verbal consent was taken from patient’s next of kin to report the case.

Discussion

This case represents exceptional challenges due to the patient's complex medical history, including hyponatremia, syndrome of inappropriate antidiuretic hormone, a positive syphilis profile, hypercalcemia, 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 they can influence the disease progression. Our 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. One important concept is the immune process led by the infiltration of CD+8 T cells within muscles triggered by inflammation, production of differentiated cells results which further exerts its cytotoxic properties causing the production of autoantibodies like cN1A which is detected in 60% of patients. Moreover, another nonimmune 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 like amyloid seen by congo red, ubiquitin, B-amyloid, and tau. But more recently, degenerative muscle biomarkers like 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 fibers.[4,10] Genetic predisposition with the presence of some HLA 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 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 patterns associated with IBM distinguishing it over the remaining myositis. For instance, Magnetic resonance might demonstrate features like muscle atrophy, edema, 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 summarized to help in diagnosing IBM. For example, in PET scans using F-18 FDG, specific tracers are used to detect potential markers like Beta amyloid and tau proteins in affected muscles and to monitor the progression of the disease. Moreover, dual energy x-ray absorptiometry (DEXA) 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 inclusion body myositis 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 emphasized. [7,11]

Swallowing dysfunction, falls, and a decline in quality of life are common in IBM and significantly affect morbidity and mortality. Around 40% of patients complain of dysphagia at diagnosis and around 80% have dysphagia with the advancement of disease. For evaluation of dysphagia in IBM, rosenbek penetration aspiration scale, video-fluoroscopy, and endoscopic evaluation of swallowing along with magnetic resonance can quantify swallowing dysfunction. Several measures like the Mendelsohn maneuver and expiratory muscle strength trainer device to reduce the risk of aspiration were proposed for prevention, however, no role was identified for improving swallowing function. Similarly, ankle foot orthosis has been proposed for prevention of recurrent falls which correlate with disease progression, however a definitive role in the prevention of falls has not been established.[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 like arimoclomol, bimagrumab, follistatin, oxandrolone, and rapamycin were proposed in recent clinical trials.[3]

In one study (n=43), 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 at -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 (-1.03%), and mycophenolate mofetil treatment showed a more favorable prognosis at -0.67%. These findings emphasize 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. In this case, we not only emphasized the significance of this multimodality approach and clinical acumen but also emphasize 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 arriving at an accurate diagnosis 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 related description. HF managed the case. AA managed the case and critically revised the manuscript. All authors approved the final version of the manuscript.

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Table 1: Laboratory results values with normal ranges

Test	Result Value	Normal ranges
Total white cell count	10.7 10^9/L	2.4-9.5 10^9/L
Neutrophils	10 10^9/L	1-4.8 10^9/L
Lymphocytes	0.4 10^/L	1.2-3.8 10^9/L
Hemoglobin	10 g/dL	11-14.5. g/dL
Serum Sodium	126 mmol/L	135-145mmol/L
Serum Calcium	2.68 mmol/L	1.15-2.55 mmol/L
Creatine kinase	54 U/L	26-192 U/L
Osmolality in serum	248 mOsm/kg	275-295 mOsmol/kg
Fractional excretion of sodium	124 mmol/L	135-145 mmol/L
Osmolality in urine	570 mOsm/kg	40-1400 mOsmol/kg
Cortisol	298 nmol/L	am 133-537 nmol/L
Alanine aminotransferase	Day of admission: 35 Day 10 of admission 136 Last reading before discharge 46	0-33 U/L
Aspartate aminotransferase	Day of admission: 20 Day 10 of admission 62 Last reading before discharge 28	0-32 U/L
Alkaline phosphatase	Day of admission: 103 Day 10 of admission:125 Last reading before discharge 97	35-104 U/L
Bilirubin	Day of admission: 9 Day 10 of admission:10 Last reading before discharge :5	0-17umol/L
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	
Anti-neutrophilic cytoplasmic antibody	Weak positive c-ANCA - anti-myeloperoxidase MPO: 1 U/ml -anti-proteinase 3 antibodies PR3: 1 U/ml	0.00-20.00 U/ml
Thyroid antibody	136 IU/ml	0-50 IU/ml
Free thyroxin T4	20.5 pmol/L	12.3-20.2 pmol/L
Thyroid stimulating hormone	4.59 mIU/L	0.27-4.20 mIU/L
Parathyroid hormone	6.5 pmol/L	1.6-6.9 pmol/L
Syphilis	Negative rapid plasma regain, non-reactive venereal disease research laboratory. Positive treponema pallidum hemagglutination with a titer of 320	
Anti-Hepatitis B core	Positive	
HCV antibodies	Negative	
Protein electrophoresis, serum	Immunoglobulin G 41.9 g/L remaining immunoglobulin within normal. No abnormal protein bands were detected and confirmed by IFE	7-16g/L
Protein electrophoresis, urine	Urine protein 0.70 g/L	0.00-0.15 g/L
Free light chain profile	Normal	

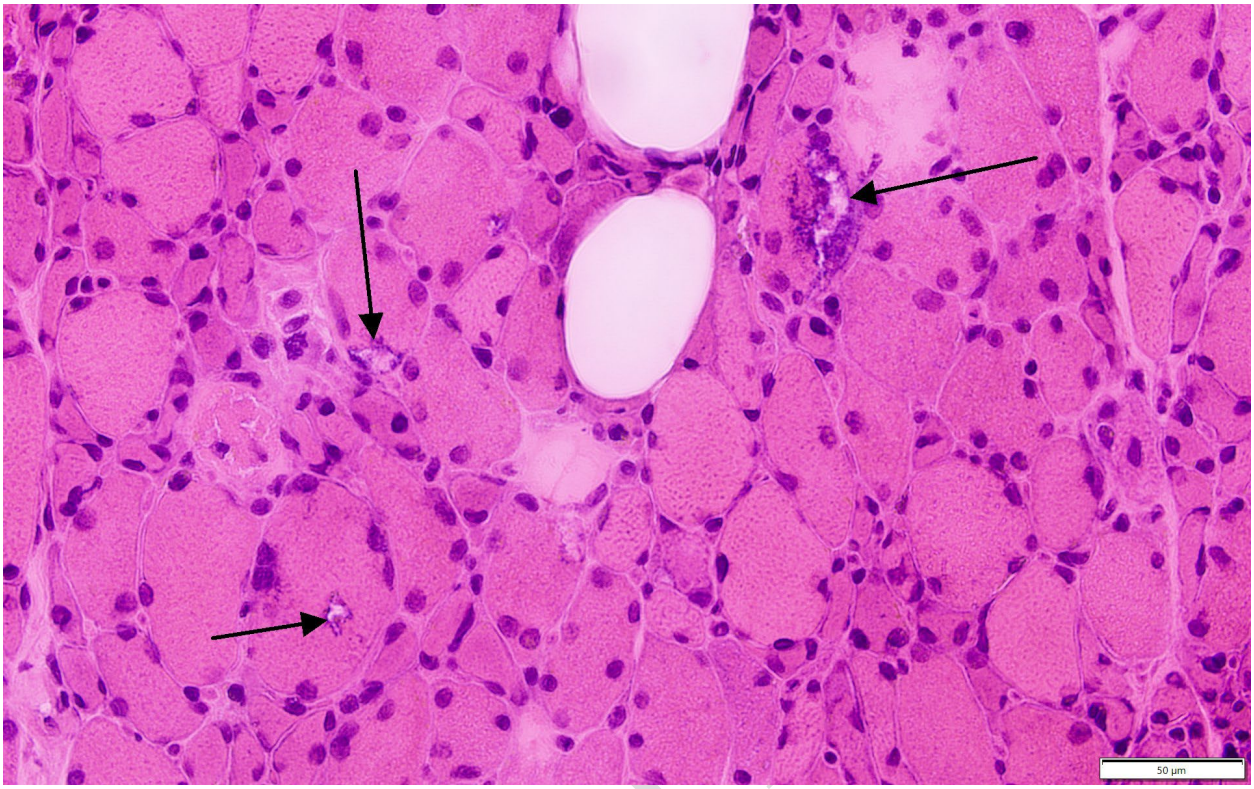

Figure 1: H&E stain of frozen skeletal muscle tissue showing variation in myofiber size and striking rimmed vacuoles in occasional myofibers (black arrows) [magnification= x400].

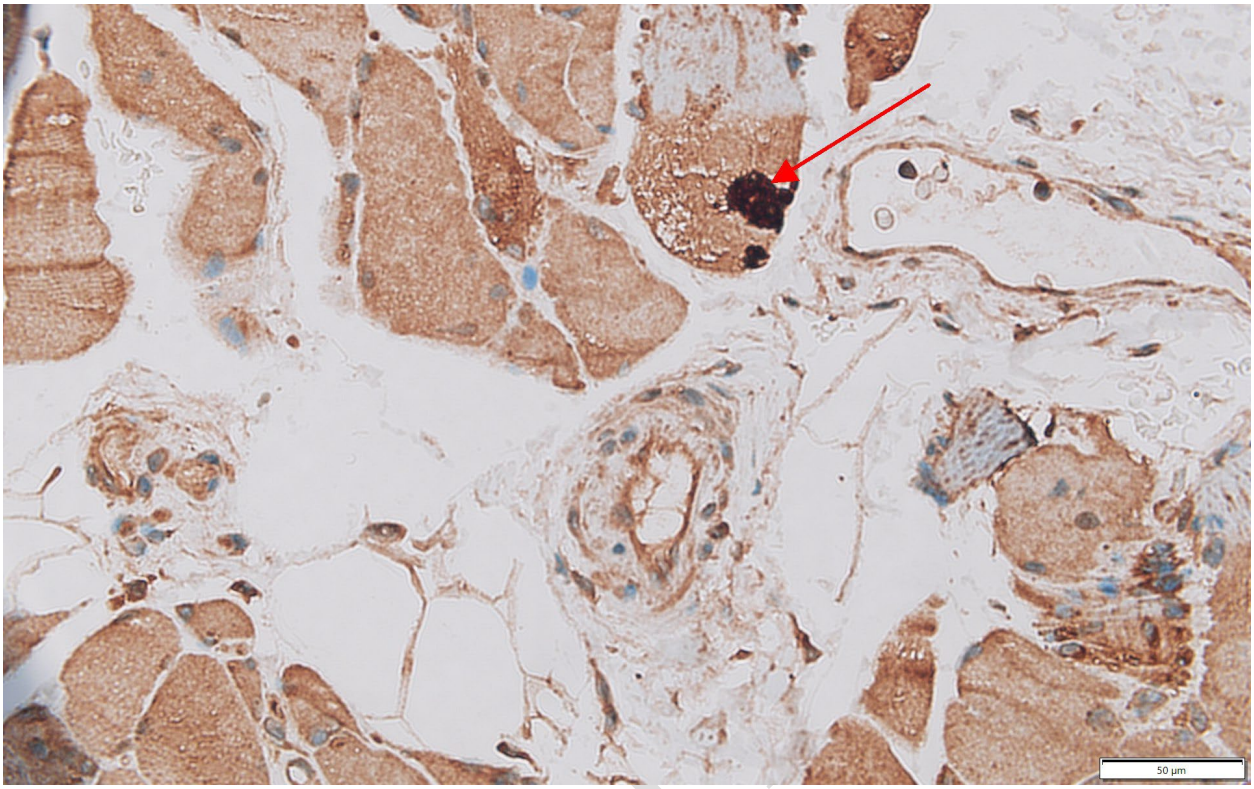

Figure 2: Immunohistochemical stain of skeletal muscle tissue showing strong positive immunoreactivity of **p62** in a rimmed vacuole (red arrow) [magnification= x600].

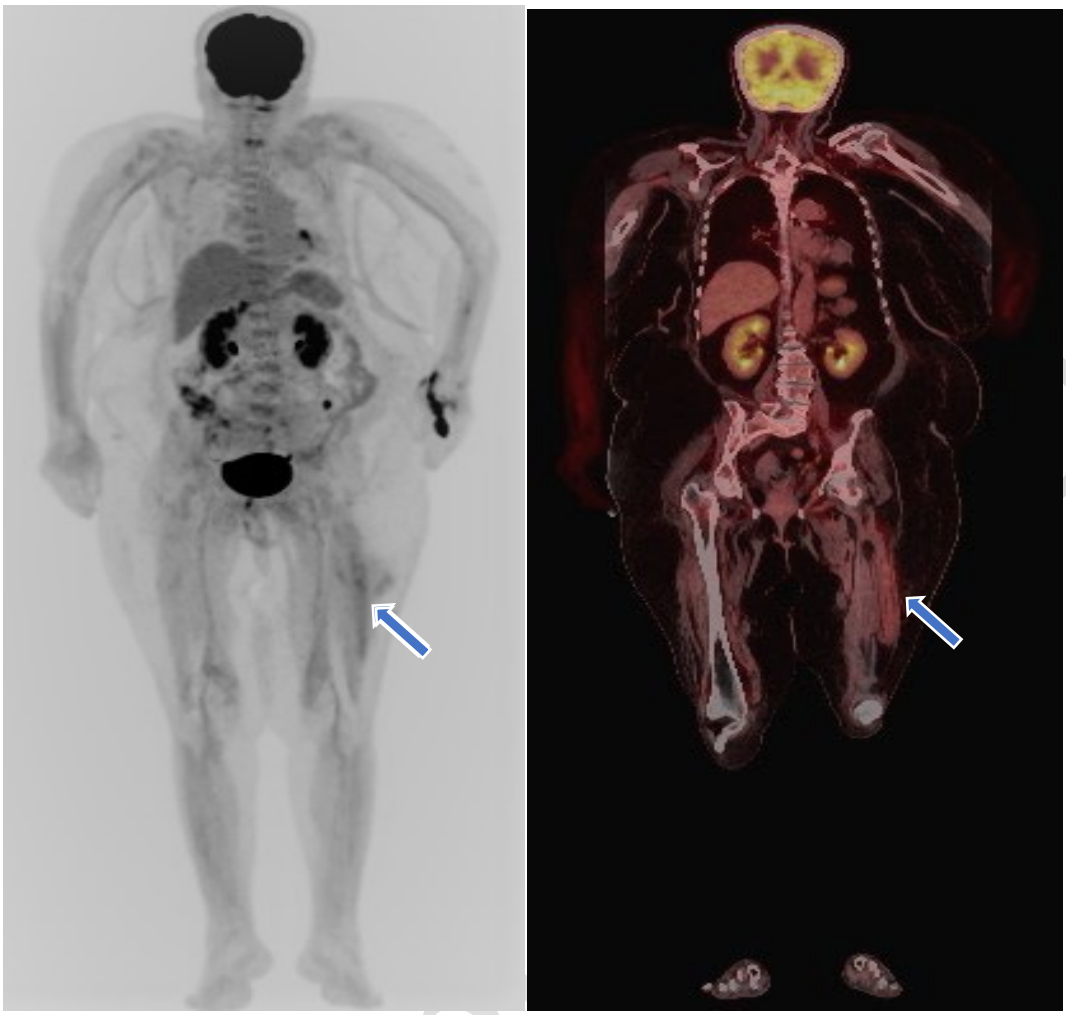

Figure 3: F-18 FDG PET-CT: showing low grade homogenous increased FDG uptake involving the muscles and subcutaneous tissue of the left lateral thigh, worse on the vastus lateralis, these findings are consistent with myositis (see arrow).