

Comorbidity of Polymyositis and Myasthenia Gravis in HIV Patients Treated with Rituximab

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Abstract

Background: Comorbidity of Myasthenia Gravis (MG) and Polymyositis (PM) is uncommon. In places like South Africa, where the prevalence of HIV is very high, any combination of associated diseases is possible. Few cases of MG/PM have been reported in the medical literature, and different therapeutic modalities have been applied. The primary aim of this study is to review the medical literature looking for the frequency of this comorbidity, its clinical features, and therapeutic modalities.

Methods: We searched the medical literature, looking for published articles on "comorbidity of MG"; "Association of MG/PM/DM/HIV/AIDS"; "MG and Immune disorders"; OR "Treatment of MG/PM/DM/HIV/AIDS"; OR "Management of MG/AD"; OR "Rituximab in MG/PM/DM/HIV/AIDS" OR "MG/PM/DM/HIV myopathy"; OR "MG/Myositis" OR "Neuromuscular Junction Disorders (NMJD)/PM/DM/HIV/AIDS, OR "Inflammatory Myopathy (IM)/MG/HIV/AIDS".

Results: All selected manuscripts were peer-reviewed, and no one included MG/NMJD/PM/DM/HIV/AIDS treated with RTX.

Case report: A 24-years-old HIV female on HAART complaining of the progressive bilateral and symmetrical proximal weakness of the four limbs with an inability to climb stairs and even lift the head off the bed, get up from a sitting position, lift heavy objects, and overhead abduction of the arm. Laboratory investigations show significantly elevated CK level in the blood, AChR ab positive, EMG findings confirmed diagnosis of MG and muscle biopsy confirmed PM. The patient was treated with RTX and improved dramatically.

Comments and concluding remarks: We have hypothesized the pathophysiology of this comorbidity and their good respond to RTX. However, further well-designed investigations should be done to clarify the overall immune mechanisms that cause these complicated pathologic features. This is the first article on this issue reported in the medical literature, as far as we know.

Keywords: Myasthenia gravis • Polymyositis • HIV/AIDS • Rituximab • Systematic review • Case report

Abbreviations: anti-AChR: Anti-acetylcholine Receptor; AchR Acetylcholine Receptor; CK: Creatine Kinase; ADL Activities of Daily Living; CTLA-4: Cytotoxic T-Lymphocyte-Associated protein 4 CI Confidence Interval; IBM: Inclusion Body Myositis; AMSTAR 2: Measurement Tool to Assess systematic; Reviews ICE: Immune Checkpoint Inhibitor; DAMP Damage Associated Molecular Pattern; IM: Inflammatory Myopathy DC Dendritic Cell; MG: Myasthenia Gravis; OMG: Early Onset Myasthenia Gravis; MHC: Major Histocompatibility complex EBV Epstein Barr Virus; MSA: Myositis-specific Autoantibody GC Germinal Centre; PD-1: Programmed Cell Death 1; IF: Interferon; PD-L1: Programmed Cell Death Ligand 1 IFNAR Interferon- α/β Receptor; PM: Polymyositis; IgG: Immunoglobulin G; PSL: Prednisolone; IL: Interleukin JAK1: Janus Kinase 1; LOMG Late-Onset Myasthenia Gravis RNS Repetitive Nerve Stimulation; LRP4 Low-Density Lipoprotein Receptor-related Protein 4; SFEMG: Single-Fibre Electromyogram; MFA: Myasthenia Gravis Foundation of America MGT Thymoma Associated Myasthenia Gravis; MG-QOL: Myasthenia Gravis-specific Quality of Life; miRNA: Micro RNA; MuSK: Muscle Specific Kinase; PAMP: Pathogen Associated Molecular Pattern; QMG: Quantitative Myasthenia Gravis PBMC Peripheral Mononuclear Blood Cell; RCT: Randomized Controlled Trial; RIG-1 Retinoic Acid Inducible Gene 1 SOCS Suppressor of Cytokine Signaling; SD: Standard Deviation; STAT Signal Transducer and Activator of Transcription TEC Thymic Epithelial Cell; Th17cell T Helper 17 cell TLR Toll-like Receptor; TNF α Tumour Necrosing Factor Alpha; INF γ : Interferon Gamma; TSA: Tissue-specificAntigen; USP18: Ubiquitin-specific Peptidase 18.

Introduction

Myasthenia Gravis (MG) is an uncommon B-cell-mediated autoimmune disease that affects the post-synaptic receptor and the mechanism of neurotransmission at the Neuromuscular Junction (NMJ). Clinical features of MG are characterized by a variable combination of fatigable weakness of the extraocular muscles, all limbs, and even bulbar muscles, and respiratory muscles due to antibodies attacking the Acetylcholine Receptor (AChR) and other proteins located at the NMJ like Muscle-Specific tyrosine Kinase (MuSK) and Lipoprotein Receptor-related Protein 4 (LRP4) and its incidence varies with age, sex, and ethnic groups and range from 0.3 to 2.8 per 100,000 all over the world. Therefore, the remarkable presence of these autoantibodies is quite common. Clinical outcomes fluctuate between benign to fatal prognosis and can be managed with anticholinesterase medications, fast immunomodulatory therapy, and chronic immunosuppressive drugs with or without thymus removal. Notwithstanding, despite the last novel and valuable therapeutic modalities, sometimes patients present clinical relapses and fatal complications. Although, some patients in this group

remain symptomatic despite adequate therapy. High concentrations of anti-AChR or anti-MuSK antibodies through radioimmunoassay, cell-based assays (CBA), and Enzyme-Linked Immune Assay (ELISA) confirm MG's diagnosis. When patients presenting muscle weakness and AChR or MuSK antibodies are not confirmed by the before-mentioned investigations, they could be grouped as "seronegative", and the final diagnosis should be confirmed through Electromyography (EMG), Nerves Conduction Velocity test (NCV) and Single Fibre Electromyography (SFEMG) abnormalities [1].

Polymyositis (PM), Dermatomyositis (DM), immune-mediated necrotizing myopathy and inclusion body myositis are included in the classification of idiopathic Inflammatory Myositis (IIM). Unfortunately, the target autoantigens have not been found yet, but the evidence of inflammatory infiltration and autoantibodies in the muscle's biopsy suggests that IIM, without a doubt, is an autoimmune condition [2]. The criteria of Peter/Bohan are still used to support the final diagnosis, which includes bilateral symmetric proximal muscle weakness of the limbs, elevated serum muscle enzymes, myopathic changes in Electromyography (EMG), characteristic muscle biopsy abnormalities, and typical rash in patients

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with dermatomyositis [3]. The currently accepted incidence of PM/DM is around 1.2-19 per million persons at risk per year, and the prevalence is 5-22/100000 people. The female-to-male incidence ratio is 2 to 3:1. The initial measuring muscle enzyme includes aspartate aminotransferase, Lactate Dehydrogenase (LDH), Creatine Phosphokinase (CPK), alanine aminotransferase, aldolase, inflammatory markers (ESR, CRP), muscle imaging, electrophysiologic examination, muscle biopsy and autoantibodies like (1) Myositis-Specific Antibodies (MSA) and (2) Myositis-Associated Antibodies (MAA). The first one includes dermatitis-associated antibodies and antisynthetase (target the cytoplasmic aminoacyl-tRNA synthetase enzymes), anti-Jo-1 (the most detected antisynthetase antibody), and anti-TIF, anti-Mi-2, anti-SAE, anti-MDA5, and anti-NXP (DM-associated Ab). The MAA included anti-La, anti-Ku, anti-PM SCL, anti-Ro, and anti-U1RNP (less specific). EMG assesses muscle inflammation showing polyphasic potential, short duration, low amplitude, increased membrane irritability, spontaneous fibrillation and early recruitment. The MRI using short tau inversion recovery sequence can document focal inflammation (bright signals and a T1 sequence) and serves to identify muscle atrophy and scarring and select the best place for muscle biopsy. A chest x-ray will detect lung involvement in cases presenting an interstitial lung disease. If patients with DM have positive anti-NXP2 or anti-TIF one antibody (high risk of cancer), then PET/CT scans should be performed [2].

The comorbidity of MG/PM/DM was studied many years ago. In 1975 some authors compared the lymphocyte proliferative response induced by muscle extract, phytohaemagglutinin, and pokeweed mitogen in peripheral blood of MG/PM/DM and concluded that cell-mediated immunity to muscle or lymphocyte impairment response to mitogen does not occur in those patients [4]. One year later, the same authors found an increased level of Ig in those cases reported in 1976 [5]. Since 1997 the skeletal muscle involvement seen in HIV patients has been classified into different groups as follows: zidovudine myopathy (reversible mitochondrial myopathy), HIV-wasting syndrome and other AIDS-associated cachexia, HIV-associated myopathy (PM), tumour infiltrations of the skeletal muscle and opportunistic infections, HIV-associated myasthenia gravis, iron pigment deposits and vasculitis, acquired nemaline myopathy, and rhabdomyolysis and the author established that histochemical reaction for cytochrome oxidase and major histocompatibility complex class I antigen serves to make the correct classification [6]. In 2015, Nacu et al. documented that patients presenting one Autoimmune Disorder (AD) have a higher risk of developing another one, and MG patients have an elevated risk of being affected by other AD compared to the non-MG population. In myasthenic patients, an additional associated AD frequency is 13–22%, highest in young females at the Early Onset MG (EOMG). Ten percent of the AD-associated MG is represented by Autoimmune Thyroid Disease (ATD) [7].

Fang and collaborators calculated the Odds ratios and their 95% confidence intervals for the association between MG and other autoimmune diseases in their series. MG shares risk factors with other autoimmune diseases (Rheumatoid arthritis, PM/DM, systemic lupus erythematosus and Addison's disease) regulated by the HLA-B8-DR3 haplotype [8]. Recently, other authors made a retrospective cross-sectional study on a large Chinese cohort (1,132 naïve patients) showed that autoimmune thyroid disease like hyperthyroidism (8.5-fold increase, $p < 0.001$), is the most common autoimmune disease (AD) associated with MG, followed by systemic lupus erythematosus (SLE), rheumatoid arthritis (RA: 1.4-fold increase, $p < 0.001$), autoimmune haemolytic anaemia (7.4-fold increase, $p < 0.001$), immune thrombocytopenic purpura, and PM (11.5-fold increase, $p < 0.001$) among others like Sjögren's syndrome, psoriasis, Hashimoto's thyroiditis, vitiligo, neuromyelitis optica spectrum disorder, autoimmune hepatitis all presenting a mild clinical expression, low proportion of MuSK-positive mainly seen in young females at the onset of clinical features of MG [9].

As we will comment later, all immune checkpoint inhibitor-induced myopathy can present various clinical manifestations of NMJ disorders, including myasthenic emergencies (crisis), myocarditis, PM, DM, and rhabdomyolysis, as has been reported before [10-13]. Nonetheless, it has been well documented that immunotherapy with Programmed Death 1 (PD-1) inhibitor, like siltuximab, shows promising results in patients with a metastatic tumour. However, immune-

related Adverse Events (irAEs) can be characterized by an increased prevalence of myositis/MG and myocarditis with increased levels of cardiac troponin I, Myoglobin (MYO), and Creatine Kinase (CK). However, the routine test for MG and myositis-specific and myositis-related antibodies can be harmful and cardiac MR examination-quantitative myocardial T1 mapping is also negative despite the immune-related cardiac toxicity of this agent [14]. Camrelizumab, another PD-1 inhibitor used to treat oesophageal cancer, can induce severe/fatal PM/MG. Therefore, early diagnosis and effective management of irAEs are mandatory [15]. The comorbidity of MG/PM and myocarditis with the occurrence of antistriational AB binding to cardiac and skeletal muscle proteins have been reported in humans and dogs as well [16]. Recently, some authors reported an elderly male patient affected by urothelial cancer receiving pembrolizumab (PZ-monoclonal antibody) to target PD-1 who developed PM, MG, thyroiditis, and myocarditis. The authors concluded it as an adverse event of PZ, considered an Immune Checkpoint Inhibitor (ICI). PD-1 is expressed on activated T cells that commonly link to PDL-1, hugely highly expressed by malignant cells to evade the immune system. Pembrolizumab blocks the PD-1 receptor activating the immune system against tumoral cells. The immune checkpoint inhibition PD-1/PDL-1 enhances cytotoxic T lymphocyte activity against cancer by upregulation, changing the outcome of metastatic diseases [17]. Uchio et al. provided evidence that idiopathic Inflammatory Myopathy (IM) associated with MG is usually associated with thymoma and PM pathology and shares clinicopathologic characteristics with IM induced by ICIs. The rare comorbidity of IM and MG in cases with immune-related adverse events induced by ICIs targeting PD-1 or Cytotoxic T-Lymphocyte-Associated protein 4 (CTLA-4) has been reported either. Rhabdomyolysis-like features with high serum CK levels were also reported [18]. The main aims of this study are to review all studies published on the comorbidity of MG/PM/DM/HIV/AIDS to answer the following research question: What are the clinical features and therapeutic results with Rituximab (RTX) in this combination of the pathological process.

Materials and Methods

We searched the medical literature comprehensively, looking for published Medical Subject Heading (MeSH) terms like "comorbidity of MG"; "Association of MG/PM/DM/HIV/AIDS"; "MG and Immune disorders"; OR "Treatment of MG/PM/DM/HIV/AIDS"; OR "Management of MG/AD"; OR "Rituximab in MG/PM/DM/HIV/AIDS" OR "MG/PM/DM/HIV myopathy"; OR "MG/Myositis" OR "Neuromuscular Junction Disorders (NMJD)/PM/DM/HIV/AIDS, OR "Inflammatory Myopathy (IM)/MG/HIV/AIDS". We also searched at <https://www.clinicaltrials.gov/>, a website facility from the US National Library of Medicine for unpublished clinical trials, using the same MeSH terms as above, but applying the filters "full publication" AND "summary", published in English, Spanish, or Portuguese.

Inclusion and exclusion criteria and screening process

Publications eligible to be included in this study had to meet the following inclusion criteria:

1. Human beings involved.
2. The full article was written in English, Spanish or Portuguese.
3. The central aspects are MG, PM, DM, IM, HIV/AIDS Muscular diseases, RTX.
4. Published in the medical journal after being approved by the peer-review process.

The exclusion criteria were: (1) publication did not refer to issues numbered 3. (2) review articles, letters, medical hypotheses, newspaper publications or manuscripts that did not meet the criteria of an original study (3) Medical conference proceedings; (4) clinical trials with less than ten cases per treatment arm; (5) duplicate articles or manuscript written by the same author using the same data; (6) publication without corresponding authors.

All abstracts were screened twice in a blinded fashion. Those found to meet any exclusion criteria were not included in the analysis, and any discrepancy among authors was solved by close scientific discussion.

Literature search strategy

We included case reports, case series, observational cohort studies, systematic reviews and meta- analyses, cross-sectional studies, and clinical trials. During the initial search, we looked for inclusive articles published between January 1, 1975, and December 30, 2022. We searched the following databases: Science Direct, Google Scholar, Medline, Scopus online databases, Scielo, Search of Sciences, BioRxiv, medRxiv and Cochrane library. All studies were retrieved by utilizing MeSH, as before cited. We did not include other aspects beyond the current work scope.

Study and cohort selection

We select prospective and retrospective cohort studies, case reports, case series, case-control studies, controlled clinical trials, reviews, and meta-analysis reporting data on listed topics.

Data collection process

The relevant information was extracted from each publication using Microsoft Excel in a structured coding scheme. The data collected included the Neuromuscular Junction Disorder (NMJD), clinical features, population size, age distribution, the means used to diagnose NCC, MRI studies for MLS or GS, and Immunological investigations where applicable. In any case, when there was uncertainty regarding the interpretation of the data obtained or how it could be used, the authors discussed the situation in question until they reached a unanimous consensus.

Data synthesis

Our investigation used aggregate data where possible, following the PRISMA guidelines.

Quality assessment of included studies

All studies were initially screened for bias using the Jadad scoring system, mainly for clinical trials [19]. Trials with a Jadad score <4 were removed, while investigations with a Jadad score ≥ 4 were selected for further assessment.

Results

Study selection

This study aims to update the scientific information released about these issues. A total of 2757 manuscripts were retrieved from electronic databases up to December 30, 2022. After removing irrelevancy and duplicates, 174 manuscripts were taken for full-text screening, and, finally, 06 publications delivering outcomes of interest were included for review. All selected manuscripts were peer-reviewed, and no one included MG/NMJD/ PM/DM/HIV/AIDS treated with RTX. A PRISMA flow chart for the literature searched is shown in below Figure 1.

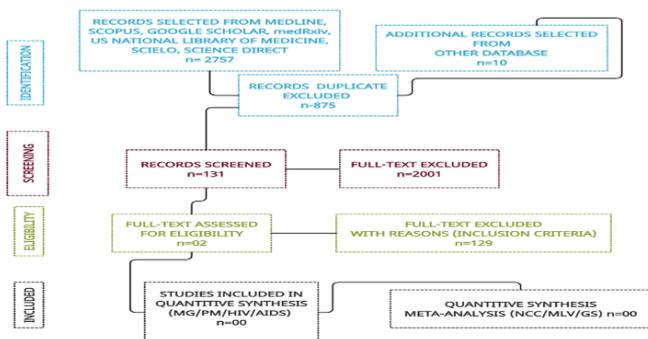


Figure 1. PRISMA Flow diagram of selected manuscripts.

Case report

A 24-years-old female.

Background: RVD positive TFE since 2016: VL – LDL, CD4 – 495

(08/09/2021).

Presentation at level 1 hospital:

- C/o generalised body weakness: 3/12 duration.
- Proximal > distal
- Symmetrical distribution.

History of complaint:

- Had progressively worsened, now couldn't talk for long periods of time, but no difficulty in swallowing
- Lifting the head off the bed was difficult.
- Couldn't turn in bed
- Symptoms were worse during the day and better as the day progresses.
- All the symptoms had reached a plateau, no more worsening now.
- No bladder/bowel involvement
- Complaining of difficulty in climbing stairs, getting up from a sitting position, lifting heavy objects, and overhead abduction of the arm.
- No preceding infections: fever/SOB/cough/diarrhoea/vomiting
- Nil previous history of COVID/COVID vaccination.

Brief medical history and physical examination findings from this patient can be seen in Table 1-5.

Table 1. Summary of the past medical history and others.

Past medical history	
•	HIV positive no TFE since 2016: VL - LDL, CD4 - 495
•	No previous treatment with penicillamine, interferon (IFN)-alpha, or anti-tumour necrosis factor, (TNF) inhibitors or environment risk factors like drug abuse, Coxsackie virus infections, exaggerated ultraviolet light exposition, vitamin D deficiency, smoking, HLA DRB1 *0301 or linked DQA1 *0501
Family history	
•	None of relevance
Social history	
•	Lives with family members
•	Unemployed
•	No use of ROH, Tobacco or other illicit substances

Table 2. Finding from general examination.

General appearance	Vitals	General exam
•On skin examination: Heliotrope rash, Gottron papules, Gottron sign, Shawl sign, Mechanic's hands, Holster sign were not identified.	•BP - 104/50mmHg •HR - 82bpm •SATA - 98%	• JACCOLD - negative

Table 3. Physical examination findings.

Focused exam - CNS	
Level of consciousness	
• Awake, alert	
Higher functions	
• Oriented to time, place, person and situation (AAO 4)	
• MMSE 30/30	

Meningism
• Nil signs suggestive of Meningism
Cranial Nerves
• CN VI palsy B/L • Nystagmus

Table 4. Findings from motor system examination.

Motor Exam					
		RUL	LUL	RLL	LLL
Inspection		Bedridden Patient			
Power	Proximal	2	2	4	4
	Distal	3	3	5	5
Tone		Hypotonia		Hypotonia	
Reflexes		Areflexia		Areflexia	

Table 5. Blood test results.

Sensory Exam	
Modality	Distribution
Pain/Temp	Globally intact
Crude touch	Globally intact
Pinprick	Globally intact
Vibration	Globally intact
Proprioception	Globally intact
Light touch	Globally intact
Coordination and Gait	
Difficult to assess on account of weakness	

The laboratory blood test results can be seen in Table 6-9, which include the highest levels of CK, ESR, CRP, and antibodies, among other investigations.

Table 6. Blood test results.

Blood Results					
Parameter	Value	Comment	Parameter	Value	Comment
Na	143	Normal	Total Protein	71	Normal
K	4	Normal	Albumin	42	Normal
Cl	105	Normal	ALT	42	High
HCO3	19	Normal	AST	78	High
Urea	4	Normal	ALP	53	Normal
Creatinine	27	Normal	GGT	14	Normal
HbA1c	5.50%	Normal	Vit B12	471	Normal
Ca	2.27	Normal	Serum Folate	30.8	Normal
Mg	0.88	Normal	WCC	6.6	Normal
PO4	1.29	Normal	Hb	12.9	Normal
Uric acid	0.29	Normal	Platelet	328	Normal
CK	120928	High	ESR	20	Normal

Table 7. Blood test results.

Blood Results					
Parameter	Value	Comment	Parameter	Value	Comment
CD4	883	Normal	NCC ELISA	Negative	

HIVVL	LTD	Normal	TOXO	IgG Negative
TSH	2.14	Normal		IgM Negative
T4	14.2	Normal	HBSAG	Negative
Amylase	68	Normal	CLAT	Negative

Table 8. Blood test results.

Blood Tests	
Parameter	Value
Rheumatoid factor	Negative
Anti-nuclear Antibodies (IFA)	Positive
Anti-nuclear Antibodies screen (CTD)	Positive
Anti-double stranded DNA antibody (FEIA)	Negative
Anti-SS-A (Ro) antibody (FEIA)	Negative
Anti-SS-B (La) antibody (FEIA)	Negative
Anti-U1RNP antibody (FEIA):	Negative
Anti-Sm (deamidated) antibody (FEIA):	Negative
Anti-Ribosomal P antibody (FEIA):	Negative
Anti-cyclic citrullinated peptide (CCP) antibody (FEIA)	Negative
Acetylcholine receptor antibody	Positive

Table 9. Blood test results.

Blood Tests	
Parameter	Value
Anti-Jo-1 antibody	Negative
Anti-Scleroderma-70 antibody	Negative
Anti-Mi-2 antibody	Positive
Anti-smooth muscle antibody (FEIA)	Negative

The CSF results are summarized in Table 10.

Table 10. Blood test results.

CSF Analysis		
Parameter	Value	Comment
CSF Glucose	3.2 mmol/L	Normal
CSF Protein	0.37 g/l	Normal
Appearance	Clear Colourless Absent	Normal
Cell count	Polymorphs – 0 Lymphocytes – 0 Erythrocytes – 0	Normal
PCR	Mycobacterium tuberculosis complex NOT detected	Not detected
Bacterial culture	No growth after 2 days	
Cysticercosis ELISA	Negative	

The nerve conduction velocity tests were standard. The needle EMG shows polyphasic potential, short duration, low amplitude, increased membrane irritability, spontaneous fibrillations, and early recruitment, and

the repetitive nerve stimulation showed the classic MG pattern. The muscle biopsy showed several sections of transverse and horizontal sections of skeletal muscle tissue and surrounding fibro fatty connective tissue. A moderate endomysial lymphocytic inflammatory reaction and secondary degenerate skeletal muscle fibres are identified. Mild perifascicular atrophy is also noted. A moderate variation in fibre size and shape is evident. A mild perivascular mature lymphocytic inflammatory reaction is also identified.

No increased internalized muscle nuclei or rimmed vacuoles are identified. No dystrophic changes, vasculitis, or necrotic muscle fibres were noted, while granulomas were evident. No congophilic material is identified. See Figure 2.

Histochemical and immunohistochemical profile (with appropriate controls):

- PAS: this stain highlights the muscle glycogen
- Masson trichrome: fibrosis is noted adjacent to the degenerate fibers
- Reticulin: a normal staining profile is noted in the residual muscle
- CD3: A prominent CD3-positive T-lymphocytic component is evident and exhibits a predominant endomysial distribution and a minor perivascular distribution.
- CD20: Muscle inflammatory reaction does not exhibit CD20 positive B-cell component.

- CD4 and CD8: The T-lymphocytic inflammatory response consists of both CD4 and CD8 positive T- lymphocytes with the CD4 lymphocytic component predominating. Presented in Figures 3 and 4

The overall features are in keeping with an inflammatory myopathy with perifascicular atrophy and remarkably CD-4 predominant T-lymphocyte inflammatory response. A second pathologist's opinion highlighted: *variation in fibre size and shape; *random degenerate and regenerate muscle fibres including areas of perifascicular atrophy; *perivascular, perimysial and endomysial mature lymphocytic inflammatory reaction; *the endomysial inflammatory reaction associated with degenerate fibres (predominantly) as well as with non-degenerate muscle fibres. *no vasculitis, inclusion bodies/rimmed vacuoles or dystrophic changes are noted; *the CD3 and CD20 stains demonstrate a predominant T cell lymphocytic response; *both CD4 and CD8 positive T lymphocytes are noted with CD4 positive lymphocytes predominating. The overall features are in keeping with an inflammatory myositis (*Polymyositis and *HIV-associated inflammatory myopathy)

The clinical neurophysiological tests (EMG/nerves conduction velocity tests) showed T2-weighted Magnetic Resonance Imaging (MRI) confirmed multifocal high-signal-intensities in the psoas bilaterally and paraspinal muscles. Apart from the HIV treatment, our patient received RTX IV weekly, and remarkable clinical improvement was noted. Other medications used can be seen in Figure 5.

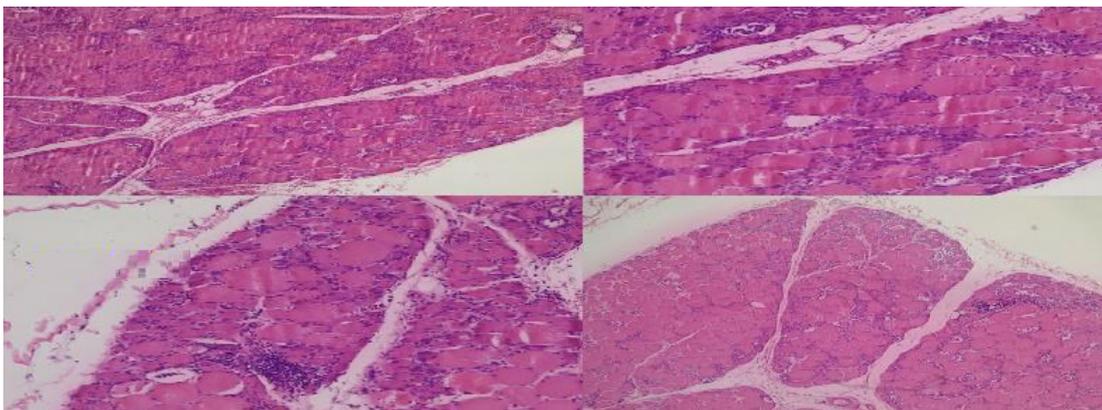


Figure 2. Hematoxylin-eosin staining showing a remarkable presence of numerous endomysial inflammatory cells, which lead to myofiber degeneration, myophagocytosis, and atrophy. A higher power image (20x) confirmed a numerous internalized nuclei which involve the majority of myofibers, and one myofiber with an intramyofibrillar vacuole. The inflammatory cells are predominately composed of CD3 and CD8 positive T-lymphocytes and CD68 positive macrophages.

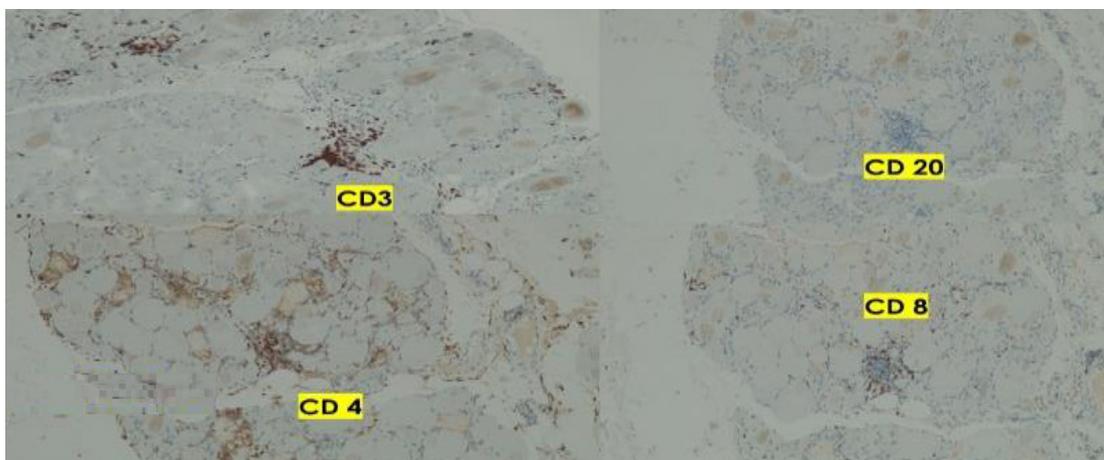


Figure 3. Muscle biopsy: Immunohistochemical staining for CD8 showing CD8-positive cells invading non-necrotic muscle fibers with antibodies against inflammatory cells, such as T and B lymphocytes (CD4, CD8 and CD20), macrophages (CD68), major histocompatibility complex (MHC) class I antigen and membrane attack complexes (MACs). immunohistochemical staining for CD20 showing perimysial aggregation of CD20-positive cells are seen.

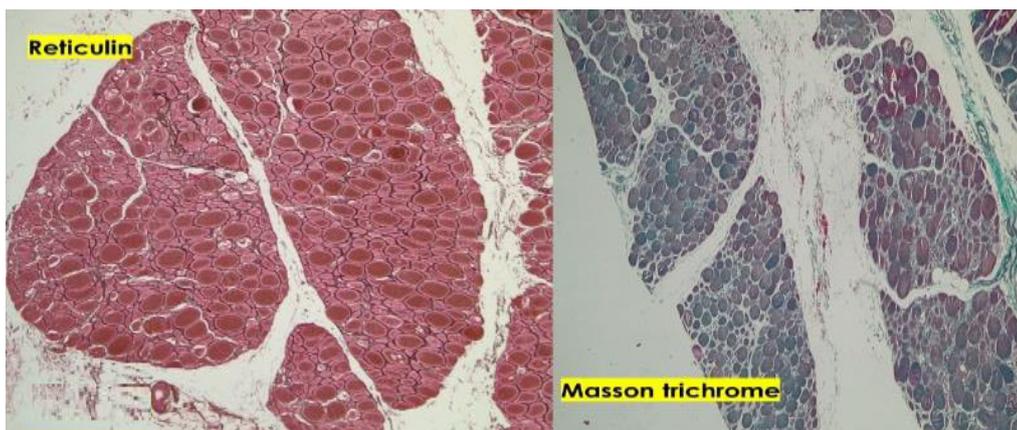


Figure 4. Muscle biopsy: Reticulin and Masson Trichromic.

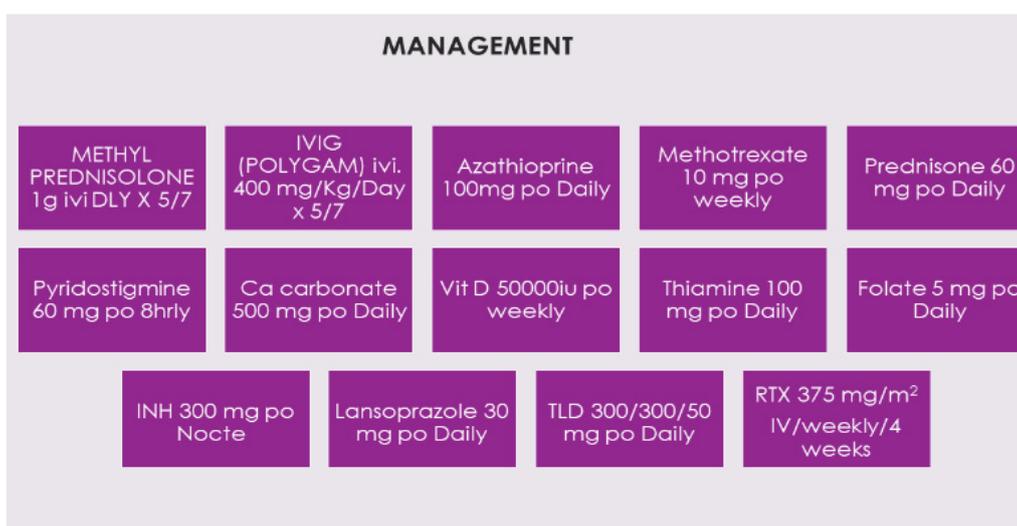


Figure 5. Treatment used for this patient.

Discussion

After completing our systematic review and removing duplicates, manuscripts with no inclusion criteria and other parameters, we did not find any publication regarding MG/PM/DM/HIV/AIDS/RTX therapy. Clinical manifestations, laboratory results, neurophysiological investigations, muscle biopsy, and response to treatment confirmed the final diagnosis. The more recent proposal for the pathogenic mechanisms of PM/DM was released by Cheeti and colleagues [2], narrowing related to inflammatory cell infiltration direct effect including CD4+ and CD8+ T cells, macrophages, B cells, and dendritic cells. In addition, the indirect effects of interleukins, interferons, and TNF plays a crucial role in this process. This mechanism also included the presence of autoantibodies, complement, and IgG, as shown in the muscle biopsy. On top of that, the microvasculature involvement leading to significant thickening of the endothelial cells has been described in patients with myositis as our patient with relevant inflammatory cell infiltration in the muscle. In Figure 6, we represent B Lymphocytes (BL), better known as B cells (type of blood cell) and one component of the adaptive immune system, which is the capacity to produce antibodies molecules which are inserted/secreted into the plasma membrane working as B-Cell Receptors (BCRs). This figure shows a memory cell (naïve cell) activated by an antigen replicating into a plasmablast/plasma cell (antibody-secreting effector cell). These B lymphocytes present antigens classified as Antigen- Presenting Cells (APCs), which secretes cytokine. Among pro-inflammatory cytokines expression, we will comment on IL-6. One crucial difference between B cells and other lymphocytes (T cells and natural killer cells) is the presence of

BCRs at the cellular membrane. These BCRs allow the B lymphocytes to bind to an antigen by initiating an antibody response (Figure 6).

Histopathology

In DM, the hallmark pathologic feature is the presence of muscle fibre atrophy in a perifascicular fashion. Nevertheless, the absence of dermatological manifestation is crucial for the differential diagnosis. We managed DM cases with poor muscular involvement and even with associated ophthalmoplegias, which is relatively uncommon. As we report here, the presence of mononuclear cell infiltration/degeneration/regeneration of muscle fibres is a histopathologic feature of this condition.

Immunopathology

The muscle biopsy of our patient confirmed a marked endomysial inflammatory infiltration with abundant CD8+T cells, CD4+T cells, dendritic cells, and macrophages. In patients with PM, normal- appearing muscle fibres and increased expression of MHC class I and II molecules on regenerating fibres can be observed in cases of myositis. However, the mechanism by which the MHC expression in muscle is induced has not been reported. The MHC Class I antigen expression is more commonly observed than MHC class II. Endomysial infiltration of T-lymphocytes (lymphorrhagia) in muscle biopsy of patients with MG has been documented for many years back, mainly in thymomatous MG cases, and we have hypothesized this finding can be present in myopathies HIV/AIDS-related and associated immunologic disorders as can be seen in Table 11.

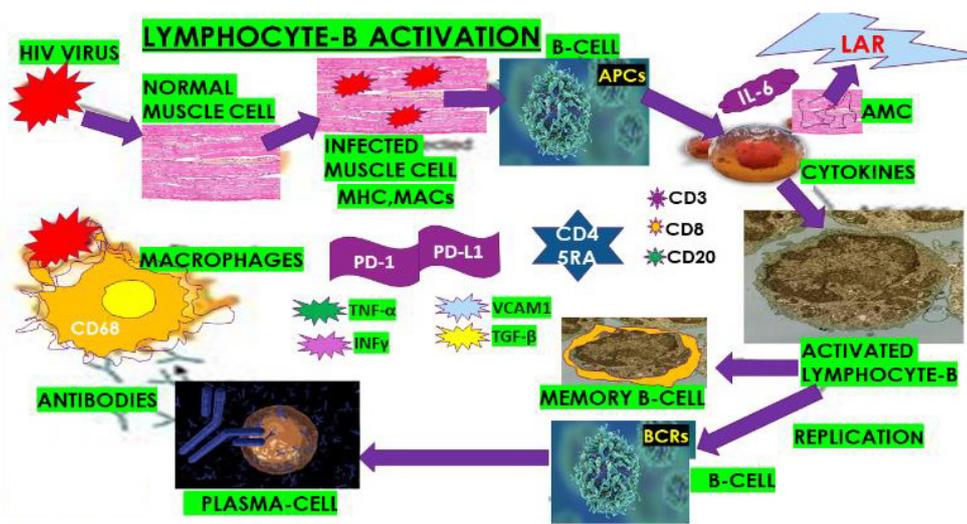


Figure 6. Shows B lymphocytes activation scheme. PD-1: endomysial programmed positive cell death–1, PD-L1: programmed cell death ligand 1, BCRs: B cell receptors, CDC: complement- Dependent Cytolysis, ADCC: antibody-dependent cell-mediated cytotoxicity of circulating lymphocytes, APC: antigen-presenting cell, TGF-β: transforming growth factor beta, VCAM1: vascular cell adhesion molecule 1, INFγ interferon gamma, TNF-α: and tumour necrosis factor-alpha, AMC: antigen muscle cell, LAR: leading to autoimmune response..

Table 11. List of myositis-specific antibodies associated to IIM.

Myositis-specific autoantibodies	Isolation is a key risk factor for shared psychosis
Myositis-specific autoantibodies are associated with clinical syndromes within the IIM spectrum.	Antisynthetase antibodies
	Anti-SRP antibody
	Anti-Mi-2 antibody
	Anti-MDA5 antibody
	Anti-NXP-2 antibody
	Anti-TIF-1 gamma antibody
	Anti-SAE antibody
	Anti-HMGCR antibody

Interleukin 6

The mechanism of elevated expression of IL-6 was explained recently by one of us [1]. This pro-inflammatory interleukin is a highly pleiotropic glycoprotein element which modulates adaptative-innate immunity and many functions of the metabolism like fatty acid oxidation, oxidative phosphorylation, glycolysis, and it is actively involved in maintaining body homeostasis and inflammatory response to viral infection-associated diseases, including HIV immunosuppression. HIV counteracts the host restriction factors express protein Vpr, which degrades TET2, a member of the Ten-Eleven Translocation (TET) family as α-ketoglutarate- and Fe2+-dependent dioxygenase catalysing the iterative oxidation of 5-Methylcytosine (5mC). TET2 keep the IL-6 expression favouring viral replication and progression to AIDS supported by advanced age, hypolipidemia, HIV replication, low levels of CD4+ count, epidermal growth factor receptor, non-black peoples, and elevated BMI because around 25% of circulating IL-6 is produced by subcutaneous adipose tissue active macrophages, active immune cells make the rest. Moreover, the HIV-1 Tat (auxiliary viral protein) can damage tight junctions at the micro endothelial cells in the BBB [20]. Based on this information, we have hypothesized that detecting the IL-6 level can be helpful in the management of MG/PM/ HIV-AIDS cases.

Treatment/Management

Corticosteroid drugs are the initial medication and cornerstone in managing both PM and MG. The usual practice starts with prednisone 1 to 2 mg/kg/day and later will be reduced gradually. In some patients with

poor response, we use methylprednisolone 1 gr/IV/daily for 3-7 consecutive days. Unfortunately, we have no guidelines for the initial dosing or tapering of steroids; therefore, we do it based on our clinical judgment. A health education program for patients and families should be implemented to take additional measures if steroid-related adverse effects happen, mainly steroid- induced myopathy, osteoporosis, weight gain, arterial hypertension, and hyperglycaemia. In PM cases with normal Thiopurine Methyltransferase (TPMT) activity with adverse effects to steroids, methotrexate and azathioprine can be prescribed, although MG patients add to the steroids. However, in HIV/AIDS patients, extreme precautions should be taken. If the patient presents a rapidly progressive interstitial lung disease, then Cyclophosphamide (CPP) may be a better choice. Nevertheless, we decided to use this one based on our previous experience using RTX in refractory MG patients [1].

Rituximab

Rituximab was funded by the New Drug Funding Program (NDFP) in Ontario, Canada, on January 2, 2001, as a first-line treatment for patients with aggressive-histology lymphoma and HIV-negative condition [21]. This medicine is an anti-CD 20 monoclonal antibody highly recommended for managing MG cases even in crisis (if eculizumab is not available). RTX is even practical to manage cases with myositis and myositis-related interstitial lung disease. Many investigators prefer it over CPP because of its tolerability and fewer adverse effects. Currently, other drugs like anti-TNF agents, etanercept, infliximab, alemtuzumab (anti-CD-52), tocilizumab (anti-IL-6 antibody), tofacitinib, anakinra (anti-IL one antibody), and ruxolitinib (JAK-

inhibitors). However, there is no unanimous concern about the benefits of the previously cited drugs, and most authors recommended their use only in resistant patients [2]. Last year, we conducted a systematic review on RTX and MG, which confirmed the remarkable improvement of clinical features of MG, providing a better quality of life in patients presenting AChR-MG and MuSK-MG with no severe complications during the treatment. However, the incidence/prevalence of mortality has not been reported, and results from post-mortem examinations were not published. Apart from the clinical benefits obtained with RTX, a substantial number of patients were able to reduce doses and frequency of associated immunomodulatory agents. On top of that, we delivered a proposal for the mechanism of action of RTX in these patients supported by the roles played by lymphocytes B, macrophages, eosinophils and nerves, elaborating Complement-Dependent Cytolysis (CDC), Antibody-Dependent Cell-mediated Cytolysis (ADCC) of circulating lymphocytes, Antigen-Presenting Cell (APC), Transforming Growth Factor beta (TGF- β), Vascular Cell Adhesion Molecule 1 (VCAM1), Interferon-gamma (INF γ), and Tumour Necrosis factor- alpha (TNG- α). Here, we include the before-cited components in the pathogenesis of the comorbidity of MG/PM/HIV-AIDS, as represented in figure 6. Other HIV-related conditions have been treated with RTX with Imagenology investigations done in cases with HIV. RTX-associated PML patients confirmed mild contrast enhancement, with punctuate appearance at the cortical level without remarkable improvement on treatment [22]. However, in five patients with HIV histologic-proven Castleman disease after receiving four infusions of RTX, three remained free remission of Castleman disease with a follow-up of 4 to 14 months. These preliminary results suggest that RTX may effectively control Castleman disease, although it may exacerbate concomitant Kaposi sarcoma [23]. Other authors reported the first prospective evidence that HAART and RTX plus HD-MTX lead to a high response rate, long-term survival, CD4+ lymphocyte reconstitution, and preserve or improve neurocognitive function [24]. Although, Gaillard and collaborators documented that RTX can increase the replication of hepatitis B virus and cytomegalovirus while keeping an undetectable viral load in a patient treated with RTX without antiretroviral therapy in 2011. Apart from this patient, no other cases have been reported [25]. Confident results from large clinical trials are necessary to support the use of RTX as the therapy of choice for patients with MG/PM/HIV-AIDS; however, because there is no RTX contraindication, we recommend being prescribed in cases of MG/PM/HIV-AIDS.

HIV-Muscular disorders can be secondary to antiretroviral therapy (mitochondrial toxicities), HIV myositis itself, and infectious, neoplastic, metabolic, or autoimmune processes, among other causes. HIV-associated polymyositis is the most common muscular disease associated with HIV infection, although its prevalence remains unknown. HIV-PM is clinically and pathologically quite like the autoimmune PM in HIV-negative patients. The histopathologic studies, prove that HIV-associated inflammatory myopathy predominantly comprised of CD8+ T cells and macrophages. In 15 patients with HIV-PM, histologic features were identical to those seen in polymyositis in non-HIV-affected individuals. HIV-PM diagnosis is based on the criteria of 2017 European League Against Rheumatism and the American College of Rheumatology for PM, based on the absence of skin manifestations and the presence of muscle weakness in lower limbs and findings on muscle biopsy [26]. Some authors have hypothesized that inflammatory cell-derived cytokines or lymphokines lead to muscle fibre damage, which precipitate muscle antigen exposure and a process where muscle fibres act as antigen-presenting cells, triggering an autoimmune response [27]. We include this hypothesis in our speculative proposal on the mechanism of immunological reaction in patients presenting MG/PM/HIV-AIDS, which is represented in figure 6. Nevertheless, the severity of inflammatory infiltrate is not correlated with a patient's symptoms or stage of HIV infection. Our reported case highlights the broad differential diagnosis of muscular diseases in HIV/AIDS patients and the need for an extensive workup, including a muscle biopsy, to reach a confident diagnosis. A novel challenge for young rheumatologists and neurologists is the successful management of patients presenting idiopathic Inflammatory Myopathies (IIM), a treatable and heterogeneous group of muscular diseases. Patients usually complain of acute or subacute

onset of proximal weakness in all limbs, sometimes accompanied by extramuscular manifestations apart from the involvement of the skin, lungs, and joints. The diagnosis is based on increased CK level, electrophysiological abnormalities, and inflammatory infiltrates in the muscle biopsy. Identifying autoantibodies is relevant because they are present in most patients [28]. The list of myositis-specific autoantibodies associated with clinical syndromes within the IIM spectrum is listed in table 11.

Around ten years ago, only PM, DM, and inclusion body myopathy were included in this group. However, immune-mediated necrotizing myopathy now overlaps myositis, and the antisynthetase syndrome is accepted as the most common presentation type of IIM in daily practice [28]. Therefore, identifying autoantibodies is crucial to provide a safe diagnosis, proper therapy, and a better outcome to these patients; being a tremendous challenge for neurologists to stay updated on the fast advances of this knowledge to offer the best management of this treatable condition.

The role of the Endoplasmic Reticulum (ER) in the maintenance of homeostasis regulating proteins and the relationship between non-immunological, immunological, and infectious processes for the activation of ER stress and autoimmunity have been documented by Corona-Sanchez and colleagues based on shreds of evidence on the participation of inflammatory cytokines, chemokines, viral processes, auto-antibodies, and involvement of MHC-I, in the activation of ER stress and the consequences on auto-antibody production in IIM [29].

MG/PM/HIV-AIDS

Unfortunately, around 38 million people were living with HIV by the end of 2019 (<http://www.unaids.org>) (most in South Africa), and there is no available routine curative treatment to date. However, anti-HIV inhibitors like reverse transcriptase inhibitors, integrase inhibitors, protease inhibitors, and entry inhibitors are in use to control HIV replication effectively. Today it is well known that the HIV reservoir defined as resting CD4+ cells that harbour replication-competent HIV is the major impediment to HIV eradication because it is not sensitive to combined antiretroviral therapy (cART) and remains quiescent in memory CD4+ cells for a long time and is also the primary cause for HIV rebound after cART treatment interruption. Patients who received bone marrow transplantation from a donor with CCR5-tropic-HIV-resistant homozygous CCR5 Δ 32 mutation is the only case acknowledged HIV cure case all over the world but "transient CD4-cell-depletion therapy (TCDT)" to eradicate HIV reservoir is currently in use after injection of specific anti-human CD4 monoclonal antibody which deplete all CD4+ cells, including CD4+ T cells, CD4+ macrophages, and CD4+ dendritic cells [30].

We have speculated on the high frequency of comorbidity of HIV/AIDS, neurozoonotic diseases, and other immunosuppressive disorders in South Africa and the establishment of ideal conditions for virus mutation/replication and the presence of immunological conditions which might facilitate the surge of the B.1.1.529 variant of SARS-CoV-2 on November 24, 2021, being this country the global epicentre of COVID-19 outbreak twice [31]. In patients with MG, endomyxial infiltration of T-lymphocytes (lymphorrhage) in the striate muscle tissue has been reported, particularly in patients with thymomatous MG when that infiltration consists of CD8+CD45RA+naive T-cell derived from lymphocyte-rich thymoma [32-34]. In our case, all types of mediastinum mass were ruled out mainly by imagenology, and lymphorrhage can be due to the underlying HIV infection.

Conclusion

Another atypical finding in our case was the massive collection of CD20+ B-cell and CD68+ granulomas. This pathologic pattern might be found in IIM and associated thymoma because the thymus provides several immunologic functions, including autoimmune dysregulation. As far as we know, PD-1+ cell infiltration and PD-L1 overexpression in cases with HIV-muscular diseases were not reported to date. Therefore, in patients complaining of similar clinical manifestation is recommended to check PD-1,

PD-L1 monoclonal antibodies and endomysial infiltration of CTLA-4+ cells despite the absence of mediastinal mass. We have hypothesized that the over-expression of PD-1, PD-L1, and CTLA-4 in MG/PM/HIV cases is due to an essential dysregulation of immune checkpoint molecules. Without a doubt, the genetic characteristic of CTLA-4 is close related to thymomatous MG cases, as has been communicated by other authors. Unfortunately, we do not have the research capacity to confirm our speculation because we do not have the necessary data to perform a cross-sectional study. Further well-designed investigations to elucidate the overall immune mechanisms that cause these complicated pathologic features.

Declaration

Consent for Publication

Written informed consent from our patient was obtained for publication, including accompanying diagnostic results. Any interested reader can obtain it by request.

Ethical approval

The WSU/NMAH Institutional Ethical Committee did not consider this report for additional ethical approval.

Competing interest

The authors declare that they performed this study without any commercial, financial, or otherwise relationships able to construe a potential conflict of interest.

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Author's contributions

Study concept and design: HFS and LFIV. Data collection from searched literature: LdeFIV and HFS. Analysis of the obtained data: LdeFIV/HFS. Drafting of the manuscript: LFIV, HFS. Revising the manuscript: HFS and LFIV. Supervised research and manuscript writing process: HFS and LFIV. Both authors have approved this version for publication.

Declaration of anonymity

Both authors certify that they did not reveal the names, initials, and other identity issues of this patient in this publication, and complete anonymity is guaranteed. Availability of data and material: The data supporting this study's findings are available on reasonable request from the corresponding author.

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