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An odd case of immune-mediated necrotizing myopathy, complicated with sagittal, transverse and sigmoid sinus thrombosis

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Abstract: INTRODUCTION: Immune-mediated necrotizing myopathy (IMNM) is a rare variant of immune-mediated inflammatory myopathy (IMIM) that exhibits a severe prognosis and is unresponsive to conventional treatment. (1,2)Notably, the incidence of immune-mediated inflammatory myopathies (IMIMs) is low, estimated at 1.16 to 19/million/year and only 3-6% of IMIMs are diagnosed as IMNM. (1,3–5). Systemic inflammation has been found to play a crucial role in promoting the onset of cerebral venous thrombosis. (6,7)
MATERIAL AND METHODS: We present the case of a 46-years-old Chinese woman, without any known prior pathology, who was referred to the Rheumatology Department for symmetrical, proximal muscle weakness of the limbs, dysphagia for solid food, and weight loss (5 kg within 2 months). The pathologic clinical examination revealed itchy erythematous plaques on the posterior thoracolumbar region and signs of muscle weakness. Laboratory workup showed significant inflammatory syndrome, severe muscle and hepatic cytolysis syndrome, and positivity for thyroid-specific autoantibodies but with normal thyroid function, positivity for antinuclear antibodies (more precisely: SS-A, Ro-52, SS-B), and myositis antibodies (SRP, Ro-52, SAE1, PM-Scl, MDA5). The CT scan of the thoracic, abdominal, and pelvis showed fibrosis of the lungs, hepatic hypertrophy, and an enlarged uterus, further diagnosed by transvaginal ultrasound as adenomyosis. The positive diagnosis is immune-mediated necrotizing myopathy. Differential diagnoses included dermatomyositis, toxic/infectious myositis, hypothyroidism, and neuromuscular diseases (5,8). The initial treatment was made with glucocorticoids (pulse therapy followed by oral therapy) and immunosuppressants (Mycophenolate Mofetil – stopped because of severe dyspepsia and myelosuppression). After five days of pulse therapy, the patient developed muscle weakness and paresthesia on the left side of the body, and the cerebral CT scan revealed sagittal, transverse, and sigmoid sinus thrombosis. Thrombophilia screening uncovered the positivity of the lupus anticoagulant. (9)
RESULTS: The patient was treated with anticoagulants (low molecular weight heparin, and afterward Vitamin K antagonist), low doses of oral glucocorticoids, and immunosuppressant (Methotrexate), without any other adverse event.
CONCLUSION: In the presence of the lupus anticoagulant, even though the antiphospholipid syndrome is not confirmed, the only anticoagulant therapy that has proven its efficacy is the Vitamin K antagonist. Immune inflammatory myopathies, like IMNMs, create a significant inflammatory status that leads to hypercoagulability and endothelial injury, which exposes collagen and tissue factors, promoting further platelet aggregation, and can even lead to cerebral thrombosis. (2,6)

Keywords: immune-mediated inflammatory myopathy, cerebral venous thrombosis, inflamma-tion, immune-mediated necrotizing myopathy, anticoagulant therapy, physical therapy

Introduction

Acquired immune-mediated inflammatory myopathies (IMIMs) are a diverse group of muscle disorders characterized by a gradual loss of skeletal muscle strength, reduced endurance, and muscle fatigue. This disease can be caused by – but not limited to – a wide range of autoantibodies, both specific and non-specific, making it a complex condition to diagnose and treat. In cases of muscle biopsy, inflammatory infiltrates are often found. These infiltrates are mainly comprised of T cells, macrophages, dendritic cells, B cells, and plasma cells. In some myopathies, necrosis is also seen.

Their incidence is estimated at 1.16 to 19/million/year, and prevalence at 2.4 to 33.8 per 100,000 people, according to a meta-analysis of forty-six articles published between 1966 and 2013. (1,4)

Patients with IMIMs may experience other systemic manifestations, depending on where autoantibodies cause damage. Among other organ involvement, the lungs are a frequent target, and the disease can be complicated with interstitial lung disease, pulmonary hypertension, alveolar hemorrhage (with high mortality), or aspiration pneumonia. Similarly, the heart may be affected, causing myocarditis, congestive heart failure, rhythm disturbances, or complete heart block. Skin manifestations include Gottron's papules, Gottron's sign, heliotrope rash, "Shawl" sign, "Holster" sign, calcinosis, "mechanic's hands", and skin ulcers with tender palmar papules. Gastrointestinal symptoms may also occur, such as esophageal dysmotility, severe proximal dysphagia, malabsorption syndrome, and "total gut failure" secondary to an atonic bowel.

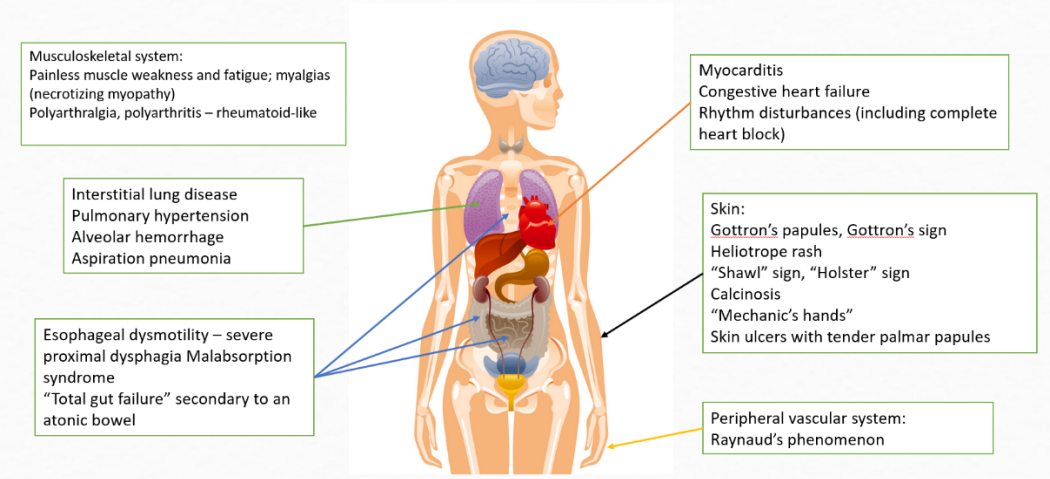


Figure 1 : Clinical features of IMIMs

Autoantibodies are essential biomarkers in identifying idiopathic inflammatory myopathies and are present in approximately 70-80% of patients with IMIMs. In addition to facilitating diagnostic procedures, they also provide crucial information on patient stratification, cancer risk, and overall prognosis. These autoantibodies are generally classified as myositis-specific autoantibodies (MSA) and myositis-associated autoantibodies (MAA).

Immune-mediated inflammatory myopathies were originally described by E. Wagner and P. Potain in the mid-1800s. (10) In 1970 – Medsger, and 1975 – Bohan and Peter – proposed the first classification and diagnostic criteria for a group of diseases. This groundbreaking work led to a more comprehensive understanding of these conditions and facilitated the development of effective treatments and therapies. Their contributions have proven

invaluable in the field of medical research. (11)The current classification criteria for IMIMs is the EULAR-ACR classification criteria: Polymyositis (PM), Dermatomyositis (DM), Immune-mediated necrotizing myopathy (IMNM), Overlap syndrome with myositis, including anti-synthetase syndrome, Inclusion body myositis (IBM). Each group has unique clinical, biological, immunological, and histopathological characteristics and responds to different treatments. (12)

Immune-mediated necrotizing myopathy (IMNM) is a distinctive type of inflammatory myopathy that is characterized by the presence of antibodies to signal recognition particle (SRP) and 3-hydroxy-3-methylglutaryl CoA reductase (HMGCR). This condition is characterized by muscle weakness, which can range from mild to severe and can affect multiple muscles in the body. The exact cause of IMNM is not fully understood, but it is believed to be an immune-mediated disorder that results from the production of autoantibodies against specific muscle proteins. The presence of these antibodies is considered to be a diagnostic hallmark of IMNM, and their detection can aid in the diagnosis and management of this condition. Understanding the underlying mechanisms of IMNM and the role of these autoantibodies in its pathogenesis may help in the development of more effective treatments for this condition.

IMNM is a type of myopathy that is considered rare, very severe, and resistant to treatment. Typically, the onset of the disease is acute or subacute (<6 months), occurs after the fourth decade of life, and predominantly affects females. Unfortunately, determining the exact prevalence and incidence of IMNM is challenging because many cases are misdiagnosed as polymyositis, and the entity itself has undergone various definition changes over the years. It is worth noting that only in 2003 was this disease separated from the other inflammatory myopathies, highlighting the complexity of diagnosing and understanding this condition. (9)

It is known that around 3-6% of all cases of inflammatory myopathies belong to anti-SRP antibody-associated necrotizing myopathy. (13)

The myopathological features of this disease are defined by diffuse necrotizing myofibers in different stages of necrosis, myophagocytosis, and regeneration, with granular complement (membrane attack complex C5b-C9) deposition around the sarcolemma. Inflammatory cells are sparse, sometimes only perivascular, composed predominantly of macrophages, and observed in severe cases. (9)

Patients with anti-SRP antibodies tend to exhibit severe symmetric proximal muscle disease, affecting the lower limbs much more than the upper ones. Muscle cytolysis syndrome is often impressive with CK levels above 10 000 U/L. (9,13)

Extra-muscular organ involvement includes predominantly the heart and lungs. Most frequently, patients have interstitial lung disease (23-38% of patients), and life-threatening myocarditis that is manifested by severe cardiac symptoms such as chest pain, palpitations, and signs of cardiac failure. (9,14–16)

A frequent comorbidity associated with IMNM is malignancy and a thorough screening should be made for all newly diagnosed cases as well as in the evolution of the disease. (9)

The disability associated with the disease in question is of a severe nature, as it tends to rapidly progress towards muscle atrophy and weakness. Patients affected by this disease face frequent challenges in their daily lives, even whilst undergoing treatment. Amongst the inflammatory myopathies, it is noteworthy that IMNM has the highest severity of muscle damage, which is known to initiate early in the course of the disease. It is worth noting that the duration of the disease, the age of onset, and the duration from the first symptoms to treatment are crucial predictors of the muscle damage burden. (9,17)

Cerebral venous thrombosis (CVT) is a type of stroke that accounts for only 0.5% to 1% of all stroke cases. One of the known risk factors for developing CVT is systemic

inflammation. When the immune system mistakenly attacks healthy cells and tissues in the body, it triggers an autoimmune-mediated inflammatory reaction. This type of reaction can cause a localized increase in blood clotting and damage to the inner lining of blood vessels, which in turn can lead to a condition known as cerebral venous thrombosis (CVT). CVT is a rare but serious condition that can occur when the veins that drain blood from the brain become blocked or narrowed, preventing normal blood flow and potentially leading to a range of neurological symptoms. CVT-induced inflammation can exacerbate brain tissue ischemic injury leading to poor clinical outcomes. Therefore, treatment strategies should target both pathological states comprehensively.

Recent research suggests that there may be a link between systemic inflammation and the onset of cerebral venous thrombosis, leading some experts to use the term "immune-thrombosis" to describe this phenomenon. This new understanding could potentially help in the development of more targeted and effective treatments for this condition.

Venous thrombus formation, regardless of the type, is primarily caused by three crucial factors known as Virchow's triad. These factors include blood flow changes, endothelial damage, and a hypercoagulable state.

Systemic autoimmune diseases are characterized by inflammatory reactions that initiate high immune system activation by engaging leukocytes, cytokines, chemokines, and adhesion molecules. The modification of the coagulation system is linked to the exacerbation of inflammation. This connection is attributed to the increase in procoagulant factors and the inhibition of natural anticoagulant pathways and fibrinolytic activity. These processes act in concert to amplify the inflammatory response and are achieved through the thrombin-induced secretion of proinflammatory cytokines and growth factors [vascular endothelial growth factor (VEGF), tumor necrosis factor-α (TNF-α), monocyte chemoattractant protein-1 (MCP-1), ICAM-1, IL-1, IL-6, and IL-8].

Endothelial damage not only compromises the natural anticoagulant, antiaggregant, and vasodilatory functions of the endothelium but also exposes collagen and tissue factors (TFs) that could lead to platelet aggregation and activate the immune system, thereby contributing to thrombus formation. (6)
Therefore, inflammation plays a critical role in the onset and development of CVT. Diagnostic and treatment strategies cannot ignore this fact.

While the link between inflammation and thrombosis is well-established and numerous studies have confirmed that thrombosis can be a potential complication of myositis, there is no other documented case of a patient with immune-mediated necrotizing myopathy and cerebral venous thrombosis in the available literature.

Material and methods:

Having the patient's consent and the approval of the Ethics Committee of "Sfânta Maria" Clinical Hospital, N.O. 6655/21.03.2022, we examine the medical history of a 46-year-old Chinese woman from a rural area who was referred to the Rheumatology Department due to symmetrical, proximal muscle weakness of the limbs, dysphagia for solid food, and weight loss (5 kilograms within 2 months). This patient did not have any known prior medical conditions. The patient experienced a sudden onset of symptoms that started two months ago and have since gradually worsened.

The patient denies smoking, and alcohol consumption and there is no significant family history of pathology. During the general clinical examination, the patient was conscious, cooperative, and afebrile but in poor general health. The patient had itchy, erythematous plaques on the posterior thoracolumbar region, as seen in Figures 1 and 2. The respiratory and cardiovascular examinations were normal; blood pressure was 110/60mmHg, heart

rate was 85 bpm, and peripheral oxygen saturation (SpO2) was 96%. There were no other pathological findings.

On the other hand, the **Neuro-Mio-Arthro-Kinetic Examination revealed:**

- Symmetrical, proximal muscle weakness quantified in Muscular force on the Medical Research Council (MRC) Scale:
  - 3/5 lower limbs proximal and intermediary bilateral, 4/5 distal bilateral
  - 3/5 upper limbs proximal and intermediary bilateral, 4/5 distal bilateral
- Weak neck extensors: 4/5 MRC at testing cervical extension
- Unable to climb or descend stairs, kneel, arise from the seated position, difficulty in hair combing, inability to overhead abduction of the arms
- Absent myalgias, no involvement of ocular muscles
- Dysphagia for solid food
- Absent spasticity
- No hypo/anesthesia, no proprioceptive or nociceptive impairments
- Preserved tendon reflexes

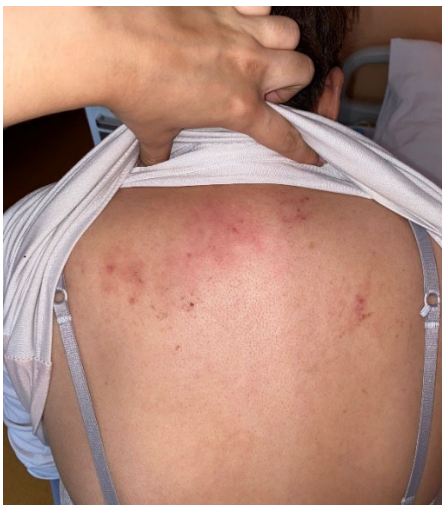


Figure 1

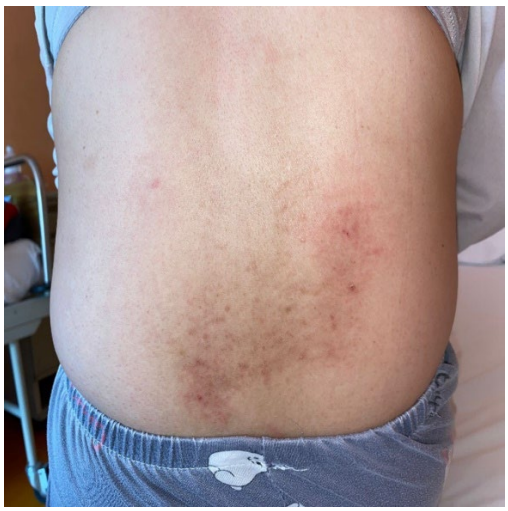


Figure 2

Considering the anamnesis and clinical examination, the clinical diagnosis is a myopathic syndrome of unknown etiology.

Here are the findings from the **laboratory tests**.

The patient has a significant inflammatory syndrome, as shown by an ESR of 61 mm/h and a C Reactive Protein level of 22 mg/L, a severe muscle and hepatic cytolysis syndrome, as indicated by a CK level of 19,200 U/L and a CK-MB level of 904.7 U/L, in addition to an ALT level of 295 U/L and an AST level of 404 U/L. The patient's LDH level is high at 1709 U/L.

Although the patient has normal thyroid function (TSH=4.21 UI/ml, FT4=1 ng/dl), they tested positive for thyroid-specific autoantibodies, including anti-thyroglobulin antibodies (379.85 UI/ml) and thyroid peroxidase antibodies (7.77 UI/ml).

The patient tested negative for viral hepatitis and HIV screening, as well as for IgM & IgG for Cytomegalovirus, Epstein Barr Virus, Toxoplasma spp., Trichinella spp., Toxocara spp, Borrelia burgdorferi.

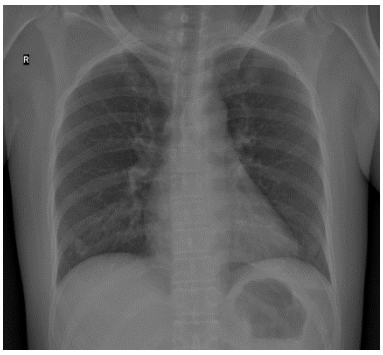
In regards to autoantibodies, the patient tested positive for antinuclear antibodies, specifically SS-A (anti–Sjögren's-syndrome-related antigen A autoantibodies) and SS-B

(anti–Sjögren's-syndrome-related antigen B autoantibodies) and for myositis-specific autoantibodies, including SRP (anti-signal recognition particle autoantibodies), Ro-52 (interferon-inducible protein of the tripartite motif family autoantibodies), SAE1 (anti-small ubiquitin-like modifier 1-activating enzyme autoantibodies) and PM-Scl (anti-Polymyositis/Systemic Sclerosis autoantibodies).

Abbreviations: ALT: alanine transaminase, AST: aspartate aminotransferase, CK: creatine kinase, CK-MB: creatine kinase-myocardial band, ESR: erythrocyte sedimentation rate, FT4: free thyroxine, HIV: Human Immunodeficiency Virus, IgG: Immunoglobulin G, IgM: Immunoglobulin M, LDH: Lactate dehydrogenase, TSH: Thyroid-Stimulating Hormone.

Given the severity of the clinical and biological markers, we conducted further investigations of the patient using the techniques available to us. These included a chest x-ray, electrocardiography (ECG), and echocardiography as standard investigations to screen for any obvious pulmonary and cardiac complications. Additionally, we performed a CT scan of the thoracic, abdominal, and pelvic regions, keeping in mind the possibility of paraneoplastic myopathic syndrome. We also conducted an Upper Gastrointestinal Series (UGI) to investigate the patient's dysphagia. Unfortunately, we could not carry out the paraclinical investigations involving electroneuromyography or muscle biopsy due to technical issues and patient refusal. We have provided detailed results of the investigations mentioned above below.

OTHER PARACLINICAL INVESTIGATIONS:



Chest x-ray revealed no acute or progressive pleuropulmonary lesions visible radiographically (Figure 3).

Figure 3: ***Chest x-ray***

The findings from the upper GI series (UGI) showcase no pathological concerns, as seen in Figures 4 and 5.

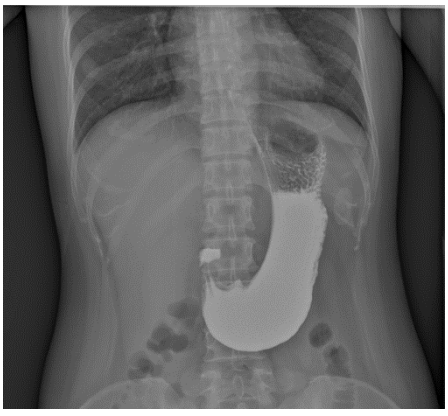


Figure 4: UGI

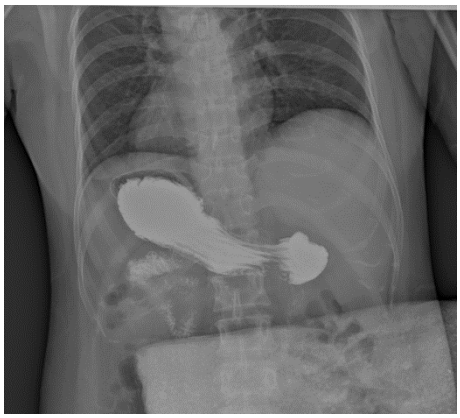


Figure 5: UGI

Furthering our examination and taking into account the possibility of a paraneoplastic myopathic syndrome, we conducted a Computer Tomography (CT) scan of the thoracic, abdominal, and pelvic regions, revealing the presence of lung fibrosis, hepatic hypertrophy, and an enlarged uterus as demonstrated in Figures 6 and 7.

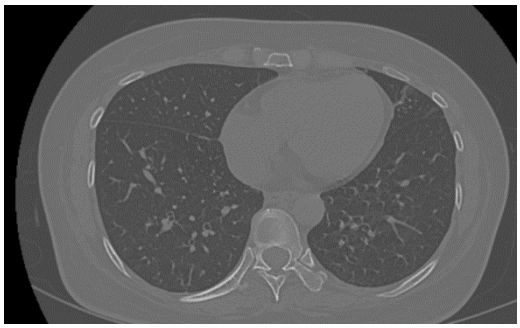


Figure 6: Lung CT scan

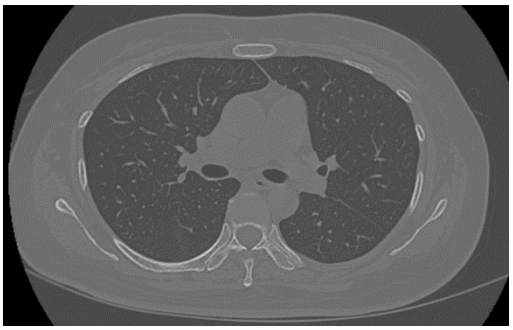


Figure 7: Lung CT scan

After reviewing the CT result, we suspected the possibility of neoplasia due to the enlarged uterus. However, upon further examination using a transvaginal ultrasound, we concluded that she was only suffering from adenomyosis of the uterus.

The ECG showed no abnormalities of electric conduction and further, the cardiac echocardiography revealed that there were no structural nor functional abnormalities in regards to the heart muscle.

Myopathic syndromes are complex disorders with over 50 different possible pathologies. In our case, we narrowed the possible causes down to five main categories:

1. **Immune-mediated Inflammatory Myopathy:** Dermatomyositis, Idiopathic Polymyositis, Immune-mediated necrotizing myopathy
2. **Endocrinologic myopathy:** Hypo/hyperthyroidism, Addison's Disease, Cushing's Disease
3. **Toxic myopathy:** most frequent in clinical practice being glucocorticoids, Hydroxychloroquine, statins, alcohol, cocaine, and Colchicine (18)
4. **Infectious myopathy:** Hepatitis B and C viruses, Cytomegalovirus, Epstein Barr virus, Toxoplasma, Trichinella, Toxocara spp., Influenza A and B, Coxsackievirus and others (19–22)
5. **Neuro-muscular diseases:** Lambert-Eaton myasthenic syndrome (LEMS); myasthenia gravis; lateral amyotrophic sclerosis, muscular dystrophy

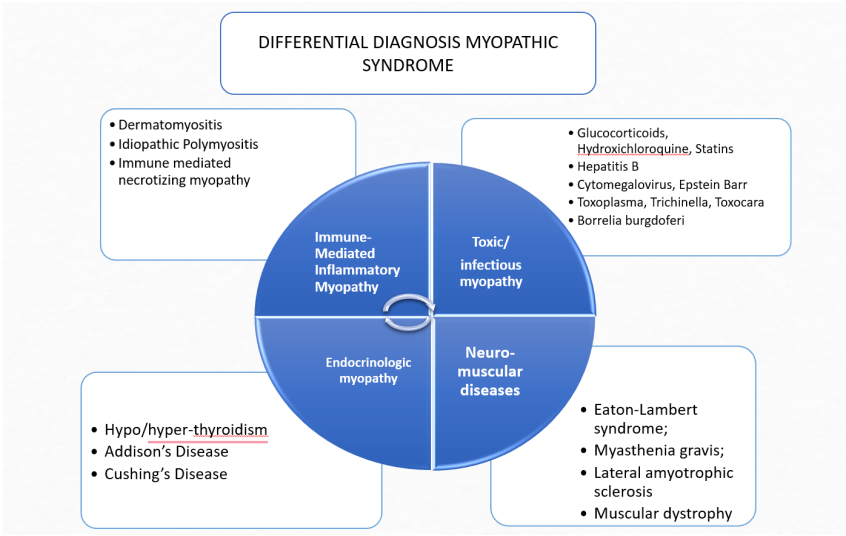


Figure 9: Differential Diagnosis of a myopathic syndrome in the presented case

The first etiologies that were excluded were toxic myopathy, given the fact that the patient did not take any aforementioned myopathy-inducing drugs, and infectious myopathy, taking into account that the contagious diseases panel aforementioned was negative.

Myasthenia gravis is a chronic autoimmune neuromuscular disease that affects people of all ages, races, and genders. It is a unique condition that is characterized by the involvement of the ocular muscles, which causes weakness in the eye muscles (ocular myasthenia), blurred or double vision (diplopia), and drooping of one or both eyelids (ptosis) – these symptoms are not exhibited in patients with an inflammatory myopathy. This condition occurs when the immune system mistakenly attacks the body's own tissues, specifically the receptor sites responsible for transmitting nerve impulses to the muscles. As a result, the muscles become weak and fatigued, making it difficult for individuals to perform even the simplest tasks. The patient presented in this paper did not exhibit any of these ocular symptoms.

Lambert-Eaton myasthenic syndrome (LEMS) is an uncommon condition that affects the way neurons communicate with muscles. Specifically, it disrupts the transmission of signals from the nerves to the muscles, leading to muscle weakness and fatigue. This disorder is similar to myasthenia gravis, as both conditions affect the muscles of the eyes. However, LEMS is typically associated with small-cell lung cancer, which can complicate prognosis and treatment. (25,26) Our patient did not have involvement of the muscles of the eyes.

Upon review of the high values of anti-thyroglobulin antibodies, although thyroid function is normal, it has been determined that the patient has autoimmune thyroiditis. This disease can result in muscle weakness (not necessarily proximal) and myalgias as part of a myopathic syndrome. It is pertinent to note that a severe myopathic syndrome akin to the one encountered by our patient would typically be accompanied by some form of thyroid function disturbance. (24, 25)

Another endocrinological cause of proximal myopathy can be found in Cushing's Disease – a pathology caused by endogenous hypersecretion of cortisol. It has an annual incidence of 2-3/million people. It has distinct clinical manifestations that are hallmarks of cortisol impregnation: increased weight, insomnia, Abnormal adipose in dorsocervical, supraclavicular, temporal areas, striae, thin skin, hyperpigmentation, hirsutism, acne, increased bruising, among many others. Our patient did not present with any of those symptoms so the cortisol levels were not tested. (27,28)

Our patient's symptoms are typical of IMIM, which is characterized by symmetrical, proximal muscle weakness in the limbs (upper and lower) and neck flexors, dysphagia, and a significant increase in serum muscular cytolysis enzymes, as well as myositis-specific autoantibodies.

Moreover, based on The European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) classification criteria for adult and juvenile idiopathic inflammatory myopathies (Appendix 1) (26, 27), the patient has accumulated a score of 8.4, which corresponds to a ≥ 90% probability of having an IMIM.

Dermatomyositis is typically characterized by pathognomonic cutaneous manifestations. The most frequent are: **Gottron papules** (symmetric overlying erythematous or purple papules and plaques with or without scaling or ulceration over dorsal metacarpophalangeal and interphalangeal joints), **Heliotrope rash** (liliac discoloration affecting both the upper eyelids with or without periorbital edema), **Gottron sign** (symmetric confluent erythematous macules or patches with or without edema over the elbows or knees), ***V sign***: (indistinct erythematous macules over the sun-exposed parts of the anterior neck and the upper chest), **Shawl sign** (widespread, flat, fixed erythema over

the posterior aspect of the upper back, neck and shoulders, which can become poikilodermatous and can worsen at ultraviolet light), **Holster sign** (poikiloderma involving the thighs, laterally), **Mechanic's hands**: (the palmar and lateral aspects of the fingers exhibit hyperkeratotic, cracked horizontal lines; these irregular lines bear a resemblance to the markings of a manual laborer and display a dirty appearance). (29–31) Upon examination, we observed a rash on the patient's back, which did not appear to be consistent with the shawl sign nor any other pathognomonic dermatomyositis skin manifestations, so this type of myopathy was excluded.

Polymyositis (PM) and IMNM have different spectra of antibodies and the muscle biopsy shows predominantly inflammatory infiltrates in PM and muscular necrosis with sparse inflammatory infiltrates in IMNM. Considering that the patient has a strong positivity for anti-SRP antibodies (anti-signal recognition particle), even though the muscle biopsy is not available, the **final positive diagnosis is immune-mediated necrotizing myopathy with muscular, pulmonary, gastrointestinal, and immunological involvement.** When it comes to IMNM, early and accurate diagnosis is crucial, especially because of its severe impact on the heart. It's important to act promptly to ensure the best possible outcome. (22,32,33)

Currently, there are no specific therapies approved for immune-mediated necrotizing myopathy. Due to low global case numbers, there is a lack of large case series available, and only one randomized clinical trial has been conducted. This study aimed to prove that zilucopan, a complement component 5 (C5) inhibitor, is an appropriate treatment for this disease. It included 27 participants from four countries who were randomized 1:1 to receive daily subcutaneous zilucoplan (0,3mg/kg) or placebo for eight weeks. This clinical trial was stopped because it did not reach its primary endpoint of efficacy. (34,35)

Therefore, the treatment guidelines for INMN follow the guidelines of IMIMs in general – corticosteroid therapy (Prednisone 1mg/kg) and steroid-sparing immunosuppressant (Methotrexate, Azathioprine, Mycophenolate Mofetil, Cyclosporine, Cyclophosphamide, Rituximab – case series). Some severe cases require intravenous immunoglobulins or plasmapheresis. (9,13,17,36,37)

The steroid-sparing immunosuppressant will be chosen according to patients' particularities, and comorbidities. Methotrexate and Azathioprine require frequent monitoring of hepatic enzymes and blood count and can cause severe dyspeptic syndrome. Mycophenolate mofetil is the drug of choice when the patient cannot be that closed-monitored and has hepatic comorbidities and Cyclophosphamide is chosen when the patient has surpassed the reproductive age and has no other gynecological pathologies. (17)

According to national and international guidelines for the treatment of IMIMs (8,38,39), the patient was started on **pulse therapy of glucocorticoids**: Solumedrol 250mg/day for 5 days (the choice of a lower dose of corticotherapy was made to prevent a concurrent glucocorticoid-induced myopathy) and i**mmunosuppressant** (Mycophenolate Mofetil (MMF) - CellCept 500 mg/day). Methotrexate and Azathioprine were not chosen because it is difficult for this patient to monitor hepatic cytolysis syndrome based on the levels of transaminase considering that they are increased also in muscular cytolysis syndrome that this patient has. Furthermore, considering the adenomyosis of the uterus, we considered it more prudent to refrain from Cyclophosphamide.

The patient's journey took a turn for the worse, even after the initial two days of improvement. She began to experience a severe dyspeptic syndrome characterized by nausea, abdominal pain, and vomiting. Furthermore, she developed myelosuppression, which was attributed to MMF intake and required immediate discontinuation and specific

intravenous treatment for dyspepsia. This new complication was a concerning development that required prompt medical attention.

On the fifth day of treatment with Solumedrol, the patient's condition worsened even further. She exhibited acute muscle weakness in both lower limbs and acute paresthesia on the left side of her body. A Neuro-Mio-Arthro-Kinetic Examination was performed to assess the patient's condition. The patient was conscious, cooperative, and fully oriented, but the results revealed an acute flaccid paraparesis that was more pronounced in the proximal areas than in the distal area. The patient exhibited no sensitivity disorders, but her muscular force was significantly reduced. The MRC scale revealed a score of 2/5 for lower limbs proximal, intermediate, and distal bilaterally, a score of 3/5 for upper limbs proximal and intermediate bilaterally, and 4/5 for distal bilaterally. The patient displayed no spasticity. This development was a cause of concern and required further medical evaluation.

It became imperative to perform urgent paraclinical investigations. The **Cerebral CT scan with contrast agent and angio-sequence of supra-aortic vessels** revealed thrombosis of the sagittal, transverse, and sigmoid sinus and at the first segment of the right jugular vein. The **Cerebral Magnetic Resonance Angiography** showed sagittal, transverse, and sigmoid sinus thrombosis with subcortical ischemia in the right parietal-frontal region. The blood tests uncovered positivity for D-Dimers and persistent muscular cytolysis syndrome. **Thrombophilia screening** revealed only the positivity of the lupus anticoagulant, but the patient was under anticoagulant treatment at the moment of collection of blood tests.

Results:

She was transferred to a Neurology department and started treatment with anticoagulants low molecular weight heparin (Clexane 0,6 ml x2/day) for 10 days, then bridging therapy with Vitamin K antagonist (Sintrom) – adjusting the dose according to the international normalized ratio (INR) of 2-3.

Despite the challenges posed by the extended venous thrombosis and the positivity of lupus anticoagulant, a definitive diagnosis of antiphospholipid syndrome cannot be made based on the Sapporo revised classification criteria used at that time. However, given the clinical suspicion of APS, it is crucial to tailor anticoagulant treatment to the individual's needs until the subsequent determination of antiphospholipid antibodies. This approach will help manage the symptoms effectively and promote better health outcomes. As per the recommendations of both national and international guidelines and clinical practice, patients afflicted with antiphospholipid syndrome (APS) and first unprovoked venous thrombosis should receive long-term treatment with vitamin K antagonists (VKA) having a target international normalized ratio (INR) of 2-3. This approach is known to be highly beneficial for patients, leading to improved health outcomes. (5,8,40)

A 2021 meta-analysis of randomized controlled trials, conducted according to the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines, aimed to highlight the risks of recurrent thrombosis and bleeding in patients with APS treated with direct-oral anticoagulant therapy (DOAC) compared to warfarin. The analysis revealed that DOAC treatment did not increase the risk of recurrent venous thromboembolism in APS patients; however, it did pose a significantly higher risk of recurrent arterial thrombosis. Moreover, the risk of recurrent arterial thrombosis was more frequent in patients with a history of arterial thrombosis. (41)

In a related 2023 meta-analysis encompassing 253 studies, patients with thrombotic antiphospholipid syndrome who were randomized to DOACs were found to have a higher

risk of arterial thrombosis when compared to those treated with vitamin K antagonists (VKAs). It has been observed that there is no significant difference in the risk of subsequent venous thromboembolism or major bleeding between patients treated with DOACs and VKAs.

Considering the immune-thrombosis theory, we need to control inflammation to further control thrombosis properly. Thus, another immunosuppressant was started: Methotrexate (MTX) 10 mg/week with Folic Acid 5 mg/week, the second day after MTX, together with oral corticoids (Methylprednisolone 8mg/day).

During the patient's regular follow-up visits to our clinic, we closely monitored her progress and witnessed a gradual amelioration in her symptoms. We also noted a considerable reduction in the prevalence of muscular cytolysis syndrome, which was encouraging. We have seen significant improvements in patients' general health and well-being as they continue to undergo therapy, which were demonstrated by the end of their subsequent follow-up.

Do we need physical therapy in IMIMs?

There has been a long-held belief that physical exercise could be harmful for patients with inflammatory myopathies. Healthcare professionals were worried that physical activity could exacerbate muscle inflammation in PM/DM patients, thereby exacerbating their muscle weakness. However, recent studies have shown that physical therapy can play a vital role in the treatment of IMIMs as long as it is practiced during periods of disease stability.

Research has shown that aerobic exercise can be extremely beneficial for patients with PM/DM, as it helps to improve their overall performance. In particular, patients who engage in aerobic exercise have been found to experience an increase in their VO2 max values, which is a measure of the maximum amount of oxygen that an individual can utilize during exercise. Additionally, aerobic exercise has been found to improve mitochondrial activity and oxygen uptake of skeletal muscles in patients with PM/DM.

For patients with PM/DM, sports activities such as cycling, walking, and jogging on level ground are the safest options. These activities typically involve concentric contractions, which are muscle contractions that shorten the muscle and help to generate force. By engaging in these types of exercises, patients can improve their overall physical fitness and reduce the risk of muscle damage or injury.

Studies have shown that active resistance training can have significant benefits for patients with DM/PM, including improvements in muscle strength, endurance, functional capacity, and overall quality of life. In particular, a combination of low-intensity resistance training with blood flow restriction therapy (LRT-BFR) has been found to be a promising approach. This technique involves using a specialized cuff to partially restrict blood flow to the muscles during low-intensity resistance exercises (usually around 20-30% of one repetition maximum [1RM]). Despite the low intensity of the exercises, this approach has been found to induce similar gains in muscle mass and strength as conventional high-intensity resistance training, without causing significant damage to the muscles. This makes LRT-BFR a safe and effective option for patients with DM/PM who may have limited mobility or other health concerns that make high-intensity exercise challenging.

Overall, healthcare providers need to encourage physical exercise and therapy among patients with IMIMs to help them achieve optimal health outcomes and improve their quality of life. (42,43)

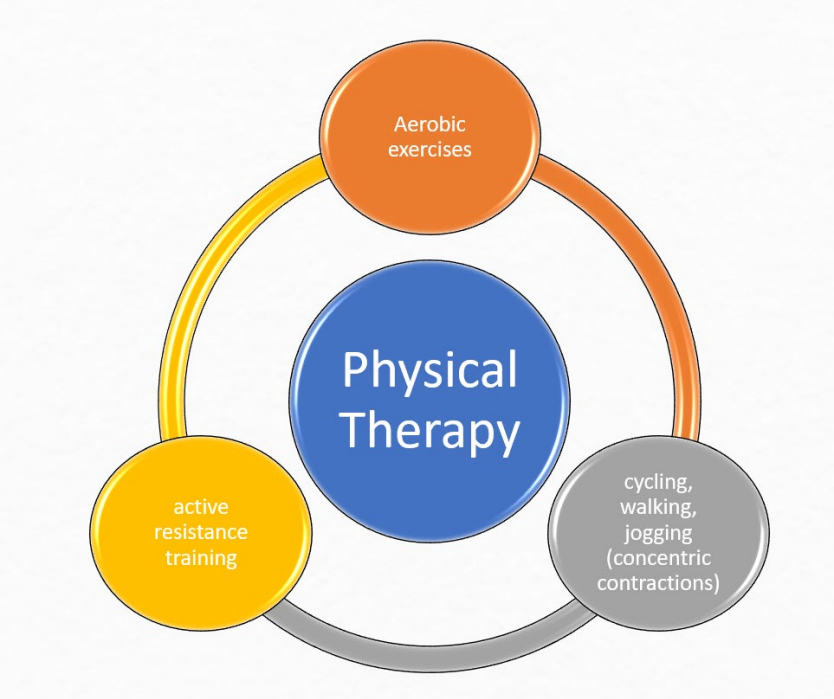


Figure 10: Physical Therapy strategies in IMIMs.

Conclusion:

In the presence of lupus anticoagulant, even though antiphospholipid syndrome is not confirmed, the only anticoagulant therapy that has proven its efficacy is Vitamin K antagonist, as proven by multiple studies and real-world data. (40,41,44)

Cerebral venous thrombosis, a rare form of stroke, is strongly linked to systemic inflammation. Immune-inflammatory myopathies, such as immune-mediated necrotizing myopathy, can increase the risk of thrombosis by creating an inflammatory response that makes the blood more susceptible to clotting and damages the inner lining of blood vessels. This damage exposes collagen and tissue factors, which can exacerbate the formation of blood clots. It is essential to understand these risk factors so that patients can receive the best possible care and treatment to reduce their risk of complications.

To our knowledge, there is no other case of immune-mediated necrotizing myopathy complicated with cerebral venous thrombosis in the available literature. Therefore, our case underlines the importance of carefully monitoring the patient for every new symptom, even uncommon, that may arise. Due to the lack of large cohorts of patients with IMNM, we should raise awareness about this disease and how it can be diagnosed. This will help in studying future treatments for the disease. In the case of a patient with acute symmetrical proximal weakness, dysphagia, and high levels of muscular cytolysis syndrome, it is essential to screen for myositis-specific autoantibodies (MSA) and myositis-associated autoantibodies. When possible, a muscle biopsy should also be performed for a proper diagnosis. A diagnostic of immune-mediated necrotizing myopathy is difficult, but it is of utmost importance for early treatment and prevention of possible life-threatening complications.

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Appendix A

Box 1 | **The EULAR–ACR classification criteria for adult and juvenile IIMs and their major subgroups**[6,7]

Muscle biopsy available

- Probable idiopathic inflammatory myopathies (IIMs): aggregated score (probability ≥55% and <90%) ≥6.7 and <8.7
- Definite IIMs: aggregated score (probability ≥90%) ≥8.7

Muscle biopsy not available

- Probable IIMs: aggregated score (probability ≥55% and <90%) ≥5.5 and <7.5
- Definite IIMs: aggregated score (≥90% probability) ≥7

Variable	Score	
	Without muscle biopsy	With muscle biopsy
Age of onset of first symptom assumed to be related to the disease ≥18 years and <40 years	1.3	1.5
Age of onset of first symptom assumed to be related to the disease ≥40 years	2.1	2.2
Muscle weakness		
Objective symmetrical weakness, usually progressive, of the proximal upper extremities	0.7	0.7
Objective symmetrical weakness, usually progressive, of the proximal lower extremities	0.8	0.5
Neck flexors are relatively weaker than neck extensors	1.9	1.6
In the legs, proximal muscles are relatively weaker than distal muscles	0.9	1.2
Skin manifestations		
Heliotrope rash	3.1	3.2
Gottron papules	2.1	2.7
Gottron sign	3.3	3.7
Other clinical manifestations		
Dysphagia or oesophageal dysmotility	0.7	0.6
Laboratory measurements		
Anti-histidyl-transfer RNA synthetase (Jo1) autoantibody present	3.9	3.8
Elevated serum levels of one of the following enzymes[a]: creatine kinase, lactate dehydrogenase, aspartate aminotransferase or alanine aminotransferase	1.3	1.4
Muscle biopsy features — presence of		
Endomysial infiltration of mononuclear cells surrounding, but not invading, myofibres	–	1.7
Perimysial and/or perivascular infiltration of mononuclear cells	–	1.2
Perifascicular atrophy	–	1.9
Rimmed vacuoles	–	3.1

Table adapted from Lundberg, I. E. et al. 2017 European League Against Rheumatism/American College of Rheumatology classification criteria for adult and juvenile idiopathic inflammatory myopathies and their major subgroups. *Ann. Rheum. Dis.* **76**, 1955–1964 (2017) (REF. 6) and with permission from REF. 7, Wiley. [a]Serum levels above the upper limit of normal.

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