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Refractory Immune-Mediated Necrotizing Myositis and Limited English Proficiency

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Statement of Significance

We report the case of a 76-year-old Spanish-speaking patient with a three-year history of statin-induced immune-mediated necrotizing myositis (IMNM) who presented with worsening symptoms and increasing creatinine kinase levels despite escalating treatment strategies. IMNM is a rare and challenging diagnosis. This case report details a myositis flare refractory to first and second-line therapies. Our report also examines limited English proficiency as a structural barrier to care in the United States, particularly in the setting of visits conducted via telehealth modalities.

Purpose: To report a rare presentation of statin-induced IMNM and the clinical impacts of language barriers and telehealth.

Methods: Case report.

Results: A 76-year-old male with a three-year history of statin-induced IMNM presented for follow-up to the rheumatology clinic. He reported worsening weakness after beginning leucovorin to mitigate side effects ascribed to methotrexate therapy. He had previously achieved baseline strength and normal creatinine kinase (CK) levels with a regimen of weekly methotrexate and monthly infusion of intravenous immunoglobulin (IVIG). His decline in condition appeared to result from inappropriate medication scheduling due to a language barrier. The patient was taking weekly leucovorin on the day before his weekly dose of methotrexate, thus mitigating the efficacy of methotrexate. However, his condition continued to decline with three months of the recommended treatment schedule. The patient was then switched to mycophenolate mofetil as an alternative immunosuppressant. This therapy has demonstrated benefit thus far and provided the patient with symptomatic relief.

DOI: 10.47265/cjim.v1i1.1465

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Case Report

A 76-year-old Spanish-speaking patient with past medical history notable for type two diabetes and hyperlipidemia initially presented to the rheumatology clinic three years prior with severe proximal muscle weakness and pain three months after beginning high dose atorvastatin. His symptoms persisted despite discontinuation of the statin. He denied any fevers, chills, rashes, joint pain, or other symptoms of infection. Physical exam was notable for reduced muscle strength. At this time, his primary care physician noted serum CK elevation to 6928 U/L (normal 24-195) and aldolase to 54.8 U/L (normal< 7.5).[1] A panel assessing auto-antibodies associated with myositis was negative for anti-synthetase and anti-jo, anti-MDA5, antiTIF1, and anti-Mi-2. Further investigation identified HMG-CoA reductase antibodies > 108 (normal < 20). A muscle biopsy revealed vacuolar myopathy and muscle fiber necrosis and regeneration, consistent with a diagnosis of IMNM.[2]

The patient received six months of high-dose corticosteroids with effective resolution of his symptoms and improvement in serum CK. Given his comorbidities, he was started on methotrexate

as a steroid-sparing agent. A year later, IVIG was added to his treatment regimen after an acute flare of muscle disease. During the first months of the COVID-19 pandemic, the patient was seen via telemedicine. At this visit, he noted nausea and mental fog associated with his continued methotrexate usage. He was prescribed leucovorin, a folic acid metabolite to mitigate methotrexate toxicity. Using a certified medical interpreter, the physician explained to the patient that this medication should be taken every week on the day following methotrexate ingestion.

Three months later, the patient returned to clinic in person. He reported a significantly increased weakness. He described difficulty performing daily activities, including walking throughout stores and carrying light loads. Routine lab work reveled an elevated serum CK to 694 U/L. When asked about medication usage, he reported taking both his methotrexate and leucovorin weekly and noted no trouble obtaining either medication. He also endorsed improvement in methotrexate-associated side effects following leucovorin initiation. Upon further questioning, it was discovered that he was taking the leucovorin on the day before methotrexate, effectively negating any antifolate drug effect.

In order to preserve the therapeutic effect of methotrexate, it is imperative that leucovorin is administered 24 hours after taking methotrexate. A medical student reviewed the appropriate dosing of methotrexate and leucovorin with the patient in Spanish. The physician later repeated this explanation with the assistance of an interpreter service via video call. The patient demonstrated his understanding using the teach-back method. He continued on weekly methotrexate and leucovorin in addition to IVIG. Unfortunately, he experienced progressively diminished strength in his upper and lower extremities. At his follow-up visit three months later, his CK level had increased to 1,440 U/L. He was subsequently treated with initiation of mycophenolate mofetil, as an alternative immunosuppressing agent, and a long prednisone taper. Thus far, these changes have yielded significant amelioration of the patient's symptoms. Continued follow-up is necessary to evaluate for improved levels of creatinine kinase and maintained resolution of his muscle weakness.

Methods

Immune-mediated Necrotizing Myositis

Immune-mediated necrotizing myositis (IMNM) is a relatively new diagnosis, first defined in 2004.[3] The clinical presentation is characterized by proximal muscle weakness, dysphagia, dysarthria, and fatigue. IMNM is known to occur secondary to statin use, as was the case in this patient, however, may also occur in the setting of other autoimmune diseases, neoplasms, or idiopathically.

IMNM triggered by statin use is associated with the development of auto-antibodies to HMG-CoA reductase.[2] Statin use is often associated with toxic myopathy, which presents similarly to IMNM with muscle pain, weakness, and elevated serum CK. Unlike IMNM however, the statin-associated muscle symptoms of toxic myopathy are common, and are estimated to occur in 10-15% of patients.[4] These symptoms also generally resolve upon discontinuation of the statin. IMNM in response to statin use is a separate entity, and occurs with much less frequency. The incidence of statin-induced IMNM is less than two per million per year.[5] This condition typically follows a chronic course and does not resolve with the removal of the statin.[6] Interestingly, while women are more likely to be affected by IMNM unrelated to statin use, there does not seem to be a gender bias in the prevalence of IMNM triggered by statins.[7]

IMNM can be detected clinically via elevated serum creatinine kinase (CK), auto-antibodies to

HMG-CoA reductase, and evidence of muscle fiber necrosis and regeneration on biopsy. The mainstay of treatment is immunosuppression, and the majority of patients require multiple therapies to reduce their symptoms effectively.[6] Corticosteroids followed by IVIG are the first-line treatment recommended by an international IMNM working group. The addition of methotrexate or rituximab is recommended for refractory cases.[2] There have been infrequent case reports of patients with IMNM benefitting from mycophenolate mofetil when they cannot tolerate methotrexate.[6]

This report details the presentation and unique treatment course of a patient with this rare condition. His limited English proficiency further impaired the efficacy of long-term treatment with methotrexate. His case demonstrates the challenges of care management for patients with IMNM requiring chronic immunosuppression.

Discussion

IMNM can significantly disable patients by causing muscle atrophy and fatty replacement of muscular tissue.[6] Early treatment with immunosuppression has shown to be critical to halting the progression of necrosis. For many patients with IMNM, a course of immunosuppression with corticosteroids followed by IVIG monotherapy is sufficient.[2] However, there are several case reports of patients with IMNM who had continued worsening of disease on monotherapy, and required the addition of methotrexate or rituximab.[5] In this case report, we describe a patient who experienced refractory IMNM despite combination therapy with methotrexate and IVIG.

Initially it appeared that the worsening of disease was due to the patient mistakenly taking leucovorin on the day prior to his methotrexate. It is recommended that leucovorin be given only once weekly, on the day after administration of methotrexate, because these two drugs are structural analogs and compete for cellular transport and enzyme binding.[8] Methotrexate is an inhibitor of folate metabolism that is often utilized in low doses in autoimmune conditions. Its mechanism of action to reduce inflammation is incompletely understood but recent literature postulates that while its inhibition of folate pathways causes side effects such as nausea and fatigue, its therapeutic benefit is found in its interaction with the JAK/Stat pathway.[9] Thus, folate replenishment with folic acid supplements or leucovorin can be given to mitigate the side effects of methotrexate without rendering the drug ineffective, when it is taken after the methotrexate has been absorbed. This case highlights the importance of appropriate timing for these two medications.

This case further elucidates limited English proficiency as a structural barrier to healthcare in the United States, especially with the recent expansion of telehealth visits. The American College of Physicians emphasizes addressing language barriers as an essential aspect of improving patient safety.[10] One out of every eleven adults living in the United States experience difficulties associated with limited English proficiency, which has a profound effect on their interactions with the healthcare system.[11] As indicated by this case report, the time and effort spent towards improved communication reduces unnecessary harm and expense for the patient and improves quality of care.

In the case presented here, the patient's risk of an adverse event due to miscommunication was compounded by his complicated chronic condition and the use of telemedicine to explain a new treatment. Maintaining open communication and timely follow-up allowed the physician to identify a critical misunderstanding. Her appropriate use of a medical interpreter and the teach-back method ultimately facilitated effective communication of her treatment plan.[12] Further research is needed

to assess the impact of telemedicine on outcomes for patients with limited English proficiency and chronic conditions. Our case demonstrates the importance of maintaining regular communication with these patients and asking about their medication adherence comprehensively and without negative judgement or assigned blame. By doing these things, the physician was able to determine that this patient required further therapy with an alternative agent.

This case report ultimately demonstrates the insidious nature of IMNM refractory to first-line treatments. There are many reasons for which methotrexate may not be an appropriate treatment for patients with IMNM including injury to hepatocytes, significant side effects, and continued progression of myositis. We present a case of IMNM in which mycophenolate mofetil in addition to IVIG offered promising benefit to a patient for whom treatment with methotrexate and IVIG was insufficient. Mycophenolate mofetil is an inhibitor of inosine-5' monophosphate dehydrogenase, which prevents B and T cell proliferation. It is approved for use as an immunosuppressing agent to prevent transplant rejections. There are also reports of Mycophenolate mofetil providing benefit to patients with autoimmune conditions like autoimmune hepatitis and lupus nephritis.[13] By reporting the use and benefit of Mycophenolate mofetil in this case, we build upon the growing body of literature on IMNM, a rare and newly described disease.

ARTICLE INFORMATION

Accepted for Publication: September 25 2021.

Published Online: September 28 2021.

DOI: 10.47265/cjim.v1i1.1465

Cite this article:

Astrike-Davis Emma. Refractory Immune-Mediated Necrotizing Myositis and Limited English Proficiency. Carolina Journal of Interdisciplinary Medicine (CJIM) 78-82.

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