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MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE WITH ASSOCIATED NECROTIZING MYOPATHY: A CASE REPORT AND REVIEW OF THE LITERATURE

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ABSTRACT

Background: Monoclonal gammopathies encompass many types of plasma cell proliferative disorders ranging from benign to malignant. Monoclonal gammopathies that meet diagnostic criteria for monoclonal gammopathies of undetermined significance (MGUS) but with clinical manifestations are now being referred to as monoclonal gammopathies of clinical significance (MGCS). MGUS associated myopathies are a rare form of MGCS.

Case description: We present a case of MGUS associated necrotizing myositis. The patient had been previously diagnosed with MGUS and myositis around the same time, but prior testing had not revealed the etiology of the myopathy. Repeat biopsy and work-up revealed a necrotizing myopathy.

Discussion: MGUS associated myopathies are rare, with the most common being sporadic late-onset nemaline myopathy (SLONM-MGUS) and amyloid light chain (AL) amyloidosis-associated myopathy. MGUS associated necrotizing myopathy is even rarer. Because this condition is so uncommon, there are no standardized guidelines on how to treat this condition. Some case reports or studies suggest treating the myositis with standard of care for the myositis type without considering the monoclonal gammopathy while other studies have suggested that treating the monoclonal gammopathy would be beneficial in treating the associated clinical syndrome.

Conclusion: Our case report of MGUS associated necrotizing myopathy encourages internists to broaden their differential diagnosis of myopathy, increasing awareness of a condition that is still not well understood.

KEYWORDS

Monoclonal gammopathy, myopathy

LEARNING POINTS

- Monoclonal gammopathy of clinical significance is a new term that refers to nonmalignant monoclonal gammopathies that exhibit significant clinical manifestations.
- Monoclonal gammopathy associated myopathies are rare but should be considered as part of the differential diagnosis for myopathy.

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INTRODUCTION

Monoclonal gammopathies are characterized by the uncontrolled production of monoclonal immunoglobulins, stemming from plasma cell proliferative disorders. These disorders encompass a spectrum, ranging from benign or smoldering conditions like monoclonal gammopathy of undetermined significance (MGUS) to malignant forms such as multiple myeloma (MM)[1,2]. An emerging type of monoclonal gammopathy that has raised clinical interest is referred to as monoclonal gammopathy of clinical significance (MGCS). This is a monoclonal gammopathy that meets the criteria for MGUS except it produces clinical manifestations attributed to a small B cell clonal population causing pathogenesis in various organs including the kidneys, eyes, peripheral nervous system, skin, and sometimes systemically[1,2]. MGCS-associated myopathies

Lab	Value	Reference Range
ESR (mm/hr)	↑ 120	2-37
CRP (mg/dl)	↑ 8.7	<0.5
CK (unit/l)	↑ 200-600*	28-319
LDH (unit/l)	↑ 260-300*	135-225
WBC (×103/µl)	↓ 2.2	4-11
C3 (mg/dl)	95	90-180
C4 (mg/dl)	↓ 3	10-40
M protein (IgG) (g/dl)	↑ 0.24	0.00
Kappa (mg/dl)	↑ 16.45	0.33-1.94
Lambda (mg/dl)	1.44	0.57-2.63
K/L ratio	↑ 11.42	0.26-1.65
Bone marrow biopsy	Plasma cell proliferative disorder with 5-9% kappa light chain-restricted plasma cell	
ANA	Negative	-
ANCA	Negative	-
Rheumatoid Factor	Negative	-
SSA 52 ab	Negative	-
SSA 60 ab	Negative	-
dsDNA	Negative	-
Smith/RNP ab	Negative	-
HMGCR ab	Negative	-
PM1/Scl-100 ab	Negative	-
Jo-1 ab	Negative	-
Mi-2 ab	Negative	-
PL-7 ab	Negative	-
PL-12 ab	Negative	-
P155/140 ab	Negative	-
Ku ab	Negative	-
EJ ab	Negative	-
SRP ab	Negative	-
OJ ab	Negative	-
SAE1 ab	Negative	-
NXP-2 ab	Negative	-
MDA5 (CADM-140)	Negative	-
TIF1-gamma	Negative	-
Fibrillarin/U3 RNP ab	Negative	-
Cryptococcus	Negative	-
Toxoplasmosis	Negative	-
Coccidioides	Negative	-
Q-Fever	Negative	-
Histoplasma	Negative	-
Brucella	Negative	-
Schistosoma	Negative	-
Tetanus	Negative	-
Diphtheria	Negative	-
TB	Negative	-
Aspergillus	Negative	-
HSV	Negative	-
Hepatitis A, B, C	Negative	-
HIV	Negative	-
EBV	IgG positive, IgM negative	-
CMV	IgG positive, IgM negative	-

*Range provided for multiple values during myositis exacerbations.

Abbreviations: ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; CK, creatine kinase; LDH, lactate dehydrogenase; WBC, white blood cell; ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibodies; ab, antibodies; dsDNA, double-stranded deoxyribonucleic acid; HMGCR, HMG-CoA reductase; TB, tuberculosis; HSV, herpes simplex virus; HIV, human immunodeficiency virus; EBV, Epstein Barr virus; CMV, cytomegalovirus.

Table 1. The patient's laboratory values including monoclonal gammopathy of undetermined significance and myositis work-up.

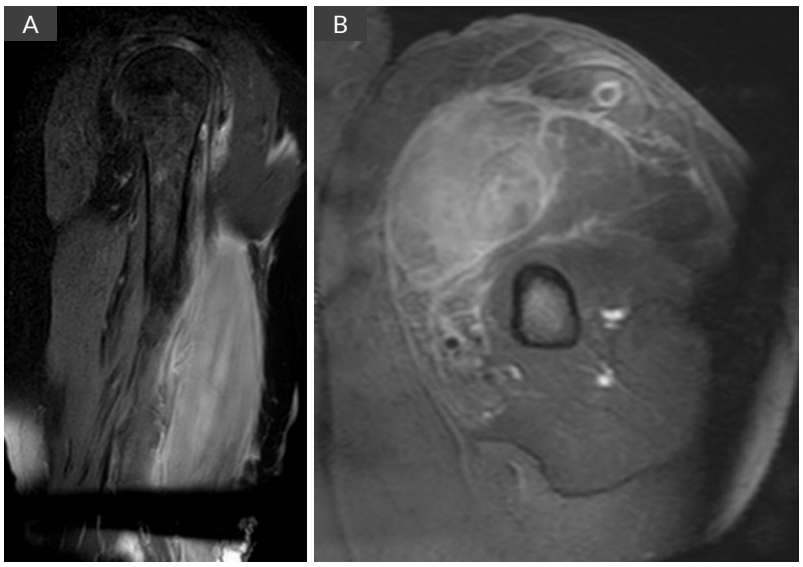

Figure 1. Magnetic resonance imaging showing bicipital myositis.

have also been reported. Although they are rare, they can be associated with very high morbidity[3,4].

The most common MGCS-associated myopathies are sporadic late-onset nemaline myopathy (SLONM-MGUS) and amyloid light chain (AL) amyloidosis-associated myopathy[3,4]. Very few reports have been published on other types of MGCS-associated myopathies. There have been rare case reports of MGCS associated inclusion body myositis, polymyositis, and a case of necrotizing autoimmune myopathy associated with POEMS syndrome[5-7]. Our case report highlights a rare case of MGCS-associated necrotizing myositis.

CASE DESCRIPTION

A 64-year-old male with a history of previously diagnosed MGUS via bone marrow biopsy and myositis of unknown etiology presented to the emergency room with extremity weakness, migratory muscle pains, swelling, and diffuse erythema over his affected limbs which had been occurring intermittently for years. He had come to the emergency room on multiple prior occasions with the same presentation. Magnetic resonance imaging (MRI) on these occasions revealed inflammatory edema consistent with focal myositis of the distal vastus lateralis and mid portion of the biceps femoris muscle, which was again present on repeat MRI *(Fig. 1)*. Upon review of the patient's medical history, prior work up had been unrevealing including electromyography, an extended myositis panel, and a muscle biopsy which had shown mild myopathy characterized by inflammation, denervation atrophy, and signs of reinnervation without an identified etiology. The patient had undergone initial treatment at the time of diagnosis with intravenous immunoglobulin (IVIG) and steroids and then had been started on methotrexate (MTX) 20 mg with a prednisone taper starting at 40 mg daily due to persistent symptoms of migratory muscle pain and swelling. Despite this initial treatment course, he continued to present to the emergency department with myopathy flares.

A repeat extended myositis panel was unremarkable revealing no specific etiology for the patient's presentation. He had chronically elevated C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), intermittently elevated creatine kinase (CK), and chronic leukopenia, but a full autoimmune workup remained negative aside from a chronically low C4 *(Table 1)*. With early concerns for pyomyositis or an infectious process, infectious disease was consulted, with a full workup for infectious etiology which was negative. After evaluation of the patient's labs and clinical course, the infectious disease team suspected the etiology was non-infectious. As he continued to have myositis flares

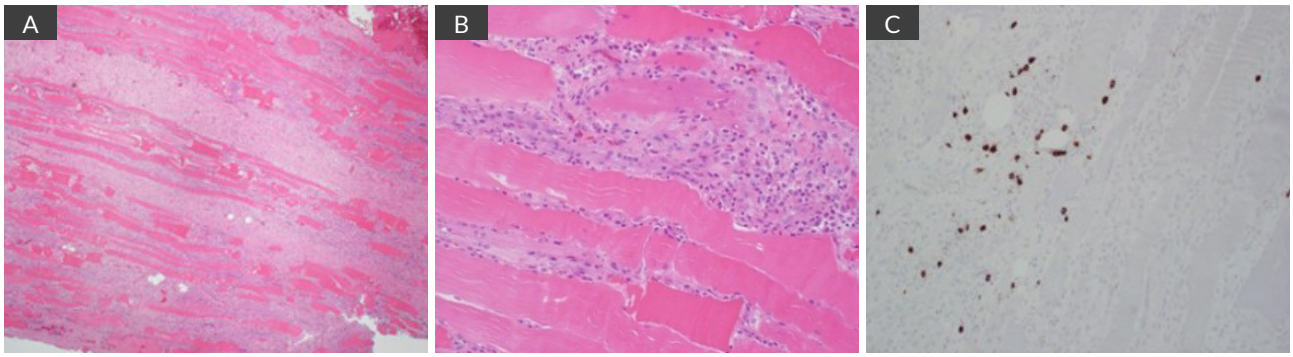

Figure 2. A) Left biceps muscle tissue with H&E stain showing necrosis and regeneration of muscle fibers; B) Magnified image of left biceps tissue showing necrotic fiber surrounded by endomysial infiltrates; C) Immunohistochemical stain showing occasional endomysial infiltrates around necrotic fibers. Per University of New Mexico pathology report findings were most consistent with necrotizing myositis.

while on MTX and there were concerns about his leukopenia, MTX was changed to azathioprine (AZA), 50 mg daily, then increased to 100 mg daily. The patient still continued to have flares and leukopenia while on AZA and it was discontinued as well. During his flares high dose prednisone did improve his symptoms, however the frequency of his flares worsened when on prednisone only.

A repeat muscle biopsy was performed of the left biceps which revealed necrotizing myopathy with both acute and chronic inflammation, featuring extensive fiber degeneration/necrosis and regeneration, severe neutrophilic inflammation, and a notable presence of macrophages and endomysial lymphocytes *(Fig. 2)*. Following this, the patient was then started on rituximab (RTX) with high dose prednisone for flares and his flares appeared to be less frequent with lab testing revealing an overall decrease in M-protein for his gammopathy *(Fig. 3)*.

DISCUSSION

MGUS-associated myopathies are rare and frequently underdiagnosed disorders that can potentially produce significant morbidity. Establishing an appropriate diagnosis at the beginning is crucial to understand potential treatment approaches. In our patient´s case the initial diagnosis of MGUS was made based on the presence of an elevated free light chain ratio, an elevated M protein, and < 10% light chain monoclonal proliferation on bone marrow biopsy. The concurrent diagnosis of myositis suggests the case could have been classified as MGCS instead. This diagnosis is supported by the patient's clinical symptoms, intermittent elevation of CK, ESR, and CRP, MRI findings, and muscle biopsy results despite a negative myositis panel. The repeat biopsy findings exclude the two main types of myopathies typically associated with MGUS, SLOMN and AL amyloidosis-associated myopathy.

Histologic examination did not support AL-amyloidosis-associated myopathy as Congo red staining did not reveal amyloid deposition. Similarly, the findings did not support SLOMN-MGUS due to the absence of nemaline rods in the myofibers[3,8]. The lack of visualized vacuoles made inclusion body myositis less likely[8]. Endomysial infiltrates surrounding necrotic fibers, excluded a diagnosis of polymyositis which would usually present with endomysial infiltrates surrounding non-necrotic fibers[8]. Finally, no perimysial inflammation was found to suggest dermatomyositis[8]. Necrotic myofibers with macrophages were visualized suggesting a diagnosis of necrotizing myositis[8].

From a clinical perspective, the patient's symptoms did

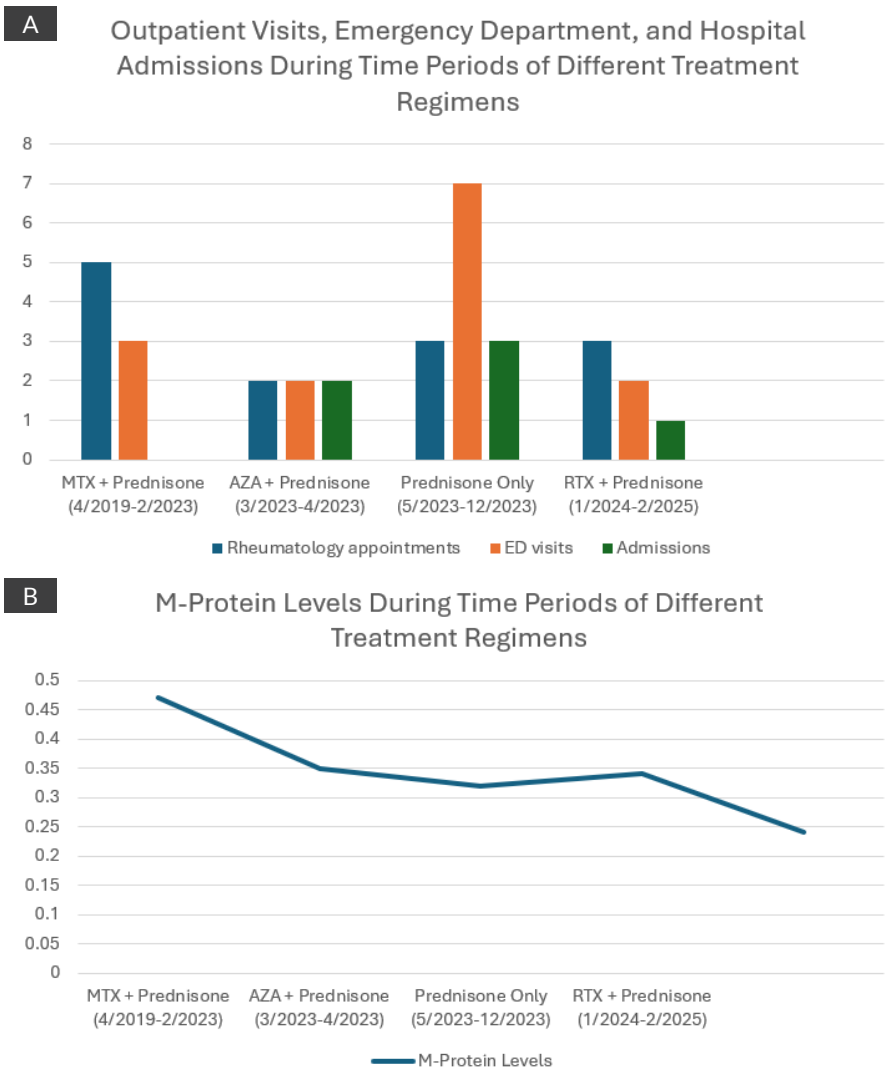

Figure 3. A) The figure shows the amount of rheumatology (outpatient visits), emergency room visits, and hospital admissions that patient had in the ascribed time period with a chief complaint related to his myositis symptoms. Overall, the patient had less total visits on RTX + prednisone compared to prednisone only and MTX + prednisone. He had the same number of total visits on AZA + prednisone compared to RTX + prednisone, but in a much shorter time period (2 months compared to 1 year). B) shows a decreased M-protein while on RTX compared to other medications.

Abbreviations: RTX, rituximab; MTX, methotrexate; AZA, azathioprine.

not include the pseudohypertrophy characteristic of AL amyloid related myositis or respiratory muscle weakness characteristic of SLOMN[3]. Furthermore, common skin manifestations seen in dermatomyositis such as Gottron's papules, heliotrope rash, poikiloderma, or mechanic's hands were absent[8]. The muscle weakness observed, while proximal, was not symmetric as typically seen in dermatomyositis or polymyositis. The acute onset of symptoms supported a diagnosis of necrotizing myositis[8].

Despite extensive diagnostic testing, no specific etiology for the likely autoimmune necrotizing myositis has been identified. Statin-induced myopathy, often associated with necrotizing myositis, was ruled out with a negative anti-HMGCR antibody testing[8].

Some literature emphasizes the challenges of establishing causation between MGUS and associated myopathies, due to limited evidence and rarity of these conditions[3]. Delayed diagnosis or misdiagnosis commonly occurs with MGCS-associated myopathy and therefore awareness of this condition is important for differential diagnosis considerations[3].

Treatment protocols for MGCS-associated myopathy lack standardization due to its low frequency. The approach varies based on subtype, with some literature advocating for treatment of the autoimmune condition while other literature suggests treatment for this entity may require treating it as a neoplastic disorder rather than an autoimmune condition, involving chemotherapy and autologous stem cell transplantation for conditions like SLOMN-MGUS[9,10].

MGUS without any clinical manifestations is not routinely treated, just monitored[1]. Per literature review, IVIG and RTX +/- steroids are used most frequently as treatment options for MGCS[11]. RTX is used as the standard of care for Waldenström's macroglobulinemia, however is not recommended as standard of care for MM[12]. Steroids are used as part of the standard of care of MM, which also typically includes stem cell transplant, chemotherapy, and/or immunotherapy[12].

Necrotizing myopathy is typically considered an autoimmune myositis[8]. Based on a review of the standard of care for this and other related myopathies, generally the standard of care includes glucocorticoids with methotrexate, mycophenolate, azathioprine, or rituximab, with IVIG thought to be beneficial as well[8].

Of the treatments that our patient underwent, all should have had efficacy against his myositis as they are consistent with the standard of care. He continued to have myositis flares despite treatment with MTX and AZA and also developed leukopenia, leading to cessation of these medications. Of the treatments that he received, per literature review as mentioned above, IVIG, RTX, and steroids are the treatments that would be most likely to influence the monoclonal gammopathy as well. During the time period he was on RTX he did appear to have a decrease in flares for an extended period of time along with a decrease in his M-protein level. This supports the idea that his monoclonal gammopathy was contributing to his necrotizing myopathy instead of them being two separate and unrelated conditions.

There are some limitations in the data we were able to collect about our patient's condition. One limitation is we do not have complete outside records of the number of flares during his initial treatment with IVIG at the time his diagnosis. Another limitation is the patient's RTX was not continuously given every 2 weeks as prescribed during 1/2024-2/2025 due to hospitalizations unrelated to his myositis symptoms, which limits our ability to analyze its actual effectiveness.

CONCLUSION

There seems to be an established association between MGUS and SLOMN/AL amyloidosis associated myopathy as this makes up the majority of case reports about MGUS associated myopathies. Further study is required to not only establish a stronger association between MGUS and other forms of myopathies/myositis but also to further investigate treatment options and how systemic treatment of MGUS in such cases may contribute to resolution of such myopathies compared to standard of care for the specific myopathy alone. The rarity and diagnostic complexity of MGCS-associated myopathies highlight the need for heightened clinical suspicion and individualized treatment strategies tailored to the underlying pathology and organ involvement.

REFERENCES

1. Fermand JP, Bridoux F, Dispenzieri A, Jaccard A, Kyle RA, Leung N, Merlini G. Monoclonal gammopathy of clinical significance: a novel concept with therapeutic implications. *Blood* 2018;**132**:1478-1485.
2. Oganesyan A, Gregory A, Malard F, Ghahramanyan N, Mohty M, et al. Monoclonal gammopathies of clinical significance (MGCS): In pursuit of optimal treatment. *Front Immunol* 2022;**13**:1045002.
3. Yu H, He D, Zhang Q, Cao B, Liu W, Wu Y. Case Report: Monoclonal Gammopathies of Clinical Significance-Associated Myopathy: A Case-Based Review. *Front Oncol* 2022;**12**:914379.
4. Wang M, Lei L, Chen H, Di L, Pang M, Lu Y, et al. Monoclonal gammopathy with both nemaline myopathy and amyloid myopathy. *Neuromuscul Disord* 2017;**27**:942-946.
5. Kiprov DD, Miller RG. Polymyositis associated with monoclonal gammopathy. *Lancet* 1984;**2**:1183-1186.
6. Gremain V, Litrowski N, Boulard C, Marguet F, Courville P, Zarnitsky C, et al. Necrotizing autoimmune myopathy associated with POEMS syndrome report. *QJM* 2018;**111**:49-50.
7. Nakayama T, Horiuchi E, Watanabe T, Murayama S, Nakase H. A case of inclusion body myositis with benign monoclonal gammopathy successfully responding to repeated immunoabsorption. *J Neurol Neurosurg Psychiatry* 2000;**68**:230-233.
8. Dalakas MC. Inflammatory muscle diseases. *N Engl J Med* 2015;**372**:1734-1747.
9. Susman D, McLean J, Kotchetkov R. Sporadic late onset Nemaline Myopathy with a monoclonal gammopathy: Comparative effectiveness of immuno- and chemotherapy. *Blood* 2019;**134**:5820.
10. Belhomme N, Maamar A, Le Gallou T, Minot-Myhié MC, Larralde A, Champtiaux N, et al. Rare myopathy associated to MGUS, causing heart failure and responding to chemotherapy. *Ann Hematol* 2017;**96**:695-696.
11. Dispenzieri A. Monoclonal gammopathies of clinical significance. *Hematology Am Soc Hematol Educ Program* 2020;**2020**: 380–388.
12. Schuster S, Rajkumar SV, Dispenzieri A, Morice W, Aspitia AM, Ansell S, et al. IgM multiple myeloma: disease definition, prognosis, and differentiation from Waldenstrom's macroglobulinemia. *Am J Hematol* 2010;**85**:853-855.