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Case Report

Internal Medicine Section

Skeletal and Cardiac Myopathy with Acquired Factor X Deficiency in a Patient with Monoclonal Gammopathy of Clinical Significance: A Rare Case Report

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ABSTRACT

Monoclonal gammopathies include several types of plasma cell proliferative disorders, which might be benign to malignant. Monoclonal Gammopathy of Clinical Significance (MGCS) refers to small plasma cell clones that cause organ damage without meeting criteria for multiple myeloma. The common MGCS syndromes include renal, neurologic and cutaneous, while there is evidence of haematological and multi-organ involvement. MGCS-associated myopathy is a rare presentation, including amyloid light chain amyloidosis and sporadic late-onset nemaline myopathy. MGCS presenting solely with myopathy may lead to misdiagnosis with other common causes of myopathies, delaying management. The condition being rare, it lacks standardised guidelines on management, while data from certain reports suggest treating monoclonal gammopathy for optimal results. This article presents a case of a 57-year-old man with progressive thigh pain, ecchymoses, and proximal muscle weakness for four months. MRI showed muscle oedema, and autoantibody positivity initially suggested immune-mediated myositis. However, recurrent bleeding with deranged coagulation revealed acquired factor X deficiency. Further evaluation demonstrated elevated lambda light chains, abnormal kappa/lambda ratio, and 5% clonal plasma cells on bone marrow biopsy. Cardiac imaging revealed infiltrative cardiomyopathy without amyloidosis. These findings confirmed MGCS with multisystem involvement (myopathy, cardiomyopathy, and coagulopathy). The patient improved on daratumumab, bortezomib, cyclophosphamide, and dexamethasone. This case illustrates the diagnostic challenge of MGCS, which may mimic autoimmune myositis. Awareness of such atypical presentations is crucial, as therapy is guided by organ injury rather than tumour burden. Early recognition and clone-directed treatment are essential to preserve organ function.

Keywords: Cardiomyopathy, Global longitudinal strain, Monoclonal gammopathy, Myositis-specific antibody

CASE REPORT

A 57-year-old gentleman with no history of any comorbidities developed insidious pain in the right thigh with difficulty in standing from the sitting position for one month. This was followed by ecchymosis and red discolouration over the right thigh [Table/Fig-1a]. Similar symptoms developed in the left thigh subsequently and Magnetic Resonance Imaging (MRI) of the thighs showed hyperintensities in the medial and posterior compartments, suggestive of muscle oedema [Table/Fig-1b]. The patient presented to the rheumatology department with the above-mentioned complaints, along with undocumented weight loss and fatigue. Clinical examination revealed blanchable erythema over the face and limbs (unnoticed by the patient), resolving ecchymosis on the right thigh, and proximal muscle weakness in the lower limbs (power 4/5 in bilateral thighs). Inflammatory markers were elevated; muscle enzymes were normal {Creatine Phosphokinase (CPK) 98 IU/L, Aspartate Transaminase (AST) 22 IU/L, Alkaline Transaminase (ALT) 19 IU/L}, but coagulation parameters were deranged {raised Prothrombin Time (PT) 20.3 sec and activated Partial Thromboplastin Time (aPTT) 41.1 sec}.

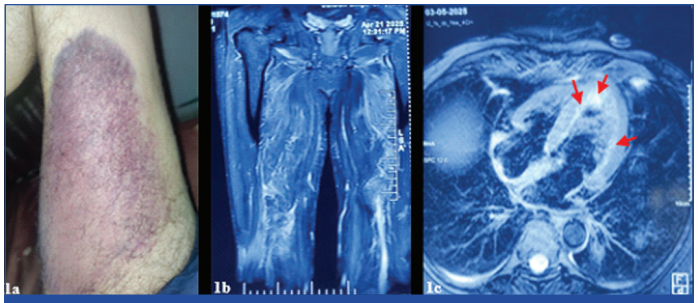
Immunological testing showed positive ANA (2+ speckled), Ro-52(1+), and anti-SAE (2+) antibodies. In view of myositis-specific antibody (SAE) and myositis associated antibody (Ro 52) positivity in the presence of muscle oedema on imaging, a provisional diagnosis of immune-mediated myositis was considered and the patient was started on intravenous methylprednisolone. FDG PET-CT of the whole body showed increased FDG avid uptake in the deep muscles of the bilateral proximal thighs. Patient developed a new ecchymotic patch on the left thigh and left eye subconjunctival haemorrhage, fresh frozen plasma was infused, steroids were increased, and this resulted in improved muscle symptoms with no further bleeding episodes.

Meanwhile, the APTT mixing study demonstrated 80% correction, suggesting a factor deficiency; subsequent individual factor assays revealed a reduced Factor X level (20%).

Hence, the patient was evaluated for plasma cell disorder, which showed normal serum protein electrophoresis and immunofixation (no M-band) but elevated lambda light chains (751.25 mg/L) and a low kappa-lambda ratio (0.03). Bone marrow biopsy (flow cytometry) confirmed the presence of 5% clonal plasma cells with lambda chain restriction.

Transthoracic echocardiography showed non-obstructive hypertrophic cardiomyopathy with asymmetrical septal hypertrophy. Speckled tracking showed borderline Global Longitudinal Strain (GLS) (-16%) with mild apical sparing. The ECHO findings were abnormal hence MRI was done. Cardiac suggested diffuse subendocardial enhancement indicative of infiltrative cardiomyopathy [Table/Fig-1c] along with elevated NT-proBNP (3338 pg/mL, normal <125) and Troponin I (59 pg/mL, normal <39). There was no family history of sudden cardiac death or the hypertrophic cardiomyopathy. In this case, amyloidosis was suspected, but the accessible tissue, which is the abdominal fat pad, did not show any evidence of amyloid.

Patient had <10% clonal plasma cells with no myeloma-defining events and no histopathological evidence of amyloidosis; hence, he fulfilled criteria for Monoclonal Gammopathy of Undetermined Significance (MGUS). But he had significant end-organ damage in terms of myopathy, cardiomyopathy and factor X deficiency; therefore, a final diagnosis of MGCS was established. The



[Table/Fig-1]: Showing large ecchymotic patch over right thigh (a); hyperintensities in coronal section of MRI thighs suggestive of muscle oedema (b); and mild diffuse/global subendocardial enhancement (red arrows) in cardiac MRI (late gadolinium enhancement), suggestive of infiltrative cardiomyopathy (c).

muscle oedema was attributed to monoclonal protein-mediated tissue damage rather than autoimmune inflammatory myositis. The patient was started on a weekly regimen of daratumumab, bortezomib, cyclophosphamide and dexamethasone, since there is no standard regimen for MGCS and the above-mentioned drugs were used for the management of multiple myeloma. For cardiac involvement patient was treated aggressively, like multiple myeloma the haematology team and gradual improvement in symptoms and clinical parameters was observed. The patient was followed by Serum Free Light Chain (SFLC) ratio, which normalised after six months and muscle power returned to normal.

DISCUSSION

Monoclonal gammopathy refers to the presence of monoclonal immunoglobulin in the serum or urine, produced by an abnormal B-cell clone. MGUS occurs in approximately 3% of persons, 50 years of age or older [1,2]. It encompasses a heterogeneous spectrum of disorders ranging from overt multiple myeloma to quiescent MGUS. Traditionally, MGUS was considered a benign precursor condition; however, the recognition of MGCS has redefined this understanding. MGCS denotes cases where monoclonal gammopathies, though not meeting the diagnostic criteria for multiple myeloma or other overt malignancies, still cause significant organ dysfunction. This paradigm shift has profound implications for risk stratification and management, as even small clones may give rise to clinically important tissue or organ damage. The kidneys, nervous system, and skin are among the most commonly affected organs in MGCS [3].

MGCS encompasses a spectrum of organ-specific disorders, including renal, neurological, and dermatological disorders that are typically defined. MGCS-associated myopathy, including AL amyloidosis-associated myopathy and Sporadic Late Onset Nemaline Myopathy (SLONM) is well described. In addition to these two, a few case reports suggest that MGCS or multiple myeloma can cause myopathy secondary to unknown pathogenic mechanisms [2]. In amyloidosis there is deposition of light chain amyloid fibrils within the muscles, deranging its architecture and functioning, causing weakness, fatigue or pseudohypertrophy. These might also deposit in the myocardium, causing stiffness, impaired ventricular relaxation, causing restrictive cardiomyopathy, arrhythmias [4].

In a case series of three patients with MGCS-associated myopathy, there was subacute, symmetrical weakness of axial and proximal muscles with stiffness [5]. There was a presence of vacuoles filled with glycogen on muscle biopsies and all three responded well to intravenous immunoglobulin and immunosuppressive agents. Another case by Soontrapa P et al., was of a case of Polyneuropathy, Organomegaly, Endocrinopathy, M protein, Skin changes (POEMS) syndrome with severe distal and mild proximal weakness along with sensory impairments [6]. None of these cases showed cardiac involvement with MGCS, while a case reported by de Berny Q et al., in a 52-year-old male with proximal muscle weakness, facial diplegia and hypertrophic cardiomyopathy [7]. He showed <10% clonal plasma cells with no evidence of myeloma or amyloidosis. In our case too, there were elevated lambda light chains as in de Berny Q et al., case. Differentiating MGCS from other myositis is crucial, such as AL amyloid-related myositis, which has the classic pseudohypertrophy. SLONM was eliminated from the diagnosis due to the absence of respiratory muscle weakness [8]. Dermatomyositis manifests with certain skin conditions along with proximal muscle weakness [9]. In our case, high risk of bleeding and resolution of muscle oedema on repeat imaging (local ultrasound) were reasons for not undergoing muscle biopsy.

Cardiac involvement in plasma cell dyscrasias is classically associated with light-chain (AL) amyloidosis in the form of infiltrative restrictive cardiomyopathy. However, recent studies suggest that MGUS may independently confer an increased risk of cardiovascular diseases and is hypothesised to be mediated through chronic low-grade inflammation, endothelial dysfunction, and possible subclinical light chain deposition even in the absence of overt amyloidosis. Speckle-tracking echocardiography has demonstrated impaired GLS in MGUS patients despite preserved left ventricular ejection fraction, suggesting early but clinically significant myocardial dysfunction. These observations may suggest the importance of cardiac screening in MGUS patients and evaluation for underlying plasma cell dyscrasias in unexplained heart failure with preserved ejection fraction [10,11]. Although this case was asymptomatic from a cardiac viewpoint and was primarily evaluated to exclude amyloidosis, such observations reinforce that subclinical cardiac involvement in MGUS may warrant reclassification of these entities under the spectrum of MGCS. Diagnostic confirmation by myocardial biopsy could not be established due to the high risk in the presence of factor X deficiency.

Acquired factor X deficiency is a rare but recognised haemostatic abnormality that is most commonly associated AL amyloidosis and is attributed to adsorption of factor X onto deposited amyloid fibrils leading to its accelerated clearance. However, only a few isolated reports have described it in patients with multiple myeloma or MGUS without detectable amyloid deposition. The precise pathophysiology remains poorly understood but may involve non-amyloid monoclonal protein binding to coagulation factors or endothelial surfaces, altering factor X bioavailability [12].

The presence of myositis-like symptoms and autoantibodies posed a diagnostic challenge. However, the absence of dermatomyositis features with persistent coagulation abnormalities prompted further evaluation, highlighting the need for tissue diagnosis and malignancy workup in atypical cases.

CONCLUSION(S)

This case report highlights the importance of considering mimics of rheumatological diseases in presence of atypical manifestations. Awareness of such MGCS presentations is crucial to avoid misdiagnosis and ensure timely therapy. The concept of MGCS emphasises that organ damage, not tumour burden, drives the need for intervention here and that clone-directed therapy, even in the absence of myeloma-defining criteria, may be warranted to preserve organ function.

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