



In the Idiopathic Inflammatory Myopathies, How Significant is Creatine Kinase Levels in Diagnosis and Prognosis? A Case Study and Review of the Literature

Travis C Sizemore*

Department of Internal Medicine, University South Carolina Greenville Health System, USA

*Corresponding author: Travis C Sizemore, Department of Internal Medicine, University South Carolina Greenville Health System, 5th floor support tower, 701 Grove Rd, Greenville, SC 29605, USA, Tel: 864-483-3147, E-mail: tsizemore@ghs.org

Abstract

Purpose/Methods: The clinical significance of creatine kinase [CK] levels in idiopathic inflammatory myopathies [IIM] has varied between studies. CK levels continue to be the most sensitive laboratory marker for muscle disease in IIM but vary depending upon the disease entity. The goal of this article was to further elucidate the clinical significance of CK levels in the setting of IIM, including role of CK in diagnostics and prognostication. A case report was described with a subsequent literature review completed by searching within high quality peer-reviewed articles in the Cochrane Review database as well as Medline 1975-2015 with Key words creatine kinase, idiopathic inflammatory myopathies, polymyositis, and dermatomyositis.

Results/Conclusion: CK was found to be the most sensitive marker of muscle damage in IIM. The levels are variable and are related to specific disease entity. CK levels were found to be most elevated in necrotizing autoimmune myositis and lowest in inclusion body myositis. CK was also found to be normal in many instances of DM, which does not appear to be required for diagnosis or related to prognosis. Normal CK levels do not rule out IIM as a diagnosis, however, instances of such are more rare than normal. In cases of normal CK levels it appears to be beneficial to investigate aldolase levels. CK levels can also be normal in other types of myopathy, including: multiple cases of statin-associated myopathy, Parvovirus B19 myositis, and in rare cases of polymyositis. Therefore, CK should not be used as primary clinical diagnostic criteria nor to predict mortality. CK can be helpful to aid in the diagnosis but must be interpreted in the context of patient's complete clinical symptoms of proximal myopathy and cutaneous involvement and investigational studies including: myopathic pattern on electromyography, muscle and skin biopsy.

Introduction

Idiopathic inflammatory myopathies (IIM) are a group of diseases characterized by inflammation of the skeletal muscle. The main subtypes of inflammatory myopathies include dermatomyositis (DM), polymyositis (PM), necrotizing autoimmune myopathies (NAM) and sporadic inclusion-body myositis (sIBM). DM is the primary focus of this article and is characterized by skin involvement in addition to inflammation of skeletal muscle. DM usually presents with elevated muscle enzymes [1]. A case is presented here with normal muscle

enzymes in a patient with characteristic clinical and histopathological features of DM. The goal of this article was to further elucidate the clinical significance of CK levels in the setting of IIM with the aid of literature review following an interesting case. Additionally, to investigate the significance and strength of the history and physical exam in the face of conflicting laboratory data.

Case Presentation

A 77 year old Caucasian female previously in excellent health without comorbidities and currently not taking any medications, presented with a three month history of rash and subsequent muscle weakness. The rash was first noted primarily in the sun-exposed areas of the tops of the ears, around the eyes, face and upper chest. Patient was seen following an evaluation by dermatology department who had performed a skin biopsy which noted streptococcal impetigo infection as well as perivascular inflammation of the dermis with eosinophilic infiltration. She was treated with penicillin with some improvement but with worsening of the rash. Prior to illness patient had been an avid swimmer with no deficits in her physical ability or functional status. She then began to experience myalgia and weakness in her legs which subsequently affected her arms and trunk. She noted difficulty rising from a chair, climbing stairs, dyspnea on exertion walking from room to room, and difficulty swallowing. She presented to the Emergency Department for evaluation of these progressive symptoms.

On physical exam she was noted to have a violaceous rash to the forehead, upper eyelids and cheeks as well as violaceous papules on the dorsal aspects of the metacarpophalangeal joints bilaterally consistent with Gottron's papules. In addition there was an erythematous V-shaped rash to the sun-exposed portion of the upper chest consistent with a shawl sign. The patient was noted to have poor strength in the proximal muscle groups of the upper and lower extremities; only able to resist against gravity. She was notably dyspneic with minimal exertion. Lab findings were notable for a normal CK, a minimally elevated aldolase (7.6 units/liter), a moderately elevated myoglobin, and elevated C-reactive protein (> 250 mg/L). ANA was positive with 1:80 titer. Jo-1 antibodies was negative. A modified barium swallow study showed increased oral transit time and moderate dysphagia. An EMG of the right upper and lower limbs revealed patchy denervation

in proximal muscles with typical myopathic waveforms consistent with myositis. Muscle biopsy revealed mild perifascicular atrophy and a chronic mononuclear inflammatory infiltrate. Neoplasia screening was conducting including CT Chest/Abdomen/Pelvis, mammography. Colonoscopy screening was normal at age of 65, as well as a normal cervical cancer screen at age of 65. The patient was started on a course of oral prednisone 80 mg daily with improvement noted to rash and improvement in her muscle weakness. A pulmonary consultation was made with unremarkable pulmonary function tests.

Methods

Following a case review, a literature review was completed by conducting a search within high quality peer-reviewed articles in the Cochrane Review database as well as Medline 1975-2015 with key words creatine kinase, idiopathic inflammatory myopathies, polymyositis, and dermatomyositis.

Results/Discussion

The IIM disease subsets are differentiated by a high degree of variability in disease presentation. The prevalence of IIM as a group is about 1 in 100,000 with annual incidence is approximately one - two per million adults and is more common in females [1]. There is an association with paraneoplastic disease and IIM in recent data, especially the subset DM [2] in addition to a DM-association with multiple pulmonary complications that can contribute to significant morbidity and mortality [3]. Cancer screening is recommended and was completed in the patient included in our case study. The different cutaneous manifestations include: 1) heliotrope rash - a purplish red rash surrounding eyes and eyelids 2) Gottron papules - raised erythematous plaques on elbows and hands 3) Shawl and V-sign - rash in shawl distribution along dorsal trunk and then a V-neck shaped sunburn like rash, respectively 4) Mechanic's hands - erythematous roughened skin changes of the palms and fingers with dirty - appearing horizontal lines across lateral and palmar aspects of fingers. Clinically amyopathic dermatomyositis (CADM) is a subset of DM that presents with little or no evidence of myositis but with typical cutaneous manifestations. CADM represents approximately 20% of cases of DM [4].

Pathophysiology

The mechanism causing myositis in IIM is poorly understood. It has been postulated that activation of the endoplasmic reticulum stress pathway contributes, specifically a disruption in this process [5], resulting in a complement-mediated microangiopathy that causes destruction of capillaries and in increase in inflammation [6]. In addition, there has been suggested a possible pathway involving aminoacyl t-RNA synthetase (ARS) molecules, and proteolytic fragments produced during inflammation [7].

Diagnosis and evaluation

There are many novel antibodies suggested to aid in diagnostics, including eight variable antisynthetases, anti-SRP, -200/100 (HMGCR), -Mi-2, -CADM-140 (MDA5), -SAE, -p155, -MJ (NXP-2), and -PMS1 [8]. The previous novel antibodies were not evaluated in the case do the overwhelming evidence of patient's diagnose without the need for further serum antibody investigation.

Clinical assessment of the patient can be assisted with the use of multiple distinct tools including: Myositis Damage Index (MDI), Myositis disease activity assessment tool (MDAAT), the Physician and Patient/Parent Global Activity (PGA) assessment, or Manual muscle testing (MM) [9]. Clinical assessment tools were not utilized in this particular case, again because of the overwhelming clinical and histopathological clinical clues. Accurate diagnosis is imperative; it is important to differentiate IIM from IIM-like conditions because of the potential for IIM-related therapy to result in toxic adverse effects in the setting of misdiagnosis [10].

CK was found to be the most sensitive marker of muscle damage in IIM. Serum elevation of CK levels are postulated to occur when

there is damage to the sarcolemma and z-disks [11-13]. The levels vary depending on the disease entity with highest CK levels observed in necrotizing autoimmune myositis and lowest in inclusion body myositis [14]. CK was also found to be normal in many instances of DM, which at first thought to be related to poor prognosis [15] however, in subsequent studies, there has been difficulty in associating normal CK levels with a poor prognosis in both DM and PM [16-18]. Normal CK levels can be seen in myopathies with an underlying etiology other than DM, such as statin-associated myopathy, Parvovirus B19 myositis, thyrotoxic myopathy and in rare cases of PM [19-22]. In addition, the case patient was observed with dermatomyositis with normal CK levels.

Treatment: IIM treatment is primarily accomplished by corticosteroids. However, there are multiple side effects, including a statistically significant increased risk of thromboembolic arterial events in IIM treated with corticosteroids [23] thus; immunosuppressive agents are increasing in frequency of use. Combination approach of corticosteroids with immunosuppressive therapy can lead to a decrease in duration and dose of corticosteroid [24]. In the present case, patient had responded to corticosteroids appropriately and taper had already been initiated. Methotrexate was considered if patient were to clinically regress during steroid taper consideration.

This particular case patient presented with highly characteristic and disabling clinical features of DM but with normal or minimal elevation in muscle enzymes and negative serologies in regard to Anti-Jo 1 antibody as well as SRP. Muscle biopsy revealed perifascicular atrophy which historically supports a diagnosis of DM [25]. Clinical improvement including decreased muscle weakness was noted with initiation of steroids in this case patient. This case demonstrates the significance and strength of the history and physical exam in the face of conflicting laboratory data as this patient was initially ignored as IIM because of the lack of rise in CK. DM should not immediately be dismissed following a normal investigation of CK levels. In addition it is important to differentiate IIM from IIM-mimics because of the many adverse effects associated with the treatment of IIM.

References

1. Iaccarino L, Ghirardello A, Bettio S, Zen M, Gatto M, et al. (2014) The clinical features, diagnosis and classification of dermatomyositis. *J Autoimmun* 48-49: 122-7.
2. Selva-O'Callaghan A, Trallero-Araguás E, Grau-Junyent JM, Labrador-Horrillo M (2010) Malignancy and myositis: novel autoantibodies and new insights. *Curr Opin Rheumatol* 22: 627-632.
3. Miller SA, Glassberg MK, Ascherman DP (2015) Pulmonary complications of inflammatory myopathy. *Rheum Dis Clin North Am* 41: 249-262.
4. Sato S, Kuwana M (2010) Clinically amyopathic dermatomyositis. *Curr Opin Rheumatol* 22: 639-643.
5. Lightfoot AP, McArdle A, Jackson MJ, Cooper RG (2015) In the idiopathic inflammatory myopathies (IIM), do reactive oxygen species (ROS) contribute to muscle weakness? *Ann Rheum Dis* 74: 1340-1346.
6. Dalakas MC (2011) Pathophysiology of inflammatory and autoimmune myopathies. *Presse Med* 40: e237-247.
7. Levine SM, Rosen A, Casciola-Rosen LA (2003) Anti-aminoacyl tRNA synthetase immune responses: insights into the pathogenesis of the idiopathic inflammatory myopathies. *Curr Opin Rheumatol* 15: 708-713.
8. Lazarou IN, Guerne PA (2013) Classification, diagnosis, and management of idiopathic inflammatory myopathies. *J Rheumatol* 40: 550-564.
9. Iaccarino L, Pegoraro E, Bello L, Bettio S, Borella E, et al. (2014) Assessment of patients with idiopathic inflammatory myopathies and isolated creatin-kinase elevation. *Auto Immun Highlights* 5: 87-94.
10. Hilton-Jones D (2014) Myositis mimics: how to recognize them. *Curr Opin Rheumatol* 26: 663-670.
11. Brancaccio P, Lippi G, Maffulli N (2010) Biochemical markers of muscular damage. *Clin Chem Lab Med* 48: 757-767.
12. Brancaccio P, Maffulli N, Buonauro R, Limongelli FM (2008) Serum enzyme monitoring in sports medicine. *Clin Sports Med* 27: 1-18, vii.
13. Brancaccio P, Maffulli N, Limongelli FM (2007) Creatine kinase monitoring in sport medicine. *Br Med Bull* 81-82: 209-30.
14. Dalakas MC (2015) Inflammatory muscle diseases. *N Engl J Med* 372: 1734-

15. Fudman EJ, Schnitzer TJ (1986) Dermatomyositis without creatine kinase elevation. A poor prognostic sign. *Am J Med* 80: 329-332.
16. Fernandez-Sola J, Pou JC, Junyent JM, Urbano-Manquez A (1991) Normal creatine kinase activity in idiopathic inflammatory myopathy: does it have prognostic implications? *J Rheumatol* 18: 1640-1641.
17. La Montagna G, Manzo C, Califano E, Tirri R (1988) Absence of elevated creatine kinase in dermatomyositis does not exclude malignancy. *Scand J Rheumatol* 17: 73-74.
18. Nicholls D (1987) Dermatomyositis without creatine kinase elevation. *Am J Med* 83: 182-183.
19. Chawla J (2011) Stepwise approach to myopathy in systemic disease. *Front Neurol* 2: 49.
20. Oliver ND, Millar A, Pendleton A (2012) A case report on parvovirus b19 associated myositis. *Case Rep Rheumatol* 2012: 250537.
21. Trøseid M, Henriksen OA, Lindal S (2005) Statin-associated myopathy with normal creatine kinase levels. Case report from a Norwegian family. *APMIS* 113: 635-637.
22. Kenyon C, Pillay K, Heckmann JM (2010) Beware of 'normal' creatine kinase levels in HIV-associated polymyositis. *S Afr Med J* 100: 156-157.
23. Tisseverasinghe A, Bernatsky S, Pineau CA (2009) Arterial events in persons with dermatomyositis and polymyositis. *J Rheumatol* 36: 1943-1946.
24. Iaccarino L, Bartoloni E, Gerli R, Alunno A, Barsotti S, et al. (2014) Drugs in induction and treatment of idiopathic inflammatory myopathies. *Auto Immun Highlights* 5: 95-100.
25. Vattemi G, Mirabella M, Guglielmi V, Lucchini M, Tomelleri G, et al. (2014) Muscle biopsy features of idiopathic inflammatory myopathies and differential diagnosis. *Auto Immun Highlights* 5: 77-85.