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Case report

Diagnostic role of technitium-99m bone scan in severe COVID-19-associated myositis ☆,☆☆

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ABSTRACT

Coronavirus disease 2019 (COVID-19), initially appreciated as a respiratory illness, is now known to affect many organs in the human body. Significant data has become available on muscle involvement, with creatinine kinase elevations present in a significant percentage of patients. For those with suspected COVID-19-associated myositis, the imaging modality of choice has been gadolinium-enhanced magnetic resonance imaging; however, the use of technitium-99 m bone scan has not been previously reported. Here, we report two cases of COVID-19 patients with severe elevation in creatinine kinase who underwent technitium-99 m bone scan. The resulting images showed diffuse symmetrical muscle involvement. Both patients developed acute renal injury due to rhabdomyolysis. To our knowledge, this is the first report of bone scan as a diagnostic imaging modality for COVID-19-associated myositis.

Introduction

Myositis is defined as inflammation of muscle, typically characterized by pain, tenderness, swelling, and weakness [1]. The most sensitive laboratory finding is elevation in creatinine kinase (CK). Small elevations in CK are often seen in asymptomatic cases, but higher elevations are associated with electrolyte imbalances, acute renal failure, disseminated intravascular congestion, and death [2].

Elevation of CK levels in patients with COVID-19 infection is relatively common, with prevalence as high as one third of patients [3,4,5]. The mechanism of this elevation, whether by direct viral infection of muscle, toxic effects of cytokines, or another mechanism, is unclear [6]. The few muscle biopsies that have been done on COVID-19-associated myositis patients have been characterized as unremarkable [7,8], or notable for HLA upregulation suggesting an inflammatory myopathy [9], or alternatively, suggestive of upregulation of type I interferon leading to the accumulation of proteins that are toxic to myocytes [6]. COVID-19-associated myositis has led to elevation in CK as high as 1,083,744 U/L, though most cases are far less severe [10]. The anatomical distribution of COVID-19-associated myositis and its imaging characteristics have yet to be fully characterized. One case report of non-contrast computed tomography (CT) imaging in COVID-associated myosi-

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tis showed symmetrical proximal upper extremity and back muscle sarcopenia with high attenuation foci presumed to represent calcifications [11], while other case reports employed gadolinium-based contrast MRI to show symmetrical paraspinal and thigh muscle edema and enhancement [9,12].

Technitium-99 m bone scan (Tc-99 m) has long been investigated as an imaging modality for characterization of skeletal muscle disease [13]. The mechanism for radiotracer uptake by affected muscle is poorly understood, though some reports have suggested the methyl diphosphonate (MDP) tracer binds readily to calcium and hydroxyapatite crystals in ischemic and necrotic muscle tissue [14,15]. Bone scans have been studied in polymyositis/dermatomyositis patients, where sensitivity was demonstrated to be 71% [16]. One case report documents the utility of a bone scan in myositis ossificans [17]. To our knowledge, Tc-99 m bone scan has not been reported as a diagnostic tool in COVID-19-associated myositis.

In comparisons of imaging techniques in skeletal muscle disease, MRI has been shown to be superior to both CT and ultrasound [18,19,20]. Advantages of bone scan over MRI include lower cost and wider field of view [16]. Furthermore, reliable identification of myositis on MRI requires gadolinium-based contrast agents that produce characteristic high signal intensity in the active phase of STIR and fat-saturated gadolinium-enhanced T1-weighted images [21]. Concerningly, gadolinium-based contrast agents have been linked to the occurrence of nephrogenic systemic fibrosis in renally impaired patients, especially those with a pre-existing pro-inflammatory state [22]. Here, we present two cases of patients found to have COVID-19 and associated severe CK elevation, and in whom novel use of Tc-99m-MDP bone scan showed diffuse symmetrical muscle myopathy. Muscle and renal biopsies were obtained from the second patient.

Case presentations

Case 1

A 64-year-old African American male with end stage renal disease was brought to the emergency department after four days of progressive malaise and weakness. He also reported abdominal pain, loss of appetite, and non-bloody, non-bilious vomiting. He denied fevers, chills, cough, shortness of breath, chest pain, diarrhea, and constipation. In addition to end stage renal disease, his past medical history was significant for insulin dependent type II diabetes, hypertension, and heart failure with preserved ejection fraction. On exam, his vital signs were normal. He had largely symmetrical weakness throughout his upper and lower extremities, and was unable to ambulate. He did not have any skin rashes. He had last been dialyzed on the day prior to presentation.

Complete blood count was normal except for an elevated neutrophil: lymphocyte ratio. Complete metabolic panel was notable for hyperkalemia of 7.1 mmol/L (Ref: 3.5-5.5 mmol/L), blood urea nitrogen of 66 mg/dL (Ref: 6-22 mg/dL), creatinine of 11.5 mg/dL (Ref: 0.8-1.6 mg/dL), and an anion gap of 21 (Ref: 3-15 mmol/L). Initial CK was 19,525 U/L (Ref: 30-200 U/L). Transaminitis was evident with AST of 1,104 U/L (Ref: 10-37 U/L) and ALT of 189 U/L (Ref: 5-40 U/L) with a normal INR. EKG showed sinus rhythm without signs of ischemia. Infectious workup included a COVID-19 RT-PCR nasal swab that resulted positive. Additionally, his interleukin-6 level was 157 pg/ml (Ref: 0-7 pg/ml), ferritin was 15,347 ng/ml (Ref: 22-322 ng/ml), and CRP was 9.9 mg/dL (Ref: 0.0-0.5 mg/dL).

Chest X-ray was unremarkable. CT scan of abdomen and pelvis with contrast showed new multifocal ground glass opacities in the lung bases, without other acute abnormality. Infectious workup, including blood cultures, respiratory viral panel, and urine antigen testing, was otherwise negative. His smear evaluation was normal. HIV and hepatitis panels were negative. His thyroid studies were normal. Blood testing was negative for all drugs of abuse, including amphetamines, cocaine metabolites, and phencyclidine. The patient did not drink alcohol. The patient did take rosuvastatin 20 mg daily, which was stopped on admission.

The patient had no history of autoimmune diseases nor past myopathies. ANA immunoassay was negative. Rheumatoid arthritis factor was not elevated. Antibody testing for anti-DNA, anti-histone, anti-Smith, anti-RNP, anti-SS-A, anti-SS-B, anti-citrulline, p-ANCA, c-ANCA, anti-MPO, anti-PR3, anti-Jo-1, anti-SCL-70, and anti-PML-SCL-75 were all negative. Accordingly, the diagnosis of COVID-19-associated myositis was made.

Given his rapidly increasing CK, the choice of imaging modality to identify the area of myopathy was discussed. The patient was not a candidate for gadolinium-enhanced MRI due to pre-existing renal disease. Accordingly, a Tc-99 m–MDP bone scan was performed, which showed abnormal radiotracer uptake throughout the torso, upper extremities including forearm, and proximal lower extremities (Fig. 1).

Case 2

A 34-year-old African American male presented to the emergency department for evaluation of body aches, fevers, and chills for one week. He had previously tested positive for COVID-19 two days prior at an outpatient clinic. He also reported loss of appetite and decreased urine output, which had become very dark. He denied chest pain, dyspnea, coughing or dysuria. He denied any significant past medical history and took no long-term medications. For his acute symptoms, he was taking over-the-counter Dayquil and ibuprofen but denied exceeding the daily limits. On examination, his vital signs were normal. He had diffuse muscle tenderness in upper and lower extremities but did not have any skin rashes.

His complete blood count was normal except for an elevated neutrophil: lymphocyte ratio. His basic metabolic panel was significant for acute kidney injury with creatinine of 7 mg/dL (Ref: 0.8-1.6 mg/dL), BUN of 74 mg/dL (Ref: 6-2 mg/dL), anion gap of 26 (Ref: 3-15 mmol/L) and hyperkalemia of 7.2 mmol/L (Ref: 3.5-5.5 mmol/L). His CK was noted to be more than 200,000 U/L (Ref: 30-200 U/L). His AST was 2,420 (Ref: 10-37 U/L), ALT was 368 U/L (Ref: 5-40 U/L) and INR was normal. EKG showed sinus rhythm without signs of ischemia. Infectious workup included a COVID-19 RT-PCR nasal swab that resulted positive. Additionally, his interleukin-6 level was 50 pg/ml (Ref: 0-7 pg/ml), ferritin was 909 ng/ml (Ref: 22-322 ng/ml), and CRP was 6.8 mg/dL (Ref: 0.0-0.5 mg/dL).

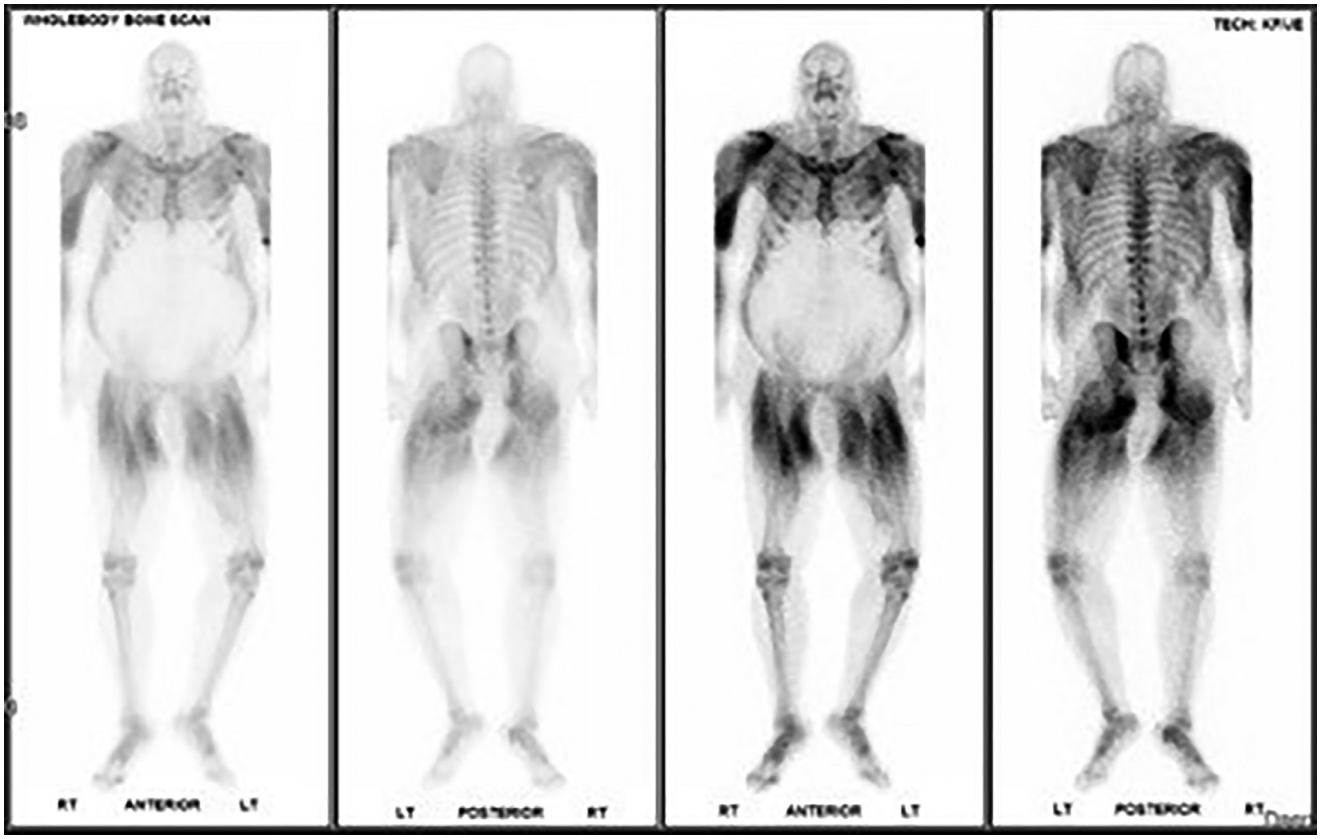

Fig. 1 – Tc-99m bone scan in Case #1 showing widespread radiotracer uptake.

Chest X-ray was unremarkable. An ultrasound of the kidneys showed increased echogenicity consistent with medical renal disease. Extensive infectious and serological workup similar to case #1 was negative and a diagnosis of COVID-19-associated myositis was made. The patient was not a candidate for gadolinium-enhanced MRI because of acute kidney injury, and accordingly underwent a Tc-99 m–MDP bone scan, which showed abnormal radiotracer uptake similar to case #1 (Fig. 2). Muscle biopsy identified active myonecrosis with some regenerative changes, and no evidence of vasculitis (Fig. 3). Renal biopsy showed tubular injury characterized by attenuation or sloughing of the apical portion of tubular epithelial cells associated with luminal accumulation of acellular clusters or globules of eosinophilic material (Fig. 4A). The cast material was strongly positive for myoglobin (Fig. 4B). Additional analysis to identify COVID-19 in both kidney and muscle tissue was performed. In situ hybridization for the presence of SARS-CoV-2 RNA was performed using RNAscope (ACD, Newark) [23] and showed no evidence of viral RNA in neither kidney nor muscle tissue sample. Similarly, no staining for COVID-19 was detected by immunohistochemistry (Leica BOND-III platform, Wetzlar, Germany) [24] in either sample.

In both cases, CK levels continued to rise despite intravenous fluids. Dialysis was initiated, which eventually led to a decrease in CK levels over several days. The patients were also treated with intravenous steroids for the duration of their in-hospital stay. They did not have any other COVID-19-related complications such as respiratory or heart failure. In the second case, there was no renal recovery, and chronic dialysis was arranged.

Discussion

These cases demonstrate novel use of Tc-99 m bone scan to characterize the distribution of COVID-19-associated myositis. As seen in the images above, the diffuse and symmetrical distribution of radiotracer uptake is striking. Notably, radiotracer uptake was not only seen in proximal muscles, but also in bilateral forearm muscles. Advantages of Tc-99 m bone scan over MR imaging include field of view enhancement, avoidance of gadolinium, lower cost, and ability to compare and select the best site for potential muscle biopsy. The avoidance of gadolinium is especially important in hospitalized COVID-19 patients, who are at increased risk for acute kidney injury and often exhibit a pro-inflammatory state—both of which are risk factors for the development of gadolinium-associated nephrogenic systemic fibrosis [22,25,26].

Furthermore, the first case illustrates a remarkably severe case of rhabdomyolysis (CK 340,180 U/L) in a COVID-19 patient who was taking a statin medication. A similar case was described by Anklesaria et al. [10], in which a 57-year-old male on 5mg rosuvastatin developed severe rhabdomyolysis and acute renal failure. In that case, CK reached 1,083,744 U/L, and while that patient did not have respiratory symptoms at

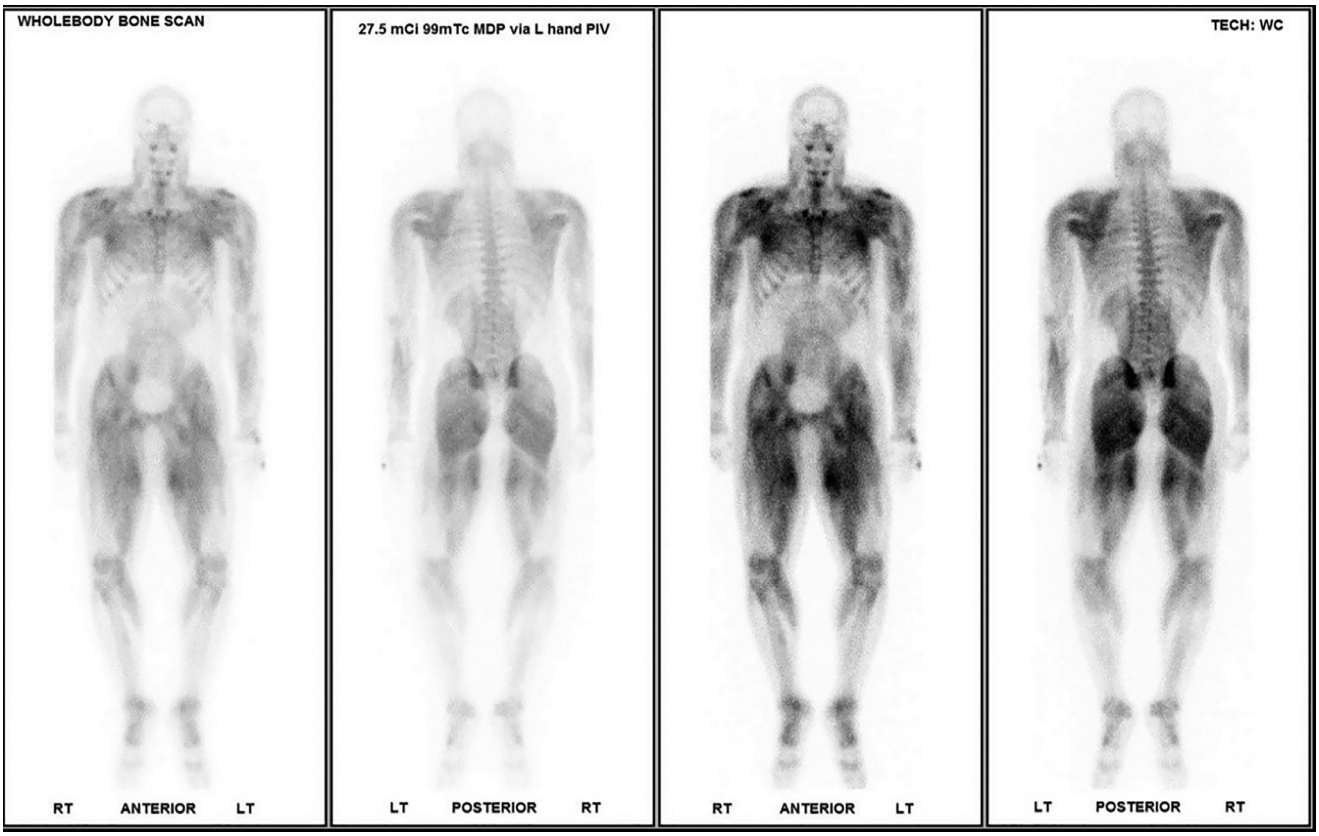

Fig. 2 – Tc-99m bone scan in Case #2 showing widespread radiotracer uptake.

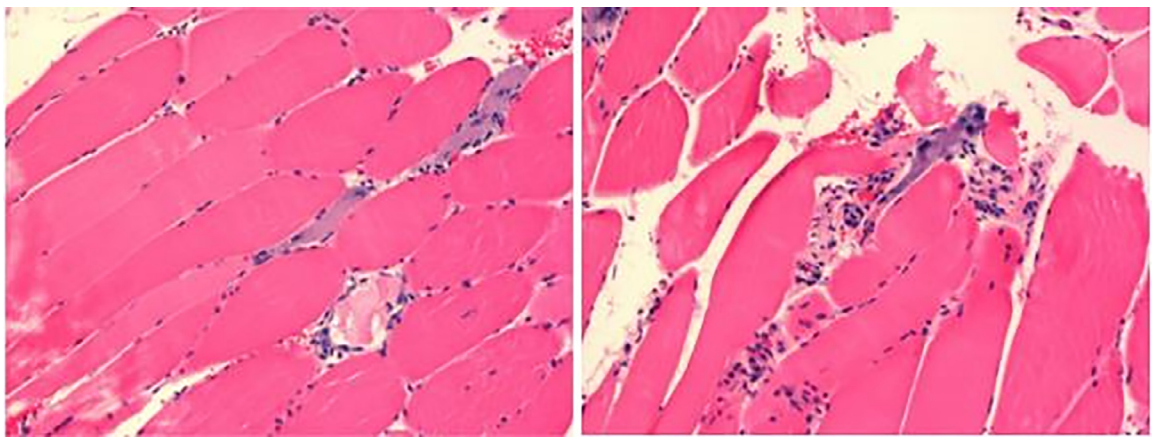

Fig. 3 – Muscle tissue from Case #2 showing myonecrosis (H&E stain; original magnification 40x).

presentation, he did eventually require intubation on HD#5 for respiratory failure. The degree to which statins, and rosuvastatin specifically, contribute to such severe COVID-19-associated myositis is not yet determined. The general mechanism of statin-associated myopathy is believed to be mitochondrial dysfunction, calcium signal disruption, and pro-apoptotic signaling [27]. It is unclear how the proposed Type I interferonopathy in COVID-19-associated myositis may interact with the cellular pathways responsible for deleterious effects of statins [6].

The patient in the second case was not on any statin medications, which suggests an alternate mechanism may play a role in COVID-19-associated myositis. Prior to presentation, he had taken substantial doses of ibuprofen, which has been reported to cause rhabdomyolysis. However, the proposed mechanism of this effect—induction of a renal tubular acidosis and subsequent hypokalemia—does not match the clinical scenario in this patient [28].

Kidney and muscle tissue samples from the second case did not show any evidence of direct COVID-19 viral invasion.

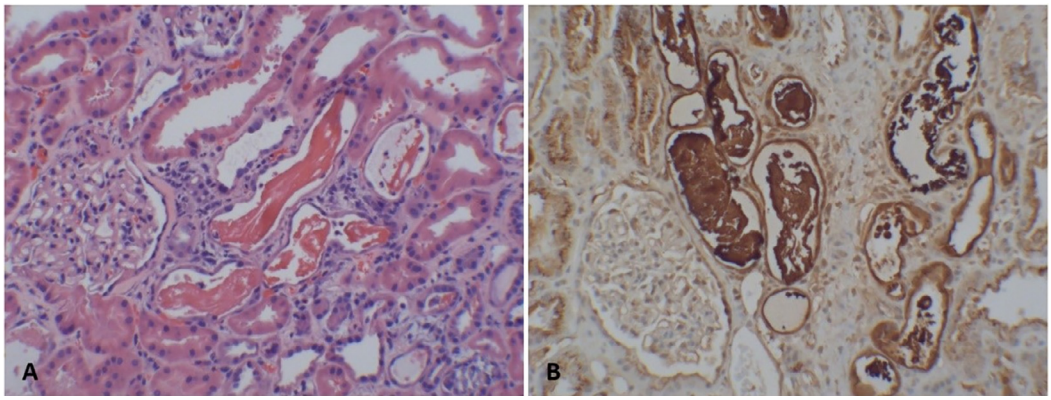

Fig. 4 – Numerous eosinophilic myoglobin casts with associated acute tubular injury in Case #2 (A); H&E stain, original magnification 200x). Strong staining of the casts for myoglobin (B); immunohistochemistry, original magnification 200x).

This finding is consistent with previously reported kidney and muscle biopsies in COVID-19 patients, and suggests an alternate pathway for the resulting inflammatory myopathy [6,24]. Further study is needed to characterize the mechanism of COVID-19-associated myositis.

Overall, there is a considerable degree of heterogeneity in the presentation of patients with COVID-19 and concomitant CK elevations, with cases presenting early or late in the disease course, and with or without the typical pneumonia syndrome [29,30]. It's notable that among severe cases with CK levels above 70,000, including the cases described here, respiratory involvement was usually a late development, if present at all [8,10,31,32,33,34,35,36]. Given that acute kidney injury and need for renal replacement therapy are common—28% and 9%, respectively—in hospitalized COVID-19 patients, the two cases presented here add to an increasing body of evidence that assessment of CK levels has a role in the assessment and risk stratification of all COVID-19 patients, even when their respiratory symptoms do not indicate severe disease [25]. Furthermore, technitium-99m bone scan appears to be a good alternative to MRI with gadolinium-based contrast agent, especially in patients with renal involvement.

Patient consent

Written informed consent was obtained from these patients for their anonymized information to be published in this article.

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