Case report

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

Glen Hookey, MD*, Qamar Ahmad, MD, Thomas McCune, MD, Jolanta Kowalewska, MD, Barbara Amaker, MD, Nadeem Inayat, MD

EVMS Critical Care Medicine, Sentara Norfolk General Hospital, 600 Gresham Drive Norfolk VA 23507, USA

ARTICLE INFO

Article history:
Received 23 April 2021
Revised 6 May 2021
Accepted 7 May 2021
Available online 14 May 2021

Keywords:
COVID
Myositis
Bone scan
Rhabdomyolysis

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.

© 2021 The Authors. Published by Elsevier Inc. on behalf of University of Washington. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/)

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 myos-
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 diposphonate (MDP) tracer binds readily to calcium and hydroxypatite 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 large symmetrical weakness throughout his upper and lower extremities, and was unable to ambulate. He did not have any skin rashes. He had last been diazylated 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 rosvastatin 20 mg daily, which was stopped on admission.

The patient had no history of autoimmune diseases nor past myopathies. ANA immunosassay 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).
Chest X-ray was unremarkable. An ultrasound of the kidneys showed increased echogenicity consistent with medica
t 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 candi-
date 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). Re-
nal 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 anal-
ysis 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 plat-
form, Wetzlar, Germany) [24] in either sample.

In both cases, CK levels continued to rise despite intra-
venous 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 sec-
don 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 myosi-
tis. 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, avoid-
ance of gadolinium, lower cost, and ability to compare and se-
lect 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 nephro-
genic 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 de-
scribed 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. 1 – Tc-99m bone scan in Case #1 showing widespread radiotracer uptake.
presentation, he did eventually require intubation on HD#5 for respiratory failure. The degree to which statins, and rosvastatin 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.
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, technetium-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.

**REFERENCES**

[1] Crum-Cianflone NF. Bacterial, fungal, parasitic, and viral myositis. Clin Microbiol Rev 2008;21:473–94.
[2] Huerta-Alardin AI, Varon J, Marik PE. Bench-to-bedside review: rhabdomyolysis – an overview for clinicians. Crit Care 2005;9:158–69.
[3] Guidon AC, Amato AA. COVID-19 and neuromuscular disorders. Neurology 2020;94:959–69.
[4] Guan W-J, Ni S-Y, Hu Y, Liang W-H, Ou C-Q, He J-X, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;382:1708–20.
[5] Li L-Q, Huang T, Wang Y-Q, Wang Z-P, Liang Y, Huang T-B, et al. COVID-19 patients’ clinical characteristics, discharge rate, and fatality rate of meta-analysis. J Med Virol 2020;92:577–83.
[6] Manzano GS, Woods JK, Amato AA. Covid-19-associated myositis caused by type I interferonopathy. N Engl J Med 2020;382:1708–20.
[7] Almadani M, Shiferson A, Swearingen B, Shih M, Jacob T, Rhee R. Compartment syndrome secondary to viral myositis as initial presentation in COVID-19 patient. J Vasc Surg Cases Innov Tech 2020;6:524–7.
[8] Cunha M, Pinho J, Lopes M, Trigueiros F, Braz S, Medeiros F. A case of corticosteroid-responsive SARS-CoV-2 related massive rhabdomyolysis. IDCases 2020;22:e00946.
[9] Zhang H, Charmchi Z, Seidman RJ, Anziska Y, Velayudhan V, Perk J. COVID-19-associated myositis with severe proximal and bulbar weakness. Muscle Nerve 2020;62:537–60.
[10] Anklesaria Z, Frankman J, Gordin J, Zhan J, Liu AK. Fatal rhabdomyolysis in a COVID-19 patient on rosuvastatin. Cureus 2020;12:e11186.
[11] Husain R, Cucuerla-Solano I, Dayan E, Jacobi AH, Huang M. Rhabdomyolysis as a manifestation of a severe case of COVID-19: a case report. Radiol Case Rep 2020;15:1633–7.
[12] Mehan WA, Yoon BC, Lang M, Li MD, Rincon S, Buch K. Parasplinal myositis in patients with COVID-19 infection. AJNR Am J Neuroradiol 2020;41:1949–52.
[13] Brown M, Swift TR, Spies SM. Radiosotope scanning in inflammatory muscle disease. Neurology 1976;26:517–20.
[14] Siegel BA, Engel WK, Derrr EC. Localization of technetium-99m diphosphonate in acutely injured muscle: relationship to muscle calcium deposition. Neurology 1977;27:230.
[15] Vita G, Harris JB. The uptake of 99m technetium diphosphonate into degenerating and regenerating muscle: a correlational histological and biochemical study. J Neurol Sci 1981;51:339–54.
[16] An YS, Suh CH, Jung JY, Kim HA. Role of bone scan in the assessment of polymyositis/dermatomyositis. Clin Rheumatol 2015;34:699–706.
[17] Drane WE. Myositis ossificans and the three-phase bone scan. AJR Am J Roentgenol 1984;142:179–80.
[18] Yu JS, Habib P. MR imaging of urgent inflammatory and infectious conditions affecting the soft tissues of the musculoskeletal system. Emerg Radiol 2009;16:267–76.
[19] Lamminen AE, Hekali PE, Tiula E, Suramo I, Korhola OA. Acute rhabdomyolysis: evaluation with magnetic resonance imaging compared with computed tomography and ultrasonography. Br J Radiol 1989;62:326–30.
[20] Moratalla MB, Braun P, Fornas GM. Importance of MRI in the diagnosis and treatment of rhabdomyolysis. Eur J Radiol 2008;65:311–15.
[21] Schulze M, Köttler I, Ernemann U, Fenchel M, Tzaribatchev N, Claussen C, et al. MRI findings in inflammatory muscle diseases and their noninflammatory mimics. AJR Am J Roentgenol 2009;192:1708–19.
[22] Khawaja AZ, Cassidy DB, Al Shakarchi J, McGrogan DG, Inston NG, Jones RG. Revisiting the risks of MRI with gadolinium based contrast agents—review of literature and guidelines. Insights Imaging 2015;6:553–8.
[23] Wang F, Flanagan J, Su N, Wang LC, Bui S, Nielson A, et al. RNAscope: a novel situ RNA analysis platform for formalin-fixed, paraffin-embedded tissues. J Mol Diagn 2012;14:22–9.
[24] Sharma P, Uppal NN, Wanchoo R, Shah HH, Yang Y, Parikh R, et al. COVID-19-associated kidney injury: a case series of kidney biopsy findings. J Am Soc Nephrol 2020;31:1948–58.
[25] Silver SA, Beaubien-Souilgy W, Shah PS, Hare S, Blum D, Kishibe T, et al. The prevalence of acute kidney injury in patients hospitalized with COVID-19 infection: a systematic review and meta-analysis. Kidney Medicine 2021;3:83–98.
[26] Manjili RH, Zarei M, Habibi M, Manjili MH. COVID-19 as an acute inflammatory disease. J Immunol 2020;205:12–19.
[27] Turner RM, Pirmohamed M. Statin-related myotoxicity: a comprehensive review of pharmacokinetic, pharmacogenomic and muscle components. J Clin Med 2019;9:22.
[28] Dang MH, Wu S, Sia C. Ibuprofen-induced renal tubular acidosis—a rare cause of rhabdomyolysis: a case report. Oxford Med Case Rep 2016;8:212–14.
[29] Singh B, Kaur P, Mechineni A, Maroules M. Rhabdomyolysis in COVID-19: report of four cases. Cureus 2020;12:e10686.
[30] Buckholz AP, Kaplan A, Rosenblatt RE, Wan D. Clinical characteristics, diagnosis, and outcomes of 6 patients with COVID-19 infection and rhabdomyolysis. Mayo Clin Proc 2020;95:2557–9.
[31] Chedd NR, Udit S, Solhiou Z, Panawala MY, Sheridan AM, Barkoudah E. COVID-19 and rhabdomyolysis. J Gen Intern Med 2020;35:3087–90.
[32] Gefen AM, Palumbo N, Nathan SK, Singer PS, Castellanos-Reyes LJ, Sethna CB. Pediatric COVID-19-associated rhabdomyolysis: a case report. Pediatr Nephrol 2020;35:1517–20.
[33] Alrubaye R, Choudhary H. Severe rhabdomyolysis in a 35-year-old woman with COVID-19 due to SARS-CoV-2 infection: a case report. Am J Case Rep 2020;21:e926733-1–e926733-5.
[34] Solis JG, Pineda AE, Minuti PA, Sanchez AA. Case report: rhabdomyolysis in a patient with COVID-19: a proposed diagnostic-therapeutic algorithm. Am J Trop Med Hyg 2020;103:1158–61.
[35] Shanbhag A, Manaktala PS, Rizvi H, Frey K, Narayanan R. COVID-19 presenting as severe rhabdomyolysis with normal renal function. Cureus 2020;12:e9556.
[36] Samies NL, Pinninti S, James SH. Rhabdomyolysis and acute renal failure in an adolescent with coronavirus disease 2019. J Pediatric Infect Dis Soc 2020;9:507–9.