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Rhabdomyolysis as the main manifestation of coronavirus disease 2019

Rheumatology key message

- Creatine kinase levels should be monitored in patients with COVID-19, especially when complaining about muscle pain and weakness.

SIR, Coronaviruses mainly affects the respiratory tract in humans [1]. Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first reported in Wuhan, China in the late December 2019. It rapidly spread worldwide and was declared a pandemic in March 2020. COVID-19 patients commonly present with fever, myalgia, dyspnoea and dry cough. Symptoms that are reported less often include expectoration, headache, haemoptysis and diarrhoea. Mild muscle damage and increased creatine kinase (CK) levels have commonly been observed in Wuhan patient cohorts [1–3]. We present the case of a patient infected by novel coronavirus in Madrid (Spain) whose primary symptoms were indicative of a musculoskeletal pathology.

A 78-year-old white man was admitted with a 2 week history of asthenia that had progressively worsened. He occasionally presented fevers up to 38°C and severe disabling myalgia and muscle weakness, with dark-coloured urine in the last 48 h (Fig. 1).

Pre-morbidly he had hypertension and type 2 diabetes mellitus. Cough, dyspnoea and other respiratory symptoms were not reported, nor were previous trauma, vigorous exercise or intramuscular injections. He denied statin use, new medication (both prescription and over the counter), alcohol ingestion or illicit drugs.

On initial review he was afebrile, haemodynamically stable, with a respiratory rate of 18 breaths/min and peripheral oxygen saturation of 96%. Skin and mucous membranes had no signs of dehydration. On auscultation, his lungs had bilateral and equal air entry, but rough breath sounds. Muscle power was normal and neither haematoma nor cutaneous lesions were found. Nasopharyngeal swab SARS-Cov-2 PCR was positive and on chest X-ray there was bilateral lung infiltration. Blood tests showed elevated CK of 22511 U/l (normal 6–174), aspartate aminotransferase (AST)/glutamic oxaloacetic transaminase (GOT) 937 U/l (normal 40–50), lactic acid dehydrogenase (LDH) 972 U/l (normal 140–240), D-dimer 1400 ng/ml (normal 100–200) and CRP 131.2 mg/l (normal 0–5). His renal function had declined [serum creatinine 3.20 mg/dl (normal 0.3–1.3), urea 131 mg/dl (normal 15–45)] and myoglobinuria was detected. Electrolytes were normal except for mild hyponatremia [sodium 134 mmol/l (normal 135–145)]. Complete blood count indicated that haemoglobin was 16.2 g/dl (normal 13–17.5) and the neutrophil:lymphocyte ratio was 7.25.

He was diagnosed with bilateral pneumonia caused by SARS-Cov-2, rhabdomyolysis and acute renal failure. The patient was hospitalized and treated with aggressive fluid therapy, hydroxychloroquine and ritonavir/lopinavir. In the following days his muscle pain resolved and his urine samples normalized. Throughout his hospital admission he displayed no signs of fever or respiratory symptoms. CK levels dropped to 11 200 (2 days later) and 559 U/l (4 days later). The biochemistry results [AST/GOT, ALT/glutamic pyruvic transaminase (GPT), LDH and CPR] and the renal function improved completely. Six days after admission he was discharged, his primary symptoms had resolved and he only complained of remaining asthenia.

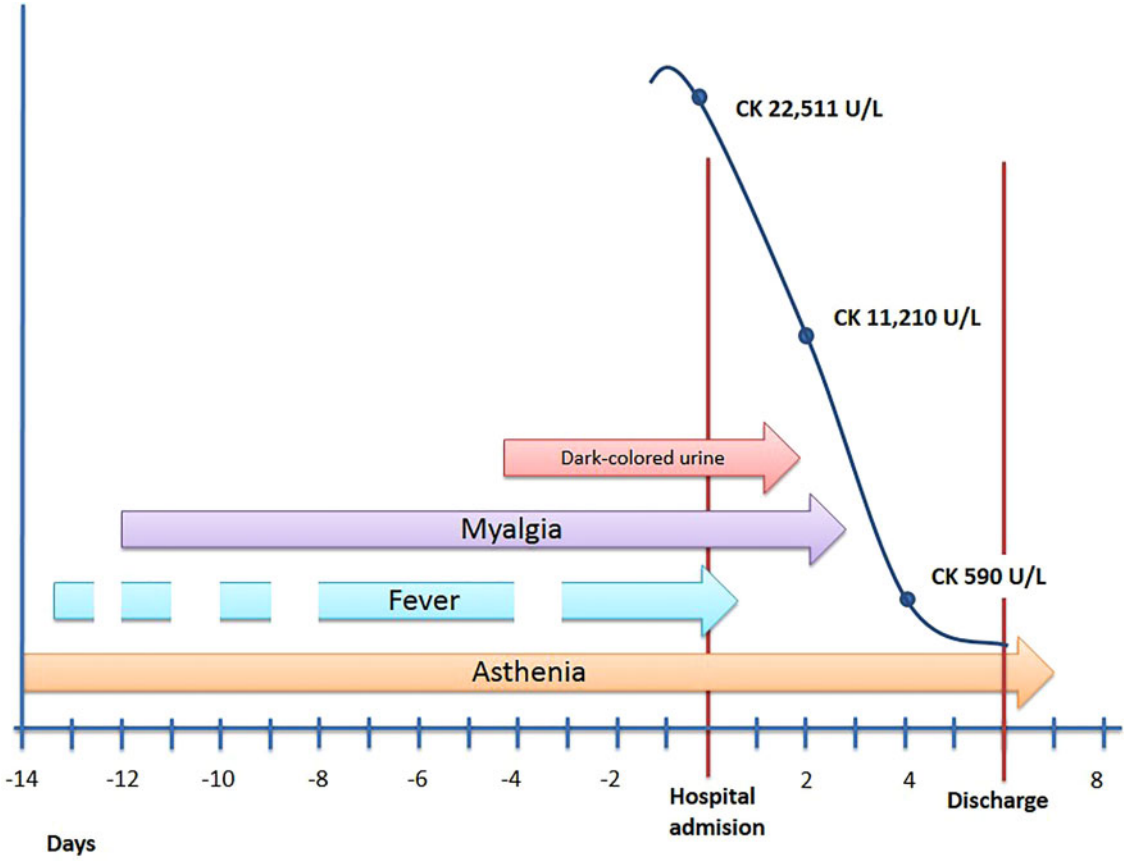
Myalgia, fatigue and weakness are frequently related to viral infections, included in the coronavirus family group. Recent patient case series published in the setting of COVID-19 infection in China have described myalgia and elevated CK as frequent findings. The Lancet published a report of 41 patients hospitalized with pneumonia: 33% of them showed CK elevation and that number increased up to 46% in intensive care unit patients [1]. Along the same line, muscle pain was present in 11% of patients and 13% had elevated CK in another 99 patient case series [2]. High levels of CK-MB (muscle and brain isoform) were found in 4.5% of a 201 patient case series in Wuhan, [3] showing a significant association with acute respiratory syndrome distress development. Further research is needed in order to determine whether these data are applicable to European patient cohorts.

Muscle weakness and elevated serum CK levels were also commonly found in coronavirus case series reported in the 2003 outbreak of SARS and the 2012 outbreak of Middle East respiratory syndrome (MERS) [4]. Myopathic changes with focal myofibril necrosis were described in histological post-mortem examination. Farcas et al. [5] found SARS-CoV in 12% of muscle samples during the Toronto outbreak. Furthermore, authors of a recent study [6], found viral particles in macrophages infiltrating skeletal muscles in MERS-CoV patients during histopathological analyses. These findings may concern human coronavirus pathogenesis. Zhou et al. [7] confirmed that SARS-CoV-2 uses the same cellular entry receptor, angiotensin converting enzyme 2 (ACE2), as SARS-CoV. Interestingly, ACE2 is expressed in many of the organs in which we observed SARS-CoV dissemination, including skeletal muscle.

Rhabdomyolysis usually manifests with myalgia, an increase in CK levels (reasonably >10 times the upper limit), myoglobinuria and acute renal failure. The main causes of rhabdomyolysis include autoimmune myopathies, septicaemia, alcohol use, drug abuse or infection. Bacterial and viral infections represent 5% of rhabdomyolysis cases and influenza virus accounts for 42% of the total cases of virus-mediated rhabdomyolysis [8].

Even if myalgia and CK elevation are relatively frequent, rhabdomyolysis symptoms have been rarely reported in SARS-CoV-2 outbreaks. Jin and Tong [9] describe a 60-

Fig. 1 Time course of patient's symptoms and signs



year-old man, COVID-19 confirmed, with fever and cough as initial manifestations, who suffered pain, weakness, high CK elevation and myoglobinuria, indicating the diagnosis of rhabdomyolysis.

It is relatively common that COVID-19 patients have clinical signs of dehydration, and hypovolaemia may contribute to renal impairment and consequently to a mild increase in CK levels. However, our patient presented with extremely high levels of CK together with severe muscular symptoms, whereas clinical signs of dehydration were not present. Thus we assume rhabdomyolysis as the main cause of elevated CK and the decline in renal function in this case.

In conclusion, we report a case of rhabdomyolysis associated with novel coronavirus infection. COVID-19 commonly presents with respiratory symptoms ranging from mild to fatal. However, this case suggests that muscle damage and CK elevation, even without respiratory symptoms, should still be considered as a potential COVID-19 presentation. Consequently it is important to monitor CK levels in COVID-19 patients, especially when they complain of muscle pain and weakness.

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Comment on: The reliability of immunoassays to detect autoantibodies in patients with myositis is dependent on autoantibody specificity

Sir, I was interested to read the article by Tansley *et al.* published in the February 2020 issue of Rheumatology [1]. The authors tried to address the reliability of commercial assays to identify myositis-specific and -associated autoantibodies. They aimed to compare the results of two commercial immunoassays with the results obtained by protein immunoprecipitation. Autoantibody status was determined using radiolabelled protein immunoprecipitation for patients referred to their laboratory for myositis autoantibody characterization. For each autoantibody of interest, the sera from 25 different patients were analysed by line blot (Euroline Myositis Antigen Profile 4, EuroImmun, Lübeck, Germany) and dot blot (BlueDiver, D-tek, Mons, Belgium). Sera from 134 adult healthy controls were analysed. They reported that overall commercial assays performed reasonably well, with high agreement (Cohen's $\kappa > 0.8$). Notable exceptions were the detection of rarer anti-synthetases, with $\kappa < 0.2$, and detection of anti-TIF1γ, where κ was 0.70 for the line blot and 0.31 for the dot blot. Further analysis suggested that the proportion of patients with anti-TIF1γ may recognize a conformational epitope, limiting the ability of blotting-based assays that utilize denatured antigen to detect this clinically important autoantibody. A false-positive result occurred in 13.7% of samples analysed by line blot and 12.1% analysed by dot blot.

Although this article has provided valuable information, there are some substantial points that need to be considered to help clarify the method and accurately interpret the study. It is important to know that two important weaknesses of Cohen's κ to assess agreement are as follows. First, it depends on the prevalence in each category, which means it is possible to have different κ values having the same percentage for both concordant and discordant cells. This means the prevalence of concordant cells can be 90% (85% and 5% *vs* 45% and 45%) and discordant cells 10%; however, we get different κ values (0.4 as moderate for 85% and 5% *vs* 0.8 as very good for 45% and 45%, respectively). The κ value also depends on the number of categories [2–5]. It is crucial to know that agreement (reliability, precision, repeatability) and validity (accuracy) are two completely different methodological issues [2]. False positive and false negative as well as sensitivity, specificity, positive predictive value, negative predictive value and positive and negative likelihood ratios are among the estimates to assess validity (accuracy) of a diagnostic test and have nothing to do with agreement [6–8]. Agreement (precision), as a different methodological issue, should be assessed using appropriate tests. For qualitative variables, weighted κ can be applied with caution. Regarding quantitative variables, the intraclass correlation coefficient and Bland–Altman plot are among well-known approaches [2].

The authors concluded that the assays analysed do not perform well for all myositis-specific and -associated autoantibodies and overall false positives are relatively common. Such a sweeping conclusion should be supported by the above-mentioned methodological and statistical issues on agreement and validity. In this letter I emphasize two important weaknesses of Cohen's κ to assess agreement as well as methodological differences between agreement and validity. These differences should be taken into account by clinical researchers when assessing agreement and validity issues, otherwise misinterpretation of the results may occur.

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