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Harish Gopalakrishna
hkgp44@gmail.com

Ahmad Al-abdouh

Gayatri Nair

Vinod Solipuram

Ammer Bekele

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Reply to Letter to the Editor Titled “Before Blaming Legionella for Severe Rhabdomyolysis, Consider Alternative Triggers”

Harish Gopalakrishna*, Ahmad Al-Abdouh, Gayatri B. Nair, Vinod Solipuram

Department of Medicine, Saint Agnes Healthcare, Baltimore, MD, USA

Dear Editor,

We appreciate the interest shown by the reviewers and their comments regarding our article titled “Immensely High Creatine Kinase Levels in a Case of Rhabdomyolysis Due to Legionnaires' Disease in a Patient on Tofacitinib: A Case Report and Literature Review”.¹

Severe hypokalemia with potassium levels less than 2–2.5 mmol/L has been shown to cause rhabdomyolysis with creatinine kinase (CK) elevation to less than 20,000 IU/L.^{2,3} But in our patient, hypokalemia (potassium of 3 mmol/L) was mild and was immediately corrected to normal reference range and so is unlikely to trigger rhabdomyolysis with CK elevation up to 512,820 IU/L.¹ Hyponatremia can also trigger rhabdomyolysis and Legionella pneumonia is known to cause hyponatremia, a retrospective analysis by Fiumefreddo et al. showed that about 46% of patients with legionella pneumonia had hyponatremia with sodium levels less than 131 mmol/L.⁴ In an observational study by Lim et al. looking into association between hyponatremia and rhabdomyolysis showed that prevalence of rhabdomyolysis in mild (sodium between 130 and 134 mmol/L), moderate (sodium between 125 and 129 mmol/L) and severe (sodium <125 mmol/L) hyponatremia was 9.4%, 2.5%, and 2.1%, respectively. The peak CK elevation seen in this study in moderate hyponatremia was 40,000 IU/ml.⁵ However, considering CK elevation of about 500,000 IU/L in our patient and the known fact hyponatremia is a common finding in legionella pneumonia, we cannot blame the transient hyponatremia to be etiology for the rhabdomyolysis.

Drugs especially losartan was another possible trigger as reported in the past was considered as etiology in our case. Even though losartan could be a possible culprit, dose at which it can cause rhabdomyolysis is not certain.⁶ Our patient was on low dose losartan 25 mg once daily monotherapy for hypertension and no other diuretics¹ making it less likely the cause for rhabdomyolysis. Even though Tofacitinib was immediately discontinued after admission, it could have played a role to potentiate the degree rhabdomyolysis seen in our patient as mentioned in the title of the case report.¹ On initial presentation patient was lethargic and slow to respond to commands possibly due to underlying sepsis, hypoxemia and electrolyte abnormalities. However, as mentioned in case report she did not have any focal neurological deficits, neck rigidity or signs of meningeal irritation. She had Computed tomography of the head without contrast done on admission which showed no acute intracranial abnormality. On subsequent days, with treatment of hypoxemia, management of sepsis and correction of underlying electrolyte abnormalities her mental status improved. So, additional work up for initial lethargy was not indicated as patient returned to baseline mental status within 24 h of admission.

Macrolides especially azithromycin or fluoroquinolones like levofloxacin are the mainstay of treatment for legionella pneumonia.⁷ Our patient received azithromycin. Even though there was initial increase in creatinine kinase on azithromycin, she completed 14 days course of azithromycin with subsequent decline and eventual resolution of rhabdomyolysis.¹ This makes azithromycin induced CK elevation unlikely. This patient was admitted

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* Corresponding author.
E-mail address: hkqp44@gmail.com (H. Gopalakrishna).

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and treated in 2019 before the first case of COVID 19 was identified in USA.⁸ Cultures obtained from endotracheal secretions are gold standard for diagnosing legionella pneumonia, but previous antibiotic exposure and expertise needed for its isolation can limit the sensitivity.⁹ Reviewers have raised some interesting thoughts. As we have explained in this reply, we believe we have ample evidence to consider legionella pneumonia along with tofacitinib to be the major contributors for this patient's rhabdomyolysis as we mentioned in the original case report.¹

Conflicts of interest

None of the authors have any conflicts of interest.

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