CASE REPORT

TANGO-2 with Severe and Prolonged Rhabdomyolysis in a 2-year Old Male with Human metapneumovirus Infection

Rowida Kheireldin [a] **Sameer Imdad** [a] **Waseem Ostwani** [b]

Coresponding author(s): waseem.ostwanimd@promedica.org

[a] Divisions of Pediatrics, Department of Pediatrics, University of Toledo, College of Medicine and Life Sciences, Toledo, OH 43614, USA, and [b] Divisions of Critical Care Medicine, Department of Pediatrics University of Toledo College of Medicine and Life Sciences, Toledo, OH 43614, USA

We report a unique case of prolonged acute rhabdomyolysis in a 2-year-old male with known TANGO-2 mutation with delayed peak in creatinine kinase levels secondary to human metapneumovirus infection. Creatinine kinase peaked at 424,760 U/l on day 9 of hospitalization. Resolution of rhabdomyolysis was achieved using aggressive management with intravenous fluids with optimal urine output and no kidney injury. TANGO-2 patients may develop severe and prolonged rhabdomyolysis with a delayed peak suggesting the need for prolonged inpatient hospitalization to prevent life-threatening complications.

TANGO-2 | rhabdomyolysis | creatinine kinase | infection

TANGO-2 Mutation usually presents with metabolic encephalomyopathies, hypoglycemia, recurrent rhabdomyolysis, developmental delay and seizures. Acute rhabdomyolysis with TANGO-2 presents with a wide array of symptoms ranging from profound muscle weakness and disorientation to coma (1). When it comes to rhabdomyolysis in patients with TANGO-2 mutation, CK can be significantly elevated up to greater than 200,000 U/l (1).

Case Report

Patient Information

A 2-year-old male with a known TANGO-2 mutation presented to the emergency department with a 3-day history of fever, upper respiratory symptoms along with decreased oral intake. Mother also noted that the urine was darker in color. The rest of the review of symptoms was non-contributory.

Objective for Case Reporting

Rhabdomyolysis may progress over a week with extremely high CK levels. We suggest prolonged inpatient hospitalization for patients with TANGO-2 mutation and rhabdomyolysis in order to prevent life-threatening complications.

Case

In the ED, labs were significant for decreased bicarbonate level at 19 mmol/L with an anion gap of 17 mmol/L and a mildly elevated creatinine kinase of 232 U/L. Electrocardiogram showed a normal QT interval. Patient was given a fluid bolus of normal saline then admitted to the pediatric floor where he was continued on 1.5 times maintenance intravenous fluids with dextrose 10% and Levocarnitine as per his emergency management plan. The on-call geneticist was consulted and recommended monitoring CK levels and following EKG daily for the increased risk of QT prolongation. Respiratory pathogen panel was positive for Human metapneumovirus. IV fluids were cut to 1/2 maintenance on day 3 of admission to help stimulate better oral feeds. On day 4 of hospitalization, the patient's urine started to look more concentrated and CK levels were increased to 7,031 indicating continued rhabdomyolysis. IV fluids were increased to twice maintenance as CK level increased steadily to 43,000 U/L, patient was refusing to walk due to pain with total

Submitted: 05/20/2020, published: 08/11/2020.

Freely available online through the UTJMS open access option

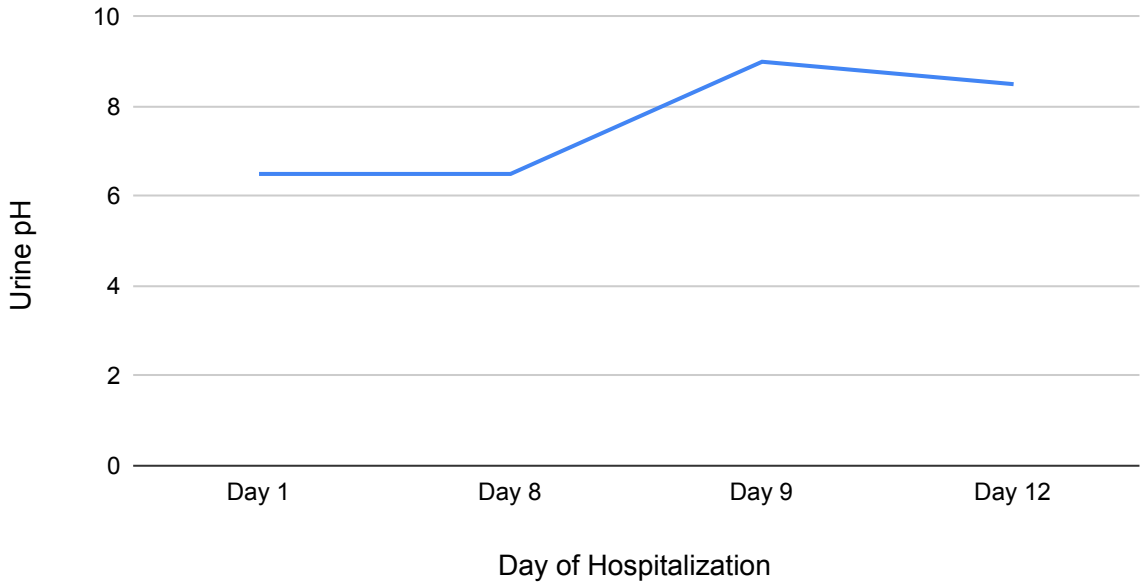

Fig. 1. Urine pH during hospital course

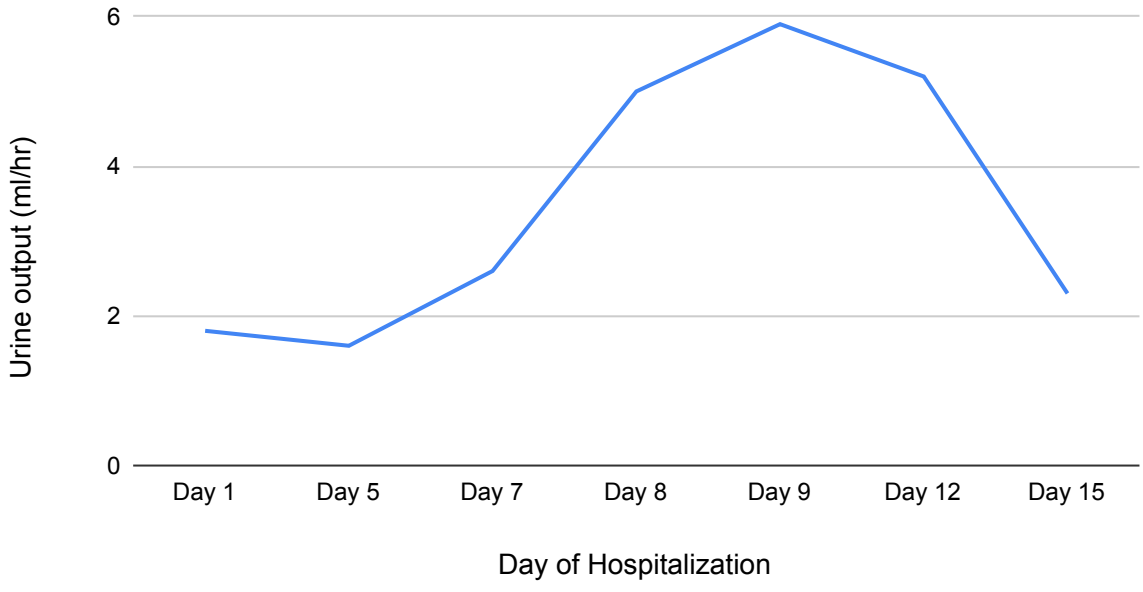

Fig. 2. Urine output during hospital course

body aches and he was transferred to the Pediatric Intensive Care Unit for close monitoring, foley catheter was placed and urine output was maintained at 3 ml/kg/hr with subsequent alkalinization of IV fluids utilizing sodium bicarbonate to achieve urine PH of 6-8 (Fig. 1, 2).

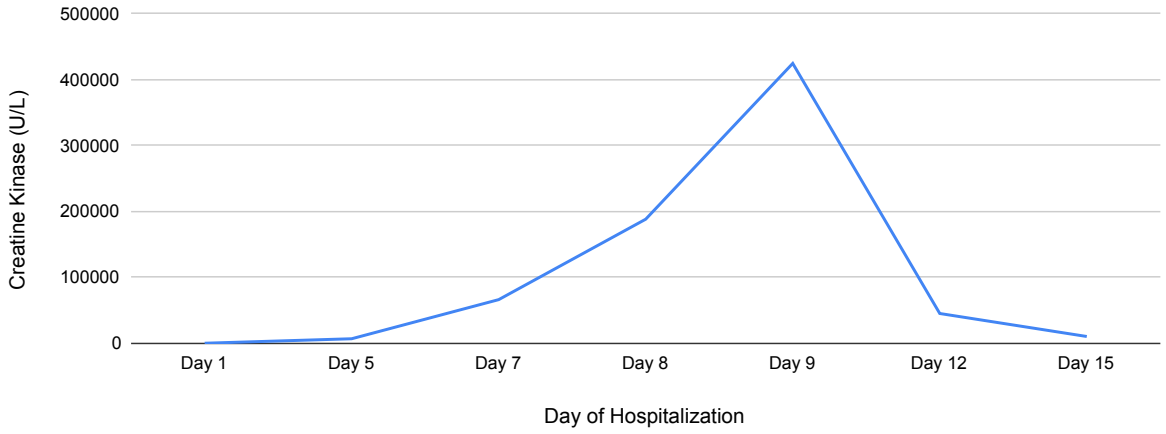

Fig. 3. Creatine kinase (CK) levels during hospital course

Infection work-up did not reveal any bacterial infection as a secondary cause of this ongoing rhabdomyolysis. Patient's CK level peaked at 424,760 U/L on day 9 of hospitalization (Fig.3). Renal function remained stable despite increasing CK levels with aggressive medical management. Liver enzymes were elevated up to the 1000 range with normal synthetic liver function and bilirubin, which was attributed to acute illness. Blood pressure throughout hospital stay remained normal with mild hypertension during the PICU stay that was resolved. This could be attributed to the high rate of fluids administration during the management of rhabdomyolysis. Aggressive medical management for rhabdomyolysis was deescalated due to downtrending CK levels and transaminitis, along with clinical improvement.

Discussion

TANGO-2 Mutation is an autosomal recessive disorder characterized by metabolic encephalomyopathies, hypoglycemia, hyperammonemia, recurrent rhabdomyolysis, developmental delay and seizures. It is caused by variations in the transport and Golgi organization 2 (TANGO2) gene responsible for creating the proteins that play a critical role in many functions of the body (2). The TANGO2 Research Foundation reports fewer than 30 individuals affected with the disorder worldwide (2). The onset of first symptoms may occur as early as 4 months and up to 27 months of age (3). During an acute illness, affected individuals may develop arrhythmias with QT prolongation, being the leading cause of death in children with TANGO-2 mutations. During a metabolic crisis, some patients may develop acute rhabdomyolysis. Acute rhabdomyolysis with TANGO-2 presents with symptoms that vary from profound muscle weakness, ataxia, and disorientation to coma (1). Myoglobinuria can lead to renal failure.

Mechanisms leading to metabolic crises and rhabdomyolysis among patients with TANGO-2 are not well understood or reported in the literature (2). Rhabdomyolysis has been reported in patients with TANGO-2 with age ranging between 5 months up to 13 years of age (5). It can be recurrent resulting in acute renal tubular damage, acute kidney injury and renal failure(6). Recurrent rhabdomyolysis can be fatal in severe cases with 8-10 % mortality rate. Acute kidney injury with cardiac arrhythmia due to hyperkalemia are the main causes of increasing mortality(5). Triggers for rhabdomyolysis associated with genetic abnormalities include fever, exercise, infection, general anesthesia, drugs, emotional stress and changes in diet (7). Human metapneumovirus infection was the trigger factor in our case.

CK serum level is useful in the diagnosis and management for rhabdomyolysis. CK levels gradually increase in the first 12 hours of rhabdomyolysis with a peak at 3-5 days, and return to baseline within 6-10 days (8,9). Serum CK levels exceeding five times the upper limit of normal are commonly used for diagnosing rhabdomyolysis(8). In rhabdomyolysis secondary to viral myositis, the serum CK level usually peaks at 1-5 days (10,11).

There is no available data regarding the range of CK levels when it comes to rhabdomyolysis in patients with TANGO-2 mutation. CK can be significantly elevated up to greater than 200,000 U/l (1). Lalani et al reported CK ranging from 16,674 U/l and up to 287,230 U/l (5). In a case report of a 3-year-old patient with TANGO and rhabdomyolysis, the peak for CK was 225,000 IU/l on day 4 of his illness (6). Dines et al study showed CK elevation was present in 11 out of 14 patients ranging from 14,000 to 278,000 U/l with rhabdomyolysis documented in 9 of these patients, with 1 patient presenting at 4 months with elevated creatinine kinase secondary to rhinovirus (3). In our patient, the highest CK was 424,760 U/l on day 9 of hospitalization which is the highest reported CK number in the literature for rhabdomyolysis secondary to TANGO-2 mutation.

Complications of rhabdomyolysis include high anion gap metabolic acidosis, hyperkalemia, acute kidney injury and disseminated intravascular coagulopathy(12). Acute kidney injury is the most common systemic complication of rhabdomyolysis and occurs in 5-50 % of the patients with poor outcome (12,13). Elevated serum CK has not been shown to correlate with the severity of AKI (13,14). In spite of the highly elevated CK level in our patient, with close monitoring and aggressive management, his renal function remained stable with no evidence of AKI.

There is a lack of guidelines for the best treatment in children with rhabdomyolysis (8,10). Management of acute rhabdomyolysis involves hydration and alkalinization of the urine in order to prevent development of AKI, monitoring for electrolyte imbalance, correction of metabolic acidosis, and management of other complications. An emergency plan for patients with TANGO-2 should be

in place in order to minimize the risk of life-threatening rhabdomyolysis and cardiac arrhythmias. Aggressive hydration with fluids to achieve urine output of 3 ml/kg/hr is recommended. The role of mannitol and bicarbonate in the treatment of rhabdomyolysis in pediatric patients remains controversial, although urine alkalinization to pH of ≥ 7.0 using sodium bicarbonate-containing fluids has been recommended in some studies (1,13). Hemodialysis may be indicated for severe fluid overload and electrolyte abnormalities (1). The rhabdomyolysis in our case peaked at day 9 of hospitalization highlighting the importance of close monitoring and management for rhabdomyolysis in TANGO-2 patients to a longer extent compared to other causes of rhabdomyolysis.

The small number of reported cases, the lack of large clinical studies, and the recent identification of TANGO-2 is not allowing complete understanding of the prognosis and clinical course of this genetic abnormality (2). Further research is needed to help understand this mutation and the mechanism behind the associated rhabdomyolysis.

Conclusion

Acute rhabdomyolysis in TANGO-2 patients presents with various levels of illness severity. Even with mild illness, rhabdomyolysis may take over a week until it peaks with extremely high CK levels suggesting the need for prolonged inpatient hospitalization in order to prevent life-threatening complications.

Conflict of interest

Authors declare no conflict of interest.

Authors' contributions

RK and SI wrote the initial draft of this case report. WO edited the manuscript and reviewed the paper. All authors read and approved the final document.

1. **Lalani S, et al. (2018), TANGO2-Related Metabolic Encephalopathy and Arrhythmias. GeneReviews.**
2. **Shott B, Miyake C, Neu D, Lalani S. (2019), Engaging Patients in Outcomes Research in TANGO2-related disorder. The Baylor College of Medicine and the TANGO2 Research Foundation Family Conference. Houston, Texas. Available at https://tango2research.org/.**
3. **Dines J, et al. (2019), TANGO2: expanding the clinical phenotype and spectrum of pathogenic variants. *Genet Med.* 21(3):601-607.**
4. **Elsayed E, Reilly R. (2010),Rhabdomyolysis: a review, with emphasis on the pediatric population. *Pediatr Nephrol.* 25(1):7-18.**
5. **Lalani S, et al. (2016) Recurrent Muscle Weakness with Rhabdomyolysis, Metabolic Crises, and Cardiac Arrhythmia Due to Bi-allelic TANGO2 Mutations. *Am J Hum Genet.* 98(2):347-357.**
6. **Ricci F, et al. G. (2017) Multi-system disorder and severe recurrent rhabdomyolysis due to TANGO2 mutations in a 3 year-old child. *Neuromuscular disorders.* Volume 27, Supplement 2, S207, October 01.**
7. **Scalco R, et al. (2015) Rhabdomyolysis: a genetic perspective. *Orphanet J Rare Dis.* 10:51.**
8. **Chavez L, Leon M, Einav S, Varon J.(2016) Beyond muscle destruction: a systematic review of rhabdomyolysis for clinical practice. *Crit Care* 20, 135.**
9. **Cervellin G, et al. (2017) Non-traumatic rhabdomyolysis:Background, laboratory features, and acute clinical management. *Clin Biochem.* 50(12):656-662.**
10. **Attanasi M, et al.(2018) A pediatric case of rhabdomyolysis with acute renal failure due to co-infection with Epstein-Barr virus and Human herpesvirus 6. *Arch Med Sci.* 14(1):254-256.**
11. **Goldsmith B, Hicks J. (1985)Rhabdomyolysis: two pediatric case reports., *Clinical Chemistry*, Volume 31, Issue 2, 314{317**
12. **Williams J,Thorpe C. (2014) Rhabdomyolysis, Continuing Education in Anaesthesia, *Critical Care and Pain*, Volume 14, Issue 4, 163{166**
13. **Chen CY, et al. (2013) Clinical spectrum of rhabdomyolysis presented to pediatric emergency department. *BMC Pediatr.* 13:134.**
14. **De Meijer A, Fikkers B,De Keijzer M, Van Engelen B, Drenth J. (2003) Serum creatine kinase as predictor of clinical course in rhabdomyolysis: a 5-year intensive care survey. *Intensive Care Med.* 29(7):1121-1125.**
15. **Lalani S, Miyake C, Burrage L. (2018) TANGO2-Related Metabolic Encephalopathy and Arrhythmias. National Organization for Rare Disorders (NORD).**