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Case Report: Herein, we report a case of *S. enteritidis* gastroenteritis complicated by rhabdomyolysis and acute kidney injury, which was successfully treated with hydration and antibiotics without dialysis. In this report, we reviewed all the previously published cases of rhabdomyolysis associated with *Salmonella* infection in English literatures and discussed the prevalence, pathogenesis and treatment.
Conclusion: Rhabdomyolysis was thought to be a rare complication of *Salmonella* infection. However, due to the variable manifestations that depend upon the extent and severity of muscle damage, rhabdomyolysis is perhaps under diagnosed as an extra-intestinal manifestation of *Salmonella* infection. Therefore, it is critical to recognize the condition promptly, initiate early antibiotics treatment and provide good supportive care. A high index of suspicion may help to reduce significant co-morbidities associated with the development of rhabdomyolysis in *Salmonella* infection.

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Keywords: Acute kidney injury, Gastroenteritis, Rhabdomyolysis, *Salmonella* infection

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INTRODUCTION

Salmonella is estimated to cause more than 1.2 million illnesses every year in the United States [1], with 19,000 hospitalizations and 380 deaths every year. Among over 2500 serotypes of *Salmonella*, only a few of them can cause human infection [2], which can be divided into two categories–those cause typhoid fever and those cause gastroenteritis. *Salmonella typhimurium* and—*enteritidis* are the two most common serotypes in the United States. *Salmonella* infection may have different clinical presentations. The elderly, children, and immunocompromised patients are more likely to have severe disease. The most common manifestation of salmonellosis is gastroenteritis, including fever, diarrhea, and abdominal pain 12–72 hours after infection, which accounts for 70% of cases. Extraintestinal manifestations are not uncommon and have been reported both in immunocompromised and immunocompetent patients involving a variety of organ systems, including acute cholecystitis [3], pancreatitis [4], acute pyelonephritis [5], osteomyelitis [6], myocarditis [7], encephalopathy [8], disseminated intravascular coagulation (DIC) and

multi-organ failure [9]. Rhabdomyolysis secondary to *Salmonella* infections was thought to be a rare complication and has only been reported a few times. Here, we present a case of rhabdomyolysis and acute kidney injury with *Salmonella enteritidis* infection in a middle-aged male.

CASE REPORT

A previously healthy 42-year-old African-American male presented to the emergency department with 20–30 watery stools daily for three days, accompanied by nausea and vomiting. Three days prior to admission, the patient ate lunch at a local restaurant and later that night, he developed fever, chills, muscle cramping and watery diarrhea. There was no dysuria, melena, no history of recent illness or antibiotic use or contact with persons with similar illness prior to admission. He denied any recent travel outside the United States. Only past medical history was asthma. The patient was a healthy and active man with no history of alcohol, tobacco or illicit drug use.

On physical examination, he appeared ill-looking and dehydrated. He was afebrile, with blood pressure of 122/89 mmHg. His pulse was weak but regular at 87 beats/min. Bowel sounds were present and active. Generalized abdominal tenderness without guarding or rebound or organomegaly was noted on palpation. No skin rash was appreciated. No muscular weakness was elicited.

Hematological laboratory findings and blood chemistry values on the day of admission and subsequent days are given in Table 1. Pertinent laboratory data on admission included leukocytosis $13.3x10^9$/L, and hemoglobin 16.6 g/dL. The serum creatinine level was elevated to 10.5 mg/dL, with an estimated glomerular filtration rate (GFR) of 5 mL/min per 1.73 m^2, suggesting acute kidney injury. The patient was found to have pure metabolic acidosis (anion gap 35). ALT and AST were mildly elevated. The creatinine kinase (CPK) level significantly elevated at 21 481 U/L. Urinalysis showed a specific gravity of 1.010 and a pH 5.5. A spot urine test showed urinary sodium of 9 mEq/L and creatinine 113 mg/dL, sample was positive for myoglobin. Rapid influenza and HIV tests were both negative. *Salmonella Group D enteritidis* was isolated from stool, while the blood and urine culture remained sterile. An abdominal ultrasound showed normal liver, spleen and kidney. Electrocardiogram showed sinus tachycardia and no ST-T wave changes.

The patient initially was managed by intravenous hydration and alkalization by sodium bicarbonate, he responded well to hydration. Patient was not on antibiotics until day 5 of admission when revealed *Salmonella* in stool culture. Ceftriaxone was initiated and one day later switched to oral ciprofloxacin. Good clinical response and complete normalization of most of the laboratory parameters were observed during treatment. On discharge, 7 days after admission, the patient was asymptomatic, enzyme levels had returned to normal, and serum creatinine decreased to 1.3.

DISCUSSION

Rhabdomyolysis is characterized by muscle pain and markedly elevated CPK level [10]. An elevated serum CPK to at least five times the upper limit of normal and usually greater than 5,000 U/L is diagnostic of rhabdomyolysis. Myoglobinuria may be present in rhabdomyolysis. Rhabdomyolysis has been reported in numerous disorders including the common etiologies [10] such as trauma, ischemic disorders, autoimmune diseases, drugs and toxins. It has also been associated with both viral and bacterial infections [11, 12] such as influenza, Coxsackievirus, Epstein-Barr virus, echovirus, HIV, *Legionella*, *Staphylococcus* and *Escherichia coli*. Rhabdomyolysis secondary to *Salmonella* infection has also been described in literature [4, 9, 13]. However, the mechanisms remain not fully elucidated. It was proposed that dehydration, hypoxia, electrolyte disturbances, bacterial invasion of the muscle, and *Salmonella* toxic effects on muscle cell metabolism could be responsible for muscle cell injury [14].

Acute kidney injury (AKI) is a well-known complication of rhabdomyolysis. The reported frequency of acute kidney injury ranges from 13% to approximately 50% [10]. Acute renal failure due to rhabdomyolysis in typhoid was first described as early as 1977 [13]. Later, non-typhoid *Salmonellae*, *i.e. Salmonella enteritidis, Salmonella bonariensis, Salmonella group C and Salmonella typhimurium,* have also been reported with this complication [4, 15, 16]. Therefore, rhabdomyolysis and AKI are potential complications of salmonellosis. Table 2 gives the characteristics of all the reported individual cases of rhabdomyolysis associated with microbiologically proven *Salmonella* infection in English language journals. Janssen et al. [17] reviewed over a two-year period of 44 hospitalized adult patients with *Salmonella* gastroenteritis, and reported 36% of the cases complicated with acute renal failure. However, during the course of *Salmonella* infection, the muscle involvement in some cases may or may not be clinically evident. Therefore, rhabdomyolysis is perhaps under diagnosed and may constitute an extraintestinal manifestation of the infection. In addition, the associated risk of renal failure is not correlated with the peak CPK level. Clinicians should be aware of this possibility of muscular involvement and development of acute renal failure. The occurrence of acute kidney injury in many patients is believed due to dehydration from gastroenteritis, tissue hypoxia from sepsis, rhabdomyolysis, nephrotoxicity of myoglobin [14]. Other rare causes of acute kidney injury in *Salmonella* infection include glomerulonephritis, acute tubular necrosis (ATN) and interstitial nephritis [4, 18].

The overall prognosis of acute kidney injury from *Salmonella* infection based on our review of reported

Table 1: Hematological and blood chemistry laboratory values

Day of admission	1	2	3	4	5	6	7
WBC (10^9/L)	13.3	8.1	6.3	5.3	6.8	8.8	9.5
Hg (g/dL)	16.6	15.0	13.2	12.7	12.7	12.5	12.2
PLT(10^9/L)	218	173	161	171	168	195	206
BUN (mg/dL)	54	68	62	37	18	13	14
Creatinine (mg/dL)	10.5	9.4	5.5	2.1	1.7	1.3	1.3
Serum Na (mEq/L)	127	126	131	131	133	136	137
Serum K (mEq/L)	5.5	4.5	3.6	3.1	3.4	3.3	3.6
Serum HCO_3^- (mEq/L)	16	17	18	27	32	35	25
ALT (U/L)	74	100	110	100	94	97	110
AST (U/L)	467	528	492	356	267	51	58
CPK (U/L)	21 481	25 102	--	11 426	5 660	1 241	849

WBC: white blood cell, Hg: hemoglobin, PLT: platelets, BUN: blood urea nitrogen, CPK: creatinine kinase

Table 2: Details of reported cases of rhabdomyolysis associated with *Salmonella* infection in English literature

Author (Reference)	Age	Sex	*Salmonella* Subtype/ Source	CPK (U/L)	WBC (10^9/L)	Serum Creatinine (mg/dL)	Treatment
Blaauw et al. [3]	27	F	*S. enteritidis*/Urine, stool, blood	45429	9.7	1.37	Ceftriaxone
Abdulla et al. [4]	56	M	*S. enteritidis*/Blood	2801	8	9.09	Ciprofloxacin Hemodialysis
	50	M	*S. enteritidis*/Stool	3200	4.8	7.16	Ciprofloxacin
Retornaz et al. [9]	58	M	*S. enteritidis*/Blood	2104	12	3.05	Tazocillin Ciprofloxacin
Brncic et al. [14]	58	F	*S. infantis*/Blood	>64000	17.1	3.30	Hemodialysis
Sirmatel et al. [15]	21	M	*S. paratyphi B*/Blood	4070	2.5	5.70	Ceftriaxone Ciprofloxacin Deceased
Gingold-Belfer et al. [16]	24	M	*S. group C*/Stool	24073	5.92	1.06	Ofloxacin
Fisk et al. [20]	25	M	*S. entericaserovartyphi*/ Blood	31410	11.8	1.79	Ceftriaxone Ciprofloxacin
Ali et al. [21]	42	M	*S. typhi*/Blood	17000	Normal	12.7	Ciprofloxacin
Jhawar et al. [22]	64	M	*S. typhi*/Stool	9473	3.2	3.7	Cefoperazone, Ciprofloxacin, Imipenemcilastin Hemodialysis
Al-aqeedi et al. [23]	34	M	*S. typhi*/Blood	6341	4.5	2.38	Ceftriaxone
Khan et al. [24]	23	M	*S. typhi*/Blood, urine stool	5350	2.2	6.03	Ceftriaxone
Neau et al. [25]	72	M	*S. enteritidis*/Stool	3008	--	1.22	Ofloxacin
	73	F	*S. enteritidis*/Stool	213	--	1.26	Ofloxacin
	37	M	S. enteritidis/Stool	1124	--	8.05	Ofloxacin
Campistol et al. [26]	43	M	*S. enteritidis*/Stool	1870	14.6	9.9	Ampicillin
	51	M	*S. enteritidis*/Stool	4300	11.8	12	Ampicillin
	38	M	*S. enteritidis*/Stool, blood	2270	11.7	13	Ampicillin

cases, in addition to the current case, seems to have a benign course. Among all 18 reported cases in Table 2, one patient died because of multi-organ failure [15]. Hemodialysis was not required before renal failure resolved in majority of the reported cases. Abdulla et al. [4] described two adult patients with severe rhabdomyolysis due to *S. enteritidis* complicated by ATN requiring hemodialysis in one case. In a retrospective study of 44 adult patients with *Salmonella* infection induced acute renal failure, kidney function recovered in all but 1 patient [17]. However, rhabdomyolysis induced acute kidney injury from *Salmonella* infection in previous reported pediatric cases has largely in the need for dialysis [19]. It is unclear whether there is any difference between adult and pediatric cases in terms of pathogenesis, treatment and prognosis in rhabdomyolysis associated with *Salmonella* infection.

In the current case, the patient's presenting symptoms of fever and diarrhea were typical of *Salmonella* gastroenteritis. We considered his rhabdomyolysis due to *Salmonella* infection since other causes of rhabdomyolysis such as trauma, medications, illicit drugs, ischemic disorders and infection like influenza were all ruled out. Despite having elevated muscle enzymes, he had no muscle weakness on examination, therefore, *Salmonella*-induced myopathy was also ruled out. His kidney function responded well to conservative management and returned to baseline within seven days of admission. Aggressive early recognition of the rhabdomyolysis, extensive fluid replacement and appropriate treatment with antibiotic may have lead to successful management of *Salmonella*-induced rhabdomyolysis and renal failure without progression to ATN in our patient [20–26].

CONCLUSION

In summary, depending upon the extent and severity of muscle damage, the manifestations of rhabdomyolysis secondary to *Salmonella* infection can vary from mild myalgia to severe pain with weakness. The associated risk of renal failure may not correlate with the peak creatinine kinase (CPK) level. Therefore, a high index of suspicion may help to reduce significant co-morbidities associated with the development of rhabdomyolysis in *Salmonella* infection.

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Author Contributions

Ziqiang Zhu – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published
Sina Aghaie – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published
Andrei Bandarchuk – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published
Anjula Gandhi – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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