

Rhabdomyolysis in the Context of Infections: Combining the Elements

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Abstract

Rhabdomyolysis is a severe, potentially fatal disorder resulting from muscle necrosis and the subsequent release of intracellular muscle components into the bloodstream. Trauma is the predominant etiology of rhabdomyolysis. Infections account for 5%-10% of all rhabdomyolysis cases and may result from endotoxins, direct muscle invasion or tissue hypoxia. While Influenza and *Legionella* infections are most linked numerous other viral, bacterial, fungal and protozoal diseases can induce rhabdomyolysis, resulting in detrimental consequences. Prompt recognition of the underlying infection is essential for the effective care of rhabdomyolysis and the prevention of impacts, particularly acute renal injury. Rhabdomyolysis associated with infections has been minimally examined. This article examines the current understanding of rhabdomyolysis linked to infections and its clinical implications.

Keywords: Rhabdomyolysis; Infections; Viral; Bacterial; Malaria; Candida

Introduction

Rhabdomyolysis is a medical condition marked by the degradation of muscle tissue, leading to the release of intracellular constituents into the bloodstream [1]. Myoglobin is an important myocyte protein secreted into plasma and its excess may lead to Acute Kidney Injury (AKI) by renal tubular blockage, direct nephrotoxicity and intrarenal vasoconstriction. AKI is the most important and potentially fatal complication of rhabdomyolysis, occurring in 10%-40% of patients [2,3].

Clinically, rhabdomyolysis is defined by a triad of myalgia, muscle weakness and myoglobinuria (tea-colored urine) nevertheless, this trio is observed in less than 10% of individuals. Most individuals are asymptomatic or may exhibit non-specific symptoms such as fever, lethargy, nausea or vomiting. Complications of rhabdomyolysis encompass electrolyte imbalances (e.g., hyperkalemia, hypocalcemia, hyperphosphatemia and hyperuricemia), acute renal injury, disseminated intravascular coagulation, dysrhythmias, respiratory failure, acute respiratory distress syndrome and hepatic dysfunction [4,5]. Myoglobin in serum or urine is indicative of rhabdomyolysis however, its reliability is compromised due to swift renal clearance. Serum Creatine Kinase (CK) is the most dependable and sensitive marker of rhabdomyolysis. The typical plasma CK level ranges from 45 IU/L to 260 IU/L. A CK cut-off value exceeding 1000 IU/L or CK larger than 5 times the upper limit of normal indicates mild rhabdomyolysis, while a level of 5000 U/L or higher is linked to the risk of AKI [6]. Rhabdomyolysis can result from either traumatic or non-traumatic factors.

Trauma is the predominant cause of rhabdomyolysis, which may include crush injuries, electrical shocks, intense exercise or extended immobilization. Non-traumatic etiologies encompass drugs, toxins, myopathies, seizures and infections. In a patient with recurrent rhabdomyolysis, one should consider hereditary metabolic myopathies [7]. The management of rhabdomyolysis focuses on addressing the underlying cause, ensuring sufficient fluid resuscitation, undertaking serial electrolyte and creatine kinase monitoring and implementing urinary alkalization in specific individuals. Infections account for 5%-10% of all rhabdomyolysis cases [8].

Numerous bacterial, viral, fungal and protozoal infections have been linked to rhabdomyolysis [Table 1]. The suggested mechanisms of rhabdomyolysis in infections cause tissue hypoxia resulting from sepsis or dehydration, endotoxins, direct bacterial invasion of muscle or elevated lysosomal enzyme activity [9-12]. Here, we summarize the existing literature on rhabdomyolysis associated with infections and its clinical implications.

Viruses	Influenza virus, HIV, SARS-CoV, Cytomegalovirus, Coxsackie virus, Epstein-Barr virus, Adenovirus, Herpes simplex virus, Parainfluenza virus and Varicella-zoster virus
Bacteria	<i>Legionella</i> species, <i>Streptococcus pneumoniae</i> , <i>Salmonella</i> species, <i>Staphylococcus aureus</i> , Group B <i>Streptococcus</i> , <i>Streptococcus pyogenes</i> , <i>Mycoplasma pneumoniae</i> , <i>Francisella tularensis</i> , <i>Listeria</i> species, <i>Vibrio</i> species, <i>Staphylococcus epidermidis</i> , <i>Brucella</i> species, <i>Bacillus</i> species, <i>Escherichia coli</i> , <i>Herbicola lathyri</i> , <i>Leptospira</i> species, <i>Borrelia burgdorferi</i> , <i>Clostridium perfringens</i> and <i>Viridans streptococci</i>
Others	<i>Plasmodium</i> species, <i>Candida</i> species and <i>Aspergillus</i> species

Table 1: Infections associated with Rhabdomyolysis.

Literature Review

Viral infections are a significant cause of rhabdomyolysis, often leading to muscle damage through direct invasion or inflammatory responses.

Rhabdomyolysis and viral infections

Influenza A virus is more commonly linked to rhabdomyolysis than other viral infections, including Human Immunodeficiency Virus (HIV), Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV), Cytomegalovirus (CMV) and Epstein-Barr Virus (EBV) [11-16]. Rhabdomyolysis linked to Influenza A virus infection is correlated with unfavorable outcomes. During the 2009 Influenza A (H1N1) epidemic, of the 18 hospitalized pneumonia cases, 10 individuals (62%) exhibited increased creatinine kinase values. An elevation in creatinine kinase levels correlated with the severity of the illness [17]. Subsequent to the epidemic, numerous instances of rhabdomyolysis associated with the H1N1 Influenza virus were documented [18-20]. A study by Borgatta et al., including 505 patients admitted with severe H1N1 pneumonia across 148 Intensive Care Unit (ICUs) in Spain found that high creatinine kinase occurred in 23.8% of patients, correlating with increased renal dysfunction and prolonged duration of mechanical

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Received: 11-Nov-2024, Manuscript No. JIDT-24-152169; **Editor assigned:** 13-Nov-2024, PreQC No. JIDT-24-152169 (PQ); **Reviewed:** 27-Nov-2024, QC No. JIDT-24-152169; **Revised:** 04-Dec-2024, Manuscript No. JIDT-24-152169 (R); **Published:** 11-Dec-2024, DOI: 10.4172/2332-0877.24.S4.002.

Citation: Shapoo N, Boma N (2024) Rhabdomyolysis in the Context of Infections: Combining the Elements. J Infect Dis Ther S4:002.

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ventilation [21].

Rhabdomyolysis is more prevalent in the HIV-infected population and can manifest at any stage of HIV infection. A study by Towner et al., discovered a tenfold increase in the incidence of rhabdomyolysis in HIV-positive people compared to their HIV-negative counterparts [22]. Research by Koubar et al., reported an incidence of rhabdomyolysis in the HIV population of 943 cases per 1,00,000 person-year [23]. The cause of rhabdomyolysis in this demographic is unique, with infection being the predominant contributor. The degree of rhabdomyolysis in HIV infection varies from asymptomatic increases in blood creatine kinase to possibly fatal electrolyte disturbances and acute renal failure. Elevated HIV viral load correlates with increased muscle catabolism, heightening the risk of severe acute kidney injury and necessitating renal replacement treatment. Rhabdomyolysis in HIV correlates with a higher death rate compared to the general population [24].

During the COVID-19 pandemic, rhabdomyolysis frequently occurred in hospitalized individuals. Haroun et al., conducted an observational cohort analysis involving 140 COVID-19 patients, revealing that the incidence of new-onset renal replacement therapy and in-hospital mortality was elevated in patients who experienced rhabdomyolysis [16]. In a study conducted by Samardzic et al., among 984 patients hospitalized due to COVID-19 infection, rhabdomyolysis was identified in 39 individuals [25]. The prevalence was elevated among individuals with AKI and those necessitating ICU stay. Patients with rhabdomyolysis experienced an extended hospital stay compared to those without the condition. Multiple findings indicate an increased risk of acute kidney injury associated with rhabdomyolysis in individuals infected with COVID-19, showing the necessity of early consideration of this diagnosis in patients presenting with COVID-19 and myalgia [26-28].

Coxsackieviruses (groups A and B) have been associated with rhabdomyolysis in numerous instances [29-31]. The extraction of Coxsackieviruses from the myocardium in individuals with acute myocarditis demonstrates its affinity for striated muscle tissue. Among all documented cases, a minority experienced acute renal impairment nevertheless, all patients recuperated following appropriate treatment. Cytomegalovirus (CMV)-associated rhabdomyolysis has been seen in both immunocompromised and immunocompetent individuals. Jung HY et al., documented two instances of rhabdomyolysis related to cytomegalovirus in kidney transplant recipients [32,33]. Both patients convalesced without problems following ganciclovir therapy. Other viral illnesses infrequently linked to rhabdomyolysis encompass Epstein-Barr virus, adenovirus, parainfluenza virus, herpes simplex and Varicella zoster virus [34-38].

Rhabdomyolysis and bacterial infections

Rhabdomyolysis is frequently linked to both gram-positive and gram-negative sepsis, with gram-positive bacterial infections being the predominant cause. Betrosian et al., identified bacterial sepsis-induced rhabdomyolysis in 7.1% of 491 individuals studied [39]. They noted that infections caused by gram-positive pathogens, particularly *Staphylococcus aureus* and *Streptococcus faecalis*, were more commonly linked to rhabdomyolysis than those caused by gram-negative pathogens, with the lungs being the primary site of sepsis in most patients, followed by urosepsis, gallbladder infections, pancreatitis and catheter-related infections. A study by Kumar et al., demonstrated the predominance of gram-negative pathogens, particularly *Pseudomonas*, *Escherichia coli* and *Klebsiella*, over gram-positive pathogens, including *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Streptococcus viridans* [40]. The lungs were the predominant location of infection.

Kumar et al., described the prevalence of gram-negative bacteria to the significant proportion of diabetes individuals in their study [40]. Acute renal failure was the primary consequence in both studies and patients with rhabdomyolysis had elevated fatality rates.

Discussion

Legionella is strongly linked to rhabdomyolysis. Since the initial case report in the 1980's over 20 publications have documented the correlation between rhabdomyolysis and legionnaires' illness [41-43]. Rhabdomyolysis and acute renal failure may manifest as initial symptoms in people with legionnaires' illness [44]. According to the reports, the combination of legionnaire's illness, rhabdomyolysis and acute renal injury has resulted in an elevated demand for dialysis and a mortality rise of up to 40%. Rhabdomyolysis has been observed as an extra pulmonary manifestation of *Mycoplasma pneumoniae* in certain instances, particularly in patients lacking radiographic signs of pneumonia [45-48]. It has been proposed that Tumor Necrosis Factor-Alpha (TNF- α) may be responsible for rhabdomyolysis in mycoplasma, however this remains unverified [49]. The severity of rhabdomyolysis associated with mycoplasma varies among cases and affected patients may also experience other extrapulmonary problems, including neurological, dermatological and gastrointestinal issues.

Salmonella infections have been linked to rhabdomyolysis. Over 30 instances of rhabdomyolysis have been documented in both adult and pediatric populations [50-52]. *Salmonella* infections may result from *Salmonella typhi* infection and non-typhoidal salmonellosis, both of which have been linked to rhabdomyolysis. Rhabdomyolysis may be worsened by acute kidney injury, particularly in patients with *salmonella gastroenteritis*. Rhabdomyolysis associated with tularemia was initially documented in 1985. Tularemia is an uncommon, tick-transmitted disease caused by the bacteria *Francisella tularensis*. Ulceroglandular tularemia, the most prevalent variant, is marked by cutaneous lesions and localized lymphadenopathy, with the potential for ulceration and suppuration if not addressed therapeutically. To date, twelve cases of tularemia complicated with rhabdomyolysis have been documented [53]. Among those, four cases resulted in fatalities and the elevated mortality was believed to be associated with high CK levels and advanced age [54].

Rhabdomyolysis and other infections

Rhabdomyolysis has been identified as a cause of acute kidney injury in malaria, particularly in patients with a significant parasite load [55-58]. Miller et al., proposed that red blood cell sequestration in skeletal muscles, toxins from the parasite or host, or lactic acidosis may induce myonecrosis.

Tumor necrosis factor, a recognized myotoxin, has been implicated in patients who experience elevated fevers [59]. Rhabdomyolysis is typically documented because of *Plasmodium falciparum* malaria, although it has also been observed in a limited number of cases associated with infection [60]. Patients attained full recovery following timely intervention. Candida infections are linked to rhabdomyolysis, particularly in immuno-compromised individuals. Reports indicate that *Candida krusei* and *Candida parapsilosis* fungemia are linked to rhabdomyolysis in patients with acute myeloid leukemia following appropriate therapy for candida infections, rhabdomyolysis was resolved [61,62].

Conclusion

Numerous bacterial, viral, protozoan and fungal infections can induce rhabdomyolysis. The pathophysiology involves direct muscle

invasion, endotoxins or tissue hypoxia. In cases of unexplained rhabdomyolysis, infections must be examined and the diagnosis should be substantiated by isolating the causal organism using culture or serological methods. Timely identification of the underlying infection might avert life-threatening consequences of rhabdomyolysis, including acute renal injury. Additionally, complete supportive care, including hydration and monitoring is essential to optimize patient outcomes in such cases.

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