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Case Report,

A Case of Rickettsiosis in a Patient with Glucose-6-Phosphate Dehydrogenase (G6pd) Deficiency

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Introduction:

Rickettsia is a group of Gram-negative intra cellular obligatory bacteria. Rickettsia species are an important cause of infectious disease in people and animals. Fleas, ticks, mite, lice etc., serve as vectors who transfer the rickettsia from animal to humans.Rickettsiosis is one of the oldest known vector-borne diseases(Blanda et al., 2020).

Usually it is a nonspecific self-limiting febrile illness without major complications. Fever, headache, mild-rash, myalgia's and anorexia are the most common presenting signs and symptoms. Laboratory findings include elevated transaminase levels, hyponatremia, thrombocytopenia and anemia (Merhej et al., 2014).

The disease is usually of benign nature. Severe complications are reported in about 6% of cases. Patients may present with organ involvement, severe vasculitis and multi organ failure (Oteo and Portillo, 2012) and the mortality rate is up to 2.5%(Giammanco et al., 2005; Raoult et al., 1986).

Case Description:

We report a case of a54-year-oldman admitted to the internal ward due to fever of 39.8^{C}that began two days prior to his admission.

Past medical history revealed diabetes mellitus (type 2), hypertension, chronic heart failure, dyslipidemia and cigarette smoking.

At the time of admission, the patient was hemodynamically stable. Chest radiography and urine sample were normal. Fever measured up to 38.9 ^{C} was the only symptom reported. Upper respiratory tract infection (URTI) was suspected.

During his hospitalization in the internal medicine wardhis respiratory status deteriorated and he reported dyspnea, tachypnea up to 30 breaths per minute with high fever up to 40^{C} rapidly developed.

A new chest radiography reveled right-side infiltrates with diffuse interstitial opacities.

Blood analysis revealed elevated inflammatory markers: CRP33.5 mg/dl (normal range 0-0.5 mg/dl), WBC 24.10^9/land platelet 150L/10^9, elevated liver enzymes spartate amino Transferase 359 IU/L (AST), Alanine aminotransferase 124 IU/L (ALT), Gamma-glutamyl transferase 95 U/L(GGT) and hyponatremia 127 mEq/L, hypochloremia 95 mEq/L. Albumin level was 2.1 g/dl, blood cultures were sterile.

Empiric antibiotic therapy was initiated with intravenous (IV) Ceftriaxoneand laboratory panel for atypical infections was performed, including: SARS cov-2,Human Respiratory syncytial virus, Influenza virus, Cytomegalovirus, Epstein-Bar virus, Hepatitis A virus, Hepatitis B virus, Hepatitis C virus, Human immunodeficiency virus, Brucella, Syphilis; urine test for Legionella, all were negative.

The patient's respiratory status further deteriorated and oro-trachealintubation was performed.

Antibiotic treatment was changed to IV Piperacillin/ tazobactam and Levofloxacin.

The patient was transferred to the ICU. Due to hemodynamic instability pressorsupport was initiated. The patient developed acute kidney injury with creatinine level of 2.97 mg/dl and anemia (hemoglobin 7.3gr/dl).

The patient required blood products to keep his hemoglobin level stable. No source of active bleeding was found. Blood smear was preformed presenting polychromasia and immature cells.

LDH levels was elevated up to 2677U/L, absolute reticulocyte count was elevated (Reticulocyte production index >3), haptoglobin was less than 5 mg/dl, indirect bilirubin 0.9 mg/dl. Thus, a diagnosis of hemolytic anemia was made. Coombs test was border line-positive. No pharmacological cause for hemolysis was found. Autoimmune panel was performed: Anti nucleus antibody (ANA); Antiphospholipid syndrome was both normal, Complement C3-C4, 242mg/dl and 88mg/dl respectively. The diagnosis of autoimmune vasculitis was ruled out. We performed a workup for Hemophagocytic Lymphohistiocytosis (HLH) due to the combination of persistent fever, respiratory distress, rash, anemia, and elevated liver enzymes. Interleukin 2(IL-2) receptor level was elevated up to 4891 units and ferritin maximal level was 13,000ng/ml further supported this diagnosis. However, he did not fulfill the 5 HLH criteria out of 8 required for diagnosis. Paroxysmal Nocturnal Hemoglobinuria (PNH) was considered as a cause for non-immune hemolysis. Flow cytometry was performed and CD59 and CD55 were within normal ranges making this diagnosis improbable.

We considered the possibility of Glucose-6-phosphate dehydrogenase (G6PD)

Deficiencyhemolysis.The patient's Mediterranean origin was supportive and the result was positive. However, this could not account for the fever and elevated inflammatory markers. We therefore considered atypical infection coupled with G6PD deficiency hemolysis that could encompass all the findings. We took serology for: Q fever, murine typhus and spotted fever infection. Serial serology tests for: Q fever, murine typhus and spotted fever infection are shown in table1. Doxycycline therapy was initiated pending results.

Table I: Blood Fluorescence Analysis (FA)

	Spotted Fever		**Murine Typhus**		**Q Phase II**		**Q phase I**	
Date	IgG	IgM	IgG	IgM	IgG	IgM	IgG	IgM
25-10-20					Borderline	Neg	Neg	Neg
27-10-20	Borderline	Neg	Borderline	Positive	Borderline	Neg	Neg	Neg
03-11-20	Borderline	Neg	Borderline	Positive				
04-11-20	400AU/ml	Positive	800AU/ml	Positive				
13-12-20	1600AU/ml	Positive	1600AU/ml	Positive				

Negative: <100AU/ml
Borderline: 100AU/ml
Positive: <100AU/ml

The patient received doxycycline treatment and improved. He was weaned of mechanical ventilation and discharge from ICU to the internal ward after 5 days. The striking response to the antibiotic therapy was indeed in favor of rickettsia infection rather than HLH.

Discussion:

Rickettsia species are an important cause of infectious disease in people and animals. Rickettsiosis is one of the oldest known vector-borne diseases(Blanda et al., 2020). The pathogen is transmitted by arthropods such as ticks, fleas, lice, or mites. For some rickettsia species (Rickettsia Felis) mosquito vector may also exist(Adem, 2019; Dieme et al., 2015; Oteo and Portillo, 2012). The rickettsia genus includes several species. The most common classification includes the spotted fever group(SFG),typhus group(TG),Rickettsia belli group, and Rickettsia Canadensis group(Merhej and Raoult, 2011). The spotted fever group include the Mediterranean spotted fever(MSF) that is most common ,caused by R.conorii(Parola et al., 2005).

MSF due to R. conorii is common in North Africa and the Mediterranean area(Parola et al., 2009). In recent years the incidence of rickettsia disease has been growing. Global warming might be the cause of the growing tick population translating into more cases of this vector borne diseases(Parola et al., 2008).

Murine (endemic) typhus is a flea-borne infectious disease caused by Rickettsia Typhi. The Infection occurs worldwide, with majority of cases occurring in areas habituated by a large number of rats(Tsioutis et al., 2017).

The disease can be mild, self-limited, and clinically similar to other causes of rash and fever, without significant complications. This is the case in the vast majority of patients .Severe illness rarelydevelopsand can cause a diagnostic challenge(Civen and Ngo, 2008).

Patients with severerickettsial disease may present with neurologic, hepatic, cardiac, renal, and /or pulmonary dysfunction as a result of capillary leak and septic shock(Khairallah et al., 2009; McKelvey et al., 1991; Purcell et al., 2007; Shaked et al., 1994).complications develop in 28% of cases of adult flea born typhus(Civen and Ngo, 2008; Nogueras et al., 2013).

The presence of G6PD and advanced age appear to be associated with severe rickettsia diseases, sometimes even leading to fatality. The association with G6PD deficiency was first described in American soldier who developed acute renal failure and severe hemolysis after contracting murine typhus in Vietnam(Whelton et al., 1968).Several studies found an association between G6PD deficiency, severe or fulminant Rocky mountain spotted fever(RMSF) and severe infection with Rickettsia conorii (Walker,1990).

A case report of severe rickettsiaconorii infection in a patient with G6PD was published in Israel. A 35 year old man from Iraqi origin, owner of three dogs, was hospitalized with high fever, fatigue, headache and rash. During hospitalization he became irritable, lethargic and then lapsed into a coma. This was followed by renal failure, hepatic insufficiency, hemolysis and respiratory failure that required assisted ventilation(Regev-Yochay et al., 2000).

Zoonotic diseases are of public health importance; therefore, they are reported mandatorily to a central registry reporting system of the Israeli Ministry of Health. Identifying the Rickettsia species is necessary in order to prevent the disease from spreading to other people and animals (Israel Ministry of Health, 2006).

In our case report, the identification of the exact rickettsiaspecies is impossible. No real time PCR test for rickettsia species was taken during the acute phase of the patient' sillness. Serology testing was taken on several occasions, during the acute illness and after recovery (table 1).The diagnosis of rickettsiosis may be done in several methods. Serological tests are done frequently but data interpretation is often complicated by cross-reactivity among the different rickettsial species(Pennisi et al., 2012). Molecular methods based on PCR amplification and sequencing are used for rickettsialspeciesidentification(Fournier et al., 2003; Kidd et al., 2008; Segura et al., 2016; Stenos et al., 2005). Using Blood Fluorescence Analysis alone rickettsial species cannot be identify. In our case rickettsial infection was present, but the pathogen is unclear (table1).According to our patient's history – a dog owner with no known ticks who is rarely exposed to cats at home or in his work place, as well as working in a bakery where rodents can be found albeit a rare occasion – we could not determine the species. However, Rickettia Conori was more plausible because the patient had not worked at all during the two months prior to his hospitalization. Another option could be Rickettia Felis. The latter, transmitted via a cat flea (Ctenocephalides felis) can produce anti R. Conorii antibodies as well as anti R. typhi antibodies (expert experience, Israel's Rickettia reference laboratory, biological research Institute, Nes Zionna, Unpublished data).

Our patient was of an Arabicoriginand he had no knowledge of having G6PD deficiency. G6PD deficiency is quite common in the Middle East and Africa, although the major group that has G6PD deficiency in Israel are Iraqi Jews.

The association of G6PD deficiency with severe rickettsia disease was not conclusively established, but it has been proposed that G6PD-associated hemolysis may aggravate or potentiate rickettsia-induced vasculitis (Walker, 1995).

The condition of our patient improved dramatically after antibiotic treatment and he was weaned from mechanical ventilation and pressor after 3 days in the ICU. A rapid and sometime life-threatening rickettsia infection can occur. Therefore, rickettsia infection should be included early in the differential diagnosis of nonspecific fever (Lynn et al., 2018).

Conclusion:

We describe a case report of a young 54 years old patient with rickettsia infection and G6PD deficiency that required an ICU admission due to hemodynamically and respiratory insufficiency. Special attention should be given to patients withG6PD disorder as it can aggravate an already albeit rare life-threatening rickettsia infection. Awareness and early treatment are lifesaving.

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