Case Report,

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

Garin-kol Avrahami Ret1,4, Zerbib Olivier 2,4, Gafter- Gvili Anat3,4, Lev Shaul2,4, Sahaf Levin Gal2,4, Gottesman Tamar1,4

1Department of Infectious Diseases and Infection Control Service, Hasharon Hospital, Rabin Medical Center, Petah Tikva, Israel;
2Intensive Care Unit, Hasharon Hospital, Rabin Medical Center, Petah Tikva, Israel;
3Internal Medicine Department A, Beilinson hospital, Rabin Medical Center, Petah Tikva, Israel;
4Sackler School of Medicine, Tel Aviv University, Ramat Aviv, Israel;

**E-mail Address:** reutyreuty@yahoo.it

**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 a 54-year-old man 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 ward his 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 revealed right-side infiltrates with diffuse interstitial opacities.

Blood analysis revealed elevated inflammatory markers: CRP 33.5 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) Ceftriaxone and 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-tracheal intubation was performed.
Antibiotic treatment was changed to IV Piperacillin/tazobactam and Levofoxacin. The patient was transferred to the ICU. Due to hemodynamic instability pressor support was initiated. The patient developed acute kidney injury with creatinine level of 2.97 mg/dl and anemia (hemoglobin 7.3 gr/dl). The patient required blood products to keep his hemoglobin level stable. No source of active bleeding was found. Blood smear was performed presenting polychromasia and immature cells. LDH levels was elevated up to 2677 U/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, 242 mg/dl and 88 mg/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 13,000 ng/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) Deficiency hemolysis. 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 table 1. Doxycycline therapy was initiated pending results.

Table I: Blood Fluorescence Analysis (FA)

| Date       | Spotted Fever | Murine Typhus | Q Phase II | Q phase I |
|------------|---------------|---------------|------------|-----------|
|            | 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: &lt;100AU/ml
Borderline: 100AU/ml
Positive: &lt;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.
Several studies found an association with G6PD deficiency, severe or fulminating Rocky mountain spotted fever (RMSF) and severe infection with Rickettsia conorii. A case report of severe rickettsiosis 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. 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 rickettsial species is impossible. No real time PCR test for rickettsia species was taken during the acute phase of the patient's illness. 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. Molecular methods based on PCR amplification and sequencing are used for rickettsial species identification. Using Blood Fluorescence Analysis alone rickettsial species cannot be identify. In our case rickettsial infection was present, but the pathogen is unclear (table 1).

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, Rickettsia Conori was more plausible because the patient had not worked at all during the two months prior to his hospitalization. Another option could be Rickettsia 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 Rickettsia reference laboratory, biological research institute, Nes Ziona, unpublished data).
Our patient was of an Arabic origin and 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 with G6PD disorder as it can aggravate an already albeit rare life-threatening rickettsia infection. Awareness and early treatment are lifesaving.

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