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Case Report

Transfusion-Transmitted Malaria in an Omani Patient with β Thalassemia: Out of Mind; Late to Diagnose

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Abstract

Transfusion-transmitted malaria (TTM) is very rare in non- endemic areas, including Oman. Hereby, we present the first case of TTM in a female patient with transfusion dependent β thalassemia major. A 16 year-old female receiving regular blood transfusion every 3 - 4 weeks, was admitted to hematology ward at Sultan Qaboos University Hospital for evaluation of pyrexia of unknown origin. For 1.5 months before admission, she had recurrent fever spikes, reaching 39 - 40ºC, associated with shivering, sweating and headache. There was no history of contact with sick people or travel/transfusion outside Oman. Clinical examination was unremarkable, but she had documented weight loss of 1.5 kg over 1 month. CBC showed mild thrombocytopenia ranging between 90 - 140 x 10^3/uL. Blood and urine cultures, multi-transfused patient screening were negative, chest x-ray and abdominal US were normal. Blood tested positive for malaria (non- falciparum species). Examination of blood film revealed heavy parasitemia. Tracing of the possible source was difficult, because she had been exposed to multiple donors. She was treated with Riamet@ (artemether 20 mg and lumefantrine 120 mg/tab) for 6 doses with good response. She remained fever free, and parasitemia decreased, and on follow up malaria antigen detection tests were negative. There was no indication for primaquine as transfusion related malaria has no hepatic phase.

Conclusion: TTM should be suspected in patients with classic clinical presentation, even in non- endemic areas. Mild thrombocytopenia could be the only laboratory hint.

Keywords: *Fever of Unknown Origin; Transfusion Transmitted Malaria; Oman; β Thalassemia; Thrombocytopenia*

Abbreviations

TTM: Transfusion Transmitted Malaria; CMV: Cytomegalovirus; EBV: Epstein Bar Virus; ANA: Antinuclear Antibody

Case Report

A 16 year old female patient with β thalassemia major was admitted to the hematology ward for evaluation of pyrexia of unknown origin. She has no HLA matching sibling donor for bone marrow transplantation, so, she was on regular transfusion every 3 - 4 weeks, and she received deferiprone at 100 mg/kg/day for iron chelation. For 1.5 months before admission, she had recurrent fever spikes 2 - 3 times/week, reaching 39 - 40ºC, associated with shivering, sweating and headache. There was no history of contact with sick people or travel/transfusion outside Oman. During that period, she lost 1.5 kg of her body weight, otherwise, she had no other symptoms and her clinical examination was unremarkable. Initial laboratory assessment revealed Hb : 10.8 g/dl, platelet 119 x 10^3/cmm, WBC 4.7 x 10^3/cmm, (differential N61%, L24%, M8%, E4%, B3%) ESR 47/hr, CRP 52 - 58, and normal kidney and liver function tests.

Blood and urine cultures, PCR for adenovirus, CMV, EBV were negative, respiratory viral screen and Brucella serology were negative, Chest x ray was normal, and abdominal US revealed only mild hepatosplenomegaly with no other abnormalities.

During that period, the patient looked clinically well when afebrile, and no antibiotics were started for her. She had been reviewed by ID team who decided to go for stage II investigations: Q fever (Coxiella Burnettii Serology IgG, IgM, IgA), Yersinia serology, HIV, chronic hepatitis screening: all were negative. Thyroid function tests and complement levels were normal, rheumatoid factor and ANA were negative. An ECHO cardiography and Galium bone scan were arranged.

During admission, temperature monitoring revealed one spike of fever that would last for several hours, followed by fever - free interval of 48 - 72 hours, a fever pattern that is consistent with relapsing fever of malaria. The second hint was the mild thrombocytopenia that was observed on her serial CBCs. Blood testing for malaria was requested, and malaria antigen detection test was positive for *P. Vivax, P. Ovale*, and *P. Malariae*, but negative for *P. Falciparum*. A blood film was requested, and revealed heavy mixed parasitemia.

The patient was treated with Riamet (artemether 20 mg and lumefantrine 120 mg/tab)@ (Novartis Pharmaceuticals UK Ltd) for 6 doses with good response. She remained fever free, and parasitemia decreased, the follow up antimalarial tests were negative. There was no indication for primaquine as transfusion related malaria has no hepatic phase.

Discussion

The current case report highlights the first case of transfusion-transmitted malaria (TTM) in Oman, a country that is not endemic for malaria. The patient had no history of travelling to endemic areas, or receiving transfusion abroad. Delay in her diagnosis was attributed to lack of high index of suspicion of that entity. Although the transmission of malaria by blood transfusion was one of the first recorded incidents of transfusion-transmitted infection, in general, the risk of transfusion transmitted parasitic infection is considerably low compared to bacterial and viral infection [1].

During 1950s and 1960s, Oman was endemic for malaria, and almost one third of the population were infected. In 1970s, Malaria Control Program was launched with substantial drop of the number of infected cases, till 1990, when the number of infected population surged to 37,720 cases. In 1991, the Ministry of Health started the National Malaria Eradication Program. Since then, the annual parasite incidence remained at low level of 0.1/10000. Most cases were imported from East Africa. Few cases were reported in certain provinces (North Sharqiyah and Dakhliyah). In general, malaria is considered to be under control in Oman and malaria chemoprophylaxis is currently not recommended by the CDC for travel to Oman [2].

The encounter of the current case provoked questioning whether it was naturally acquired or transfusion- transmitted malaria. Living in Muscat, which is considered free of malaria, and lack of history of visiting endemic areas for 3 years before the symptoms, made naturally acquired malaria unlikely. As a patient with β thalassemia on regular transfusion, the most likely source of malaria is thought to be through transfusion with contaminated blood. The next step was to identify the possible donor. Compared to natural malaria which is transmitted by the bite of an infective female Anopheles mosquito, TTM is caused by injection of asexual forms (trophozoites). Pre-erythrocytic development of the parasite in the liver is absent and relapses does not occur. Incubation period for natural malaria ranges between 7 - 30 days, depending on the species. On the other hand, the incubation period of TTM depends on the number of parasites infused. It is usually short but may be up to two months. Based on that speculation and upon tracing her transfusion records, 6 potential donors were identified as possible source of TTM. Reviewing their donation questionnaire, none of them admitted history of malaria or travelling to an endemic area within 6 months of blood donation. They have been called by the blood bank for further diagnostic tests, but unfortunately they were not willing to be screened. Absent history of infection or travel to endemic areas for 6 months does not completely exclude the possibility of transmitting the parasite. Following an attack of malaria, the donor may remain infective for years: 1 - 3 years in *P. falciparum*, 3 - 4 years in *P. vivax*, and 15 - 50 years in *P. malariae*. Partially immune, asymptomatic carriers of malaria constitute the major risk for the recipients of their blood [3].

The clinical course of the patient also favored being TTM. She received treatment with Riamet (artemether 20 mg and lumefantrine 120 mg/tab) for 6 doses with good response. She remained fever free, and parasitemia decreased. On follow up visits, malarial antigen detection tests were repeatedly negative and she had no recurrence of fever or other symptoms. Pre-erythrocytic schizogony does not occur and hence relapses due to dormant hepatic forms also does not occur in TTM. That is why treatment with primaquine post therapy was not indicated.

The frequency of transfusion-transmitted malaria in non- endemic countries like Oman is estimated at less than 0.2 cases per million recipients, in contrast to 50 cases per million in endemic ones. Patients with β thalassemia, who are receiving regular blood transfusion are theoretically at higher risk of TTM than casual blood recipients.

In Oman, blood banking started in mid 70s, and was initially relying on imported blood that had been already screened for infectious agents. Formal blood screening for transfusion transmitted infections was initiated in 1984. By 1991, no more imported blood was needed, and local voluntary donors provided sufficient blood for the local demand [4]. The National Donor and Donation Registry (NBDR) system integrates different blood banks within Oman to build a central donor and donation registry, blood product inventory, and a transfusion database so that a nation-wide safe blood donation and transfusion environment can be achieved.

Currently, there are no reliable cost effective serologic tests available to screen donors for malaria, and the focus for prevention remains on adherence to donor screening guidelines that address travel history and previous infection with malaria [1].

In non-endemic countries, some measures are followed to minimize recipient exposure to the parasite. These measures include donor deferral and screening for specific antimalarial immunoglobulin. As suggested by the American Association of Blood Banks, travelers may donate blood 6 months after returning from endemic areas if they have been free of symptoms and have not taken antimalarial drugs. Persons who have had malaria or who had been taking chemoprophylaxis shall be deferred from donating blood for 3 years after either becoming asymptomatic or stopping therapy or chemoprophylaxis [5]. Despite sticking with those guidelines, breakthrough TTM, like the current case continue to be encountered.

In the current case, beside the classical clinical picture, mild thrombocytopenia was the only laboratory hint of malaria infection. Mild thrombocytopenia was reported earlier as the most common hematologic complication of *P. vivax*, and *P. falciparum* malaria. Gupta., *et al*. reported an incidence of 76 - 90%, variable with the species [6].

The speculated mechanisms included non-immunological (coagulation disturbances, oxidative stress, sequestration in spleen, direct lytic effect of the parasite on the platelets, platelet phagocytosis), and antibody mediated platelet destruction. Muley., *et al*. [7] correlated the depth of thrombocytopenia with more severe disease, a correlation that had been confirmed also by Hanson., *et al* [8]. Fortunately, thrombocytopenia in our patient was mild, asymptomatic, and did not require medical intervention.

Conclusion

TTM should be suspected in patients with classic clinical presentation, even in non- endemic areas. Mild thrombocytopenia could be the only laboratory hint. Awareness of that rare incidence might lead to earlier diagnosis and avoidance of more expensive and invasive tests.

Conflict of Interest

The authors declare that no financial interest or conflict of interest exists.

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