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Positive malaria rapid test in asymptomatic blood donor – Undetectable parasitemia or false positive?

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Abstract:

A 35-year-old male, first-time whole blood donor, cleared for donation by physical examination and donor questionnaire, tested reactive for malaria by rapid diagnostic test (RDT). Tests done in triplicate with bag segment samples gave the same results. He had no history of travel to endemic areas or of features suggestive of or a confirmed diagnosis of malaria or its treatment. There was also no history of any prolonged illness or medications. Repeat physical examination was unremarkable, he had no history of fever postdonation and repeat samples showed a normal hemogram, negative for malaria parasite by thick and thin smears and RDT. Further work-up, such as nucleic acid testing or quantitative polymerase chain reaction, was not done due to financial constraints and nonsuggestive history, physical examination, and laboratory tests. The unit was discarded, however, since asymptomatic, low-dose parasitemia could not be ruled out, it could not be definitively labeled false positive.

Keywords:

Asymptomatic donor, malaria, rapid diagnostic test

Introduction

In India, testing every unit of donated blood for malaria is mandatory.[1] One of the techniques used commonly involves rapid diagnostic testing (RDT) kits.[2] Malaria is a febrile disorder caused by *Plasmodium* species and spread through the bite of the female *Anopheles mosquito*.[3] Reports of transmission through transfusion and transplant are present,[4,5] re-infection is also possible[6] and owing to globalization, cases have been reported from nonendemic regions as well.[7] *Plasmodium falciparum*, *Plasmodium vivax*, and *Plasmodium malariae* are most frequently implicated in transfusion-transmitted malaria (TTM).[8] "Semi-immune" asymptomatic donors with a low parasite load pose a serious issue with respect to transfusion safety as they may remain undetected by methods such as microscopy.[8] This is a case of a whole blood donor at a stand-alone blood center in South India who was found to be reactive for malaria by rapid card test and the workup that followed.

Case Report

The donor was a 35-year-old male, donating blood for the first time. He had been declared fit during his predonation counseling and physical examination. He was afebrile on the day of donation with a pulse rate of 80/min and blood pressure of 130/86 mm of Hg. Whole blood was collected in a 450 mL quadruple bag and packed red cells, fresh frozen plasma and platelets had been separated. As per

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National AIDS Control Organization and Drug and Cosmetics Act, 1945 mandate,[1] this unit, as all others, was tested for hepatitis B and C, HIV, syphilis, and malaria.

For malaria, a rapid testing kit was used (Malascan, Viola Diagnostic Systems, Uttarakhand). It is a qualitative, two-site sandwich immunoassay detecting pan-specific aldolase and *P. falciparum*-specific histidine-rich protein-2.[2] The results showed reactivity for "Pan" antigen and for *P. falciparum*. Figure 1 shows the rapid testing cards with the results of his sample. The test was repeated in triplicate with samples from the bag segment and returned the same results.

Evaluation

The donor was called back for more blood samples and a more detailed history. He had no history of travel or settling anywhere other than his native state in India, or of confirmed or suspected malaria or its treatment. He had no drug history or any other prolonged illness. His physical examination was also unremarkable. Fresh samples collected from him were sent for complete blood counts, repeat malaria tests with rapid kit, and by thick and thin Leishman smears.

His test results were as follows: hemoglobin - 13.7 g/dL, hematocrit - 44.5, white blood cell count - 7300/μL, and platelet count - 2.6 lakhs/μL. Two mL samples in EDTA vacutainers were sent to a third-party laboratory for Leishman staining of thick and thin smears for malaria parasite and came back negative for the parasite. The repeat sample yielded negative results by rapid testing when done in triplicate. Hence, no further testing or donor counseling was done. The unit was discarded and the concerned personnel of the company manufacturing the RDT kit was informed for any further action on their end.

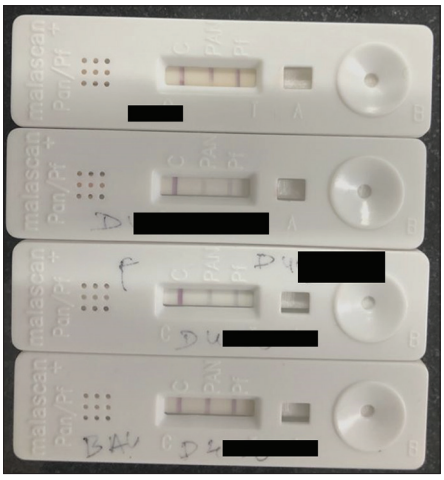

Figure 1: Malaria rapid diagnostic test reactive for pan malaria antigen and *Plasmodium falciparum*, tested in triplicate including samples from the bag segment. The three lines in each card from left to right: Control, pan antigen, *P. falciparum*. (Page 2)

Discussion

Reports of malaria positivity in healthy blood donors without past history of disease or travel to malaria-prevalent areas, cleared for donation by standard donor questionnaire and physical examination, are very rare. As such, a reactive unit was a cause for grave concern. In addition, TTM has no preerythrocytic stage and, therefore, has higher complication rates,[9] *Plasmodium* parasites retain their viability for as long as 10 days even when refrigerated[10] and can be transmitted by a minimal number of infected red blood cells[11] and the donors can remain infective over years.[8]

However, ruling out false positives and confirmation of results were the top priority. Rapid diagnostic tests for malaria can be false positive in cases of human African trypanosomiasis (HAT) and in cases with positive rheumatoid factor (RF) and human anti-mouse antibody.[12,13] The aggregated results from six rounds of the WHO Malaria RDT product testing program have indicated that false-positive results against specific sample types are most likely related to the manufacturing process and/or specific antibody used in the RDT, which most probably varies between products.[12] In the presence of HAT, RDT specificity has been found to be lower in some kits.[13] As far as RF is concerned, a correlation between RF concentration and malaria false positivity has been observed in a few studies.[12] History still remains the first line of inquiry in ruling out such cases and the donor elicited clearly negative history that was suggestive of these conditions (e.g.: fever, joint pain, skin lesions, specialized medication, or treatment of any kind).

Features such as anemia and thrombocytopenia can be useful indirect markers of malaria. Complete blood counts ruled them out.[7]

Thick and thin smears are considered to be gold standard for the detection of malaria parasites.[14] This donor's sample did not show any parasites. Follow-up 1 week after the date of donation revealed that the donor was in good health. Some protocols suggest supplementing nucleic acid testing (NAT) and quantitative polymerase chain reaction (qPCR) for effective diagnosis of malaria parasites, specifically in cases with low parasitemia.[8] However, in view of financial constraints, negative tests on repeat samples by two modalities and the absence of any suggestive history, NAT and qPCR were not done. However, asymptomatic malaria still cannot be ruled out in this donor as reports of PCR-positive malaria, negative by

rapid testing and/or microscopy, exist.[4] After all the relevant history and testing as available in the literature assured us of donor safety, the concerned unit was discarded to ensure recipient safety.

Conclusion

Any transfusion-transmitted infection reactivity is grounds for the discard of concerned units. Therefore, testing is a precarious endeavor, balancing safety, and undue wastage. The incidence of malaria reactivity in healthy donors being particularly low, this case raised an immediate alert in the blood center. Reporting of such cases is essential because no clear guidelines exist for situations such as this. A systematic work-up of these must be elucidated. In case of proven false positives, any kit-related preventive and corrective actions that can be taken, require detailed information on such cases to reduce their incidence. Since tests such as qPCR are not easily available for malaria testing in blood donors, donor history and questionnaire still remain our main preventive measures and the most valuable supplements to serological and microscopic testing.[8]

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that his name and initials will not be published and due efforts will be made to conceal his identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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