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Imported malaria from Africa with false negative rapid diagnostic test for P. falciparum due to deletion of the histidine-rich protein 2 gene

Aldert Bart*[1], Nienke Verhaar[2], Jarne Van Hattem[1], Michèle Van Vugt[2], Godelieve de Bree[3], Tom Van Gool[1]

[1]*Academic Medical Center; Medical Microbiology*

[2]*Academic Medical Center*

[3]*Academic Medical Center; Infectious Diseases*

Background: Microscopic examination of stained thick and thin blood smears is the gold standard for detecting and identifying malaria parasites. However, in developed and non-endemic countries, many laboratories lack sufficient samples to build-up and maintain sufficient microscopic expertise. As a result, rapid diagnostic tests (RDTs) are increasingly used as first line screening for malaria in Europe, especially outside opening hours. In most RDTs, histidine-rich protein 2 (PfHRP2) is used as indicator of P. falciparum infection, and aldolase or pLDH for demonstration of non-falciparum malaria. False negative results with RDTs, especially with P. falciparum, may result in severe complications and even fatality of patients involved.

False negative RDT results for PfHRP2 due to deletion of the genes encoding PfHRP2 and the cross-reacting PfHRP3 have been reported, mainly from South America. We present a case of imported malaria in The Netherlands caused by a PfHRP2 and PfHRP3-negative P. falciparum from East-Africa.

Material/methods: As part of routine laboratory diagnosis for malaria, microscopical analysis of quantitative buffy coat (QBC), stained thick and thin blood films, and the BinaxNOW RDT were performed. Diagnosis was complemented by species-specific qPCR and illumigene Malaria and illumigene Malaria Plus assays, and by testing with the Clearview Malaria Dual test, which detects both P. falciparum-specific PfHRP2 and Plasmodium-specific pLDH. (Nested) PCRs were performed to detect pfhrp2, pfhrp3 and flanking genes. In each PCR reaction, negative controls were included, PfHRP2 positive samples with similar qPCR Cq value served as positive controls.

Results: In September 2016, a 77 year old male presented with fever, 14 days after returning from Eritrea where he had visited friends and relatives. He denied having travelled to other countries. The QBC was positive for malaria parasites. In thick smear and thin smears *P. falciparum* was observed with a parasitemia of 1.6%. The BinaxNOW Malaria RDT repeatedly was negative for PfHRP2, but did show a positive aldolase band. The Clearview RDT was also repeatedly negative for PfHRP2, but had positive pLDH results. Both illumigene Malaria assays detected *Plasmodium* DNA. Species-specific qPCR confirmed *P. falciparum* to be the causative malaria parasite. PCRs for PfHRP2 and its upstream flanking gene were negative, but positive for the downstream flanking gene. Neither *pfhrp3* nor its flanking genes were detected.

Conclusions: To our knowledge, this is the first description of imported malaria from Africa to Europe with false negative PfHRP2 RDT results due to deletion of the encoding gene. PCRs targeting the pfhrp2 region, showed that at least part of the gene and the upstream gene were deleted in the causative strain. The gene pfhrp3 and its flanking genes were deleted as well.

This observation underscores that RDT results should be interpreted with caution when used as screening test for malaria.