CASE STUDIES

Transfusion Transmitted Malaria in the Western Cape, South Africa

Le paludisme transmis par la transfusion à l'Ouest du Cap, Afrique du Sud

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ABSTRACT

Background: The Western Province Blood Transfusion Service is situated in the non-endemic malaria province of the Western Cape in South Africa.Transfusion Transmitted Malaria (TTM) is uncommon in the Western Cape with only three cases having been reported to date.

Objective: The objective of this presentation is to report on three cases of TTM that have occurred in the Western Cape, and to describe the look-back processes that were involved in the diagnosis, and resolution of the cases.

Case reviews: In 2001, a 35-year-old male patient tested positive for *Plasmodium falciparum* malaria post red cell concentrate transfusion. The second case occurred in 2010 when *Plasmodium falciparum* malaria was transmitted via a platelet transfusion. The donors involved in these cases of TTM had both originated from malaria endemic countries outside South Africa. In December 2012, the third case of TTM was reported. An 81-year-old female patient with an unexplained febrile illness tested positive for *Plasmodium malariae* after transfusion. The red cell donor had left his country of origin Nigeria in 2007.

Conclusion: Despite revised deferral strategies, there still remains a risk of TTM as people infected with *Plasmodium malariae* and *Plasmodium falciparum* may remain asymptomatic carriers longer than the three year deferral period. Consequently, TTM must always be considered as a differential diagnosis in any patient with an unexplained febrile illness following transfusion.

RÉSUMÉ

Contexte: Le service de transfusion sanguine de la province occidentale est situé dans la province du sud-ouest où le paludisme n'est pas endémique. Le paludisme transmis par transfusion (TTM) est rare dans la province du Cap occidental. Trois cas seulement ont été rapportés à ce jour.

Objectif: L'objectif de cette présentation est de rapporter trois cas de TTM survenus dans la province du Cap occidental et de décrire les processus d'étude rétrospective impliqués dans le diagnostic et la résolution des cas.

Examens de cas: En 2001, un patient de 35 ans a été testé positif pour le Plasmodium falciparum après la transfusion de concentrés de globules rouges. Le deuxième cas s'est produit en 2010, lorsque le paludisme à *Plasmodium falciparum* avait été transmis par transfusion de plaquettes. Les donneurs impliqués dans ces cas de MTT étaient tous deux originaires de pays d'endémie palustre à l'extérieur de l'Afrique du Sud. En décembre 2012, le troisième cas de TTM a été signalé. Une patiente de 81 ans atteinte d'une maladie fébrile inexpliquée a été testée positive pour *Plasmodium malariae* après une transfusion. Le donneur de globules rouges avait quitté son pays d'origine, le Nigéria, en 2007.

Conclusion: Malgré la révision des stratégies d'ajournement, il existe toujours un risque de TTM car les personnes infectées par *Plasmodium malariae* et *Plasmodium falciparum* peuvent rester des porteurs asymptomatiques plus longtemps que la période d'ajournement de trois ans. Par conséquent, le TTM doit toujours être considéré comme un diagnostic différentiel chez tout patient présentant une maladie fébrile inexpliquée après une transfusion.

INTRODUCTION

South Africa has limited areas which are endemic for malaria and these are situated in the provinces of Mpumalanga, Limpopo Province and Northern KwaZulu-Natal. The Western Province Blood Transfusion Service is situated in the non-malaria endemic province of the Western Cape. There has been a decrease in malaria risk in South Africa in the past 10 years, but an increase in imported malaria from a growing migrant population from other malaria endemic sub-Saharan African countries.[1]

Transfusion transmitted malaria (TTM) is uncommon in South Africa, with only three cases being reported in the past 30 years. These cases occurred in the Western Cape in 2001, 2010 and 2012. Two were as a result of red cell transfusions and the third from a pooled platelet product. The investigation of these cases is presented in this report.

Donations in South Africa are not routinely screened for malaria. Prevention of TTM depends on exclusion of potentially infected donors prior to donation with questions about previous malarial infection, recent febrile illness and travel to or residence in malaria endemic areas. Deferral criteria in malaria endemic areas of the country differ marginally from those in non-endemic areas. These malaria deferral policies have been effective at maintaining a low prevalence of TTM.

CASE STUDIES

The look-back investigation of these cases involved re-interviewing the donors regarding past malarial infection, history of travel, country of origin and any significant symptoms suggestive of malaria at the time of donation. Archived samples and any blood products still in the blood inventory were recalled for malaria testing. Once donors had been identified as infected with malaria, the other recipients of blood products from the index donation or from previous donations were traced and, where possible, tested for malaria.

Case 1

A 35-year-old male patient received 5 units of red cell concentrate and 6 units of random donor platelets in August 2001 during hip replacement surgery following an injury at work. A further 4 units of red cell concentrate were transfused to this patient on 05 December 2001. He developed pyrexia and rigors one week later, and *Plasmodium falciparum* was identified on a peripheral blood smear. The patient had been hospitalised since August 2001 and had not travelled to or resided in any malaria endemic areas. He was successfully treated with quinine sulphate.

Fifteen donors were investigated and 12 donors had no significant risk factors for malarial infection. One donor had visited a malaria area 11 months prior to donation but had no symptoms of malaria. A second donor had resided in a malaria endemic area up to 6 months before donation, but tested negative for malaria. The third donor, a 24-year old man from Nigeria, tested positive for Plasmodium falciparum malaria on 21 December 2001 using antigen testing. He was retested on 31 January 2002 and found to be negative on malaria antigen testing, indicating a clearance of malaria infection. He was referred for further management.

During interview at the time of donation, the donor had given a history of malarial infection six years previously with no recurrent symptoms. He advised the interviewer that he was from Nigeria but had not been "home" for two years. On follow-up interview during the look-back process, it became apparent that the donor did not equate the question of whether he had been "home" with recent residence in Nigeria. He had not been back to his family home in two years but had travelled extensively in Nigeria and had only been in South Africa for a few weeks at the time of donation. This donor should have been excluded from donating based on the malaria deferral policy in place at the time. Misinterpretation of his history of travel arose as a result of the interview being conducted in English, which was second language for both interviewer and donor. This case highlighted the importance of accurate donor interviewing at pre-donation screening.

Case 2

A 32-year-old woman with pre-eclampsia was admitted to hospital on 23 August 2010 in active labour at 39 weeks gestation. She complained of headache and was noted to have pedal oedema. Blood pressure on admission was 170/100mmHg and proteinuria, noted on urinalysis. An emergency caesarean section was performed for foetal distress and a healthy child was delivered. On 24 August 2010, her platelet count was $25x10^9$/L with a haemoglobin (Hb) level of 6.5g/dL. She was transferred to the referral hospital with a differential diagnosis of Gestational Proteinuric Hypertension (GPH) or HELLP Syndrome.

On 25 August 2010 the patient was transfused with 3 units of red cell concentrate and one unit pooled random donor platelets. On 27 August 2010 she had mild pyrexia, her Hb was 6.1 g/dL and platelet count $28x10^9$/L. Red cell fragmentation was noted on the peripheral blood smear and malaria antigen testing was negative. Thrombotic thrombocytopaenic purpura (TTP) was diagnosed and plasmapheresis was commenced on 31 August 2010. Her course was complicated with renal impairment, urinary tract infections and convulsions, and was persistently pyrexial from 16 September 2010. During review of peripheral blood slides on 18 September 2010, Plasmodium falciparum malaria was identified with a parasitaemia of <1% and she tested positive for malaria antigen on 20 September 2010. The patient responded rapidly to treatment with artemether/lumefantrine Her condition improved and she was discharged on 26 October 2010.

This patient had no prior treatment for or symptoms of malaria and had not travelled to malaria endemic areas. She had travelled to Durban in KwaZulu-Natal in 2009, and had not left Cape Town since then. During her hospitalisation (23 August 2010—26 October 2010), she received 17 units of red cell concentrate, 2 units of pooled platelets and 205 units of fresh frozen plasma.

As there have been no reports of malaria having been transmitted via fresh frozen plasma,[2,3] only the donors of the cellular products were contacted for malaria testing. The 27 donors involved were interviewed about history of malarial illness, symptoms and travel to malaria areas within the 6 months preceding their donations. Malaria PCR testing was performed on all donors. In addition, malaria smears and antigen testing were performed on 7 donors who gave a history of travel or described symptoms of malaria. One random platelet donor tested positive for malaria PCR, had an equivocal antigen testing result for Plasmodium falciparum, and a low level of parasitaemia on peripheral blood smear. This donor's platelet donation had been part of the pooled product transfused on 25 August 2010.

The donor was a 38-year-old male who originated from the Democratic Republic of Congo. He had been residing in Cape Town, South Africa since June 2008 and had not travelled out of Cape Town since his arrival. On interview he gave a history of night rigours when he first arrived in Cape Town and had experienced two episodes of nocturnal pyrexia with headaches in the three months prior to his index donation. These episodes resolved without medical intervention. He had not seen a doctor or required medication since arriving in Cape Town. He was referred for further management.

The red cell recipient from the index donation was traced and tested negative on malaria PCR, antigen testing and peripheral smear. This was possibly due to treatment with high doses of the chemotherapy (etoposide) for acute lymphocytic leukaemia. The plasma from this donation and the archived segment tested positive for malaria on PCR testing.

Further look-back was performed on the donor's previous donations in February and May 2010. The red cell recipients from these two donations both tested negative on malaria PCR, antigen testing and smear examination.

Case 3

An 82-year-old female patient was hospitalised in October 2012 for insertion of arterial shunts. She was transfused with units of red cell concentrate. In December 2012, she developed pyrexia of unknown origin and malaria testing was done, despite no history of recent travel to malaria endemic areas. She tested positive for Plasmodium malariae on PCR testing.

Of the two donors, one had no history of travel and tested negative for malaria on PCR and antigen testing. The second donor had donated three times and fulfilled all the donor acceptance criteria relating to malaria at the time of donation. He tested negative for malaria on antigen testing and no malaria parasites were detected on thin or thick blood smears. However, PCR testing was positive and Plasmodium malariae was identified. These results were confirmed on repeat PCR testing four days later.

The donor was a 23 year old male who originated from Nigeria. He and his family left Nigeria in 2007 and had not returned. He had not visited any malaria endemic areas during his time in South Africa. He had a good understanding of the symptoms of malaria. During interview he disclosed that he had experienced shivering and headaches once a year in Nigeria, but had never required treatment. He had experienced a similar episode about 4 months prior to donation, which resolved again without treatment. He had no symptoms at time of donation. The donor was referred for treatment which he seemed reluctant to comply with.

DISCUSSION

Blood donor deferral criteria

Donors in South Africa are deferred from donating blood for three years after successful treatment of malaria. Deferral criteria for donors travelling to malaria endemic areas changed during the period under review. Criteria in 2001 stated that travel to a malaria endemic area resulted in a 2 week deferral period after which the donor could continue to donate, but for the next five and a half months their cellular products would be discarded and the plasma utilized for fractionated products only. This was changed in 2006 to the current policy, which is a 4 week deferral after leaving a malaria endemic area, followed by a 2 month period where cellular products are discarded and plasma is only utilised for fractionated products.

In order to defer donors who may be semi-immune asymptomatic carriers of malaria, an additional deferral criterion was introduced in 2011. Donors who spent the majority of their childhood (i.e. birth to 15 years) in a malaria endemic area are deferred for 3 years after their departure from the area, and are deferred for a further 3 years if they visit any malaria endemic area thereafter.

The donor in the first case should have been excluded from donation based on the criteria in place in 2001. In this instance the donor interview failed, which emphasises the importance of accurate interviewing techniques prior to donation. The third case of TTM occurred despite adherence to the current guidelines.

The second case prompted a change in the malaria deferral policy in August 2011 in order to defer donors who may be semi-immune asymptomatic carriers of malaria. Persons who have spent their formative years in malaria endemic areas may have acquired natural immunity with asymptomatic parasitaemia, which can persist for long periods depending on the parasite involved. Plasmodium vivax may persist for 2.5years, Plasmodium ovale for 7 years, Plasmodium falciparum for 5 to 8 years and Plasmodium malariae for up to 44 years.[2] However, immune carriers who have resided in malaria endemic areas for extended periods may transmit Plasmodium falciparum and Plasmodium vivax for periods which exceed those mentioned above.[3]

The second case was unusual in that malaria was transmitted through a platelet transfusion by a donor with a low parasitaemia, indicating that even a small number of infected red cells can transmit malaria and all products which potentially contain red cells should be followed up in malaria look-back investigations.

CONCLUSION

Increased travel to malaria endemic areas and high volumes of population movement to South Africa from malaria endemic countries in Sub-Saharan Africa could lead to an increase in the prevalence of TTM. Guidelines for malaria deferral should be reviewed regularly and criteria updated accordingly. These cases illustrate the importance of careful, and consistent adherence to donor screening policies Screening interview must be thorough, and donor and blood product documentation and archival must be strictly observed, in case extensive look-back, and traceability becomes necessary, as in this report.

TTM can have life-threatening consequences as it can often go undiagnosed. Clinicians should be alert to any undiagnosed symptoms suggestive of malaria in transfused patients. Despite implementation of strict deferral criteria, complete prevention of transmission of malaria via transfusion may not be achievable.

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