JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

Case Report

Malaria in an asylum seeker paediatric liver transplant recipient: diagnostic challenges for migrant population

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Abstract

Transplanted patients are particularly exposed to a major risk of infectious diseases due to prolonged immunosuppressive treatment. Over the last decade, the growing migration flows and the transplant tourism have led to increasing infections caused by geographically restricted organisms. Malaria is an unusual event in organ transplant recipients than can be acquired primarily or reactivation following immunosuppression, by transfusion of blood products or through the transplanted organ. We report a rare case of *Plasmodium falciparum* infection in a liver transplanted two years-old African boy who presented to one Italian Asylum Seeker Center on May 2019. We outlined hereby diagnostic challenges, possible aetiologies of post-transplantation malaria and finally we summarized potential drug interactions between immunosuppressive agents and antimalarials. This report aims to increase the attention to newly arrived migrants, carefully evaluating patients coming from tropical areas and taking into consideration also rare tropical infections not endemic in final destination countries.

Key words: liver transplantation; malaria; recipient; asylum seeker; post-transplant infections.

J Infect Dev Ctries 2021; 15(1):172-178. doi:10.3855/jidc.12541

(Received 13 February 2020 – Accepted 03 May 2020)

Introduction

The recent dramatic rise in migratory flows has led to a better awareness of the phenomenon prompting the diagnosis and management of infectious diseases that are no longer endemic in Europe. Transplant tourism has increased rapidly over the past two decades, accounting for 10% of world organ transplants in 2007 [1]. The transplants occurred in 35 countries, led by China, Philippines and India [2]. India is now in the forefront of living donor liver transplant (LDLT) with survival data comparable to the best centres in the world [3]. The risk of infection during the first year of liver transplantation adds up to 80%: of these most are successfully treated, but some end up to be life-threatening [4]. Opportunistic infections are a leading cause of death during the first three years after liver transplantation and cytomegalovirus along with invasive fungal infections are the most common conditions [5]. Post-transplant malaria has been rarely reported in literature and but can be acquired by transfusion of blood products, through the transplanted organ or via mosquito bites in areas of endemicity [6].

We report the peculiar case of *Plasmodium falciparum* infection in a two year-old migrant African child liver transplanted.

Case Report

A 2-years old male from Sierra Leone arrived at the Asylum Seeker Center (ASC) of Rocca di Papa, Rome, Italy on May 2019. The health management strategy of individual people and public health is based on a screening visit on arrival at the internal health care facility (IHF) of ASC [7-18]. The visit is performed with the support of translators speaking the patient's mother language. In his past medical history, a biliary atresia treated with living donor (mother) liver transplant one year before in New Delhi, India was reported. Ever since, he had been on a long-term immunosuppressive treatment including mycophenolate mofetil, cyclosporine and steroids on a daily basis. The patient and his mother, after spending 8 months in India, returned to Sierra Leone. They flew to Italy after a stay of 4 months in Sierra Leone. No previous history of recent malaria attack or a of antimalarials intake was reported. The child only suffered from general malaise before moving to Italy. Physical examination at the arrival was completely normal. Fifteen days after the arrival at the ASC the child started to show fever and three days later was referred to the hospital.

In relation to his age the clinical examination at the emergency department (ED) admission was almost unremarkable with the exception of fever (body temperature: 38.7 C°) and the surgical scar related to previous surgery. Blood test showed haemoglobin (Hb) 12.7 g/dL, white blood cells (WBC) 5.30×10^3/µL, neutrophils (N) 2.54×10^3/µL, lymphocytes (L) 2.40×10^3/µL, platelets (Plt) 75.00×10^3/µL, total bilirubin 2.7 mg/dL, direct bilirubin 1.6 mg/dL, aspartate aminotransferase (AST) 110 UI/L, alanine aminotransferase (ALT) 40 UI/L, prothrombin time 52% and C-reactive protein (CRP) 14 mg/dL. A chest X-ray, a urinary test strips and an abdominal ultrasound were promptly performed but no clues of ongoing infection or graft rejection were pointed out.

The patient was therefore admitted to the gastroenterology ward and started off on an empiric antibiotic course of therapy including piperacillin/tazobactam i.v. 300 mg/kg/day divided q6h. However, persistent fever along with increasing inflammatory markers (CRP 19.1 mg/dL; Procalcitonin (PCT) > 100 pg/mL), prompted physicians to add teicoplanin i.v. 10 mg/kg q24h (with loading dose of 10 mg/kg q12h for 3 doses) and replace piperacillin/tazobactam with meropenem i.v. 60 mg/kg/day divided q8h. In addition to a large spectrum antibiotic treatment, the dose of cyclosporine was reduced, and steroids discontinued. The whole virology panel (cytomegalovirus, hepatitis A-B-C and E, HIV, adenovirus, parvovirus, BK virus), turned out to be negative, beside increasing EBV DNA levels (2 million genome copies). Both blood and urine cultures were negative.

Upon the 7th day of hospitalisation, the patient presented a severe drop in haemoglobin level (5.6 g/dL). Three UI of packed red blood cells (PRBCs) were urgently transfused and thick and thin blood smears for malaria were performed. Light microscopy of stained blood films was positive for *Plasmodium falciparum,* with a parasitaemia of 10%. *P. falciparum* malaria was treated with artesunate i.v. 3 mg/kg for 3 days (at 0, 12, 24, 48, 72 hours), followed by a course of oral artemether/lumefantrine (20mg/120mg at 0 and 8 hours, then every 12 hours for other 2 days). During the antimalarial treatment the patient clinical conditions progressively improved. By the time of hospital discharge, bloods parameters improved significantly and parasitaemia quickly dropped under 0.5%.

One week later, he attended a clinical follow up examination. The whole blood count showed: Hb 9.3 g/dL, WBC 13.23×10^3/µL, Plt 261.00×10^3/µL,. A complete metabolic panel showed: Alb 4.7 g/dL, ALT 11 UI/L, AST 30 UI/L, total bilirubin 1.28 mg/dL, direct bilirubin 0.69 mg/dL, PT 78%.

Regular dose of cyclosporin was then renewed. A graft biopsy was scheduled and the mother was advised to carry out further malaria-related investigations, if the fever appeared again in the child.

Discussion

The International Organization for Migration estimated the migrant population worldwide to be 258 million in 2017 and, more than ever before, migration touches all countries and people [19]. Factors promoting migration are multiple, including economic prosperity, inequality, demography, violence and conflict, and environmental change [20]. In addition to these well-known causes of migration, it is relevant to mention the growing phenomenon of health tourism, defined as "the practice of travelling to another country with the purpose of obtaining health care", which is reasonably limited in low-income countries mainly due costs, lack of availability, and/or lengthy of waiting lists [21]. India is one of the top 10 medical tourism destinations in the world, where it represents one of the most growing sectors [22]. It is estimated that up to 25% of patients undergoing live donor transplants in India come from foreign countries [23].

We presented the case of a two year-old migrant African child, who had received a liver from his mother

in India one year before and presented fever 15 days after his arrival in Italy.

Bacterial infections account for the most frequent post-transplant infections (up to 70%), followed by viral and fungal aetiologies [24]. Infection causes differ during 3 different time periods after liver transplant (<1 month, 1-6 months, and > 6 months post-transplant) [24,25]. Fever in the late post-transplant period is typically associated with ongoing rejection or infections similar to those seen in the general population. The recurrence of chronic infections such as EBV, hepatitis C virus (HCV), and hepatitis B virus (HBV) may be a further cause of fever [24-26].

On epidemiological basis, our patient was firstly considered as "fever in a transplant recipient". Later on, his condition was interpreted as "fever in traveller from tropical areas". Indeed, when our patient arrived at the Emergency Department (ED) a rejection or a bacterial infection was highly suspected, and therefore he was treated with broad-spectrum antibiotics. The hypothesis of bacterial infection was actually reinforced by elevated levels of procalcitonin (PCT), a promising marker for the diagnosis of bacterial infections. Nevertheless, high PCT values, have also been reported in several patient series with severe falciparum and non-falciparum malaria [27,28].

When the patient arrived at the ED, thrombocytopenia and hyperbilirubinemia, which are significant clues of malaria, were already present. Despite laboratory findings were consistent with a bacterial infection, the crucial information that the patient was coming from Sierra Leone, a country with high prevalence of *P. falciparum* malaria, should have been taken into account. Only at day 7, when haemoglobin level dropped to 5.6 g/dL, a thick blood smear was performed and established the diagnosis of malaria. The patient started anti-malaria drugs with improving clinical condition and recovery.

Over the last years, a growing number of tropical infections in transplant recipients have been reported [29,30]. The reasons underling this phenomenon include the increasing number of transplant tourism mainly in regions with high prevalence of tropical infectious diseases, higher rate of migrants from endemic areas for tropical infections to non-endemic settings, and increasing travel of transplanted patients to the tropics and subtropics [29-31]. Post-transplant malaria has been rarely reported in literature even in endemic areas and the infection source has not always been defined. Nevertheless, malaria remains very common in individuals travelling from endemic countries. In non-endemic areas, collecting an accurate travel history in all patients with fever is the key to making diagnosis. The clinical picture of malaria in transplant recipients is usually severe, due to impaired immune response [32]. It is characterized by pyrexia, although not always occurring with typical paroxysmal or cyclic pattern, haemolytic anaemia, occasionally hemophagocytic and often associated with thrombocytopenia [33,34].

Malaria infection can be a consequence of donor-derived infections (DDI); reactivation or recrudescence of latent infections in the recipient; and *de novo* post-transplant infection by the bite of Anopheles mosquitoes in endemic setting. DDI has been reported through transfusion of blood products, most cases have been described after renal transplantation; some cases of malaria have also been transmitted by liver, heart, lungs, and bone marrow grafts [35].

In our case, it should certainly be considered the chance of malaria infection as a consequence of DDI. Indeed, all species of *Plasmodium*, causing human infection, can be transmitted by graft. Our patient had received the liver from his mother who reported having undergone a screening before the transplant in Delhi (India). She could not provide any medical documentation but considering the level of the transplant sector in India we are confident that she was in good health and suitable to donate her liver. However, mother may have a negative thick blood smear simply as a result of lower parasitaemia. Indeed, the transplant immunosuppression can lead to a relapse of latent *P. vivax* or *P. ovale* due to the hypnozoite forms within hepatocytes for months or even years, or recrudescence of asymptomatic infection caused by other *Plasmodium* species [31]. Of note, the patient had been travelling to India, a country where *P. vivax* is also found [36]. Thus, history of travel to *P. vivax* or *P. ovale* endemic areas oblige doctors to consider the risk of relapses, regardless of pharmacological immunosuppression. Anyway, the final diagnosis was *P. falciparum* malaria, which undermines the hypothesis of relapses "hypnozoites related".

Regarding the recrudescence (without reinfection) if the patient survives without treatment, the persistence of the parasite in the human is estimated to last 1 year for *P. falciparum*, 3 to 5 years for *P. vivax* and *P. ovale*, and until 40 years for *P. malariae* [35]. During this time frame, the patient may complain few symptoms; this occurs especially in the semi-immune population of countries where the parasite is endemic [37].

Table 1. The potential for interactions between antimalarial and immunosuppressant drugs. Adapted from DrugBank, WebMD, Drugs.com, Medscape.

Antimalarial	Immunosoppressor	Severity	Interaction
Quinine	Ciclosporine	Minor	increases the level or effect of quinine by affecting hepatic/intestinal enzyme CYP3A4 metabolism. Increases QTc interval
	Tacrolimus	Monitor closely	Increases QTc interval.
	Everolimus, azathioprine, cyclophosphamide, mycophenolate, daclizumab	No	
	Prednisone, dexamethasone, methylprednisolone	Minor	Decreases the level or effect of quinine by affecting hepatic/intestinal enzyme CYP3A4 metabolism.
Chloroquine	Cyclosporine	Monitor closely	Increases levels of cyclosporine by decreasing metabolism.
	Tacrolimus	Minor	Increases levels of tacrolimus by decreasing metabolism.
	Everolimus, azathioprine, cyclophosphamide, mycophenolate, prednisone, dexamethasone, methylprednisolone, daclizumab	No	
Doxycycline	Cyclosporine, tacrolimus, everolimus, azathioprine, cyclophosphamide, mycophenolate, prednisone, dexamethasone, methylprednisolone, daclizumab	No	
Pyrimethamine/ Sulfadoxine	Cyclosporine, tacrolimus, everolimus, azathioprine, cyclophosphamide, mycophenolate, prednisone, dexamethasone, methylprednisolone, daclizumab	No	
Mefloquine	Cyclosporine	Monitor Closely	Increases the level or effect of mefloquine by affecting hepatic/intestinal enzyme CYP3A4 metabolism
	Tacrolimus	Serious-Use alternative	Increases toxicity of tacrolimus by QTc interval. Mefloquine may enhance the QTc prolonging effect of high risk QTc prolonging agents
	Everolimus	Serious - Use alternative	Increases levels of everolimus by P-glycoprotein (MDR1) efflux transporter. Increases immunosuppressive effects;
	Azathioprine	Serious-Use alternative	Increase immunosuppressive effects;
	Cyclophosphamide, mycophenolate, prednisone, dexamethasone, methylprednisolone, daclizumab	No	
Atovaquone/ Proguanil	Cyclosporine, tacrolimus, everolimus, azathioprine, cyclophosphamyde, mycophenolate, prednisone, dexamethasone, methylprednisolone, daclizumab	No	
Primaquine	Cyclosporine, tacrolimus, everolimus, azathioprine, cyclophosphamyde, mycophenolate, prednisone, dexamethasone, methylprednisolone, daclizumab	No	
Attemether/ Lumefantrine	Cyclosporine	Monitor closely	artemether/lumefantrine will decrease the level or effect of cyclosporine by affecting hepatic/intestinal enzyme CYP3A4 metabolism. cyclosporine will increase the level or effect of artemether/lumefantrine by affecting hepatic/intestinal enzyme CYP3A4 metabolism.
	Tacrolimus	Monitor closely	artemether/lumefantrine will decrease the level or effect of tacrolimus by affecting hepatic/intestinal enzyme CYP3A4 metabolism
	Everolimus	Contra indicated	artemether/lumefantrine will decrease the level or effect of everolimus by affecting hepatic/intestinal enzyme CYP3A4 metabolism.
	Azathioprine, cyclophosphamyde, mycophenolate	No	
	prednisone, metilprednisolone	Monitor closely	artemether/lumefantrine will decrease the level or effect of Prednisone and Metilprednisolone by affecting hepatic/intestinal enzyme CYP3A4 metabolism. Prednisone and Metilprednisolone will decrease the level or effect of artemether/lumefantrine by affecting hepatic/intestinal enzyme CYP3A4 metabolism.
	Dexamethasone	Contra indicated	dexamethasone will decrease the level or effect of artemether/lumefantrine by affecting hepatic/intestinal enzyme CYP3A4 metabolism. Coadministration with strong CYP3A4 inducers can result in decreased serum concentrations and loss of antimalarial efficacy. artemether/lumefantrine will decrease the level or effect of dexamethasone by affecting hepatic/intestinal enzyme CYP3A4 metabolism. Use Caution/Monitor.
	Daclizumab	No	

Our patient had been in Italy two weeks, coming from Sierra Leone, a country at high-risk for malaria transmission which reported 1,651,236 confirmed cases in 2017, but with more than 2.9 million cases estimated. *P. falciparum* is the only plasmodium species reported in Sierra Leone [38]. For this reason and considering the typical incubation time of *P. falciparum*, a falciparum attack should have been immediately suspected and a *de novo* post-transplant malaria infection by *Anopheles* mosquitoes bite was the most reasonable hypothesis to explain the fever.

Antimalarial drugs can be used safely in most patients without medical issues, although the potential drug interactions with immunosuppressive agents should be evaluated when choosing a prophylaxis or a treatment agent. Special attention should be payed when quinine is used for treatment because it may interfere with cyclosporine metabolism, decreasing its blood levels [39]. Moreover, tacrolimus together with chloroquine, artemisinin combinations, or mefloquine increases the risk of arrhythmia [40]. In Table 1 we reassumed principal antimalarials used in therapy or in prophylaxis and their interactions with immunosuppressors. Notwithstanding any possibility of personalized treatment, prevention and early individuation of patients at risk remains the most important measure. Transplant candidates and recipients travelling to malaria endemic areas or foreign- born transplant recipients returning to their country of origin may be at risk for reactivation of latent infections and for acquisition of new malaria infection. In this context, careful anamnesis and evaluation of travel and the destination's risk of infection should be always considered in malaria free areas, considering that infection can be acquired in non-endemic locations by mosquitoes unintentionally transported by aircraft ("airport malaria").

We believe that our case has multiple points of interest. First, the *unde venis* criteria should always be considered when collecting the medical history of a patient with fever, regardless of risk factors for viral or bacterial infection. The World Health Organization and other epidemiological institutions offer very detailed maps and documents that can be easily and promptly sought on the Internet. Physicians at the ED should be trained in order to collect in real time epidemiological information on malaria and other tropical diseases. Distribution and outbreaks of the most frequent travellers' infections should be well known. In addition, physicians who deals with transplant patients have to consider the chance of rare infections if the donor serological state is unknown.

Conclusions

This clinical case describes the management of a *P. falciparum* infection in a liver transplant patient presenting as a refugee in a country declared malaria-free in 1970 [41]. To sum up, we recommend increasing attention to newly arrived migrants evaluating carefully the past medical and travel history. In the patient coming from tropical areas during the diagnostic pathway we have to take into consideration also rare tropical infections not endemic in the country of final destination to avoid serious health consequences.

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Conflict of interests: No conflict of interests is declared.