Submitted: 15 February, 2021 Accepted: 12 April, 2021 Published: 08 November, 2021 DOI:10.22514/sv.2021.108

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Signa Vitae

CASE REPORT

Fatal imported case of Plasmodium mixed infection: cerebral malaria, thrombocytopenia and multi organ dysfunctions (MODs)

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Abstract

Background: Plasmodium falciparum accounts for nearly all severe malaria cases among European travellers, even though, in areas of endemicity, Plasmodium vivax seems to cause severe malaria to a degree which is comparable with P. falciparum. Furthermore, unlike countries at high risk, the incidence of mixed infections among imported cases is very low. We report the case of a man from non-endemic country with a mixed infection diagnosed after a two-year stay in Guinea.

Case Presentation: A 43-year-old male Italian patient developed hyperpyrexia and chills the day after his return to Italy. Within 7 days from fever onset, he was found unresponsive with vomiting and seizures. On admission to Emergency Room, the patient was hypotonic with flaccid tetraparesis, with a GCS score of 7. On the basis of personal and working history and clinical features, after exclusion of viral encephalitis, acute pyogenic meningitis, tubercular meningitis and pontine infarct, cerebral malaria infection was suspected. Rapid diagnostic test and peripheral blood smear were positive for plasmodium mixed infection (P. falciparum, P. vivax, Plasmodium ovale). Over the first 30 hours from admission, thrombocyte count dropped, and the patient developed disseminated intravascular coagulation. Renal failure required renal replacement therapy. Death occurred after 48 hours of ICU admission.

Conclusion: The fatal course of the severe malaria with related cerebral impairment, lung and kidney failure, disseminated intravascular coagulation, severe acidosis, circulatory collapse with refractory septic shock and subsequent multi organ failure was likely due to delayed medical presentation by the patient and the mixed plasmodium infection. Diagnosis could only be established nine days after onset of symptoms.

Keywords

Cerebral malaria; P. vivax; MODs; Thrombocytopenia; Plasmodium mixed infection

1. Background

According to WHO estimates, malaria is endemic in 87 countries with 229 million people infected in 2019. The heaviest burden is carried by sub-saharian african countries where Plasmodium falciparum accounts for most cases of severe disease and death [1].

Since the 1970s autochthonous malaria transmission in Europe has been only exceptionally documented. However, given the growing number of travelers in endemic regions, the annual number of imported cases has kept between 5000 and 7000 over the last few years, with 6199 cases confirmed in 2015 [2].

P. falciparum is detected in more than 75% of imported infections, being responsible for nearly all severe disease in developed countries, with a fatality rate of about 1% [3].

The incidence of non-falciparum cases (mostly from Plasmodium vivax), may be underestimated due to their milder progress among European travellers [4].

In areas of endemicity, however, P. vivax seems to cause severe malaria to a degree which is comparable with P. falciparum, although the two species appear to have different pathophysiological mechanisms of organ-specific involvement [5].

Furthermore, unlike countries at high risk, where the spread of different plasmodium species frequently overlaps, the incidence of mixed infections among imported cases is very low [6].

We report the case of a man from a non-endemic country with a mixed infection from P. vivax, Plasmodium ovale and P. falciparum diagnosed after a two-year stay in Guinea. Of note, the country visited by the man is currently considered an area at unstable transmission of P. vivax as a consequence

TABLE 1. Main laboratory findings.

Lab. data	T_0	T_2 (6 h)	T_3 (18 h)	T_4 (30 h)	Reference interval
pH	7.293	7.269	7.239	6.860	12–16
PLT × 10^3/mm^3	34	24	12	5	130–400
INR ratio	0.95	2.42	Nd	Nd	0.8–1.3
PCT ng/mL	5.32	7.32	80	244	<0.5
Lactate mmol/L	6.3	7.8	8.7	14.3	0.5–1
PO_2/FiO_2 ratio mmHg	323	169	123	54	>300
CSF/BC	Aerobic - Anaerobic - Fungi -				
CSF PCR Real time	Bacterial antigen: Streptococcus Pneumoniae -, Strteptococcus B -, Neisseria Meningitidis B/E/Acy -, Haemophilus Influentiae B - Virus DNA: HSV 1–2 -, CMV -, EBV -.				
CSF	IgG: 155 mg/L; Ph: 9; Pandy: ++; CSF protein: 142 mg/dL; CSF glucose: 87 mg/dL				

PLT, platelet; INR, international normalized ratio; PCT, procalcitonin; CSF, cerebrospinal fluid; BC, blood culture; PCR, polymerase chain reaction; HSV, Herpes simplex virus; CMV, Cytomegalovirus; EBV, Epstein–Barr virus.

of human genetic negativity for Duffy factor in local population [7]. Encephalopathy and thrombocytopenia were the most remarkable features of the presenting clinical picture, which rapidly evolved to multiple organ dysfunction syndrome (MODs).

2. Case presentation

A 43-year-old Italian patient, who had been working in Republic of Guinea over the past 2 years, developed hyperpyrexia and chills the day after his return to Italy. He had no previous relevant clinical records and had not taken antimalaria chemoprophylaxis. He was prescribed paracetamol and betamethasone tablets by his GP.

Seven days from fever onset, he was found unresponsive with vomiting and tonic clonic seizures.

On admission to Emergency Room (ER), the patient was already hypotonic with flaccid tetraparesis, GCS (Glasgow Coma Scale) score was 7 (E_4, V_2, M_1). Hemoglobinuria was detected and blood gas analysis showed lactic acidosis (lactate 63 mg/dL, PH 7.293) (Table 1). A Computed Tomography (CT) Angiography of the brain was obtained and proved to be negative for bleeding or ischemia.

Due to worsening hemodynamic instability, respiratory distress and GCS score of 7, the patient was intubated, put on mechanical ventilation and admitted to ICU, with a SAPS II score of 65 and SOFA score of 13 respectively.

A lumbar puncture was performed: cerebrospinal fluid analysis, culture and polymerase chain reaction (PCR) tests proved to be negative for bacterial meningitis and common neurotropic viruses (Table 1).

A Magnetic Resonance Imaging (MRI) scan and an electroencephalogram (EEG) were also obtained: both tests showed signs of encephalitic involvement of hippocampal cortex, thalami, cerebellar cortex, hypothalamus, insular cortex, periaqueductal gray matter, anterior temporal and polar cortex with bilateral distribution (Fig. 1).

Laboratory findings on admission showed thrombocytope-

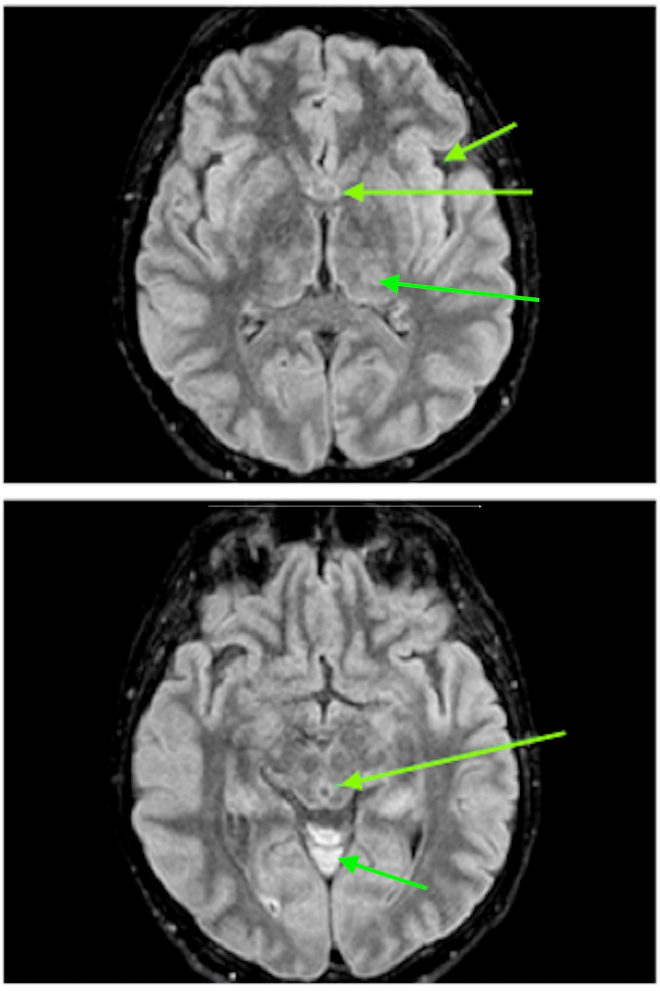

FIGURE 1. MRI: Signs of encephalitic involvement with hyperintensity of the cerebellar cortex, thalamus, hypothalamus, insular cortex, anterior temporal cortex, periaquedutal gray matter and polar cortex with bilateral distribution (green arrows).

nia and high levels of procalcitonin and CRP (259.61 mg/dL) (Table 1). On the basis of personal and working history and clinical features, after exclusion of viral encephalitis, acute pyogenic meningitis, tubercular meningitis (TBM) and pontine infarct, cerebral malaria infection was suspected. Rapid diagnostic test and peripheral blood smear were positive for plasmodium mixed infection (Fig. 2).

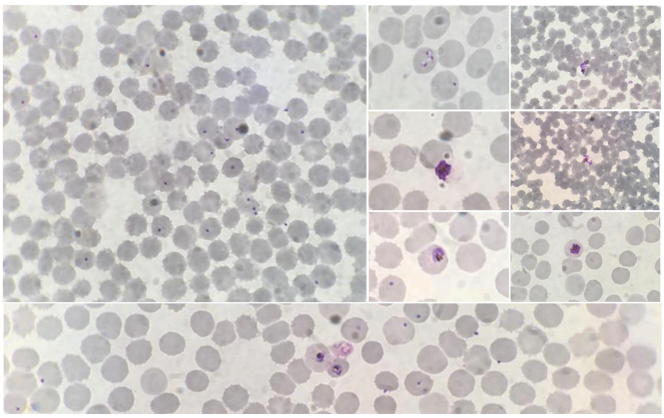

FIGURE 2. Blood smear examination showed schistocytes, split red blood cells (indicate microangiopathic hemolytic anemia) and echinocytes (burr cells), red blood cells with short, evenly spaced spicules and preserved central pallor (observed in uremia, liver disease and in severe metabolic acidosis) [28].

In vitro immuno-chromatographic assay for the qualitative detection of Plasmodium antigens circulating in human venous and capillary EDTA whole blood of individuals with sensitivity and specificity for P. falciparum of 99.7% and 94.2% respectively and sensitivity and specificity for P. vivax and P. ovale of 93.5% and 99.8% respectively, were performed.

Trophozoites and schizonts of P. vivax and P. ovale and P. falciparum trophozoites were showed. Percentage of Plasmodium parasitemia >10% was determined as (number of infected RBCs/Total number of RBCs counted) × 100.

No PCR analyses were carried out for malarial diagnosis in our case. A third level center, the Department of Infectious Diseases and Tropical Medicine at Spallanzani Hospital in Rome, was contacted. As per WHO guidelines he was started on intravenous artenusate (2.4 mg/kg) and doxycycline 100 mg twice daily.

Catecholamines had to be administered to maintain sufficient perfusion and circulation. Over the first 30 hours from admission, thrombocyte count dropped dramatically (5000/μL) and the patient developed disseminated intravascular coagulation (DIC). Platelet pools and fresh frozen plasma were transfused. Renal failure with anuria and severe creatinine increase (3.97 mg/dL) required renal replacement therapy (CVVHD, continuous veno-venous hemodiafiltration).

Death occurred within 48 hours from admission.

3. Discussion

Severe forms of malaria are most often caused by Plasmodium falciparum, but emergent health problem is represented by vivax malaria and mixed Plasmodium infections which can also lead to multiple organ dysfunction syndrome (MODS) and shock. As per severe sepsis, this clinical scenario should be regarded as a medical emergency and managed in intensive care units (ICU) [8–10].

In our case, the patient presented with altered consciousness (seizure and coma), thrombocytopenia/DIC, shock, acute respiratory distress syndrome (ARDS), renal impairment, severe metabolic acidosis, and high parasitemia level (>10%). These conditions have already been reported in recent case series and listed in the 2015 WHO criteria for severe malaria [11].

In patients who meet these criteria, mortality ranges from 8 to 30% despite treatment [10].

The fatal course in the presented case was likely due to delayed medical presentation by the patient so that diagnosis could only be established nine days after onset of symptoms. The presence of a mixed infection, however, played an important role in determining the severity of illness.

Republic of Guinea is currently considered an area at unstable transmission of P. Vivax as a consequence of human genetic negativity for Duffy factor in local population [7]. However, as the burden of P. falciparum declines, widespread distribution of non-falciparum species becomes more obvious across sub-Saharan countries. These species account for nearly 13% of infections among travelers. Of note, there is growing evidence of autochthonous P. vivax transmission in East Africa [12].

This species is characterized by a variable incubation period and the possibility of asymptomatic primary infection. However, even in the case of mildly or asymptomatic primary infection, P. vivax can survive in infected patients as liver dormant stages hypnozoites causing recrudescence or relapses through the years [13]. It has been demonstrated that coinfection with other species favors P. vivax hypnozoites activation and parasitemia [14].

Dormant stages hypnozoites and reactivations have also been described for P. ovale, which is a widespread species in all sub-Saharan countries [15].

Our patient was likely to acquire P. vivax infection during his stay in Eritrea, more than 2 years before P. falciparum infection. The latter may have reactivated vivax hypnozoites and favored P. ovale parasitemia.

A strong correlation was found between the parasite density in the peripheral blood and the severity of the disease and its complications. Especially among non-immune subjects, the patients' clinical condition can lead to exacerbation of systemic inflammatory response, until onset of MODS [8].

A parasitemia >10% found in our case is one of the criteria for the diagnosis of severe malaria as established in the revised guidelines [16]. This criterion, however, is based on studies over P. falciparum infection. Hyperparasitemia is rather uncommon with P. vivax and P. ovale which exhibit preference to invade reticulocytes rather than erythrocytes, being more difficult to detect in peripheral blood smear [15, 17]. Moreover, as long as cytoadherence and microvascular accumulation are the main characteristics of P. falciparum, the pathophysiology of P. vivax is characterized by endothelial activation and over increase of pro-inflammatory cytokines. As a consequence, organ dysfunction may occur in the presence of a lower parasite

biomass [17].

Cerebral malaria is a life-threatening complication associated with the sequestration of Plasmodium infected erythrocytes in the brain microcirculation [18]. Neuroimaging studies have shown breakdown of blood brain barrier and severe brain swelling in disease etiology [19]. The vascular dysfunction in cerebral malaria is believed to result from a combination of microvascular obstruction and tissue perfusion abnormalities [20], altered coagulation [21], systemic and local inflammatory processes, and damaging parasite products [22]. Released cytokines could lead to vascular engorgement and vasodilatation causing cerebral vasogenic and cytotoxic edema and subsequent ischemia.

Severe thrombocytopenia was also one of the main findings in our case (PLT = 35,000/μL). Significant decrease in platelet levels, especially during mixed infections and an inverse relationship between parasitemia and platelet counts across various infecting species, was observed and reported earlier [23]. Recently Punnath *et al*. [24] suggest that P. vivax infections can result in a similar degree of severe thrombocytopenia as observed in P. falciparum infection. They found that patients with thrombocytopenia, experienced severe malarial complications such as severe anemia, acute renal failure, jaundice, metabolic acidosis, spontaneous bleeding, hypoglycemia, hyperparasitemia, acute respiratory distress syndrome, pulmonary edema, and cerebral malaria. A possible role of cytokines such as TNF-α, IL-6, and IL-10 in decreased or disturbed platelet production, resulting in thrombocytopenia, was postulated.

Shock occurs in about 10% of patients with severe malaria, is uncommon in adults but frequently seen in children [10].

Lactic acidosis, as reported in the presented case, is a marker of poor prognosis. This is caused by anaerobic glycolysis in under-perfused tissues due to microcirculatory obstruction by parasitized erythrocytes. Type B lactic acidosis due to increase in lactate production by parasites and impairment of hepatic and renal lactate clearance can also coexist.

Renal failure may occur in patients with a high parasitemia following shock and hemoglobinuria from intravascular hemolysis [25]. Continuous renal replacement therapy, which was performed for our patient, is initiated in up to 35% of patients with AKI in severe malaria [26].

The rapid onset of MODS, as previously described, led to pulmonary involvement in a very short time. Most patients with ARDS will also have thrombocytopenia, renal failure and hemodynamic disturbances [10]. Malarial ARDS carries a high mortality [27].

Cerebral malaria, MODS and severe thrombocytopenia are possible presentations of severe malaria both in endemic and non-endemic industrialized areas.

Similarly, to severe sepsis, intensive care management is essential, and it can be a demanding challenge for intensivists. In case of major delay in medical diagnosis and treatment, MODS may soon develop, and even the best intensive care support and prompt institution of effective anti-malarial therapy may not prevent a fatal course of the disease.

In the last decades, population mobility changes the epidemiology of infectious diseases. The displacements of people caused by wars and poverty from disadvantaged geographical areas to industrialized and rich areas, as well as international travel play a fundamental role in mixing the population.

In this context travel medicine plays a crucial role in raising awareness to the problem and establishing good strategies to reduce the incidence of communicable diseases among travelers. Lack of pre-travel information can increase the patient delay to medical access.

4. Limits

The lack of the possibility of being able to perform a PCR analyses in our hospital, for the genetic confirmation of the identification carried out by the rapid antigenic test of the plasmodia species involved in the patient's infection, could present a diagnostic limitation. Nonetheless, traditional methods and rapid tests, despite the limitations inherent in the methods, have allowed a diagnosis of infection to be made in a reasonable time. Another possible limitation concerns the anamnestic gaps regarding the patient's history, the state of antimalarial prophylaxis and the possible period of contact with plasmodium.

5. Conclusions

This case highlights the severity of imported plasmodium mixed infection. Although known to infrequently cause severe malaria and MODS, intensivists must be vigilant of such rare case of septic shock and multi organ failure. Prompt recognition and institution of supportive therapy and early antimalarial therapy will increase survival rate. The occurrence of malaria infections could be expected in non-endemic and industrialized areas; physicians should consider the possibility of severe malaria disease, the presenting symptoms, the differential diagnosis and the anamnestic information about traveling in endemic areas to avoid delayed or misdiagnosis in primary healthcare system.

AUTHOR CONTRIBUTIONS

CA and RM Design, Writing and Revision the Manuscript; CA, MPDB, NC, GDL, FV, SCR and RM: Literature Search, Revision of References; MPDB, GDL, SCR: collected and analyzed radiological and laboratory data; CA, MPDB, GDL, SCR, NC, FV and RM approved the final version of manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the local Ethics Committee of ASL Avezzano-L'Aquila-Teramo, which waived the requirement for informed patient consent (approval no. 0041713/21). Consent to participate is not applicable.

ACKNOWLEDGMENT

The authors thank all the staff of the ICU, the laboratory of Clinical Pathology and Microbiology department the Radiol-

ogy Department of General Civil Hospital "G. Mazzini" of Teramo city, for their collaboration.

FUNDING

This research received no external funding.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

[1] World Health Organization. World malaria report 2020. 2020. Avaliable at: https://www.who.int/publications/i/item/9789240015791 (Accessed: 1 June 2021).

[2] ECDC. Annual epidemiological report for 2015. Stockholm: ECDC. 2017. Avaliable at: https://www.ecdc.europa.eu/en/publications-data/malaria-annual-epidemiological-report-2015 (Accessed: 1 June 2021).

[3] Mali S, Kachur SP, Arguin PM. Division of Parasitic Diseases and Malaria, Center for Global Health; Centers for Disease Control and Prevention (CDC). Malaria surveillance—United States, 2010. MMWR Surveill Summ. 2012; 61: 1–17.

[4] Ruas R, Pinto A, Nuak J, Sarmento A, Abreu C. Non-falciparum malaria imported mainly from Africa: a review from a Portuguese hospital. Malaria Journal. 2017; 16: 298.

[5] Naing C, Whittaker MA, Nyunt Wai V, Mak JW. Is Plasmodium vivax malaria a severe malaria? A systematic review and meta-analysis. PLoS Neglected Tropical Diseases. 2014; 8: e3071.

[6] Odolini S, Gautret P, Parola P. Epidemiology of imported malaria in the mediterranean region. Mediterranean Journal of Hematology and Infectious Diseases. 2012; 4: e2012031.

[7] Baird JK. Evidence and implications of mortality associated with acute Plasmodium vivax malaria. Clinical Microbiology Reviews. 2013; 26: 36–57.

[8] Santos LC, Abreu CF, Xerinda SM, Tavares M, Lucas R, Sarmento AC. Severe imported malaria in an intensive care unit: a review of 59 cases. Malaria Journal. 2012; 11: 96.

[9] D'Abramo A, Lepore L, Iannetta M, Gebremeskel Tekle S, Corpolongo A, Scorzolini L, *et al*. Imported severe malaria and risk factors for intensive care: A single-centre retrospective analysis. PLoS ONE. 2019; 14: e0225135.

[10] Karnad DR, Nor MBM, Richards GA, Baker T, Amin P; Council of the World Federation of Societies of Intensive and Critical Care Medicine. Intensive care in severe malaria: report from the task force on tropical diseases by the world federation of societies of intensive and critical care medicine. Journal of Critical Care. 2018; 43: 356–360.

[11] Al Farsi F, Chandwani J, Mahdi AS, Petersen E. Severe imported malaria in an intensive care unit: a case series. IDCases. 2020; 17: e00544.

[12] Twohig KA, Pfeffer DA, Baird JK, Price RN, Zimmerman PA, Hay SI, *et al*. Growing evidence of Plasmodium vivax across malaria-endemic Africa. PLoS Neglected Tropical Diseases. 2019; 13: e0007140.

[13] Kondrashin AV, Morozova LF, Stepanova EV, Turbabina NA, Maksimova MS, Morozov EN. On the epidemiology of Plasmodium vivax malaria: past and present with special reference to the former USSR. Malaria Journal. 2018; 17: 346.

[14] Commons RJ, Simpson JA, Thriemer K, Hossain MS, Douglas NM, Humphreys GS, *et al*. Risk of Plasmodium vivax parasitaemia after Plasmodium falciparum infection: a systematic review and meta-analysis. The Lancet Infectious Diseases. 2019; 19: 91–101.

[15] Okafor CN, Finnigan NA. Malaria (Plasmodium ovale). Treasure Island: StatPearls Publishing. 2020.

[16] World Health Organization. Guidelines for the treatment of malaria. Third edn. Geneva: WHO Press. 2015.

[17] Gowda D, Dayananda K, Achur R. Epidemiology, drug resistance, and pathophysiology of plasmodium vivax malaria. Journal of Vector Borne Diseases. 2018; 55: 1–8.

[18] Taylor TE, Fu WJ, Carr RA, Whitten RO, Mueller JS, Fosiko NG, *et al*. Differentiating the pathologies of cerebral malaria by postmortem parasite counts. Nature Medicine. 2004; 10: 143–145.

[19] Mohanty S, Benjamin LA, Majhi M, Panda P, Kampondeni S, Sahu PK, *et al*. Magnetic resonance imaging of cerebral malaria patients reveals distinct pathogenetic processes in different parts of the brain. MSphere. 2017; 2: e00193–17.

[20] Dondorp AM, Ince C, Charunwatthana P, Hanson J, van Kuijen A, Faiz MA, *et al*. Direct in vivo assessment of microcirculatory dysfunction in severe falciparum malaria. The Journal of Infectious Diseases. 2008; 197: 79–84.

[21] Moxon CA, Chisala NV, Mzikamanda R, MacCormick I, Harding S, Downey C, *et al*. Laboratory evidence of disseminated intravascular coagulation is associated with a fatal outcome in children with cerebral malaria despite an absence of clinically evident thrombosis or bleeding. Journal of Thrombosis and Haemostasis. 2016; 13: 1653–1664.

[22] Miller LH, Ackerman HC, Su X, Wellems TE. Malaria biology and disease pathogenesis: insights for new treatments. Nature Medicine. 2013; 19: 156–167.

[23] Margono S, Lubis B, Pasaribu S, Wijaya H, Pasaribu AP. The correlation between platelet count and parasite density in children with malaria infection. Asian Pacific Journal of Tropical Disease. 2016; 6: 199–203.

[24] Punnath K, Dayanand KK, Chandrashekar VN, Achur RN, Kakkilaya SB, Ghosh SK, *et al*. Association between Inflammatory Cytokine Levels and Thrombocytopenia during Plasmodium falciparum and P. vivax Infections in South-Western Coastal Region of India. Malaria Research and Treatment. 2019; 2019: 4296523.

[25] White NJ, Pukrittayakamee S, Hien TT, Faiz MA, Mokuolu OA, Dondorp AM. Malaria. Lancet. 2014; 383: 723–735.

[26] Cheng MP, Yansouni CP. Management of severe malaria in the intensive care unit. Critical Care Clinics. 2013; 29: 865–885.

[27] Taylor WRJ, Hanson J, Turner GDH, White NJ, Dondorp AM. Respiratory manifestations of malaria. Chest. 2012; 142: 492–505.

[28] Dai Q, Zhang G, Lai C, Du Z, Chen L, Chen Q, *et al*. Two cases of false platelet clumps flagged by the automated hematology analyzer Sysmex XE-2100. Clinica Chimica Acta. 2014; 429: 152–156.

How to cite this article: Chiara Angeletti, Sofia Chiatamone Ranieri, Gabriella Di Leonardo, Maria Paola Di Bartolomeo Maria, Nadia Carbuglia, Federica Venturoni, *et al*. Fatal imported case of Plasmodium mixed infection: cerebral malaria, thrombocytopenia and multi organ dysfunctions (MODs). Signa Vitae. 2021;17(6):145-149. doi:10.22514/sv.2021.108.