

Hemophagocytic syndrome associated with severe *Plasmodium vivax* malaria in a child in Bikaner (northwestern India)

Gajanand Singh Tanwar¹, Anil Lahoti¹, Priya Tanwar², Renu Agrawal¹, Punam Chand Khatri¹ & Dhanpat Kumar Kochar²

¹Department of Pediatrics, S.P. Medical College, Bikaner; ²Rajasthan University of Health Sciences, Jaipur, India

Key words Childhood malaria; hemophagocytic syndrome; *Plasmodium vivax*; severe vivax malaria

Hemophagocytic syndrome (HPS) is a reactive disorder of the mononuclear phagocytic system, characterized by benign, generalized histiocytic proliferation, with marked hemophagocytosis in bone marrow¹. Generally, HPS has been related with hematologic diseases, autoimmune diseases, or with various infections¹. There are plenty of reports on hemophagocytic syndrome associated with *Plasmodium falciparum* monoinfection^{2–9}, but reports on the association with *P. vivax* monoinfection are very scanty^{9–14}. In most of these case reports, the diagnosis was made by peripheral blood smear (PBS) and rapid diagnostic test (RDT) without molecular diagnostic confirmation. Thus, there are always chances of species misidentification and missing the mixed infection thereby lacking authenticity. In this case report, the species diagnosis was confirmed by polymerase chain reaction (PCR) and possibilities of other diseases were ruled out by stringent laboratory and biochemical investigations to establish the firm association of hemophagocytic syndrome with *P. vivax* monoinfection.

Case report

On March 28, 2012, a female child was admitted with history of high grade fever with chills and rigor, emesis and abdominal pain since last seven days to the Department of Pediatrics, S.P. Medical College, Bikaner, Rajasthan, India. She had history of epistaxis and her parents also noticed petechiae spots on trunk and extremities since Day 1. There was no history of weight loss, bone pain, seizure, frequent infections, previous blood transfusion and any contact of tuberculosis. Past medical history and family history were also unremarkable. On physical examination, there was severe pallor, icterus, petechial spots, palpable cervical lymph nodes and hepatosplenomegaly (spleen 5 cm below the left costal margin). Vital signs were 100/60 mm Hg of blood pressure, 108/min of pulse rate, 36.9°C of temperature, and 26/min of respiration rate. Hematological findings revealed hemoglobin 5.2 g/dl, total leukocyte count

2100/mm³, differential leukocyte count: 41% polymorphs, 53% lymphocytes, 3% monocytes, 3% eosinophils, and platelet count: 16,000/mm³, hematocrit 22.6%, peripheral smear showing pancytopenia with all stages of *P. vivax* (density 8000/mm³) (Fig. 1).

The RDT results, based on the detection of species-specific *Plasmodium* lactate dehydrogenase (LDH) (OptiMal test; Diamed AG, CressiersurMorat, Switzerland) and histidine rich protein-2 (HRP-2) (Falcivax test; Zephyr Biomedical Systems, Goa, India), were positive for *P. vivax* and negative for *P. falciparum*. The PCR study targeted against the 18S ribosomal RNA gene of the parasite and used 1 genus-specific 5' primer and 2 species-specific 3' primers in the same reaction mixture, confirmed the *P. vivax* monoinfection. The details are described in our previous studies¹⁵.

Abnormal liver function tests were as follows: aspartate aminotransferase, 104 IU/L (reference: 5–45 IU/L); alanine aminotransferase, 106 IU/L (reference: 5–45 IU/L); total bilirubin, 3.3 mg/dl (reference: 0.2–1.13 mg/dl); and alkaline phosphatase, 856 IU/L (reference: 122–378 IU/L). Other investigations, results were as follows: serum ferritin level, 1070 ng/ml (reference: 15–332 ng/ml); fasting triglyceride levels, 297 mg/dl (reference: 30–160 mg/dl); serum fibrinogen levels, 102 mg/dl (reference: 233–496 mg/dl); and D-dimer assay, 25.7 µg/ml (reference: <1 µg/ml). Prothrombin time, activated partial thrombin time, renal function test, serum electrolytes and glucose-6-phosphate dehydrogenase enzyme levels were in normal range. Ultrasonography of the abdomen showed enlarged liver and spleen (12 cm). Immunohistochemistry including natural killer (NK) cells activity, soluble IL-2 and soluble CD25 measurement could not be done due to non-affordability by the patient.

Repeated culture (BACTEC-ALERT) of blood, urine and stool, and relevant serology tests for typhoid, *Leptospira*, rickettsia, hepatitis A/B/C viruses, HIV, infectious mononucleosis, dengue infection and fungal infec-

tion were all negative. Bone marrow was examined due to pancytopenia. Bone marrow aspirate smears showed normal cellularity and myeloid/erythroid ratio, adequate numbers of megakaryocytes/granulocytes/erythroid cells and sufficient hemosiderin particles. Intracellular parasites were rare but prominent hemophagocytic histiocytes were seen (Fig. 2). Diagnosis of malaria-associated HPS was made.

The child was treated with i.v. artesunate 2.4 mg/kg stat at 12 h, 24 h and then once daily for 2-days and then with oral artemether and lumefantrine for 3-days. Primaquine was given for 14 days as radical treatment. On Day 3, hematological findings were: hemoglobin 7.6 g/dl; total leukocyte count 7,600/mm³; platelet count 146,000/mm³ and peripheral smear showing disappearance of *P. vivax*. After 14 days of antimalarial medication, the child was discharged in hemodynamically stable state. Serum ferritin level and fibrinogen level were normalized during follow up.

Pancytopenia in a febrile patient may be the manifestation of bone marrow suppression induced by aplastic

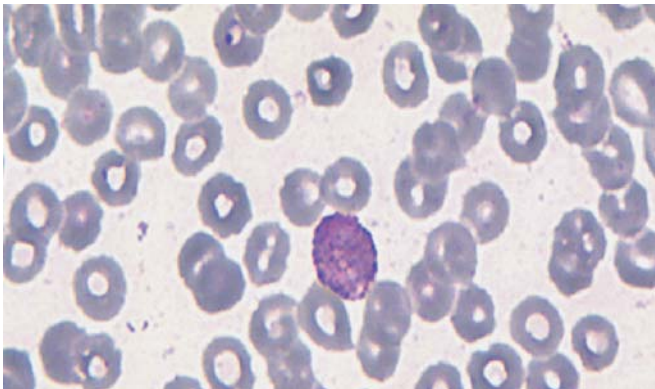


Fig. 1: Peripheral blood smear showing ring and schizont stages of *P. vivax*.

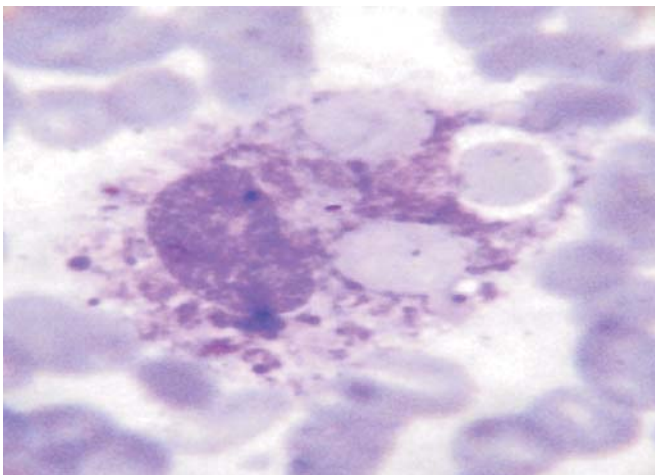


Fig. 2: Bone marrow aspiration smear showing hemophagocytosis (Leishman stain).

anemia, hematologic malignancies, metastatic cancer, infection, and or inflammation¹⁶. HPS, a rare cause of pancytopenia and fever, results from impaired functions of natural killer and cytotoxic T-cells and augmented activities of lymphocytes and histiocytes induced by overexpressed inflammatory cytokines such as tumour necrosis factor- α (TNF- α), interferon- γ (IFN- γ) and macrophage colony stimulating factor (M-CSF), soluble IL-2 receptor, IL-1 and IL-6, resulting in monocyte activation and leading to phagocytosis of hematopoietic cells¹⁹⁻²⁰. Strikingly high levels of these cytokines have been observed in patients with malaria and could trigger HPS initiation¹⁷⁻¹⁸. Our patient presented with fever, hepatosplenomegaly, pancytopenia, hyperferritinemia, hypertriglyceridemia, hypofibrinogenemia and hemophagocytosis in the bone marrow, fulfilling the diagnostic criteria for HPS¹⁷⁻¹⁸.

Severe *P. vivax* malaria has been recently reported in pediatric age from this community¹⁹. After extensive literature search, our case is the first PCR confirmed *P. vivax* associated HPS in childhood age. The etiological role of *P. vivax* monoinfection is suggested by the confirmation of species by PCR, ruling out the possibilities of other concurrent disease by scientific pattern and the total clinical and haematological recovery after antimalarial treatment. HPS is one of the causes of pancytopenia in these infections. Bone marrow examination is not usually undertaken for the purpose of diagnosis of malarial infection. Therefore, it is difficult to determine the prevalence of malaria complicated by HPS.

HPS could play a role in the pathogenesis of cytope-
nia observed during Plasmodia infestation. As its frequency has not been systematically studied during malaria, it is difficult to assume its pathophysiological consequences on prognosis. We recommend a marrow examination in malarial cases with severe or persistent decrease in hemoglobin or pancytopenia. However, it could be implicated in life-threatening complications due to the infection by Plasmodium species, justifying further studies on this syndrome to reduce disease burden.

ACKNOWLEDGEMENTS

We are especially thankful to Dr Gajendra N. Gupta, Head of Department (Pathology and Transfusion Medicine), Santokba Durlabhji Memorial Hospital-cum-Medical Research Institute, Jaipur, Rajasthan, India for his expert opinion about bone marrow histopathology.

REFERENCES

1. Imashuku S. Differential diagnosis of hemophagocytic syndrome:

- Underlying disorders and selection of the most effective treatment. *Int J Hematol* 1997; 66: 135–51.
2. Anwar M, Salcem M, Malik A. Severe hemophagocytic syndrome in falciparum malaria. *J Pak Med Assoc* 1995; 45: 302–3.
 3. Ohno T, Shirasaka A, Sugiyama T, Furukawa H. Hemophagocytic syndrome induced by *Plasmodium falciparum* malaria infection. *Int J Hematol* 1996; 64: 263–6.
 4. Retormaz F, Seux V, Arnoulet C, Durand JM, Sainty D, Soubeyrand J. *Plasmodium falciparum* malaria infection complicated by haemophagocytic syndrome in an old man. *Acta Haematol* 2000; 103: 224–5.
 5. Sermet-Gaudelus I, Abadie V, Stambouli F, Hennequin C, Lenoir G, Gendrel D. Haemophagocytic syndrome in *Plasmodium falciparum* malaria. *Acta Paediatr* 2000; 89: 368–9.
 6. Abdelkefi A, Othman TB, Torjman L, Ladeb S, Lakhal A, Belhadj S, et al. *Plasmodium falciparum* causing hemophagocytic syndrome after allogeneic blood stem cell transplantation. *Hematol J* 2004; 5: 449–50.
 7. Saribeyoglu ET, Anak S, Agaoglu L, Boral O, Unuvar A, Devecioglu O. Secondary hemophagocytic lymphohistiocytosis induced by malaria infection in a child with Langerhans cell histiocytosis. *Pediatr Hematol Oncol* 2004; 21: 267–72.
 8. Ohnishi K, Mitsui K, Komiya N, Iwasaki N, Akashui A, Hamabe Y. Clinical case report: Falciparum malaria with hemophagocytic syndrome. *Am J Trop Med Hyg* 2007; 76: 1016–8.
 9. Pahwa R, Singh T, Khurana N. Hemophagocytic syndrome in malaria and kala-azar. *Indian J Pathol Microbiol* 2004; 47(3): 348–50.
 10. Aouba A, Noguera ME, Clauvel JP, Quint L. Hemophagocytic syndrome associated with *Plasmodium vivax* infection. *Br J Haematol* 2000; 103: 832–3.
 11. Zvulunov A, Tamary H, Gal N. Pancytopenia resulting from hemophagocytosis in malaria. *Pediatr Infect Dis J* 2002; 21: 1086–8.
 12. Park TS, Oh SH, Choi JC, Kim HH, Chang CL, Son HC, et al. *Plasmodium vivax* malaria complicated by hemophagocytic syndrome in an immunocompetent serviceman. *Am J Hematol* 2003; 74: 127–30.
 13. Ram Kumar TV, Baghmar S. *Plasmodium vivax* malaria complicated by neurological, jaundice and haemophagocytic syndrome. *J Nepal Paediatr Soc* 2010; 30(3): 168–70.
 14. Bae E, Jang S, Park CJ, Chi HS. *Plasmodium vivax* malaria-associated hemophagocytic lymphohistiocytosis in a young man with pancytopenia and fever. *Ann Hematol* 2011; 90: 491–2.
 15. Kochar DK, Saxena V, Singh N, Kochar SK, Kumar SV, Das A. *Plasmodium vivax* malaria. *Emerg Infect Dis* 2005; 11: 132–4.
 16. Young N. Aplastic anemia, myelodysplasia, and related bone marrow failure syndromes. In: Fauci AS, Braunwald E, Kasper DL, Hauser SL, Longo DL, Jameson JL, Lascenzo J, editors. *Harrison's principles of internal medicine*, 17th edn. New York: McGraw-Hill Medical 2008; p. 663–71.
 17. Roupael NG, Talati NJ, Vaughan C, Cunningham K, Moreira R, Gould C. Infections associated with haemophagocytic syndrome. *Lancet Infect Dis* 2007; 7: 814–22.
 18. Filipovich AH. Hemophagocytic lymphohistiocytosis and other hemophagocytic disorders. *Immunol Allergy Clin North Am* 2008; 28: 293–313.
 19. Kochar DK, Tanwar GS, Khatri PC, Kochar SK, Sengar GS, Gupta A, et al. Clinical features of children hospitalized with malaria: A study from Bikaner, northwest India. *Am J Trop Med Hyg* 2010; 83(5): 981–9.

Correspondence to: Dr D.K. Kochar, C-54, Sadul Ganj, Bikaner-334 003, Rajasthan, India.
E-mail: drdkkochar@yahoo.com; drdkkochar@indiatimes.com

Received: 17 September 2012

Accepted in revised form: 20 June 2013