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CASE REPORT

Plasmodium Vivax Malaria: Usual Illness with Dysregulated Immune Profile

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ABSTRACT

Afebrile *Plasmodium vivax* disease is believed to be extremely rare; and so is the association of a secondary immune thrombocytopenia due to *Plasmodiun vivax malaria*. This is a case of malaria presenting in an atypical manner. A middle aged male (31 years) came with occasional bleeding around gums, small petechial haemorrhages over chest and abdomen, and blood in stools for a few months, but no fever. In addition, the cervical lymph nodes were slightly enlarged. Spleen was 3 cm below costal margin. Platelets were found to have markedly decreased with clusters of megakaryocytes in bone marrow. A possibility of Immune thrombocytopenic purpura was considered and immunoglobulin started intravenously, however platelet counts remained low. Later, in a follow up smear, trophozoites of *P. vivax* were discovered. Antimalarial drugs (Artesunate) were administrated for the patient along with IV immunoglobulins, to which he responded. It was revealed by flow cytometry that there was reversal of helper to cytotoxic ratio (0.9). This highlighted a rare case of afebrile malaria in association with immune dysregulation. Accordingly, malaria, though uncommon, could trigger immune thrombocytopenia.

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Keywords: Afebrile, Immune thrombocytopenia, Plasmodium Vivax Malaria

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INTRODUCTION

Plasmodium vivax (*P. vivax*) infection is known to be a prevalent illness in several parts of the world and characteristically presents with fever, chills and rigors. Fever serves as a surrogate indicator for malaria diagnosis, particularly in resource limited malaria endemic zones (1). An infection with *P. vivax* without fever is extremely rare. Furthermore, malaria is known to be associated with transient thrombocytopenia, yet secondary immune thrombocytopenia (ITP) as a manifestation of *P.vivax* malaria has been rarely reported. In the present study, we reported a case of *P. vivax* malaria with these unusual features.

CASE REPORT

A 31-year-old male patient, resident of Meerut, Uttar Pradesh (India), presented with complaints of petechial hemorrhages, gum bleeding, and melena started from 3 months before. There was no history of cough, cold, fever, diarrhea or vomiting. On the examination, he had splenomegaly (Spleen size 14 cm, soft in consistency) and bilateral cervical lymphadenopathy, largest node measuring 1 X 0.5 cm. The provisional clinical diagnosis was hematological malignancy or immune thrombocytopenia. Hemogram revealed hemoglobin -10.3g/dl, WBC count- 7800/ µL, and severe thrombocytopenia (platelets count- 7000/ µL). Peripheral blood smear (PBS) revealed platelet anisocytosis with few large platelets and normocytic red cells. There were few (10%) atypical/ reactive lymphoid cells with moderate blue-grey cytoplasm, fine cytoplasmic granules, and inconspicuous nucleoli (Figure 1A). Certain neutrophils demonstrated platelet phagocytosis (Figure 1B). A flow cytometric immuno-phenotyping was carried out to evaluate the nature of atypical cells which were confirmed as large lymphocytes; ELISA for HIV I and II, hepatotropic viruses (Hepatitis B and C) and IgM for Dengue were negative. Rheumatoid factor and antinuclear antibodies were observed to be within the normal range. A bone marrow aspiration and biopsy were performed after transfusing random donor platelets (4 units). The bone marrow was cellular (70% cellularity), which revealed trilineage hematopoiesis along with megakaryocytic hyperplasia with an increased number of immature megakaryocytes. Focal clustering of megakaryocytes was also noted. Myeloid and erythroid series showed normal maturation and reaction, respectively. No atypical cells were detected in the bone marrow (Figure 1C and D). Hence, a diagnosis of Immune thrombocytopenia was suggested. The patient was started on Intravenous immunoglobulin (1g/kg/day X 2 days). Subsequent hemogram revealed only partial correction of thrombocytopenia (Platelets – 50 × 10^9/L). Surprisingly, repeating PBS showed trophozoites of *P. vivax* malaria (Figure 1A) even though the parasite density was quite low (approximately 25/ µL of blood). The patient was started on antimalarial drugs (IV Artesunate, 120 mg stat followed by 120 mg/IV after 12 hours, followed by 120 mg/IV OD) along with a repeated bolus dose of IV immunoglobulin, after which the patient responded well with complete correction of thrombocytopenia (Platelet count: 160,000/µL). Lymphadenopathy also subsided within one month following the treatment. Such unusual manner of presentation prompted us to review the previous papers. We found that the absence of fever in malaria was attributed to a defective immune system. Thus, a screening flow cytometric analysis was carried out for lymphocytic populations and helper to cytotoxic cell ratio.

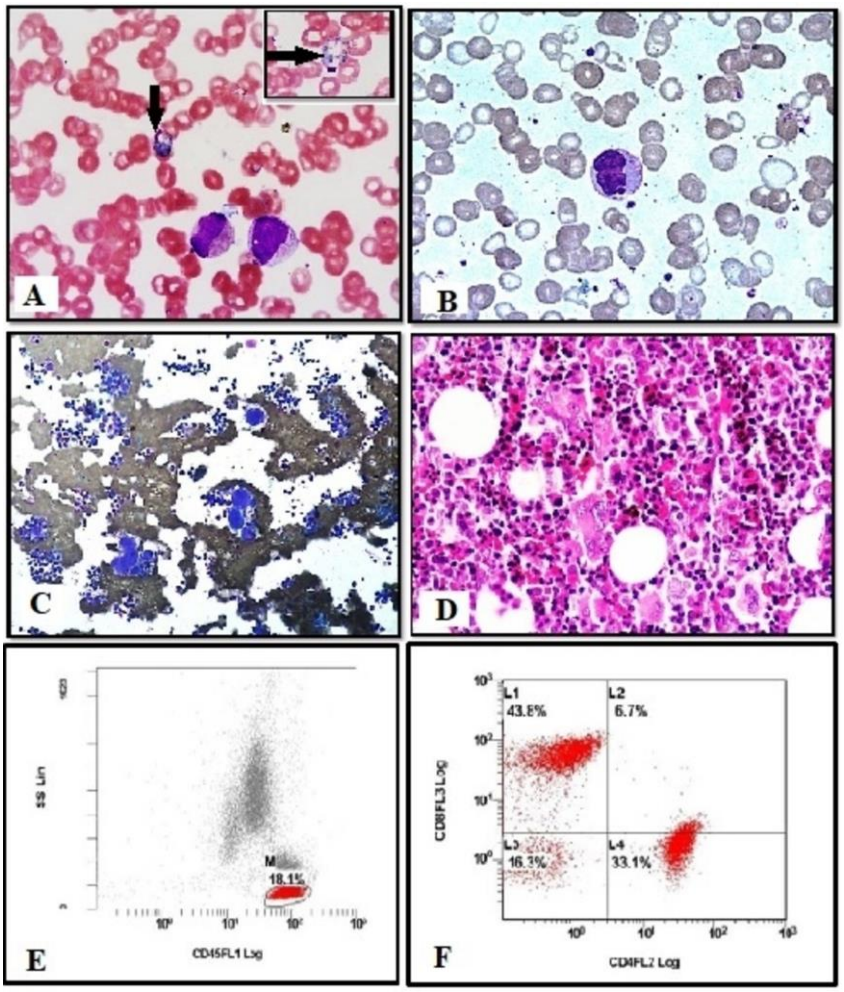

Figure 1. (A) PBS shows normocytic normochromic to microcytic hypochromic RBCs, monocytoid cells and thrombocytopenia along with trophozoites of *P. vivax* malaria (In inset also). (B) PBS represents platelet phagocytosis by neutrophil. (C) Bone marrow aspirate smears show megakaryocytic hyperplasia with both mature and immature forms and focal clustering. (D) Bone marrow biopsy illustrate megakaryocytic hyperplasia. (E) Immunophenotyping by flowcytometry CD45 vs SS: 18% gated population. (F) Immunophenotyping by flowcytometry 40% population is CD4 positive and 44% is CD8 positive (CD4:CD8 ratio-0.9).

A disturbance in distribution of T and B cells (88% - T cells (increased); B cells – 9.5%; NK cells – 2.5%) was noted with reversal of helper to cytotoxic cell ratio (0.9) (Figure 1E and F). This was indicative of immune dysregulation.

DISCUSSION

Malaria is a major public health problem worldwide, in developing countries in particular. The disease is still endemic in several parts of India, including Andhra Pradesh, Chhattisgarh, Gujarat, Jharkhand, Madhya Pradesh, Maharashtra, Orissa, Rajasthan and Sikkim (2). The two major plasmodium species in India are *Plasmodium*

falciparum and *vivax*. *Plasmodium malariae* infection has only been reported in Eastern India whereas the infection triggered by a *Plasmodium ovale* species is extremely rare (3). Our patient was from Meerut, Uttar Pradesh, which does not lie in the malaria endemic zone. The prevailing clinical manifestations of malaria infection are fever, characteristically with chills and rigors, sweating, headache, myalgia and fatigue. *P. vivax* infection without fever is extremely rare. Hotz *et al.* described a case of afebrile malaria in an immunosuppressed female on Methotrexate therapy for rheumatoid arthritis. They explained that immunosuppression due to methotrexate therapy might have suppressed the fever (1). The present case was also afebrile, but there was no history of immunosuppression due to medication or disease. On flow cytometry, we could observe CD4:CD8 ratio (4). Few authors have studied the profile of CD4 and CD8 cells in malaria and found either no alteration in the CD4 and CD8 cells in malaria or a mild increase in the effector CD4 cells (5,6). The reversal of CD4:CD8 ratio has not been observed in malaria and thus, it cannot be presumed to be a consequence of the disease. The reduction in CD4 cells in this particular patient may have led to a poor cytokine response necessary for the production of fever. However, on extensive literature search, no association was found between afebrile malaria and an altered CD4/CD8 ratio. Mild to moderate thrombocytopenia is one of the common hematological alterations seen in *P. vivax* infection. However severe thrombocytopenia due to *P. vivax* infection, which leads into bleeding manifestations is extremely rare (7). The reasons of thrombocytopenia due to *P. vivax* infection include coagulation disturbances, splenomegaly, bone marrow alterations, platelet aggregation and antibodies mediated platelet destruction (8). Immune thrombocytopenia (ITP) occurs due to deposition of antiplatelet antibodies and immune complexes on the membrane of platelets, leading to their premature destruction. It might be primary or secondary. Causes of secondary ITP include infections, collagen vascular disease, lymphoproliferative disorders, solid tumors and drugs. Infections associated with ITP are HIV, Hepatitis C, Helicobacter pylori, Tuberculosis, Cytomegalovirus and Varicella or Zoster. To the best of our knowledge, a secondary ITP induced by a *P. vivax* infection is a rare event, and only three cases have been previously reported (8,9). *P. vivax* antigen binds to the surface of platelets to which antimalarial antibodies also bind, leading to the formation of immune complexes. These immune complexes most probably lead to platelet destruction and thrombocytopenia in these patients. However, the exact mechanism of malaria induced ITP is not yet well understood (8). These patients also exhibit an increase in the macrophage-colony stimulating factor suggesting that macrophages play a pivotal role in the destruction of these particles. Platelet phagocytosis by neutrophils in peripheral smear was observed in this patient. To rule out EDTA induced platelet phagocytosis, a repeated peripheral smear with fresh blood sample was performed, which again implied phagocytosed platelet by neutrophils, suggesting that it was not due to EDTA effect. Thrombophagocytosis by neutrophils is a rare peripheral smear finding. Antiplatelet antibodies formed due to ITP could be a cause of neutrophilic thrombophagocytosis, which activate the neutrophilic granulocytes to ingest selectively opsonized platelets (10). Consequently, fever is a consistent symptom associated with malaria, but it should be used as a surrogate marker with caution in immunocompromised patients. Thrombocytopenia is commonly seen in *P. vivax* infection, yet secondary ITP due to *P. vivax* has rarely been reported. Thrombophagocytosis by neutrophils suggests the presence of antiplatelet antibodies.

CONSENT

Written informed consent was obtained from the patient`s legal guardians for publication of this case report and its accompanying information. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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