Chronic Myeloid Leukemia (CML) Complicated by Mixed Malaria Infection- An Unusual Presentation

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Abstract
Objective: To report an unusual case of Chronic Myeloid Leukemia (CML) undergoing chemotherapy complicated by co-infection with Plasmodium vivax and Plasmodium falciparum.

Case presentation: A 31 years Kashmiri male who was a known case of Philadelphia positive Chronic Myeloid Leukemia and on chemotherapy for last 1 year, presented with high grade fever, left flank pain, vomiting and one episode of epistaxis. The oncologist suspected CML progressing to Accelerated phase or chemotherapeutic drug (Tasigna) associated adverse effects leading to thrombocytopenia. He was diagnosed with mixed malarial infection based on positive blood smear and bone marrow aspirate showing gametocytes of both Plasmodium Vivax and Plasmodium Falciparum. Patient was treated successfully with anti malarial drugs and showed marked improvement in platelet count.

Conclusion: It is suggested that malaria should be considered as a complicating factor in the patients of hematological malignancies or those on chemotherapy in form of fever or thrombocytopenia, especially in malaria-endemic areas.

Keywords: Chronic Myeloid Leukemia (CML), Plasmodium vivax, Plasmodium falciparum, Thrombocytopenia.

Introduction
Malaria continues to be a cause of high mortality and morbidity throughout the developing world1. It is also called Poor man’s disease and affect 0.5 million Pakistanis every year 2. Though this region is endemic for malaria but a co-infection with Plasmodium Vivax and Plasmodium Falciparum complicating a hematological malignancy is very unusual. Nirmala et al3 reported multiple cases of leukemias (n = 24) and lymphomas (n = 7) in children complicated by drug resistant Plasmodium falciparum malaria. Tapper and Amstrong4 reported two cases of neoplastic diseases which had transfusion-induced malaria. Rapoport and Uys5 reported three cases (one with Hodgkin’s disease and other two with acute lymphoblastic leukemia) undergoing chemotherapy, developed febrile neutropenia and malaria infection concurrently.

Case Presentation: A31 year male resident of Azad Jammu Kashmir (AJK) Pakistan, diagnosed case of Philadelphia positive Chronic Myeloid Leukemia (CML) presented with high grade fever, left flank pain, vomiting and single episode of epistaxis.

Chronic Myeloid Leukemia (CML) was diagnosed by bone marrow biopsy in some other institute one year ago. PCR confirmed the BCR-ABL fusion gene. Chemotherapy was started in January 2013 and he was on Tasigna (Nilotinib) a Tyrosine Kinase Inhibitor for almost 2 months.

On admission, he was having high grade fever of 104 °F with a pulse rate of 115 beats/min, blood pressure of 100/80 mmHg and was well oriented and alert. General physical examination revealed marked pallor and yellow discoloration of sclera. There was no rash, petechiae or bruises and no lymphadenopathy. Patient had a hemoglobin of 10.1 g/dL with hematocrit of 27.0%, TLC- 4,700/uL and platelet count of 24,000/uL. Antibiotic cover of Tazocin & Vancomycin was given along with Steroids (Deltacortril) and I/V fluids. Multiple transfusions of red cell concentrates and Platelets were also given but platelets continued to drop. Finally Tasigna was with held. A provisional diagnosis of Tasigna associated adverse effects or Chronic Myeloid Leukemia (CML) progressing to
accelerated phase was made and bone marrow biopsy was ordered. At time of biopsy patient had a hemoglobin of 9.2 g/dL with hemotocrit of 25.6%, TLC 3,300/uL and platelet count of 19,000/uL. DLC revealed slight neutropenia with neutrophils; 38 %, Lymphocytes; 43 %, Monocytes; 13 %, Myelocytes; 02% Metamyelocytes; 01 %, Basophils; 03 %, NRBC; 02 NRBC/100 WBC. Peripheral blood film revealed Anisocytosis ++, Poikilocytosis ++, Microcytosis +, Hypochromia +, Target cells ++. Trophozoites and Schizonts of Plasmodium vivax and few Gametocytes of Plasmodium falciparum were also seen. (Figure. 1, 2, 3)

Bone marrow aspirate from posterior superior iliac spine revealed a hypocellular smear with low erythropoietic and myelopoietic activity and decreased megakaryocytes. Platelets were also decreased on smear. Lymphocytes, plasma cells and histiocytes were not increased and no atypical cells seen. Trophozoites and Schizonts of P.vivax and Gametocyte of P.falciparum were seen in the aspirate. (Figure. 4, 5, 6)

A diagnosis of Chronic Myeloid Leukemia with mixed malaria infection was made and the patient was treated with anti malarial drugs, his fever subsided and counts became normal. Steroids were tapered off, Tasigna was started again and patient was discharged after one week.

Discussion

Bone marrow trephine revealed hypocellular bone marrow fragments with decrease in Erythroid, Myeloid and Megakaryocytic cells series along with marked fibrosis. (Figure. 7, 8)

Malaria remains one of the major health problems in tropical and subtropical countries. Despite the intensive worldwide efforts to reduce its transmission, it is the most serious and widespread protozoal infection of humans. Over 40% of world population lives in malaria endemic area. Pakistan being a part of endemic belt has an incidence of one case per thousand persons. Malaria is caused by four species of plasmodium parasites which spread through the bites of infected Anopheles mosquitoes as a vector. These species include: Plasmodium falciparum, vivax, malariae and ovale. P. falciparum and vivax are...
the most common and P. falciparum is the most deadly.
The clinical features of malaria can be misinterpreted in patients with a hematological malignancy especially when the patient is on chemotherapeutic drugs and presents with persistent fever and thrombocytopenia. Malaria is accompanied by various hematological changes which are more pronounced in P. falciparum infection, most likely due to higher levels of parasitemia. These changes include anemia, thrombocytopenia, splenomegaly, and mild-to-moderate atypical lymphocytosis and rarely disseminated intravascular coagulation (DIC). There have also been reports of leucopenia and leucocytosis. Other hematological reactions that have been reported include neutropenia, eosinophilia, neutrophilia and monocytes. Thrombocytopenia being the most common of these with incidence ranging from 40.5-85%. It is thought to be caused by increased splenic sequestration, immune mediated destruction, and a shortened platelet survival.

Tasigna (nilotinib) is a Tyrosine kinase inhibitor indicated for the treatment of newly diagnosed adult patients with Philadelphia chromosome positive Chronic Myeloid Leukemia (Ph+ CML) in chronic phase. Its hematologic side effects include thrombocytopenia (up to 37%), neutropenia (up to 37%), anemia (up to 23%), febrile neutropenia, pancytopenia, thrombocytosis, and leukocytosis. In this case bone marrow of the patient revealed a WBC count of 3,300/μL with no blasts in the peripheral blood film and in bone marrow, ruling out the provisional diagnosis of Chronic Myeloid Leukemia (CML) progressing to accelerated phase (associated with leukocytosis, thrombocytosis or thrombocytopenia, persistent fever & bone pain). The only differential of Tasigna (nilotinib) associated adverse effects was left, which include thrombocytopenia and febrile neutropenia. However the presence of Trophozoites and Schizonts of P.vivax and Gametocytes of P.falciparum not only in peripheral blood film but also in bone marrow aspirate ruled out any other possible differential and mixed malaria infection is established as a root cause.

**Conclusion**
In the patients of hematological malignancies and those who are on chemotherapy presenting with persistent fever and thrombocytopenia, malaria should be considered as a differential especially in malaria endemic areas.

**References**
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**Contribution of authors**
Kanwal Zahra conception and study design and planning and manuscript writing
Lubna Naseem conception and study design, Critical Review and facilitation