CASE REPORT

Fever with Thrombocytopenia—Look beyond Infection: A Case Report

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Abstract

Introduction: Patients having fever with thrombocytopenia [febrile thrombocytopenia (FT)] is a common observation in the intensive care unit (ICU). The majority of the cases of FT are infective in origin, and rarely, FT is due to a noninfectious cause.

Case Description: This is a case of a 33-year-old male who presented with complaints of fever, myalgia, and loose stools. His routine blood investigation showed thrombocytopenia but was negative for tropical infection tests. The peripheral blood smear had blast cells. Bone marrow aspiration showed hypercellular marrow with blasts of occasional Auer rods. Flow cytometry revealed polymyelocytic (PML)/retinoic acid receptor alpha (RARA) fusion-M3 type of acute myeloid leukemia (AML). This patient was diagnosed as having acute promyelocytic leukemia (APML) and treated with all-trans retinoic acid (ATRA) and arsenic trioxide (ATO).

Discussion: Febrile thrombocytopenia is one of the common causes of intensive care unit (ICU) admission. It narrows the differential diagnosis among patients admitted to the hospital. Tropical infections/sepsis are the major causes of FT. Hematological malignancies account for <1–2% of FT.

Conclusion: This case highlights a rare cause of FT (due to APML). High suspicion of hematological malignancies in patients having FT and early initiation of treatment can reduce morbidity and mortality.

Keywords: Case report, Fever, Promyelocytic leukemia, Thrombocytopenia, Tropical infection.

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Introduction

The fever associated with low platelet count is called febrile thrombocytopenia (FT). Thrombocytopenia is defined as platelet count of <1,50,000/mm^3, and fever is defined as temperature of >98.9°F. FT is one of the common causes of intensive care unit (ICU) admission. Tropical infections/sepsis are the major causes of FT. Hematological malignancies account for <1–2% of FT. This is a rare case of FT secondary to hematological malignancy. This case report emphasizes the importance of having hematological malignancy as a part of differential diagnosis in patients presenting with FT.

Case Description

This is a case of a 33-year-old male with no prior comorbidities with a history of travel presented to a tertiary care hospital with fever, myalgia, and loose stools for 3–4 days. There was no history of vomiting, abdomen pain, chest pain, cough, and bleeding manifestations. The patient was evaluated initially at an outside hospital and later referred to our hospital in view of low platelets. On examination in the emergency room (ER), the patient was febrile with a temperature of 101°F, heart rate of 126/minute, blood pressure of 110/54 mm Hg, saturation of peripheral oxygen of 97% on room air, and respiratory rate of 18/minute. The patient was conscious, alert, and cooperative. Another systemic examination was unremarkable. A blood test revealed Hb of 13.5 gm/dL, total leukocyte count of 6,500/cm^3, platelet count of 12,000, serum creatinine of 0.8 mg/dL, blood sugar of 110 mg/dL, and normal liver function tests. Investigations for dengue and other tropical were negative. Ultrasound abdomen showed mild fatty liver with mild splenomegaly. The peripheral blood smear showed blast cells. A bone marrow aspiration study was done, which revealed hypercellular marrow, sheets of blasts, and occasional Auer rods. Flow cytometry revealed polymyelocytic (PML)/RARA fusion suggestive of M_3 type of acute myeloid leukemia (AML) [(15; 17) translocation]. The patient was treated with all-trans retinoic acid (ATRA) and arsenic trioxide (ATO). The patient improved, was stable, and was discharged home without any symptoms.

Discussion

Most of the patients admitted to ICU will have fever with thrombocytopenia. The diagnosis is usually due to dengue fever, rickettsia diseases, malaria, leptospiral infection, typhoid, and sepsis. Noninfectious causes such as hematological malignancies account for <1–2%. Radhika et al. analyzed 855 patients who were admitted with FT between January 2016 and December 2018 and found that dengue fever was the major cause of FT (51.9%), whereas acute leukemia was 0.23%.[1] The incidence of hematological malignancies by Yadav and Gandhi et al. was 0.6[2] and 1.79%, respectively.[3]

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Acute myeloid leukemia (AML) is one such rare cause that presents with FT. In 1957, French and Norwegian physicians first described APML as a hyperacute fatal illness.[4] Myeloid leukemia is a cancer of marrow cells. Acute promyelocytic leukemia (APML) is an M_3 subtype of AML. The APML occurs due to the reciprocal translocation of the RARA gene on chromosome 17 with the promyelocytic leukemia gene on chromosome 15 [(15; 17) (q24; q21).[4]

The incidence of APML is about 0.23/100,000 persons. The median age of occurrence is about 20–50 years. It is seen in 10–12% of all AML cases.[5] Patients usually present with fever, recurrent infections, easy fatigability (due to anemia), breathlessness, loss of appetite, bleeding tendencies, and bone pain.

The diagnosis is to demonstrate multiple Auer rods (Faggot cells) on microscopy with peripheral blood smear. The PML/RARA fusion gene can be demonstrated using polymerase chain reaction, fluorescence *in situ* hybridization (FISH), or cytogenetics. The APML patients are classified as low risk (white blood count ≤10,000 cells/μL) and high risk (white blood count >10,000 cells/μL) based on white blood count.[6] The low-risk patients are treated with less intensive regimens. The APML is very sensitive to ATRA.[4] This drug helps to differentiate immature granulocytes from mature granulocytes by dissociating the N-CoR-HDAC3 complex from RAR. Later, these differentiated granulocytes undergo spontaneous apoptosis. Over a period of time, the APML has transferred from highly fatal to most curable disease (80% or more). If untreated, the patient may succumb within a month. Most of the deaths in APML are due to bleeding complications. In those days, the median survival rate was <1 week, but nowadays, the 10-year survival rate is up to 80–90%.[7,8] The use of ATA as concurrent chemotherapy[9] has shown a remission rate of up to 90% (7/2). Methotrexate, mercaptopurine, and ATRA are used as maintenance therapy following remission. In patients having persistent minimal residual disease, even after medical treatment, stem cell transplantation can be done.

Differentiation syndrome is seen in APML patients occasionally during treatment. It is due to the release of cytokines from the differentiating promyelocytes. The cytokines that cause capillary leak lead to peripheral edema, dyspnea, and fever.

This case report highlights the rare cause of APML-related fever with thrombocytopenia. In the ICU, patients with FT always consider hematological malignancies as one of the differential diagnoses.

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