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Covid-19 Coinfection and Dengue Fever in Patients with Myelodysplastic Syndrome: A Case Report

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ABSTRACT

Introduction: This case report aims to describe the manifestation and management of severe thrombocytopenia in Myelodysplastic Syndrome (MDS) patients with concomitant viral coinfection that also reduce platelet levels. ***Case Illustration:*** A female patient aged 77 years came with complaints of gum bleeding, coughing, shortness of breath, fluctuating fever and weakness. Patient was diagnosed with dengue fever with confirmed NS-1 test. One week before admission to the hospital, the patient received 10 units of platelet transfusion. The result of the SARS-CoV-2 Reverse Transcriptase Real Time PCR examination was positive, laboratory examinations showed severe thrombocytopenia and minimal pneumonia on chest X-Ray. The patient was diagnosed with moderate COVID-19 pneumonia, dengue infection and myelodysplastic syndrome. ***Discussion:*** Thrombocytopenia is one of the frequently observed manifestations in MDS, dengue infection and COVID-19 due to decreased platelet production in bone marrow and increased platelet destruction in peripheral blood.

Keywords: severe thrombocytopenia; myelodysplastic syndrome; coinfection; dengue; COVID-19

INTRODUCTION

Myelodysplastic syndrome (MDS) is a clonal bone marrow disease associated with ineffective hematopoiesis, which manifests as morphological dysplasia of the hematopoietic elements and peripheral cytopenias. The incidence of MDS increases with age, with a 5-fold increase in risk between patients aged 60 and > 80 years.[1] Bleeding complications are a major cause of morbidity and mortality in MDS patients. Thrombocytopenia is an independent factor in reducing survival rates in MDS.[2]

Dengue infection is a disease caused by the dengue virus, belonging to the Flaviviridae family and there are 4 serotypes, including DEN-1, DEN-2, DEN-3, and DEN-4. Dengue infection is transmitted by female Ae. aegypti and Ae. albopictus. Symptoms that appear can include fever, nausea and vomiting, weakness, reddish spots on the skin (petechiae) and in severe cases shock and bleeding can occur. [3,4]

In MDS patients who have a low platelet count, coupled with the presence of COVID-19 and Dengue infection can cause a more severe decrease in platelet count, so stricter management and monitoring is required. Here we report a case of a patient with MDS who experienced co-infection with COVID-19 and Dengue and management of thrombocytopenia.

CASE ILLUSTRATION

A 77-year-old woman came with complaints of bleeding gums since 1 week ago. Complaints are accompanied by fever, weakness, cough and shortness of breath. The patient was diagnosed with MDS 2 years ago, from a pathological examination taken from a bone marrow puncture.

On examination, the general condition was weak, alert, vital signs within normal limits, with a temperature of 38'C. Laboratory results showed positive NS antigen, SARS-CoV2 PCR (+). A complete blood count showed Hb 12.6g/dL, leukocytes 10.610/uL, HCT 38% very low platelets 2000/uL. Liver Function Test and Renal Function Test within normal limits. The chest X-ray shows mild pneumonia.

Our patient was diagnosed with a moderate degree of COVID-19 infection, dengue fever, and MDS. The patient was treated in an isolation room, and a thrombocyte concentrate transfusion was performed. During treatment the patient was given an antiviral, Remdesivier 200 mg/day intravenously which was continued 100 mg/day until day 5, as well as symptomatic drugs. The patient's condition was getting better, and he was allowed to go home after the 13th day of treatment with a platelet count of 47,000/uL.

DISCUSSION

The myelodysplastic syndromes represent a heterogeneous group of myeloid neoplasms characterized by inefficient hematopoiesis, cytopenia and risk of progression to acute myeloid leukemia (AML). The incidence of MDS in the normal population is 4.5 per 100,000 people per year, but the incidence increases in male patients compared to female patients with a ratio of 6.2 vs 3.3 per 100,000 people per year and the number will increase with age. The incidence of MDS is low in patients aged <40 years, which is around 0.1 per 100,000 people per year and increases to 26.9 per 100,000 people per year in patients aged 70-79 years and reaches 55.4 per 100,000 people per year in age group > 80 years. (5,6)

The clinical presentation of MDS patients is dominated by symptoms that arise due to cytopenias.[7,8] Based on the study of Lindberg et al., approximately 11% and 42% of newly diagnosed MDS patients had hemoglobin levels <8 g/dL and 8-10 g/dL, respectively, besides that approximately 50% of patients required erythrocyte transfusions, 40% of patients had platelet count < 100 x 109 L and 5% required platelet transfusion and 20% of MDS patients had neutrophil count < 0.8 x 109/L. Thus, symptoms of anemia such as dyspnea and fatigue predominate in the clinical picture in MDS patients. (9) Complications of bleeding and infection will become more evident as the course of MDS disease progresses. Some MDS patients also have systemic inflammation and are diagnosed with autoimmune diseases before, concurrently with or after the diagnosis of MDS has been made, such as systemic vasculitis, connective tissue disease, inflammatory arthritis and neutrophilic disease. A significant association was observed between chronic myelomonocytic leukemia and systemic vasculitis. Other symptoms such as fever and skin manifestations such as Sweet syndrome and bleeding due to coagulation disorders may also occur. In patients with this clinical spectrum, it is important to think about the diagnosis of MDS because early treatment can help improve the symptoms and condition of the patient. (10)

Although abnormal findings on routine blood tests may help guide the diagnosis of MDS, definitive diagnosis should be confirmed by examination of bone marrow aspiration (cellular morphology and blast percentage), bone marrow biopsy (cellularity and architecture) and molecular genetic or cytogenetic analysis. Other criteria that can help establish the diagnosis of MDS include abnormal bone marrow histology, abnormal immunophenotypes and the presence of molecular markers such as abnormal CD34. (11)

The patient in this case report had previously been diagnosed with MDS and now came with complaints of bleeding gums, fever with fluctuating temperatures and decreased platelet levels leading to a diagnosis of dengue infection. The results of a complete blood count showed a platelet count of 2,000/µL. Thrombocytopenia in MDS is defined when the platelet level is <100,000/µL with a prevalence ranging from 40-65%. The mechanism of thrombocytopenia in MDS includes suppression of megakaryocyte differentiation by cytokines, increased megakaryocyte apoptosis, abnormal TPO signaling transduction, increased platelet destruction and gene mutations associated with thrombocytopenia in MDS. Megakaryocyte cells originate from differentiation of pluripotent hematopoietic cells under the influence of various cytokines such as IL-3, IL-6, IL-11 and TPO. Progenitor cell studies in MDS patients showed that there was an increase in myeloid progenitors while megakaryocyte erythroid progenitors experienced a significant decrease in the bone marrow. Disruption of differentiation at this early stage is caused by the presence of inhibitory cytokines. Bone marrow biopsy results in MDS patients show intramedullary megakaryocyte apoptosis in large numbers. Increased programmed cell death is a mechanism for premature intramedullary cell death in MDS. Megakaryocyte growth unresponsive to TPO was also observed in MDS, this defective response is probably caused by a dysregulated c-Mpl signaling pathway. Nearly 50% of MDS patients were observed to have decreased platelet survival which indicates that there is increased peripheral platelet destruction mediated by both immune and non-immune mechanisms. Finally, mutations in the RUNX1, TP53 and NRAS genes are strongly associated with severe thrombocytopenia and increased bone marrow blasts. (3,15)

Dengue co-infection in MDS patients as observed in this case report can exacerbate hemorrhagic complications. Thrombocytopenia is the predominant clinical manifestation in mild and severe dengue infection and correlates with disease severity. There are 2 mechanisms that cause thrombocytopenia in dengue infection, the first is increased destruction and clearance of platelets from the peripheral blood and the second is a decrease in platelet production in the bone marrow. Inhibition of megakaryocyte development in the bone marrow is one of the mechanisms underlying thrombocytopenia in experimental animals infected with dengue virus. (13) Hemorrhagic complications due to thrombocytopenia as observed in MDS patients and dengue infection vary, ranging from minor symptoms such as bruising and petechiae, to manifestations which can be life threatening, such as gastrointestinal and intracranial bleeding. In both MDS and dengue patients, significantly higher mortality due to bleeding complications was observed in patients with low platelet counts at diagnosis. (9,15)

Prevention of bleeding complications due to thrombocytopenia in MDS and dengue infection can be prevented by proper and prompt treatment of thrombocytopenia. The standard management of thrombocytopenia in MDS is platelet transfusion. Platelet transfusion is the most important supportive management of clinically significant thrombocytopenia. Research in the United States shows that 6 – 33% of patients with MDS require platelet transfusions. Another cohort study conducted in Australia showed that approximately 45% of MDS patients had thrombocytopenia with a platelet count < 100 x 10 9 cells/L at diagnosis. Nearly half of the MDS patients in this cohort had received platelet transfusions with a median amount of thrombocyte concentrate (TC) transfused of 11 units. Two platelet products are available, namely whole blood platelets and single donor platelets. Although platelet transfusion is the most effective method for increasing platelet count, platelet transfusion is not only expensive, but is associated with various risks such as allergic transfusion reactions or fever, transmission of viral or bacterial infections and transfusion-associated acute lung injury. Platelet transfusions routinely will induce "alloimunization" which ultimately makes the patient refractory to transfusion. (16)

The management of thrombocytopenia and administration of platelet transfusions in patients with dengue infection are still controversial. Several guidelines recommend giving platelet transfusions at a cut point value of <20,000/µL if there are no clinically significant signs of bleeding. However, reducing the cut point to <10,000/µL in patients with acute myeloid leukemia did not increase the risk of bleeding, but reduced the number of patients receiving platelet transfusions. Guidance from The British Committee recommends platelet transfusion at the 10,000/µL cut point for patients with stable thrombocytopenia without risk of bleeding. (19, 20)

The patient in this case report is also infected with COVID-19. The manifestations of COVID-19 infection observed in this patient were coughing, shortness of breath, weakness and fever. The COVID-19 pandemic in dengue endemic areas is a challenge in itself because clinical manifestations (such as fever, headache and body aches) and laboratory results (thrombocytopenia and leukopenia) often overlap. Coinfection between the two diseases is associated with higher morbidity and mortality than single infection. Fever is the most common manifestation of dengue infection and COVID-19, additional symptoms such as cough, headache, ageusia will lead to a diagnosis of COVID-19 infection and need to be confirmed by testing for SARS-CoV-2.

Based on the results of systematic studies, the dominant laboratory test observed in SARS-CoV-2 and dengue co-infection is thrombocytopenia. Thrombocytopenia results from decreased platelet synthesis due to virus-induced bone marrow suppression and immune-mediated platelet clearance. Autoantibodies and immune complexes in response to SARS-CoV-2 infection and dengue infection can also destroy platelets. Based on a study by Nham et al., the treatment of thrombocytopenia observed in COVID-19 resembles the treatment of thrombocytopenia in MDS and dengue infection, namely by administering thrombocyte concentrate (TC). (22)

COVID-19 infection affects multiple organs including the hematopoietic system. In the peripheral blood, quantitative and qualitative abnormalities have been reported. CBC and peripheral blood smear findings commonly reported in COVID-19 patients include anemia, leukopenia, leukocytosis, neutropenia, neutrophilia, lymphopenia, monocytosis, monocytopenia, eosinopenia, thrombocytopenia, thrombocytosis, and leukoerythroblastic features.

Morphological abnormalities especially in leukocytes and platelets have been reported, including changes usually found in MDS such as dysplastic neutrophils with hypogranular cytoplasm and/or hyposegmented nuclei (Pelger-Huët anomaly) and giant thrombocytes. Taken together, COVID-19 and MDS could present with a similar appearance on peripheral blood findings. Further studies are needed to understand whether and how hematopoiesis is involved in the pathogenesis of COVID-19, and whether COVID-19 patients have a higher susceptibility to secondary hematological disease. (23)

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