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Case Report

Transfusion associated graft versus host disease following whole blood transfusion: an unusual case of expanded dengue syndrome

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ABSTRACT

Dengue infection presents in a diverse array of manifestations, including dengue fever (DF), dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS). To include cases that do not fit the criteria for either DHF or DSS and show atypical manifestations across multiple organ systems, world health organization (WHO) coined the term expanded dengue syndrome (EDS). A 47-yr-old female presented with fever, chills, blanchable rash, itching and burning sensation all over body with skin peeling over the last 5 days. In the outside hospital, she developed melena and thrombocytopenia, for which she received 1unit packed red blood cells, 1 unit of single donor platelets from her brother. After 1 week she developed above symptoms and was referred to us for pancytopenia. On evaluation her platelets, leucocyte count was low with normal Hb levels. The bone marrow biopsy revealed a hypoplastic marrow accompanied by significant proliferation of pre-progenitor megakaryocytes. She had mild transaminitis, without hyperbilirubinemias. Blood culture grew candida spp, *Enterococcus faecium*. She received appropriate antibiotics along G-CSF. Skin biopsy revealed basal vacuolation, spongiosis in epidermis, necrotic epidermis, apoptotic keratinocytes scattered in intact epidermis suggestive of acute GVHD Gr-III. Consequently, she was commenced on pulsed steroid regimen followed by maintenance dose. Within a week, her clinical condition improved and was discharged on tapering dose of steroids. The existence of donor-derived cells or DNA in the recipient's blood or afflicted tissues must be documented to make conclusive diagnosis of TA-GVHD.

Keywords: Transfusion associated GVHD, Thrombocytopenia, Blood transfusion, Expanded dengue syndrome

INTRODUCTION

Dengue fever (DF) is a tropical disease caused by a single-stranded RNA virus belonging to the genus Flavivirus and family Flaviviridae and spread by Aedes aegypti mosquitoes.[1] The clinical presentation of dengue fever can vary widely, ranging from asymptomatic cases to severe conditions such as dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS).[2] It is predominantly a self-limiting illness, accompanied by symptoms such as fever, arthralgias, myalgias, nausea, abdominal pain, diarrhea, hepatomegaly, lymphadenopathy, maculopapular rash, transaminitis, thrombocytopenia and leukopenia.[3] However, the disease can also present with a range of rare but severe complications, which are collectively referred to as the expanded dengue syndrome (EDS) by the world health organization (WHO).[4]

The identification of characteristic symptoms associated with the expanded dengue syndrome (EDS) is crucial for determining appropriate treatment strategies. Transfusion-associated graft-versus-host disease (TA-GVHD) represents a relatively infrequent but potentially lethal complication related to blood transfusions. Clinical signs like fever, skin rash, jaundice, diarrhea and pancytopenia usually appear two to thirty days following the transfusion.[5] It arises from the interaction between immunologically competent cells within the graft, all

antigens present in the host that are absent in the graft and an immunocompromised host. The disease is often characterized by a fulminant course with a mortality rate exceeding 90% in most cases.[6] In this case study, we have meticulously outlined the scenario of a 47-year-old female patient who subsequently developed transfusion-associated graft-versus-host disease (GVHD) as a consequence of receiving a blood transfusion from a related donor. The requirement for the blood transfusion was necessitated by thrombocytopenia condition resulted from the prior dengue fever infection.

CASE REPORT

A 47-year-old female has presented to our clinic with symptoms like fever, chills, blanchable rash, itching and burning sensation across her body accompanied by skin peeling over the past five days. Subsequently, she was referred to us due to persistent symptoms and was diagnosed with pancytopenia. Prior to her admission, she had been hospitalized in another hospital for one week with a diagnosis of dengue fever, which was initially suspected due to the presence of warning signs.

During her hospitalization period, she developed melena and thrombocytopenia for which she received a unit of packed red blood cells (pRBCs) and a unit of single donor platelet (SDP) from her brother. She was discharged from the hospital after four days. However, one week after her discharge, she began experiencing the aforementioned symptoms. Upon assessment, the patient exhibited hemodynamic stability. The patient had a uniformly distributed red rash with normal haemoglobin levels along low platelet and leukocyte count. She did not have pustules, discharge or necrotic tissue. The evaluation for sepsis, tropical diseases, autoimmune diseases, hemophagocytic lymph histiocytosis (HLH), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and adverse reactions to medications were all negative. The bone marrow biopsy indicated a state of hypoplastic marrow with an abnormal proliferation of megakaryocytes in the pre-production phase. The patient demonstrated mild transaminitis without hyperbilirubinemias. Laboratory cultures revealed the presence of candida species and enterococcus faecium. The patient was prescribed suitable antimicrobial agents in conjunction with granulocyte-colony stimulating factor (G-CSF).

A skin biopsy was conducted, revealing basal vacuolization and spongiosis in the epidermis, necrotic epidermal layers and scattered apoptotic keratinocytes within the intact epidermis (Figure 1). These findings are indicative of acute graft-versus-host disease (GVHD) of the Gr-III subtype.

Therapeutic intervention

Upon admission, the patient received intravenous fluid therapy, cefipime (IV, 2 g every eight hours), G-CSF (granulocyte colony stimulating factor), leucovorin (LCV, IV 500 mg/m2 once daily) and additional supportive treatments. Consequently, the patient was commenced on a pulsed steroid regimen followed by a maintenance dose. Her clinical condition showed improvement, leading to her discharge with a gradual reduction in steroid dosage over a period of one week.

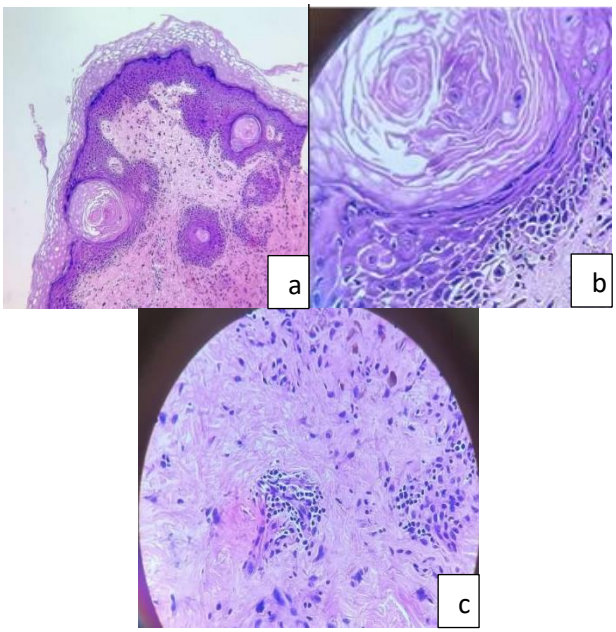

Figure 1 (a-c): Skin biopsy images revealing basal vacuolization and spongiosis in the epidermis, necrotic epidermal layers, and scattered apoptotic keratinocytes within the intact epidermis manifesting TA-GVHD grade III.

DISCUSSION

Expanded dengue syndrome (EDS) encompass the atypical manifestations of dengue virus (DENV) characterized by severe damage to vital organs including kidneys, liver, heart, bone marrow and brain.[7] These manifestations may be attributed to pre-existing co-morbid conditions, concurrent infections or extended states of shock.[8] Our patient was admitted in outside hospital earlier with a skin rash and fever, subsequently diagnosed with a DENV infection.

Thrombocytopenia, defined by decreased number of platelets, is a prevalent clinical symptom associated with dengue virus (DENV) infection. Despite extensive research, the exact mechanisms responsible for thrombocytopenia and the occurrence of bleeding during dengue virus (DENV) infection remain largely unknown.[9]

It is hypothesized that dengue virus (DENV) may directly or indirectly disrupt the function of bone marrow progenitor cells, thereby reducing the capacity of hematopoietic cells to proliferate.[10] Studies suggest that dengue infection may result in bone marrow hypoplasia during the acute phase of the disease, destruction of

platelets followed by their clearance from peripheral. Our patient's bone marrow biopsy revealed hypoplastic marrow with aberrant megakaryocyte proliferation during the pre-production stage. According to clinical guidelines, platelet transfusions are recommended for individuals who exhibit severe haemorrhagic symptoms or possess platelet counts that have significantly decreased, with counts falling below 10–20×109/l.[11] In this instance, the patient necessitated the administration of a unit of packed red blood cells (pRBCs) in addition to a unit of packed cell volume (PCV).

This patient presented with clinical manifestations indicative of graft-versus-host disease (GVHD). Given the patient's history of blood transfusions, it was imperative to consider the possibility of transfusion-associated graft-versus-host disease (TA-GVHD) in this individual. It was crucial to exclude other potential diagnoses to ensure accurate management, including the ruling out of any active viral infection that could present with symptoms similar to graft-versus-host disease (GVHD). Transfusion-associated viruses such as hepatitis B, HIV and cytomegalovirus have also been known to cause illnesses with similar symptoms as those of GVHD.[12] Typically, it affects individuals with compromised cell-mediated immunity; however, it has been documented in individuals who appear to have a fully functional immune system.

Following the initial report of Transfusion-associated graft-versus-host disease (TA-GVHD) in an immunocompetent individual, there has been a significant increase in the number of cases of TA-GVHD in immunocompetent patients, predominantly originating from recipients who were transfused from family members.[13-15] Here our patient had blood transfusion administered from her own brother and later on she was diagnosed with Transfusion-associated graft-versus-host disease (TA-GVHD) grade III with skin reactions and peeling.

Nonetheless, the suspicion of Transfusion-associated graft-versus-host disease (TA-GVHD) should be entertained in patients who exhibit cytopenia within the first 30 days following blood product transfusion. A high level of suspicion, coupled with a recent transfusion and the presence of clinical features indicative of TA-GVHD, is essential for an early diagnosis.[16] The diagnosis of Transfusion-associated graft-versus-host disease (TA-GVHD) frequently presents a significant challenge due to non-specific symptoms, which resemble other diseases, including viral infections, drug reactions, liver failure, autoimmune disorders, aplastic anaemia, immunodeficiency syndrome and hematologic malignancies.[17]

The traditional clinical manifestations of TA-GVHD encompass fever, skin rash, diarrhoea, liver dysfunction, and bone marrow suppression. Nonetheless, it is important to note that not all patients with Transfusion-associated graft-versus-host disease (TA-GVHD) will display these symptoms and some may exhibit atypical or delayed manifestations. Our patient exhibited fever, skin rashes with blanching and burning sensation.

The histopathological analysis of skin, rectum, liver, bone marrow biopsy samples can reveal characteristic alterations such as lymphocytic infiltration, necrosis and epithelial damage which indicate GVHD. Biopsy from any of the aforementioned organs is considered the definitive test for confirming the diagnosis of TA-GVHD. However, a skin biopsy is generally the least invasive and simpler to perform compared to liver or bone marrow biopsies.[18-20] Our patient condition was confirmed with skin biopsy.

A variety of immunosuppressive agents, including corticosteroids, antithymocyte globulin, methotrexate, cyclosporine, azathioprine, serine protease inhibitors, chloroquine, and OKT3, have been utilized with suboptimal outcomes.[21] Our patient underwent steroid treatment with which her discharge was uneventful.

CONCLUSION

A rare but dangerous side effect of blood transfusion is TA-GVHD, which happens when the immune cells of the donor target several recipient tissues. When a triad of symptoms, including fever, pancytopenia and skin rash, appear a few days or weeks after a blood transfusion, there should be a strong suspicion of TA-GVHD among clinicians, especially when working with a high-risk patient group. Timely initiation of appropriate treatment for TA-GVHD depends on an early diagnosis.

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