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Dengue virus infection in hematopoietic stem cell transplant recipients: A case series and comparative literature review from dengue endemic region

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Abstract

This case series describes the wide spectrum of clinical presentation, laboratory findings, and morbidity/mortality associated with dengue fever in hematopoietic stem cell transplant recipients, treated in a dengue endemic region. The risk of acquiring viral infections increases manifold after transplant due to the severely immunocompromised state amid conditioning toxicity and immunosuppressive therapy. The classical warning signs of dengue viremia are often masked in posttransplant patients, leading to a missed diagnosis of dengue and grave consequences observed in some of the patients. Accurate and timely diagnosis of dengue fever especially in dengue prevalent areas can prevent the unwarranted complications and reduce the morbidity and mortality associated with dengue in allogeneic/autologous transplant recipients.

Keywords

Hematology, infectious diseases, dengue fever, hematopoietic stem cell transplantation

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Background

Hematopoietic stem cell transplant (HSCT) is the established curative treatment option for various life-threatening hematological disorders, such as leukemia, bone marrow failure syndromes, immunological, and genetic disorders. Comprehensive understanding of transplant immunology, stringent patient selection, and patient tailored conditioning regimens has led to an improved outcome of transplant.[1]

Infectious complications are still considered the chief cause of morbidity and mortality in HSCT recipients.[2] Immune deficiency occurring as result of intensive chemotherapy is the main factor predisposing to posttransplant infections.[3] B cell function and virus-specific antibodies are the main defense mechanisms against viral infections, thus reducing the risk for reinfection in already seropositive individuals.[4] On the other hand, cytotoxic T cell function is the main mechanism for preventing severe viral diseases.[5]

Dengue fever transmitted by the bites of *Aedes aegypti* and *Aedes albopictus* mosquitoes, which act as vectors for the dengue virus (a RNA flavivirus), poses significant life-threatening risks to immunocompromised patients, especially those who have undergone hematopoietic stem cell

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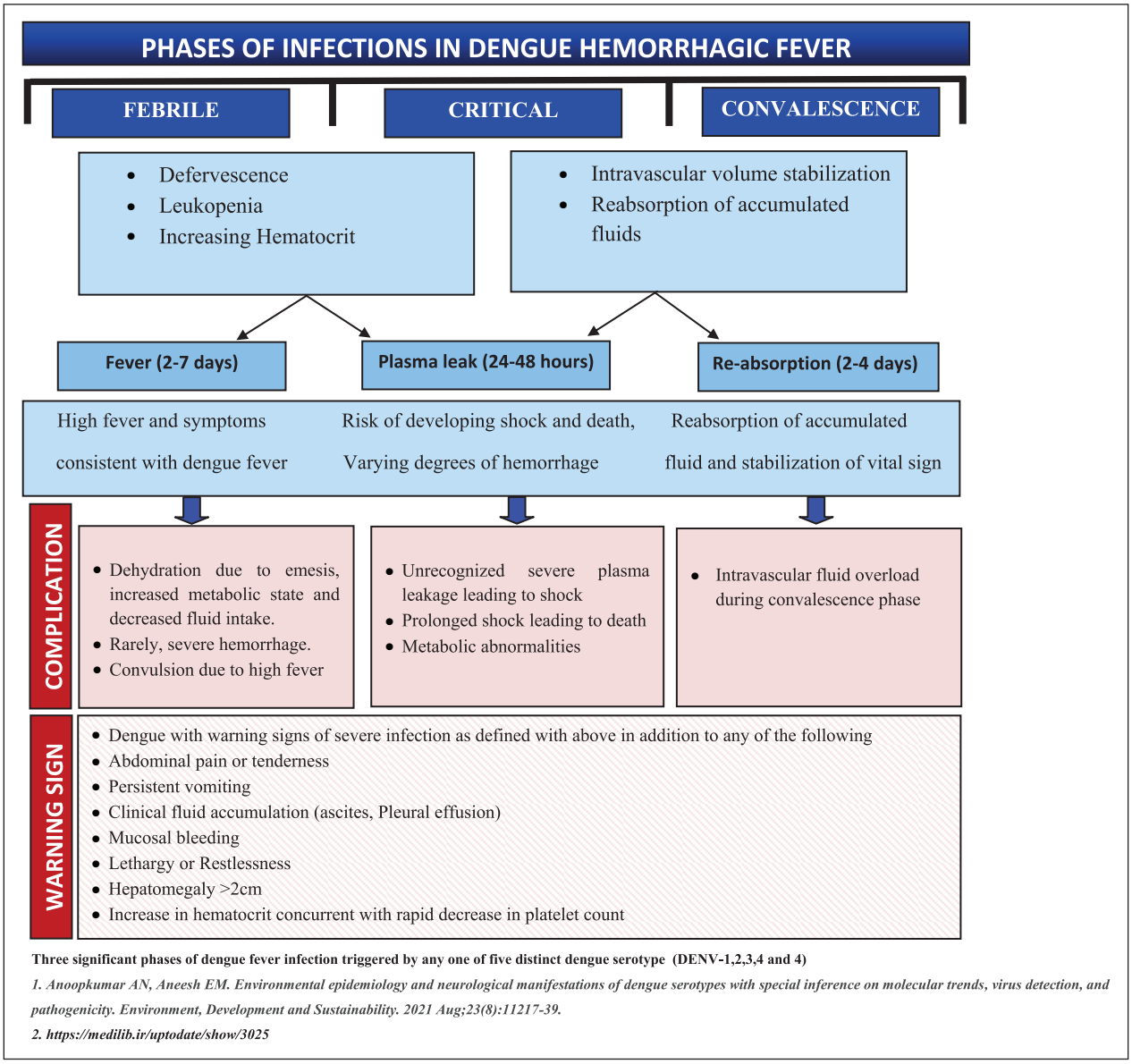

Figure 1. Phases of infections in dengue fever.

transplantation (HSCT). The early posttransplant phase, up to 30 days patients are more susceptible to dengue fever because of extreme immunosuppression, neutropenia, and mucositis. Though the risk persists later on due to ongoing immunosuppression. Currently four serotypes of dengue virus presumptively cause dengue fever in human beings. Early symptoms of dengue are similar to common flu, headache followed by body aches, myalgia, nausea, and vomiting.[6] In late febrile phase, few cases develop severe plasma leakage termed as Severe Dengue according to WHO 2009 guidelines (Figure 1), which needs meticulous medical attention otherwise it may consequently lead to dengue shock syndrome. Laboratory findings of dengue include leukopenia, thrombocytopenia, raised hematocrit, deranged coagulation, and in many cases, elevations of serum aminotransferase concentrations. The number of dengue cases are multiplying worldwide particularly in Asian countries. Reportedly, South East Asian region including Pakistan is the most severely affected region with an estimated 1.3 billion people harboring the risk of dengue virus infection. In Pakistan, seasonal outbreaks of dengue occur every 2–3 years with mass infectivity reported over the past decade.[7]

Among HSCT recipients, apart from clinical factors like immunodeficiency state posttransplant, a variety of social factors including literacy, low social class, and poor water sanitation and storage practices are attributable to the acquisition of dengue fever. This case series and literature review aims to address the clinical course, management, and outcome of nine consecutive HSCT recipients who had a

confirmed laboratory or clinical diagnosis of dengue fever during an outbreak at our institute.

Case presentation

A total of nine posttransplant cases with dengue infection were recruited in the study with a median (interquartile range) age of 16 (6–18) years, while the onsets of symptoms were reported in posttransplant cases at 130 (57–428) days. Moreover, demographic characteristics of all cases were demonstrated in Table 1, after further evaluation, one (11.1%) patient clinically presented with true features of dengue fever with negative NS1 antigen. The outcomes after management of dengue infection are displayed in Figure 2 while the clinical status and laboratory parameters of all cases are shown in Table 2. Baseline and serial complete blood count (CBC) parameters of patients are presented in Table 3. Rapid antigen detection through immunochromatographic method was utilized for detection of NS1 antigen with sensitivity of 92.4% along with detection of immunoglobulin (Ig)G and IgM antibodies.

Case 1

A 17-year-old male recipient of matched-sibling donor transplant for myelodysplastic syndrome, on immunosuppressive agent, presented with fever and body ache on day +317. Donor chimerism at day +180 was >90%. At presentation, CBC showed Hb = 16.5 g/dL, hematocrit (HCT) = 48%, platelet = 90×10^9/L. Physical examination revealed harsh vesicular breathing. Dengue NS1 antigen was detected. Blood cultures were negative. He was managed conservatively for 1 week as inpatient with intravenous hydration, analgesics, and antipyretics. Platelet count dropped to 24×10^9/L followed by recovery without need for transfusion.

Case 2

A 16-year-old boy, with severe aplastic anemia, presented in transplant emergency with high-grade fever associated with shivering, pain in right hypochondrium and loose watery stools for 2 days, on day +88 posttransplant. Pan cultures and other infective workup were negative while Dengue NS1 antigen was detected. His platelet count declined rapidly with rising hematocrit level. He was managed aggressively with supportive care, intravenous hydration, and platelet transfusions during critical phase. He also had slightly deranged renal function and liver enzymes were elevated two times upper normal limit. However, the coagulation profile was normal. Mild pleural effusion and moderate ascites were also observed on ultrasound. He stayed in the hospital for 15 days for management of dengue fever.

Case 3

A 10-year-old boy with transfusion-dependent β-thalassemia along with secondary hemophagocytic lymphohistiocytosis (proven on bone marrow biopsy) received matched-related donor transplant. On day +130 posttransplant, he reported in emergency department with 1 day history of continuous high-grade fever and myalgias. He was on tacrolimus, mycophenolate mofetil, and oral prednisolone for Graft vs host disease (GVHD) prophylaxis along with eltrombopag for poor graft function and incomplete blood count recovery. His blood counts revealed Hb = 10.5 g/dL, white blood cell (WBC) = 7.0×10^9/L, Absolute neutrophil count (ANC) = 4.2×10^9/L, Platelet = 16×10^9/L. Dengue NS1 antigen was detected. Supportive treatment was offered along with platelet transfusion. Coagulation profile was slightly deranged. He developed vomiting, loose stools, abdominal distension and periorbital puffiness, and rising creatinine and deranged liver function test. On the fourth day of admission, he became restless, his urine output decreased with increasing abdominal distension, developed tachycardia, tachypnea, and severe hypotension. Cardiac support was started following crystalloid administration, platelet, and Fresh frozen plasma (FFP) transfusion along with all other emergency measures but unfortunately he collapsed and could not be revived.

Case 4

A 3.5-year-old boy presented with high-grade fever and body ache for 1–2 days after 8 months of allogeneic stem cell transplant for transfusion-dependent β-thalassemia major. He was on cyclosporine for GVHD prophylaxis and antitubercular treatment for pulmonary tuberculosis which he developed 4 months after transplant. He was diagnosed with dengue fever and developed thrombocytopenia and leucopenia rapidly with deranged coagulation during febrile phase. After 5 days of febrile illness, his platelet counts further dropped to a nadir of 15×10^9/L, followed by recovery phase. There were no signs of plasma leakage. Child was discharged uneventfully after 10 days.

Case 5

A 19-year-old male diagnosed case of T cell acute lymphoblastic leukemia presented on day +103 of matched-sibling donor transplant with fever, throat pain, and flu-like symptoms. His dengue NS1 antigen was positive, with mild thrombocytopenia. His posttransplant course remained uneventful with full donor chimerism and negative Measurable residual disease (MRD) status at day +100 posttransplant. No admission was required as he was managed with supportive care and serial monitoring of blood counts in outpatient department.

Table 1. Demographic characteristics of the patients.

Serial No.	Gender	Age (years), median (IQR)	Primary diagnosis	Type of HSCT	Conditioning regimen	Source stem cell	Immunosuppressive therapy	Posttransplant antimicrobial prophylaxis	Neutrophil engraftment (day+)	Graft vs host disease (GVHD)	Days of onset of symptoms (posttransplant), median (IQR)
1.	Male	17	MDS	Allogeneic	MA	PBSC	Cyclosporin 5 mg/kg/day	No	+11	No	317
2.	Male	16	Aplastic anemia	Allogeneic	RIC	BM and PBSC	Cyclosporin 5 mg/kg/day	No	+11	No	88
3.	Male	10	Thalassemia	Allogeneic	MA	PBSC	Tacrolimus 0.15 mg/kg, Mycophenolate mofetil (MMF) 600 mg/m^2/dose Steroid 1 mg/kg/day	No	+11	No	130
4.	Male	3.5	Thalassemia	Allogeneic	MA	BM	MMF 600 mg/m^2/dose	Yes	+16	No	250
5.	Male	19	T cell ALL	Allogeneic	MA	PBSC	Cyclosporin 3 mg/kg/day	Yes	+15	No	103
6.	Male	64	Multiple Myeloma	Autologous	MA	PBSC	No	No	+9	No	730
7.	Male	16	AML	Allogeneic	MA	PBSC	No	No	+10	No	540
8.	Male	8	Thalassemia	Allogeneic	MA	BM	Tacrolimus 0.15 mg/kg/day MMF 600 mg/m^2/dose	No	+24	No	26
9.	Male	4	Thalassemia	Allogeneic	MA	BM	Cyclosporin IV 3 mg/kg/day	No	+11	No	9

IQR: interquartile range; MA: Myeloablative; RIC: reduced intensity conditioning; HSCT: hematopoietic stem cell transplantation; MDS: myelodysplastic syndromes; ALL: acute lymphoblastic leukemia; AML: acute myeloid leukemia; PBSC: peripheral blood stem cell; BM: bone marrow.

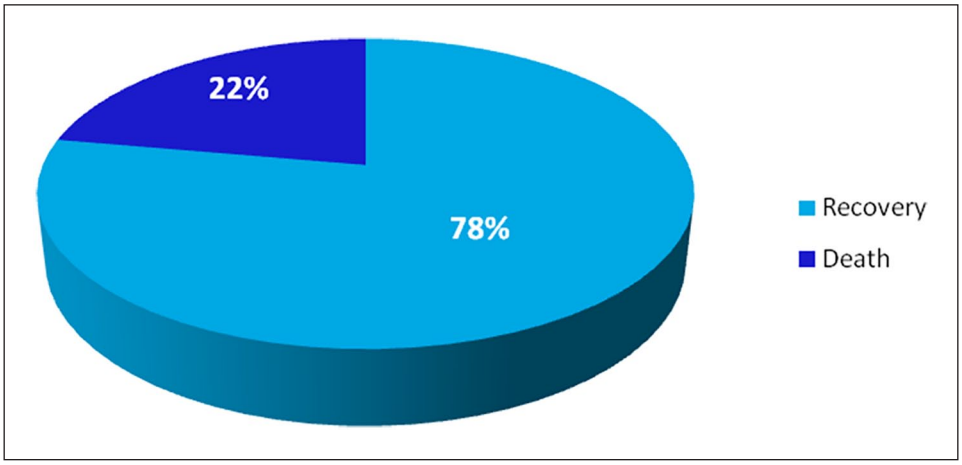

Figure 2. Outcome of posttransplant patients.

Table 2. Clinical status and laboratory parameters of organ function.

Cases	Dengue NS1 antigen	Bacterial cultures	Elevated transaminase level	Deranged renal function	Deranged coagulation profile[a]	Features of severe dengue	Platelet transfusion requirement	Fresh frozen plasma (FFP) transfusion requirement	Lowest Platelet count (10^9/L), median (IQR)
1.	Positive	Negative	No	No	Yes	No	No	No	24
2.	Positive	Negative	Yes	Yes	No	Yes	Three times	No	10
3.	Positive	Negative	Yes	Yes	Yes	Yes	Two times	No	16
4.	Positive	Negative	Yes	Yes	Yes	No	No	No	15
5.	Positive	Negative	No	No	No	No	No	No	150
6.	Negative (IgG+ve)	Negative	No	Yes	No	Yes	Three times	No	25
7.	Positive	Negative	Yes	No	No	No	No	No	29
8.	Positive	Positive	Yes	No	No	Yes	Four times	No	13
9.	Positive	Negative	Yes	No	Yes	Yes	Four times	No	19

IQR: interquartile range.
[a]Prothrombin time (PT), Activated prothrombin time (APTT), Fibrinogel level D-Dimer.

Table 3. Baseline and serial Complete blood count (CBC) parameters of patients.

Cases	Baseline Hemoglobin before dengue (g/dL)	Mean Hemoglobin (g/dL)	Baseline WBC before dengue (1×10^9/L)	Mean WBC (1×10^9/L)	Baseline hematocrit before dengue (%)	Mean hematocrit (%)	Baseline platelets (1×10^9/L) before dengue	Mean platelets (1×10^9/L)
1	11.2	9.64	4.5	4.67	27	28.4	172	34.9
2	13.9	14.98	9.9	4.04	30	41.4	183	51.9
3	10.5	10.9	7	5.54	28	33.7	16	16.3
4	11.9	10.1	12.2	8.3	30	31.4	237	66.6
5	10.2	11.7	4.9	7.76	33	36	202	151
6	9.1	8.3	6.4	5.2	24	24.3	223	31.4
7	13.7	11.8	4.4	6.4	40	38	114	86.8
8	9.5	8.3	2.6	3.8	27	28.5	13	13.4
9	12.1	9.8	0.5	0.9	37	28.5	87	15

WBC: white blood cell.
Before dengue infection.

Case 6

A 64-year-old gentleman, post-autologous stem cell transplant for multiple myeloma, presented with persistent fever and cough. Though dengue NS1 antigen and serology were negative, clinical and laboratory parameters favored the diagnosis of dengue fever. Chest X-ray was normal. His platelet count fell from 123×10^9/L at baseline to 30×10^9/L and serum creatinine increased along with gross hematuria. Nephrologist was taken on board and patient was managed conservatively with hydration, continuous bladder irrigation, and platelet transfusion support. On ninth day of his admission, he was discharged after improvements were seen in his renal function, and his thrombocytopenia and hematuria were resolved.

Case 7

A 16-year-old male with acute myeloid leukemia underwent matched-sibling donor transplant. Eighteen months post-transplant, off immunosuppressant, he presented with intermittent fever for 24–48 h and found to be positive for dengue NS1 antigen. He only had thrombocytopenia, without any significant complications. He was successfully managed as an in-patient with hydration, analgesics, antipyretics, and serial monitoring of blood counts for 5 days.

Case 8

An 8-year-old child, admitted in transplant unit for haploidentical stem cell transplant for β-thalassemia major, developed fever spike on day +26 posttransplant. Pan cultures were sent with all other infective workup. Piperacillin/tazobactam and amikacin were started empirically. He grew *Escherichia coli* in urine culture with raised C-reactive protein and procalcitonin. Laboratory workup was negative for dengue NS1, malarial parasite, galactomanan, BKV, and Cytomegalovirus (CMV). Antibiotics were continued according to culture and sensitivity report. Second fever spike occurred 4 days later and that time dengue serology turned out to be positive. He also developed features of plasma leak syndrome confirmed on ultrasound of whole abdomen and chest X-ray. He was successfully managed with Intravenous immunoglobulin (IVIG) rescue therapy and supportive care treatment.[8]

Case 9

A 4-year-old boy, with transfusion-dependent β-thalassemia major, underwent second stem cell transplantation at our institute. He developed fever on day +1, which persisted intermittently for 10 days. He was initially managed on febrile neutropenia protocol. All of his infective workup turned out to be negative. Multiple sets of cultures were also negative along with dengue NS1 antigen. Afterward, after a fever-free interval of 72 h, he developed a new fever spike and dengue NS1 antigen was detected at that time. Neutrophil engraftment was achieved on day +11. He was managed with hydration and broad-spectrum antibiotics (Meropenem 40 mg/kg) during neutropenic phase. Ultrasound abdomen revealed flattened bowel mucosa, edematous gallbladder, moderate ascites, and mild pleural effusion. His peripheral film showed rings of plasmodium falciparum, for which antimalarial therapy was immediately started but on the very next day (day +22) he succumbed to respiratory failure.

Discussion

This case series highlights the impact of dengue-related complications on the outcome of immune-compromised transplant recipients. Because of scarcity of prospective data of dengue virus infection in this population, the extent of morbidity/mortality secondary to dengue in transplant recipients is still not known. Few case reports published previously have shown mortality rates around 40% in immune-compromised patients after dengue virus infection.[9–11] All patients except case 8 and 9 presented as an outpatient exposure to mosquito. The clinical and laboratory manifestations of dengue infection like fever, vomiting, headache, diarrhea, bleeding diathesis, and thrombocytopenia mimic with the findings observed in posttransplant patients especially during early neutropenic phase because of high-dose chemotherapy administration combined with immunosuppressive agents; therefore, suspicion of dengue fever is often delayed even in areas where dengue is highly prevalent. The male predominance in this case study reflects the cultural preference of prioritizing medical care for male children as compared to female children within the families in Pakistan.[12] Majority of the patients received myeloablative conditioning regimen in combination with antithymocyte globulin for GVHD prophylaxis which perhaps contributed to the prolonged immunodeficiency, and resultant viral infections in these patients. The delayed T cell immune reconstitution is largely responsible for life-threatening viral and fungal infections, occurrence of graft-versus-host disease, and relapse after allogeneic stem cell transplantation.[4] The median time to dengue infection after transplant in our patients was 130+ days which correlates with the impaired B and T cell function perpetuating the latent viral infections. The diagnosis of dengue in almost all patients was established by routine detection of NS1 antigen; however, in one patient, serological testing was required to confirm the diagnosis. NS1 is considered a surrogate marker for viremia, with the level of NS1 proportionate with viral load. However, combining NS1 detection with IgM and/or IgG detection has led to nearly 100% increase in sensitivity of dengue diagnosis from the onset of illness through recovery.[13] The lowest platelet count observed was 10×10^9/L (median 16×10^9/L) with no major grade 3–4 bleeding episodes in any of the patients except for multiple myeloma patient (case#6). Five out of nine patients required platelet transfusions during the course of illness. Most of our patients

were receiving immunosuppressive therapy; therefore, blood counts were at low normal limit. However, we found slight increase in hemoglobin and hematocrit from day 2 and it persisted throughout the infective period. The majority of patients developed thrombocytopenia and leucopenia from day 2 to 5 in this case study. Two of the patients were in early posttransplant phase (case#8–9), both of them were already neutropenic and thrombocytopenic. All of our patients had developed thrombocytopenia except for one patient (case#5). Chaloemwong et al. reported decrease in WBC count from day 2 to 10 (lowest on day 4), decreased platelet count from day 3 to 10 (lowest on day 6), and higher hemoglobin and hematocrit from day 3 to 10 (highest on day 7) of dengue infection.[14] Management of dengue was based on updated GCP guidelines 2020, including appropriate fluid replacement (0.9% normal saline), antipyretics, antiemetics, proton-pump inhibitors, analgesics, and platelet transfusions if indicated. Assessment of warning signs, hemodynamic status, capillary refill time, bleeding, changes in mental state, urine output were performed every 4–6 h in all patients. A comparison of intravenous fluids in dengue shock syndrome among 230 Vietnamese children reported no clear advantage of dextran, normal saline, gelatin, or ringer lactate over one another.[15] Two patients died due to severe plasma leakage and severe dengue leading to shock. All remaining patients are alive and are being followed up at the outpatient department according to WHO 2009 guidelines. The first patient was a 10-year-old thalassemic who acquired dengue infection after an outdoor activity in neighborhood. He developed signs of plasma leakage within 48 h of onset of fever along with tachypnea, acidotic breathing, pleural effusion, ascites, and hepatosplenomegaly. Family mistook it for a common viral fever and brought him late to hospital. All measures were taken to control plasma leakage, but he developed multi-organ failure. The second patient was a young thalassemic boy who acquired dengue during early neutropenic phase of second bone marrow transplant. His donor was evaluated for dengue but it turned out negative. Due to severe neutropenia, thrombocytopenia, and co-infection with malaria, the child went into septicemia/multi-organ failure and could not survive. Immunosuppression was withheld in both the patients, but it was not helpful in these patients. There are few case reports showing advantage of withholding the immunosuppression to avoid further worsening of viral infections. Nasim et al. reported increased mortality among dengue affected patients who were on tacrolimus treatment ($n=102$, $p=0.031$), but no statistical significance was obtained in the final analysis ($n=131$, $p=0.28$).[16]

Conclusion

This case series indicate the importance of dengue infection in immune-compromised hematopoietic transplant recipients and prompts the clinicians to improve their understanding of delayed immune reconstitution so that new strategies could be determined to prevent dengue-related deaths after transplant. Accurate and timely diagnosis of dengue fever especially in dengue prevalent areas can prevent the unwarranted complications and reduce the morbidity and mortality associated with dengue in hematopoietic stem cell transplant recipients.

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Author contributions

W.S. and U.Z. generated the concept and design of the study, However, Data editing and collection by F.F. and A.R. whereas Data analysis and interpretation was done by M.N. and M.A. Therefore, all the cases were reviewed by A.J., S.A.S., Z.G., A.H., D.S. which ensured that they met the study criteria. U.Z. drafted this article, which was subsequently critically reviewed by T.F. and revised by U.Z.

Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical approval

This study was approved by the Institutional Review Board (IRB) of the National Institute of Blood Diseases (NIBD), Pakistan Ethics Committee, and written informed consent was taken from the study participants. All work must be conducted in accordance with the Declaration of Helsinki (1964). Our institution does not require ethical approval for reporting individual cases or case series.

Informed consent

Written informed consent was obtained from the patient(s) and a legally authorized representative(s) for anonymized patient information to be published in this article.

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References

1. Juric MK, Ghimire S, Ogonek J, et al. Milestones of hematopoietic stem cell transplantation—from first human studies to current developments. *Front Immunol* 2016; 7: 470.
2. Ullmann AJ, Schmidt-Hieber M, Bertz H, et al. Infectious diseases in allogeneic haematopoietic stem cell transplantation:

prevention and prophylaxis strategy guidelines 2016. *Ann Hematol* 2016; 95: 1435–1455.
3. Kurosawa S, Mizuno S, Arai Y, et al. Syngeneic hematopoietic stem cell transplantation for acute myeloid leukemia: a propensity score-matched analysis. *Blood Cancer J* 2021; 11: 159.
4. Düver F, Weißbrich B, Eyrich M, et al. Viral reactivations following hematopoietic stem cell transplantation in pediatric patients—a single center 11-year analysis. *PLoS One* 2020; 15(2): e0228451.
5. Ogonek J, Kralj Juric M, Ghimire S, et al. Immune reconstitution after allogeneic hematopoietic stem cell transplantation. *Front Immunol* 2016; 7: 507.
6. Shabbir W, Pilz J and Naeem A. A spatial-temporal study for the spread of dengue depending on climate factors in Pakistan (2006–2017). *BMC Public Health* 2020; 20: 995.
7. Khan J, Adil M, Wang G, et al. A cross-sectional study to assess the epidemiological situation and associated risk factors of dengue fever; knowledge, attitudes, and practices about dengue prevention in Khyber Pakhtunkhwa Province, Pakistan. *Front Public Health* 2022; 10: 923277.
8. Padmaprakash KV, Jha VK, Karantha CS, et al. Rescue therapy with intravenous immunoglobulin in severe refractory dengue: a pilot study. *Med J Armed Forces India* 2022; 78(2): 204–212.
9. Chacko B, John GT, Jacob CK, et al. Dengue shock syndrome in a renal transplant recipient. *Transplantation* 2004; 77(4): 634–635.
10. Tan FL-S, Loh DLSK and Prabhakaran K. Dengue haemorrhagic fever after living donor renal transplantation. *Nephrol Dial Transpl* 2005; 20(2): 447–448.
11. Garcia JHP, Rocha TDS, Viana CFG, et al. Dengue shock syndrome in a liver transplant recipient. *Transplantation* 2006; 82(6): 850–851.
12. Qadir F, Khan MM, Medhin G, et al. Male gender preference, female gender disadvantage as risk factors for psychological morbidity in Pakistani women of childbearing age—a life course perspective. *BMC Public Health* 2011; 11: 745.
13. Muller DA, Depelsenaire ACI and Young PR. Clinical and laboratory diagnosis of dengue virus infection. *J Infect Dis* 2017; 215(Suppl 2): S89–S95.
14. Chaloemwong J, Tantiworawit A, Rattanathammethee T, et al. Useful clinical features and hematological parameters for the diagnosis of dengue infection in patients with acute febrile illness: a retrospective study. *BMC Hematol* 2018; 18: 20.
15. Ngo TN, Cao XT, Kneen R, et al. Acute management of dengue shock syndrome: a randomized double-blind comparison of 4 intravenous fluid regimens in the first hour. *Clin Infect Dis* 2001; 32(2): 204–213.
16. Nasim A, Anis S, Baqi S, et al. Clinical presentation and outcome of dengue viral infection in live-related renal transplant recipients in Karachi, Pakistan. *Transplant Infect Dis* 2013; 15(5): 516–525.