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The Impact of Endothelial Injury in Hematopoietic Stem Cell Transplant (HSCT)

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Damage to Endothelial Cells Can Occur in Many Ways—Physically, Chemically and Immunologically[1-3]

Before, during, and after transplant, multiple factors can lead to endothelial injury syndromes (EIS)[1-3]

The HSCT process

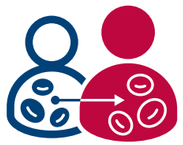
Chemoradiotherapy included in conditioning regimens

Cytokines released by injured tissues

Immunosuppressive therapies

Bacterial endotoxins translocated through gastrointestinal (GI) damage

Engraftment process



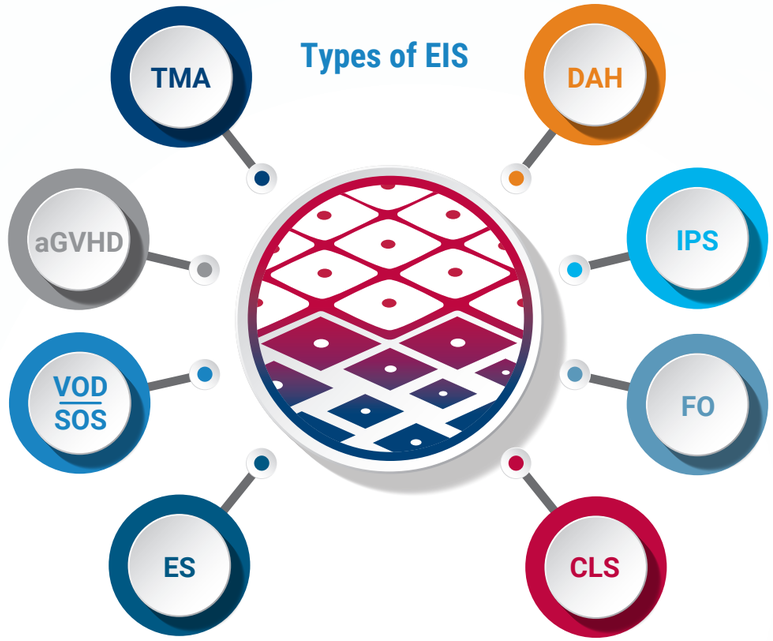
Allogeneic reactions with donor-derived immune cells

HSCT and **adoptive cell therapy** require careful monitoring to manage the risk of EIS.

Various Endothelial Injury Syndromes May Result From HSCT[1,4]

Several syndromes result from transplant-related endothelial damage and can overlap in presentation and classification[1-4]

Endothelial injury plays a significant role in a host of potentially lethal syndromes, including HSCT-associated thrombotic microangiopathy (HSCT-TMA), and can occur prior to, during, and after HSCT.[1,4-12]



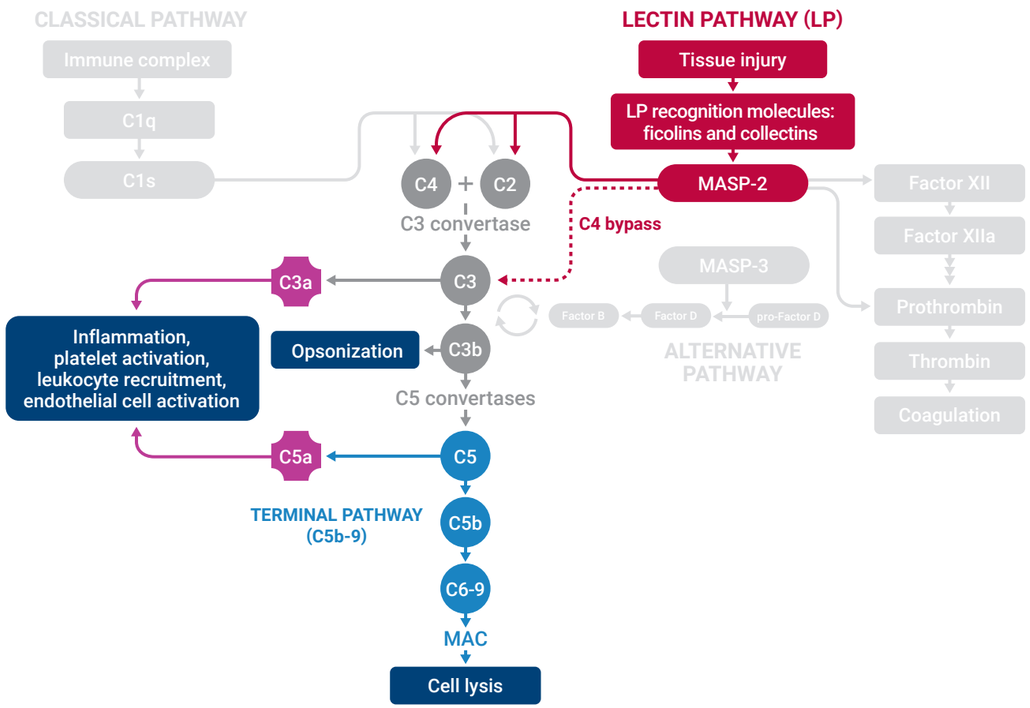
- Thrombotic microangiopathies (TMA)
- Acute graft-vs-host disease (aGVHD)
- Veno-occlusive disease (VOD)/sinusoidal obstruction syndrome (SOS)
- Engraftment syndrome (ES)
- Capillary leak syndrome (CLS)
- Fluid overload (FO)
- Idiopathic pneumonia syndrome (IPS)
- Diffuse alveolar hemorrhage (DAH)

The complement system becomes activated in many of these syndromes[1,4,9-11,13-18]

The complement system is an important part of the innate immune system that protects against foreign cells and helps remove damaged host cells.[19]

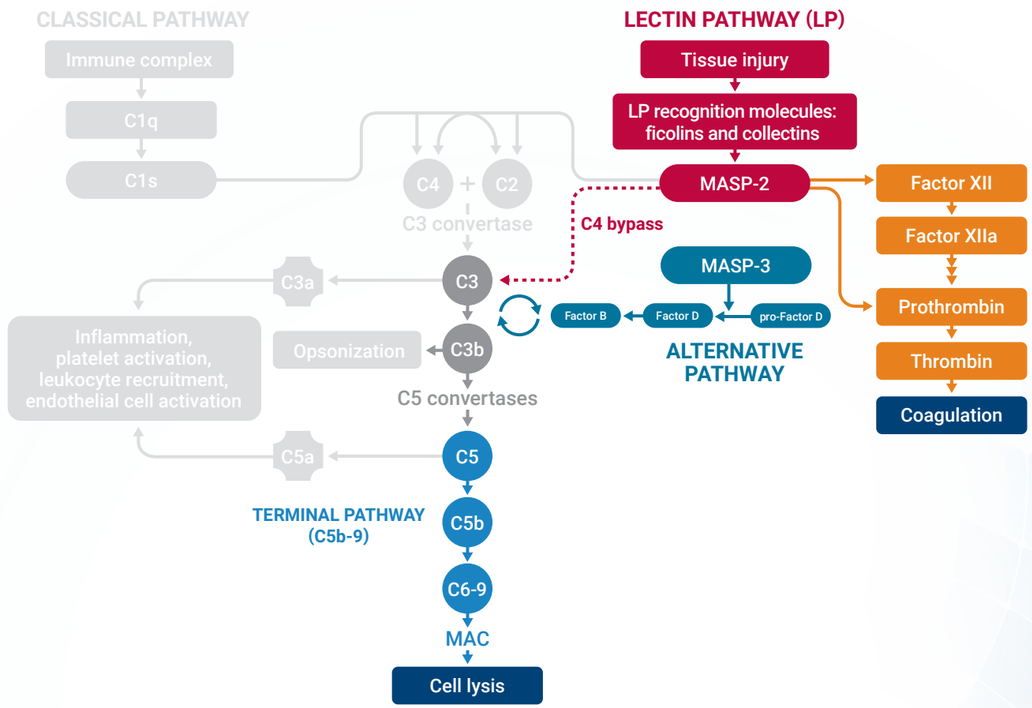
The Role of the Lectin Pathway of Complement

Injured endothelial cells can activate the lectin pathway of the complement system—a key factor contributing to post-transplant complications, including HSCT-TMA[10,11,13]



- Three distinct pathways (classical, lectin, and alternative) can activate the complement system—leading to a common, terminal pathway[19]
- **Lectin pathway activation is initiated via binding of pattern recognition molecules** called lectins (mannose-binding lectin [MBL], ficolins, collectins). Lectins recognize damage-associated molecular patterns (DAMPs) on the surface of injured cells[20-24]
- Lectin complexes containing **MBL-associated serine protease-2 (MASP-2) bind to DAMPs**[20,23]
- Complement proteins located early in the lectin pathway are **cleaved by MASP-2**, triggering a cascade of **protein cleavage and complex formation**[20]
- Two important cleavage products—**C3a and C5a**—are both proinflammatory, prothrombotic, chemotactic anaphylatoxins[22,23,25]
- **Membrane attack complexes (MACs) are formed** from C5b-9 protein complexes, leading to **cell lysis and further damage to the endothelium**[26]

The Role of the Lectin Pathway of Complement
(continued)



- MASP-2 can activate the **coagulation cascade** in two ways: by cleaving factor XII to factor XIIa or through cleavage of prothrombin to generate thrombin. Activated thrombin is a key driver of **fibrin deposition and clot formation**, which may contribute to the progression of HSCT-TMA and other EIS[23,27,28]
- Lectin pathway cleavage of C3 generates C3b, which results in an amplification loop with the alternative pathway, increasing terminal pathway activity and **formation of the MAC**[19,29]

A Closer Look at HSCT-TMA

HSCT-induced endothelial injury is caused by a 3-hit process—the process begins with underlying predispositions to complement activation or preexisting endothelial injury and is exacerbated by conditions associated with transplant and post-transplant events[30]

Inherent/nonmodifiable risk factors[30-32]

1

Underlying predispositions

- Female sex
- African American ethnicity
- Severe aplastic anemia
- Cytomegalovirus (CMV) seropositive recipient
- Prior stem cell transplant
- Genetic variants, including complement-related genes
- High baseline lactate dehydrogenase (LDH) levels
- High/very high disease risk index

Transplant-associated risk factors[10]

2

Endothelial injury and complement activation

- Transplant conditioning
- Total-body irradiation (TBI)
- Unrelated donor transplants
- Human leukocyte antigen (HLA) mismatch
- Administration of growth factor
- Prolonged immobilization
- Venous thromboembolism
- Other factors

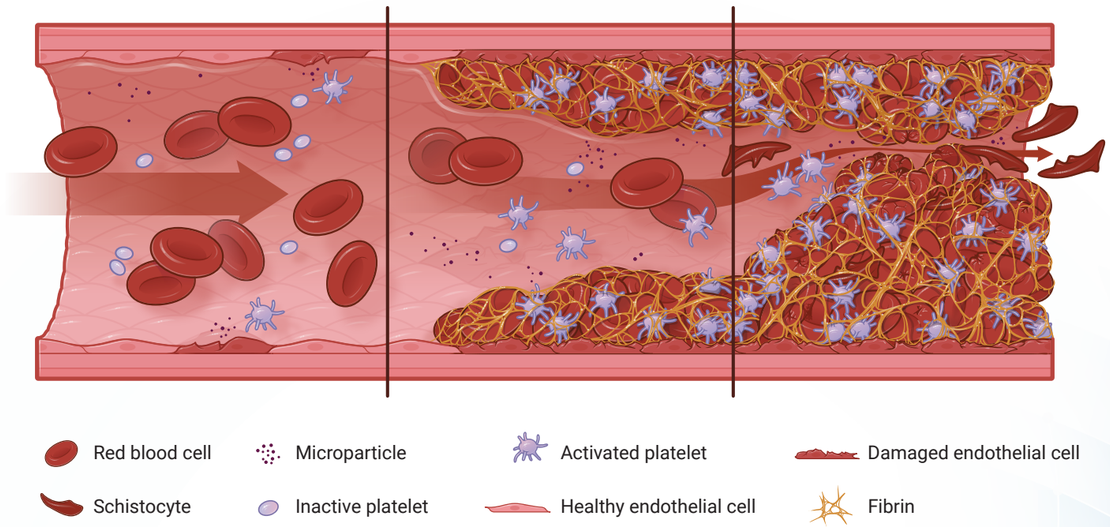
Post-transplant event risk factors[10,30]

3

Continued endothelial injury and complement dysregulation

- aGVHD
- Infection

HSCT-TMA Pathophysiology: 3-Phase Model



Phase 1

Initiation[10]

TMA pathogenesis has been thought to be initiated when various factors associated with HSCT lead to **endothelial damage**

- Calcineurin and mTOR inhibitors
- aGVHD
- Infection
- TBI

Phase 2

Progression[10,13,33]

- Injured endothelial cells present carbohydrate patterns, activating the **lectin pathway of complement**, and activated complement proteins cause further endothelial damage
- Injured endothelium releases procoagulant microparticles, causing platelet aggregation and microthrombi formation

Phase 3

Outcome[10]

Worsening endothelial damage leads to further microthrombi formation, mechanical damage to red blood cells (RBCs), and lumen obstruction, leading to TMA, organ damage, and organ failure

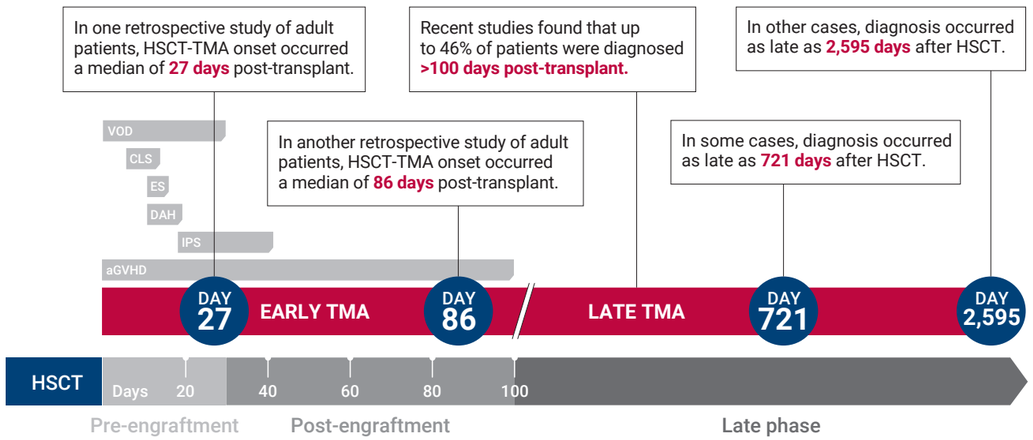
HSCT-TMA Can Be Difficult to Differentiate

Shared elements of graft-vs-host disease (GVHD) and HSCT-TMA

Mechanistic link	Risk factors	Compound risks
Endothelial injury and complement activation[34]	**GVHD is a risk factor for developing HSCT-TMA**[34]	**Worsened outcomes when presenting together**[34]
The endothelium is a key mediator of end-organ damage in aGVHD, and increasing evidence suggests that endothelial dysfunction and complement activation may contribute to the pathophysiology of aGVHD[34-36]	Rates of overlap between patients with steroid-refractory GI GVHD and HSCT-TMA have approached 80%—and GVHD almost always preceded the diagnosis of HSCT-TMA	In grades 3/4 GI GVHD, decreased overall survival (OS) and longer hospital stays are associated with patients having concomitant HSCT-TMA (vs grades 3/4 GI GVHD alone)

HSCT-TMA Is a Significant, Often Lethal Complication—Particularly in Allogeneic Transplants[10,12,37]

Onset of HSCT-TMA can vary widely in the period after transplantation[1,7,32,38-49]



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Incidence of HSCT-TMA

Severe HSCT-TMA

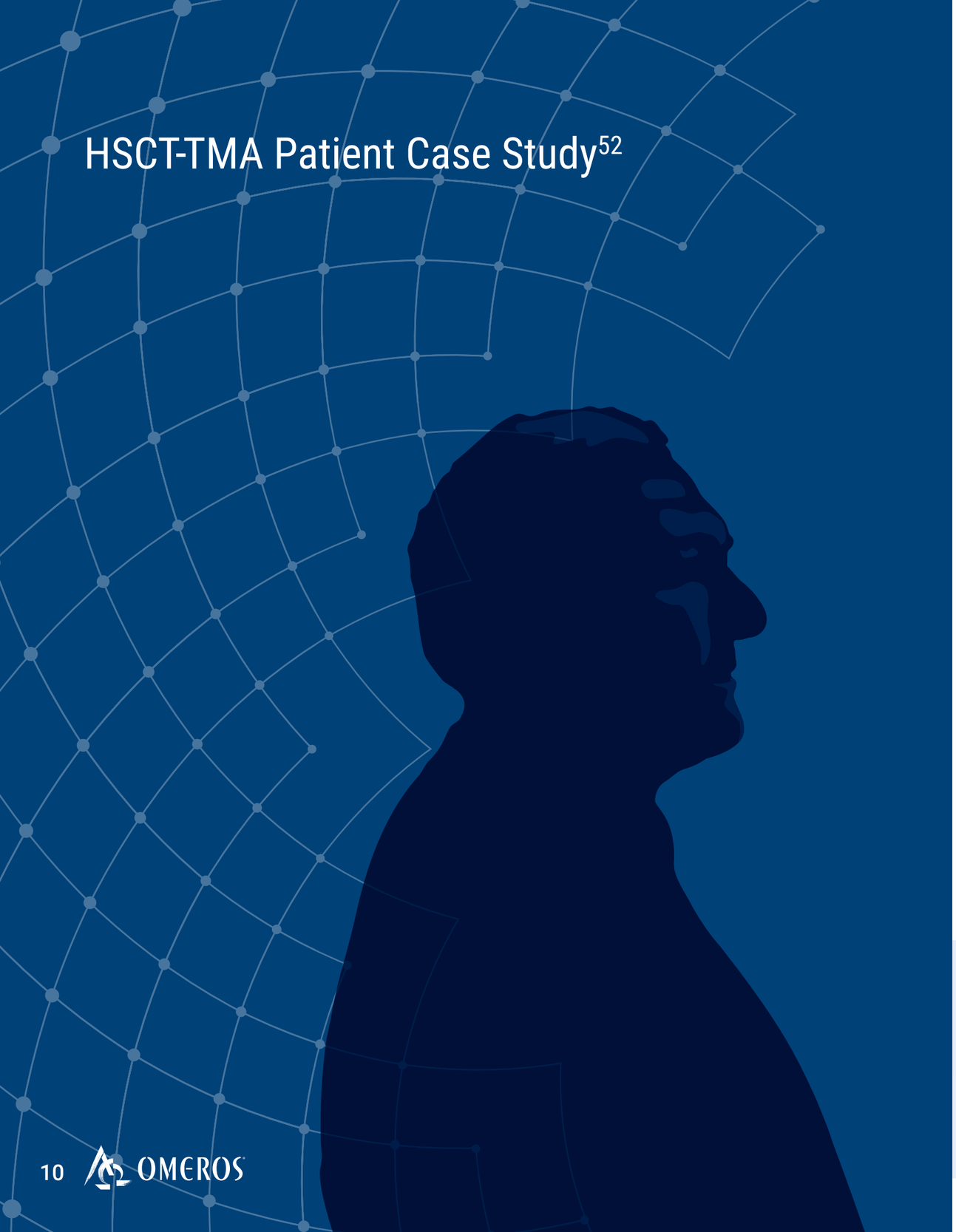
of patients with HSCT-TMA display at least one **high-risk** feature[50]

50% of HSCT-TMA cases may be **severe**[11]

of severe cases of HSCT-TMA can be **fatal**[50,51]

Patients with severe disease may be defined by multiorgan impairment, uncontrolled hypertension, worsening renal function, and a lack of response to therapeutic plasma exchange (TPE); predicting severity at initial diagnosis can be difficult.[11,37]

HSCT-TMA Patient Case Study[52]

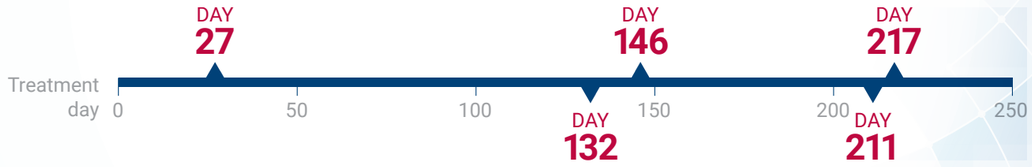


Presentation

- 54-year-old male with multiple myeloma
- Allo-HSCT from HLA-matched, unrelated donor after conditioning with reduced-intensity chemotherapy

Interventions

- GVHD prophylaxis consisted of sirolimus tacrolimus, and methotrexate
- **On day +27** post-treatment, the patient developed acute kidney injury (creatinine of 2.6 mg/dL)
- Patient was switched to mycophenolate mofetil and corticosteroids for GVHD prophylaxis
- **On day +132**, patient returned to hospital with diarrhea, GI bleeding, and thrombocytopenia (93,000/µL); colonic biopsies revealed CMV infection and GVHD
- Patient was started on ganciclovir, and prednisone dose was increased
- Patient remained hospitalized for 2 weeks
- Patient was readmitted **on day +146** with profuse bloody diarrhea and was restarted on tacrolimus
- Patient continued to have maroon-colored stool output, persisting thrombocytopenia (30,000-50,000/µL range), elevated LDH levels (731 U/L), and low haptoglobin (22 mg/dL); colonic biopsy again suggested CMV infection and GVHD
- Tacrolimus was discontinued, sirolimus was reintroduced, and patient was maintained on a combination of sirolimus, mycophenolate mofetil, and steroids for GVHD treatment
- Patient was readmitted **on day +211** with melenic stool, low platelet count (37,000/µL), and elevated LDH (1,254 U/L)
- Sirolimus was again discontinued
- The patient remained anemic and intermittently refractory to RBC transfusions. **On day +217**, patient was transferred to intensive care unit (ICU) for high-volume, bloody stool as well as low hemoglobin (6.3 g/dL), and light-headedness



Outcome

- The patient expired **on day +217** secondary to uncontrolled GI bleeding
- A postmortem analysis revealed extensive TMA involving numerous arteries and arterioles in the GI submucosa as well as in the muscularis propria and deep lamina propria of the mucosa
- A retrospective review of the patient's previous colonic biopsies was performed, and additional subtle features of TMA were found

Significant Mortality

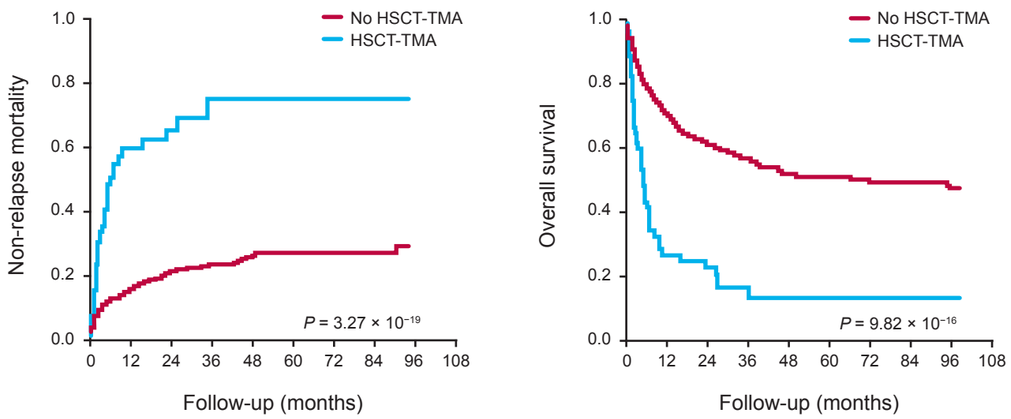
In a retrospective analysis, the risk of transplant-related mortality was ~3.5 times higher in patients with confirmed HSCT-TMA than in patients without HSCT-TMA.[53]

($P < 0.001$)[a]

3.5×
mortality risk

[a] In a retrospective analysis of 672 patients who underwent allo-HSCT and were diagnosed with probable or definite HSCT-TMA. Definite HSCT-TMA was defined by the Blood and Marrow Transplant Clinical Trials Network (CTN) criteria, including normal coagulation assay, schistocytosis (≥2/high power field), increased serum LDH, concurrent renal and/or neurologic dysfunction without other explanations, and negative Coombs test.

In another retrospective analysis, patients with HSCT-TMA demonstrated significantly higher non-relapse mortality and lower OS than those without HSCT-TMA[54]

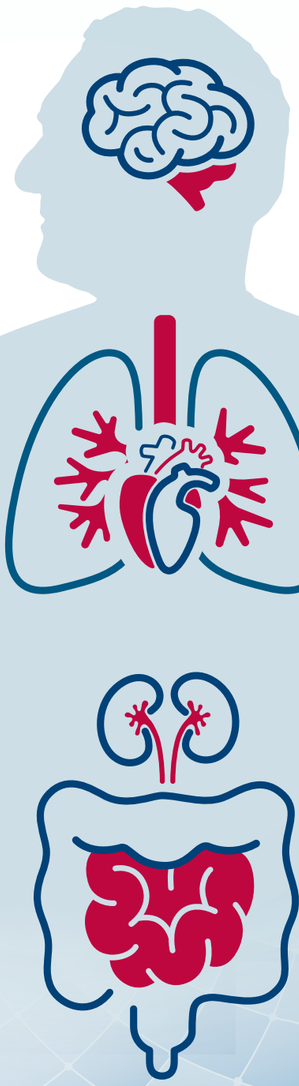


This is a single-center, retrospective analysis of 660 patients with various hematologic diseases who underwent allo-HSCT between January 2006 and April 2016. Of these patients, 65 matched established diagnostic criteria for HSCT-TMA.

Long-Term Challenges for Patients With HSCT-TMA

Patients with nonlethal cases of HSCT-TMA have an increased risk of chronic organ injury and other conditions, including[32,51,55]:

- Central nervous system complications
  (e.g., infections, cerebrovascular lesions, metabolic disturbances)
- Hypertension
- Pulmonary hypertension
- Chronic kidney disease (CKD)
- GI disease



Patients With HSCT-TMA May Face Significant Kidney Complications

Poor outcomes, as measured by 2 major types of complications[32]

City of Hope diagnostic criteria for TMA

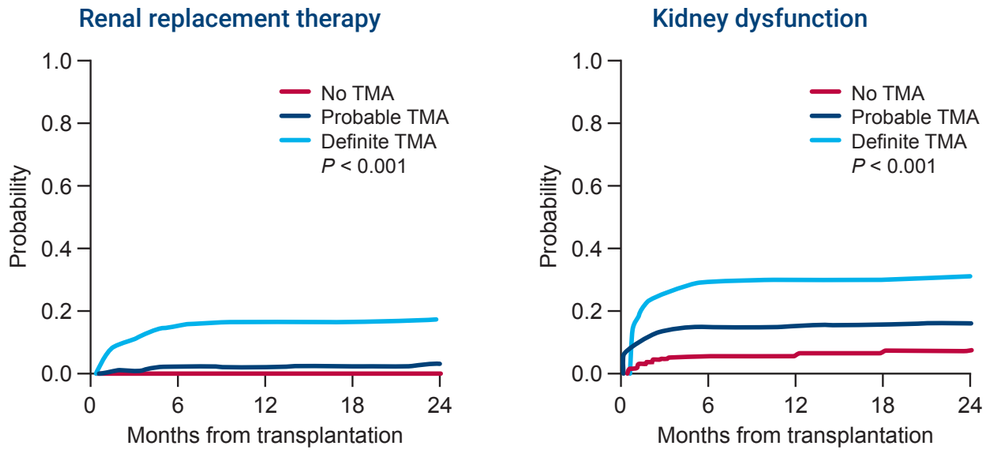
1. Presence of schistocytes or nucleated RBCs
2. Thrombocytopenia
3. LDH >2 × upper limit of normal
4. Serum creatinine >1.5 × baseline

"Probable" TMA

- 3 criteria

"Definite" TMA

- 4 criteria



- Measured 6 months post-HSCT
- Significant difference maintained 2 years post-HSCT

In those who survive, HSCT-TMA can be associated with chronic organ injury that begins early in the TMA process. This organ injury invariably leads to long-term morbidity, which may require ongoing hospital visits and continued patient care.[32,51]

Economic Burden: Cost of HSCT-TMA

Costs associated with treatment for patients with HSCT-TMA may be affected by:

- ICU length of stay (LOS)
- Non-ICU hospital LOS
- Dialysis sessions
- RBC transfusions
- Platelet transfusions
- Pulmonary disease
- Cardiovascular complications
- GI complications
- CKD
- End-stage renal disease
- aGVHD

Be aware of signs that may indicate the presence of HSCT-TMA in post-transplant patients[56]

Markers can include thrombocytopenia and microangiopathic hemolytic anemia (MAHA) plus clinical manifestations in one or more organ systems:

- Kidney
- GI tract
- Central nervous system
- Cardiopulmonary

Terms

aGVHD, acute graft-vs-host disease

allo-HSCT, allogeneic hematopoietic stem cell transplant

CKD, chronic kidney disease

CLS, capillary leak syndrome

CMV, cytomegalovirus

CTN, Clinical Trials Network

DAH, diffuse alveolar hemorrhage

DAMPs, damage-associated molecular patterns

EIS, endothelial injury syndromes

ES, engraftment syndrome

FO, fluid overload

GI, gastrointestinal

GVHD, graft-vs-host disease

HLA, human leukocyte antigen

HSCT, hematopoietic stem cell transplant

HSCT-TMA, hematopoietic stem cell transplant–associated thrombotic microangiopathy

ICU, intensive care unit

IPS, idiopathic pneumonia syndrome

LDH, lactate dehydrogenase

LOS, length of stay

LP, lectin pathway

MACs, membrane attack complexes

MAHA, microangiopathic hemolytic anemia

MASP-2, mannose-binding lectin-associated serine protease-2

MBL, mannose-binding lectin

mTOR, mammalian target of rapamycin

OS, overall survival

RBC/RBCs, red blood cell/red blood cells

SOS, sinusoidal obstruction syndrome

TBI, total-body irradiation

TMA, thrombotic microangiopathy

TPE, therapeutic plasma exchange

VOD, veno-occlusive disease

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The Impact of Endothelial Injury in Hematopoietic Stem Cell Transplant (HSCT)

- Endothelial injury may be caused by a variety of factors resulting from HSCT and can contribute to a number of syndromes[1-4,34-36]
- Injured endothelial cells can activate the lectin pathway of complement—a key factor contributing to post-transplant complications[10,11,13]
- HSCT-associated thrombotic microangiopathy (HSCT-TMA) is a significant and often lethal endothelial injury syndrome—particularly in allogeneic transplants[10,12,37]
  - Results in fatality in over 90% of severe cases[37]
  - Can be difficult to differentiate from graft-vs-host disease and other primary thrombotic microangiopathies, which often occur concomitantly with HSCT-TMA[12,34,57,58]
  - Lacks consensus on diagnostic parameters across current guidelines[58]
- Historical treatment regimens for HSCT-TMA have limitations[12,34,51,58,59]

Be aware of signs that may indicate the presence of HSCT-TMA in post-transplant patients.[56]

Markers can include thrombocytopenia and microangiopathic hemolytic anemia (MAHA) plus clinical manifestations in one or more organ systems:

- Kidney
- GI tract
- Central nervous system
- Cardiopulmonary

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