

Early Complications of Endothelial Origin

42

Enric Carreras and Maribel Diaz-Ricart

42.1 Introduction

A group of complications that occur after transplant share several common characteristics:

- (1) They appear early after HSCT (between day 0 and day +100).
- (2) Their diagnosis is usually based on the presence of medical signs and symptoms, and consequently they are classified as syndromes. Their clinical manifestations are overlapping, making their differential diagnosis difficult.
- (3) They seem to begin at the capillary level, in a systemic way or in one or more affected organs.
- (4) If not properly treated, they can evolve into an irreversible MODS/MOF.

The animal models of SOS showed that the first morphological alterations observed occurred

in endothelial cells (EC) of the hepatic sinusoids (DeLeve et al. 1996). Similarly, multiple ex vivo and in vitro studies have shown that, in auto- and allo-HSCT, there is a pro-inflammatory and pro-thrombotic state secondary to endothelial damage (Carreras et al. 2010; Palomo et al. 2009, 2010; Carreras and Diaz-Ricart 2011). Therefore, all these complications are nowadays grouped under the name of “early complications of endothelial origin”:

- Sinusoidal obstruction syndrome (SOS) of the liver (formerly denominated VOD)
- Capillary leak syndrome (CLS)
- Engraftment and peri-engraftment syndrome (ES and peri-ES)
- Diffuse alveolar hemorrhage (DAH) (see Chap. 42)
- Thrombotic microangiopathy associated with HSCT (TA-TMA)
- Posterior reversible leukoencephalopathy syndrome (PRES)

Initially, idiopathic pneumonia syndrome (IPS) was included in this group. However, even if endothelial damage plays a role in its pathogenesis, other more relevant factors seem to be present.

Probably along the next years, GVHD will be included in this group since every day it is more evident that endothelial dysfunction is the origin and not the consequence of this complication.

E. Carreras (✉)

Spanish Bone Marrow Donor Registry, Josep Carreras Foundation and Leukemia Research Institute, Barcelona, Catalunya, Spain

Hospital Clinic Barcelona, Barcelona University, Barcelona, Catalunya, Spain
e-mail: enric.carreras@fcarreras.es

M. Diaz-Ricart

Hemostasis and Erythropathology, Hematopathology Section, Pathological Anatomy Department, CDB, Hospital Clinic, University of Barcelona, Barcelona, Spain

42.2 Sinusoidal Obstruction Syndrome (See Chap. 49)

42.3 Engraftment Syndrome

42.3.1 Definition

High and well-tolerated fever of a noninfectious origin developed when the first neutrophil appears in peripheral blood indicating the engraftment. This syndrome has also been called CLS of the engraftment, autoaggression syndrome, respiratory distress of the engraftment, aseptic–septic shock, and autologous GVHD.

42.3.2 Pathogenesis

It seems to appear as a result of a systemic endothelial damage produced by the massive release of pro-inflammatory cytokines (IL-2, TNF- α , IFN- γ , IL-6), M-GSF, EPO, and products of degranulation and oxidative metabolism of neutrophils. In some cases, the concomitant administration of G-CSF, potent endothelial toxicant, contributes to its development.

42.3.3 Clinical/Biological Manifestations of ES

Around the day when engraftment starts ^a	
Classical (main criteria)	Fever ≥ 38.3 °C well tolerated Skin rash (>25% of body surface) ^b Pulmonary edema (non-cardiogenic) / hypoxia Sudden increase in CRP values (≥ 20 mg/dL) ^c
Occasional (minor criteria)	Weight gain (>2.5%) Creatinine increase ($\geq 2 \times N$ values) Hepatic dysfunction (bilirubin ≥ 2 mg/dL or AST/ALT $\geq 2 \times N$) Diarrhea ^d Encephalopathy

^aFirst day with neutrophil counts greater than $0.5 \times 10^9/L$

^bVery similar to an acute GVHD

^cValues higher than those observed in a febrile neutropenia. Due to its recent description, this parameter is not

included in the classical diagnostic criteria. The cutoff point of 6 mg/dL has a high sensitivity and specificity (90%). Additionally, CRP allows monitoring the response to the treatment since it normalizes completely in a few days (Carreras et al. 2010)

^dAt least two fluid depositions per day without microbiological documentation of infection

42.3.4 Diagnostic Criteria

Spitzer (2001)	More specific but too much complex. 3 major criteria or 2 major + 1 minor criteria within the 96 h around engraftment
Maiolino et al. (2003)	Simplest and enough specific. Noninfectious fever + another major criteria or diarrhea since 24 h before engraftment

42.3.5 Incidence and Risk Factors

ES is classically observed after autologous HSCT although it has also been described after NMA allo-HSCT (Gorak et al. 2005) and after CBT (see pre-ES).

Incidence: Ranging between 5 and 50% depending of the population analyzed and criteria used.

Most relevant *risk factors* for ES are:

- Auto-HSCT for diseases not intensively treated with chemotherapy before HSCT (AID, AL, POEMS, breast cancer, etc.)
- Intensity of the conditioning (NMA < MEL < BEAM < CY/TBI)
- In myeloma patients, previous treatment with BOR or LENA (Cornell et al. 2013)
- Use of PBSC or G-CSF

42.3.6 Prophylaxis and Treatment (Cornell et al. 2015)

Prophylaxis: Avoid the use of G-CSF after HSCT in the high-risk patients.

Treatment:

- When suspected, stop immediately G-CSF.
- If fever persists after 48 h of ATB treatment and cultures are negative, start methyl-PRD 1 mg/kg q12h (3 days) and progressive tapering in 1 week.
- When PRD is stopped, some recurrences of ES could be observed; treat again with steroids.
- With an early treatment, 90% of CR, any delay can favor the evolution to MOF.

42.4 Pre-engraftment Syndrome

ES-like was described in 2003 after CBT. Its pathogenesis is similar to ES + alloreactivity and cytokine storm (also denominated “early immune reaction” in this scenario) (Lee and Rah 2016).

Main differences with classical ES are:

- Development in the context of MAC–RIC allo-HSCT
- Earlier presentation (around day +7; up to 10–11 days before engraftment)
- Fluid retention in 30% of cases
- Higher incidence than ES (20–70% of CBT) (Lee and Rah 2016)

Patients with pre-ES have less graft failure and more GVHD without impact in TRM (Park et al. 2013).

42.5 Capillary Leak Syndrome

42.5.1 Definition

Idiopathic systemic capillary syndrome was described in healthy patients that presented episodic crisis of hypotension/hypoperfusion, hypoalbuminemia, and severe generalized edema (Clarkson disease). Usually, these manifestations could be reversed with steroids, vasopressors, fluid, and colloids, but some patients could die during this recovery phase due to a cardiopulmonary failure (Druey and Greipp 2010).

Very similar episodes have also been described after the administration of IL-2, IL-4, TNF- α ,

GM-CSG, and G-CSF and in the context of HSCT (Nünberger et al. 1997; Lucchini et al. 2016).

42.5.2 Pathogenesis

Many mechanisms have been suspected, but nowadays, due to the duration of the capillary leak and its reversibility, the endothelial injury seems to be the main cause for the capillary damage. The high levels of VEGF and angiopoietin-2 (potent inducers of vascular permeability) observed in these patients could play a role (Xie et al. 2012).

42.5.3 Diagnostic Criteria in the Context of HSCT (Lucchini et al. 2016)

Early after HSCT (\approx days +10 to 11).

Unexplained weight gain >3% in 24 h.

Positive intake balance despite furosemide administration (at least 1 mg/kg) evaluated 24 h after its administration.

42.5.4 Incidence and Risk Factors

Mainly observed in children

True incidence unknown (variable diagnostic criteria): 5.4% in the largest series (similar incidence between MAC and RIC-HSCT)

Apparently no relationship with G-CSF administration but higher incidence among patients receiving this treatment more than 5 days.

42.5.5 Treatment and Evolution

When suspected, stop immediately G-CSF
Steroids; supportive therapy (catecholamines, colloids, and plasma)
A rapid improvement has been observed in a patient treated with bevacizumab (Yabe et al. 2010)
Sixty-seven percent of patients required ICU admittance and 47% mechanical ventilation
Fourty-seven percent reach a complete remission
TRM at day +100: 43% vs only 5% in patients w/o CLS (Lucchini et al. 2016)

42.6 Thrombotic Microangiopathy Associated with HSCT (TA-TMA)

42.6.1 Definition and Classification

TMA are a heterogeneous group of diseases characterized by microangiopathic hemolytic anemia and thrombocytopenia due to platelet clumping in the microcirculation leading to ischemic organ dysfunction. As this phenomenon could be observed in different clinical situations, a consensus on the standardization of terminology has been recently proposed by an International Working Group (Scully et al. 2017) (Fig. 42.1).

42.6.2 Pathogenesis

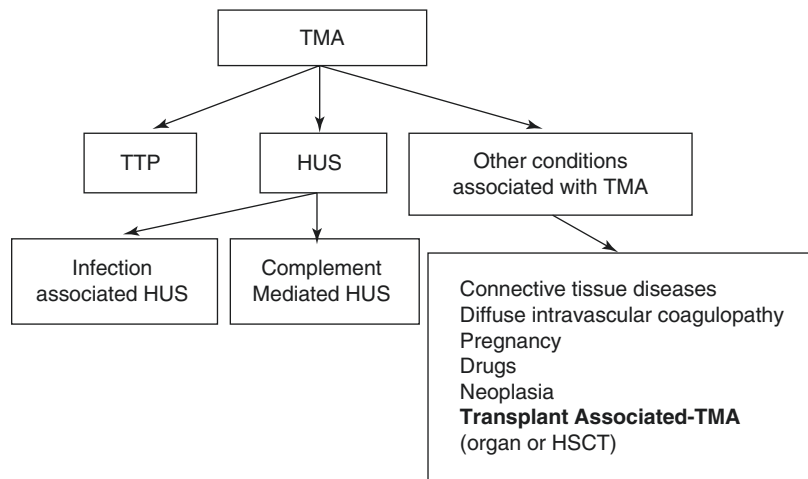
Like in the other vascular–endothelial syndromes after HSCT, the endothelial injury due to the action of different factors (conditioning, lipopolysaccharides, CNI, alloreactivity, GVHD) plays a crucial role in its development. Endothelial injury

generates a prothrombotic and pro-inflammatory status that favors capillary occlusion.

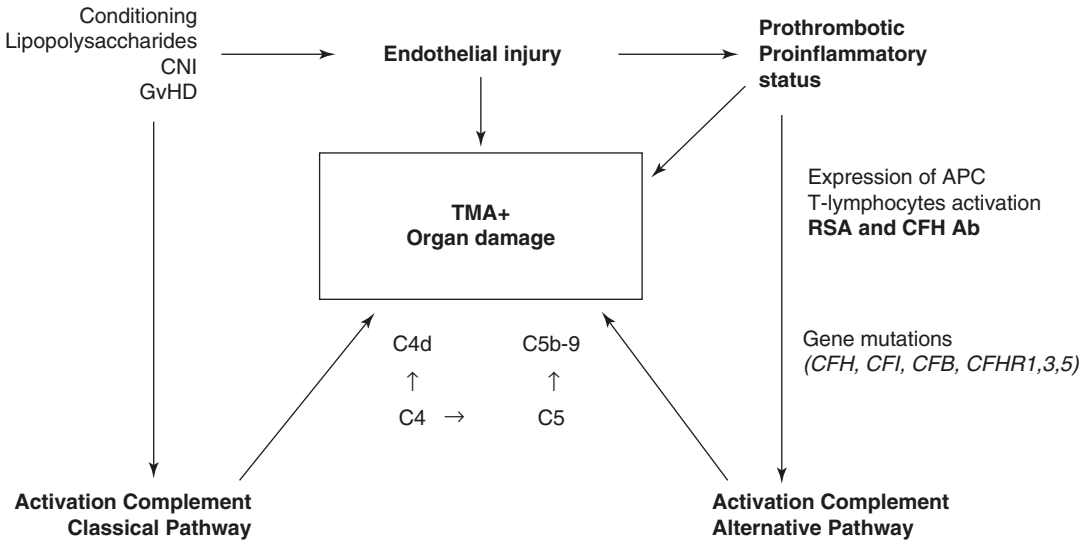
However, unlike in other endothelial syndromes, the dysregulation of the complement system and the possible presence of specific antibodies (donor- or recipient-specific Ab, as anti-factor H Ab) could play a relevant role in some TA-TMA. The activation of the classical pathway of the complement system (by chemotherapy, infections, GVHD) and the activation of the alternative pathway (favored by a genetically determined mutation of several genes [*CFH*, *CFI*, *CFB*, *CFHR1,3,5*]) produce deposits of C4d or C5b-9 (membrane attack complex) fractions, respectively (Jodele et al. 2016b).

Recently, the two-hit hypothesis tries to unify all these pathogenetic mechanisms (Khosla et al. 2018). The first hit will be produced by the normal input signals that any EC could receive (cell interaction soluble mediators, oxygenation, hemodynamic, temperature, pH) plus predisposing risk factors as prolonged immobilization, bacterial–fungal infection, leukemia not in remission, G-CSF administration, URD HSCT, HLA mismatch, RIC (fludarabine), or high-dose BU.

Fig. 42.1 Terminology of TMA



TTP=Thrombotic Thrombocytopenic Purpura; HUS=Hemolytic Uremic Syndrome



Adapted from Jodele, 2014. RSA=recipient specific antibodies: APC=Antigen Presenting Cells

Fig. 42.2 Pathogenesis of TA-TMA

The second hit will be produced by CNI, mTOR inhibitors, severe infections, or TBI. All these events would trigger the succession of events that are observed in Fig. 42.2.

Manifestations of organ damage	
Polyserositis	Refractory pericardial/pleural effusion, and/or ascites, without generalized edema

42.6.3 Clinical Manifestations

Manifestations of microangiopathic hemolytic anemia	
De novo anemia	
De novo thrombocytopenia	
Increased transfusion requirements	
Elevated LDH	
Schistocytes in the blood	
Decreased haptoglobin	
Manifestations of organ damage	
Kidney	Decreased glomerular filtration rate Proteinuria Hypertension; ≥2 medications
Lungs	Hypoxemia, respiratory distress
GI tract	Abdominal pain/GI bleeding/ileus
Central nervous system	Headaches/confusion Hallucinations/seizures

42.6.4 Diagnostic Criteria

The gold standard for diagnosis is a biopsy of the damaged organ. However, to obtain these samples is almost impossible in these patients. Consequently, along the last years, several attempts have been carried out to reach consensus criteria for the diagnosis of this complication. The most relevant advance in this area has been to recognize some clinical data, not previously included in the diagnostic criteria, that could appear even before the classical ones and that are indicative of very bad prognosis. Unlike other TMA, the activity of ADAMTS13 never reaches levels below 5–10%.

Criteria	BMT-CTN ^a	IWG ^b	Chao ^c	Jodele ^d
Schistocytes	≥2/HPF	≥4% ^e	≥2/HPF	Yes
Elevated LDH ^f	Yes	Yes	Yes	Yes
De novo thrombocytopenia	–	Yes	Yes	Yes
Decreased Hb ^g	–	Yes	Yes	Yes
Coombs (–ve)	Yes	–	Yes	–
↓ Haptoglobin	–	Yes	Yes	–
Renal/neurological dysfunction	Yes	–	–	–
Coagulation normal	–	–	Yes	–
Proteinuria ^{f,h}				±
Hypertension ^{f,i}				±
Increased serum C5b-9 levels	–	–	–	±

Yes: required, ± (bold): factors not necessary for TA-TMA diagnosis, but their presence indicate a high-risk TA-TMA.

HPF high-power field

^aHo et al. (2005)

^bRuutu et al. (2007)

^cCho et al. (2010)

^dJodele et al. (2014)

^e≥4% in 8/HPF

^fEarlier clinical signs of TMA

^gOr increased red cell transfusion

^hOr protein/creatinine ratio ≥2 mg/mg

ⁱHypertension refractory to ≥2 antihypertensive drugs

42.6.5 Clinical Forms, Incidence, Risk Factors, and Prognosis

Forms: (1) TA-TMA associated to CNI—the most frequent form with good prognosis and a real incidence unknown; (2) TA-TMA not associated to CNI—bad prognosis, requiring specific measures.

Clinical manifestations: Onset day, median time day +32 to +40 (>92% before day +100).

Incidence: Unknown due to the different diagnostic criteria—literature focused on allo-HSCT, from 0.5% to 76%; EBMT survey (IWG criteria), 406 allo-HSCT, 7% (Ruutu et al. 2002); meta-analysis (variable criteria), 5423 allo-HSCT, 8.2% (George and Selby 2004); and prospective (Cho criteria), 90 allo-HSCT, 39% (Jodele et al. 2014). Similar incidence in MAC tan in RIC.

Risk factors: Use of CNI (more if associated to SIR), viral (CMV, ADV, BK virus, etc.) or fungal infection, active GVHD, URD/mismatch HSCT (probably due to more infections and GVHD), and several gene polymorphisms (predominate in non-Caucasian).

Prognosis: Despite the resolution of TA-TMA, these patients have an increased relative risk of chronic kidney disease, 4.3; arterial hypertension, 9; and TRM, 5.

42.6.6 How to Prevent/Manage TA-TMA?

Systematic screening:	LDH 3 times a week Proteinuria × 3 times per week Blood pressure (daily)	
If any data of TA-TMA evaluate:	Schistocytes in PB Quantitative proteinuria Haptoglobin and serum C5b-9 levels	
If TA-TMA criteria	w/o proteinuria and w/o increased sC5b-9	→ Stop CNI, treat any possible triggering cause (infection, GVHD)
	With proteinuria ≥30 mg/dL or increased sC5b-9	→ All the previous measures + specific treatment (see later)

42.6.7 Treatment

Supportive	Stop CNI (substitute by PRD or MMF) Treat intensively any infection, GVHD, and AHT
Therapeutic plasma exchange (TPE)	In recent prospective studies, 59–64% of CR (better if started early) In patients with Ab anti-factor H, better/good results with TPE ± RTX RTX should be administered after TPE Do not associate TPE with eculizumab
Rituximab (RTX)	Reported 12/15 responses to RTX + TPE (Uderzo et al. 2014) RTX should be administered immediately after TPE
Defibrotide (DF)	Recent report with 46 adults and children: 77% of CR (Yeates et al. 2017)
Eculizumab	Indicated in TA-TMA with proteinuria ± > sC5b-9: 67% of responses Children could require higher doses (quantify CH50 to adjust the doses) (Jodele et al. 2015, 2016a)

CH50: Total hemolytic complement activity

Key Points

- Although endothelial dysfunction syndromes are rare, HSCT physicians should be aware of their main manifestations to establish an early diagnosis.
- Given the limited effectiveness of the available therapeutic measures, all modifiable risk factors that may favor their development should be avoided.
- Early diagnosis is essential to make effective the few available therapeutic measures.
- When one of these syndromes progresses to MOF, the prognosis is very poor.

- Even in those patients where resolution of the syndrome is achieved, the probability of survival of the procedure is clearly reduced

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