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Thrombotic microangiopathy following CAR T-cell therapy: a case series from the EBMT Complications Working Party

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Authors' contributions
GD, CG and OP conceived and designed the study. WB, CP, and MA performed data collection and statistical analysis. EG, EG, MG, MF, GS, GD contributed clinical data. GD, CG, OF drafted the manuscript. All authors reviewed, revised, and approved the final version.

Running head: CAR T-associated TMA: EBMT data

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

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Chimeric antigen receptor T-cells (CAR-T) therapies have transformed the management of relapsed or refractory B-cell malignancies. Alongside remarkable clinical efficacy in patients with otherwise poor prognosis, CAR-T treatments have also introduced a new spectrum of immune-mediated toxicities: Cytokine release syndrome (CRS), immune effector cell–associated neurotoxicity syndrome (ICANS), and immune effector cell–associated hemophagocytic syndrome (IEC-HS) are now well-recognized complications[1].

Increasing evidence suggests that endothelial injury plays a central role in the pathophysiology of CAR-T–related toxicities[2]. Biomarkers of endothelial activation, including angiopoietins and von Willebrand factor (VWF), have been shown to increase in patients developing severe CRS and ICANS[3, 4]. Furthermore, systemic inflammation associated with CRS has been linked to cardiovascular complications, with early interleukin-6 blockade appearing partially protective[5]. These findings collectively highlight the importance of endothelial dysfunction and coagulation disturbances in the toxicity profile of CAR-T therapy.

Transplant-associated thrombotic microangiopathy (TA-TMA) is a well-described life-threatening complication following hematopoietic cell transplantation (HCT)[6]. It is characterized by microangiopathic hemolytic anemia, thrombocytopenia frequently associated with renal or neurologic dysfunction. A consensus definition[7] has refined diagnostic criteria and emphasized the multifactorial pathophysiology of the syndrome, involving systemic inflammation, complement activation, platelet activation and endothelial injury.

Despite growing recognition of endothelial injury in CAR T-cells related toxicities, thrombotic microangiopathy following CAR-T therapy remains poorly characterized. Only isolated case reports have been described to date and no systematic multicenter description is available[1]. Since timely recognition of this complication has important implications for patient monitoring and management, the EBMT Complications Working Party (CWP) conducted a retrospective multicenter survey to identify and characterize cases of CAR-T–associated thrombotic microangiopathy, describing their clinical features, management, and outcomes.

Following approval by the CWP Board (internal approval number 84110139), EBMT CAR-T centers were contacted to identify cases of thrombotic microangiopathy (TMA) occurring after CAR T-cells therapy. Overall, 215 EBMT CAR-T centers were contacted. Ninety centers responded indicating that they had not observed eligible cases and 7 centers agreed to participate in a detailed retrospective clinical data collection. Diagnostic

of TMA was based on current consensus criteria[7]. Variables collected included demographic information, disease characteristics, and clinical outcomes following CAR T-cell therapy.

Seven cases of TMA occurring after CAR-T therapy were identified. All patients had undergone CAR-T treatment for B-cell malignancies, including diffuse large B-cell lymphoma (n=2), mantle cell lymphoma (n=1), follicular lymphoma (n=1), monomorphic post-transplant lymphoproliferative disorder, diffuse large B-cell lymphoma-type (monomorphic PTLD, DLBCL-type, n=1), and high-grade B-cell lymphoma (n=1). None of the patients had a history of prior autologous hematopoietic cell transplantation (auto-HCT) before CAR T-cell infusion. One patient had B-lymphoblastic leukemia (B-ALL) and had previously undergone an allogeneic HCT 617 days (1.7 years) before CAR T-cell infusion.

The median age at CAR-T infusion was 63 years (range 41–75), and six patients had an ECOG performance status ≤2 at infusion. CAR-T products included axicabtagene ciloleucel (n=4), brexucabtagene autoleucel (n=2), and tisagenlecleucel (n=1). All patients received standard lymphodepleting chemotherapy with fludarabine and cyclophosphamide prior to CAR-T infusion. Two patients had refractory disease, one had stable disease, and one had untreated relapse at the time of CAR T-cell infusion. The remaining three patients were in complete remission. Detailed baseline patient characteristics are summarized in Supplementary Table 1.

All patients developed a CRS prior to the diagnosis of TMA, mostly grade 1–2, although two patients experienced grade 3 and 4 CRS. ICANS occurred in five of the seven patients, preceding TMA in four cases and coinciding with TMA diagnosis in one case. All patients suffered from infectious complications after CAR-T, with three patients presenting with clinically active infections at the time of TMA diagnosis (one CMV infection and two bacterial blood stream infections). Of note, one patient developed a proven invasive fungal infections (*Geotrichum*, patient 1), one other patient had an invasive pulmonary aspergillosis (patient 6) and two additional patients had suspected fungal infections (*Candida spp*), highlighting the morbidity of this patient population. No acute GVHD was reported at time of TMA in the patient who had previously undergone an allogeneic HCT.

TMA developed after a median of 8 days following CAR-T infusion (range 6 – 442). Diagnostic features included thrombocytopenia and elevated lactate dehydrogenase (LDH) in all patients, anemia in six patients, hypertension in four patients, proteinuria in four patients and schistocytes in four patients. As data were registry-derived, severity grading of individual diagnostic criteria was not systematically available. Complement activation marker C5b-9 was assessed in five patients and was elevated in one case. One patient had biopsy-proven TMA. Supplementary Table 1 details TMA presentation and treatment. Five patients presented high-risk features according to consensus definition[7], including peak LDH greater than twice the upper limit of normal, concurrent systemic infection or significant organ involvement. Isolated central nervous system, renal (proteinuria ≥30 mg/dL), or pulmonary involvement occurred in three patients; one had combined renal and pulmonary involvement, and one developed multisystem involvement (cardiovascular, serosal, CNS and gastrointestinal).

Four patients received specific treatment for TMA, initiated at the time of diagnosis in three cases and on day 55 following TMA onset in patient 5. Treatment regimens included corticosteroids, antihypertensive therapy, complement inhibition with ravulizumab, or multimodal therapy including plasma exchange and eculizumab. The temporal relationship between CAR-T infusion, CRS and ICANS occurrence and TMA onset is illustrated in Figure 1. Two patients presented a notably late onset of TMA occurring 237 and 442 days after CAR-T infusion, without evidence of relapse of the underlying disease. One of these patients had previously undergone allo-HCT and developed severe multisystemic TMA with biopsy confirmation and elevated sC5b-9. She was treated with corticosteroids, plasma exchange, tocilizumab and long-term complement inhibition with eculizumab, and remains alive in complete remission of her B-ALL.

Regarding oncologic outcomes, four patients achieved complete remission of their underlying malignancy, one achieved partial remission and two had progressive diseases. At last follow-up, four patients had died, including two from lymphoma progression and two from treatment-related infectious complications: one from invasive geotrichosis and one from prolonged aplasia complicated by invasive pulmonary aspergillosis.

This multicenter case series provides the first systematic description of TMA occurring after CAR T-cell therapy. Although rare, this complication appears clinically significant, may require dedicated therapeutic management and may represent a broader state of clinical deterioration in this fragile patient population.

CRS preceded TMA in all patients and ICANS was observed in five out of seven patients, occurring prior to TMA in four cases and concurrently on the day of TMA diagnosis in one case. This chronology suggests that CAR-T driven inflammation may contribute to endothelial injury and microvascular damage, potentially leading to coagulation disturbances and microangiopathy[4, 8, 9]. Consistent with this, CAR-T–related toxicities are closely linked to endothelial activation, with elevated endothelial biomarkers correlating with toxicity severity and supporting a central role for endothelial dysfunction in their pathophysiology [2, 8]. Complement activation may further amplify endothelial damage and promote microvascular thrombosis, as described in transplant-associated TMA. In this context, markers of endothelial stress summarized in the Endothelial Activation and Stress Index (EASIX) have recently been associated with adverse events following CAR T-cell therapy[9]. Together, these observations support the concept that CAR-T–associated TMA may represent the end of an inflammatory endothelial injury spectrum.

Most cases of TMA in our cohort occurred early after CAR-T infusion, within the first weeks following treatment, consistent with a mechanism driven by acute inflammatory toxicity. However, two patients developed TMA at notably later timepoints, approximately 8 months and more than one year after CAR T-cell infusion, suggesting that delayed endothelial injury may also occur. Such late presentations, in the absence of hematologic relapse, may reflect persistent immune dysregulation, cumulative endothelial damage or additional risk factors such as prior transplantation, concomitant infections, or concurrent medications known to promote endothelial injury. This diagnostic complexity is further compounded by the potential co-occurrence of overlapping inflammatory syndromes: although complement activation marker C5b-9 was not systematically assessed across all patients, its elevation in a subset of cases raises the possibility that HLH may have been concurrently present but underdiagnosed, given the nosological overlap between TMA and HLH following CAR T-cell therapy.

Our study has several limitations mainly linked to its low response rate, its retrospective design with limited granularity of data and the fact that our definition of TMA was based on a transplant-associated TMA consensus, which has not been specifically validated in a CAR-T population. The retrospective collection of biomarker data also limits interpretation, as measurements were not standardized over time, particularly for EASIX score and sC5b-9. Finally, the limited sample size precludes estimation of incidence and prevents identification of clear risk factors or optimal therapeutic strategies.

In conclusion, TMA represents a rare but clinically relevant complication of CAR T-cell therapy. Its association with CRS and ICANS supports a shared pathophysiological pathway driven by inflammatory endothelial injury. Increased clinical awareness and prospective studies incorporating systematic assessment of endothelial and complement biomarkers are needed to better define its incidence, mechanisms, and risk factors.

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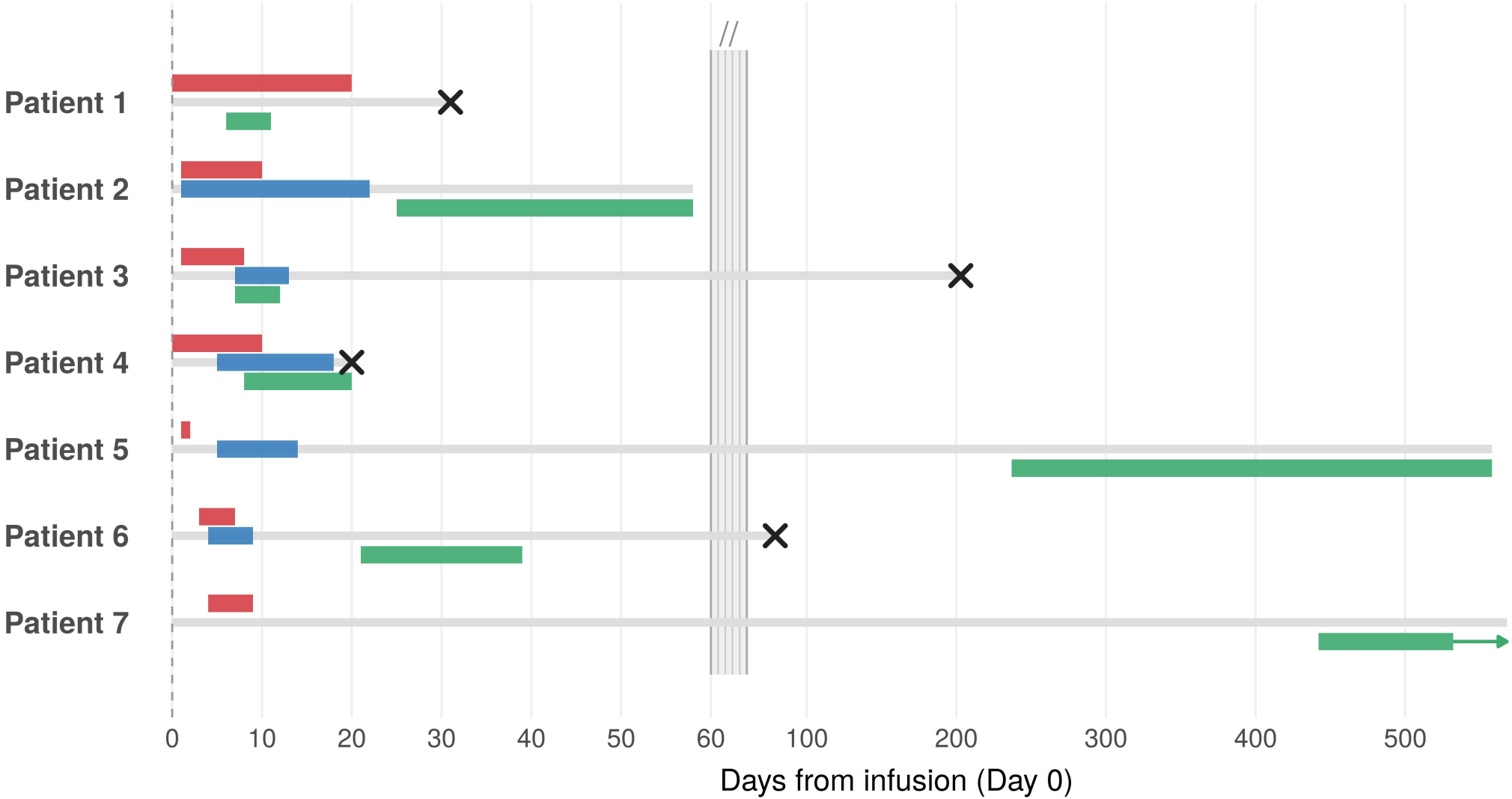
Figure legend

Figure 1. Swimmer plot illustrating the temporal relationship between CAR T-cell infusion, CRS, ICANS, and thrombotic microangiopathy onset.

Each horizontal bar represents one patient, with Day 0 corresponding to the date of CAR T-cell infusion. Grey lines indicate the duration of follow-up for each patient. Colored bars represent the onset and duration of cytokine release syndrome (CRS, red), immune effector cell-associated neurotoxicity syndrome (ICANS, blue), and thrombotic microangiopathy (TMA, green). Arrows indicate events that are ongoing at date of last follow-up. Death is represented by a cross (×). The time axis is continuous up to Day 60 and compressed sixfold beyond Day 60 to accommodate the wide range of follow-up durations. CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; TMA, thrombotic microangiopathy; CAR T, chimeric antigen receptor T-cell.


Patient 1
Patient 2
Patient 3
Patient 4
Patient 5
Patient 6
Patient 7
0
10
20
30
40
50
60
100
200
300
400
500
Days from infusion (Day 0)

Supplementary material.

Sup Table 1. Baseline characteristics, clinical presentation and outcomes of seven patients with thrombotic microangiopathy following CAR T-cell therapy.

	Patient 1	**Patient 2**	**Patient 3**	**Patient 4**	**Patient 5**	**Patient 6**	**Patient 7**
Baseline Characteristics							
Patient age at CAR-T infusion	75	64	63	56	41	67	42
Sex of the patient	Male	Female	Male	Male	Female	Female	Female
Disease	Mantle cell lymphoma	Follicular lymphoma	DLBCL, NOS	DLBCL, NOS	PTLD	High-grade BCL	B-ALL
Prior allo-HCT (Y/N)	No	No	No	No	No	No	Yes
Product infused	brexu-cel	axi-cel	axi-cel	tisa-cel	axi-cel	axi-cel	brexu-cel
Dose of Flu / Cy (total dose, mg/m²)	90 / 900	90 / 1500	90 / 1500	75 / 750	90 / 1500	90 / 1500	75 / 900
Disease status at lymphodepletion	Stable disease	Refractory	Untreated relapse	Refractory	CR	CR	CR
Refractory to any prior line (Y/N)	Yes	Yes	No	Yes	No	No	–
Total number of prior lines of treatment	3	≥5	2	2	2	1	NR
ECOG at CAR-T infusion	3	2	1	2	1	0	0
Outcomes post CAR-T							
CRS occurrence (grade)	4	2	2	2	1	2	1
ICANS occurrence (grade)	No	2	3	1	4	3	No
Infections post CAR-T (until last FU)? (Y/N)	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Infection before / at time of TMA Diagnosis	No	Yes	No	Yes	Yes	Yes	Yes
Type of infection before TMA Diagnosis	NA	CMV, D+21	NA	Staph coag neg spp, D+7	RSV, D+92	K. Pneumoniae, D+13	E. Coli, D+63
Best response	PR	CR	PD	PD	CR	CR	CR
Delay CAR-T infusion - last FU (days)	31	730	203	20	601	76	699
Survival status at last follow-up	Dead	Alive	Dead	Dead	Alive	Dead	Alive
Main cause of death	CAR-T related (infectious complication)	NA	Relapse / Progression	Relapse / Progression	NA	CAR-T related (infectious complication)	NA
TMA Characteristics							
Anemia (Y/N)	**Yes**	**Yes**	**Yes**	**Yes**	No	**Yes**	**Yes**
LDH passed threshold (Y/N)	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**
Thrombocytopenia (Y/N)	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**

Proteinuria (Y/N)	**Yes**	**Yes**	No	No	**Yes**	**Yes**	No
Hypertension (Y/N)	No	**Yes**	**Yes**	**Yes**	**Yes**	No	No
Schistocytes (Y/N)	No	**Yes**	No	No	**Yes**	**Yes**	**Yes**
Elevated C5b9 (Y/N)	No	No	No	No	Not tested	Not tested	**Yes**
Other indication of TMA (Y/N)	NR	NR	NR	NR	NR	NR	Biopsy proven
High Risk Features for TMA							
Peak LDH > 2x ULN	**Yes**	**Yes**	No	**Yes**	**Yes**	No	**Yes**
Concurrent organ dysfunction, included CNS manifestation	No	**Yes**	**Yes**	**Yes**	**Yes**	No	**Yes**
Treatment	No	**Yes**	**Yes**	No	**Yes**	No	**Yes**
Treatment regimen	NA	Amlodopine / Furosemide / Urapidil	Corticosteroids	NA	Ravulizumab	NA	Corticosteroids + Plasma Exchange followed by tocilizumab and eculizumab

Abbreviations: Brexu-cel, brexucabtagene autoleucel; axi-cel, axicabtagene ciloleucel; tisa-cel, tisagenlecleucel; allo-HCT, allogeneic hematopoietic cell transplantation; auto-HCT, autologous hematopoietic cell transplantation; Flu, fludarabine; Cy, cyclophosphamide; CR, complete remission; PR, partial remission; PD, progressive disease; LDH, lactate dehydrogenase; ULN, upper limit of normal; CNS, central nervous system; CMV, cytomegalovirus; RSV, respiratory syncytial virus; CT, CAR T-cell therapy; NR, not reported; NA, not applicable. Grades of CRS and ICANS are reported according to ASTCT consensus criteria. TMA severity and high-risk features are defined according to the Schoettler et al. consensus criteria.