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Endothelial injury at the crossroads of CAR-T toxicity and thrombotic microangiopathy

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The remarkable success of chimeric antigen receptor T-cell (CAR-T) therapy has shifted attention from efficacy toward a growing spectrum of immune-mediated toxicities. While cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), and immune effector cell-associated hemophagocytic syndrome are now recognized complications, endothelial injury has emerged as a common biological denominator linking many of these syndromes. Increasing evidence indicates that endothelial activation accompanies severe CRS and ICANS and may contribute directly to organ dysfunction, coagulopathy, and vascular complications [1-5]. In this issue of *Haematologica*, Dachy and colleagues [6] provide the first multicenter case series of thrombotic microangiopathy (TMA) following CAR-T-cell therapy, offering important clinical insights while simultaneously raising fundamental questions regarding pathogenesis.

The study describes seven patients who developed TMA after CAR-T treatment for B-cell malignancies. Despite the modest number of cases, a few observations merit consideration. Prior to receiving a TMA diagnosis, every patient had CRS, and the majority also acquired ICANS. First, all patients experienced CRS before the diagnosis of TMA, and most also developed ICANS. Second, the majority fulfilled criteria for high-risk TMA, with evidence of organ involvement and substantial morbidity. Third, two patients developed TMA remarkably late, at 237 and 442 days after CAR-T infusion, expanding the temporal boundaries of this complication far beyond what many clinicians would currently consider.

From a clinical perspective, the immediate message is clear: whenever unexplained thrombocytopenia, hemolysis, hypertension, proteinuria, renal dysfunction, or neurological deterioration follow CAR-T therapy, TMA should be included in the differential diagnosis. These manifestations are often attributed to disease progression, infection, prolonged cytopenias, or treatment-related toxicity. The present report reminds us that a microangiopathic process may underlie at least a subset of such presentations. Importantly, several patients received targeted interventions, including complement inhibition, suggesting that early recognition may have therapeutic consequences. However, the true significance of this report may lie less in the description of a rare entity than in what it reveals about the biology of CAR-T-associated toxicities. The chronology observed by the authors strongly supports a model in which

endothelial injury occupies a central position in the pathophysiological cascade. The consistent occurrence of CRS before TMA, and the frequent association with ICANS, argues against TMA being an isolated complication. Instead, TMA appears to represent one of the most severe manifestations of a continuum of endothelial damage initiated by inflammatory cytokines and amplified by coagulation and complement pathways. This interpretation is supported by studies demonstrating elevations of angiopoietin-2, von Willebrand factor, soluble thrombomodulin and other endothelial markers in patients experiencing severe CAR-T-related toxicities [1-5]. Yet the data also caution against an overly simplistic interpretation. If acute cytokine-mediated endothelial activation were the sole mechanism, one would expect TMA to occur predominantly within the first weeks following infusion. Indeed, five of the seven cases fit this paradigm, with a median onset of only eight days after CAR-T administration. These early cases are biologically consistent with the intense inflammatory milieu accompanying CRS and ICANS, conditions characterized by profound cytokine-driven endothelial activation [1-5].

The two late-onset cases, however, challenge the hypothesis of a single mechanism. The occurrence of TMA eight months and more than one year after CAR-T infusion suggests that endothelial vulnerability may persist long after resolution of acute toxicity. Such observations are reminiscent of the “three-hit hypothesis” proposed for transplantation-associated TMA, in which baseline endothelial vulnerability is followed by cumulative endothelial insults and finally by triggering events that precipitate overt microangiopathy [7-9].

Therefore, one possibility is that CAR-T therapy acts as an additional endothelial insult within a broader multistep process. Prior transplantation, infections, persistent immune activation, medications, and inherited or acquired complement susceptibility may all contribute to the eventual development of TMA. The observation that one of the late cases occurred in a patient with prior allogeneic transplantation is particularly intriguing and supports the possibility that pre-existing endothelial injury may interact with CAR-T-associated inflammation.

The complement findings are equally provocative. Elevated soluble C5b-9 was documented only in a minority of evaluated patients, but testing was neither systematic nor longitudinal. Consequently, the

study cannot determine whether complement activation is a primary driver of disease or merely a downstream amplifier of endothelial injury. This distinction is critical because complement activation is increasingly recognized as a central effector pathway in TA-TMA after allogeneic transplantation and constitutes the biological rationale for therapies such as eculizumab or ravulizumab [8-10]. Whether CAR-T-associated TMA shares this dependency remains unknown.

Perhaps the most important implication concerns biomarkers and surveillance strategies. The heterogeneity in timing observed in this cohort suggests that a single biomarker assessment performed around the time of CRS would almost certainly be adequate but not sufficient. Current investigations of endothelial biomarkers in CAR-T recipients have largely focused on the peri-infusion period, seeking predictors of acute CRS and ICANS [3-5]. However, the present data indicate that such an approach may capture only part of the risk landscape. For early-onset TMA, biomarker monitoring should likely concentrate on the period extending from lymphodepletion through the first month after infusion, when endothelial activation, cytokine release, and complement engagement are most intense. Markers such as angiopoietin-2, von Willebrand factor, soluble thrombomodulin, C5b-9, and the Endothelial Activation and Stress Index (EASIX) are attractive candidates. Indeed, EASIX has already been associated with severe endothelial complications and inferior outcomes after CAR-T therapy [11].

Conversely, the existence of very late presentations suggests that biomarker surveillance should not necessarily end once CRS and ICANS have resolved. Longitudinal assessment may be warranted in selected high-risk populations, particularly patients with previous transplantation, persistent cytopenias, recurrent infections, chronic inflammatory states, or evidence of ongoing endothelial stress (Figure 1). The concept emerging from this series is that biomarkers may need to be interpreted dynamically rather than as single-point predictors. The biological signals identifying imminent TMA may differ substantially between the acute inflammatory phase and the late post-CAR-T period.

Indeed, the swimmer plot presented by the authors may ultimately prove to be one of the most informative aspects of the report because it visually demonstrates that CAR-T-associated TMA is not confined to a single temporal window. Rather than a discrete event, endothelial injury may represent a

dynamic process whose clinical manifestations emerge whenever cumulative endothelial stress exceeds an individual threshold. This interpretation is consistent with contemporary models of endothelial dysfunction across transplantation and cellular therapy [7-9].

The next challenge is not simply to determine how frequently TMA occurs after CAR-T therapy, but to understand whether it represents the extreme end of a shared endothelial injury spectrum or a distinct biological syndrome with multiple pathogenic routes. Prospective studies integrating serial endothelial, coagulation, inflammatory, and complement biomarkers before infusion, during CRS, after resolution of acute toxicity, and throughout long-term follow-up will be required to answer this question.

Until then, the report by Dachy and colleagues [6] serves as an important reminder: endothelial injury may be one of the central organizing principles of CAR-T toxicity, and TMA may represent its most clinically visible, and potentially most preventable, expression.

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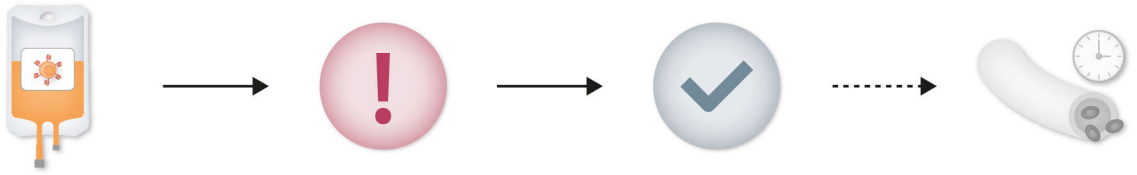
Figure 1. Dynamic interpretation of biomarkers for the detection of late TA-TMA after CAR-T-cell therapy. Biomarker surveillance for transplant-associated thrombotic microangiopathy (TA-TMA) should not necessarily cease after resolution of cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). The occurrence of very late TA-TMA presentations suggests that ongoing biological risk may persist beyond the acute phase. Longitudinal monitoring may therefore be warranted in selected high-risk patients. Rather than serving as static, single-point predictors, biomarkers should be interpreted dynamically within the temporal context of disease evolution, endothelial injury, and host-specific risk factors.

Key concept

Biomarker surveillance after CAR-T should extend beyond CRS and ICANS resolution



Biomarkers should be interpreted dynamically

Biological signals and risk factors evolve over time