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Recurrent oral ulceration after CD19 CAR T-cell therapy defines a delayed mucosal inflammatory phenotype

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Author contributions
JS, LdH, EK, TD en JSVP conceived the Letter, wrote the manuscript, and prepared the figures and tables. All other authors contributed to the intellectual content of the manuscript, critically revised the text for important scientific content, and approved the final version of the manuscript.

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Key points

- Recurrent oral ulceration occurring months after CD19 CAR T-cell therapy defines a reproducible, steroid-responsive inflammatory phenotype distinct from chemotherapy-associated mucositis.

- These findings suggest that barrier tissues may represent a vulnerable axis of delayed immune dysregulation following CAR T–induced immune remodeling.

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Data sharing statement
The data that support the findings of this case series were obtained from a national registry database. Anonymized data may be made available upon reasonable request to the corresponding author, subject to approval by the registry authority and in accordance with applicable data protection regulations. A data-sharing agreement may be required.

CD19-directed chimeric antigen receptor (CAR) T-cell therapy has improved outcomes in relapsed or refractory diffuse large B-cell lymphoma (DLBCL).[1] Early toxicities, including cytokine release syndrome (CRS), immune effector cell–associated neurotoxicity syndrome (ICANS), are well characterized and linked to cytokine-driven immune activation during CAR T-cell expansion, as well as the immune effector-cell hemophagocytic lymphohistiocytosis-like syndrome (IEC-HS).[2] However, increasing clinical experience suggests that CAR T-cell therapy induces more durable immune perturbations extending beyond the early post-infusion period.[3]

Emerging reports of gastrointestinal ulceration and immune effector cell (IEC)–associated enterocolitis following both CD19- and probably more commonly, BCMA-directed CAR-T cells suggest that mucosal barrier tissues may represent a vulnerable axis of delayed immune dysregulation following cellular immunotherapy.[4,5] Yet, involvement of localized oral mucosa has not been systematically described. Here, we report a multi-center case series of five patients who developed recurrent, steroid-responsive oral ulceration several months after anti-CD19 CAR T-cell therapy. We propose that this phenotype represents delayed barrier tissue immune remodeling rather than classical chemotherapy-induced mucositis or opportunistic infection.

The index patient, a 67-year-old female treated with axicabtagene ciloleucel (axi-cel) for refractory DLBCL, presented with a painful ulcer on the lateral tongue (**Figure 1**). She was initially diagnosed with stage III DLBCL and received six cycles of R-CHOP. Six months later, recurrence in a submandibular lymph node was diagnosed and treated with platinum-based salvage therapy (R-GDP). Although an initial response was achieved, disease recurred in the submandibular region, allowing next-line CAR T cell therapy. Axi-cel infusion was complicated by grade II CRS and grade III ICANS, both of which were treated with tocilizumab and dexamethasone with full recovery. CAR T-cell count in peripheral blood peaked at 92 * 10^6 cells/L at day 11 and gradually declined to 8 * 10^6 cells/L at day 30 and 1 * 10^6 cells/L at six months. She achieved complete metabolic remission one month after therapy. Five months later, she presented with painful ulcers on the lateral tongue that had arisen abruptly without preceding trauma or prior aphthous history. Smoking history was negative. Comprehensive clinical, laboratory and microbiological evaluation excluded infectious, nutritional and autoimmune etiologies. Infectious workup included HSV PCR, fungal cultures and bacterial swabs, all of which were negative. Pathological evaluation (**Figure 1**) showed epithelial loss with fibrin deposition. A dense and deep mixed infiltrate was present within the stroma, primarily comprising histiocytes (CD68+), along with occasional small lymphocytes and neutrophilic and eosinophilic granulocytes. The lymphocytes present were predominantly small T-cells, with a predominance of cytotoxic T-cells with CD8, TIA and Granzyme B expression. PD1 was sporadic weak positive. B-cells were absent (CD20-, PAX5-, CD79a-). Additionally, CD30, HSV1 and stains for micro-organisms were negative. Immunohistochemical detection of CAR-positive T cells within the inflammatory infiltrate was attempted repeatedly but could not be reliably interpreted due to the absence of a suitable positive control.

Initial treatment of the ulcerative lesion consisted of topical corticosteroids that was intensified to systemic corticosteroid treatment (prednisone 30 mg daily) for a duration of several weeks due to rapidly recurring

lesions at various attempts to taper steroid therapy. The lesion eventually resolved but relapsed six months later, requiring an additional two-week course of systemic prednisone to achieve sustained remission.

After the initial description of this case, patients treated with CD19-directed CAR T-cell therapy at Dutch CAR-T treatment centers between 2020 and June 2025 were identified through review of institutional CAR-T follow-up registries for persistent or recurrent oral ulceration occurring ≥1 month after infusion without any clinical signs of concomitant enterocolitis. Cases with documented infection, nutritional deficiency, active autoimmune disease, or lymphoma involvement were excluded. Among 410 patients treated with anti-CD19 CAR T-cell therapy during the study period and reviewed through institutional CAR T-cell follow-up registries, five patients (1.2%) met the inclusion criteria for delayed oral ulceration. For these patients, clinical data were extracted from medical records, including lymphoma characteristics, prior therapies, CAR-T product administered, occurrence and grade of CRS and ICANS, timing of ulcer onset, laboratory parameters, treatments administered for ulceration and clinical outcomes. Where available, immune reconstitution parameters (peripheral blood T- and B-cell counts, immunoglobulin levels and circulating CAR T-cell counts) were reviewed from routine clinical monitoring.

Four additional patients exhibited a similar phenotype (**Table 1**). In all cases, the onset occurred between 1 and 6 months after CAR T infusion, while the patients remained in sustained complete metabolic remission at the time of occurrence. None of the patients had concurrent CRS or ICANS. HSV PCR testing was negative for all, as well as bacterial swabs. Positive fungal cultures (C. albicans and C. tropicalis) in two cases were considered colonization of the ulcerative lesion rather than its causal agent. CMV PCR at ulcer onset was negative in one CMV IgG-positive patient and was not performed in the remaining patients. CMV immunohistochemistry or in situ hybridization was not performed, because CMV disease was not clinically suspected at the time of biopsy. None of patients had prior history of recurrent aphthous stomatitis. Ulcers were relatively large (ranging from 1 to 2 cm in diameter), deep and painful, most commonly affecting tongue and buccal mucosa. Apart from the index patient (Patient 4 in **Table 1**), two patients were treated with topical corticosteroids (budesonide, triamcinolone), resulting in rapid clinical improvement (**Figure 2**). Recurrence during steroid taper occurred in several cases, suggesting persistent immune activation. In two other patients ulcers resolved without use of corticosteroids. Despite complete clinical recovery, one ulcer recurred 2.5 years later in Patient 5 and again responded well to treatment with topical steroids.

At ulcer onset, none of the cases suffered from neutropenia. Despite the presence of local T-cell–dominant inflammatory infiltrates, peripheral T-cell counts remained low due to lymphodepletion. At the time of ulcer onset, CD4+ T-cell counts were below 200 × 10^6/L in all of three evaluated patients, while only one patient showed rapid CD8+ T-cell reconstitution (**Figure 2**). Also profound B-cell aplasia resulted in severe hypogammaglobulinemia, present in all evaluated patients, potentially impairing humoral immunity within mucosal barrier tissues. As for peripheral CAR T-cell expansion, circulating CAR T cells peaked at levels ranging from 23 to 220 *10^6/L at day 7-14 post-infusion and were detectable at low to medium-high levels at time of ulcer onset, ranging from 1 to 47 *10^6 cells/L (expansion data available in 3 of 5 evaluated patients).

CAR T-cell therapy leads to profound remodeling of the immune system. Persistent CAR T-cell activity results in sustained B-cell aplasia, ongoing antigenic stimulation, and may contribute to sustained immune activation that perturbs mucosal immune homeostasis. Barrier tissues such as oral and intestinal mucosa depend on tightly regulated interactions among T cells, antigen-presenting cells, regulatory B cells, cytokines and microbiota. Disruption of this equilibrium may predispose to localized inflammatory s .yndromes.[6-9] Interestingly, the intestinal microbiome has emerged as an important determinant of CAR T-cell therapy outcomes, with specific microbial compositions associated with improved response and reduced toxicity, while the CAR T treatment process (including lymphodepleting chemotherapy, broad antimicrobial exposure, and immune activation) disturbs microbiome composition, potentially altering barrier immune homeostasis.[10,11] Disturbances in oral microbiome composition are indeed believed to contribute to ulcer formation in the general population, and altered microbiota–immune crosstalk may therefore represent a plausible contributing or amplifying factor.[12] The T-cell– and histiocyte-rich inflammatory infiltrate observed in biopsy specimens supports a T-cell–driven local inflammatory process. Direct identification of CAR T cells within affected tissue was technically not feasible, and we therefore cannot distinguish between CAR-positive and bystander T cells as contributors to the infiltrate. However, a substantial level of circulating CAR T cells in one patient and detectable levels in the two other assessed patients, together with profound B-cell aplasia and hypogammaglobulinemia, support ongoing post–CAR T immune disequilibrium as a plausible background for mucosal inflammation. Importantly, all patients were in durable complete metabolic remission at ulcer onset, arguing against lymphoma infiltration as an explanatory mechanism. Moreover, extensive infectious work-up did not support a causative infectious etiology; positive fungal cultures in two cases were interpreted as colonization rather than the primary cause. Together, these observations suggest that delayed oral ulceration after CAR T-cell therapy may represent a clinically visible manifestation of disturbed immune homeostasis at mucosal barrier interfaces.

Delayed oral ulceration shows similarities with IEC-associated enterocolitis, as both may occur beyond the acute CRS/ICANS window, involve mucosal barrier tissues, and show predominantly T-cell–rich inflammatory infiltrates. These parallels suggest that oral ulceration may represent an anatomically restricted manifestation within a broader spectrum of delayed barrier tissue inflammation after CAR T-cell therapy. Important differences remain. IEC-associated enterocolitis has been described mainly after BCMA-directed CAR T-cell therapy and available reports suggest a more directly CAR T-cell–mediated, IBD-like phenotype, supported by detection of CAR-positive tissue-infiltrating T cells, enrichment of α4β7-expressing circulating CAR T cells, and response to vedolizumab. By contrast, our cases occurred after CD19-directed CAR T-cell therapy, presented without gastrointestinal symptoms suggestive of enterocolitis, and did not allow direct CAR T-cell detection in oral tissue. To our knowledge, IEC-associated enterocolitis reports have not described concomitant oral ulcerations, and the clinical picture is dominated by colitis. Moreover, oral ulcers in our series were highly corticosteroid-responsive, whereas IEC-associated enterocolitis may require targeted immunosuppression, directed at TNFα or α4β7-integrins. We therefore consider delayed oral ulceration potentially related to, but clinically and anatomically distinct from, IEC-associated enterocolitis.

Classical chemotherapy-induced mucositis typically occurs within weeks of cytotoxic exposure, correlates with neutropenia, and resolves with marrow recovery. In contrast, the ulcerations in this series occurred several months after lymphodepletion, developed in the absence of severe neutropenia, showed a recurrent pattern, and required immunosuppressive therapy. Recognition of delayed mucosal inflammatory phenotypes following CAR T-cell therapy is clinically relevant. Misclassification as infectious stomatitis may lead to unnecessary antimicrobial escalation. Early initiation of immunosuppressive therapy may reduce morbidity and improve quality of life. Based on our clinical experience, we recommend to initiate therapy with topical corticosteroids and if ineffective escalate to systemic treatment with sufficient tapering time before discontinuation.

Because case ascertainment was retrospective and depended on clinical documentation in institutional follow-up registries, the observed frequency should not be interpreted as a definitive incidence estimate. Incomplete CMV assessment, including the absence of systematic CMV PCR and tissue-based CMV testing, represents an additional limitation of the retrospective dataset. In addition, the study lacks in-depth mechanistic tissue profiling, and prospective studies incorporating immunophenotyping, CAR T-cell tissue detection, and cytokine profiling are needed to validate and mechanistically define this entity.

In conclusion, we describe a reproducible phenotype of delayed, recurrent, steroid-responsive oral ulceration occurring several months after CD19 CAR T-cell therapy. Together with recent reports of immune effector cell–associated enterocolitis, these findings suggest that mucosal barrier tissues may represent a shared site of delayed inflammatory toxicity after CAR T-cell therapy. As CAR T-cell therapy expands into earlier treatment lines and broader patient populations, long-term surveillance for organ-specific inflammatory sequelae will become increasingly important. Recognition of barrier tissue inflammatory phenotypes may refine long-term risk stratification and survivorship monitoring in CAR T recipients.

This research was conducted in line with the Declaration of Helsinki. Ethical approval of the Medical Ethical Committee was obtained for the registry database study “Follow that CAR! A prospective observational cohort study on CAR T-cell therapy for B-cell malignancies in the Netherlands” (NL76835.018.21).

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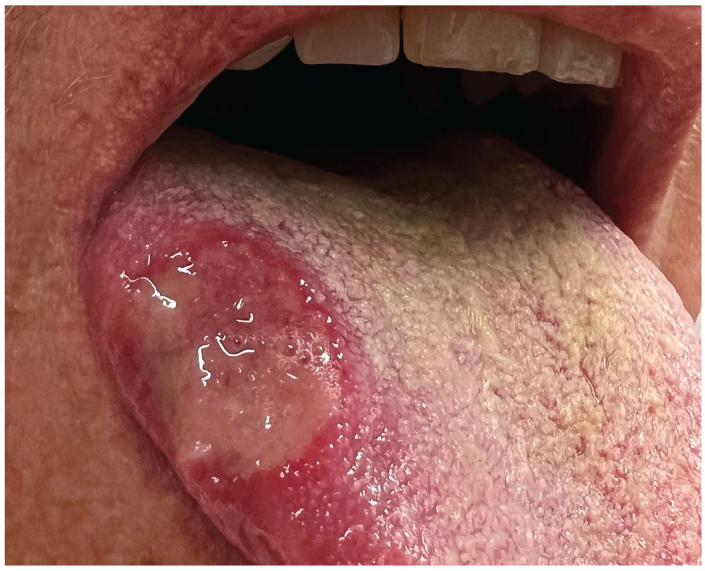
Patient ID	Gender	Age	Diagnosis by pathology	Stage	Extranodal localization	Product	CRS grade	ICANS grade	Timing of ulcer onset (days)	ANC at ulcer onset (*10^9 /L)	Remission status	Smoking status	HSV PCR	Treatment	Treatment response
Patient 1	Female	58	HGBCL	IV	Bone (skull)	Axi-cel	Grade 1	Grade 2	134	1.57	CMR	Past smoker	Negative	Antibiotic	Complete recovery
Patient 2	Female	69	HGBCL	IIE	Soft tissue (abdominal)	Axi-cel	Grade 0	Grade 0	167	0.60	PMR	Never smoked	Negative	Antifungal	Partial recovery
Patient 3	Male	66	DLBCL	IV	Spleen, bone marrow	Axi-cel	Grade 1	Grade 4	34	0.37	CMR	Never smoked	Negative	Local steroid	Complete recovery
Patient 4	Female	67	DLBCL	I	None	Axi-cel	Grade 2	Grade 3	165	0.98	CMR	Never smoked	Negative	Local and systemic steroid	Complete recovery
Patient 5	Male	56	DLBCL	II	None	Axi-cel	Grade 2	Grade 1	120	2.40	CMR	Past smoker	Negative	Local steroid	Complete recovery

Table 1 presenting characteristics of patients at baseline with toxicity and efficacy of axi-cel treatment and clinical evaluation and management of tongue ulcers.

Figure 1 - *Macroscopic image of the described ulcerative lesion on the tongue in patient 5 with corresponding histopathological images, showing an immune infiltrate of CD68+ histiocytes and T cells, predominantly CD8+ with weak expression of PD-1. CD79a immunohistochemical staining shows no infiltration of lymphoma cells.*

Figure 2. Systemic immune context and clinical course of delayed oral ulceration after CD19-directed CAR T-cell therapy. *Upper panels depict longitudinal routine laboratory and immune reconstitution parameters after CAR T-cell infusion: absolute neutrophil count, B-cell count, serum IgG level, circulating CAR T-cell count, CD8+ T-cell count, and CD4+ T-cell count. Each colored line represents an individual patient. Dashed horizontal lines indicate clinically relevant reference thresholds where applicable. The lower swimmer plot summarizes the clinical course of oral ulceration, including first response assessment after CAR T-cell therapy, time to ulcer onset, corticosteroid treatment, ulcer recovery, and ulcer recurrence. CMR indicates complete metabolic response; PMR, partial metabolic response.*

** Solid lines denote CAR-T cell measurements from fresh peripheral blood samples, whereas dotted lines denote measurements from frozen biobank samples, which should be interpreted descriptively because freeze–thawing may affect viable cell recovery.*



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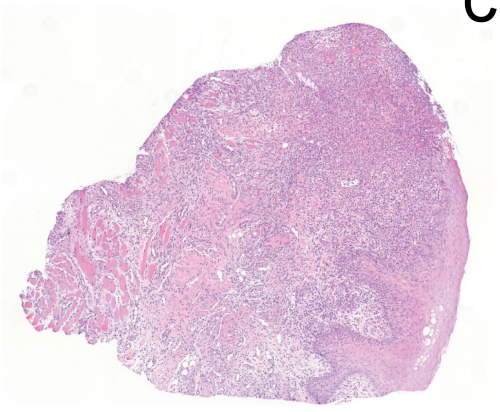

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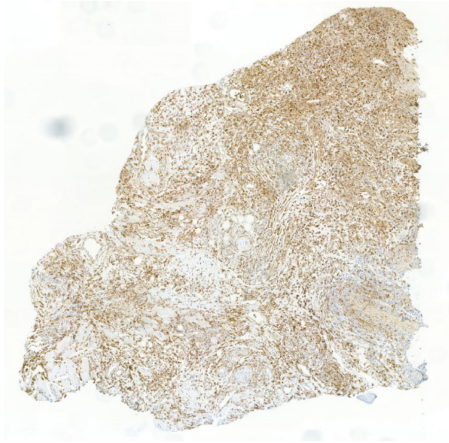

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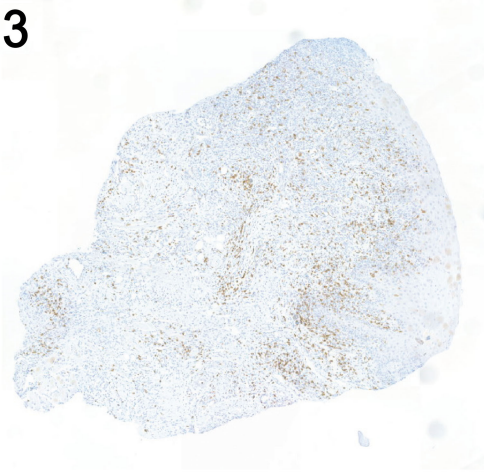

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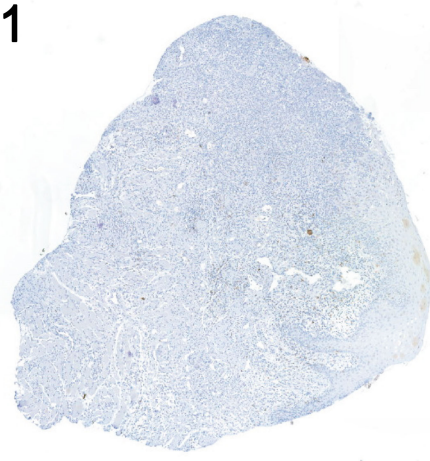

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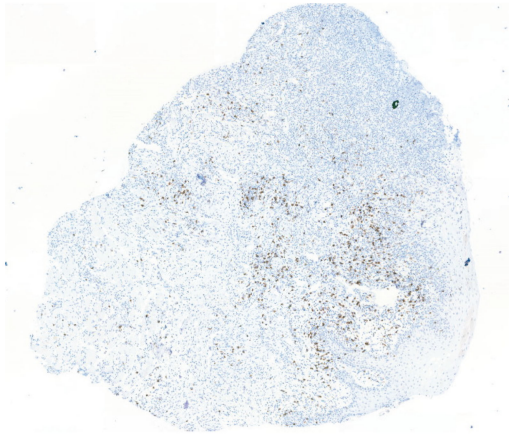
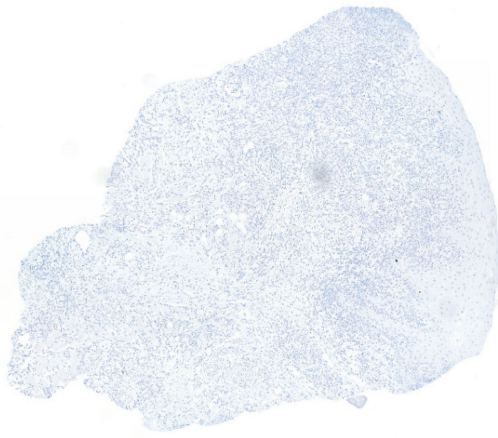
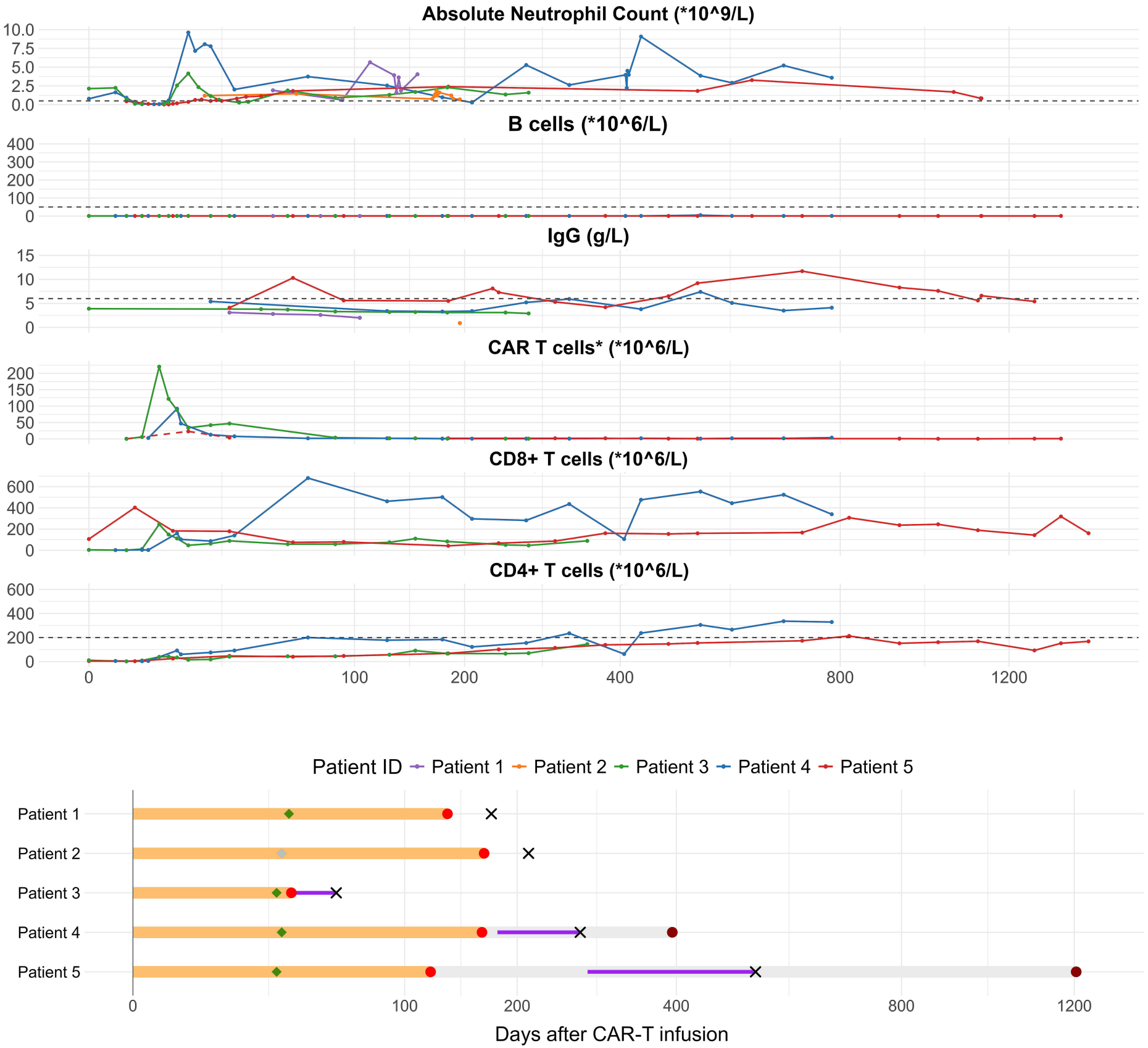


CD79a

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CAR T cells* (*10^6/L)
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Days after CAR-T infusion
Clinical events
Time until ulcer recurrence
Time until ulcer onset
Steroid Treatment
Ulcer Onset
Ulcer Recurrence
Ulcer Recovery
CMR
PMR