Local cytokine release syndrome with cervical angioedema following CAR-T cell therapy

Chimeric antigen receptor T-cell (CAR-T) therapy is associated with a spectrum of immune-related toxicities, most notably cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS), which are well characterized and managed through consensus grading systems.[1] However, as CAR-T indications expand, novel toxicities are increasingly recognized, including localized inflammatory reactions outside established CRS/ICANS frameworks.[2,3] Among these, local cytokine release syndrome (L-CRS) manifesting as cervical and laryngeal edema in the absence of local lymphadenopathy represents a distinct and potentially life-threatening complication that has not been completely characterized.[4-12] Here we present the first systematic evaluation of prevalence of L-CRS in a real-world setting. All patients who developed *de novo* cervical and/or laryngeal edema following CD19-directed or B-cell maturation antigen (BCMA)-directed CAR-T therapy between December 2020 and March 2025 were retrospectively identified from two CAR-T centers: Rambam Healthcare Campus, Haifa, Israel, and Soroka University Medical Center, Beer-Sheva, Israel. The study was approved by the institutional review boards (IRB) of Rambam Healthcare Campus (IRB #0475-24) and Soroka University Medical Center (IRB #0064-25).

As there are no consensus diagnostic criteria, following previously published reports,[4-12] L-CRS was defined clinically at both institutions as: 1) *de novo* cervical and/or laryngeal edema presenting post CAR-T infusion; 2) exclusion of pre-existing cervical lymphadenopathy per positron emission tomography-computed tomography (PET-CT) prior to CAR-T; 3) exclusion of infectious etiology based on clinical assessment, negative cultures and/or viral workup when indicated; 4) exclusion of drug-related hypersensitivity, supported by careful review of the electronic medical records to ensure no temporal relation to prior medication initiation, absence of urticaria and eosinophil elevations (noting that L-CRS appeared during the white blood cell [WBC] nadir) and rapid response to corticosteroids without discontinuation of concurrent medication; and 5) response to corticosteroid therapy. ICANS and CRS were diagnosed according to the European Society for Blood and Marrow Transplantation (EBMT)/European Hematology Association (EHA) CAR-T best practice recommendations.[1] In addition, we performed a comprehensive literature review, identifying 14 published cases meeting similar criteria.[4-12] The combined dataset encompasses 22 patients with well-characterized L-CRS (Table 1, *Online Supplementary Table S1*).

The two-center cohort of 173 CAR-T recipients had a median age of 65 years; 78 (45.1%) were female and 95 (54.9%) male. The predominant disease was diffuse large B-cell lymphoma (DLBCL, 71.7%), with the remainder comprising mantle cell lymphoma, follicular lymphoma (FL), high-grade B-cell lymphoma, primary mediastinal B-cell lymphoma, B-cell acute lymphoblastic leukemia (ALL), multiple myeloma (MM), and B-cell lymphoblastic lymphoma. CAR-T products were axicabtagene ciloleucel (axi-cel, 71.1%), tisagenlecleucel (tisa-cel, 22.0%), brexucabtagene autoleucel (5.8%), and idecabtagene vicleucel (ide-cel, 1.2%) (*Online Supplementary Table S2*).

In our two-center cohort, L-CRS prevalence was 4.6% (8/173), with marked inter-institutional variation: 1.6% (2/122) at Rambam *versus* 11.8% (6/51) at Soroka. These L-CRS patients included 4 males and 4 females with a median age of 67 years (range: 45-76). Underlying diseases were DLBCL (N=3), transformed FL (tFL, N=2), FL (N=1), and MM (N=2). The CAR-T products received included axi-cel (N=5), ide-cel (N=2), and tisa-cel (N=1) (*Online Supplementary Tables S1, S2*). An additional 5 patients who developed cervical lymphadenopathy during CAR-T therapy were excluded from the study: 2 cases were judged more consistent with tumor flare, 2 had pre-existing involvement of cervical lymph nodes at CAR-T initiation, and one had a cervical abscess in the region of the lymphadenopathy.

Local cytokine release syndrome onset occurred at a median of day 4 (range: 2-6) post infusion with a median duration of four days (range: 3-6). Patients presented with neck swelling, submandibular involvement, facial edema and dysphagia. One patient developed laryngeal involvement with dyspnea and underwent Ear, Nose and Throat (ENT) examination, revealing laryngeal narrowing (*Online Supplementary Figure S1*). Systemic CRS was present in all patients (8/8, 100%; grades 1-2) with median onset at day 1 (range: 0-2) and, notably, systemic CRS was ongoing at L-CRS onset in 7/8 patients (87.5%). ICANS developed in 5/8 patients (62.5%), with onset during or at L-CRS resolution in 4/5 cases (Table 1).

All 8 patients received corticosteroid therapy after L-CRS occurrence. In over half of the patients (5/8, 62.5%), steroids had already been initiated for systemic CRS prior to L-CRS onset (median: 1 day before; range: 0-3 days). In these cases, L-CRS developed despite ongoing steroid treatment, and dose escalation or additional dosing were required upon L-CRS presentation. One patient received steroids one day after L-CRS onset, but the indication for treatment was prolonged systemic CRS (Figures 1, 2).

Table 1. Clinical manifestations and outcomes of local cytokine release syndrome cases: two-center cohort and cases from literature review.

Case	CRS Gr, days	CRS Tx (start)	ICANS Gr, days, Tx (start)	L-CRS days, location	L-CRS treatment	Ref
1	Gr2 D1-5	Toci (D2) Steroids (D3)	Gr3, D5-9 Anakinra (D5)	D3-5 Neck swelling	Steroids	-
2	Gr2 D1-6	Toci (D3) Steroids (D4)	Gr3, D7-22 Anakinra (D8)	D5-8 Neck swelling followed by facial swelling	Steroids	-
3	Gr1 D1-6	Toci (D2) Steroids (D2)	Gr1, D7-9 Steroids (D2)	D4-7 Parotid and submandibular gland enlargement	Steroids	-
4	Gr1 D1-5	Toci (D3)	None	D4-7 Parotid and submandibular gland enlargement, dysphagia	Steroids Antihist	-
5	Gr1 D1-3	Toci (D2) Steroids (D1)	Gr1, D1-2 Steroids (D2)	D4-6 Neck and throat swelling, dysphagia, mild dyspnea	Steroids	-
6	Gr2 D0-3	Toci (D1) Steroids (D1)	None	D2-6 Parotid and submandibular gland enlargement	Steroids	-
7	Gr1 D1-6	Toci (D3)	Gr1, D6-7 Steroids (D5)	D5-7 Neck swelling	Steroids	-
8	Gr1 D2-9	Toci (D5) Steroids (D7)	None	D6-11 Left neck swelling, then bilateral swelling	Steroids	-
9	Gr2 D6–8	Toci (D7) NSAID	Not reported	D8-11 Facial edema, neck swelling, dyspnea	Steroids, diuretic, FFP	Luan *et al.* (2021)[4]
10	Gr1 D1-7	Toci (D3)	Not reported	D5-7 Neck swelling, bilateral parotid and submandibular glands enlargement	None	Inoue *et al.* (2023)[5]
11	Gr1 D0-4	Toci (D2)	Not reported	D3-4 Cervical swelling, muffled voice	Steroids	Inoue *et al.* (2023)[5]
12	Gr1 D1-11	None	Not reported	D5-11 Cervical, parotid and submandibular swelling	Steroids	Ko *et al.* (2024)[6]
13	Gr1 D2-5	Toci (D2)	Not reported	D5 Cervical, parotid and submandibular swelling, laryngeal and pharyngeal edema, mild hypoxia and fever	Steroids Toci	Kawase *et al.* (2024)[7]
14	Gr1 D1-4	Toci (D1) Steroids (D1)	Not reported	D4 Cervical, parotid and submandibular swelling, pharyngeal edema, mild hypoxia and fever	Steroids Toci	Kawase *et al.* (2024)[7]
15	Gr1 D2-4	Toci (D2)	Not reported	D4 Bilateral parotid and submandibular gland swelling, laryngeal and pharyngeal edema, hoarseness and fever	Steroids	Kawase et al. (2024)[7]
16	Gr1 D2-6	Toci (D2)	None	D4-5 Cervical edema, dyspnea	Steroids	Nakamura *et al.* (2025)[8]

Continued on following page.

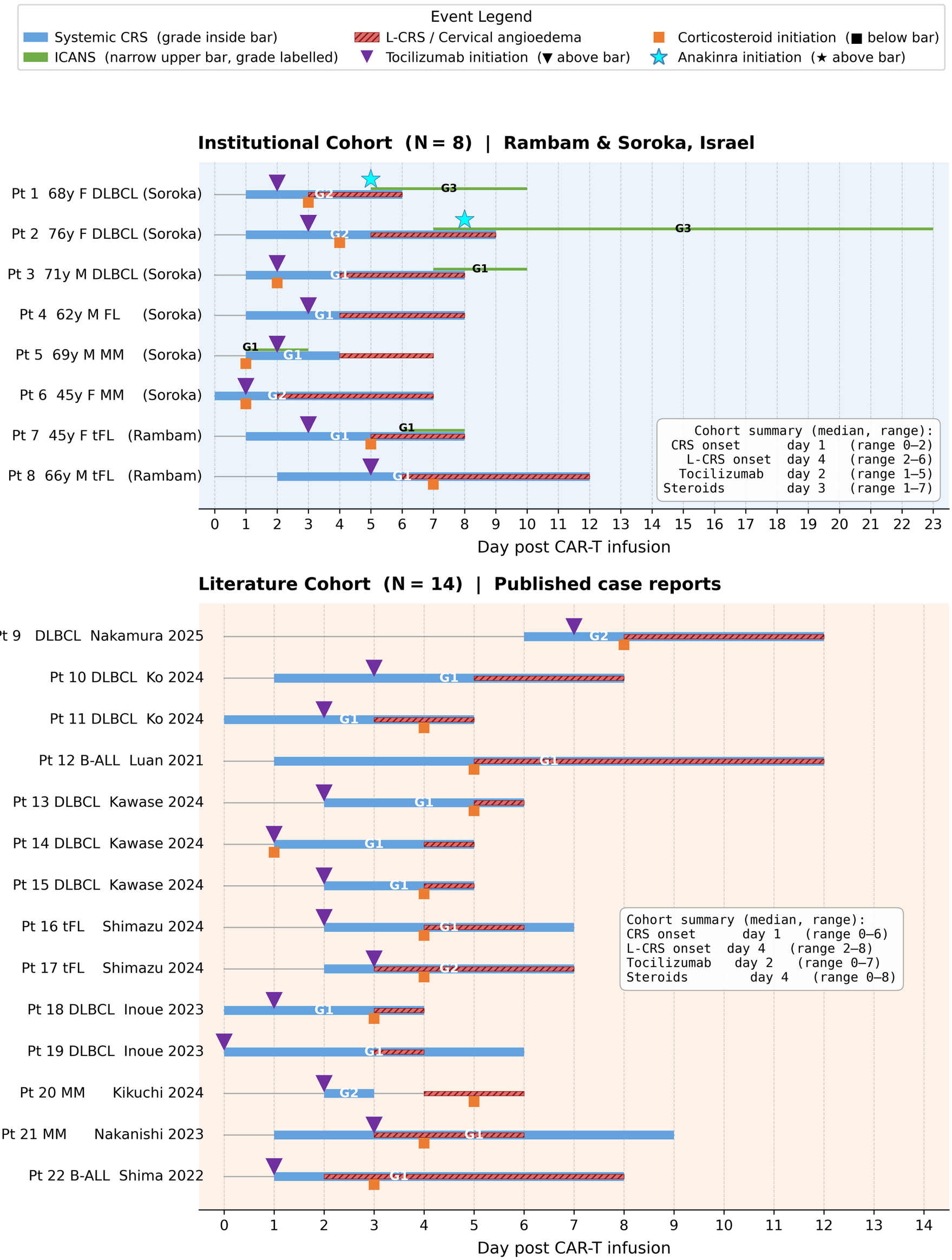
Case	CRS Gr, days	CRS Tx (start)	ICANS Gr, days, Tx (start)	L-CRS days, location	L-CRS treatment	Ref
17	Gr1 D2-6	Toci (D3)	None	D3-6 Facial and cervical swelling. Intubation	Steroids Toci	Nakamura *et al*. (2025)[8]
18	Gr1 D0-3	Toci (D1)	Not reported	D3 Cervical swelling, parotid and submandibular gland enlargement	Steroids	Kikuchi *et al*. (2024)[9]
19	Gr1 D0-5	Toci (D0) Steroids (D1)	Not reported	D3 Eyelid, cervical and parotid swelling	Steroids	Kikuchi *et al*. (2024)[9]
20	Gr2 D2	Toci (D2)	None	D4-5 Hoarseness, dyspnea, laryngeal edema	Steroids	Nakanishi *et al*. (2023)[10]
21	Gr1 D1-8	Toci (D3)	Not reported	D3-5 Neck swelling, laryngeal edema, difficulty swallowing	Steroids Toci	Shima *et al*. (2022)[11]
22	Gr1 D1-5	Toci (D1)	Not reported	D2-7 Cervical and facial swelling. Intubation	Steroids Toci	Shimazu *et al*. (2024)[12]

Cases 1-8: institutional cohort; Cases 9-22: literature cohort. Antihist: antihistamine; CAR-T: chimeric antigen receptor T-cell therapy; CRS: cytokine release syndrome; D: day post CAR-T; FFP: fresh frozen plasma; Gr: grade; ICANS: immune effector cell-associated neurotoxicity syndrome; L-CRS; local CRS; NSAID: non-steroidal anti-inflammatory drug; Ref: reference; Toci: tocilizumab; Tx: treatment.

The literature cohort comprised 14 cases from Asian centers[4-12] (Japan N=12, China N=1, Korea N=1) with similar demographics: median age 64.5 (range: 15-75); underlying diseases: DLBCL (N=6), tFL (N=2), B-ALL (N=3), and MM (N=3); CAR-T products: tisa-cel (N=8), ide-cel (N=3), liso-cel (N=2), and investigational anti-CD19 (N=1). Clinical presentations included neck swelling, new massive cervical lymphadenopathy, and laryngeal edema, with 2 cases (9.1%) requiring intubation or tracheostomy for life-threatening airway compromise[8,12] (Table 1). L-CRS onset was at a median of day 4 (range: 2-8), and median duration was two days (range: 1-7), with universal concurrent systemic CRS (14/14, 100%; grades 1-2). Notably, ICANS was not reported in any literature cases (0/14), contrasting with the 62.5% rate in our cohort. Tocilizumab was administered in 13/14 cases (93%), with L-CRS developing a median of two days after initiation of tocilizumab (range: 0-3 days) in all 13 recipients. Corticosteroids were administered in 13/14 cases (93%), with 2/14 patients (14.3%) having steroids initiated prior to L-CRS onset[4-12] (Table 1, Figures 1, 2).

Cytokine release syndrome is mediated by cytokines released from activated CAR-T cells and amplified by monocytes and macrophages.[13,14] The pathophysiology of L-CRS remains incompletely understood but appears related to CAR-T cell accumulation in cervical lymphoid tissues, triggering localized inflammatory cascades.[4,5,14] Across both cohorts, L-CRS emerged 0-3 days after tocilizumab initiation (median: 2 days), with 95% of cases developing despite prior or concurrent IL-6 receptor blockade (Figures 1, 2). This parallels CAR-T-associated neurotoxicity, for which Norelli *et al*. demonstrated that IL-1 receptor antagonism with anakinra prevented both CRS and neurotoxicity in a murine model, while tocilizumab prevented only CRS mortality.[13] These observations provide a rationale for investigating IL-1 receptor antagonism in L-CRS. Notably, in 2 patients in our cohort, L-CRS resolved on the same day anakinra was initiated for ICANS. The striking discordance in ICANS rates (62.5% in our two-center cohort *vs*. 0% in published case reports) most likely reflects reporting bias, but differences in patient populations, the CAR-T products used, and management protocols cannot be excluded. Whether L-CRS and ICANS share a common IL-1-driven mechanism warrants investigation.

Local cytokine release syndrome, as demonstrated in our two-center cohort and in previously published cases, can occur in lymphoid-rich cervical areas regardless of disease involvement at CAR-T infusion.[4-12] The cervical region contains abundant normal lymphoid tissue including tonsils, adenoids, and extensive lymph node chains, likely explaining the predilection for head and neck manifestations even in the absence of cervical disease.[5,11] CAR-T cell redistribution to these tissues following systemic overflow from tumor sites or bone marrow may explain why L-CRS typically follows systemic CRS onset.[4,5] Notably, Hagen *et al*. recently described an analogous phenomenon, local immune effector cell-associated toxicity syndrome



Continued on following page.

Figure 1. Swimmer plot depicting the temporal course of local cytokine release syndrome and associated events following chimeric antigen receptor T-cell infusion. (A) The two-center cohort (N=8; Rambam and Soroka, Israel) and (B) the literature cohort (N=14; published case reports). Each horizontal row represents one patient; the x-axis represents days post-chimeric antigen receptor T-cell (CAR-T) infusion; day 0 = day of CAR-T cell infusion. Blue bars indicate the duration of systemic cytokine release syndrome (CRS) (CRS grade labeled inside bar); red hatched bars indicate the duration of local cytokine release syndrome (L-CRS)/ cervical angioedema; narrow upper green bars indicate the duration of immune effector cell-associated neurotoxicity syndrome (ICANS) (grade labeled above bar). Symbols: orange squares (■) below the bar mark corticosteroid initiation; purple inverted triangles (▼) above the bar mark tocilizumab initiation; cyan stars (★) above the bar mark anakinra initiation. Cohort summary statistics (median and range) are displayed in the inset box for each panel.

(LICATS), affecting 77% of autoimmune disease patients receiving CD19-targeting CAR-T cells.[2] They proposed that rapid CAR-T-mediated killing of tissue-resident B cells overwhelms local phagocytic clearance, triggering localized inflammation.[2] Whether a similar mechanism underlies L-CRS in lymphoid-rich cervical tissues remains speculative and warrants further investigation. Alternatively, this may represent a more general phenomenon, but cervical involvement receives greater clinical attention because swelling in this region can result in life-threatening airway compromise.

Wei *et al*. proposed that L-CRS precedes and triggers systemic CRS through local CAR-T cell convergence on tumors with subsequent "overflow" into circulation.[14] However, across all 22 cases in the combined cohort (8 institutional and 14 from previous literature), systemic CRS preceded or coincided with L-CRS onset, suggesting that it is more likely that L-CRS represents a late localized manifestation within an already-activated systemic inflammatory response rather than its initiating trigger. The marked inter-institutional difference (11.8% at Soroka *vs*. 1.6% at Rambam) likely reflects differences in clinical vigilance, recognition practices, and patient populations. One notable institutional difference is that all CAR-T recipients at Soroka received prophylactic levetiracetam, whereas this was given to only a minority of patients at Rambam. Levetiracetam prophylaxis varies considerably across CAR-T centers; in a recent multicenter propensity-matched study, centers routinely prescribing it showed higher rates of grade 2-4 CRS (57.9% *vs*. 26.8%, *P*<0.001) and greater use of tocilizumab and steroids, suggesting that levetiracetam use reflects a higher-risk patient profile and more intensive institutional toxicity management.[15]

Notably, in our two-center cohort, L-CRS was observed disproportionately among the small MM subgroup treated with ide-cel, though limited numbers and disease-product co-linearity preclude any conclusions; this finding warrants further investigation. Furthermore, it should be noted that MM patients were exclusively treated at Soroka during the study period, and this may have also contributed to inter-institutional differences.

Combined, these findings have important clinical implications. With a prevalence of 4.6%, L-CRS is a clinically meaningful complication that warrants a standardized diagnostic approach and systematic surveillance. Importantly, L-CRS seems to develop despite treatment with tocilizumab and can emerge under ongoing corticosteroid therapy, often necessitating steroid dose escalation; therefore, IL-1 receptor antagonism warrants investigation as an alternative therapeutic target.[13] The striking discordance in ICANS rates (62.5% in our cohort *vs*. 0% in published cases) also deserves investigation, as does the apparent difference in prevalence between our two centers. Clinically, early recognition of progressive neck swelling, even in patients already receiving tocilizumab or steroids, mandates immediate evaluation for potential

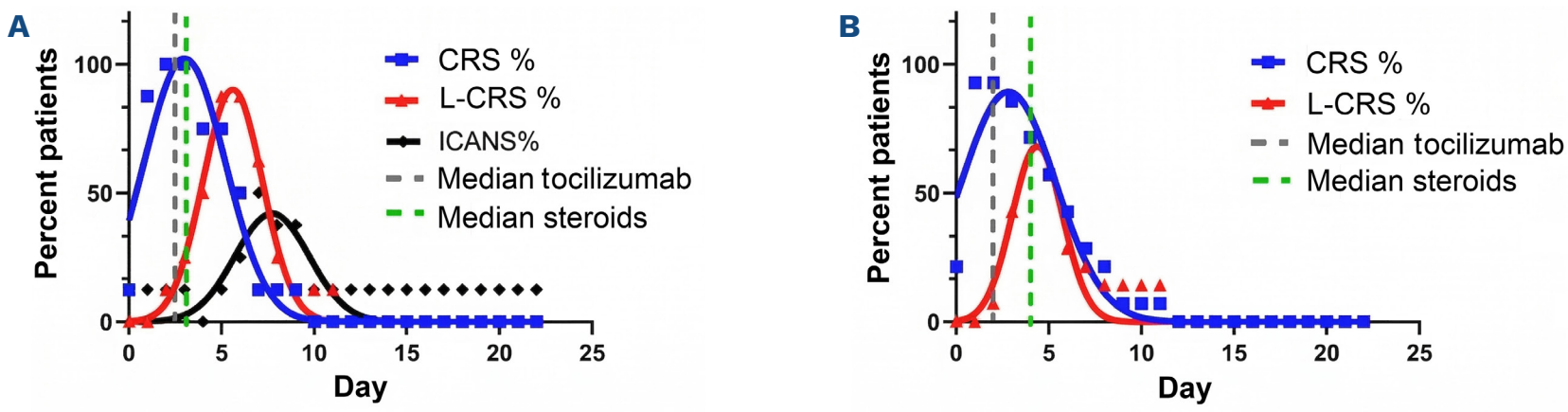


Figure 2. Timeline of toxicities and treatments following chimeric antigen receptor T-cell infusion in the 2-center cohort and literature review cohort. (A) The 2-center cohort and (B) the literature review cohort. Curves depict the percentage of patients experiencing systemic cytokine release syndrome (CRS) (blue), local cytokine release syndrome (L-CRS)/ (red), and immune effector cell-associated neurotoxicity syndrome (ICANS) (black, only (A)) at each day following chimeric antigen receptor T-cell (CAR-T) infusion. Data points represent observed percentages; lines represent locally fitted smoothing curves. Vertical dashed lines indicate the median day of first tocilizumab (gray dashed) and corticosteroid (green dashed) administration. Day 0 = day of CAR-T cell infusion.

airway involvement and steroid administration or dose escalation.[8,12]

Authors

Karney Lahad,[1,2*] Ofrat Beyar-Katz,[1,2*] Mohamad Dallasheh,[1,2] Niveen Shibli,[1,2] Shimrit Ringelstein-Harlev,[1,2] Maria Zektzer,[3,4] Dana Yehudai-Ofir,[1,2] Tsila Zuckerman,[1,2] Noam Tomasis Damri,[3,4] Uri Greenbaum[3,4#] and Limor Cohen[5#]

[1]Department of Hematology and Bone Marrow Transplantation, Rambam Health Care Campus, Haifa; [2]Ruth and Bruce Rappaport Faculty of Medicine, Technion, Haifa; [3]Department of Hematology, Soroka University Medical Center, Beer Sheva; [4]Faculty of Health and Science, Ben Gurion University of the Negev, Beer Sheva and [5]Department of Nursing, Faculty of Health Sciences, Ben Gurion University, Beer-Sheva, Israel

**KL and OB-K contributed equally as first authors.*
[#]UG and LC contributed equally as senior authors.

Correspondence:
K. LAHAD - karneylahad482@gmail.com

https://doi.org/10.3324/haematol.2026.300481

Received: January 10, 2026.
Accepted: April 14, 2026.
Early view: April 23, 2026.

©2026 Ferrata Storti Foundation
Published under a CC BY-NC license

Disclosures
No conflicts of interest to disclose.

Contributions
OB-K and UG conceived the study, contributed substantially to study design, data collection and analysis, and to manuscript drafting and revision. KL and LC led the team in carrying out the study, contributed substantially to study design, data collection and analysis, and to manuscript drafting and revision. MD, NS, SR-H, MZ, DY-O, TZ and NTD provided patient care and contributed to data collection.

Data-sharing statement
The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

1. Hayden PJ, Roddie C, Bader P, et al. Management of adults and children receiving CAR T-cell therapy: 2021 best practice recommendations of the European Society for Blood and Marrow Transplantation (EBMT) and the Joint Accreditation Committee of ISCT and EBMT (JACIE) and the European Hematology Association (EHA). Ann Oncol. 2022;33(3):259-275.
2. Hagen M, Müller F, Wirsching A, et al. Local immune effector cell-associated toxicity syndrome in CAR T-cell treated patients with autoimmune disease: an observational study. Lancet Rheumatol. 2025;7(6):e424-e433.
3. Rejeski K, Hill JA, Dahiya S, Jain MD. Noncanonical and mortality-defining toxicities of CAR T cell therapy. Nat Med. 2025;31(7):2132-2146.
4. Luan C, Zhou J, Wang H, et al. Case report: local cytokine release syndrome in an acute lymphoblastic leukemia patient after treatment with chimeric antigen receptor T-cell therapy. Front Immunol. 2021;12:707191.
5. Inoue Y, Fujino T, Chinen S, et al. Cervical local cytokine release syndrome following chimeric antigen receptor T-cell therapy in patients with relapsed or refractory diffuse large B-cell lymphoma. Cureus. 2023;15(5):e38905.
6. Ko JS, Lee JH, Yoon DH, et al. CT demonstration of local cytokine-release syndrome involving the head and neck following chimeric antigen receptor T cell infusion therapy. Korean J Radiol. 2024;25(4):399-402.
7. Kawase S, Sakurai M, Masuda K, et al. Salivary gland swelling as a characteristic manifestation of local cytokine release syndrome after anti-CD19 chimeric antigen receptor T cell therapy: a case series. J Clin Exp Hematop. 2024;64(3):261-267.
8. Nakamura N, Jo T, Arai Y, et al. Severe cases of local cytokine release syndrome (CRS); craniocervical edema soon after chimeric antigen T-cell (CAR-T) therapy. Oxf Med Case Reports. 2025;2025(1):omae164.
9. Kikuchi T, Tsukada N, Kunisada K, Nomura-Yogo M, Ishida T. Local cytokine release syndrome after idecabtagene vicleucel therapy in patients with multiple myeloma: two case reports. Cureus. 2024;16(10):e72364.
10. Nakanishi Y, Marumo Y, Ri M, et al. Laryngeal edema as a symptom of local cytokine release syndrome after BCMA-targeting CAR-T therapy for relapsed and refractory multiple myeloma. Int J Hematol. 2023;118(5):647-651.
11. Shima H, Kurosawa T, Oikawa H, et al. Cervical edema extending to the larynx as local cytokine release syndrome following chimeric antigen receptor T-cell therapy in a boy with refractory acute lymphoblastic leukemia. Case Rep Oncol. 2022;15(1):257-262.
12. Shimazu R, Nakamura N, Goto T, et al. Transformed follicular lymphoma with laryngeal edema requiring tracheal intubation after tisagenlecleucel treatment: a case report. Medicine (Baltimore). 2024;103(36):e39630.
13. Norelli M, Camisa B, Barbiera G, et al. Monocyte-derived IL-1 and IL-6 are differentially required for cytokine-release syndrome and neurotoxicity due to CAR T cells. Nat Med. 2018;24(6):739-748.
14. Wei J, Liu Y, Wang C, et al. The model of cytokine release syndrome in CAR T-cell treatment for B-cell non-Hodgkin lymphoma. Signal Transduct Target Ther. 2020;5(1):134.
15. Galli E, Di Blasi R, Di Rocco A, et al. Routine prophylaxis with levetiracetam offers no benefit in CD19 CAR-T for LBCL: a multicenter propensity-matched study. Blood Adv. 2025;9(21):5501-5509.