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

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Running head: L-CRS with cervical angioedema after CAR-T

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CAR-T cell 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 been incompletely characterized[4-12]. Here we present the first systematic evaluation of L-CRS prevalence in a real-world setting.

All patients who developed de novo cervical and/or laryngeal edema following CD19- or 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 of Rambam Healthcare Campus (IRB #0475-24) and Soroka University Medical Center (IRB #0064-25).

As no consensus diagnostic criteria exist, L-CRS was defined clinically at both institutions, following prior published reports,[4–12] as: (1) de novo cervical and/or laryngeal edema appearing post-CAR-T infusion; (2) exclusion of pre-existing cervical lymphadenopathy per 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 revealing no temporal relation to prior medication initiation, absence of urticaria and eosinophil elevations (noting that L-CRS appeared during the 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 EBMT/EHA CAR-T best practice recommendations[1]. Additionally, we performed a comprehensive literature review, identifying 14 published cases meeting similar criteria[4-12]. The combined dataset (Table 1, Supplementary Table S1) encompasses 22 patients with well-characterized L-CRS.

The two-center cohort of 173 CAR-T recipients had a median age of 65; 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, 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%). (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. The cohort included 4 males and 4 females with a median age of 67 years (range 45-76). Underlying diseases compromised DLBCL (n=3), transformed FL (tFL, n=2), FL (n=1), and MM (n=2). CAR-T products included axi-cel (n=5), ide-cel (n=2), and tisa-cel (n=1). (Supplementary tables S1 and S2) An additional five patients who developed cervical lymphadenopathy during CAR-T therapy were excluded from the study: two cases were judged more consistent with tumor flare, two had pre-existing involvement of cervical lymph nodes at CAR-T initiation, and one had a cervical abscess in the region of the lymphadenopathy.

L-CRS onset occurred at median day 4 (range 2-6) post-infusion with a median duration of 4 days (range 3-6). Patients presented with neck swelling, submandibular involvement, facial edema and dysphagia. One patient developed laryngeal involvement with dyspnea and underwent ENT examination, revealing laryngeal narrowing (Supplementary figure 1). Systemic CRS was universally present (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 eight 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 and 2).

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 encompassed neck swelling, new massive cervical lymphadenopathy, and laryngeal edema, with two cases (9.1%) requiring intubation or tracheostomy for life-threatening airway compromise[8,12] (table 1). L-CRS onset was at median day 4 (range 2-8), median duration 2 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 2 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 and 2).

CRS 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 and 2). This parallels CAR-T-associated neurotoxicity, where 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 two 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 versus 0% in published case reports - most likely reflects reporting bias, but differences in patient populations, CAR-T products, and management protocols cannot be excluded. Whether L-CRS and ICANS share a common IL-1-driven mechanism warrants investigation.

L-CRS, as demonstrated in our 2-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 (LICATS), affecting 77% of autoimmune disease patients receiving CD19-targeting CAR-T cells, proposing 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 L-CRS more likely 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 versus 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 only a minority at Rambam did. 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 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 versus 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 airway involvement and steroid administration or dose escalation[8,12].

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Table 1. Clinical Manifestations and Outcomes of L-CRS Cases- Two- center cohort and cases from literature review (n=22)

Case	CRS (Gr, Days)	CRS Treatment (start)	ICANS (Gr, Days, Tx)	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	4
10	Gr1 D1–7	Toci (D3)	Not Reported	D5–7 Neck swelling, bilateral parotid and submandibular glands enlargement	None	5
11	Gr1 D0–4	Toci (D2)	Not Reported	D3–4 Cervical swelling, muffled voice	Steroids	5
12	Gr1 D1–11	None	Not Reported	D5–11 Cervical, parotid and submandibular swelling	Steroids	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	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	7
15	Gr1 D2–4	Toci (D2)	Not Reported	D4 Bilateral parotid and submandibular gland swelling, laryngeal and pharyngeal edema, hoarseness and fever	Steroids	7
16	Gr1 D2–6	Toci (D2)	None	D4–5 Cervical edema, dyspnea	Steroids	8
17	Gr1 D2–6	Toci (D3)	None	D3–6 Facial and cervical swelling. Intubation	Steroids Toci	8
18	Gr1 D0–3	Toci (D1)	Not Reported	D3 Cervical swelling, parotid and submandibular gland enlargement	Steroids	9
19	Gr1 D0–5	Toci (D0) Steroids (D1)	Not Reported	D3 Eyelid, cervical and parotid swelling	Steroids	9
20	Gr2 D2	Toci (D2)	None	D4–5 Hoarseness, dyspnea, laryngeal edema	Steroids	10
21	Gr1 D1–8	Toci (D3)	Not Reported	D3–5 Neck swelling, laryngeal edema, difficulty swallowing	Steroids Toci	11
22	Gr1 D1–5	Toci (D1)	Not Reported	D2–7 Cervical and facial swelling. Intubation	Steroids Toci	12

Cases 1–8: Institutional cohort; Cases 9–22: Literature cohort. Abbreviations: Gr = grade; D = day post-CAR-T; Tx = treatment; Toci = tocilizumab; Antihist = antihistamine; FFP = fresh frozen plasma; NSAID = nonsteroidal anti-inflammatory drug.

Figure 1. Swimmer plot depicting the temporal course of L-CRS and associated events following CAR-T cell infusion.

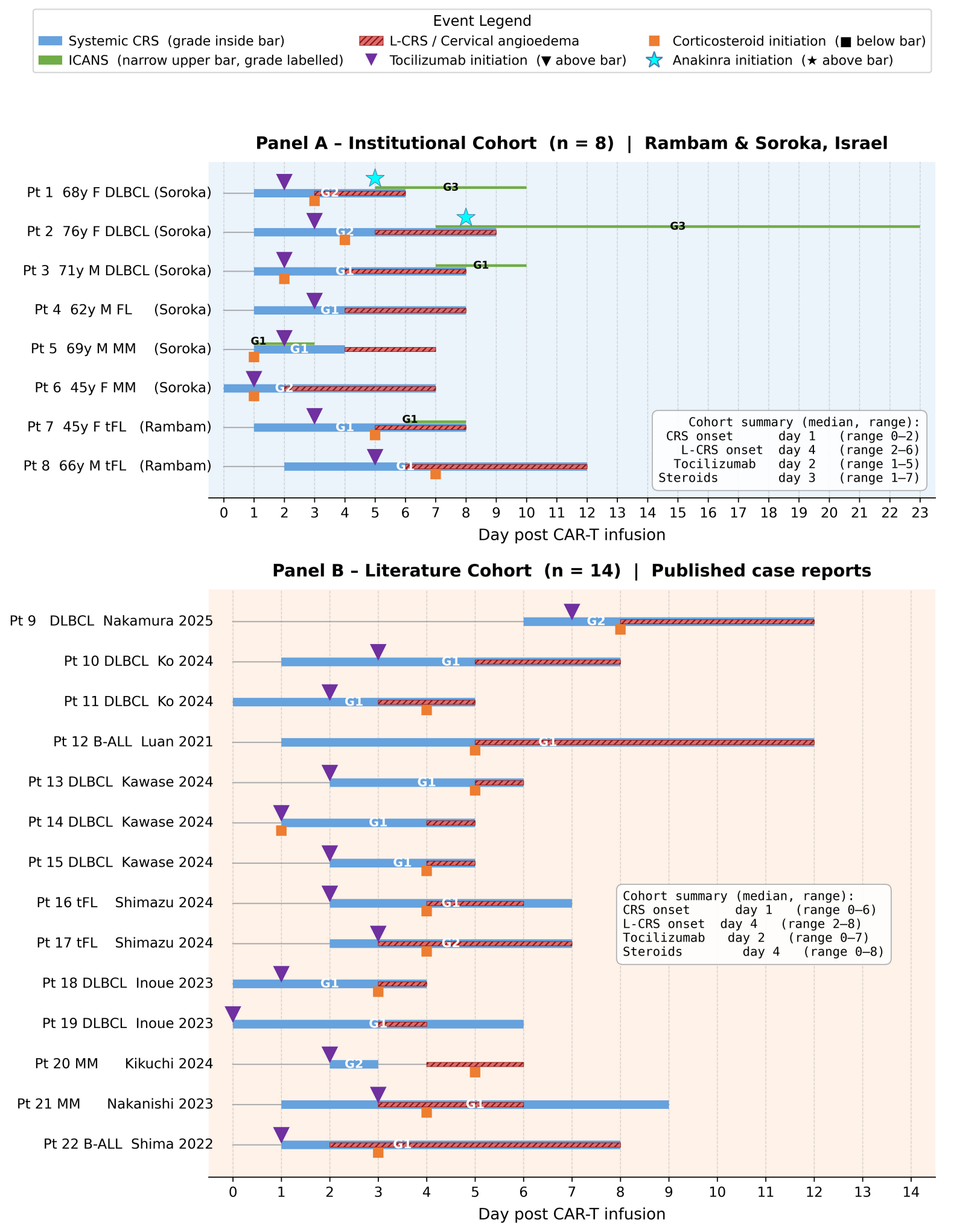
Panel A shows the 2-center cohort (n=8; Rambam and Soroka, Israel) and Panel B shows the literature cohort (n=14; published case reports). Each horizontal row represents one patient; the x-axis represents days post-CAR-T infusion, day 0 = day of CAR-T cell infusion. Bar colors: blue bars indicate the duration of systemic CRS (CRS grade labeled inside bar); red hatched bars indicate the duration of L-CRS/cervical angioedema; narrow upper green bars indicate the duration of 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.

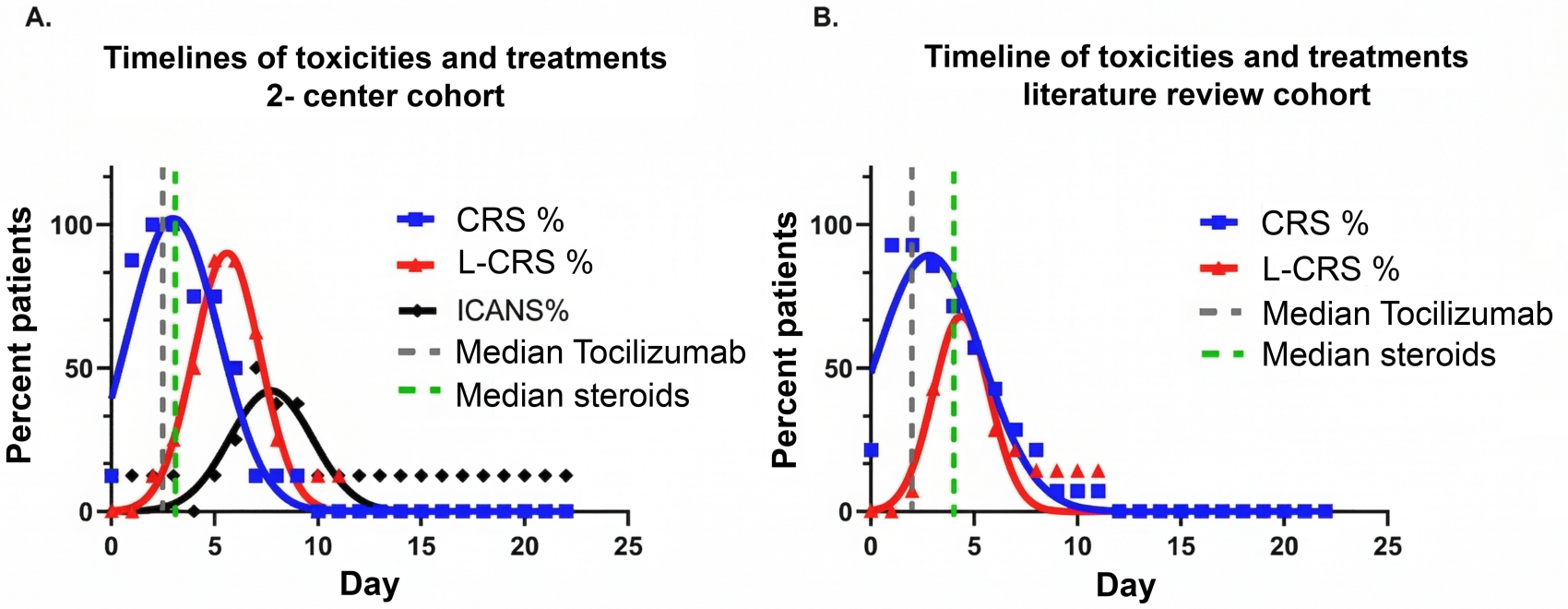
CAR-T, chimeric antigen receptor T-cell; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; L-CRS, local cytokine release syndrome.

Figure 2. Timeline of toxicities and treatments following CAR-T cell infusion in the 2-center cohort and literature review cohort.

Panel A shows the 2-center cohort and Panel B shows the literature review cohort. Curves depict the percentage of patients experiencing systemic CRS (blue), L-CRS (red), and ICANS (black, Panel A only) at each day following 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.

CAR-T, chimeric antigen receptor T-cell; CRS, cytokine release syndrome; L-CRS, local cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome.


Event Legend
Systemic CRS (grade inside bar)
L-CRS / Cervical angioedema
Corticosteroid initiation (■ below bar)
ICANS (narrow upper bar, grade labelled)
Tocilizumab initiation (▼ above bar)
Anakinra initiation (★ above bar)
Panel A – Institutional Cohort (n = 8) | Rambam & Soroka, Israel
Pt 1 68y F DLBCL (Soroka)
Pt 2 76y F DLBCL (Soroka)
Pt 3 71y M DLBCL (Soroka)
Pt 4 62y M FL (Soroka)
Pt 5 69y M MM (Soroka)
Pt 6 45y F MM (Soroka)
Pt 7 45y F tFL (Rambam)
Pt 8 66y M tFL (Rambam)
Cohort summary (median, range):
CRS onset day 1 (range 0–2)
L-CRS onset day 4 (range 2–6)
Tocilizumab day 2 (range 1–5)
Steroids day 3 (range 1–7)
Day post CAR-T infusion
Panel B – Literature Cohort (n = 14) | Published case reports
Pt 9 DLBCL Nakamura 2025
Pt 10 DLBCL Ko 2024
Pt 11 DLBCL Ko 2024
Pt 12 B-ALL Luan 2021
Pt 13 DLBCL Kawase 2024
Pt 14 DLBCL Kawase 2024
Pt 15 DLBCL Kawase 2024
Pt 16 tFL Shimazu 2024
Pt 17 tFL Shimazu 2024
Pt 18 DLBCL Inoue 2023
Pt 19 DLBCL Inoue 2023
Pt 20 MM Kikuchi 2024
Pt 21 MM Nakanishi 2023
Pt 22 B-ALL Shima 2022
Cohort summary (median, range):
CRS onset day 1 (range 0–6)
L-CRS onset day 4 (range 2–8)
Tocilizumab day 2 (range 0–7)
Steroids day 4 (range 0–8)
Day post CAR-T infusion


A.
Timelines of toxicities and treatments
2- center cohort
Percent patients
100
50
0
0
5
10
15
20
25
Day
CRS %
L-CRS %
ICANS%
Median Tocilizumab
Median steroids
B.
Timeline of toxicities and treatments
literature review cohort
Percent patients
100
50
0
0
5
10
15
20
25
Day
CRS %
L-CRS %
Median Tocilizumab
Median steroids

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

Supplementary Table S1. Patient Demographics and Disease Characteristics in patients with L-CRS from the 2-center cohort and from literature review (n=22)

Case	Age/Sex	Disease	CAR-T	Bridging	Ref
1	68/F	DLBCL	Axi-cel	GEMOX	-
2	76/F	DLBCL	Axi-cel	HD-MTX	-
3	71/M	DLBCL	Axi-cel	GEMOX	-
4	62/M	FL	Tisa-cel	None	-
5	69/M	MM	Ide-cel	None	-
6	45/F	MM	Ide-cel	None	-
7	45/F	FL→DLBCL	Axi-cel	RT	-
8	66/M	FL→DLBCL	Axi-cel	GEMOX	-
9	61/F	B-ALL	CD19 CAR-T	Dasatinib+VP	4
10	60/M	DLBCL (ref)	Tisa-cel	Pola-BR+RT	5
11	70/M	DLBCL (rel)	Tisa-cel	R-GCD	5
12	20/F	B-ALL	Tisa-cel	Not clear	6
13	75/M	DLBCL	Liso-cel	Pola-BR+CHASER	7
14	73/M	DLBCL	Liso-cel	R-DEVIC	7
15	71/F	DLBCL	Tisa-cel	Pola-BR	7
16	64/M	DLBCL	Tisa-cel	RT+Pola-BR	8
17	59/F	FL→DLBCL	Tisa-cel	R-ESHAP	8
18	65/F	MM	Ide-cel	Carfilzomib+dexa	9
19	65/M	MM	Ide-cel	Carfilzomib+dexa	9
20	54/F	MM	Ide-cel	RT	10
21	15/M	B-cell precursor ALL	Tisa-cel	Inotuzumab+imatinib	11
22	67/F	FL→DLBCL	Tisa-cel	Pola-BR	12

Cases 1–8: Institutional cohort; Cases 9–22: Literature cohort. Abbreviations: DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; MM = multiple myeloma; B-ALL = B-cell acute lymphoblastic leukemia; ref = refractory; rel = relapsed; Axi-cel = axicabtagene ciloleucel; Tisa-cel = tisagenlecleucel; Liso-cel = lisocabtagene maraleucel; Ide-cel = idecabtagene vicleucel; HD-MTX = high-dose methotrexate; GEMOX = gemcitabine + oxaliplatin; RT = radiotherapy; Pola-BR = polatuzumab + bendamustine + rituximab; VP = vincristine + prednisone; dexa = dexamethasone. R-GCD=Rituximab, Gemcitabine, Carboplatin, and Dexamethasone; CHASER=Cyclophosphamide, High-dose Cytarabine, Dexamethasone, Etoposide, and Rituximab; R-DeVIC= Rituximab, Dexamethasone, Etoposide, Ifosfamide and Carboplatin; R-ESHAP= Etoposide, Methylprednisolone Cytarabine and Cisplatin.

Supplementary Table S2. Baseline characteristics of the two-center institutional CAR-T cohort (n = 173)

Characteristic	Overall cohort (n = 173)	L-CRS (n = 8)	No L-CRS (n = 165)
Demographics			
Median age, years (range)	65.2 (range 19-86)	67 (range 45–76)	65.0 (range 19-86)
Female sex, n (%)	78 (45.1%)	4 (50.0%)	74 (44.8%)
Male sex, n (%)	95 (54.9%)	4 (50.0%)	91 (55.2%)
Underlying disease, n (%)			
DLBCL‡	124 (71.7%)	5 (62.5%)	119 (72.1%)
Mantle cell lymphoma	14 (8.1%)	0 (0.0%)	14 (8.5%)
Follicular lymphoma	13 (7.5%)	1 (12.5%)	12 (7.3%)
High-grade B-cell lymphoma	8 (4.6%)	0 (0.0%)	8 (4.8%)
PMBCL	6 (3.5%)	0 (0.0%)	6 (3.6%)
B-ALL	5 (2.9%)	0 (0.0%)	5 (3.0%)
Multiple myeloma	2 (1.2%)	2 (25.0%)	0 (0.0%)
B-cell lymphoblastic lymphoma	1 (0.6%)	0 (0.0%)	1 (0.6%)
CAR-T product, n (%)			
Axicabtagene ciloleucel (axi-cel)	123 (71.1%)	5 (62.5%)	118 (71.5%)
Tisagenlecleucel (tisa-cel)	38 (22.0%)	1 (12.5%)	37 (22.4%)
Brexucabtagene autoleucel (brexu-cel)	10 (5.8%)	0 (0.0%)	10 (6.1%)
Idecabtagene vicleucel (ide-cel)	2 (1.2%)	2 (25.0%)	0 (0.0%)

Abbreviations: DLBCL, diffuse large B-cell lymphoma; PMBCL, primary mediastinal B-cell lymphoma; B-ALL, B-cell acute lymphoblastic leukemia; L-CRS, local cytokine release syndrome.

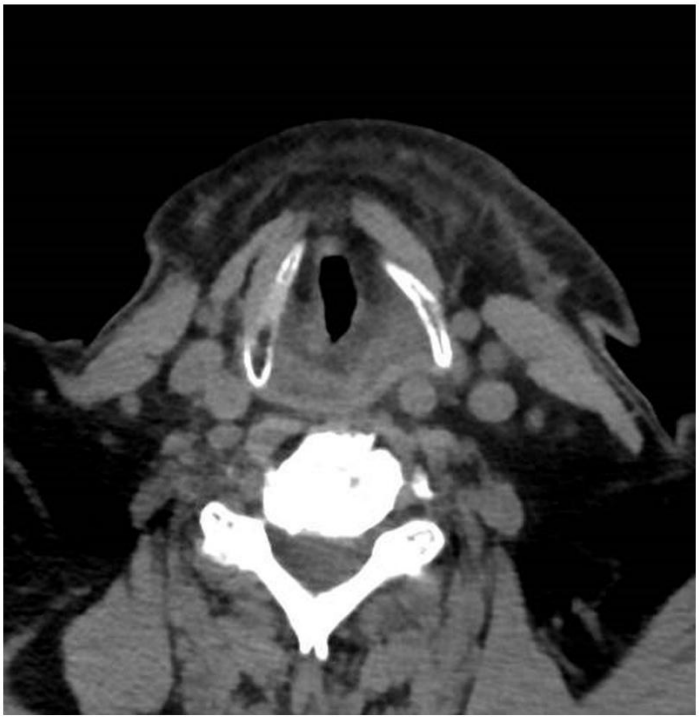
‡ Includes 2 cases of FL transformation to DLBCL (both in the L-CRS group).

No formal statistical comparisons were performed given the small number of L-CRS events (n = 8).

Supplementary Figure S1. Computerized tomography images demonstrating rapidly progressing, pending airway obstruction in a patient with L-CRS from our cohort.

Panel A shows an axial view at the level of the oropharynx; Panel B shows an axial view at a lower cervical level demonstrating narrowing of the airway lumen. Symptoms resolved after steroid administration without reaching intubation.

A



B