IO-Nebenwirkungen: Fokus auf seltene “Adverse Events” der CAR-T Zelltherapie

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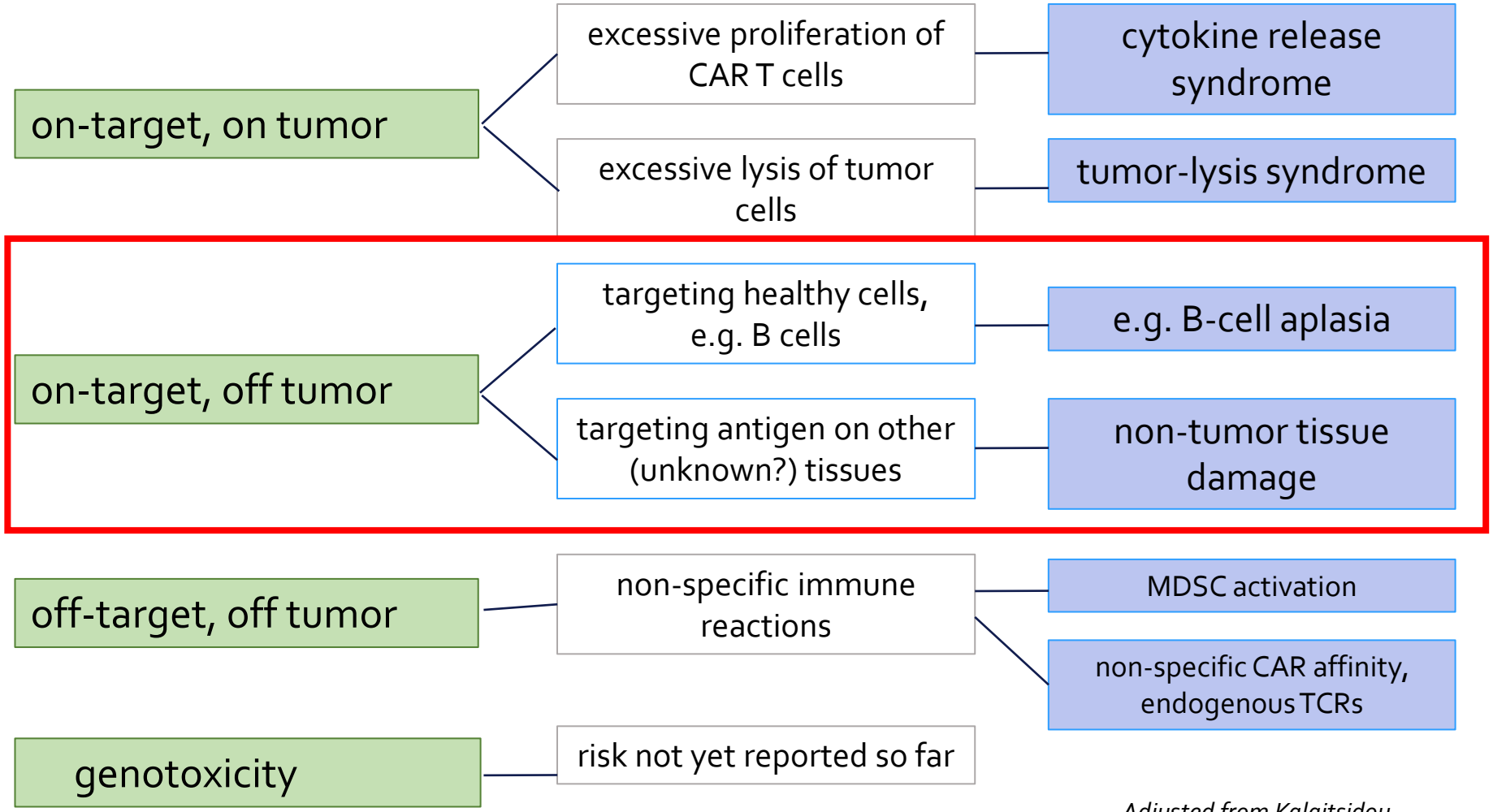
Professor of Cell Therapy and Transfusion Medicine

13.10.2023

Offenlegung Interessenskonflikte

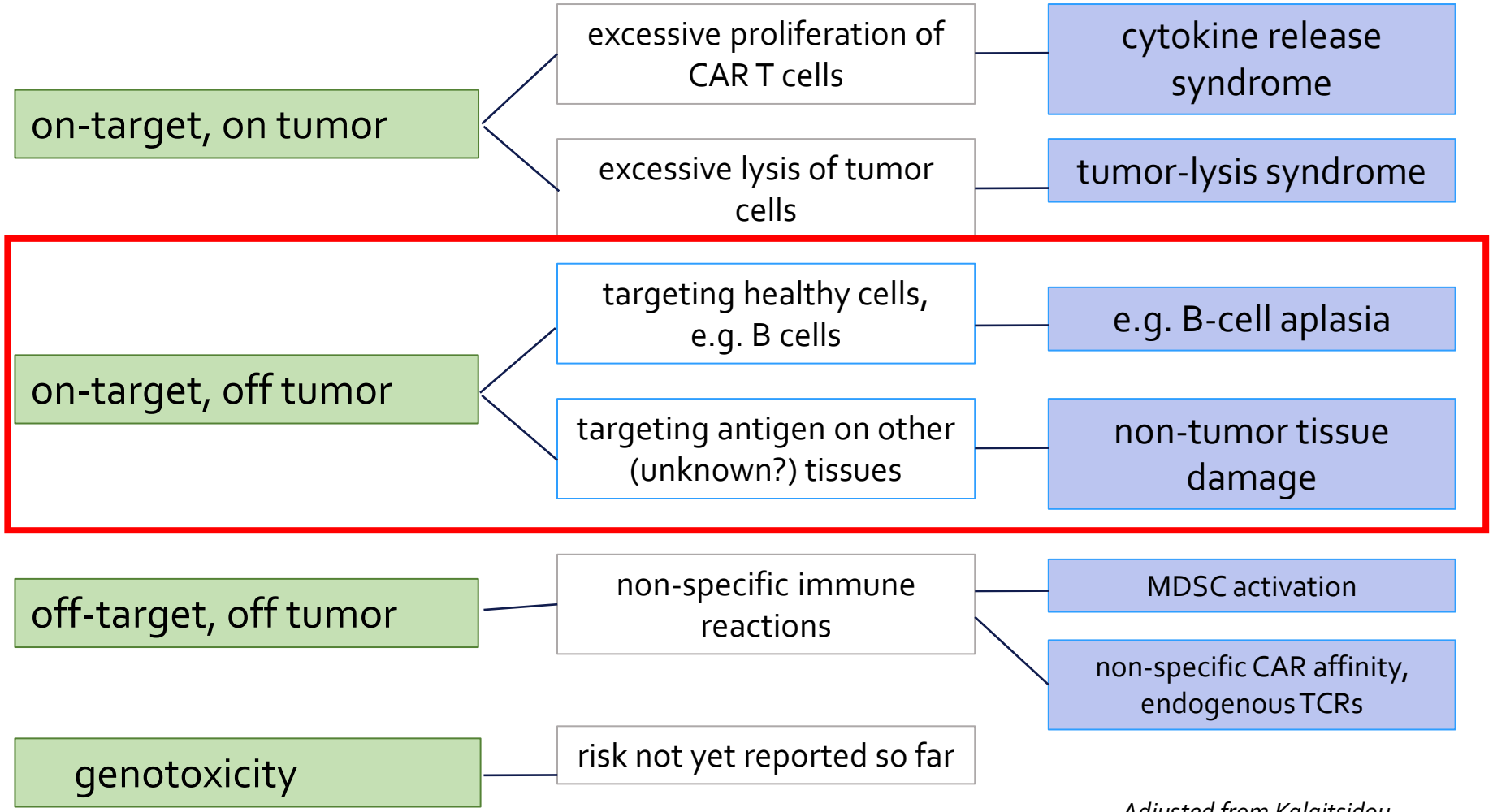
1. Anstellungsverhältnis oder Führungsposition:	keines
2. **Beratungs- bzw. Gutachtertätigkeit:**	**Novartis, KITE/Gilead, Janssen**
3. Besitz von Geschäftsanteilen, Aktien oder Fonds:	keine
4. Patent, Urheberrecht, Verkaufslizenz:	keine
5. **Honorare für Vorträge / Advisory Boards:**	**Novartis, KITE/Gilead, Janssen, Celgene/BMS**
6. Finanzierung wissenschaftlicher Untersuchungen:	keine
7. Andere finanzielle Beziehungen:	keine
8. Immaterielle Interessenkonflikte:	keine

CAR-T toxicities



Adjusted from Kalaitsidou, Immunotherapy 2015

CAR-T toxicities



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CAR-T cells for solid tumors

- *Clinicaltrials.gov* >1300 registered studies on CAR-T
- many "new" targets
  - GPC3 (glypican-3; hepatocellular carcinoma)
  - GD2 (neuroblastoma)
  - IL13Ra2 (glioblastoma)
  - EGFRvIII (epidermal growth factor receptor variant 3) → Glioblastoma
  - CEA / CEACAM5(GIT tumors)
  - ERBB2
  - EpCAM
  - ICAM-1 (thyroid cancer)
- most tumor-associated antigens are only weakly immunogenic
- most TAA are not exclusive, but are also found on other healthy cells

Case Report of a Serious Adverse Event Following the Administration of T Cells Transduced With a Chimeric Antigen Receptor Recognizing *ERBB2*

Richard A Morgan[1], James C Yang[1], Mio Kitano[1], Mark E Dudley[1], Carolyn M Laurencot[1] and Steven A Rosenberg[1]

- Pt. with metastatic ERBB2⁺ colon cancer (mets in lung, liver)
- optimized γ-retroviral CAR vector containing CD28, 4-1BB, CD3ζ
- within 15min after cell infusion respiratory distress → pulmonary infiltrates / edema → intubation @ 1h post infusion → death after 5 days
- Post-mortem / autopsy
  - multiple organs exhibited signs of systemic ischemia and microangiopathic injury
  - lungs: diffuse alveolar damage
  - highest levels of vector-containing cells in the lung + abdominal and mediastinal LN, but no particular accumulation in metastatic sites

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Postulation on cause of death

- transfer of highly active anti-ERBB2 directed T cell
- upon first-pass clearance in the lung recognition of ERBB2 on normal lung cells
- release of inflammatory cytokines
- pulmonary toxicity with edema
- + cascading cytokine storm
- multi-organ failure
- investigators speculated that CAR-Ts localized in the lung due to low expression of ERBB2 on epithelial cells

Common Adverse Reactions in ≥ 10% of Patients Treated with YESCARTA in ZUMA-7

Table 3. Adverse Reactions in ≥ 10% of Patients Treated with YESCARTA in ZUMA-7

Adverse Reaction	YESCARTA N = 168	
	Any Grade (%)	Grade 3 or Higher (%)
Febrile neutropenia	31	31
Cardiac Disorders		
Tachycardia [a]		
Arrhythmia [b]		
Gastrointestinal Disorders		
Diarrhea [c]		
Nausea		
Abdominal pain [d]		
Constipation		
Vomiting		
Dry Mouth		
General Disorders and Administration Site C		
Fever [e]		
Fatigue [f]		
Chills		
Edema [g]		
Immune System Disorders		
Cytokine release syndrome		
Hypogammaglobulinemia		
Infections and Infestations		
Infections with pathogen unspecified	25	8
Viral infections	15	4
Bacterial infections	10	5
Fungal infections	10	1

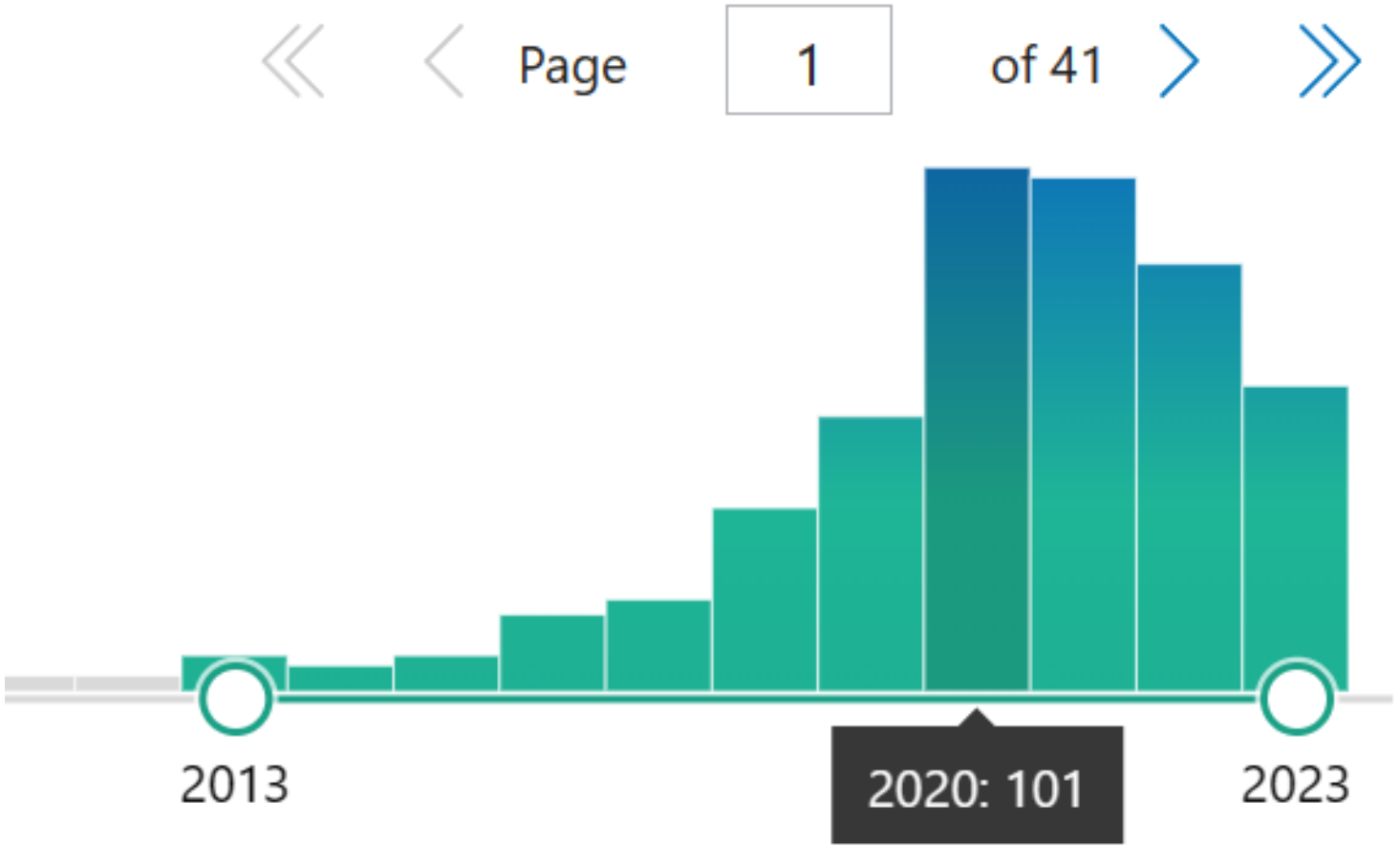
- Cytokine Release Syndrome
- Neurologic Toxicities
- Hypersensitivity Reactions
- Serious Infections
- Prolonged Cytopenias
- Hypogammaglobulinemia

Adverse Reaction	YESCARTA N = 168	
	Any Grade (%)	Grade 3 or Higher (%)
Metabolism and Nutrition Disorders		
Decreased appetite	24	4
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain [h]	40	1
Motor dysfunction [i]	15	4
Nervous System Disorders		
Encephalopathy [j]	46	18
Headache [k]	41	3
Tremor	25	1
Dizziness [l]	25	4
Aphasia	20	7
Neuropathy peripheral [m]	11	2
Psychiatric Disorders		
Insomnia [n]	13	0
Delirium [o]	12	4
Renal and Urinary Disorders		
Renal insufficiency [p]	11	2
Respiratory, Thoracic and Mediastinal Disorders		
Cough [q]	27	1
Hypoxia	21	9
Skin and Subcutaneous Tissue Disorders		
Rash [r]	17	1
Vascular Disorders		
Hypotension [s]	47	11

Other clinically important adverse reactions that occurred in less than 10% of patients treated with YESCARTA include the following

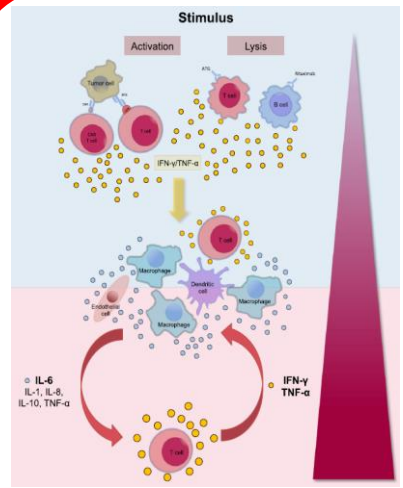
- Blood and lymphatic system disorders: Coagulopathy (9%)
- Cardiac disorders: Cardiac failure (1%)
- Eye Disorders: Visual impairment (7%)
- Infections and infestations: Pneumonia (8%), Sepsis (4%)
- Nervous system disorders: Ataxia (6%), seizure (3%), myoclonus (2%), facial paralysis (2%), paresis (2%)
- Respiratory, thoracic and mediastinal disorders: Dyspnea (8%), pleural effusion (6%), respiratory failure (2%)
- Vascular disorders: Hypertension (9%), thrombosis (7%)

Pubmed Search „Chimeric Antigen Receptor T cells and Case Report“



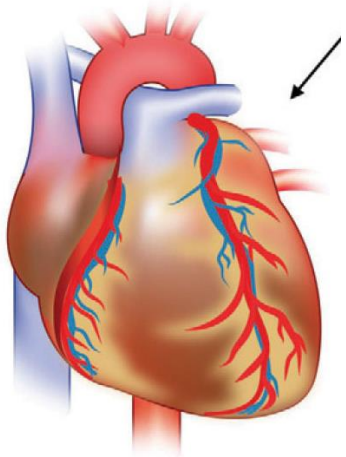
Rare toxicities and complications can be grouped

Cellular infiltration, Inflammation, cytokine release

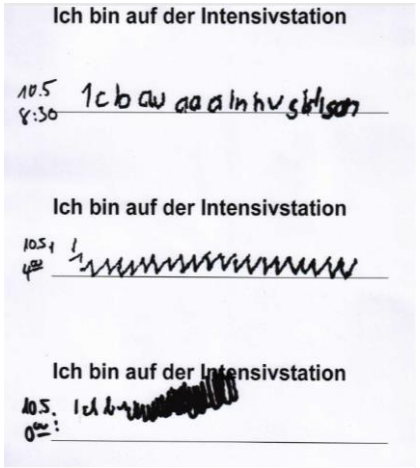


Shimabukuro-Vornhagen et al. Journal for Immuno Therapy of Cancer (2018) 6:56

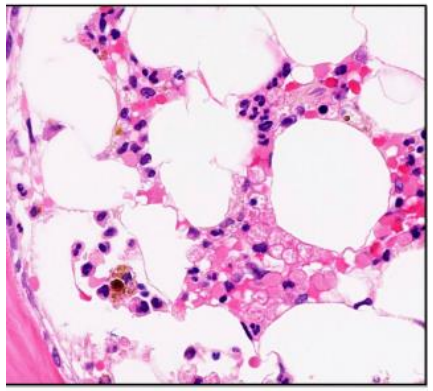
Cardiovascular complications



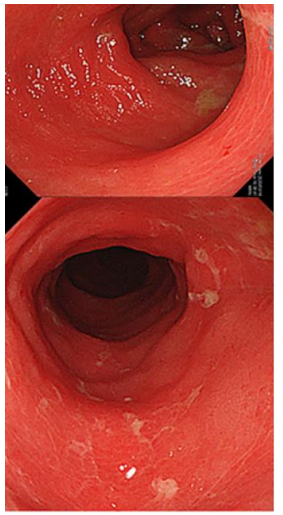
Complications affecting neuronal structures a/o functions



Hematopoietic complications



"Other" complications



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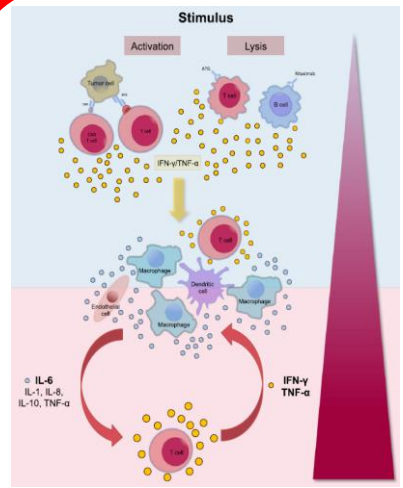

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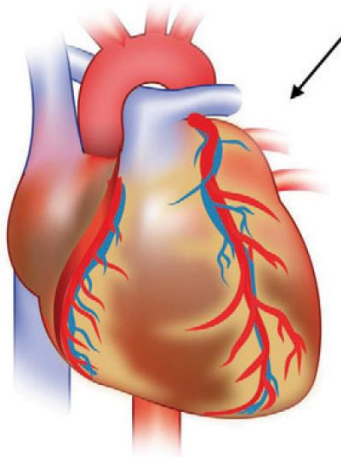

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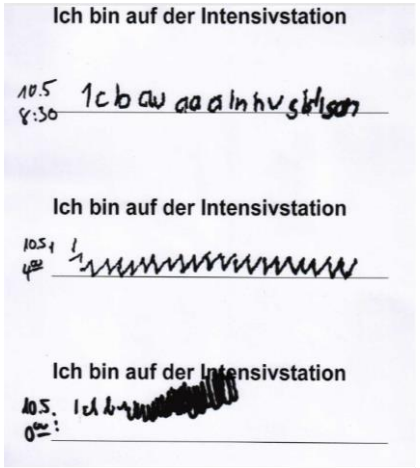

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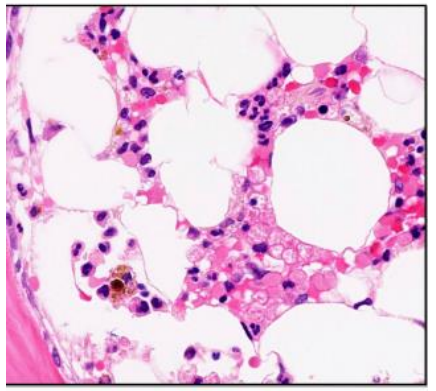

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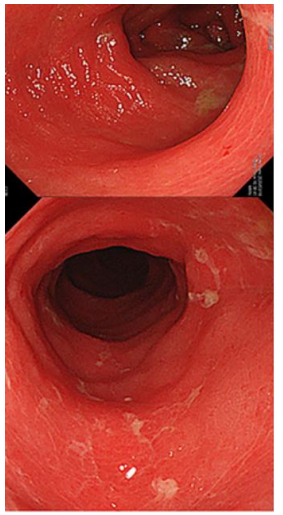


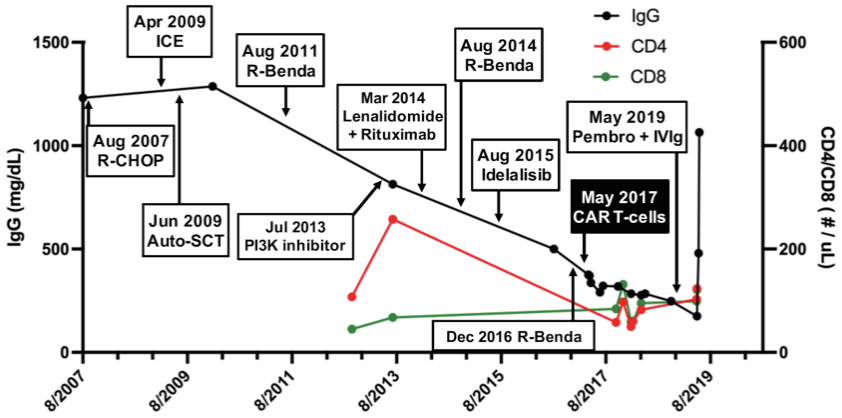
Infectious complications

Infectious complications related to immune dysfunction (not specifically CAR-T)

Case Report J Hematol. 2021;10(5):212-216

Progressive Multifocal Leukoencephalopathy After Chimeric Antigen Receptor T-Cell Therapy for Recurrent Non-Hodgkin Lymphoma

Jared T. Ahrendsen[a], Kartik Sehgal[b], Sasmit Sarangi[c], Erik J. Uhlmann[c], Hemant Varma[a], Jon Arnason[b], David Avigan[b, d]



Serum immunoglobuline levels

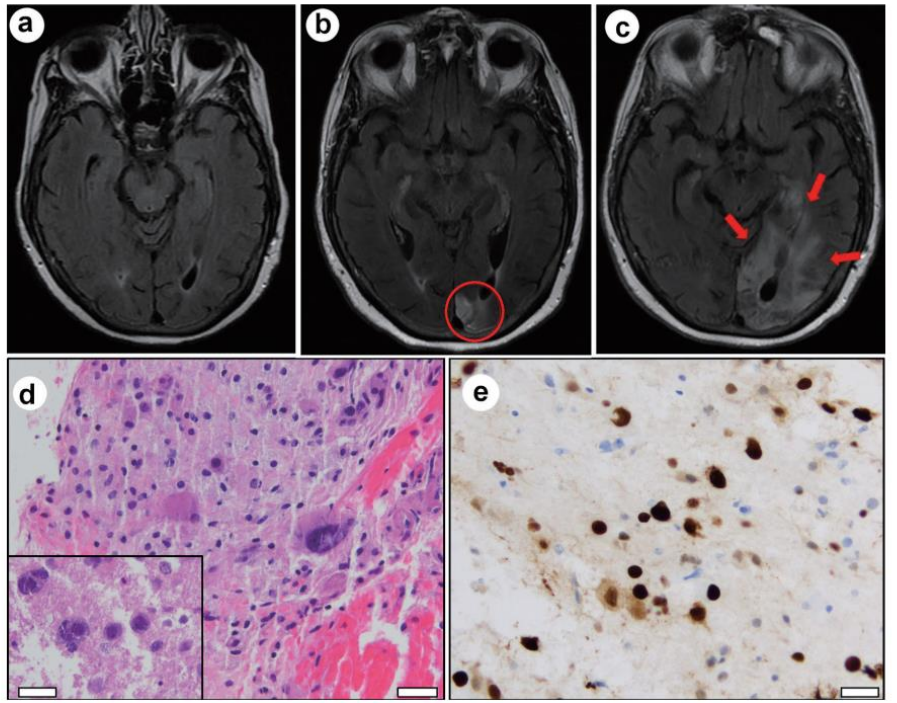
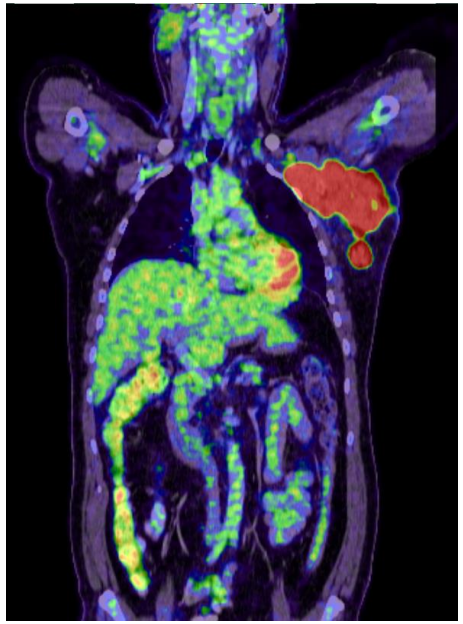


Figure 2. Magnetic resonance imaging evolution and brain biopsy. (a) FLAIR signal abnormality was absent in May 2017 at the time of CAR T-cell infusion and prior to onset of neurological symptoms. (b) FLAIR signal abnormality in the left occipital lobe at the time of initial presentation for visual disturbance in April 2018 (red circle). (c) Expansion of FLAIR signal (red arrows) involving the left occipital lobe and left posterior temporal lobe in April 2019 after presentation with progressive word finding difficulty. Hematoxylin and eosin (H&E) stained sections from left occipital brain biopsy show (d) bizarre-appearing astrocytes and violaceous oligodendroglial nuclear inclusions (inset). Immunohistochemistry demonstrates strong nuclear positivity for SV-40 (e). White scale bars = 100 μm.

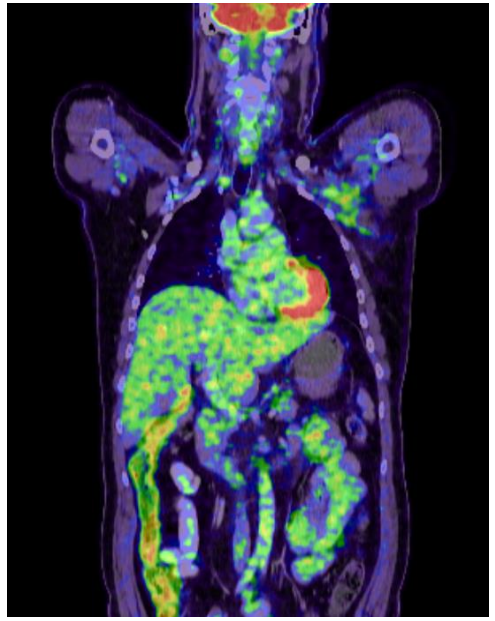
Infectious complications

Rare toxicities – related to CAR-T induced inflammation and cytokine release

- Patient L.C., diffus-large B cell lymphoma, refractory to 2 lines of therapy
- initially no CAR-T toxicities
- after 2 wks pain in the area of lymphoma/axillary LN, swelling, color, rubor

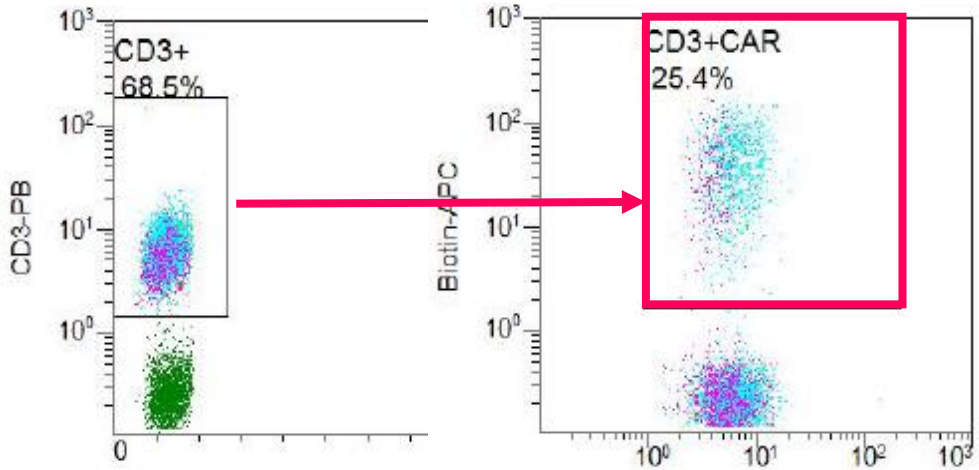


Pre-CART



2 m post CART

25% of T cells = CAR-T cells in blood!



DOI 10.3389/fimmu.2022.995496

Case report: Hashimoto's thyroiditis after CD19 chimeric antigen receptor T-cell therapy

Panpan Chen[1†], Yongming Xia[2†], Wen Lei[1], Shuhan Zhong[1], Huawei Jiang[1], Lingling Ren[1], Wenbin Qian[1] and Hui Liu[1*]

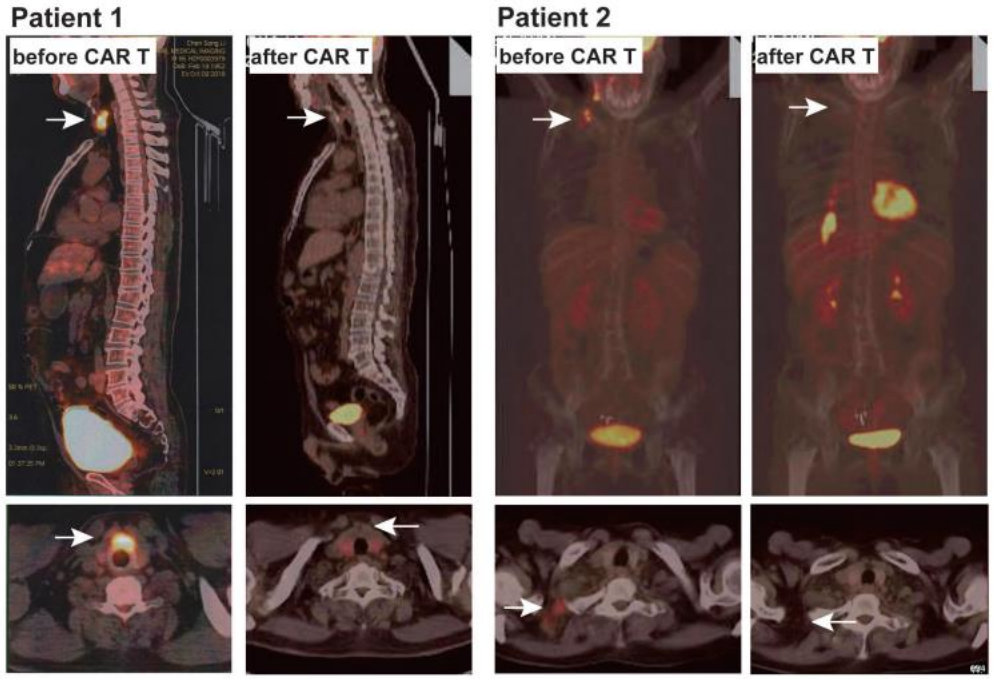


FIGURE 1
PET-CT images of two patients before and after CART treatment.

Patient 1

- 65y/o man with R/R DLBCL in thyroid
- → CAR-T → @3m in CR
- Ultrasound suggested thyroid nodule and thyroid inflammation
- Elevated anti-thyroid peroxidase antibody and thyroglobulin antibody, but normal thyroid function (T_3, T_4, TSH)

Patient 2

- 52y/o woman with R/R cervical DLBCL
- CAR-T → CR @1m post CAR-T
- Elevated TGAb, TMAb and TPOAb, but normal thyroid function

- **→ possibly direct toxicity of CAR-T cells or localized CRS/inflammatory damage**

DOI: 10.7759/cureus.38905

Cervical Local Cytokine Release Syndrome Following Chimeric Antigen Receptor T-cell Therapy in Patients With Relapsed or Refractory Diffuse Large B-cell Lymphoma

Yu Inoue [1], Takahiro Fujino [1], Shotaro Chinen [1], Yui Niiyama-Uchibori [1], Daisuke Ide [1], Moe Kawata [2], Keiko Hashimoto [2], Tomoko Takimoto-Shimomura [3], Ai Nakayama [3], Taku Tsukamoto [1], Shinsuke Mizutani [1], Yuji Shimura [1], Shigeru Hirano [2], Junya Kuroda [1]

1. Division of Hematology and Oncology, Department of Medicine, Kyoto Prefectural University of Medicine, Kyoto, JPN
2. Department of Otolaryngology-Head and Neck Surgery, Kyoto Prefectural University of Medicine, Kyoto, JPN 3. Department of Hematology, Otsu City Hospital, Otsu, JPN

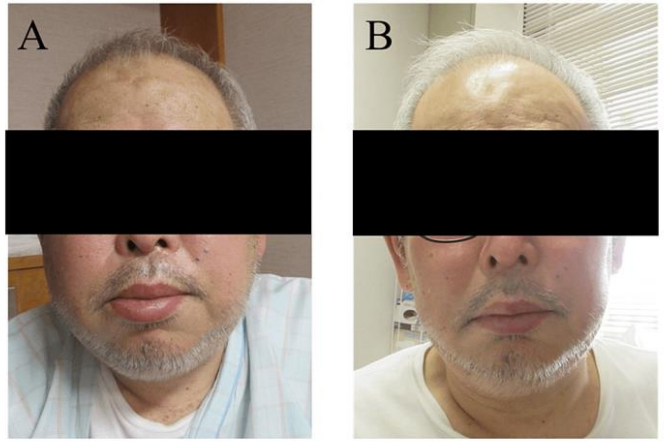


FIGURE 3: Gross appearance of cervical swelling in Case 2.

A. At the emergence of local cytokine release syndrome (CRS) on day four post-CAR-T cell infusion. B. The day after administration of dexamethasone (day five).

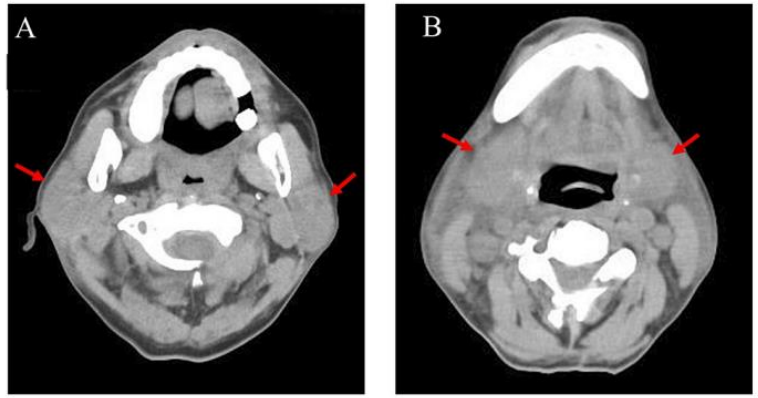


FIGURE 2: Plain computed tomography scan of the neck on day six post-chimeric antigen receptor T-cell (CAR-T) cell infusion in Case 1.

A. Swelling of bilateral parotid glands (red arrows). B. Swelling of submaxillary glands (red arrows).

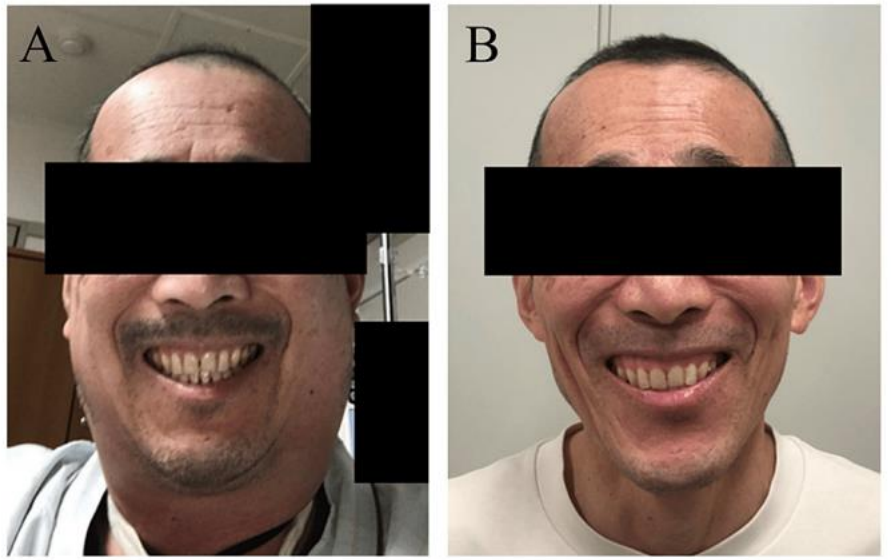


FIGURE 1: Gross appearance of cervical swelling in Case 1.

A. At the emergence of local cytokine release syndrome (CRS) on day five post-CAR-T cell infusion. B. After the resolution of local CRS.

Case Reports in Oncology

Case Rep Oncol 2022;15:257–262
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Case Report

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

Haruko Shima Takumi Kurosawa Hiroyuki Oikawa Hisato Kobayashi
Emiri Nishi Fumito Yamazaki Kentaro Tomita Hiroyuki Shimada

Department of Pediatrics, Keio University School of Medicine, Tokyo, Japan

15y/o boy with refractory B-ALL

→ CRS → toci

→ D+3: cervical edema involving soft tissue and larynx

→ Dexa → resolution of symptoms within hours

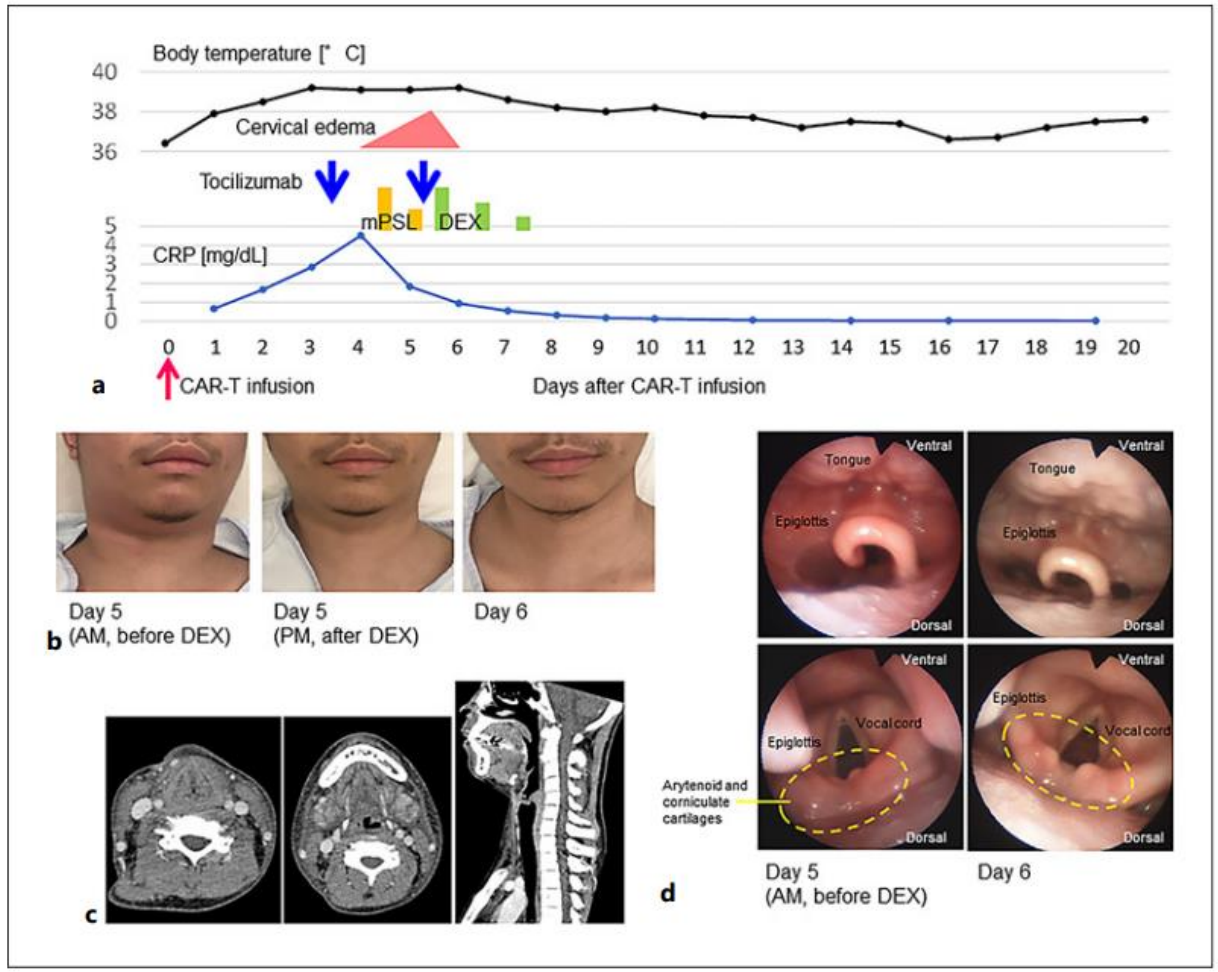


Fig. 1. Clinical course after CAR T-cell therapy. **a** Changes in body temperature and the CRP level after CAR T-cell therapy. The change in cervical edema status is also shown. Tocilizumab was administered on days 3 and 5, methylprednisolone on days 4 and 5, and DEX from days 5 to 7. **b** Cervical edema aggravated on day 5 (left) and immediately resolved within 2 h after intravenous administration of DEX (middle and right). **c** Cervical computed tomography on day 5 revealed extensive edema of the cervical soft tissues extending to the larynx. **d** Laryngoscopic findings on day 5 (left) and day 6 (right) revealed that the epiglottis, arytenoid, and corniculate cartilages were edematous. CRP, C-reactive protein; DEX, dexamethasone.

Case Report: Local Cytokine Release Syndrome in an Acute Lymphoblastic Leukemia Patient After Treatment With Chimeric Antigen Receptor T-Cell Therapy: A Possible Model, Literature Review and Perspective

Chengxin Luan[1], Junjie Zhou[1], Haixia Wang[1], Xiaoyu Ma[1], Zhangbiao Long[1], Xin Cheng[1], Xiaowen Chen[1], Zhenqi Huang[1], Dagan Zhang[2], Ruixiang Xia[1†] and Jian Ge[1†]*

[1] Department of Hematology, The First Affiliated Hospital of Anhui Medical University, Hefei, China, [2] Institute of Translational Medicine, The Affiliated Drum Tower Hospital of Nanjing University Medical School, Nanjing, China

61y/o woman with Ph-like B-ALL

→ CR

→ Relapse

→ No response to standard salvage therapy

→ CAR-T

- Pre-CAR-T no evidence of cervical lymphadenopathy, swollen gums, hepatosplenomegaly….
- Within 12h post CAR-T infusion fever (39°C), blood pressure drop, CRS°2
- → toci + steroids + NSAR + antibiotics
- D+8: foreign body sensation in the larynx, dyspnea, facial edema, rapidly growing neck circumference
- **→ local CRS despite systemic disease**

Submit a Manuscript: https://www.f6publishing.com World J Clin Cases 2022 September 16; 10(26): 9398-9403
DOI: 10.12998/wjcc.v10.i26.9398 ISSN 2307-8960 (online)

CASE REPORT

Cytokine release syndrome complicated with rhabdomyolysis after chimeric antigen receptor T-cell therapy: A case report

Lan Zhang, Wei Chen, Xiao-Min Wang, Shu-Qing Zhang

22y/o woman with relapsed B-ALL, 35kg

→ CAR-T → CRS°3, mild hypotension, hypoxia and rhabdomyolysis

→ Fever >40.3°C

→ Symptoms of irritability, photophobia, confusion, dizziness, headache, blurred vision, projectile vomiting

- D+7: severe pain and weakness in both lower limbs, local skin was painful to touch
- D+8: myoglobin and CK levels massively elevated
- + ICANS
- → ICU → plasma exchange
- **Myalgia is a classic symptom of RM and is easily overlooked in severe CRS after CAR-T**

Table 1 Clinical observations

	IL-6 (0-5 pg/mL)	Ferritin (13-150 ng/mL)	Creatine kinase (40-200 U/L)	Myoglobin (0-118 ng/mL)	LDH (120-250 U/L)	AST (13-35 U/L)	ALT (7-40U/L)	Cr (49-90 μmol/L)	BUN (2.8-7.6 mmol/L)
day1	8	1561	13		243	20	25	32	3
day2	21	1444	179		216	26	29	34	2
day3	289	1597	99		201	35	46	28	2
day4	499	1688	190		171	29	41	35	2
day5	3983	9673	103		238	61	85	41	1
day6	16745	16459	522		428	76	80	39	1
day7	33561	37968	512		446	174	99	45	4
day8	61369	> 40000	64941	22050	6948	1085	194	96	16
day9	10508	> 40000	35500	1170	4713	830	135	102	19
day10	2141	> 40000	27887	814	4941	701	143	118	9
day11	1024	> 40000	13804	667	3799	513	113	52	9
day12	513	> 40000	12804	173	4140	453	129	57	13
day13	400	> 40000	9489	89	3468	246	111	48	12
day14	386	> 40000	7195	64	3186	288	118	41	9
day15	238	38707	4720	31	2735	301	136	27	7
day16	152	21939	2678	24	2182	349	182	21	7
day17	81	15533	1395		2032	447	234	26	6
day18	41	7437	774		1746	164	148	25	4

IL: Interleukin; LDH: Lactate dehydrogenase; AST: Alaninetransaminase; ALT: Alaninetransaminase; Cr: Creatinine; BUN: Blood urea nitrogen.

Clinical Case Report

Medicine®

OPEN

Arthritis of large joints shown as a rare clinical feature of cytokine release syndrome after chimeric antigen receptor T cell therapy

A case report

Li-Xin Wang, MD, PhD[a,*], Xiaoping Chen, PhD[a], Mingming Jia, PhD[b], Shengdian Wang, PhD[b], Jianliang Shen, MD, PhD[a]

34y/o man with B-ALL

D+18 (?) post CAR-T: muscle soreness, fever 39.8°C, bilateral wrist, hip, knee, ankle joint swelling and pain

- simultaneously massive expansion of CAR-T in blood

→ Excrutiating pain require high-dose combination pain medication

Effusions into 3rd space

Clinical Case Report 2017 Medicine OPEN

Pleural cavity cytokine release syndrome in CD19-directed chimeric antigen receptor-modified T cell therapy

A case report

Lijuan Ding, MD[a], Yongxian Hu, MD[a], Kui Zhao, MD[b], Guoqing Wei, MD[a], Wenjun Wu, MD[a], Zhao Wu, MD[c], Lei Xiao, PhD[c], He Huang, PhD[a,*]

28y/o woman with DLBCL (non-GCB) presenting as mediastinal mass, cervical LN, later also chest

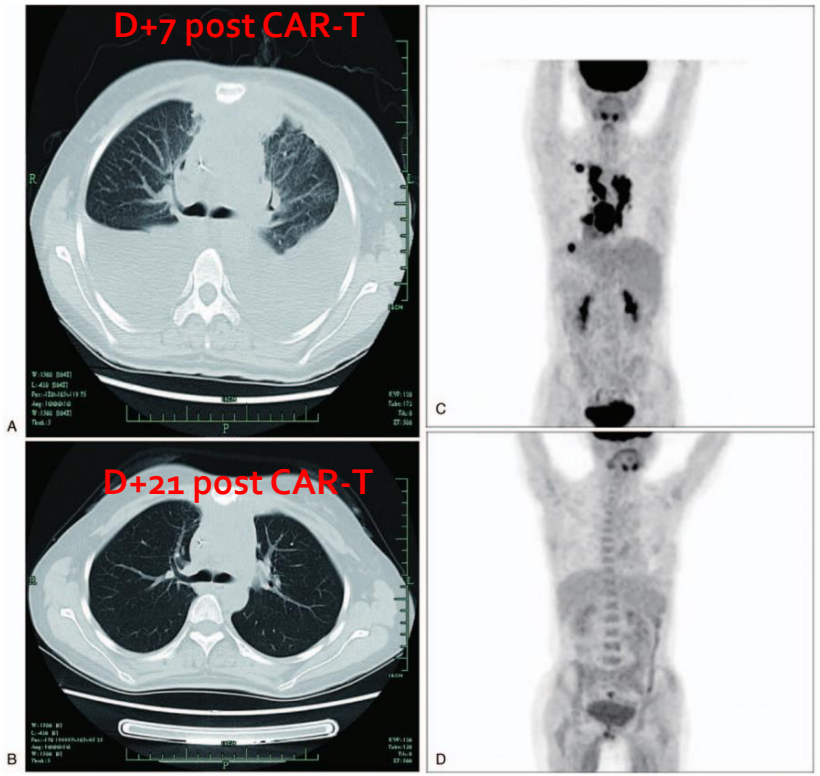
→ D+1 post CAR-T CRS

→ Antiinflammatory treatment

→ D+4 (?) progressive cough → pleural effusions

→ Thoracocentesis

→ Resolution of symptoms by d+9



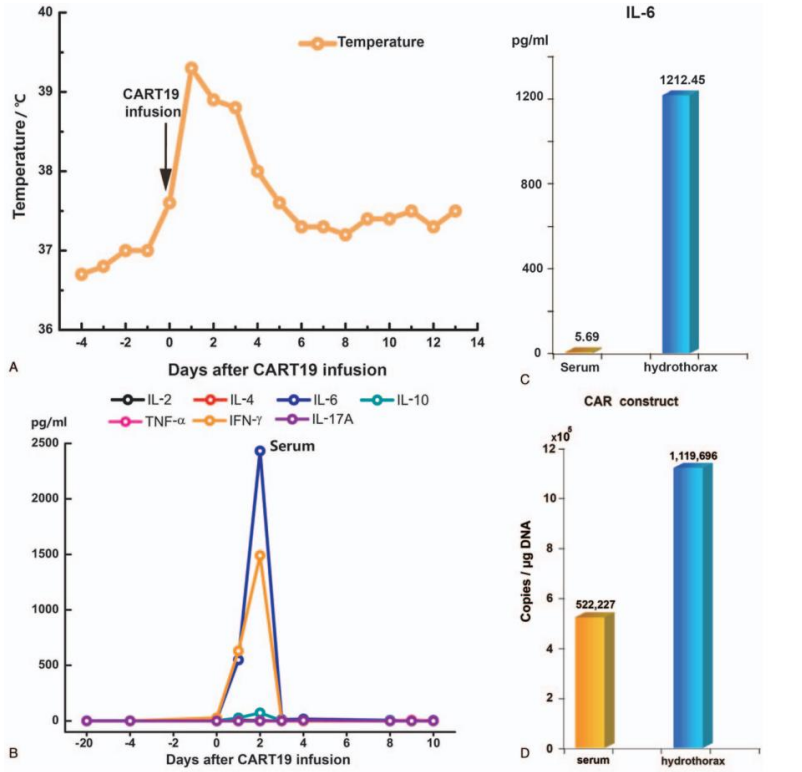


Figure 2. Changes of hydrothorax and masses of lymphoma infiltration after CART19 infusion. (A) Lung CT image on day 7 after CART19 infusion showing bilateral pleural effusion. (B) Lung CT image on day 21 after CART19 infusion showing that the pleural effusion on both sides were completely absorbed. (C) PET/CT before treatment showing high metabolic area in the chest. (D) The patient's chest was clean on day 28 after treatment. CART19 = CD19-directed CAR-T cell, CT = computed tomography, PET = positron emission tomography.

. (A) Changes in body temperature after CART19 infusion, with a maximum temperature within 24 hours as indicated by the profile. (B) Cytokine levels in erum at different time points after CART19 infusion. (C) IL-6 level in peripheral serum and hydrothorax, respectively, on day 8. (D) DNA copies of CAR t in blood serum and hydrothorax, respectively. CART19 = CD19-directed CAR-T cell.

Frontiers in Cardiovascular Medicine

TYPE Case Report
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Case report: CAR-T cell therapy-induced cardiac tamponade

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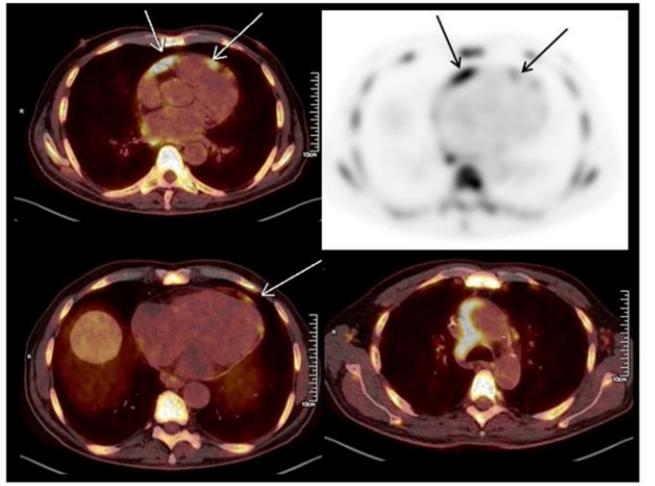


FIGURE 1
Positron emission tomography-computed tomography performed before CAR-T cell therapy showing multiple lymphoma lesions including in the pericardium (arrows).

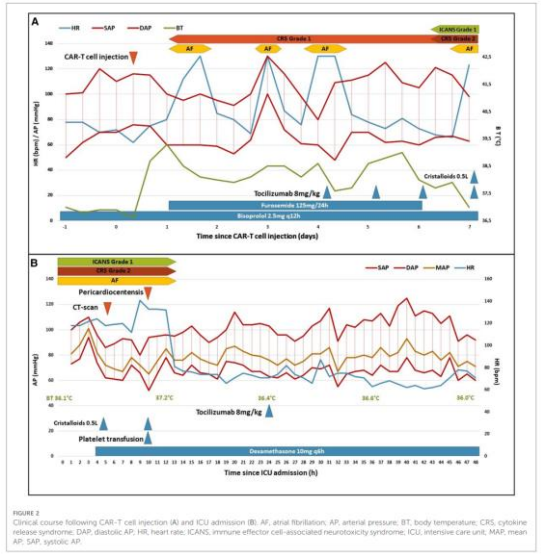


FIGURE 2
Clinical course following CAR-T cell injection (A) and ICU admission (B). AF, atrial fibrillation; AP, arterial pressure; BT, body temperature; CRS, cytokine release syndrome; DAP, diastolic AP; HR, heart rate; ICANS, immune effector cell-associated neurotoxicity syndrome; ICU, intensive care unit; MAP, mean AP; SAP, systolic AP.

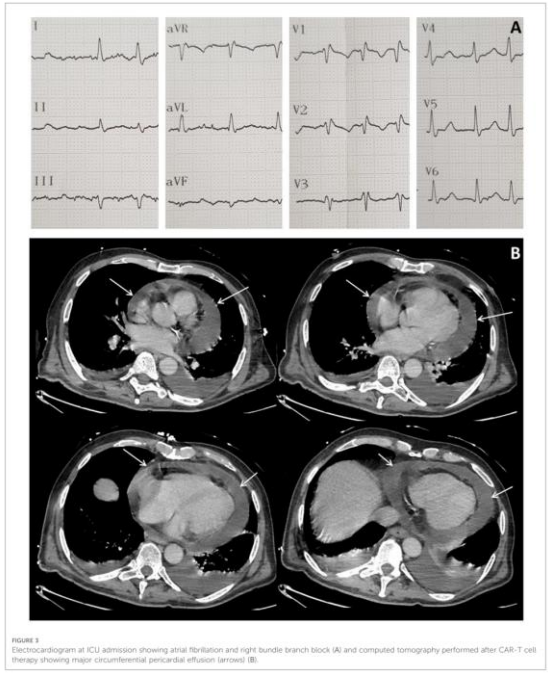


FIGURE 3
Electrocardiogram at ICU admission showing atrial fibrillation and right bundle branch block (A) and computed tomography performed after CAR-T cell therapy showing major circumferential pericardial effusion (arrows) (B).

Blood | Pericardiac effusion

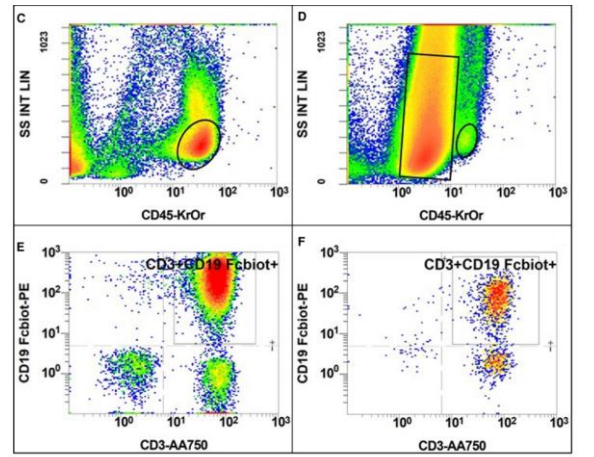


FIGURE 4
Evolution of CAR-T cell absolute number (A) and percentage of total lymphocytes (B) following injection, in blood (blue dots and line) and in pericardial fluid (red dot). Flow cytometry analysis of blood (C) and pericardial fluid (D) according to size (SS INT LIN) and CD45 expression (CD45-KrOr). Black ovals represent lymphocyte population. The black rectangle represents lymphoma population only present in pericardial fluid. Among lymphocyte population, CAR-T cells were selected according to CD3 and CD19 Fc-biotine expression in blood (E) and pericardial fluid (F). Colors from blue to red indicate an increase in cell count.

65y/o man with refractory DLBCL with pericardial involvement

→ D+1 post CAR-T CRS → toxi + steroids

→ Pericardiocentesis → improvement

Echo: pericardial effusion with RV heart failure due to cardiac tamponade

Pericardiocentesis showed large number of lymphoma cells with 73% CAR-T cells/lymphocytes

CAR-T infiltrates in critical locations

Bilateral retinal detachment after chimeric antigen receptor T-cell therapy

Christopher C. Denton,[1,2] William S. Gange,[3,4] Hisham Abdel-Azim,[1,2] Sonata Jodele,[1,5] Neena Kapoor,[1,2] Matthew J. Oberley,[6] Kenneth Wong,[1,7] Jonathan Kim,[3,4] Abby Vercio,[8] Parisah Moghaddampour,[8] K. V. Chalam,[8] David Sierpina,[8] Rebecca A. Gardner,[9,10] Michael A. Pulsipher,[1,2] Michael C. Jensen,[9] and Aaron Nagiel[3,4]

13y/o girl with B-ALL with CNS involvement

- → Following apheresis for CAR-T sudden worsening of vision
- → Fundoscopy: poor retinal perfusion
- → Orbital XRT 4Gy + steroids + chemo
- → Persistent leukemic infiltration pre-CAR-T
- → Post CAR-T: CRS°1, worsening of vision bilaterally
- → CSF and aqueous fluid: T cells (no leukemic cells)
- → **Hypothesis: Local CAR-T expansion and CRS**

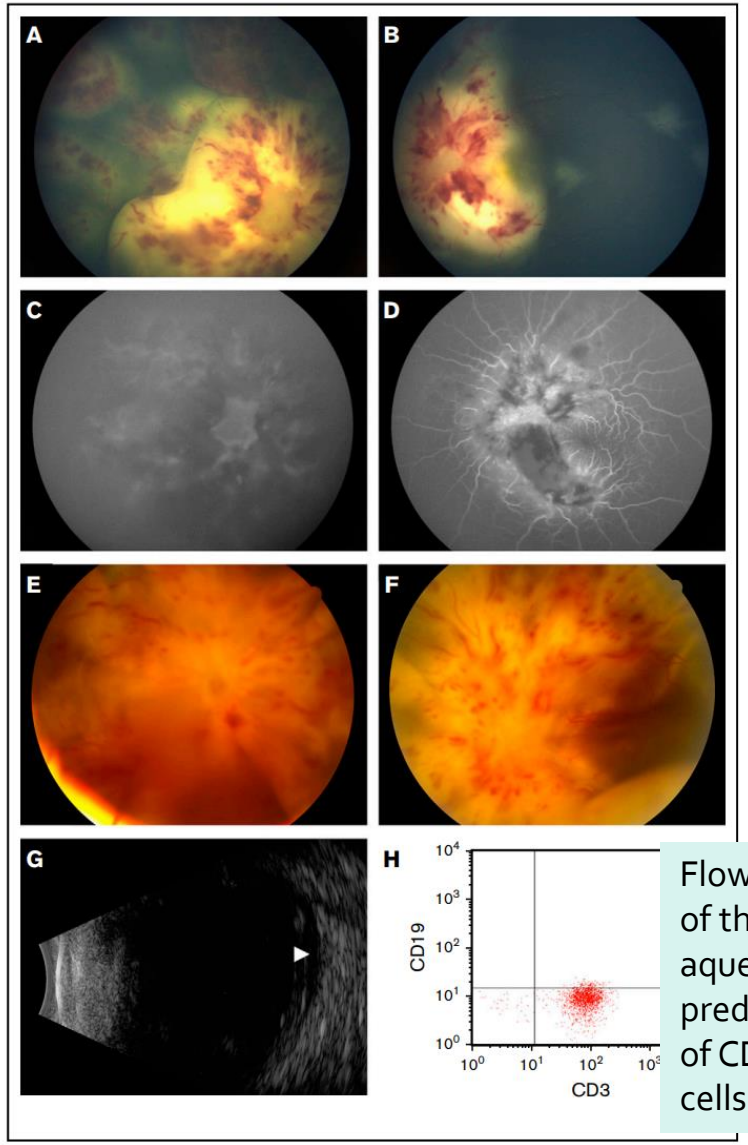
Pre-CAR-T: Leukemic optic disc infiltration and leukemic retinal infiltrates and hemorrhages

Fluorescein angiography: impaired perfusion of the choroidal and retinal circulations, with blockage in areas of leukemic infiltration and hemorrhage.

Post-CAR-T: worsened retinal whitening, hemorrhages, and optic disc edema with total exudative retinal detachments

Ocular ultrasound: subretinal fluid (arrowhead)

Ocular findings at presentation and following CAR T- therapy.



Flow cytometry of the right aqueous humor: predominance of CD3+CD19- cells

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CLINICAL CASE CHALLENGES

Fulminant Cardiotoxicity in a Patient With Cardiac Lymphoma Treated With CAR-T Cells

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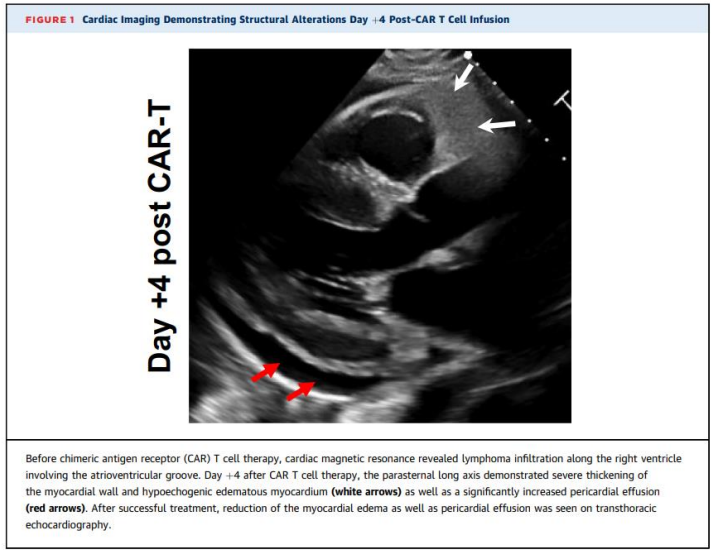


FIGURE 1 Cardiac Imaging Demonstrating Structural Alterations Day +4 Post-CAR T Cell Infusion

Before chimeric antigen receptor (CAR) T cell therapy, cardiac magnetic resonance revealed lymphoma infiltration along the right ventricle involving the atrioventricular groove. Day +4 after CAR T cell therapy, the parasternal long axis demonstrated severe thickening of the myocardial wall and hypoechogenic edematous myocardium **(white arrows)** as well as a significantly increased pericardial effusion **(red arrows)**. After successful treatment, reduction of the myocardial edema as well as pericardial effusion was seen on transthoracic echocardiography.

44y/o woman with r/r DLBCL with CNS+ cardiac involvement

→ Response to salvage therapy in CNS, but not in heart

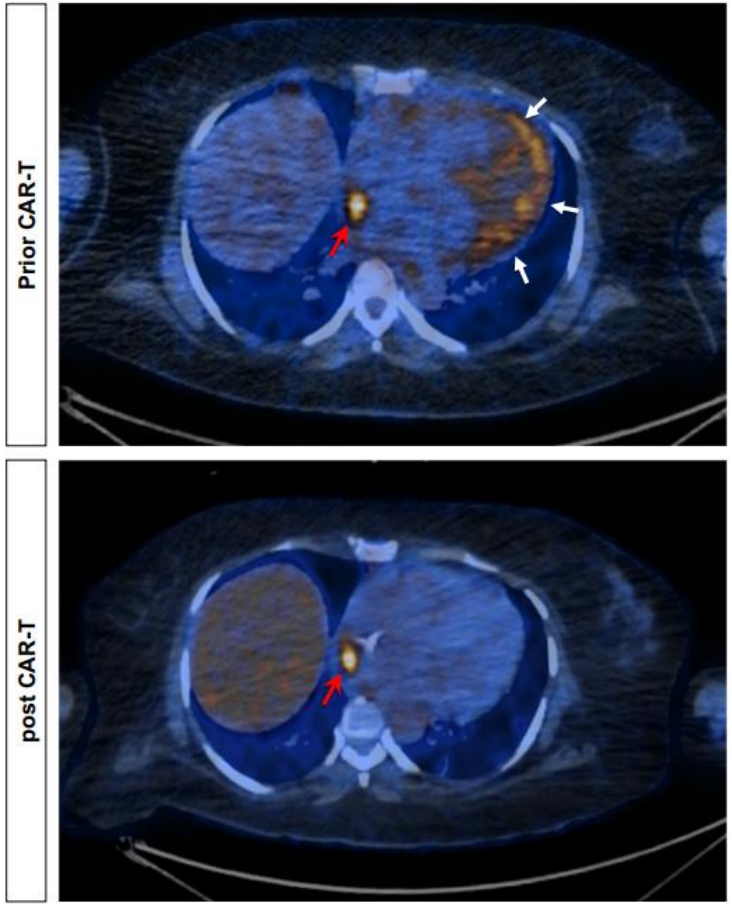
→ MRI + PET-CT: infiltration of pericardium surrounding RV and L+R atria, infiltration of interatrial septum and atrioventricular (AV) junction

→ Echo: normal LV EF, atrial tachycardia with variable conduction

→ CAR-T → CRS → D+4: rapid deterioration, heart failure, shock

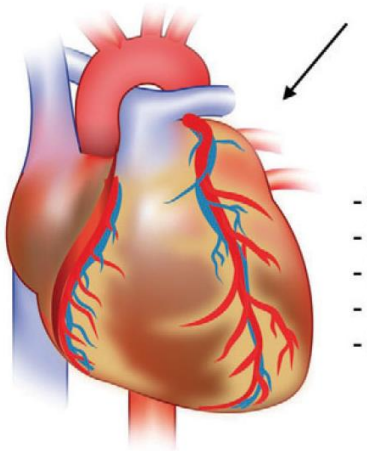
→ Deterioration despite HD-steroids, toci and vasopressors, Respiratory and renal failure

→ Supraventricular tachycardia, intermittend right bundle branch block, AV-nodal re-entry tachycardia/atrial flutter → bradycardic flutter with 3:1 conduction, high-grade AV-block, bigemini, Trop T (peak 651 ng/L).... → transvenous pacemaker

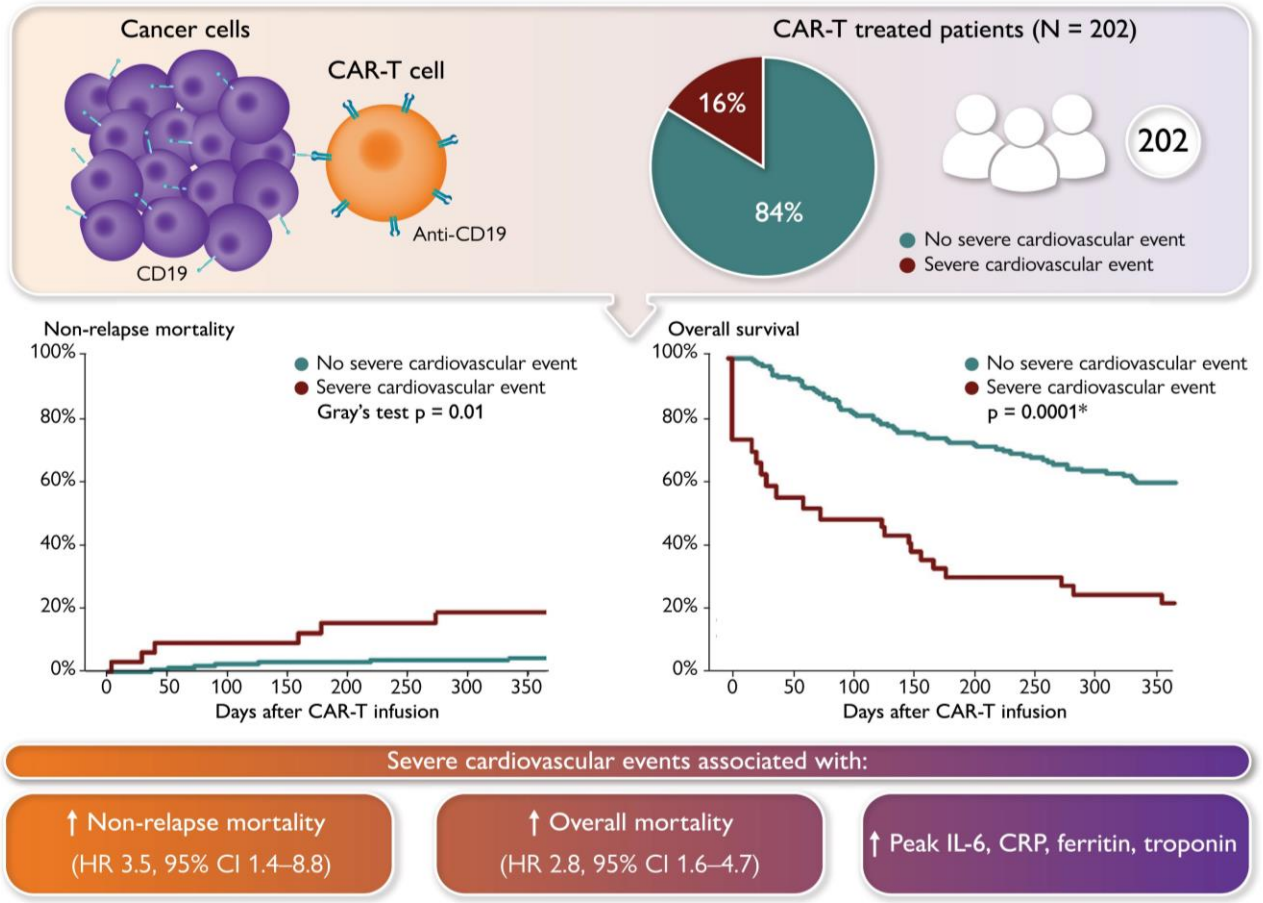


Cardiovascular complications: not so rare

Cancer patients treated with chimeric antigen receptor T-cell therapy (CAR-T) who experience severe cardiovascular events, including heart failure, cardiogenic shock or myocardial infarction are common following CAR-T



- Tachyarrhythmia
- Hypotension
- Left Ventricular Systolic Dysfunction
- Cardiac Arrest
- Elevated Troponin



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Eur Heart J, Volume 44, Issue 22, 7 June 2023, Pages 2029–2042, https://doi.org/10.1093/eurheartj/ehad117

ESC European Society of Cardiology
European Heart Journal - Case Reports (2023) 7, 1–5
https://doi.org/10.1093/ehjcr/ytad342

CASE REPORT
Coronary intervention

Coronary vasospasm during infusion of CD-19 directed chimeric antigen receptor T-cell therapy: a case report

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Time zero	Initiation of CAR-T infusion
4 min after infusion start	Patient develops symptoms concerning for acute coronary syndrome as well as hypotension and tachycardia.
10 min after infusion start	EKG shows inferior ST elevations.
10–50 min after infusion start	Patient receives aspirin 325 mg, intravenous heparin, sublingual nitroglycerin, and morphine. Due to concern for an acute infusion reaction, also receives diphenhydramine, famotidine, Epi-pen, and 1L of normal saline. Started on an epinephrine infusion for hypotension.
2 h after infusion start	Emergent coronary angiography shows nonobstructive coronary artery disease.
1 h post-catheterization	Post-catherization EKG shows resolution of ST changes. Patient symptoms have resolved.
2 days after infusion	Re-evaluated by outside cardiologist. Started on diltiazem 60 mg twice daily and aspirin 81 mg daily.
1.5 weeks after infusion	Decision is made not to re-challenge the patient with CAR-T therapy. Diltiazem is discontinued.
2 weeks after infusion	At oncology follow up, outpatient oncologist confirms the decision not to re-challenge the patient with CAR-T therapy.

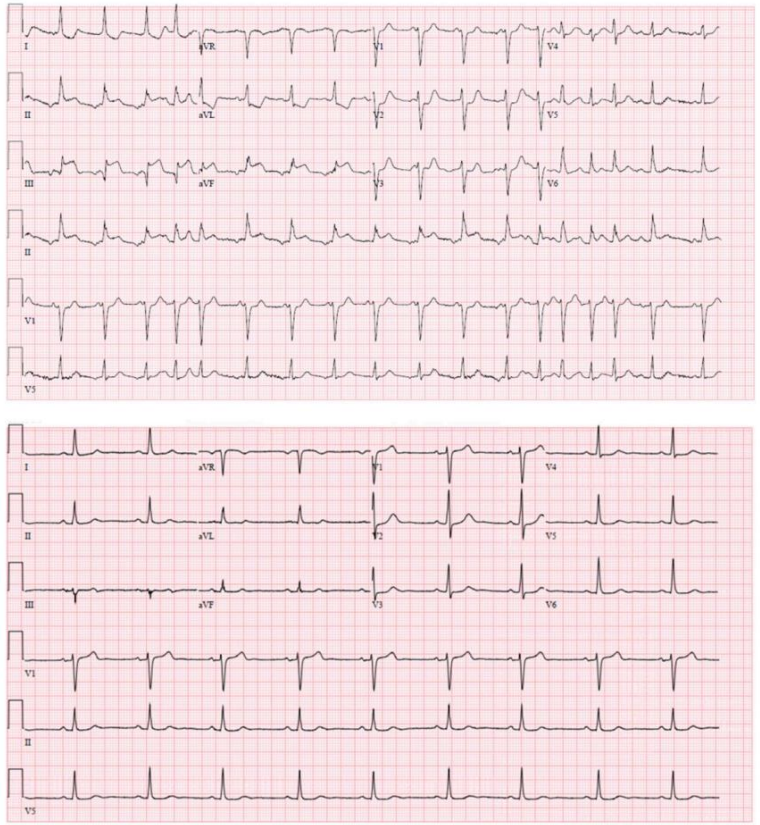


Figure 1 Pre- and post-catheterization EKG. EKG before (top) and after (bottom) catheterization. Pre-catheterization EKG shows infer tions with reciprocal lateral ST depressions. Post-catheterization EKG shows normal sinus rhythm with resolution of ST changes.

- 76y/o man with R/R DLBCL
- No known cardiovascular disease

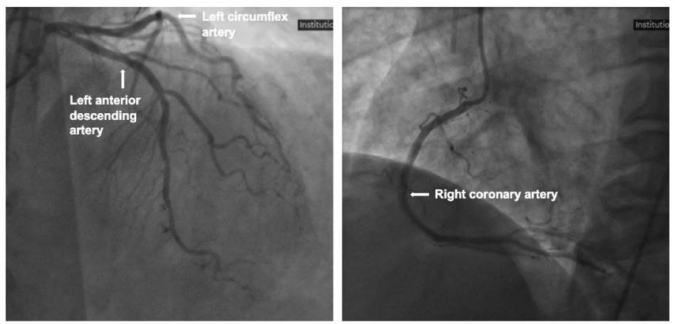


Figure 2 Coronary angiography. Coronary angiography revealed mild non-obstructive coronary disease.

Impact of cytokine release syndrome on cardiac function following CD19 CAR-T cell therapy in children and young adults with hematological malignancies

Haneen Shalabi ,[1] Vandana Sachdev,[2] Amita Kulshreshtha,[1] Julia W Cohen,[1] Bonnie Yates,[1] Doug R Rosing,[2] Stanislav Sidenko,[2] Cindy Delbrook,[1] Crystal Mackall,[1,3] Brandon Wiley,[4,5] Daniel W Lee,[1,6] Nirali N Shah[1]

Table 1 Patient demographics

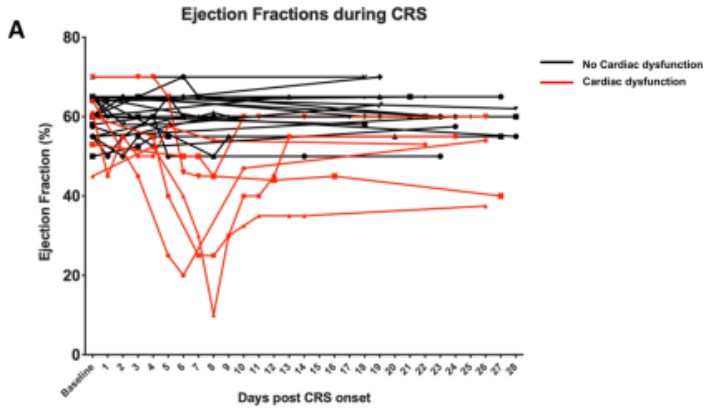
		All treated subjects n=52	Cardiac dysfunction n=6	No cardiac dysfunction n=46	P value*
Age, median (range), year		13 (4–30)	18 (10–30)	13 (4–27)	0.059
Male, n (%)		41 (78.8)	6 (100)	35 (76.1)	0.32
Diagnosis	ALL, n (%)	50 (96.1)	5 (83.3)	45 (97.8)	0.22
	NHL, n (%)	2 (3.8)	1 (16.7)	1 (2.2)	
Primary refractory		13 (25)	3 (50)	10 (21.7)	0.34
Prior lines of therapy	>4, n (%)	9 (17.3)	0 (0)	9 (19.6)	
	2–4, n (%)	43 (82.7)	6 (100)	37 (80.4)	
Prior HSCT	0, n (%)	29 (55.8)	3 (50)	26 (56.5)	1.00
	1, n (%)	18 (34.6)	3 (50)	15 (32.6)	
	2, n (%)	5 (9.6)	0 (0)	5 (10.9)	
Prior TBI, n (%)		23 (44)	3 (50)	20 (43.4)	1.00
Prior immunotherapy, n (%)		11 (21.1)	1 (16.7)	10 (21.7)	1.00
Prior anthracycline exposure, median (range), doxorubicin equivalents		205 (70–620)	275 (110–571)	205 (70–620)	0.23
Baseline left ventricular ejection fraction, median (range), %		60 (50–70)	61 (50–70)	60 (50–72)	0.59
Baseline left ventricular global strain, median (range), % n=37		16.8 (11.6 to 23.5)	14.4 (11.6 to 18.7)†	17 (14.1 to 23.5)	0.04
Performance status, median (range) %		90 (40–100)	80 (40–90)	90 (50–100)	0.07

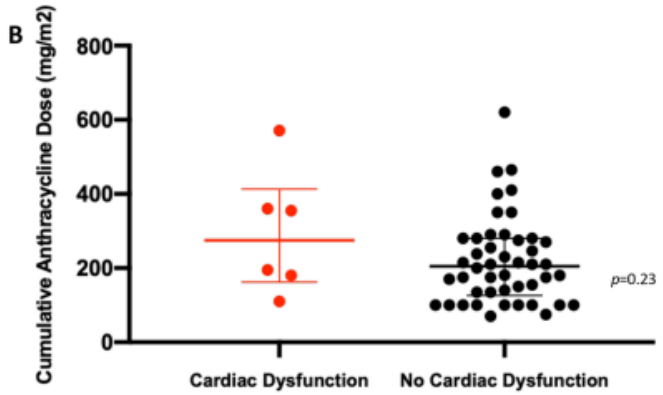
Cardiac dysfunction is defined as a >10% absolute decrease in left ventricular ejection fraction (LVEF) compared with baseline or new onset left ventricular systolic dysfunction ≥grade 2, LVEF <50%. Any biological therapy used to treat cancer, for example, CAR T cells, antibody-based therapy.
*The p value is comparing baseline characteristics of those with and without cardiac dysfunction. Global longitudinal strain (GLS) is presented in absolute numbers (%).
†Only four patients had baseline GLS measured.
ALL, acute lymphoblastic leukemia; CAR, chimeric antigen receptor; HSCT, Hematopoietic stem cell transplant; NHL, non-Hodgkin's Lymphoma; TBI, total body irradiation.

Table 2 Characteristics of patients with cytokine release syndrome (CRS)

		Subjects with CRS n=37	Cardiac dysfunction n=6	No cardiac dysfunction n=31	P value*
Time to onset of CRS, median (range), d		5 (1–12)	2.5 (1–5)	5.5 (1–12)	0.015
CRS max grade†	1, n (%)	14 (37.8)	0	14 (45.1)	0.022‡
	2, n (%)	14 (37.8)	2 (33)	12 (38.7)	
	3, n (%)	6 (16.2)	2 (33)	4 (12.9)	
	4, n (%)	3 (8.1)	2 (33)	1 (3.2)	
ASTCT CRS Max Grade§	1, n (%)	16 (43.2)	0	16 (51.6)	0.0004†
	2, n (%)	9 (24.3)	0	9 (29.0)	
	3, n (%)	9 (24.3)	4 (66.7)	5 (16.1)	
	4, n (%)	3 (8.1)	2 (33.3)	1 (3.2)	
Duration of fever >38, median (range), d		5 (1–14)	5 (4–8)	5 (1–14)	0.67
Duration of fever >40, median (range), d		3 (1–6)	4 (3–6)	2.5 (1–6)	0.059
Duration of tachycardia¶, median (range), d		6 (1–30)	8 (6–9)	5 (1–30)	0.10
ICU transfer, n (%)		21 (56.8)	6 (100)	15 (48.4)	0.026
Received Tocilizumab, n (%)		7 (18.9)	4 (66)	3 (9.7)	0.006
Received steroids, n (%)		4 (10.8)	3 (50)	1 (3.2)	0.11
Required vasopressor support	One agent	6 (16.2)	2 (33)	4 (12.9)	0.14**
	>1 agent	3 (8.1)	1 (16.7)	2 (6.5)	
Required milrinone, n (%)		1 (2.7)	1 (16.7)	0	0.16
Required mechanical ventilation, n (%)		4 (10.8)	3 (50)	1 (3.2)	0.009

Cardiac dysfunction is defined as a >10% absolute decrease in left ventricular ejection fraction (LVEF) compared with baseline or new-onset left ventricular systolic dysfunction >grade 2, LVEF <50%.





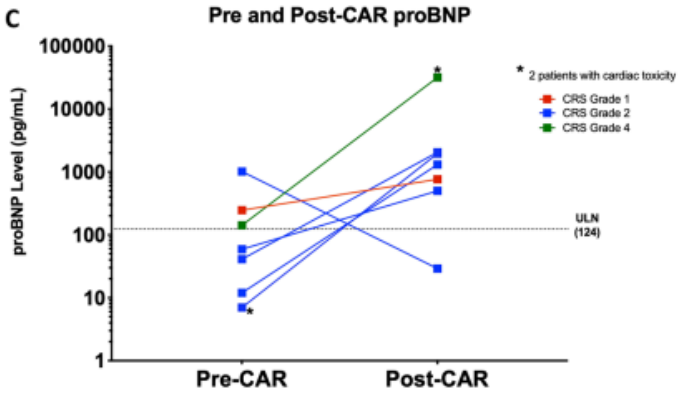


Table 3 Characteristics of patients with cardiac dysfunction

Patient	Prior anthracycline exposure (mg/m^2)	Baseline LVEF, %	Lowest LVEF, %	Max CRS* grade	Vasoactive support?	Troponin elevation?	Peak troponin (ng/mL)
14	360	64	20	4	Yes	Yes	6.23
16	110	70	45	4	No	Yes	0.117
39	195	60	25	3	No	Yes	0.113
45	570	55	10	4	Yes	No†	<0.010
51	355	50	40	2	No	No†	<0.010
52	180	61	45	2	Yes	Yes	0.016

Cardiac dysfunction is defined as a >10% absolute decrease in left ventricular ejection fraction (LVEF) compared with baseline or new onset left ventricular systolic dysfunction >grade 2, LVEF <50%.

Rare toxicities – affecting neuronal structures and functions

Recurrent Status Epilepticus in the Setting of Chimeric Antigen Receptor (CAR)-T Cell Therapy

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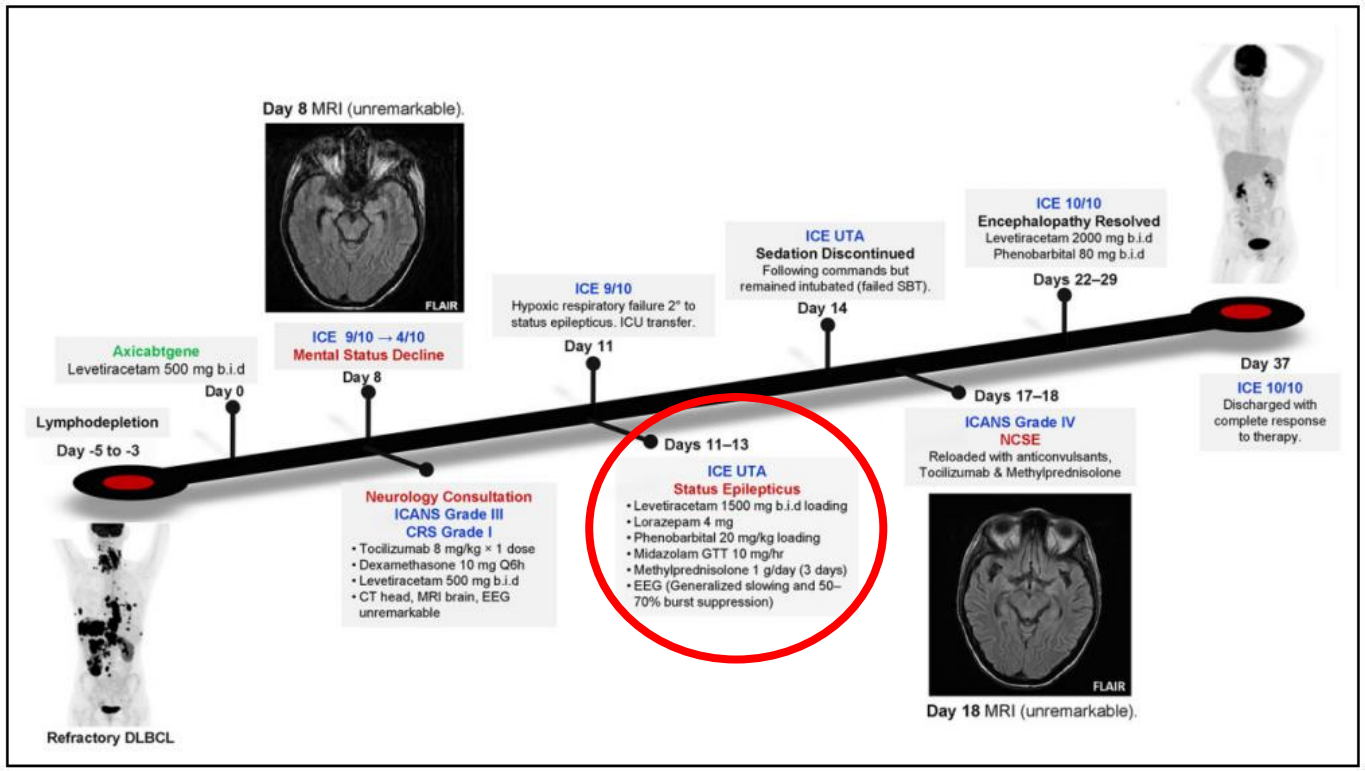

Figure 1. Summary of 42-day hospital course. Diffuse large B-cell lymphoma (DLBCL), drip (gtt), immune effector cell-associated encephalopathy (ICE) score, intensive care unit (ICU), non-convulsive status epilepticus (NCSE), spontaneous breathing trial (SBT), unable to assess (UTA).

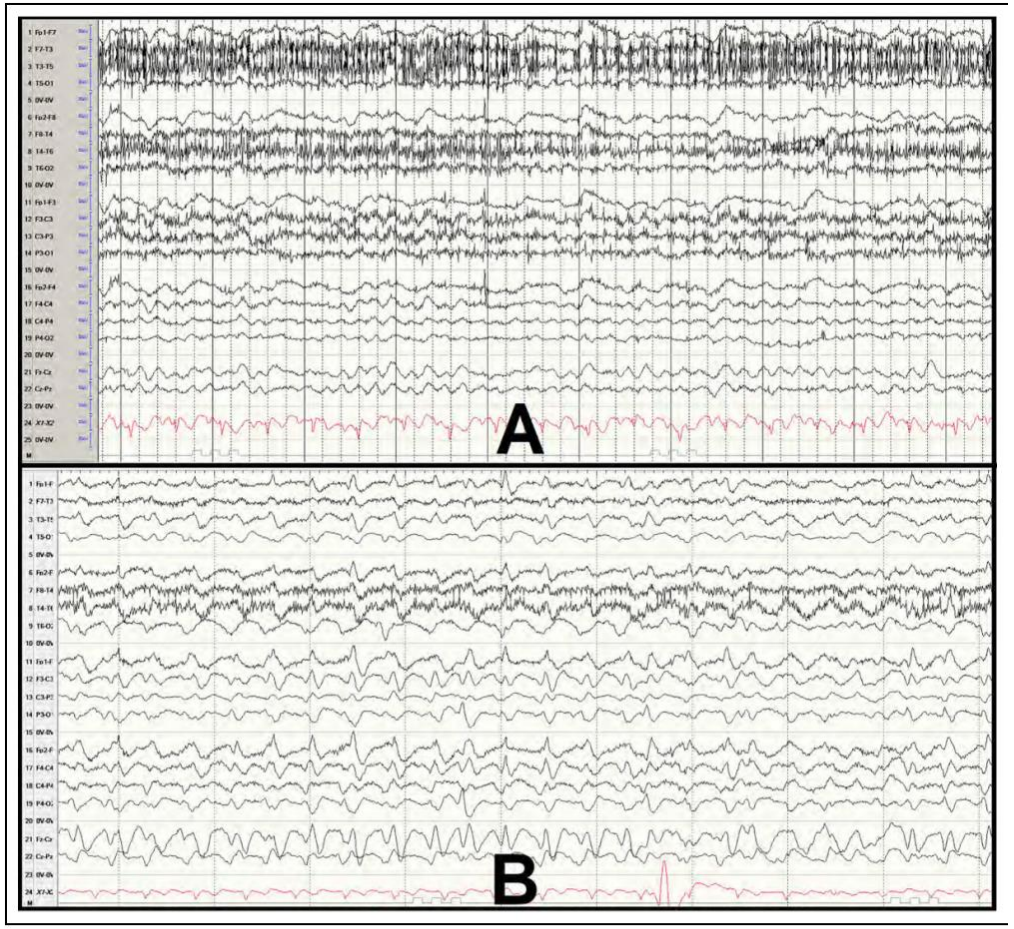

Figure 2. Day 8, 17–18 post-CAR-T infusion continuous video electroencephalography. (A) Day 8: generalized delta frequency slowing (longitudinal bipolar-double banana montage). (B) Day 18: sharply contoured 2.5–3 Hz generalized periodic discharges with frontal predominance consistent with non-convulsive status epilepticus (longitudinal bipolar-double banana montage).

→ Extremely refractory and difficult to treat status epilepticus

Chimeric Antigen Receptor-T Cell Mediated Bilateral Facial Nerve Palsy: A Case Report

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Sage

- 76y/o man with MM IgGkappa
- 60% BM infiltration
- 7x VRD + RTx → °1 PNP
- BCMA CAR-T → °1 CRS
- @2wks post CAR-T: bilateral palsy: dysarthric speech, unable to raise eyebrows, gap between eyelids, unable to smile….
- Otherwise neurologically and cognitive normal

Table 1. Diagnostic Evaluation Performed during Hospital Stay to Investigate Cause of Bilateral Facial Nerve Palsy.

Basic	Day +1	Blood: WBC 2.2X10E9/L, Lymphocytes 0.8X10E9/L CSF: WBC 13x10E6/L, Protein 0.46 g/L, Glucose 3.4 mmol/L CRP 4.1 mg/L
	Day +8	CSF: WBC 2.2x10E6/L, Protein 0.4 g/L Glucose 4.4 mmol/L
Infectious	Day +1	Fungal stain and culture negative, blood cultures negative Toxoplasma, adenovirus, CMV, EBV, enterovirus, parechovirus NAT negative CSF: Culture, fungal stain, HSV 1 + 2, HHV-6 A + B, VZV negative
Cytology	Day +1	Cytopathology report: Increased cellularity with **atypical cells** is observed Flow cytometry of CSF: CD3+ (90%) CD3+4+ (60%) CD3+8 + (32%) No immunophenotypic evidence of a B cell neoplasm No analyzable CD19/CD20 positive B cells are identified in this sample **The lymphocyte population is composed of T cells (91%) demonstrating a CD4:CD8 ratio of 4:1 and loss of CD7 expression**, accompanied by NK cells (2%)
	Day +8	Flow cytometry of CSF: CD3+ (92%) CD3+4+ (51%) CD3+8 + (42%) ; no atypical cells reported No immunophenotypic evidence of a B cell neoplasm; no analyzable CD19/CD20 positive B cells are identified in this sample **The lymphocyte population is predominantly composed of CD3/CD5-positive T cells (97%) demonstrating a CD4:CD8 ratio of 2.5:1. There is only a minor subset loss of CD7 expression (25% of cells)**
Imaging	Day +6	MR Brain, orbits; Gadolinium enhanced MRI demonstrated mild CNVII enhancement. No other intracranial pathology identified

Abbreviations: CMV = cytomegalovirus; CN = cranial nerve; CRP = C reactive protein; CSF = cerebrospinal fluid; EBV = Epstein barr virus; HHV = human herpes virus; HSV = herpes simplex virus; NAT = nucleic antigen test; NK = natural killer; VZV = varicella zoster virus; WBC = white blood cells.

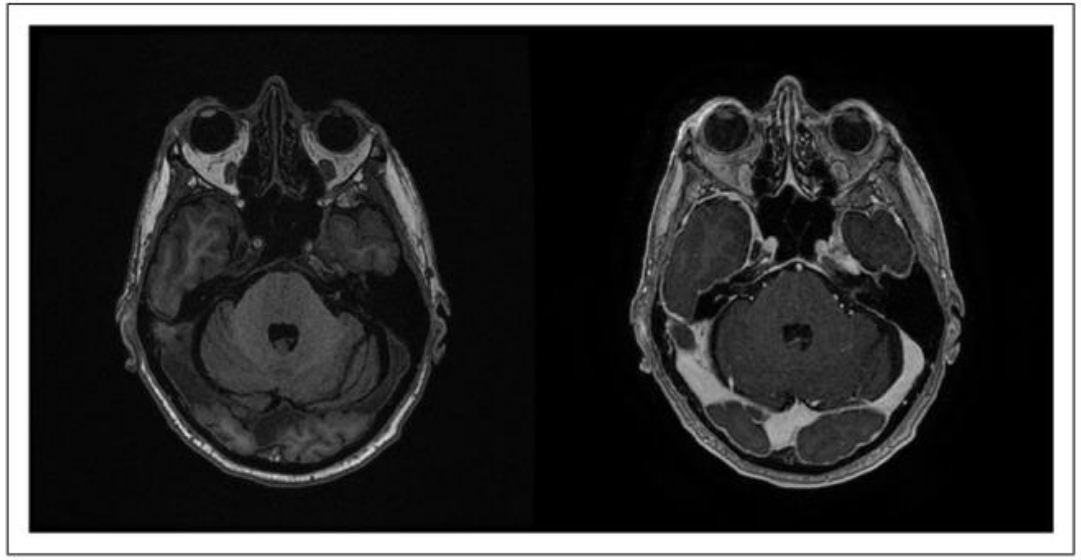


Figure 1. Bilateral facial nerve palsy after CAR-T therapy. T1 pre- (left) and post- (right) gadolinium enhancement demonstrating mild bilateral cranial nerve VII enhancement.

Journal for ImmunoTherapy of Cancer

Diabetes insipidus and Guillain-Barré-like syndrome following CAR-T cell therapy: a case report

2023

Christian Koch,[1] Juliane Fleischer,[2] Todor Popov,[3] Karl Frontzek,[4] Bettina Schreiner,[3] Patrick Roth,[3] Markus G. Manz,[1] Simone Unseld,[2] Antonia M. S. Müller,[5] Norman F. Russkamp [1,6]

- 40y/o man with LBCL with CNS involvement
- Pre-existing PNP°1 after 4 lines of therapy
- Within 24h post CAR-T infusion CRS°1
- D+5 facial nerve palsy and motor weakness of limbs , ICANS°2
- Despite treatment neuromuscular weakness deteriorated → quadriparesis + impaired respiratory muscle function and loss of upper airway reflexes → intubation
- Bronchoscopy: mucus plug in airways
- Polyuria with urine output of >900 ml/h, response to desmopressin
- CAR-T cells present in CSF (37% of lymphocytes), higher fraction compared with blood

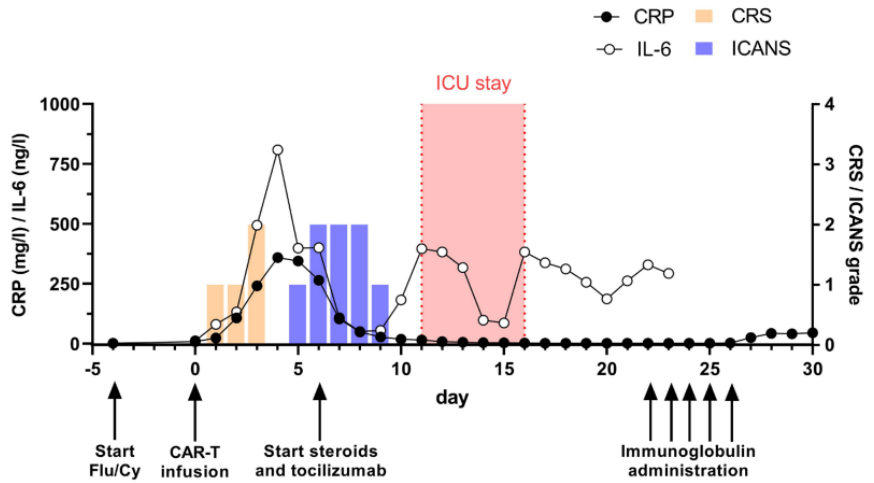
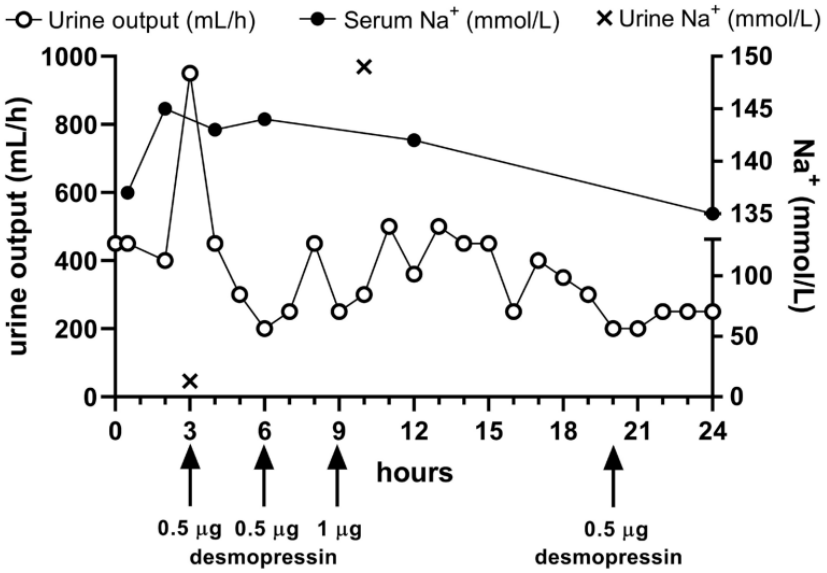


Figure 1b

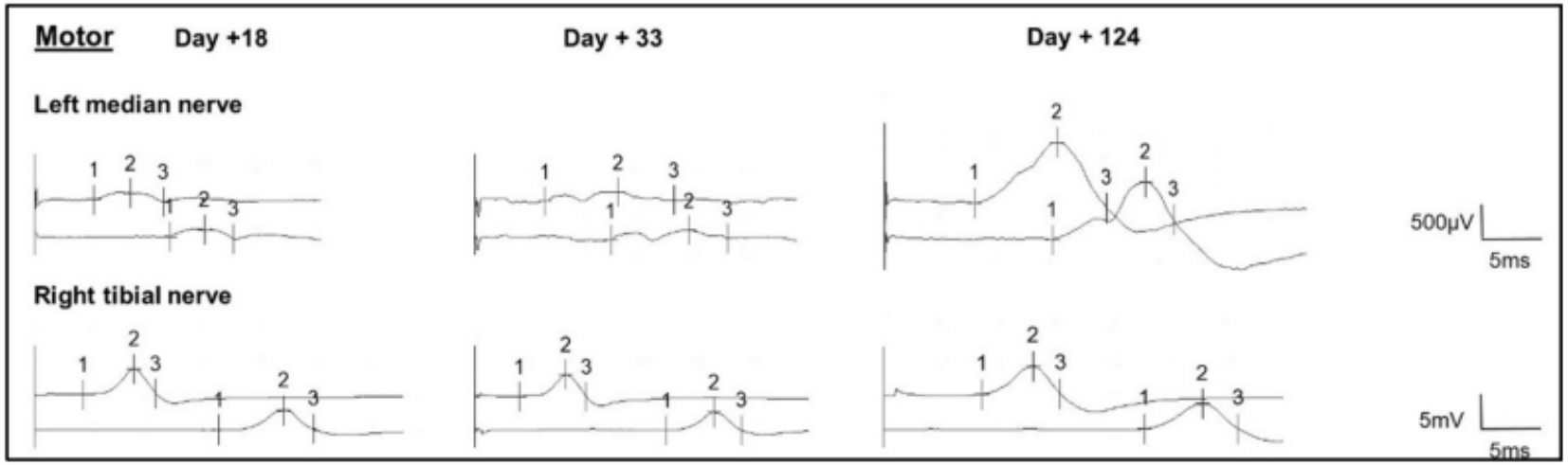


Journal for ImmunoTherapy of Cancer

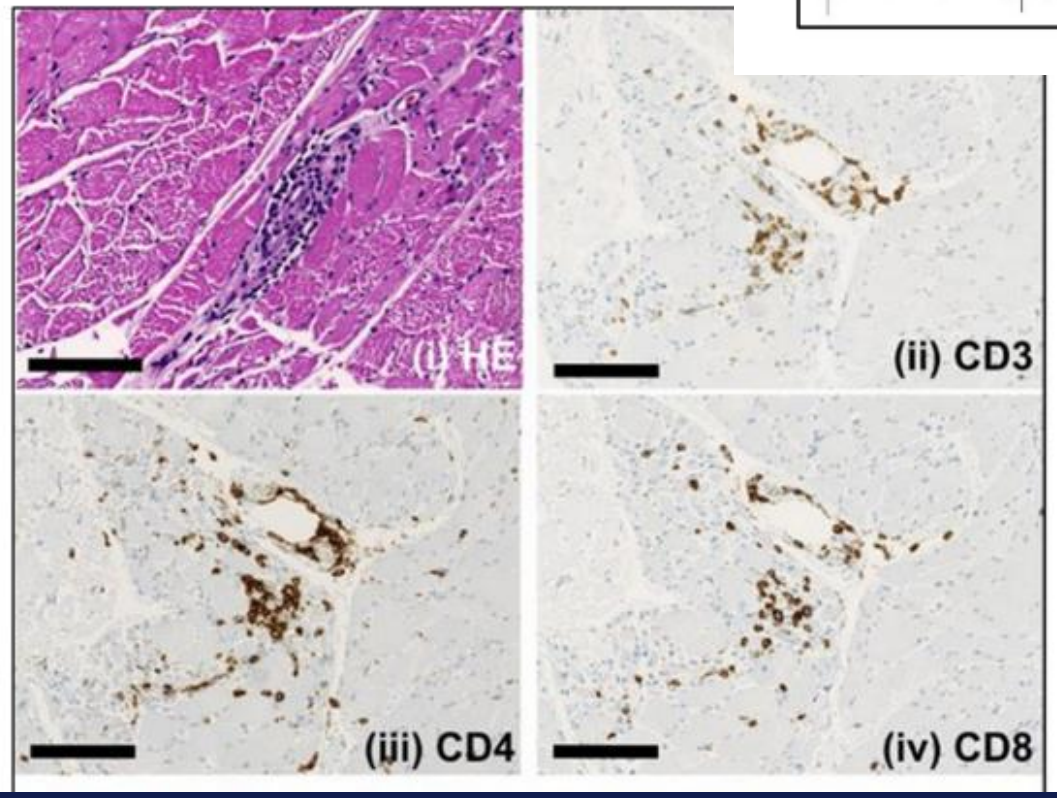
Diabetes insipidus and Guillain-Barré-like syndrome following CAR-T cell therapy: a case report

Christian Koch,[1] Juliane Fleischer,[2] Todor Popov,[3] Karl Frontzek,[4] Bettina Schreiner,[3] Patrick Roth,[3] Markus G. Manz,[1] Simone Unseld,[2] Antonia M. S. Müller,[5] Norman F. Russkamp [1,6]

Guillain-Barré like syndrome



Drastic reduction of compound muscle action potentials



Gastrocnemius muscle biopsy
→ predominant perivascular immune cell infiltration, chronic muscular atrophy

→ CAR-T transgene detectable also in biopsy

Received: 2 December 2021 | Revised: 4 January 2022 | Accepted: 6 January 2022

DOI: 10.1002/jha2.381

eJHaem

CASE REPORT

Extensive myelitis with eosinophilic meningitis after Chimeric antigen receptor T cells therapy

Baptiste Le Calvez[1,7] | Marion Eveillard[2,4] | Paul Decamps[5] | Jesus Aguilar[6] | Amélie Seguin[5] | Emmanuel Canet[5] | Audrey Grain[2,7] | Cyrille Touzeau[1,2,3] | Benoît Tessoulin[1,2,3] | Thomas Gastinne[1]

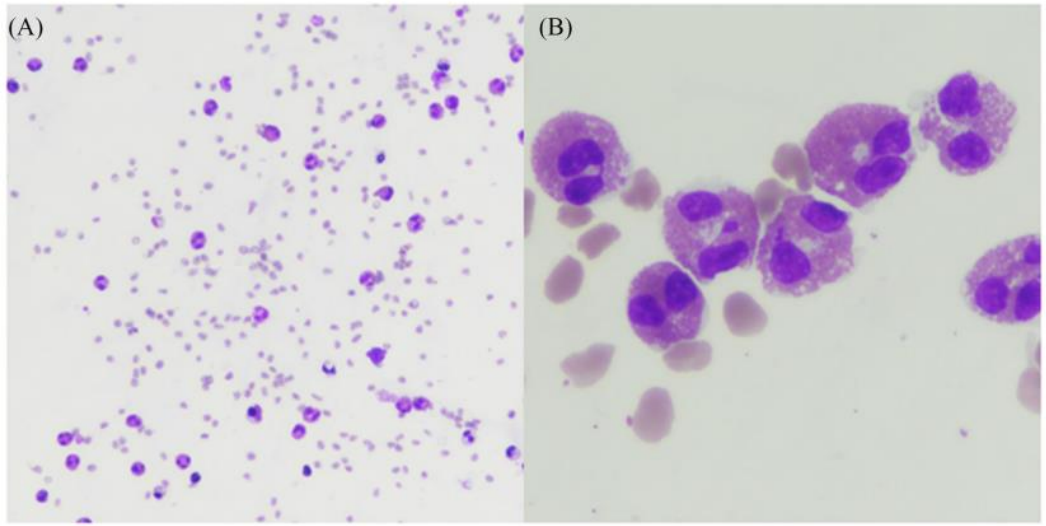


FIGURE 2 Cerebrospinal fluid (CSF) May Grunwald Giemsa cytospin stain, magnification 10x (A) and 50x (B)

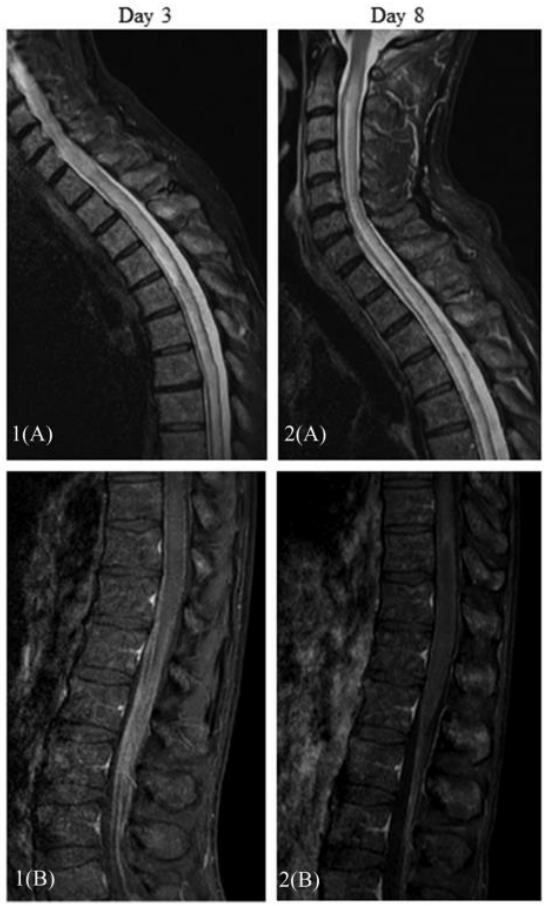


FIGURE 1 (1A) D3 magnetic resonance imaging (MRI)/sagittal short tau inversion recovery (STIR) images: extensive T2 hypersignal of the medulla, tumor-like appearance. (1B) D3 MRI/sagittal T1 fat-saturated post-contrast images: poorly delineated thoracic medulla contrast patches. Clear contrast of the roots of the cauda equina. (2A) D8 MRI/sagittal STIR images: decrease of the tumescent aspect of the medulla. Stability of the T2 hypersignal extent of the medulla. (2B) D8 MRI/sagittal T1 fat saturated post-contrast images: significant decrease in medullary contrast, especially in the roots of the cauda equina

The Laryngoscope

Case Report

Head and Neck Dystonia Following Chimeric-Antigen Receptor T-Cell Immunotherapy: A Case Report

Daniel D. Lee, MD; Yufan Lin, BS; Lisa T. Galati, MD; Stanley M. Shapshay, MD, FACS

- 55y/o female with FL → transformation in DLBCL
- → CAR-T well tolerated with some mild hypotension and dizziness
- After discharge: progessive shortness of breath, dysphonia, intermittend stridor
- → symptoms were exacerbated by stress and exertion, but resolved while sleeping
- Normal pulmonary function tests, CT of head and neck and chest, MRI brain, bronchoscopy
- CR @ 4m post CAR-T
- Laryngoscopy: involuntary movement of the palate and pharynx with spasmodic adductor vocal fold involvement → symptomatic relief could not be achieved despite conservative management (speech therapy, clonazepam, gabapentin… → improvement by botox injections

Rare toxicities – affecting the hematopoietic system

- As a consequence of long-term bone marrow inflammation (CAR-T)
- In a heavily pre-treated population

DOI: 10.7759/cureus.44677

Myelodysplastic Syndrome After Anti-CD19 Chimeric Antigen Receptor T-cell Therapy: A Case Series

Armaan Dhaliwal [1] , Soumiya Ravi [1]

1. Department of Internal Medicine, Univ

Lymphoma type	Prior ASCT	MDS or CCUS diagnosis	Time to MDS/CCUS diagnosis	Response to CAR-T cell	CRS grade	CAR-T cell dose and construct	Lines of chemotherapy prior to CAR-T cell
DLBCL	No	CCUS	2 months	CMR	1	$3.7x10^8$ (Kymrlah)	3; rituximab-ienalidomide, R-EPOCH, R-ICE
DLBCL	No	MDS	10 months	CMR	-	$2.4x10^8$ (Kymrlah)	3; R-CHOP, ICE, venetoclax and polatuzumab
DLBCL	No	CCUS	1 month	Partial near CMR. Lunago score of 4	-	$1.8x10^8$ (Kymrlah)	2; bendamustine and rituximab, R-ECHOP
DLBCL	Yes	MDS	26 months	CMR. Lunago score of 2	-	$2.3x10^8$ (Kymrlah)	2; CHOP, ICE

TABLE 1: Outcomes of each of the four DLBCL cases post CAR-T cell therapy

DLBCL: diffuse large B-cell lymphoma; ASCT: autologous stem cell transplant; MDS: myelodysplastic syndrome; CCUS: clonal cytopenias of undetermined significance; CAR-T cell: chimeric antigen receptor T-cell; CRS: cytokine release syndrome; R-EPOCH: rituximab, etoposide, prednisone, cyclophosphamide, and doxorubicin; R-ICE: rituximab, ifosfamide, carboplatin, and etoposide; R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; ICE: ifosfamide, carboplatin, and etoposide; R-ECHOP: rituximab, etoposide, cyclophosphamide, doxorubicin, vincristine, and prednisone; CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisone; CMR: complete metabolic response

DOI: 10.7759/cureus.44677

Myelodysplastic Syndrome After Anti-CD19 Chimeric Antigen Receptor T-cell Therapy: A Case Series

Armaan Dhaliwal [1] , Soumiya Ravi [1]

1. Department of Internal Medicine, University of Arizona College of Medicine, Tucson, USA

Case	Flow cytometry	Karyotype	Double-hit MYC and BCL2 rearrangement	FISH panel	BM biopsy post-CAR-T cell	NGS post-CAR-T cell
1	Pre- and post-CAR-T cell showed no monotypic B-cells, antigenically aberrant T-cells, or myoblast populations	Pre- and post-CAR-T cell showed a normal karyotype	Yes	FISH high-grade lymphoma panel: normal pre- and post-CAR-T cell. FISH MDS panel not done at any point	Variably cellular and shows trilineage hematopoiesis with no evidence of residual/persistent lymphoma. There are no blasts and overt dysplasia present	TP53 mutation on chromosome 17 with c.589G>A VAF-5.15%. DNMT3A mutation on chromosome 2 with c.2580>A VAF-3.15%
2	Pre- and post-CAR-T cell showed no monotypic B-cells, antigenically aberrant T-cells, or myoblast populations	Pre- and post-CAR-T cell showed a normal karyotype	Yes	FISH high-grade lymphoma panel: normal pre- and post-CAR-T cell. Post-CAR-T cell FISH MDS panel deletion of 7q (seen in therapy-related MDS). FISH MDS panel not done pre-CAR-T cell	Normocellular with erythroid predominant trilineage hematopoiesis and <1% blasts. Mild trilineage dysplasia.	DNMT3A mutation on chromosome 2 with C.2098A>G and VAF of 4.95%. TP53 on chromosome 17 with c.535C>T VAF of 4.55%
3	Pre- and post-CAR-T cell showed no monotypic B-cells, antigenically aberrant T-cells, or myoblast populations	Pre- and post-CAR-T cell showed a normal karyotype	Yes	FISH high-grade lymphoma panel: normal pre- and post-CAR-T cell. FISH MDS panel not done at any point	Variably cellular marrow with trilineage hematopoiesis and mildly left-shifted myeloid maturation	TET2 mutation on chromosome 4 with c.623delC VAF of 4.22%
4	Pre- and post-CAR-T cell showed no monotypic B-cells, antigenically aberrant T-cells, or myoblast populations	Pre-CAR-T cell showed a normal karyotype, post-CAR-T cell showed deletions of 5q and 7q, consistent with MDS with a poor prognosis	No	FISH high-grade lymphoma panel: normal pre- and post-CAR-T cell. FISH MDS post-CAR-T cell showed 5q and 7q deletions, consistent with MDS. FISH MDS panel not done pre-CAR-T cell	50% cellularity with trilineage dysplasia, 11% ring sideroblasts, and no increase in blasts	TP53 mutation on chromosome 17 with c.370_371insT VAF of 23.72%

TABLE 2: Genetic and tissue characteristics of each of the four DLBCL cases

DOI: 10.7759/cureus.44677

Myelodysplastic Syndrome After Anti-CD19 Chimeric Antigen Receptor T-cell Therapy: A Case Series

Armaan Dhaliwal [1] , Soumiya Ravi [1]

1. Department of Internal Medicine, University of Arizona College of Medicine, Tucson, USA

Case	Flow cytometry	Karyotype	Double-hit MYC and BCL2 rearrangement	FISH panel	BM biopsy post-CAR-T cell	NGS post-CAR-T cell
1	Pre- and post-CAR-T cell showed no monotypic B-cells, antigenically aberrant T-cells, or myoblast populations	Pre- and post-CAR-T cell showed a normal karyotype	Yes	FISH high-grade lymphoma panel: normal pre- and post-CAR-T cell. FISH MDS panel not done at any point	Variably cellular and shows trilineage hematopoiesis with no evidence of residual/persistent lymphoma. There are no blasts and overt dysplasia present	TP53 mutation on chromosome 17 with c.589G>A VAF-5.15%. DNMT3A mutation on chromosome 2 with c.2580>A VAF-3.15%
2	Pre- and post-CAR-T cell showed no monotypic B-cells, antigenically aberrant T-cells, or myoblast populations	Pre- and post-CAR-T cell showed a normal karyotype	Yes	FISH high-grade lymphoma panel: normal pre- and post-CAR-T cell. Post-CAR-T cell FISH MDS panel deletion of 7q (seen in therapy-related MDS). FISH MDS panel not done pre-CAR-T cell	Normocellular with erythroid predominant trilineage hematopoiesis and <1% blasts. Mild trilineage dysplasia.	DNMT3A mutation on chromosome 2 with C.2098A>G and VAF of 4.95%. TP53 on chromosome 17 with c.535C>T VAF of 4.55%
3	Pre- and post-CAR-T cell showed no monotypic B-cells, antigenically aberrant T-cells, or myoblast populations	Pre- and post-CAR-T cell showed a normal karyotype	Yes	FISH high-grade lymphoma panel: normal pre- and post-CAR-T cell. FISH MDS panel not done at any point	Variably cellular marrow with trilineage hematopoiesis and mildly left-shifted myeloid maturation	TET2 mutation on chromosome 4 with c.623delC VAF of 4.22%
4	Pre- and post-CAR-T cell showed no monotypic B-cells, antigenically aberrant T-cells, or myoblast populations	Pre-CAR-T cell showed a normal karyotype, post-CAR-T cell showed deletions of 5q and 7q, consistent with MDS with a poor prognosis	No	FISH high-grade lymphoma panel: normal pre- and post-CAR-T cell. FISH MDS post-CAR-T cell showed 5q and 7q deletions, consistent with MDS. FISH MDS panel not done pre-CAR-T cell	50% cellularity with trilineage dysplasia, 11% ring sideroblasts, and no increase in blasts	TP53 mutation on chromosome 17 with c.370_371insT VAF of 23.72%

TABLE 2: Genetic and tissue characteristics of each of the four DLBCL cases

Parameters	Shouse et al. [8]	Strati et al. [9]	Our series
Median age	74 years (range 57-76)	-	72.5 years (range 63-76)
Type of malignancy	DLBCL		DLBCL
Median lines of therapy prior to CAR-T cell	5	5	3
Patients with prior ASCT	4	1	1
Median time to MDS/CCUS diagnosis	3 months	13.5 months	6 months
Response to CAR-T cell	1 partial, 3 complete		4 complete
Pre-CAR-T cell mutations/dysplasia	1	Unknown	Unknown
CRS post-CAR-T cell	2		1
Patients who relapsed	2		None
Pre-CAR-T cell somatic mutations	1	2	None

TABLE 3: Comparison among similar studies that have studied post-CAR-T cell MDS/CCUS development

CAR-T cell: chimeric antigen receptor-modified T-cell, ASCT: autologous stem cell transplant, MDS: myelodysplastic syndrome, CCUS: clonal cytopenias of undetermined significance, CRS: cytokine release syndrome, DLBCL: diffuse large B-cell lymphoma

IMMUNOTHERAPY, VOL. 15, NO. 6 | CASE REPORT

normal

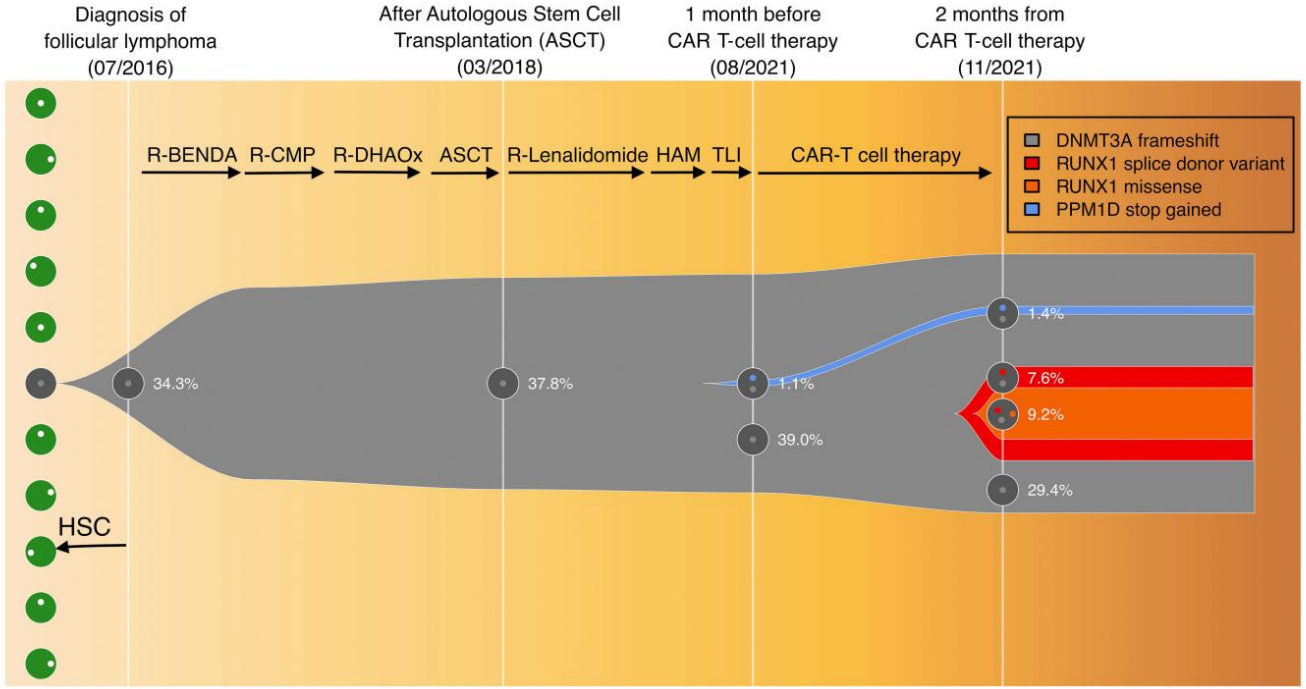
Myelodysplastic syndrome following chimeric antigen receptor T-cell therapy treated with allogenic stem cell transplantation

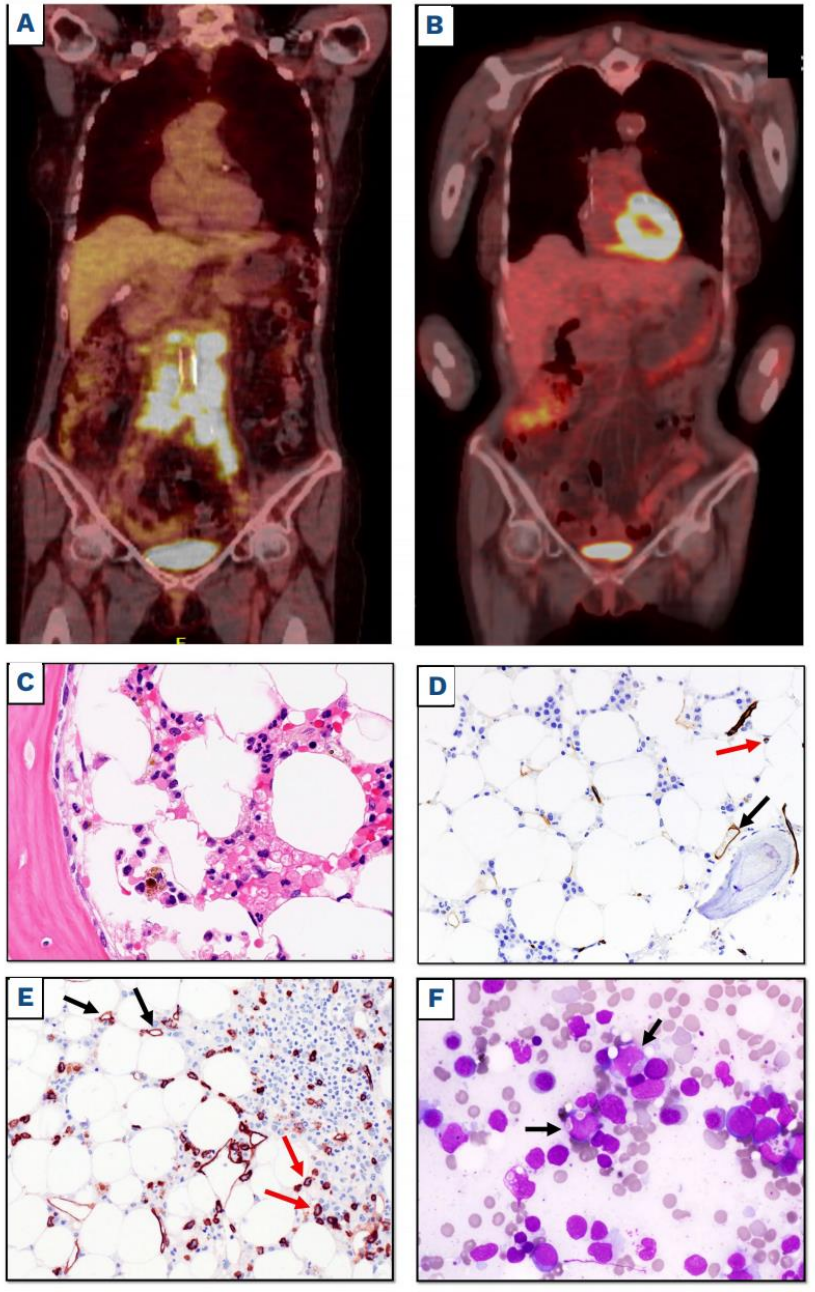
Khalil Saleh, Ahmadreza Arbab, David Ghez, Camille Bigenwald, Sophie Cotteret, Christophe Marzac, Florence Pasquier, Sylvain Pilorge, Véronique Saada, Véronique Vergé, Vincent Ribrag & Cristina Castilla-Llorente

Published Online: 23 Mar 2023 | https://doi.org/10.2217/imt-2022-0205

Acute myeloid leukemia development soon after anti-CD19 chimeric antigen receptor T-cell infusion in a patient with refractory diffuse large B-cell lymphoma and pre-existing clonal hematopoiesis

L Falini et al. Haematologica. 2023 Jan 1; 108(1): 290–294.
Published online 2022 Jul 28. doi: 10.3324/haematol.2022.281351





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DOI: 10.1002/pbc.27265

BRIEF REPORT

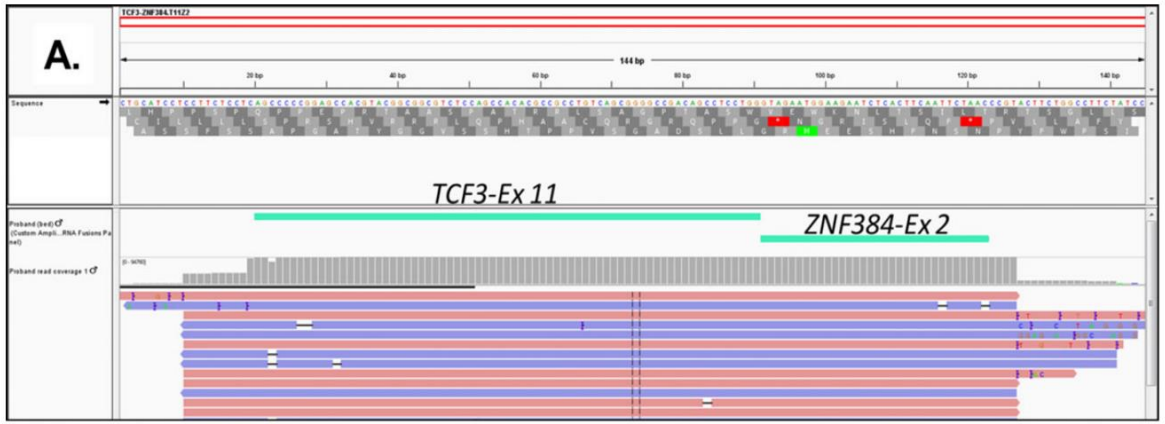
WILEY Pediatric Blood & Cancer | SIOP International Society of Paediatric Oncology | aspho The American Society of Pediatric Hematology/Oncology

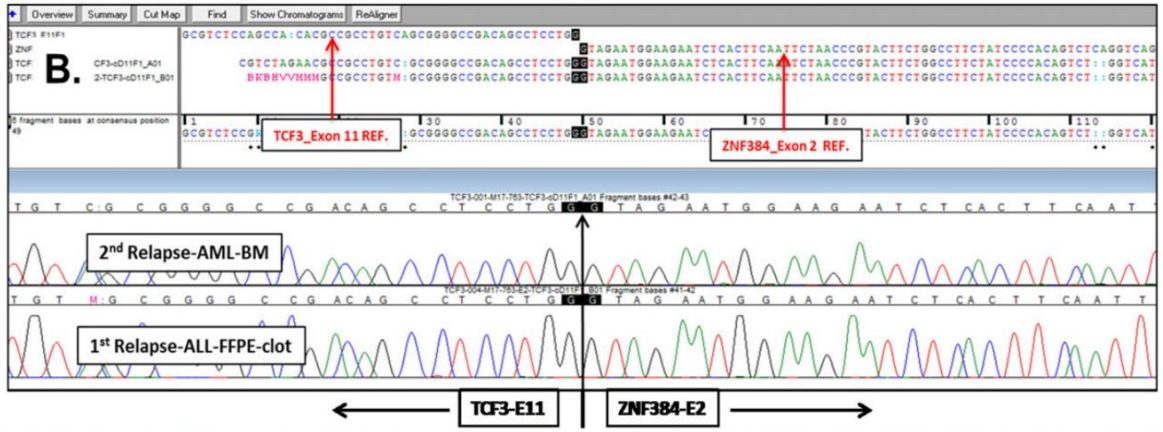
Myeloid lineage switch following chimeric antigen receptor T-cell therapy in a patient with TCF3-ZNF384 fusion-positive B-lymphoblastic leukemia

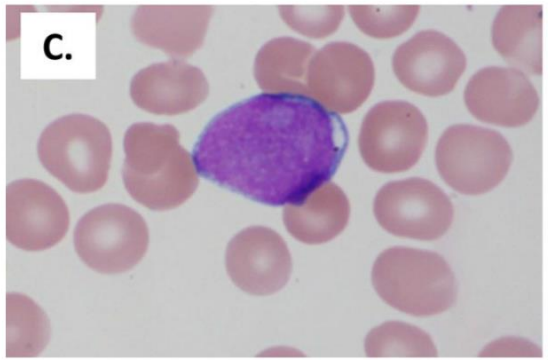
Matthew J. Oberley[1] | Paul S. Gaynon[2] | Deepa Bhojwani[2] | Michael A. Pulsipher[2] | Rebecca A. Gardner[3,4] | Matthew C. Hiemenz[1] | Jianling Ji[1] | Jennifer Han[1] | Maurice R.G. O'Gorman[1] | Alan S. Wayne[2] | Gordana Raca[1]

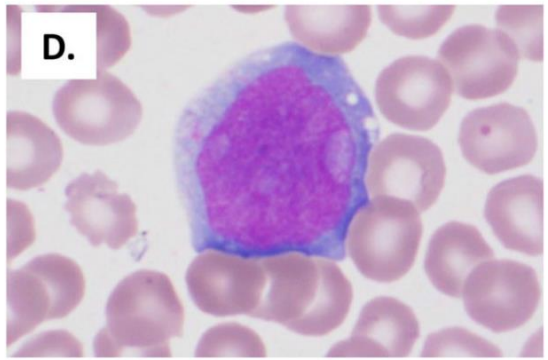
TABLE 1 Pathology and genetic testing results for tumor samples

	Pathology	Karyotype	FISH	Chromosomal microarray analysis	DNA mutations (OncoKids)	Gene fusions (OncoKids and/or RT-PCR)
Diagnosis	Immunophenotype (flow cytometry): positive for CD19, CD20 (partial), CD22, CD34, CD38, CD13, CD33 (partial), and HLA-DR; negative for CD10, MPO, and TdT	46,XY,del(12)(p13)[3]/46,XY[27]	Negative for BCR/ABL1, ETV6/RUNX1, PBX1/TCF3 fusions and PDGFRB and KMT2A (mixed lineage leukemia) rearrangements	Not performed	Not performed	TCF3 Exon 11 (ENST00000262965)-ZNF384 Exon 2 (ENST00000396795)
B-ALL relapse, CD19-positive	Immunophenotype (flow cytometry): CD19 variable (dim to moderate), CD22 bright, CD10 variable (negative to dim), TdT, CD34, CD38, CD58, HLA-DR bright, CD123; negative for CD24, CD13, CD33, and MPO	46,XY[1]//46,XX[19] (posttransplant chimerism)	Positive for a loss of ETV6 (12p13) signal in 20% of the cells	Not performed	Not performed	TCF3 Exon 11 (ENST00000262965)-ZNF384 Exon 2 (ENST00000396795)
AML relapse, lineage switch	Immunophenotype (flow cytometry): positive for CD13, CD33 (partial, dim), CD34, CD117, CD123, CD11b (partial), CD38 (moderate) and CD7; negative for CD19, CD10, CD20, CD24, MPO, TdT, and CD22	46,XY[20]	Positive for a loss of ETV6 (12p13) signal in 18% of the cells	Copy number loss in: 7q36.1q36.3 (10.8 Mb), 12p13.31p12.3 (9.8 Mb), 13p13.31p12.3 (86.5 Mb), 16 q12.2q23.1 (19.6 Mb), 18 p11.32p11.21 (11.6 Mb) and 21q21.3q22.11 (5 Mb) Copy number gain in 8q21.11q24.3 (71.4 Mb)	NM_004119 (FLT3) c.1788_1789ins GGCCCTGATTT CAGAGAA (p.Glu596_ Tyr597insGlyPro AspPheArgGlu)	TCF3 Exon 11 (ENST00000262965)-ZNF384 Exon 2 (ENST00000396795)









„Other“ rare toxicities

Case Report

Blood Cell Therapy
The official journal of APBMT

Severe bloody diarrhea due to cytokine release syndrome after chimeric antigen receptor T cell therapy for refractory acute lymphoblastic leukemia

Haruko Shima[1], Takahiro Ishikawa[1], Jumpei Ito[1], Katsura Emoto[2], Takumi Kurosawa[1], Dai Keino[3], Fumito Yamazaki[1], Hiroaki Goto[3], Hiroyuki Shimada[1]

Blood Cell Therapy-The official journal of APBMT- Vol. 5 Issue 1 No. 4 2022

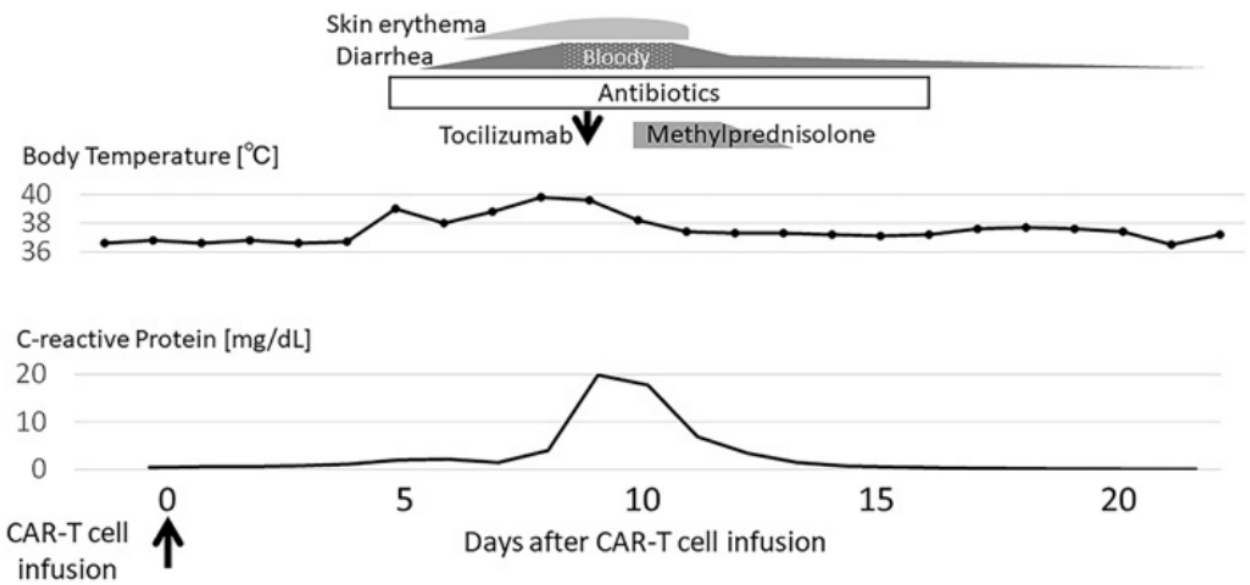


Figure 1. The clinical course after chimeric antigen receptor (CAR) T cell infusion

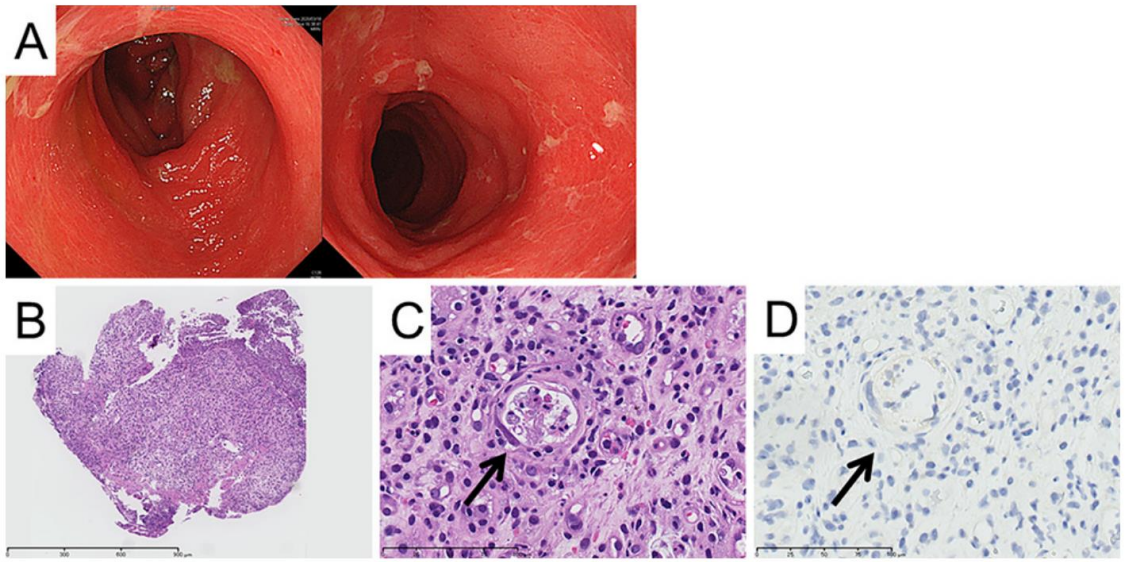


Figure 2. Lower gastrointestinal endoscopic findings and representative intestinal tissue
(A) Edematous mucosa and a geographical ulcer with mucous adhesions are observed. (B) Ulcerative change with severe inflammation is observed. No crypts and epithelial cells are seen. (C) Inflammatory cells are mainly composed of lymphocytes, plasma cells, and neutrophils. Some nuclei (allow) in capillary vessels are atypical and swollen, with differential diagnoses including viral infection. (D) Immunohistochemistry for CMV was negative.

Clinical Nephrology – Case Studies, Vol. 11/2023 (17-21)

Thrombotic microangiopathy following chimeric antigen receptor T-cell therapy

Matthew S. Wu[1] and Abbal Koirala[2]

[1]Department of Medicine, and [2]Section of Nephrology, Department of Medicine, University of Washington Medical Center, Seattle, WA, USA

Kidney Medicine

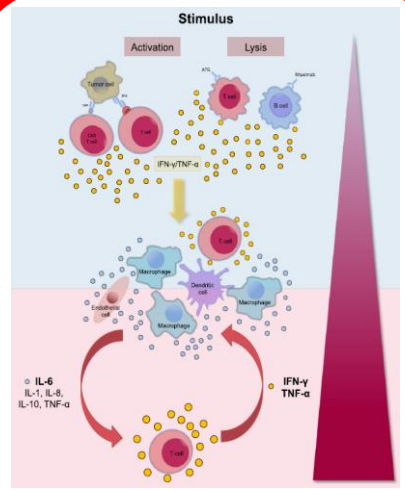
Case Report

Collapsing Focal Segmental Glomerulosclerosis and Acute Kidney Injury Associated With Chimeric Antigen Receptor T-Cell (CAR-T) Therapy: A Case Report

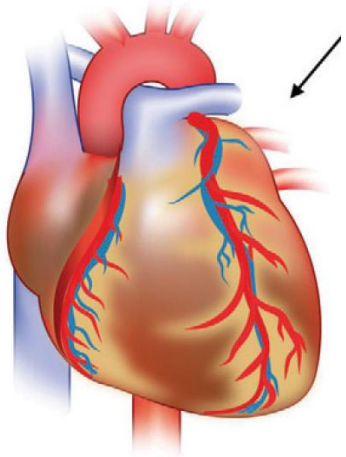
Ratna Acharya, Biljana Horn, Xu Zeng, and Kiran Upadhyay

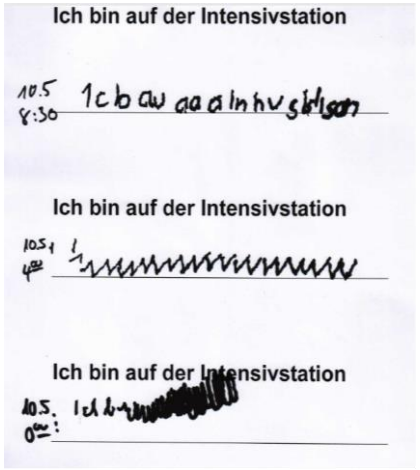
Kidney Med Vol 3 | Iss 6 | November/December 2021

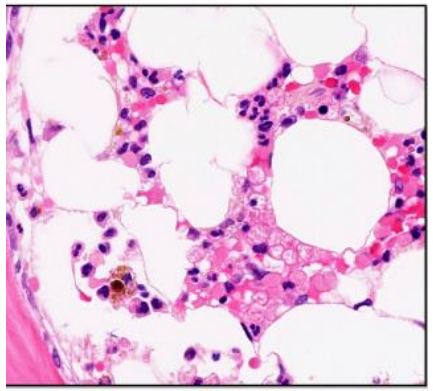
Conclusions

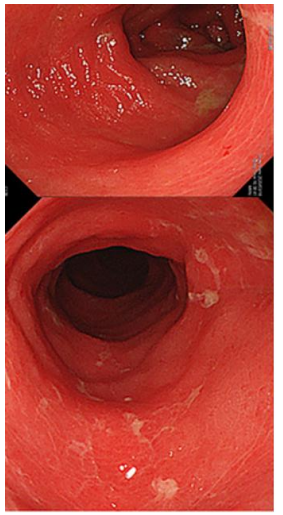


Shimabukuro-Vornhagen et al. Journal for Immuno Therapy of Cancer (2018) 6:56









Cellular infiltrations, Inflammation and cytokines can affect many cell types. Particularly when local inflammation affects critial locations particular care needs to be considered

Cardiovascular complications are common in this frail and often heavily pre-treated population.
Cytokines contribute to cardiac dysfunction

Complications affecting neuronal structures a/o functions are diverse, and incompletely understood.
CAR-T cells easily reach neuronal tissues

Hematopoietic complications are common. Malignant transformation within a chronically inflammed environment and heavy pre-treatment is possible (particularly if CHIP is already present)

"Other"
Complications can occur.... Causal relationship to CAR-T not always convincingly demonstrated