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Title: Immune effector cell-associated acute stroke: a novel entity?**Running Title: Immune effector cell-associated acute stroke**

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Chimeric antigen receptor (CAR) T-cells may induce neurologic toxicity referred to as immune effector cell-associated neurotoxicity syndrome (ICANS). Its pathophysiology, although not fully understood, seems to be due to the permeabilization of the blood brain barrier (1,2), which induces a local capillary leak and an increase of cytokine concentration in the brain leading to cerebral edema (3). Here, we report four cases of ischemic strokes that occurred after CAR T-cell infusion.

Our monocentric retrospective cohort include 190 patients treated at the University hospital of Rennes, France. Patients were treated with axi-cel (60%), tisa-cel (20%), brexu-cel (14%) and ide-cel (5%) for large B-cell lymphoma (LBCL) (73%), acute lymphoid leukemia (ALL) (9%), mantle-cell lymphoma (MCL) (7%), follicular lymphoma (FL) (6%), or multiple myeloma (MM) (5%). All patients had clinical and paraclinical baseline assessment before CAR T-cells infusion, including an

appointment with a trained and dedicated neurologist physician. Our center policy was to perform baseline MRI for every patient, which facilitate comparison during ICANS to assess imputability of newly diagnosed brain lesions. ICANS occurred in 47% of patients (n=91), and severe ICANS, defined as ICANS grade 3 or more, occurred in 17% patients (n=33).

During the study period, 71 MRI were performed on 91 patients who developed an ICANS (78%). All of the 33 patients who developed a severe ICANS had an MRI. Interestingly, 4/33 (12%) of those patients had ischemic strokes of fortuitous findings on acute MRI compared to baseline MRI (**table 1**). No patient presented clinical symptoms associated with stroke as it was only focal strokes (**figure S1**). Two patients had an ICANS grade 3, which represent 2/21 (10%) of all grade 3, and 2 patients had an ICANS grade 4, which represent 2/12 (17%) of all grade 4. Cardiac monitoring was ensured by baseline electrocardiogram and further ones on request.

Patient 1 had an history of transient ischemic attack (TIA), for which he had antiplatelet therapy (APT), and the cardiovascular assessment founded only a non-significant 30-40% internal carotid artery stenosis in one of them, which was not suspected of being involved in the acute ischemic event. Patient 2 had no prior known cardiovascular comorbidity or cardiovascular risk factors (CVRF) (except her age), and extensive cardiovascular assessment (including ECG and Holter ECG to search for atrial fibrillation) did not find additional CVRF. Patient 3 had multiple cardiovascular risk factors and received at baseline both APT and ACT for ischemic and atrial fibrillation respectively. Patient 4 had diabetes mellitus and received ACT for atrial fibrillation at baseline.

Ischemic strokes occurring after CAR T-cell therapy have been rarely reported. We performed a systematic review of the literature using PubMed, UpToDate and Researchgate platforms with the keywords "CAR-T & Stroke" "CAR-T & MRI" "CAR-T & ischemia". We found only 4 case reports or small series reporting ischemic strokes after CAR T-cells. Strati et al. (4) described three cerebral infarcts, including one in a patient who had a prior history of atrial fibrillation, among 100 R/R DLBCL patients treated with axi-cel. In this study, every patient had a baseline neuro-imaging but only 17% patients had baseline MRI before CAR T-cells infusion, which could make comparisons difficult between acute stroke and baseline status. Moreover, systematic MRI during ICANS was less frequent, as only 56% of patients with ICANS all grades and 75% of patients grade 3 or more benefited of MRI during their ICANS. Rubin et al. (5) reported 2 cases of ischemic strokes in their retrospective cohort of 100 patients treated for various hematological malignancies, who had both cardiovascular risk factors or cardiovascular comorbidities. In this cohort, systematic baseline imaging policy was not mentioned. As Strati et. al study, a few patients (29%) benefited of MRI during their ICANS, without knowing the proportion in patients with severe ICANS. Holtzmann et al. (6) reported an isolated case of pontine acute stroke among 45 patients with R/R diffuse large-cell B lymphoma (DLBCL) treated with axicabtagene ciloleucel (axi-cel), which led to neurogenic bladder and subsequent obstructive hydronephrosis. This study did not mentioned proportion of patients with ICANS and severe ICANS who received MRI.

All of these 3 studies were designed to describe ICANS course but none of them adopted a large MRI baseline policy to assess for neurological abnormalities occurring during ICANS courses.

Finally, Wang et al. reported a case (7) of bilateral anterior cerebral artery (ACA) stroke occurring in MM treated by idecabtagene vicleucel.MM.

The real issue in this report of CAR T-cells-associated acute strokes seems to be the clinical significance of such events.

On one hand, such a relatively high frequency of occurrence (6% of all ICANS and 12% of all severe ICANS in our cohort) is two to three times more frequent than previous studies and might suggest a pathophysiological link between CAR T-cells infusion and ischemic events. Pro-inflammatory state as cytokine release syndrome (CRS) is a well-known trigger of endothelial activation (8) and is also known to activate hemostasis through platelet (9) and secondary hemostasis activation (10,11) leading to CRS-associated coagulopathy (12) which may promote ischemic events.

However, one could argue that associated strokes are just an epiphenomenon in post-CAR T-cells infusion, as they might be quite common in adults and elderly people during hospitalization, even more when considering eventual underlying CVRF and inflammatory events. By extension, active cancer, especially treated with chemotherapy-regimens including Cyclophosphamide, are well-known risk factors of strokes (13).

The underlying point is whether the CAR T-cells-associated stroke occur in predisposed condition (hospitalized elderly patients, underlying CVRF) in situations at risk for ischemic events (active cancer, chemotherapy including cyclophosphamide), regardless to the CAR T-cells infusion, or whether the CAR T-cells-mediated inflammatory state plays a role in the occurrence of such events.

CAR T-cells-associated strokes seems to be highly under-reported in the literature compared to our cohort, mainly due to a broad MRI policy before CAR T-cells infusion and during ICANS, which could allow systematic assessment for acute strokes with comparison to baseline. Strikingly, clinical significance and management of these ischemic events in the post CAR T-cells setting require further studies.

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Authors contributions

G.M. and R.H. designed the research. M.M. performed the research. M.M. and G.M. wrote the paper. R.H. and S.L. reviewed the paper.

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Table 1. Description of patients with acute stroke event after CAR T-cells

Patient characteristics	Patient 1	Patient 2	Patient 3	Patient 4
Hematologic malignancy	DLBCL	MM	DLBCL	DLBCL
Hemopathy status at lymphodepletion	PD	PR	PD	PD
CAR T-cells	Axi-cel	Ide-cel	Axi-cel	Axi-cel
Sex	Man	Woman	Man	Man
Age (years)	76	70	70	76
Dyslipidemia *	No	No	Yes	No
BMI (kg/m ²)	22,1	24,7	34,5	24,6
Hemostasis trouble	No	No	No	No
Tobacco users **	No	No	Yes	No
Diabetes mellitus	No	No	Yes	Yes
Hypertension	No	No	Yes	No
Chronic renal failure	No	No	Yes	No
Cardiac diseases	None	None	Ischemic cardiopathy and atrial fibrillation	Atrial fibrillation
Stroke history	Transient ischemic attack	No	No	No
APT before CAR T-cells	Acetylsalicylic acid 75 mg	None	Acetylsalicylic acid 75 mg	None
Preexistent ACD	None	None	Apixaban 5mg	Apixaban 5mg
Baseline MRI	Normal	Vascular leucopathy	Normal	Normal
CRS				
CRS grade maximum	1	1	1	2
CRP level (mg/l)	14	334	50	10
Ferritin level (ug/mL)	3369	764	440	3369
ICANS				
ICANS starting day	D6	D2	D8	D3
Maximum ICANS grading	3	3	4	4
Maximum ICANS grading day	D10	D4	D8	D8
Day of MRI	D10	D5	D9	D7
ICANS grading the day of MRI	3	3	4	1
MRI results	Basal nuclei and right cerebellum strokes	Left punctiform parietal stroke	Minimal hippocampic stroke	Left microlacunar parietal stroke
Thorough cardiovascular work-up				
DUSSAT results	30-40% internal carotid artery stenosis	Normal	Not realized	Normal
ECG results	Normal	Normal	Normal	Atrial fibrillation
Holter-ECG results	Normal	Normal	Normal	Normal
TTE results	Normal	Normal	Dilated cardiomyopathy	Normal

Follow-up and treatment changes				
Treatment modification	Acetylsalicylic acid upgraded to 160mg	Acetylsalicylic acid 75 mg introduction	None	None

ACD, Anticoagulant drug; APT, Antiplatelet therapy; ECG, Electrocardiogram ; DLBCL, diffuse large B-cell lymphoma; DUSAT, Doppler ultrasound of the supra-aortic trunk ; MM, Multiple Myeloma; TTE, Transthoracic echocardiogram ; PD, progressive disease ; PR, Partial response

* Patients were classified as "Dyslipidemia" if they had an history of dyslipidemia or hyperlipidemia in their medical record or had a statin treatment.

** Patients were classified as "tobacco users if they had an history of tobacco use in their medical record or reported tobacco use at baseline assessment

Declaration of Competing Interest

R.H. reports honoraria from Kite/Gilead, Novartis, Incyte, Janssen, MSD, Takeda and Roche; and consultancy at Kite/Gilead, Novartis, Bristol-Myers Squibb/Celgene, ADC Therapeutics, Incyte, Miltenyi.

G.M. reports honoraria from BMC-cellgene and Gilead-Kite.

M.M. and S.L. report no conflict of interest.