RESEARCH LETTER

blood advances

TO THE EDITOR:

Inflammatory reactions mimic residual or recurrent lymphoma on [^{18}F]FDG-PET/CT after CD19-directed CAR T-cell therapy

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Chimeric antigen receptor T-cell (CAR-T) therapy, an immunotherapy in which T cells are genetically modified to target tumor surface antigen(s), transformed the treatment landscape in hemato-oncology, with durable responses in ~50% of the patients with relapsed or refractory large B-cell lymphoma (LBCL) and mantle cell lymphoma (MCL).[1-4]

2-Deoxy-2-[^{18}F]fluoro-D-glucose–positron emission tomography and computed tomography ([^{18}F]FDG-PET/CT) imaging is routinely used for staging and response evaluation in patients with aggressive lymphoma. The Lugano classification, including the Deauville score (a 5-point scale to grade the intensity of [^{18}F]FDG uptake), is used for imaging assessment in these patients.[5-7]

It is known that within the field of immunotherapy, adequate determination of treatment outcome can be challenging because of abnormalities on [^{18}F]FDG-PET/CT caused by active inflammation, resulting in phenomena such as pseudoprogression and sarcoid-like reactions (SLRs).[8-10] This study reports on 2 types of inflammatory reactions (IRs) mimicking residual/recurrent lymphoma on [^{18}F]FDG-PET/CT after CD19-directed CAR-T therapy.

Based on clinical, radiological, and pathological findings among patients treated with CD19-directed CAR-Ts, 2 IRs, an SLR and a histiocytic reaction (HR), were identified by experts of the Dutch CAR-T tumorboard, a platform for nationwide referral, eligibility assessment, and data collection for CAR-T therapy for adult patients with LBCL. Based on the literature, SLR was defined as mostly symmetric bilateral hilar and mediastinal lymphadenopathy and/or lymphadenopathy in other regions with increased [^{18}F]FDG uptake and, in a biopsy specimen, noncaseating epithelioid cell granulomatous inflammation without evidence of lymphoma.[11-13] HR was defined as increased [^{18}F]FDG uptake at the original tumor localization early (ie, ±1 month) after CAR-T infusion, with sheets of (foamy) histiocytes and necrotic lymphoma cells in the biopsy specimen.

We included adult patients with LBCL and MCL treated with CD19-directed CAR-Ts (axicabtagene ciloleucel [axi-cel], tisagenlecleucel, lisocabtagene maraleucel, and brexucabtagene autoleucel [brexu-cel]) from November 2016 to June 2022 in The Netherlands, either in a clinical trial

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Table 1. Clinical characteristics of patients with 2 distinct IRs after CD19-directed CAR-T therapy, split based on biopsy confirmation

	SLR			HR		
	Total (n = 11*)	Confirmed by biopsy (n = 5*)	Not confirmed by biopsy (n = 6*)	Total (n = 9*)	Confirmed by biopsy (n = 3)	Not confirmed by biopsy (n = 6*)
Median age†, y (range)	61 (35-73)	61 (35-73)	61 (46-72)	58 (47-66)	52 (47-66)	59 (54-66)
Male sex†, n (%)	7 (64)	2 (40)	5 (83)	7 (78)	2 (67)	5 (83)
Histological subtype†, n (%)						
DLBCL	8 (73)	4 (80)	4 (67)	6 (67)	1 (33)	5 (83)
tFL	2 (18)	1 (20)	1 (17)	3 (33)	2 (67)	1 (17)
MCL	1 (9)	–	1 (17)	–	–	–
Ann Arbor stage†, n (%)						
I-II	1 (10)	–	1 (17)	2 (22)	1 (33)	1 (17)
III-IV	10 (90)	5 (100)	5 (83)	7 (78)	2 (67)	5 (83)
Prior lines of systemic therapy†, n (%)						
1	2 (18)	2 (40)	–	1 (11)	–	1 (17)
2	7 (64)	3 (60)	4 (67)	6 (67)	2 (67)	4 (67)
≥3	2 (18)	–	2 (33)	2 (18)	1 (33)	1 (17)
Prior stem cell transplantation†, n (%)						
No	8 (73)	4 (80)	4 (67)	9 (100)	3 (100)	6 (100)
Auto-SCT	3 (27)	1 (20)	2 (33)	–	–	–
Allo-SCT	–	–	–	–	–	–
Bridging strategy, n (%)						
No bridging	6 (55)	5 (100)	1 (17)	4 (44)	1 (3)	3 (50)
Systemic therapy	2 (18)	–	2 (33)	–	–	–
RT	1 (9)	–	1 (17)	5 (56)	2 (67)	3 (50)
Best response to CAR-T therapy, n (%)						
CMR	10 (90)	5 (100)	5 (83)	7 (78)	3 (100)	4 (67)
PMR	1 (10)	–	1 (17)	2 (22)	–	2 (33)
Response to CAR-T therapy at last assessment, n (%)						
CMR	9 (82)	5 (100)	4 (67)	6 (67)	2 (67)	4 (67)
PMR	1 (9)	–	1 (17)	2 (22)	–	2 (33)
PD	1 (9)	–	1 (17)	1 (11)	1 (33)	–
Median follow-up from the onset of IR (d), median (range)	755 (133-1558)	1140 (949-1558)	530 (133-755)	550 (180-1397)	584 (383-1126)	396.5 (180-1397)
Time between CAR-T infusion and onset of IR (d), median (range)	116 (−259 to 548)	184 (−259 to 268)	70.5 (−105 to 548)	28 (21-31)	28 (28-29)	28 (21-31)

allo-SCT, allogeneic stem cell transplantation; auto-SCT, autologous stem cell transplantation; CMR, complete metabolic response; CRP, C-reactive protein; DLBCL, diffuse large B-cell lymphoma; LDH, lactate dehydrogenase; PD, progressive disease; PMR, partial metabolic response; RT, radiotherapy; tFL, transformed follicular lymphoma.

*Two patients experienced both an HR and an SLR simultaneously; thus, a total 20 IRs were observed in 18 patients.

†At screening for CAR-T therapy.

Table 1 (continued)

	SLR			HR		
	Total (n = 11*)	**Confirmed by biopsy (n = 5*)**	**Not confirmed by biopsy (n = 6*)**	**Total (n = 9*)**	**Confirmed by biopsy (n = 3)**	**Not confirmed by biopsy (n = 6*)**
Time between IR onset and resolution (d), median (range)	190 (13-585)	459 (187-494)	181 (13-585)	141 (102-427)	284 (141-427)	102 (–)
Ongoing, n (%)	3 (27)	2 (40)	1 (17)	6 (67)	1 (33)	5 (83)
Duration if ongoing (d), median (range)	989 (402-1321)	1155 (989-1321)	402 (–)	285.5 (85-1035)	329 (–)	242 (85-1035)
Any B symptoms reported at the time of onset of IR						
Yes, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Missing, n (%)	1 (9)	1 (20)	–	0 (0)	–	–
LDH levels at the time of onset of IR, n (%)						
≤ULN	5 (45)	3 (60)	2 (33)	6 (67)	1 (33)	5 (83)
>ULN	3 (27)	–	3 (50)	3 (33)	2 (67)	1 (17)
>2 × ULN	–	–	–	–	–	–
Missing, n (%)	3 (27)	2 (40)	1 (17)	–	–	–
CRP at time of onset of IR, median (range)	3.3 (1.1-7)	2.5 (1.7-3.3)	4.5 (1.1-7)	1.5 (0.3-53)	0.9 (0.7-43)	2 (0.3-53)
Missing, n (%)	6 (55)	3 (60)	3 (50)	1 (11)	–	1 (17)
IR in irradiated field if patient received RT, yes, n (%)	–	–	–	5 (100)	2 (100)	3 (100)

allo-SCT, allogeneic stem cell transplantation; auto-SCT, autologous stem cell transplantation; CMR, complete metabolic response; CRP, C-reactive protein; DLBCL, diffuse large B-cell lymphoma; LDH, lactate dehydrogenase; PD, progressive disease; PMR, partial metabolic response; RT, radiotherapy; tFL, transformed follicular lymphoma.

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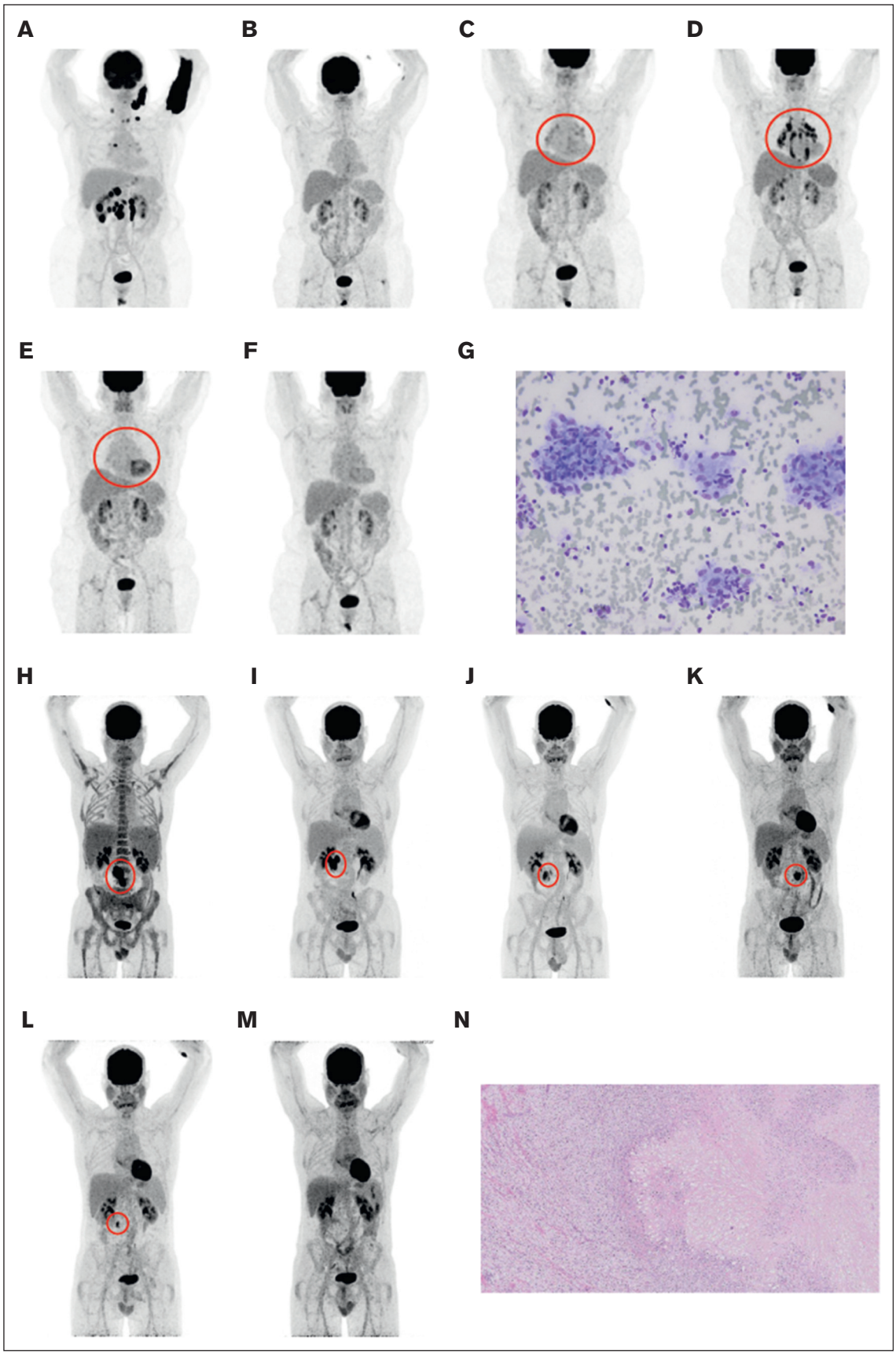

Figure 1.

(NCT02348216, NCT03391466, NCT02601313, NCT02445248, NCT0357089, NCT03484702, and NCT03575351) or as a standard of care, with [^{18}F]FDG-PET/CT abnormalities suspected for an SLR or HR at routine response evaluation(s) after CAR-T therapy. [^{18}F]FDG-PET/CT abnormalities were defined as increased [^{18}F]FDG uptake without evidence of residual/recurrent lymphoma, either biopsy proven or after a "wait-and-see" strategy, when biopsy was unfeasible. Only patients with ≥3 months of follow-up, including ≥1 [^{18}F]FDG-PET/CT scan(s), after the onset of [^{18}F]FDG-PET/CT abnormalities suspected of a SLR or HR were included. An incidence could be estimated using the nationwide registry of patients treated with commercially available CAR-Ts and the total number of patients treated in the aforementioned clinical trials in The Netherlands. Ethical approval was obtained. Data were retrospectively collected by reviewing medical records with a cutoff date of 31 January 2023. Care was provided according to study protocols or institutional guidelines. More specifically, [^{18}F]FDG-PET/CTs were performed at ~1, 3, 6, and 12 months after CAR-T infusion, and additional scans were performed according to study protocol or institutional guidelines. The study was performed in accordance with the Declaration of Helsinki.

Of the 236 patients treated with CD19-directed CAR-Ts (axi-cel: n = 200, brexu-cel: n = 12, lisocabtagene maraleucel: n = 11, and tisagenlecleucel: n = 13), 18 (7.6%) were identified with abnormalities suspected for an SLR or HR on routine [^{18}F]FDG-PET/CT (median age, 60.5 years; range, 35-73 years). Most patients were diagnosed with diffuse LBCL, followed by transformed follicular lymphoma and MCL; 50% of these patients (n = 9) received bridging therapy before CAR-T therapy (radiotherapy: n = 5, and systemic therapy: n = 4). The best overall response rate was 100% (complete response rate: 89% [n = 16]). All patients were asymptomatic at onset of the IR. No clinical signs of disease progression, such as B symptoms, clinical lymphadenopathy, or >2× upper limit of normal lactate dehydrogenase levels, were present. Median follow-up from the onset of the IR was 657.5 days (range, 133-1558 days). Two patients experienced both an SLR and HR, resulting in a total of 20 IRs observed. Eleven patients were suspected to have an SLR (axi-cel: n = 10, and brexu-cel: n = 1), and 9 patients were suspected to have an HR (axi-cel: n = 9; Table 1). No additional treatment was given for the IRs. Estimated incidences of SLRs and HRs in patients treated with CAR-Ts were 4.7% and 3.8%, respectively, whereas a total of 116 patients (49.2%; 116 of 236) had progressive disease after CAR-T therapy.

In 11 of 18 patients, an SLR was suspected using the aforementioned definition. A representative case is shown in Figure 1A-F. Of these 11 patients, biopsy was performed in 5 and showed non-caseating epithelioid cell granulomatous inflammation without evidence of lymphoma or pathogens such as *Mycobacterium tuberculosis*, fungus, or yeast (Figure 1G). The median time to onset was 116 days (range, −259 to 548 days) from CAR-T infusion. In retrospect, SLR was already existent before CAR-T infusion in 2 patients but became more evident after CAR-T therapy. The SLR resolved in 8 of 11 patients, with a median time to resolution of 190 days (range, 13-585 days). In 3 patients, the SLR was still ongoing, with a median duration of 989 days (range, 402-1321 days).

Using the aforementioned definition of HR, 9 of 18 patients were suspected of having this IR. A representative case is shown in Figure 1H-M. Histopathological examination, performed in 3 of 9 patients, showed sheets of (foamy) histiocytic cells with necrotic lymphoma cells and without granulomatous processes (Figure 1N). HRs occurred early after CAR-T infusion (median time to onset: 28 days; range, 21-31 days). In 3 of 9 patients, the HR resolved with a median time to resolution of 141 days (range, 102-427 days). In the other 6 patients, the HR was still ongoing, with a median duration of 285.5 days (range, 85-1035 days). All HRs were located in the irradiated field if patients received radiotherapy as bridging strategy (n = 5).

We describe cases of SLR and HR occurring at different time points after CAR-T therapy, illustrating that after CAR-T therapy also, similar to other immunotherapies, IRs can mimic residual/recurrent disease on [^{18}F]FDG-PET/CT.[11]

Cases of SLRs are extensively described in literature in non-Hodgkin lymphoma at diagnosis, after systemic treatment or stem cell transplantation, and in solid cancers after treatment with immune checkpoint inhibitors.[12,14-16] However, the exact pathophysiological mechanism is still unknown. The association of an interferon-γ–producing T helper 17 (Th17) T-cell subset with the occurrence of sarcoidosis after immune checkpoint inhibitors led to

Figure 1. Representative case of an SLR and an HR. A 66-year-old patient diagnosed with transformed follicular lymphoma, with an SLR after CAR-T therapy. No therapy was given during the bridging phase. (A) [^{18}F]FDG-PET/CT maximum intensity projection (MIP) overview before CAR-T infusion shows widespread localizations of lymphoma and extravasation of contrast. The [^{18}F]FDG-PET/CT at 1 (B), 3, and 6 months after infusion showed disappearance or normalization in size and metabolic activity of the previously described lymphoma localizations, consistent with a metabolic complete response. (C) The routine [^{18}F]FDG-PET/CT 9 months after infusion revealed new symmetric bilateral hilar and mediastinal lymphadenopathy with increased [^{18}F]FDG uptake, without suspicion of recurrent disease at the other original localizations. Biopsy of 1 of the [^{18}F]FDG-avid lymph nodes revealed nonnecrotic granulomatous changes, so follow-up was chosen. (D) On the [^{18}F]FDG-PET/CT 12 months after infusion, the hilar and mediastinal lymphadenopathy persisted and the intensity increased. Again, biopsy of [^{18}F]FDG-avid lymph nodes was performed, which again showed tissue with reactive changes consisting of nonnecrotic granulomas. Tuberculosis was ruled out via polymerase chain reaction and culture. Because our patient was doing fine and the radiological pattern and pathology findings were consistent with an SLR, we considered this the working diagnosis, and no treatment was administered. Fifteen (E), 18, and 24 (F) months after infusion of CAR-Ts, lymphadenopathy spontaneously disappeared. To date, this patient is in remission of lymphoma. (G) Histopathological results from [^{18}F]FDG-avid lymph nodes after CAR-T infusion showed reactive changes consisting of nonnecrotic granulomas, without evidence of lymphoma (Giemsa stain, scale 200x). (H) A 47-year-old patient diagnosed with DLBCL stage IV with a HR after CAR-T therapy. [^{18}F]FDG-PET/CT MIP overview at screening for CAR-T therapy shows a movable mesenterial lymphoma lesion. (I) Partial regression of the lesion after radiotherapy during the bridging phase. (J) At response evaluation, 28 days after infusion, a region with high [^{18}F]FDG uptake is visible at original tumor localization. (K) Compared with [^{18}F]FDG-PET/CT at 28 days after infusion, the residual high [^{18}F]FDG uptake region increased. A biopsy was performed, and histopathological examination showed an HR with no lymphoma. (L) Partial regression of [^{18}F]FDG uptake at the 9-month evaluation. (M) Complete regression of the HR 12 months after CAR-T infusion. (N) Histopathological results from the biopsy at 3 months showed a necrotic center of lymphoma cells surrounded by sheets of foamy histiocytes (Hematoxylin and eosin staining, scale 50x).

the hypothesis that (re)activation of CD4 Th1 cells could lead to macrophage activation, aggregation, and, thereby, induction of granuloma formation.[11,17] Recently, this hypothesis was supported by the presence of interferon-γ–producing Th17 T-cell subset cells in a case of SLR after anti–B-cell maturation antigen CAR-T therapy for multiple myeloma.[18] However, the reaction of the host to released tumor antigens after treatment is also proposed as an underlying mechanism.[11]

Concerning HR, it has been described that histiocytic infiltration can cause increased [^{18}F]FDG uptake.[10] The accumulation of necrotic lymphoma cells probably triggers this infiltration. Furthermore, Kuhnl et al have shown that a subgroup of patients who received radiotherapy as bridging strategy with high [^{18}F]FDG uptake (Deauville score of 4) in the irradiated field on [^{18}F]FDG-PET/CT early after CAR-T therapy only had a 10% risk of progressive disease at 6 months compared with 46% in the other patients with Deauville score–4 [^{18}F]FDG uptake.[19] Similarly, we also found a low relapse rate in patients with increased [^{18}F]FDG uptake in the irradiated field, after receiving radiotherapy as bridging strategy (n = 5).

Moreover, pseudoprogression, a well-known IR after immunotherapy, has been described early after CAR-T infusion (4-21 days) and is associated with a favorable outcome. In contrast to HR, pseudoprogression is characterized by initial tumor enlargement due to immune cell infiltration before decreasing tumor burden.[20-24]

In 2016, an adjusted version of the Lugano classification to account for pseudoprogression and tumor flare in the context of immunotherapies was published: the Lymphoma Response to Immunomodulatory Therapy Criteria.[25] Further adjustment of the Lugano criteria, taking into account SLRs and HRs as well, could enhance the identification of IRs after CAR-T.

A limitation of our study is that cases were identified using expert opinion instead of extensive medical record/imaging review of all patients treated with CAR-T therapy in The Netherlands; therefore, the number of IRs could have been underestimated.

In conclusion, our findings highlight that SLRs and HRs can occur after CAR-T therapy and should be considered as potential causes of [^{18}F]FDG uptake. This emphasizes the importance of histological proof of suspected residual/recurrent lymphoma, when feasible, to prevent potential misclassification of response and unnecessary treatment. This is particularly important, given the growing indications for CAR-T therapy use, probably resulting in a higher incidence of [^{18}F]FDG uptake because of IRs.

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