



Case Report

Temporal Dynamics and Efficacy of CAR-T Cell Therapy in B-ALL with Extramedullary Cutaneous Involvement: A Case Report and Discussion

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Abstract

Introduction: Chimeric antigen receptor-modified T cell (CAR-T) therapy is emerging as a useful therapy for B-cell acute lymphoblastic leukemia (B-ALL) with remaining uncertainty regarding the timing of response. We present a patient with extramedullary cutaneous involvement, initially stimulated by CAR-T infusion, with a rapid resolution of the lesions and serial biopsies providing information on the timing of reactivity. **Case presentation:** An 18-year-old male with relapsed and refractory B-ALL developed extramedullary involvement, leukemia cutis. After receiving chemotherapy, the lesion resolved, and he then proceeded to CAR-T therapy. Starting 9 days post-CAR-T infusion, he experienced progression of leukemia cutis. Skin biopsy confirmed leukemia cutis with less than 1% of T-cells. Due to worsening, he underwent another biopsy on day 13 of CAR-T therapy, which showed CAR-T cells comprising ~50% of all cells while peripheral blood CAR-T counts were negligible. The leukemia cutis lesions then cleared over the next week, and he achieved remission, lasting 5 months. **Discussion:** These findings suggest an initial stimulation of residual leukemia cutis cells, likely in response to chemokine and cytokine release related to CAR-T cell infusion. This was followed by an expansion of CAR-T cells at the site of involvement but not in the peripheral blood, and subsequent eradication of the leukemia. The time course of events and the biopsies 5 days apart provide insight into the timing of potential responses. The latter highlight the need to give CAR-T cells time to respond and that the correlation between peripheral blood CAR-T levels and activity can be disparate.

Keywords: Acute Lymphoblastic Leukemia; CART Therapy; Leukemia Cutis; Cytokine Release Syndrome

Introduction

B-cell acute lymphoblastic leukemia (ALL) remains a formidable disease with a low overall survival rate, particularly when accompanied by extramedullary involvement [1, 2]. The infiltration of leukemic cells into extramedullary sites serves as a predictor of poor chemotherapy response and an inferior prognosis [3, 4]. Notably, cutaneous involvement in B-cell ALL is a rarely observed manifestation that often signifies an aggressive disease state [5]. Chimeric antigen receptor-modified T cell (CART) therapy targeting CD19 has demonstrated therapeutic benefits for patients with relapsed and refractory B-cell ALL, even in the presence of extramedullary disease. However, comprehensive data elucidating the underlying mechanisms of CART cell migration to extramedullary sites in relation to clinical and laboratory dynamics is limited. In this report, we present a case study of a patient with refractory B-cell ALL experiencing extramedullary relapse, who received CART therapy. The patient initially exhibited progression of leukemia cutis, followed by near complete resolution of the extramedullary disease.

Case Presentation

An 18-year-old male with a one-month history of fatigue, intermittent blurry vision, and dyspnea initially presented to the UT Southwestern Medical Center in August 2022. His initial lab work revealed a WBC count of 138.7k, H/H of 6.0/18.7, and PLT of 11k. A bone marrow biopsy (BMB) with the flow cytometric analysis showed 90% blasts supporting a diagnosis of acute B-cell ALL was established: CD79a (+), CD38 (partial dim +), CD34 (+), CD22 (+ 100%), CD25 (partial +), CD20 (few +/-positive in 100.00% of the total blast population), CD19 (variably +), CD10 (bright +), HLA-DR (+), TdT (+), CD123 (-), CD45 (-), CD5 (-), surface immunoglobulin light chain (-), myeloperoxidase (-). Next-generation sequencing revealed JAK2 R867Q and IGH-CRLF2 rearrangements consistent with a diagnosis of Philadelphia-like ALL while cytogenetic analysis showed a normal male karyotype. The patient was started on induction chemotherapy with the CALGB 10403 protocol (intrathecal cytarabine, prednisone, vincristine, daunorubicin, pegaspargase, intrathecal methotrexate). Post-induction bone marrow biopsy on C1D37 revealed residual

ALL with 10% blasts. For reinduction the patient was switched to hyperCVAD (cyclophosphamide, vincristine sulfate, doxorubicin hydrochloride, and dexamethasone) with rituximab and intrathecal (IT) cytarabine and methotrexate. Repeat BMB (C1D18) showed persistent disease with 5% blasts, and the patient was started on Blinatumomab salvage therapy. On the C1D26 of therapy with Blinatumomab BMB was negative for the minimal residual disease (MRD). Patient was started on the second cycle of the Blinatumomab with the plan for stem cell transplantation (SCT) due to refractory nature of his disease. During the second cycle of blinatumomab on the C2D8 the patient developed bilateral neck and ear pain as well as asymptomatic slightly raised reticular lesions with no surrounding erythema (Figure 1, provided by family) and was started on amoxicillin due to concern for the infection. On the C2D13 his condition has not improved, and he presented to the hospital with cervical and mandibular lymphadenopathy. PET/CT showed extramedullary ALL relapse involving the scalp, salivary glands, cervical lymph nodes, mediastinum, and retroperitoneum. The patient was therefore started on mini-hyperCVD (lower doses of cyclophosphamide, vincristine, dexamethasone) and Inotuzumab salvage therapy. After the first cycle of the mini-hyperCV and Inotuzumab, he presented to the MD Anderson Cancer Center (MDACC) for the second opinion in January 2023. The plan was to continue with miniCVD with Inotuzumab and adding dexamethazone and Blinatumomab in preparation for potential CART therapy. On the C2D11 of the therapy, the patient has developed neutropenic fever along with bilateral parotid glands swelling. He was admitted and started on broad spectrum antibiotics. A biopsy of the parotid gland was performed which confirmed extramedullary relapse with leukemic involvement. Due to disease progression, CART therapy was deemed necessary and after the discharge from the hospital, on C2D26 in February patient underwent T-cell collection for the CART therapy. On C2D33 a planned PET/CT confirmed active leukemic involvement of the scalp, parotid gland, spleen, and right lower lung lobe (Figure 2 A, B, C). A skin biopsy also performed at that time confirmed leukemia cutis with immunohistochemistry (ICH) showing diffusely CD19-positive cells with 2-3% of CD3 positive cells (Figure 3 A, B, C). The patient was hospitalized on March 8, 2023, for salvage chemotherapy with cladribine, idarubicin, cytarabine, and pegasparginase which led to improvement in the rash after the completion of chemotherapy by the time he was discharged.



Figure 1: Patient's developing rash on the scalp with slightly raised reticular lesions and no surrounding erythema four month prior to CART therapy.

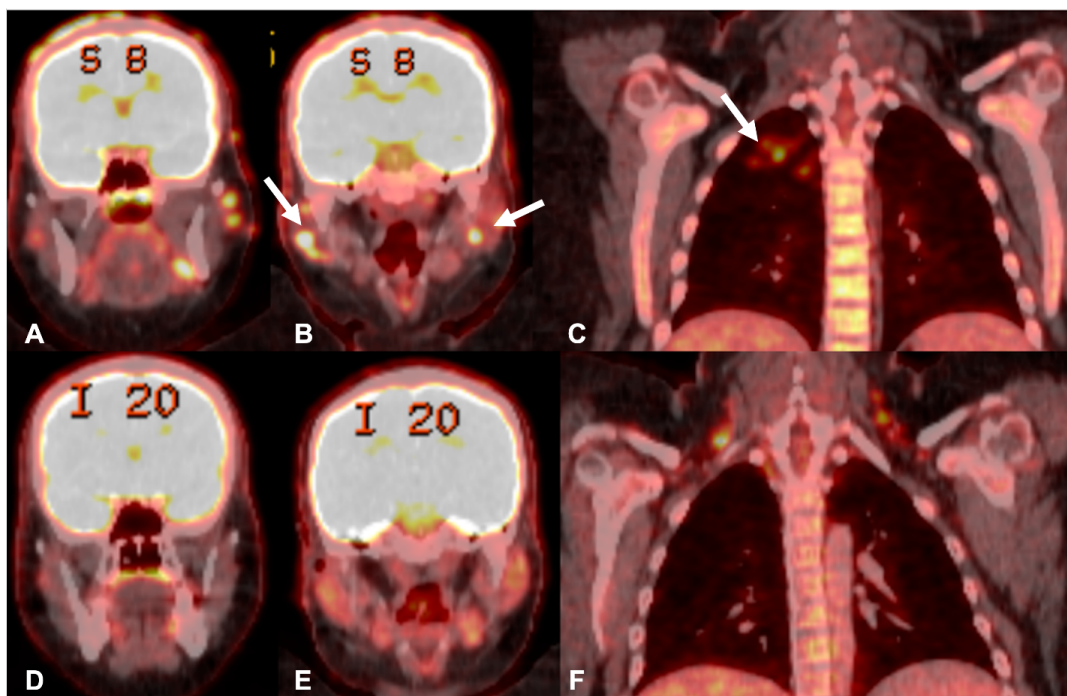


Figure 2: A – FDG-active extramedullary disease in the scalp (arrow); B - FDG-active extramedullary disease in the bilateral parotid glands (arrow); C - FDG-active extramedullary disease in the right upper lung lobe (arrow); D, E, F – no signs of FDG-active extramedullary disease.

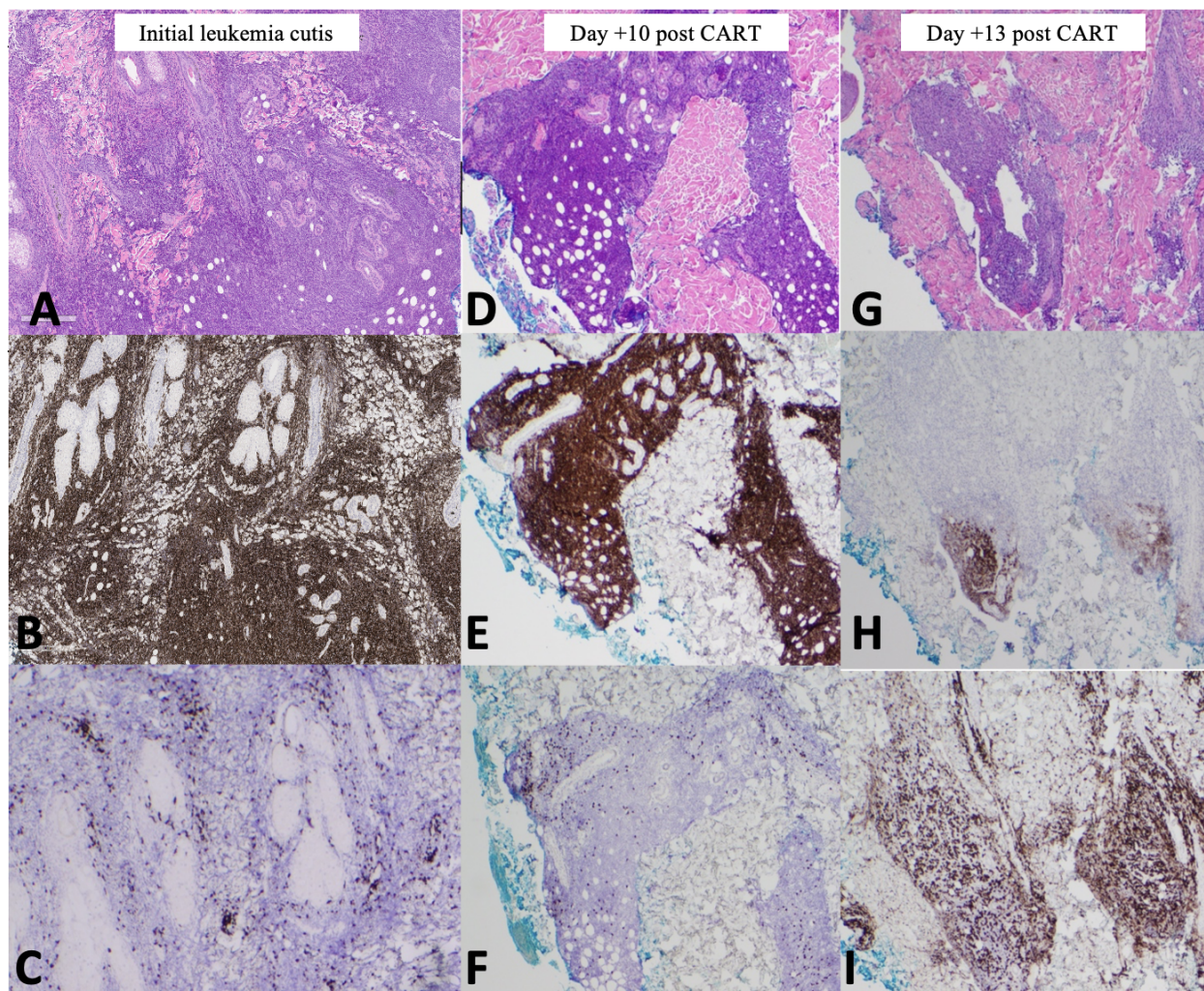


Figure 3: A – Initial skin biopsy prior to CART therapy initiation; hematoxylin and eosin (H&E) showing leukemic cell infiltration of the skin consistent with a diagnosis of leukemia cutis; B - Initial skin biopsy prior to CART therapy initiation; CD19 immunohistochemistry (ICH) staining showing cells diffusely positive for CD19; C - Initial skin biopsy prior to CART therapy initiation, CD3 ICH staining showing 2-3% cells positive for CD3; D – First skin biopsy after the initiation of the CART therapy on the day +10; H&E showing leukemic cell infiltration of the skin; E – First skin biopsy after the initiation of the CART therapy on the day +10; CD19 ICH staining showing cells diffusely positive for CD19; F - First skin biopsy after the initiation of the CART therapy on the day +10; CD3 ICH staining showing 1% cells positive for CD3; G - Second skin biopsy after the initiation of the CART therapy on the day +13; CD3 ICH staining showing 1% cells positive for CD3; H – Second skin biopsy after the initiation of the CART therapy on the day +13; H&E showing leukemic cell infiltration of the skin; H - Third skin biopsy, CD19 ICH staining showing 50% cells positive for CD19; I - Second skin biopsy after the initiation of the CART therapy on the day +13; CD3 ICH staining showing 50% cells positive for CD3

In late March, he presented with neutropenic fever, was admitted, and was started on broad spectrum antibiotics. On presentation, his WBC was 0.2, Hb 9.1, platelet count 29k. His infectious workup remained negative, and one week after admission, he exhibited no signs of infection and was started on a lymphodepletion regimen with fludarabine and cyclophosphamide. Of note, his scalp rash has resolved completely by that time. Four days later, on March 27, 2023, the patient received brexucabtagene autoleucel (Tecartus) infusion at a dose of 1×10^6 CAR-positive viable T cells per kg. On the day of infusion, he developed hypotension with a blood pressure of 87/53, which resolved with intravenous fluids administration. He had no events between day +1, and day +8, excluding an hour

long, spontaneously resolving, and episode of depressed mood without suicidal ideations on day +5. On day +9, he developed an asymptomatic light pink slightly raised maculopapular rash on the scalp (Figure 4). By the next day (+10), the rash progressed to become more raised, had increased in size and spread to his upper back and now had bright pink coloration with a purple tinge (Figure 4). The dermatology service was consulted, and a punch biopsy of the lesion on the back was performed. Later that day, the patient developed a fever with a T max of 39.2 C and hypotension with a blood pressure of 92/60. Along with broad-spectrum antibiotics, he received tocilizumab 8 mg/kg intravenously due to concern for Grade 2 cytokine release syndrome (CRS). He remained febrile and hypotensive overnight with a blood pressure in the 80-90s over 50-60s, despite intravenous fluids, and therefore received an additional dose of tocilizumab 8 mg/kg due to ongoing concern for CRS. On day +11, he remained afebrile, and his rash progressed in size, now becoming even more raised, erythematous, non-blanching, tender, and itchy (Figure 4, C, H). His infectious workup remained negative. The skin biopsy revealed leukemia cutis with ICH showing diffusely CD19-positive cells with only 1% of CD3 positive cells (Figure 3, D, E, F). On day +12, the patient developed a fever to 38.7o C, however his rash became less raised, but more itchy and painful (Figure 4). His infectious

workup remained negative, and the fever was attributed to Grade 1 CRS. On day +13, he remained afebrile and normotensive and the area of involvement by the rash was decreased in size, and the lesions were less raised, less painful, and now non-itchy (Figure 4). The dermatology team performed a second skin biopsy on that day, which again showed leukemia cutis, but now the ICH showed CD19 positivity in 50% of cells (Figure 3, G, H, I). Through the course of days +14 to day +18, the patient remained afebrile, and his rash continued to decrease in size, becoming asymptomatic (Figure 4). The patient was successfully discharged to follow up in the outpatient setting. The summary of the clinical and laboratory parameters in relation to the timing of CART therapy is reflected in the Figure 5. Repeat PET/CT on the day +27 of CART therapy showed near complete resolution of previously noted FDG-avid lesions involving the scalp, bilateral salivary glands, nasolacrimal region, right upper lobe, gastric fundus, and bone marrow (Figure 2 D, E, F). On the day +26 BMB revealed 20-30% cellularity with 1% blasts and trilineage maturation. Flow cytometry was negative for residual B-lymphoblastic leukemia. Yet, on the day +27 CART cell level in the peripheral blood was 1 cell per uL. During the follow-up appointment in the outpatient on day +38 clinical examination did not reveal any signs of skin rash. He experienced marrow relapse after 5 months in remission.



Figure 4: Sequential changes in skin rash over time. Ten sequential sets of images of the scalp (top row) and back (second row) for Day +9, +10, +11, +12, +13, and the scalp (third row) and back (bottom row) for Day +14, +15, +16, +17, +18 are shown. Day +9: Light pink slightly raised maculopapular rash on the scalp Day +10: More raised rash with surrounding erythema. Day+11: Rash progressed in size, now becoming raised, erythematous, non-blanching. Day+12: Less raised rash. Day+13: Rash decreased in size, becoming less raised. Day+14: Rash became less erythematous. Day+15: Rash decreased in size, flattened and became less erythematous. Day+16: Minimally raised rash with light coloration. Day+17: Rash continues to decrease in size, is almost flat and minimally erythematous. Day +18: Note flattening and loss of coloration.

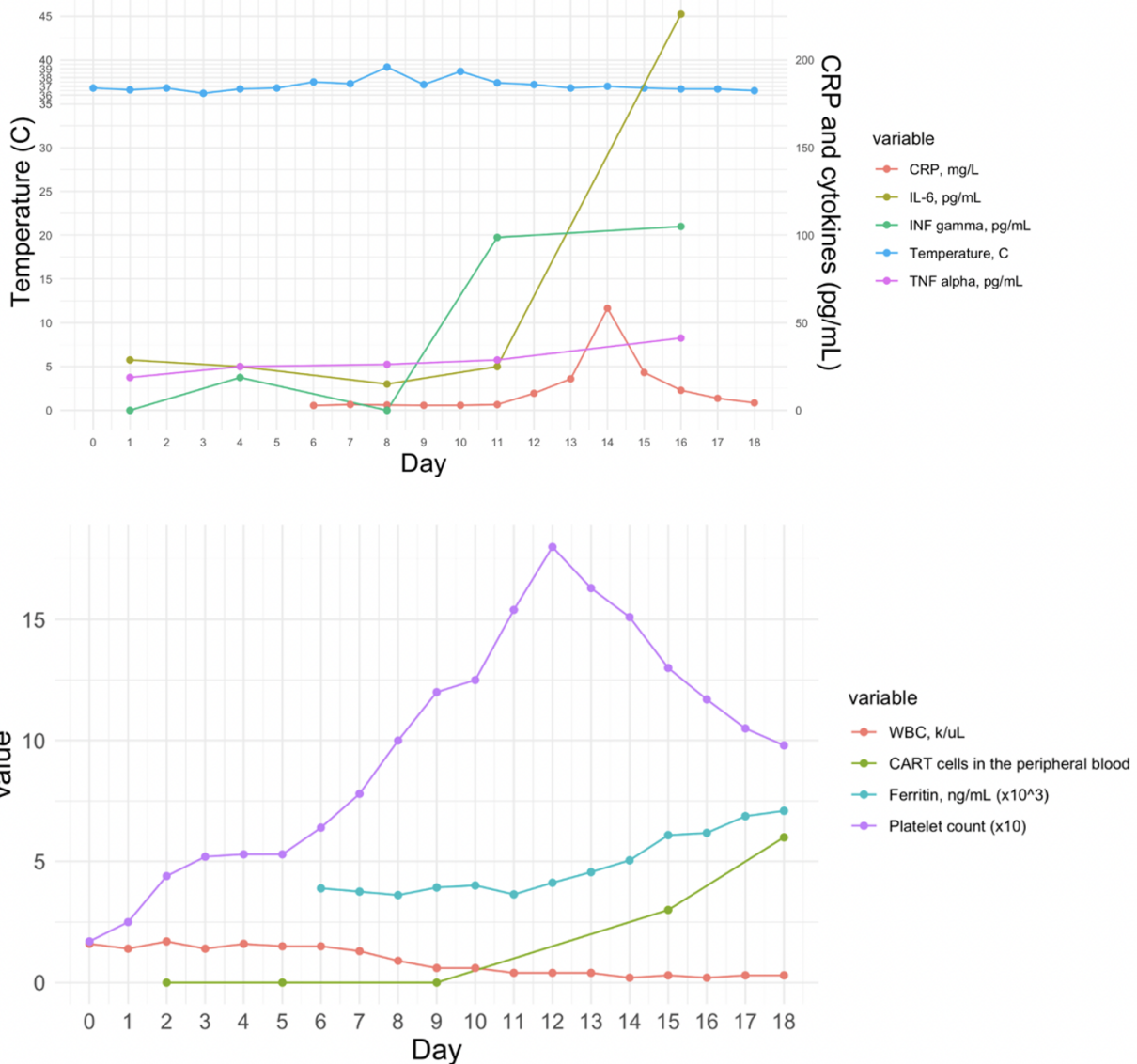


Figure 5: The summary of the clinical and laboratory parameters in relation to the timing of CART therapy

Discussion

Relapsed extramedullary B-cell ALL is associated with an extremely poor prognosis [6]. Extramedullary relapse of the B-cell ALL is a risk factor for the decreased five-year overall survival which does not exceed 10-20%, according to some studies [7,8]. Our patient, who presented with Ph-like ALL, falls into a particularly high-risk category with unfavorable outcomes and an increased risk of early relapses [9]. Leukemia cutis, characterized by the infiltration of leukemia cells or their precursors into the skin layers, is an infrequently reported extramedullary involvement, appearing as varied skin lesions. Cutaneous infiltration occurs in approximately 1% to 3% of ALL patients, and the exact mechanism underlying the specific migration of leukemic cells to the skin remains unclear [10]. It is essential to effectively manage the presence of skin involvement, given that leukemia cutis frequently acts as an indicator of aggressive illness and is commonly associated with the infiltration of other organs like the liver, spleen, and lymph nodes. The involvement of these organs collectively contributes to an unfavorable prognosis [11]. Treatment aiming to eradicate the underlying disease using chemotherapy or hematopoietic stem cell transplantation, preferably during the first remission, is essential. However, conventional chemotherapy

regimens may not effectively control cutaneous involvement. Current salvage chemotherapy demonstrates an overall response rate ranging from 25% to 50%, with complete remission rates of 30% to 40% in the first salvage and 10% to 20% in subsequent salvages, as according to the studies data [12]. In a study by Kang et al., the mean interval between leukemia cutis diagnosis and death was reported to be 8.3 months, with the majority of patients succumbing to the disease within a year, irrespective of the leukemia type [11].

CART cell therapy has emerged as a promising strategy for cancer treatment. CD19, which is universally expressed on precursor B-ALL blasts and mature B lymphocytes, serves as a target for immunotherapy in B-cell malignancies. CART cells are patient-derived T cells that are genetically engineered to combine an antigen-binding domain with T-cell signaling domains, enabling them to recognize tumor cell surface antigens in a human leukocyte antigen (HLA)-independent manner. This recognition leads to antigen-specific T-cell activation, proliferation, cytokine production, and ultimately, tumor eradication. Numerous clinical trials have demonstrated impressive overall remission rates ranging from 70% to 90% in children and adults with relapsed B-cell ALL following infusion of CD19 CART cells [13, 14]. Despite these advances, limited data exists on the mechanisms by which CART cells impact extramedullary disease sites. Recent clinical data highlight the importance of evaluating T-cell function at the site of disease. Studies have demonstrated that infused T cells effectively traffic throughout the body and home to sites where the target antigen is expressed, as supported by the detection of CART cells in post-infusion bone marrow aspirates [15, 16]. Our case report provides compelling evidence regarding the timing and quickness of the therapeutic response observed with CART cell therapy. An important observation was made when comparing the blood samples and the sequential skin biopsies. Notably, on day +10, the initial biopsy did not reveal any detectable CART cells, while on day +13, approximately 50% of the cells present in the biopsy were identified as CART cells. This unique sequential assessment of the skin biopsies provides valuable insights into the timing of the therapeutic response. To our knowledge, such detailed sequential biopsies in the context of CART cell therapy response in extramedullary B-cell ALL were not previously reported in the literature. This particular detail highlights the dynamic nature of the response to CART cell therapy, showcasing the rapid migration and accumulation of CART cells within the disease site over a short period. The kinetics of this response indicate the effectiveness of the therapy and the potential importance of assessing the disease site directly rather than relying solely on peripheral blood CART cell levels.

Interestingly, among proinflammatory markers, C-reactive protein level correlated with the level of the skin inflammation the

best, while fibrinogen did not correspond with patient's clinical picture (Figure 5).

A previous similar case reported by Yang et al. was focused on Ph-like ALL in a patient with leukemia cutis, analogous to our patient. The report revealed a significant increase in proinflammatory cytokine levels (IL-6, IL-10) between days 4 and 7 of CART therapy, paralleling our patient's experience. Furthermore, both patients received tocilizumab during their treatment. The case report documented the presence of swelling and redness in the skin during the early course of the treatment with CART cells. However, in the described patient, these skin abnormalities disappeared 20 days after the infusion of CD19 CART cells. Yet, there was no information regarding the sequential skin biopsy in the case report description. [17]. In contrast, in our patient, the skin symptoms resolved at an accelerated rate, with improvement in the rash observed by day +14 of CART therapy with almost complete rash resolution by day +18. In the other case report by Liu et al., authors described a 29-year-old patient with relapsed B-cell ALL with an extramedullary disease in the skin and testicle confirmed by skin biopsy who received CART therapy. Similar to our patient and the patient in the case report mentioned above, on the day four of the therapy patient has experienced skin inflammation as well as CRS symptoms. Analogous to our patient, the rash has disappeared in one week with biopsy on the day +7 of the CART therapy confirming the absence of the leukemia cells. These three cases elucidate the pattern of the CART cell activity in the extramedullary disease sites. The process of initial inflammation following CART cell infusion in the skin, a superficial structure, may reflect the pathophysiology of the CART cell activity in the other organs invisible to the physical examination. Initial inflammation during early stages of the CART cell therapy followed by spontaneous resolution and disease disappearance might describe the process of the CART cell migration to the extramedullary disease sites even when the CART cell level in the peripheral blood has not reached its peak or when CART cells are barely detectable [18]. The latter highlights the hypothesis that CART cell level in the peripheral blood does not reflect its activity against extramedullary leukemia and should not be used to evaluate its efficacy against leukemia. Moreover, our ICH staining findings showed that on the peak of inflammation there may be negligible level of the CART cells. Yet, the inflammation produced during the local antitumor response, seem to attract additional CART cells which appear later in the disease course when the inflammation subsides. Due to the diversity of the clinicopathological findings reported in the literature, further research is warranted to gain deeper insights into the mechanisms underlying the action of CART cells. Preclinical data with mouse models could also provide more answers on the mechanism of action of the CART cells in the extramedullary leukemia.

Another important aspect to consider is the correlation between peripheral blood levels of CART cells and clinical activity. In our case, we observed that the peripheral blood CART levels did not accurately reflect the clinical response. Despite having low levels of CART cells in the peripheral blood, the patient exhibited a successful anti-leukemic response, as evidenced by the homing of CART cells to the sites of extramedullary involvement. Interestingly, the migration of CART cells to the sites of involvement resulted in a depletion of CART cells in the peripheral blood, making it appear as if there were minimal circulating CART cells. However, this apparent reduction in peripheral blood CART levels did not indicate a lack of therapeutic efficacy. On the contrary, the localization of CART cells to the specific sites of disease involvement suggested an effective anti-leukemic response at those locations. This finding highlights the need to consider alternative methods for assessing the clinical activity of CART cell therapy, such as evaluating the presence and accumulation of CART cells at the sites of disease manifestation. Peripheral blood levels alone may not provide an accurate representation of the therapeutic response. Therefore, comprehensive monitoring and evaluation of both peripheral blood and disease-specific sites can provide a more comprehensive understanding of the therapeutic efficacy and response to CART cell therapy.

Further research is warranted to elucidate the mechanisms underlying the migration and accumulation of CART cells at specific disease sites and to determine the optimal methods for assessing the clinical activity of CART cell therapy in extramedullary manifestations of B-cell ALL.

Conclusion

In conclusion, our case study sheds light on the potential mechanisms of action of CART cells in the treatment of extramedullary B-cell ALL. We observed the migration of CART cells to sites of previous leukemic infiltration in the skin, resulting in inflammation and subsequent resolution of the extramedullary disease. This initial progression raised concerns but highlighted the therapeutic potential of CART cell therapy. Further research is needed to elucidate the precise mechanisms involved and optimize the use of CART cells in the treatment of ALL.

Ethical Considerations: Informed consent was obtained from the patient.

Conflict of Interest: No conflict of interest.

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