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ABOUT COVER

Editorial Board Member of *World Journal of Clinical Cases*, Youngmin Oh, MD, PhD, Associate Professor, Neurosurgeon, Department of Neurosurgery, Jeonbuk National University Medical School/Hospital, Jeonju 54907, Jeollabukdo, South Korea. timoh@jbnu.ac.kr

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The primary aim of *World Journal of Clinical Cases (WJCC, World J Clin Cases)* is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

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INDEXING/ABSTRACTING

The *WJCC* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Journal Citation Reports/Science Edition, Current Contents®/Clinical Medicine, PubMed, PubMed Central, Scopus, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database. The 2022 Edition of Journal Citation Reports® cites the 2021 impact factor (IF) for *WJCC* as 1.534; IF without journal self cites: 1.491; 5-year IF: 1.599; Journal Citation Indicator: 0.28; Ranking: 135 among 172 journals in medicine, general and internal; and Quartile category: Q4. The *WJCC*'s CiteScore for 2021 is 1.2 and Scopus CiteScore rank 2021: General Medicine is 443/826.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Hua-Ge Yu*; Production Department Director: *Xu Guo*; Editorial Office Director: *Jin-Lei Wang*.

NAME OF JOURNAL

World Journal of Clinical Cases

ISSN

ISSN 2307-8960 (online)

LAUNCH DATE

April 16, 2013

FREQUENCY

Thrice Monthly

EDITORS-IN-CHIEF

Bao-Gan Peng, Jerzy Tadeusz Chudek, George Kontogeorgos, Maurizio Serati, Ja Hyeon Ku

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/2307-8960/editorialboard.htm>

PUBLICATION DATE

September 16, 2022

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INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

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

Specialty type: Hematology

Provenance and peer review:

Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Kamalabadi-Farahani M, Iran; Papadopoulos VP, Greece

Received: April 14, 2022

Peer-review started: April 14, 2022

First decision: June 7, 2022

Revised: June 20, 2022

Accepted: August 6, 2022

Article in press: August 6, 2022

Published online: September 16, 2022



Lan Zhang, Wei Chen, Xiao-Min Wang, Shu-Qing Zhang, Department of Hematology, The First Hospital of Shanxi Medical University, Taiyuan 030001, Shanxi Province, China

Corresponding author: Lan Zhang, Doctor, PhD, Assistant Professor, Department of Hematology, The First Hospital of Shanxi Medical University, No. 89 Xinjian Road, Taiyuan 030001, Shanxi Province, China. qiqi994@sina.com

Abstract

BACKGROUND

Chimeric antigen receptor T-Cell (CAR-T) therapy is an effective new treatment for hematologic malignancies. Cytokine release syndrome (CRS) and neurologic toxicity are main toxicities. CRS-induced rhabdomyolysis (RM) followed by CAR-T therapy treatment has not been previously reported.

CASE SUMMARY

We report a case of a 22-year-old woman with relapsed acute lymphoblastic leukemia obtained sequential cluster of differentiation (CD) 19 and CD22 CAR-T infusion. This patient experienced grade 3 CRS with RM, mild hypotension requiring intravenous fluids, and mild hypoxia and was managed effectively with the IL-6 receptor antagonist tocilizumab. This patient had no signs of immune effector cell-associated neurologic syndrome. Restaging scans 30 d postCAR-T therapy demonstrated a complete remission, and the symptoms of muscle weakness improved through rehabilitation.

CONCLUSION

Myalgia is an easily overlooked symptom of severe CRS after CAR-T therapy. It is necessary to monitor myoglobin levels when a patient presents with symptoms of myalgia or acute renal insufficiency.

Key Words: Cytokine release syndrome; Rhabdomyolysis; Chimeric antigen receptor-T cell therapy; Relapsed acute lymphoblastic leukemia; Case report

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Core Tip: Cytokine release syndrome-induced rhabdomyolysis followed by chimeric antigen receptor-T (CAR-T) therapy treatment has not been previously reported. We report a case of a 22-year-old woman with relapsed acute lymphoblastic leukemia obtained sequential cluster of differentiation (CD) 19 and CD22 CAR-T cells infusion. This patient experienced grade 3 cytokine release syndrome with RM, mild hypotension requiring intravenous fluids, and mild hypoxia and was managed effectively with the interleukin-6 receptor antagonist tocilizumab. This patient had no signs of immune effector cell-associated neurologic syndrome. Restaging scans 30 d post CAR-T therapy demonstrated a complete remission, and the symptoms of muscle weakness improved through rehabilitation. Therefore, it is necessary to monitor myoglobin levels when a patient presents with symptoms of myalgia.

Citation: Zhang L, Chen W, Wang XM, Zhang SQ. Cytokine release syndrome complicated with rhabdomyolysis after chimeric antigen receptor T-cell therapy: A case report. *World J Clin Cases* 2022; 10(26): 9398-9403

URL: <https://www.wjgnet.com/2307-8960/full/v10/i26/9398.htm>

DOI: <https://dx.doi.org/10.12998/wjcc.v10.i26.9398>

INTRODUCTION

Chimeric antigen receptor T-Cell (CAR-T) has expanded the treatment options for patients with relapsed/refractory B-cell acute lymphoblastic leukemia (r/r B-ALL). Although CD19 CAR-T cell therapy have consistently shown high complete remission (CR) in patients with r/r B-ALL, CARTs to other targets (specifically anti-CD22) have been shown to be effective. In a large series of patients ($n = 58$), many of whom had relapsed after CD19 CAR-T therapy ($n = 51$), CD22 CAR therapy induced a CR in 70% of patients.

CASE PRESENTATION

Chief complaints

A 22-year-old woman with relapsed acute lymphoblastic leukemia relapsed and the patient did not achieve remission after the second induction chemotherapy.

History of present illness

The disease relapsed in August 2021 and the patient did not achieve remission after the second induction chemotherapy. The bone marrow blast cells were 95%. The patient underwent leukapheresis for T cells followed by bridging chemotherapy for rapid progressive disease. Although more than 90% of the bone marrow blast cells were still present, the patient was keen to undergo chimeric antigen receptor-T cell (CAR-T) therapy. She was very thin with a body weight of 35 kg. Lymphodepleting chemotherapy with fludarabine at 30 mg/m²/d intravenously (IV) and cyclophosphamide at 300 mg/m²/d IV for 3 d administered, followed by sequential infusion of CD22+ CAR-T cells (1 × 10⁶/kg) on day -2, CD19+ CAR-T cells (2 × 10⁶/kg) on day -1, and CD22+ CAR-T cells (1 × 10⁶/kg) on day 0.

History of past illness

On August 11, 2020, the patient sought treatment for progressive fatigue. Routine blood tests showed that a white blood cell count of 42.4 × 10⁹/L with 89.9% lymphocytes, hemoglobin level of 54 g/L, and platelet count of 22 × 10⁹/L. Bone marrow biopsy revealed infiltration of 90.7% lymphoblasts. Immunophenotypically, the blasts were human leukocyte antigen (HLA)-DR+, cluster of differentiation (CD) 19+, CD22+, CD34+, CD38+, terminal deoxynucleotidyl transferase (TdT)+, CD10- and cytoplasmic immunoglobulin M (cIgM)-. The *BCR/ABL1* (P190) fusion gene was negative. Cytogenetic analysis revealed a normal karyotype. Next-generation sequencing revealed a pathogenic mutation in *fms*-like tyrosine kinase 3, kirsten rat sarcoma viral oncogene homolog, paired box family of transcription factor and nonnucleoside nuclear receptor binding SET domain-protein 2. The patient was diagnosed as B cell acute lymphocytic leukemia (pro-B-ALL, adverse category). After one cycle of induction treatment with the vincristine, daunorubicin, cyclophosphamide, L-Asparaginase and prednisone regimen, the patient achieved complete remission. Five courses of consolidation therapy were administered, and the measurable residual disease (MRD) was kept negative by flow cytometry before each consolidation therapy. Allo-hematopoietic stem cell transplantation has been suggested multiple times but the patient refused.

Personal and family history

The personal and family history was normal.

Physical examination

There is no positive physical examination findings before CAR-T therapy. The patient's condition deteriorated rapidly after CAR-T therapy, the physical examination findings were described in TREATMENT part.

Laboratory examinations

The basic laboratory examination findings such as bone marrow biopsy and flow cytometry were shown in History of past illness part. The Table 1 shows several important laboratory examinations after CAR-T therapy.

Imaging examinations

The chest computed tomography showed pneumonia after CAR-T therapy. It is a very common complication. I will provide the images if they are requested.

FINAL DIAGNOSIS

Relapsed/refractory B-cell acute lymphoblastic leukemia.

TREATMENT

Intermittent fever was observed at night on day 1 after CAR-T cells infusion and the body temperature returned to normal after taking oral ibuprofen and antipyretic suppository. But on days 2-3, the body temperature gradually increased, and the highest temperature was 40.3°C. Antipyretic and analgesic drugs were not effective in reducing the temperature. Administration of methylprednisolone (40 mg q6h) reduced the body temperature to 38°C, which could only be maintained for 2-3 h. Subsequently, the patient gradually developed symptoms such as irritability, photophobia, confusion, dizziness, headache, blurred vision, and projectile vomiting. However, the patient did not have delirium or clear consciousness. Levels of interleukin (IL) -6, IL-10 and ferritin were significantly increased (Table 1). The patient developed grade 2 cytokine release syndrome (CRS) and was administered methylprednisolone 80 mg q12h, dexamethasone 15 mg q12h and tocilizumab; however, the symptoms worsened after treatment. On day 7, the patient developed severe pain in both lower limbs in the early morning, which was more severe in the knee joints, and the skin temperature was slightly higher. The patient could not stand and the local skin was painful to touch. Bone marrow suppression worsened, achieving 4 degrees. On day 8, myoglobin and creatine kinase levels were significantly increased, and IL-6 levels were much higher than normal, with undetectable high ferritin levels. The patient became more irritable and developed intermittent twitching. The vital signs were unstable, with a blood oxygen saturation of 88%, blood pressure of 86/50 mmHg, heart rate of 160-170 beats/min, facial swelling, and binocular conjunctival hemorrhage. In addition, chest computed tomography (CT) showed obvious double pneumonia, while head CT has no positive findings. This patient developed grade 3 CRS complicated with rhabdomyolysis, and CAR-T cell related encephalopathy syndrome was suspected. She was transferred to the intensive care unit (ICU), and plasma exchange was immediately performed. The doses of methylprednisolone and dexamethasone were not altered, and symptomatic and supportive treatments, such as component blood transfusion and anti-infection therapy were administered. Bilateral pneumonia was treated by meropenem, linezolid, voriconazole, aminophylline intravenous infusion, and terbutaline aerosol inhalation. On day 9, the patient's mental status improved significantly, without any convulsions. The patient heart rate was approximate 120 beats/min, blood oxygen saturation was 92%-95% (oxygen inhalation 6-8 L/min through nasal cannula), and blood pressure was 90/60 mmHg. Moreover, capillary leakage was observed. Chest CT tomography revealed massive pleural effusion and severe pulmonary interstitial edema. Symptoms, such as muscle soreness, were relieved after symptomatic treatment, such as active diuresis. However, the muscle strength of the bilateral lower limbs was level 0 with no deep or shallow sensations. Moreover, the patient experienced urinary and fecal incontinence. On days 11-12, plasma exchange and blood purification treatments were administered simultaneously. The patient's vital signs were normal and her condition was stable. Hence, the dose of methylprednisolone was gradually reduced. Physical examination showed that the patient's general condition had significantly improved; however, the muscle strength and sensation of the bilateral lower limbs did not recover. Head CT scan showed no abnormalities. After consultation with neurologists, spinal cord injury was ruled out, and rehabilitation was recommended based on the patient's condition.

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.

OUTCOME AND FOLLOW-UP

On day 14, the patient was transferred back to hematology ward from ICU. Dosages of methylprednisolone and dexamethasone were gradually decreasing, and the patient's condition was stable. The peripheral blood cells, IL-6 and ferroportin levels gradually recovered to normal range. Chest CT scan showed bilateral pneumonia absorbed mostly. Meanwhile, the muscle strength of the bilateral lower limbs gradually recovered through rehabilitation training, and have conscious of urine and feces. At the time of discharge, the patient's heart rate approximate 64-70 beats/min; the left leg muscle strength was level 1, and the right one was level 2. The patient could walk slowly with assistance, and had no specific discomfort. After 6 wk of CAR-T therapy this patient achieved completely remission with MRD negative.

DISCUSSION

Rhabdomyolysis (RM) is a disease caused by the breakdown of the cell membranes of skeletal muscle cells, leading to the release of cellular components[1]. Clinical symptoms of RM include myalgia, weakness and muscle redness[2]. However, the clinical manifestations differ vastly, ranging from asymptomatic to sharp increases in creatine kinase, myoglobin, lactate dehydrogenase, and occasionally acute renal insufficiency and disseminated intravascular coagulation, which are life-threatening. Common predisposing factors for RM are trauma, certain drugs (such as statins[3]), alcohol[4], infection [5], muscle hyperactivity, genetic diseases[6], endocrine abnormalities[7], and tumors[8]. During multiple chemotherapy sessions, this patient developed severe infections but not RM. The patient did not use any high-risk medications known to cause RM except for some over-the-counter medications. Although the patient developed infections after CAR-T cell treatment, the changes in various indicators such as creatine kinase, myoglobin, and lactate dehydrogenase were consistent with CRS indicators (IL-6 and ferritin), thereby indicating CRS. In the present case, the patient had obvious myalgia, with significantly increased creatine kinase and myoglobin levels. Therefore, a diagnosis of RM was established.

Muscle damage in RM may be caused by direct injury/trauma, direct muscle membrane damage, or adenosine triphosphate (ATP) consumption in the muscle fibers due to metabolic imbalance. ATP consumption impairs the regulation of intracellular calcium, leading in a steady increase of calcium in the sarcoplasm, energy expenditure, activation of calcium-dependent proteases and phospholipases, and the destruction of myofibrils, cytoskeleton, and membrane proteins, triggering lysosomes to digest fiber content[9]. RM is thought to be closely associated with cytokines. A study on the lethality of influenza virus showed that 81% of patients developed cytokine storms, and 36% had abnormal cytolysis[10]. Cases of RM after cytomegalovirus infection have also been reported[11]. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) binds to the angiotensin-converting enzyme 2 receptor expressed on skeletal muscle, resulting in the down-regulation of renin-angiotensin, leading to striated muscle injury[12]. After the coronavirus disease 2019 (COVID-19) infection, activated immune cells produce high levels of circulating cytokines, which can cause cell death and tissue damage[13]. Nobutaka Chiba[14] reported a case of high fever and RM caused by a cytokine storm after COVID-19 infection. The symptoms were relieved after inhibition of IL-6 release, which might be related to the energy metabolism involved in calcium. However, Cho *et al*[15] found that the cytokine storm after COVID-19 infection damaged important organs (particularly the kidneys). Hassanein *et al* [16] also believed that CRS and RM after COVID-19 infection could cause kidney damage in severe cases. RM can also induce acute kidney injury (AKI)[17], however, CRS-induced RM during CAR-T cell treatment has not been previously reported.

Theoretically, CRS treatment stops a dysregulated immune response and restores immunological homeostasis[18]. RM is typically treated with supportive treatment, including eliminating the cause, hydration, alkalization, and diuresis[19]. Severe cases can be treated using blood purification methods, such as cytokine adsorption[20]. Hemoadsorption has approved for patients with excessive cytokine levels[21], by reducing the plasma concentrations of pro- and anti-inflammatory mediators below a “toxithreshold”[22]. It remains unclear whether hemoadsorption can prevent ARF in rhabdomyolysis [21]. In the present case, the levels of IL-6 and other cytokines were reduced after treatment with corticosteroids, tocilizumab, plasma catheterization, blood purification and other related treatments. Although the patient had a persistent severe lung infection, CRS was reduced, myolysis improved significantly, and the symptoms of muscle weakness were relieved through rehabilitation. Therefore, myalgia during cytokine storm after CAR-T cell treatment should be carefully monitored to check for potential RM.

CONCLUSION

Myalgia is a classic symptom of RM and is an easily overlooked of severe CRS after CAR-T cell therapy. It is necessary to monitor myoglobin levels when a patient presents with symptoms of myalgia or acute renal insufficiency.

FOOTNOTES

Author contributions: Zhang L, Wang XM, Zhang SQ are responsible for the treatment of patient; Zhang L analyzed the data and wrote the manuscript; Chen W contributed coordination and manuscript review; all authors have read and approve the final manuscript.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: All the authors declare that they have no conflict of interest.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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Country/Territory of origin: China

ORCID number: Lan Zhang 0000-0002-2903-8059.

S-Editor: Liu JH

L-Editor: A

P-Editor: Liu JH

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