Case Reports in Oncology

Case Rep Oncol 2022;15:257–262
DOI: 10.1159/000522669
Received: December 24, 2021
Accepted: January 19, 2022
Published online: March 15, 2022

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

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Keywords
Chimeric antigen receptor T-cell therapy · Cytokine release syndrome · Laryngeal edema

Abstract
Cytokine release syndrome (CRS) is one of the major acute complications caused by massive cytokine release after chimeric antigen receptor (CAR) T-cell therapy. Patients with tumor masses were considered at high risk of local CRS induced by the expansion of CAR T cells in the tumor masses. However, even patients without any tumor burden around the neck are at risk of developing cervical edema as local CRS, which can lead to life-threatening airway obstruction. Here, we present the case of a 15-year-old boy who developed cervical edema as a local CRS after CAR T-cell therapy for refractory acute lymphoblastic leukemia. Despite administration of tocilizumab and methylprednisolone for persistent fever as a symptom of systemic CRS after CAR T-cell therapy, cervical edema occurred and extended to the larynx, resulting in dysphagia and hoarseness. Dexamethasone was remarkably effective, and the laryngeal symptoms resolved within a few hours. Local cytokine syndrome showed exacerbation with tocilizumab but exhibited considerable improvement with dexamethasone administration.

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Introduction

The efficacy of chimeric antigen receptor (CAR) T cells targeting CD19 in the treatment of hematological malignancies, such as CD19-positive B-cell acute lymphoblastic leukemia (ALL) or lymphoma, has been clearly evidenced [1, 2]. However, the administration of CAR T cells warrants careful attention to life-threatening adverse events. Cytokine release syndrome (CRS) is a major acute complication caused by massive cytokine release after CAR T-cell therapy [3]. Here, we present the case of a boy with refractory ALL who developed extensive edema from the neck to the larynx as a manifestation of CRS after CAR T-cell therapy. Local edema outside the brain or the lungs is a rare symptom of CRS [3, 4]. However, a new type of CRS, called "local CRS," has been recently proposed, which is thought to occur when CAR T cells accumulate and proliferate in the tumor local area and release a large amount of cytokines because they capture and kill tumor cells [5, 6]. This case report compares the present case with similar cases reported previously [5, 7].

Case Report

A 15-year-old Chinese boy was diagnosed with B-cell precursor ALL and initially underwent treatment according to the Japanese Pediatric Leukemia/Lymphoma Study Group ALL-B12 High-Risk Protocol. He had no extramedullary disease. However, he experienced induction failure and had difficulty continuing chemotherapy because of severe mucositis and persistent myelosuppression. NUDT15 polymorphism status of Arg/Cys may have affected the severity of the side effects. Because he was positive for the *PDGFRB* mutation, dasatinib was administered in combination with the third-line chemotherapeutics fludarabine, high-dose cytarabine, and mitoxantrone, which succeeded in achieving complete remission. However, he developed hemorrhagic enteritis, which made it difficult to continue dasatinib. He also developed grade 3 acute kidney injury – the serum creatinine level increased from 0.6 mg/dL to 2.2 mg/dL – which was probably caused by vancomycin used to treat staphylococcal sepsis during neutropenia. Despite the indication for hematopoietic stem cell transplantation for the treatment of refractory ALL, the patient was considered unable to tolerate the transplantation treatment; he was then referred to our hospital for CAR T-cell therapy. He was successfully maintained in remission by bridging therapy with one cycle of inotuzumab ozogamicin followed by imatinib monotherapy. All the chemotherapy-related complications resolved prior to CAR T-cell therapy.

CAR T cells (tisagenlecleucel) were infused in sustained complete remission. Considering that he had high fever (>39°C) that persisted from day 1, we administered 8 mg/kg of tocilizumab on day 3 (Fig. 1a). Although the high fever persisted, the respiratory and circulatory status remained stable. However, painful neck swelling was observed from the evening of day 3. He had no history of allergy and received no medication or blood transfusions that could have caused anaphylaxis prior to the onset of cervical edema. Following standard CRS management guidelines [8], we administered 2 mg/kg methylprednisolone on day 4 and a second dose of tocilizumab on day 5, but the neck swelling worsened further, and the high fever persisted (Fig. 1a, b). Because the patient experienced difficulty in swallowing and hoarseness, we performed laryngoscopy and cervical computed tomography, which revealed prominent edema extending from the neck to the larynx (Fig. 1c, d). Dexamethasone was immediately administered (10 mg intravenously), and the cervical edema and larynx-related symptoms resolved within a few hours (Fig. 1b, d). Dexamethasone was tapered over the next 2 days and stopped. Thereafter, no immunosuppressive drugs were administered. From day 8, the fever gradually subsided. He was discharged 6 weeks after CAR T-cell therapy and remains in sustained remission for 15 months. He requires regular immunoglobulin replacement therapy for hypogammaglobulinemia due to B-cell aplasia.

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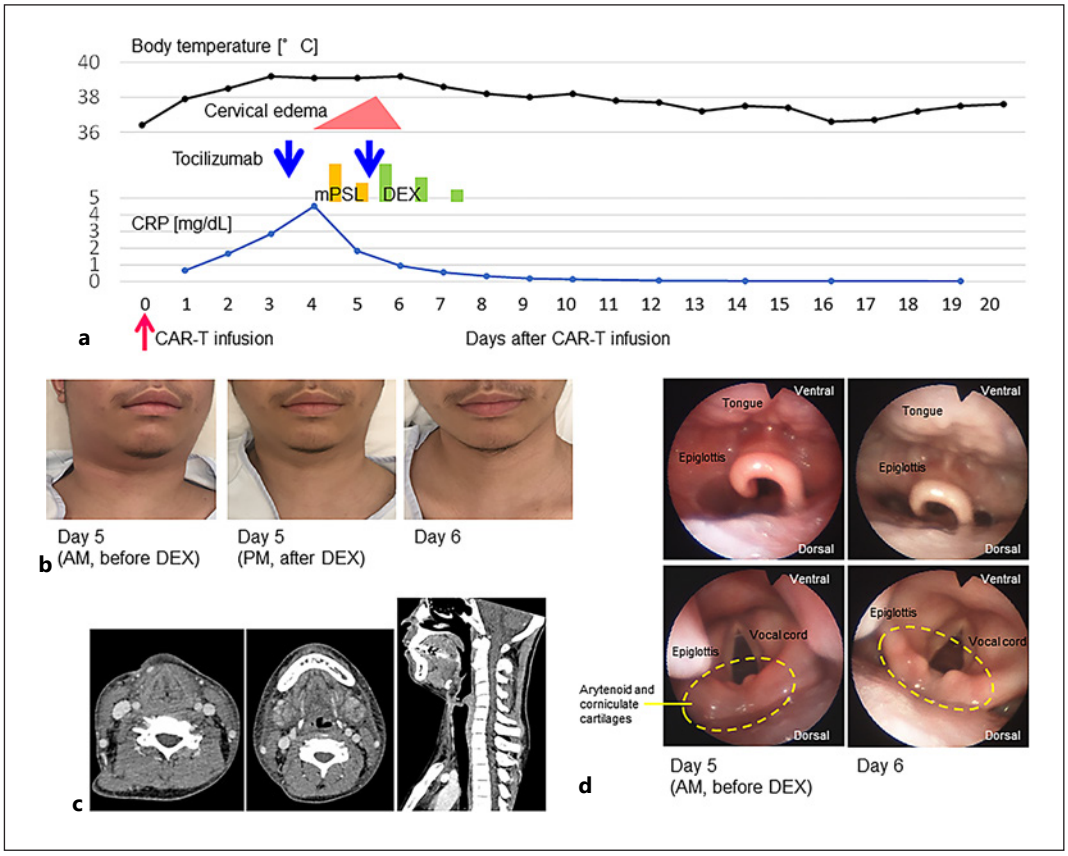

Fig. 1. Clinical course after CAR T-cell therapy. **a** Changes in body temperature and the CRP level after CAR T-cell therapy. The change in cervical edema status is also shown. Tocilizumab was administered on days 3 and 5, methylprednisolone on days 4 and 5, and DEX from days 5 to 7. **b** Cervical 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.

Discussion

CRS, which is induced by the release of inflammatory cytokines from CAR T cells or other immune cells, is the most common toxicity caused by CAR T-cell therapy [3, 9]. During the inflammatory process, body fluids may be transferred from the blood to locally stimulated tissues, resulting in edema [10]. Therefore, edemas involving organs, such as the brain and the lungs, are considered manifestations of CRS. However, edemas localized to the neck are a rarely observed manifestation of CRS after CAR T-cell therapy [3, 4]. To the best of our knowledge, only two cases of upper airway obstruction due to cervical edema after CAR T-cell therapy have been reported (Table 1). In the first case, a patient with diffuse large B-cell lymphoma developed severe dyspnea due to rapid swelling of cervical lymphadenopathy after CAR T-cell infusion [7]. Cervical lymphoma was refractory, and the patient had a bulky mass in the neck immediately before CAR T-cell infusion. Considering that the cervical mass resolved 1 month after CAR T-cell therapy, the cervical mass was presumed to have first enlarged immediately after CAR T-cell infusion and then shrunk thereafter. In the second case, a patient with refractory Ph-like B-ALL developed cervical edema and dyspnea despite

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Table 1. Patients with cervical edema after CAR T-cell therapy

Patient	Disease	Status at CAR T cell infusion	Chemotherapy before CAR T infusion	Lymphodepletion	Symptoms of CRS (day of onset)		Therapy for CRS	
					systemic	local	systemic	local
51 yr, male [7]	DLBCL	Bulky cervical mass	CHOP	Not stated	Fever (day 0)	Cervical edema and dyspnea (day 4)	Tocilizumab 4 mg/kg	DEX 10 mg
61 yr, female [5]	ALL	Nonremission (MRD 30%)	Dasatinib, vindesine, idarubicin, and DEX	FLU+CY	Fever and hypotension (day 0)	Cervical edema and dyspnea (day 8)	Tocilizumab 8 mg/kg	Torsemide 5 mg, mPSL 40 mg, and DEX 10 mg
15 yr, male (present case)	ALL	Complete remission	Imatinib	FLU+CY	Fever (day 1)	Cervical edema (day 3) and dysphagia (day 5)	Tocilizumab 8 mg/kg, mPSL 2 mg/kg	DEX 10 mg

CAR, chimeric antigen receptor; CRS, cytokine release syndrome; yr, year; DLBCL, diffuse large B-cell lymphoma; ALL, acute lymphoblastic leukemia; CHOP, cyclophosphamide/epirubicin/vinorelbine tartrate/prednisone; FLU, fludarabine; CY, cyclophosphamide; BP, blood pressure; DEX, dexamethasone; mPSL, methylprednisolone.

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treatment with tocilizumab for persistent fever and low blood pressure as symptoms of systemic CRS [5]. There are two important points to consider when comparing the present case with these previous cases. First, in the first case, the patient was presumed to have developed airway obstruction due to swelling of the cervical mass caused by the irritation associated with CAR T-cell attack on the tumor [7]. Therefore, patients with a cervical mass prior to CAR T-cell infusion are considered to be at higher risk for airway obstruction due to CRS. Such local inflammation is considered as "local CRS" and may be distinguished from systemic CRS [5, 6]. However, in the second and the present case, the patients had no history of cervical lymphadenopathy or mass during the treatment course, including the initial symptoms at ALL diagnosis. Additionally, the cervical swelling was an edema rather than lymphadenopathy. Although laryngeal edema is a well-known symptom of anaphylaxis, neither the second nor the present case had a history of allergy. Furthermore, in the present case, no medication was suspected to have caused allergies prior to the onset of cervical edema, and no cervical infections or oral problems could have induced local inflammation. Therefore, we suggest that even patients who do not have bulky neck masses are at risk of developing cervical edema such as local CRS, which can lead to airway obstruction. Second, intravenous dexamethasone administration was highly effective for cervical edema and dyspnea in a short period in all 3 cases. The present patient did not experience hypoxia or dyspnea; therefore, early intervention for CRS with tocilizumab and methylprednisolone may have been effective to some extent. However, despite these immunosuppressive treatments, the cervical and laryngeal edema aggravated. In the two previous cases, tocilizumab could not prevent the worsening of cervical edema. Based on these 3 cases, it appears that local CRS does not occur alone but develops from systemic CRS. Although dexamethasone is often used in the management of upper airway obstruction, the prophylactic administration of dexamethasone to reduce the occurrence of laryngeal edema after extubation or the effect of corticosteroids in the treatment of epiglottitis remains controversial [11, 12]. In contrast, corticosteroids have been demonstrated to be effective for the treatment of croup, a common disease caused by upper airway obstruction in children. Dexamethasone has long been used frequently for the treatment of croup despite the absence of differences in therapeutic efficacy between low-dose dexamethasone and prednisone [13, 14]. One study reported the superiority of dexamethasone in reducing the rate of return to medical care [15]. We followed the guidelines and administered tocilizumab and methylprednisolone for the treatment of CRS [8]; however, it may be beneficial to consider dexamethasone earlier in patients with cervical and laryngeal edema [14]. In the present case, although the symptoms had improved before CAR T-cell infusion, the history of severe mucositis may have placed the patient at risk for "local CRS." Because there are only two reported cases of neck edema after CAR T therapy in patients without cervical tumors, the risk of local CRS warrants further investigation.

Collectively, clinicians should consider that patients without any tumor burden in the neck region are still at the risk of developing cervical edema leading to life-threatening airway obstruction as a manifestation of CRS after CAR T-cell therapy. In such rare cases, early dexamethasone administration in addition to tocilizumab may be recommended.

Statement of Ethics

This retrospective review of patient data did not require ethical approval in accordance with local/national guidelines. Written informed consent was obtained from the patient and the parent of the patient for the clinical and treatment procedures and publication of the details of their medical case and any accompanying images.

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

No funding was received for this study.

Author Contributions

Haruko Shima, Takumi Kurosawa, Hiroyuki Oikawa, Hisato Kobayashi, Emiri Nishi, and Fumito Yamazaki treated this patient. Kentaro Tomita and Hiroyuki Shimada managed and supervised the clinical practice. Haruko Shima wrote the manuscript. Hiroyuki Shimada reviewed and edited the manuscript. All the authors contributed to discussions and agreed on the final version of the submitted manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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