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**Case Report**

# Severe cases of local cytokine release syndrome (CRS); craniocervical edema soon after chimeric antigen T-cell (CAR-T) therapy

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## Abstract

Craniocervical edema appears soon after chimeric antigen receptor T-cell (CAR-T) therapy in some cases. This phenomenon is often observed right after systemic cytokine release syndrome (CRS), and it is called local CRS (L-CRS). In severe cases, L-CRS causes airway obstruction and asphyxia, but it is not yet well known among hematologists. In this report, we present mild and severe cases of L-CRS. Tocilizumab might have limited efficacy against L-CRS, and early administration of corticosteroids can be important. We hope that this case report raises awareness of L-CRS as an acute-onset adverse event after CAR-T therapy.

**Keywords:** chimeric antigen receptor T cell therapy; cytokine release syndrome; case report

Chimeric antigen receptor T cell (CAR-T) therapy is one of the most effective treatment strategies for relapsed or refractory (r/r) B-cell malignancies [1–3]. Cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) are common acute-onset adverse events accompanying CAR-T therapy [4, 5]. Recently, it has been reported that in some cases, craniocervical edema suddenly appears right after systemic CRS [6–9]. This adverse event has been called local CRS (L-CRS) [6, 7]. The number of case reports is still very small, and L-CRS is not widely recognized by physicians. L-CRS causes airway obstruction and asphyxia in severe cases [9]. Therefore, understanding L-CRS is important for safer and more appropriate CAR-T therapy. Here, we present mild and severe cases of L-CRS after CAR-T therapy. Especially, we report the severe case requiring intubation for the first time.

A 64-year-old male (Case 1) was diagnosed with diffuse large B cell lymphoma (DLBCL) with BCL2, BCL6, and MYC expression (double-expressor lymphoma). Although he received 6 courses of R-MPV therapy (rituximab, methotrexate, procarbazine, and vincristine), 4 courses of R-CHASE therapy (rituximab, cyclophosphamide, cytarabine, and etoposide), and autologous stem cell transplantation, his lymphoma recurred 8 months after the completion of the full treatment regimen. We added radiotherapy (50.4 Gy/28 fr) for recurrent sites and 5 courses of Pola-BR therapy (polatuzumab vedotin, bendamustine, and rituximab) as salvage therapies, and complete metabolic remission (CMR) was achieved. Cervical lesions had never been observed during his treatment course. Then, he received fludarabine (25 mg/m$^2$, 3 days) and cyclophosphamide (250 mg/m$^2$, 3 days) as lymphodepletion (LD) chemotherapy followed by tisagenlecleucel (tisa-cel). He experienced grade 1 CRS with fever over 38°C 2 days after CAR-T cell infusion (day 2). Cephepim was started from day 2, and 8 mg/kg of tocilizumab were administered 4 times on days 2 and 3, but his high fever continued. In the morning of day 4, cervical edema, a sore throat, and difficulty breathing appeared. Deterioration of oxygenation was not observed. Subcutaneous edema in the craniocervical region and swelling of the epiglottis and pharynx were observed with a laryngeal fiber scope and CT scans (Fig. 1). Right after image examinations, we diagnosed L-CRS and 0.5 mg/kg of dexamethasone were initiated. His difficulty in breathing, cervical edema, and fever improved on day 5. The dose of dexamethasone was gradually decreased (0.5 mg/kg on day 4 and 5, 0.3 mg/kg on day 6, 0.15 mg/kg on day 7). His temperature also decreased from day 6, and CRS improved. ICANS was not observed. Other complications did not occur, and he was discharged on day 25. The disease continued to be CMR 4 months after CAR-T cell therapy.

A 59-year-old female (Case 2) was diagnosed with follicular lymphoma (FL) grade 3b, and received 6 courses of R-CHOP therapy (rituximab, cyclophosphamide, vincristine, doxorubicin, and prednisolone), 3 courses of R-ICE therapy (rituximab, ifosfamide, carboplatin, and etoposide), and autologous stem cell transplantation (conditioning regimen: MEAM). Her lymphoma recurred

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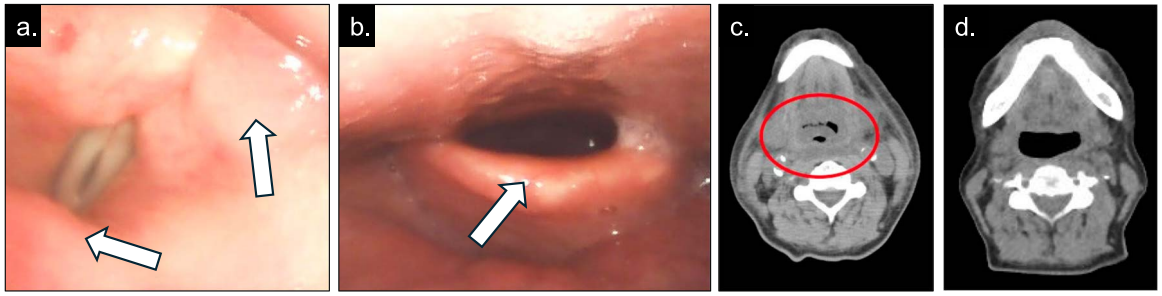


Figure 1. Laryngeal fiber (a, b) and CT scan (c, d) of case 1. Subcutaneous edema and swelling of epiglottis and pharynx were observed by laryngeal fiber scope (arrows, a, b) and CT scan (circle, c). Improvement of airway constriction with corticosteroid therapy was observed (d).

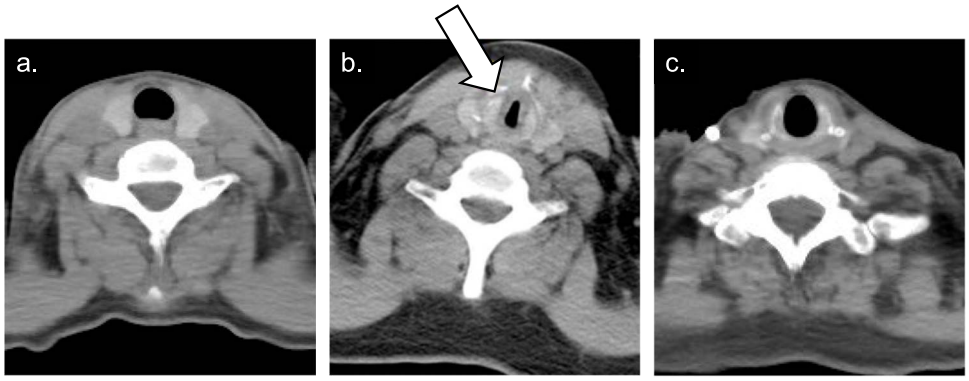


Figure 2. Comparison of cervical CT scans before lymphodepletion chemotherapy (a), on day 5 (b), and after improvement of the symptom (c) in case 2. Narrowing of upper airway from swelling of epiglottis and pharynx was observed (white arrow), and airway constriction rapidly improved after administration corticosteroid therapy (c).

9 months post-therapy. Re-biopsy of cervical lymph nodes showed histologic transformation to DLBCL. We added 3 courses of R-ESHAP therapy (rituximab, etoposide, methylprednisolone, cisplatin, and cytarabine) as a salvage therapy, and her recurrent lesions (cervical and abdominal lymph nodes) shrank. Then, she received fludarabine (25 mg/m$^2$, 3 days) and cyclophosphamide (250 mg/m$^2$, 3 days) as LD chemotherapeutics and tisa-cel. Her temperature exceeded 38°C on day 2. Piperacillin/tazobactam was initiated from day 2. Facial and cervical edema appeared on day 3. On day 3, high fever over 39°C persisted despite multiple doses of acetaminophen, and 8 mg/kg of tocilizumab were administered twice for grade 1 systemic CRS. On day 4, however, her symptoms did not improve, and airway obstruction sounds were heard with a stethoscope. Oxygen administration became necessary. Narrowing of the upper airway from swelling of the epiglottis and pharynx was observed on a CT scan (Fig. 2b). Immediately, she entered the intensive care unit (ICU). Intratracheal intubation was conducted for airway management, and 1 mg/kg of methylprednisolone was initiated. Clinical symptoms rapidly improved, and she was extubated on day 6, and discharged from the ICU on day 7. The dose of methylprednisolone was gradually decreased (1 mg/kg on day 4 to 6, to 0.5 mg/kg from day 7 to 9, to 0.25 mg/kg from day 10 to 12). ICANS was not observed. No other complications occurred. Unfortunately, on day 28 her lymphoma advanced. She received additional treatments, but died on day 801.

Here, we presented reports of mild and severe L-CRS cases after CAR-T therapy. The mechanism of L-CRS has not yet been identified, but L-CRS is regarded as a subtype of CRS from viewpoints of the timing of onset and possible treatment effect of corticosteroids [6–9]. Tocilizumab is effective for systemic CRS in many cases, but it may not be effective for L-CRS [6–10]. In our two cases and several cases previously reported, relatively rapid response was achieved with corticosteroid administration [6–10]. Corticosteroids could potentially be a key medication for managing L-CRS based on the limited cases presented. If physicians do not provide appropriate treatments with corticosteroids, L-CRS may cause airway obstruction and asphyxia as shown in case 2. Severe cases requiring intubation have not been reported previously. Several biomarkers to predict systemic CRS have already been reported, and their clinical use leads to safe CAR-T therapy [11, 12]. However, patient characteristics and biomarkers associated with L-CRS have yet to be established. Thus, accumulation of cases and further research are strongly needed. We hope that this case report calls attention to L-CRS as an acute-onset adverse event after CAR-T therapy.

## Declaration

Informed consent for publication of the text and all accompanying images was obtained from patients. No authors have conflicts of interest. This report and study were approved by the ethics committee at Kyoto University (G0697).

## Conflict of interest

None declared.

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