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CT Demonstration of Local Cytokine-Release Syndrome Involving the Head and Neck Following Chimeric Antigen Receptor T Cell Infusion Therapy

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Cytokine release syndrome (CRS) is a clinical syndrome that results from systemic immune activation, chimeric antigen receptor T (CAR-T) cell expansion, and increased levels of serum inflammatory markers and cytokines following CAR-T cell therapy for systemic hematologic malignancies [1]. A local inflammatory response occurring as an adverse effect of CAR-T cell therapy is a newly emerging concept [2-5]. Here, we describe the CT manifestations of local CRS (L-CRS) involving the head and neck.

An Exemplar Case

A 20-year-old female with an unremarkable medical history visited our hospital to undergo evaluation of petechiae in both extremities. Laboratory testing revealed a hemoglobin level of 8.0 g/dL, white blood cell of 11.5 x 10^3/uL, platelet count of 3 x 10^3/uL, and blast count of 31%. Hematologic malignancy was suspected, and bone marrow aspiration was performed. Chromosome analysis revealed t(9; 22)(q34; q11.2) *BCL/ABL1*, and the patient was diagnosed with acute lymphoblastic leukemia (ALL).

The patient was administered a hyper-CVAD regimen (a combination of cyclophosphamide, vincristine sulfate, doxorubicin hydrochloride, methotrexate, cytarabine, and dexamethasone) plus imatinib, but the disease persisted; therefore, hematopoietic stem cell transplantation (HCT) was performed. However, eight months after HCT, recurrent disease was confirmed by bone marrow examination, and the patient was scheduled for CAR-T cell therapy, a common treatment for intractable ALL. Following pretreatment with fludarabine and cyclophosphamide (FC) for one week to clear the lymphocytes, she was infused with a dose of 1.9 x 10^8 CAR-T cells (Kymriah, Novartis Pharmaceuticals; Basel, Basel-Stadt, Switzerland).

The day after infusion, the patient developed a mild fever of 37.6°C, which subsequently increased to 39.0°C. The symptoms gradually worsened, and four days later, her lower chin began to swell. Laboratory testing revealed abnormally high levels of serum interleukin-6 at 68.2 pg/mL, an erythrocyte sedimentation rate of 69 mm/hr, and a C-reactive protein level of 7.11 mg/dL. No findings indicative of end-organ dysfunction were observed. Neck CT with intravenous contrast enhancement revealed diffuse swelling and infiltration of the bilateral side of the neck, including the bilateral submandibular and parotid glands, pharynx, and supraglottis, suggesting acute

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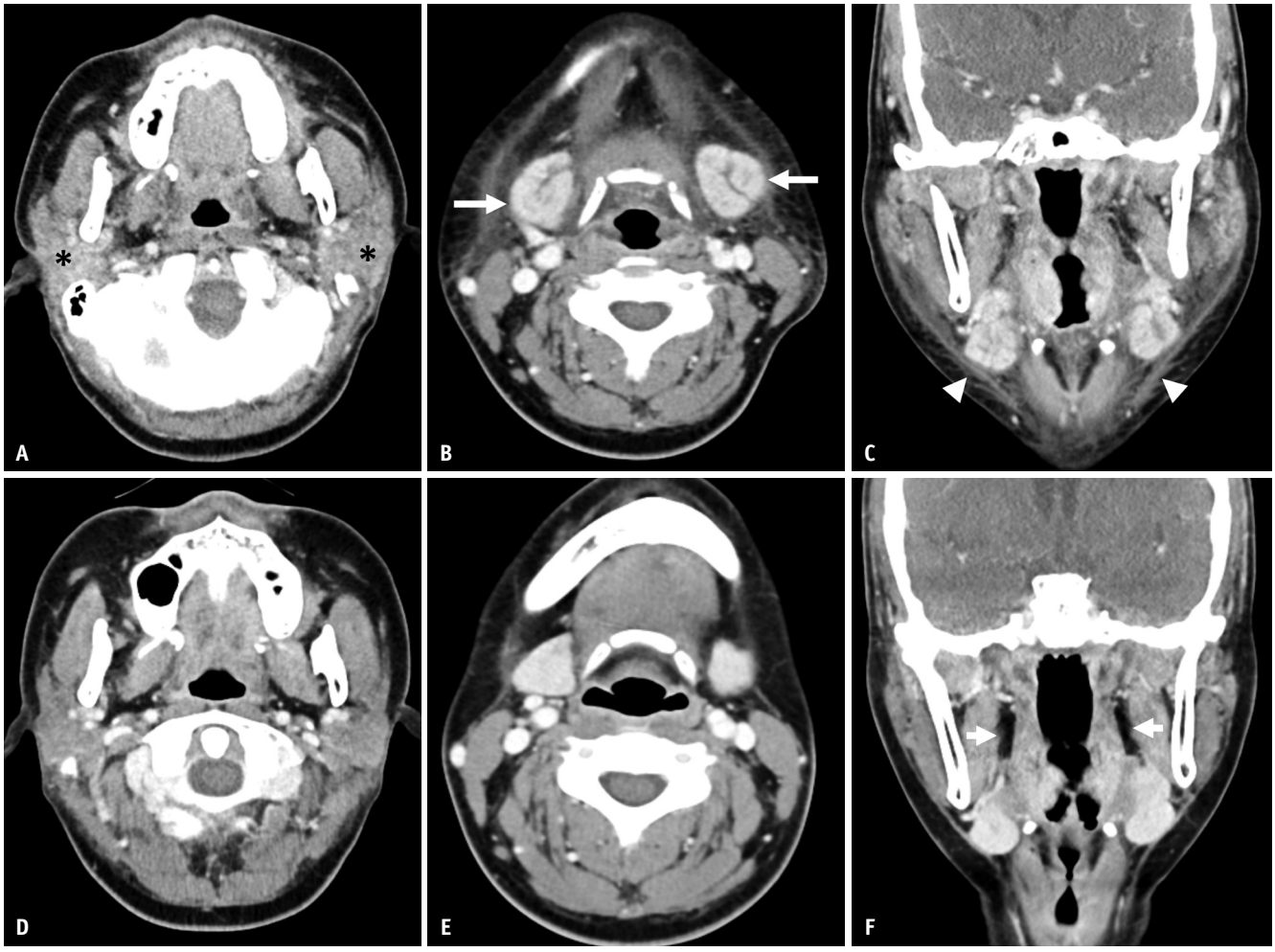

Fig. 1. An exemplar case of a 20-year-old female with acute lymphoblastic leukemia treated with CAR-T cell infusion therapy. **A-C:** Four days after CAR-T cell infusion therapy, diffuse swelling in both the parotid (asterisks, **A**)/submandibular glands (arrows, **B**), pharynx, parapharyngeal fat, and supraglottic larynx with subcutaneous and deep cervical fat infiltration can be observed. Thickening and infiltration of the platysma muscles can also be seen (arrowheads, **C**). **D-F:** One week after dexamethasone treatment for local cytokine-release syndrome, the diffuse swelling in both the parotid/submandibular glands, entire pharynx, parapharyngeal fat (arrows, **F**), and supraglottic larynx is completely resolved on axial and coronal neck CT with enhancement. CAR-T = chimeric antigen receptor T

inflammation (Fig. 1). There was no evidence of bacterial or viral infection in serological tests. These findings were classified as CRS grade 1 (the American Society for Transplantation and Cellular Therapy [ASTCT]) with localized inflammation [6,7]. Upon diagnosis of L-CRS based on clinical symptoms and elevated interleukin-6 levels, 10 mg of dexamethasone was immediately administered. After one week of dexamethasone treatment, the patient's symptoms improved, and interleukin-6 and inflammatory markers returned to normal.

Key Points for L-CRS

CAR-T cell infusion is a promising therapy for refractory ALL, and commonly results in complete response or remission among patients with various malignancies, including pediatric and adult ALL, non-Hodgkin's lymphoma, and chronic lymphocytic leukemia unresponsive to standard therapies [6]. However, adverse events, such as CRS, immune effector cell-associated neurotoxicity syndrome (ICANS), hemophagocytic lymphohistiocytosis, cytopenia, infection, and hypogammaglobulinemia, can limit the application of CAR-T cell therapy [7].

CRS is a clinical syndrome that initially presents with mild clinical symptoms such as fever, myalgia, and fatigue, which can worsen to severe CRS, characterized by life-threatening vasodilatory shock, hypoxia, electrolyte disturbance, coagulopathy, and end-organ dysfunction [6,8]. The ASTCT

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consensus includes grading scales from 1 to 5 to evaluate CRS according to the severity of fever, hypotension, and hypoxia [7]. CRS occurs in 58%–93% of patients after CAR-T cell therapy [9], and grade 3 or higher CRS is observed in 11%–47% of patients [8,9]. The CAR-T cell therapy–associated TOXicity (CARTOX) Working Group noted that CRS is most likely to occur in the first 5 days after cell infusion [7]. It is necessary to differentiate infectious conditions based on the patient's immune status.

CRS is triggered by the release of inflammatory cytokines such as interleukin-6 by host immune cells, resulting in decreased vascular integrity, vasodilation, hemodynamic instability, capillary leak, and consumptive coagulopathy [6]. Therefore, an increased serum interleukin 6 level is associated with CRS and can be used as a diagnostic biomarker. The risk factors for CRS include large tumor burden, ALL as the underlying malignancy, large numbers of infused CAR-T cells, thrombocytopenia, endothelial activation before CAR-T cell treatment, and prior lymphocyte-depleting chemotherapy with FC [6,8].

There have been several case reports of CRS involving localized regions of the body following treatment of systemic hematologic malignancies with CAR-T cell infusion. Wei et al. [2] previously reported a few cases manifesting as redness, swelling, and enlargement at the site of lymphoma involvement in the inguinal or cervicofacial area or around the periphery of lesions and suggested the term L-CRS for localized inflammation. They proposed that L-CRS is the initial stage of systemic CRS.

Luan et al. [3] previously proposed another hypothesis regarding the occurrence of L-CRS in systemic hematologic malignancies. According to this hypothesis, systemic CRS results from the release of large amounts of inflammatory cytokines when systemically infused CAR-T cells trap and kill tumor cells. Off-target effects may also occur through redistribution of CAR-T cells to attack host cells expressing the same antigens as the targeted cancer cells. The clinical course of our patient fits well with this hypothesis, as demonstrated by the occurrence of systemic symptoms of high fever, followed by local inflammation involving the bilateral parotid and submandibular glands.

CRS affects multiple organ systems and leads to inflammation and injury to the vascular endothelium [10]. As a result of vascular inflammation and injury, acute lung injury, noncardiogenic edema, periportal edema, cutaneous or mesenteric edema, and ascites can all be observed on imaging. In our experience, we noted swelling and infiltration of the salivary glands, pharynx, supraglottis, and subcutaneous and deep cervical fat on CT.

Although the underlying mechanisms and factors associated with the occurrence and severity of L-CRS require further investigation, CAR-T cell therapy, in addition to its effectiveness against hematologic cancers, has the potential to be expanded to the treatment of patients with solid tumors [11]. Radiologists need to be familiar with the new concepts of CRS and consider them when guiding the management of patients after CAR-T cell therapy.

Conflicts of Interest

Jeong Hyun Lee, Chong Hyun Suh, and Jung Hwan Baek, who hold respective positions on the Section Editor, Assistants to the Editor, and Editorial Board of the *Korean Journal of Radiology*, were not involved in the editorial evaluation or decision to publish this article. The remaining author has declared no conflicts of interest.

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