Case Report

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Extramedullary Relapse of Acute Lymphoblastic Leukemia Involving the Parotid Gland: A Case Report and Literature Review

급성 림프아구성 백혈병 환자의 이하선에 발생한 골수외 재발: 증례 보고와 문헌 고찰

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While extramedullary relapse of leukemia could occur, the parotid gland is a rare site of recurrence. Extramedullary relapse involving the parotid gland could be mistaken for other diseases. Moreover, the diagnosis of this disease is often delayed due to its rarity. Herein, we present a case of extramedullary relapse of acute lymphoblastic leukemia involving the parotid gland.

Index terms Leukemia; Recurrence; Parotid Gland

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INTRODUCTION

The parotid gland is a rare site of extramedullary relapse of recurrent leukemia other than the bone marrow. Though the diagnosis of extramedullary relapse is important since it is considered one of the main causes of treatment failure, the clinical and radiologic diagnosis of this recurrence is limited on account of the low incidence of the disease. Extramedullary relapse involving the parotid gland can be confused with other parotid gland diseases, such as idiopathic or drug-induced parotitis, which occurs more often in leukemia patients after chemotherapy. Herein, we report a case of pathologically proven extramedullary relapse of acute lymphoblastic leukemia (ALL) that was confused with parotitis, followed by a review of relevant literature.

CASE REPORT

A 21-year-old male who was diagnosed with relapsed ALL complained of parotid swelling during admission for chemotherapy. He was first diagnosed with ALL at 7 years of age and had a second recurrence when he was 14 years old. Further, after a 2-year previous remission, a third recurrence was observed in him at the age of 20 years, in September 2019. Hypercellular marrow with diffuse infiltration of immature blastic cells was noted on bone marrow biopsy with positive immunohistochemical findings on CD20 and terminal deoxynucleotidyl transferase (TdT). Anemia with increased lymphocyte and immature cell counts in peripheral blood smears was also noted at this point.

Three scheduled cycles of induction chemotherapy with blinatumomab were performed accordingly. Radiation therapy was performed after triple-drug intrathecal chemotherapy (methotrexate, cytarabine, and steroids) for central nervous system relapse when blastic cells were detected on cerebrospinal fluid examination. Immunotherapy was scheduled for an uncontrolled relapse in August 2020. In October 2020, 1 week after immunotherapy with inotuzumab ozogamicin (Besponsa; Inotuzumab ozogamicin; Pfizer, New York, NY, USA), complete remission was achieved with the maturation of all cell lines in the bone marrow biopsy, with negative conversion of CD20 and CD3 on immunohistology and absence of leukemia blast cells in the peripheral blood.

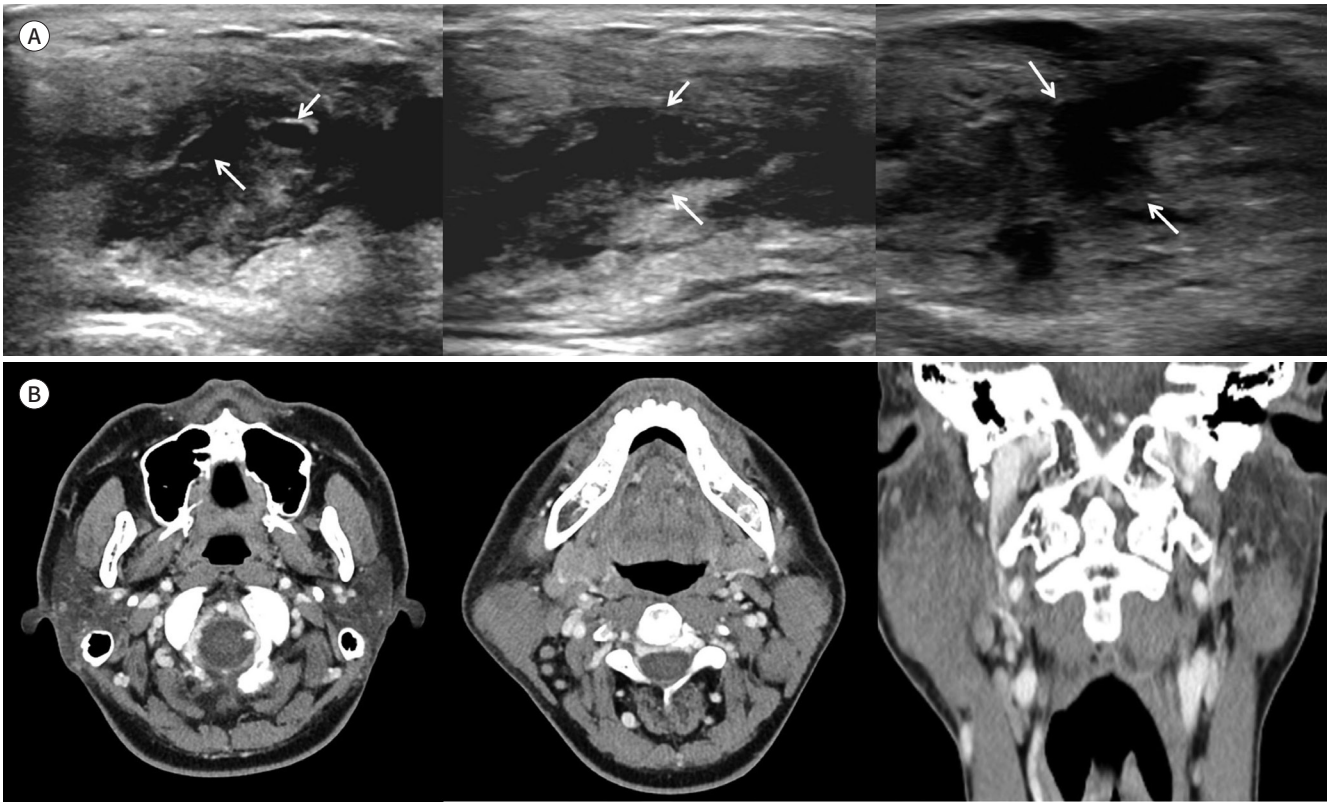
After three days, chemotherapy was discontinued because the patient developed high-grade fever (> 38.0°C) and neutropenia (absolute neutrophil count < 3000). During physical examination, right parotid swelling was noted, with erythematous changes. The patient complained of a warm sensation and severe pain in both parotid areas, which was more severe on the right side. Ultrasonography was performed for evaluation of the parotid glands. Swelling, with changes in heterogeneous echogenicity of both parotid glands, was noted with periglandular inflammatory change, that was more severe on the right side (Fig. 1A). Initially, idiopathic or drug-induced parotitis was suggested because complete remission was diagnosed before this symptom, with negative results in the bone marrow biopsy and peripheral blood examination. After conservative management with erythematous changes, the parotid swelling improved slightly.

On follow-up ultrasonography, 3 days after the initial examination, anechoic change within the enlarged parotid gland increased without detectable vascularity, suggesting fluid collection (Fig. 1A). Fine-needle aspiration was performed to differentiate parotitis from fluid collection and other pathologies. Saliva-like fluid was aspirated, and atypical lymphoid cells within the saliva and serous epithelial cells were observed on pathologic examination.

During follow-up ultrasonography, enlargement of both parotid glands improved, but a nodular mass-like palpable lesion within the parotid gland and enlargement of the left level II lymph nodes was noted on physical examination. Follow-up CT was performed 10 days after initial symptom onset. Improvement in parotid gland swelling and peri-glandular changes were noted; however, enlarged intraglandular and left neck level II lymph nodes with homogeneous enhancement were also observed (Fig. 1B).

The possibility of extramedullary involvement was minimal due to the bone marrow and peripheral blood showing complete remission in the background of parotid swelling. Al-

Fig. 1. A 21-year-old male with parotid swelling who experienced complete remission after chemotherapy for relapsed acute lymphoblastic leukemia.
A. Initial US shows swelling with heterogenous changes and periglandular inflammatory changes (left image, arrows). Follow-up US after 3 days indicates an increment of intralesional anechoic changes, suggesting fluid collection (middle image, arrows). Follow-up US after 7 days from the initial US shows an increment of intralesional anechoic changes, suggesting fluid collection (right image, arrows).
B. Follow-up contrast-enhanced axial CT image acquired 10 days after the onset of initial symptoms shows an improvement of both the parotid swellings (left image). The development of diffuse enhanced solid mass-like lesions inferior to both parotid glands is seen, with lymphadenopathy at the left neck level II (middle and right images).
US = ultrasonography



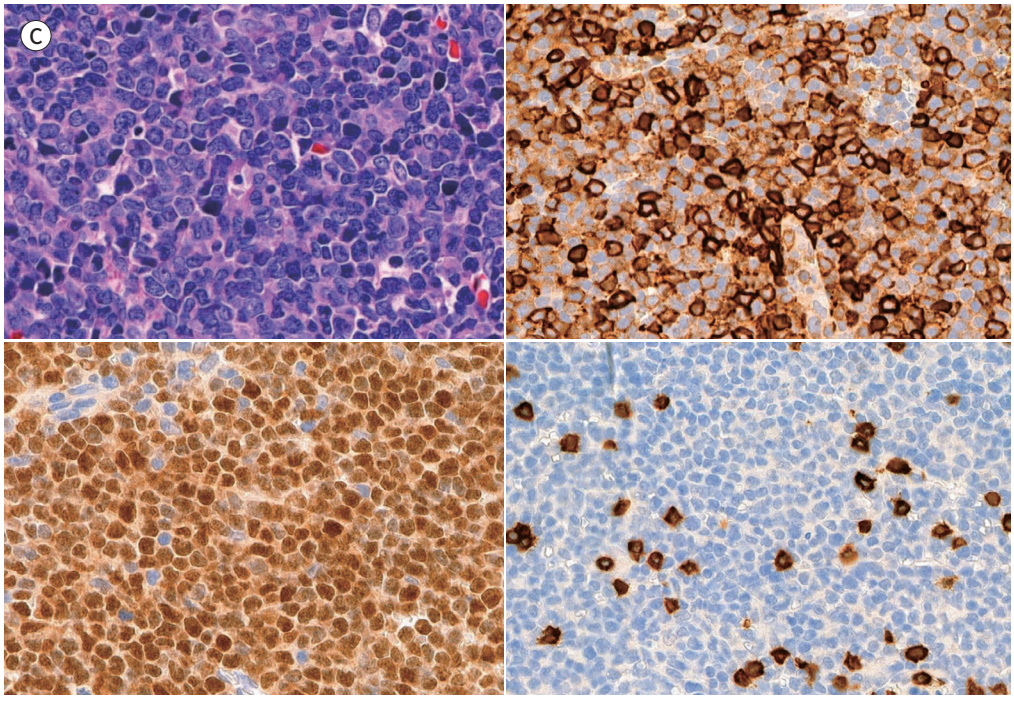
though needle aspiration revealed atypical lymphoid cells, it was necessary to discriminate between idiopathic parotitis and drug-induced parotitis, which is more common in patients with leukemia. Therefore, gun biopsy was performed for confirmation. After gun biopsy, recurrence of lymphoblastic infiltration was noted with positive immunohistochemical staining for CD20 and TdT (Fig. 1C). Parotid swelling slightly improved after prednisolone treatment, but the patient and caregivers refused active treatment and wanted hospice care. Unfortunately, the patient died soon after due to multiorgan failure.

This study was approved by the Institutional Review Board of Ewha Womans University Mokdong Hospital and the requirement for informed consent was waived (IRB No. 2021-02-042).

DISCUSSION

The parotid gland can be an extramedullary relapse site of leukemia recurrence other than

Fig. 1. A 21-year-old male with parotid swelling who experienced complete remission after chemotherapy for relapsed acute lymphoblastic leukemia.
C. Microscopic findings show diffuse atypical medium-sized lymphoid cells (upper left panel, hematoxylin & eosin stain, × 400), positive for CD20 (upper right panel, × 400), terminal deoxynucleotidyl transferase (lower left panel, × 400), but negative for CD3 (lower right panel, × 400).



the bone marrow (1, 2). Although extramedullary relapse remains an important cause of treatment failure in patients with recurrent acute leukemia (2, 3), the prognosis of patients with recurrent leukemia and extramedullary relapse is poor, with a median survival of only a few months (2, 3). Early recognition of extramedullary recurrence can be important in improving prognosis; however, clinical and radiologic diagnosis of this recurrence is limited owing to the low incidence of the disease (2, 3). It can show normal or nonspecific changes in laboratory findings (1, 4); therefore, suspicion of this unusual condition must be considered for proper diagnosis and management.

Extramedullary recurrence involving the parotid gland can show swelling of the parotid gland with or without lacrimal gland involvement (1). This nonspecific initial presentation of this disease can be confused with other parotid gland diseases, such as idiopathic or drug-induced parotitis, which occurs more often in leukemia patients after chemotherapy (5). The altered immune status of the present patient made it difficult to make a proper diagnosis of parotitis followed by suppurative change and drug-induced parotitis since he used cytarabine, which can cause parotitis (5).

Radiologic findings of extramedullary relapse were reported as nonspecific and showed variable findings according to the structures involved (5). Bulging mass formation was noted in recurrent lesions in the head and neck (5). Most lesions were discrete hypodense solid mass lesions with homogeneous enhancement, suggesting hypervascularity (5). Extramedullary relapse of the parotid gland might lead to gland swelling due to infiltration of blasts, and previously reported cases of parotid involvement of initial or relapsed disease also showed

diffuse swelling of the involved glands with homogeneous enhancement (1, 4, 6). The present case showed heterogeneous changes that did not match extramedullary release, and this unusual presentation can be due to intraglandular duct occlusion by infiltrated blasts, considering the aspirated saliva-like fluid with atypical cells on fine-needle aspiration.

Extramedullary relapse is difficult to diagnose only by clinical or radiologic evaluation; only the prior existence of extramedullary disease at the initial diagnosis can be a suggestive factor that increases the incidence of extramedullary relapse (2). The present patient was not diagnosed with extramedullary disease during the initial diagnosis, but the possibility of initial extramedullary disease cannot be completely excluded because whole body check-ups are not usually conducted during the initial workup for acute leukemia (2).

The prognosis of patients with leukemia recurrence and extramedullary recurrence is poor, and extramedullary recurrence can be seen in the form of a prior expression of bone marrow recurrence (2, 7, 8). In addition, extramedullary recurrence with concurrent bone marrow relapse exhibits a grave clinical course (9). The present patient did not undergo a follow-up bone marrow biopsy, but he experienced multiorgan failure after extramedullary relapse, which was confirmed after parotid gland biopsy.

In summary, the initial manifestation and ultrasonographic findings of the present patient posed a challenge in arriving at the initial diagnosis. Nevertheless, proper diagnosis can be accomplished through early pathological evaluation of the lesion. Therefore, regardless of the patient's bone marrow biopsy or peripheral blood examination result, if any lesion is suspected, it would be best to first consider the possibility of extramedullary recurrence.

Author Contributions

Conceptualization, C.H., data curation, C.H., L.N.; formal analysis, C.H., C.M.; investigation, C.H., L.N.; methodology, all authors; project administration, C.H.; resources, C.H., C.M.; software, C.H.; supervision, C.H., C.M.; validation, C.H.; visualization, all authors; writing—original draft, L.N.; and writing—review & editing, C.H.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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급성 림프아구성 백혈병 환자의 이하선에 발생한 골수외 재발: 증례 보고와 문헌 고찰

이 님[1] · 조현혜[1*] · 조민선[2]

백혈병의 골수 외 재발이 발생할 수 있지만 이하선은 드문 재발 부위이다. 이하선을 포함하는 골수 외 재발은 다른 질환과 혼동될 수 있으며 종종 질환의 희귀성으로 인해 진단이 지연될 수 있다. 이에 저자들은 재발성 급성 림프아구성 백혈병 환자에서 이하선의 급성 림프아구성 백혈병의 골수 외 재발 사례와 영상 소견을 보고한다.

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