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【 CASE REPORT 】

L-asparaginase-induced Parotitis in an Elderly Patient with Acute Lymphoblastic Leukemia

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Abstract:
A 67-year-old woman received induction chemotherapy comprising vincristine, daunorubicin, cyclophosphamide, L-asparaginase and prednisolone for acute lymphoblastic leukemia with a common B-cell phenotype. The administration of L-asparaginase at 3,000 U/m^2 for 6 days was planned. Before the fourth administration on day 16, left parotid swelling was identified along with increased serum amylase (991 U/L; 94% derived from salivary glands). An enlarged left parotid gland was apparent on computed tomography. The symptoms resolved after cessation of L-asparaginase, with serum amylase normalizing by day 20. This rare adverse event should be recognized as improving within a week after ceasing L-asparaginase.

Key words: parotitis, L-asparaginase, acute lymphoblastic leukemia

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Introduction

L-asparaginase is a key drug in the treatment for Philadelphia chromosome (Ph)-negative acute lymphoblastic leukemia (ALL). The outcomes of adult Ph-negative ALL are markedly improved with pediatric-inspired protocols that include an increased dose of L-asparaginase. Treatment with L-asparaginase is frequently associated with various adverse events, including hypersensitivity, elevation of ammonia levels, pancreatitis, liver dysfunction, coagulation disorder and thrombosis. However, L-asparaginase-induced parotitis appears to be extremely rare. A few cases of children with L-asparaginase-induced parotitis have been reported, but no adult cases have been described.

We herein report a case of L-asparaginase-induced parotitis in an elderly patient with ALL.

Case Report

A 67-year-old woman visited our hospital with a decreased white blood cell count (1,870/μL) and a slightly increased serum concentration of lactate dehydrogenase (258 U/L), which had been detected incidentally at a medical checkup. Bone marrow aspiration revealed numerous immature cells, which were negative for myeloperoxidase (MPO) and positive for periodic acid Schiff. Flow cytometry revealed leukemic cells that were positive for CD19, CD79a, CD10 and TdT and negative for CD3, CD4, CD8, CD13, CD33 and MPO. Reverse transcriptase polymerase-chain reaction yielded negative results for BCR-ABL mRNA, and G-banding showed a normal karyotype. Ph-negative ALL with common B-cell phenotype was therefore diagnosed.

Induction chemotherapy was administered, comprising vincristine, daunorubicin, cyclophosphamide, L-asparaginase and prednisolone. Administration of L-asparaginase (from *Escherichia coli*) at 3,000 U/m^2 (4,000 U/body) was planned for days 9, 11, 13, 16, 18 and 20 (1). Before the fourth administration of L-asparaginase on day 16, however, left parotid swelling appeared with an increase in serum amylase to 991 U/L (94% derived from salivary glands; Fig. 1). No symptoms of infection, such as a fever, redness of the skin or gingival abnormality, were evident. An enlarged left parotid gland was detected without ptyaloliths or a parotid tu-

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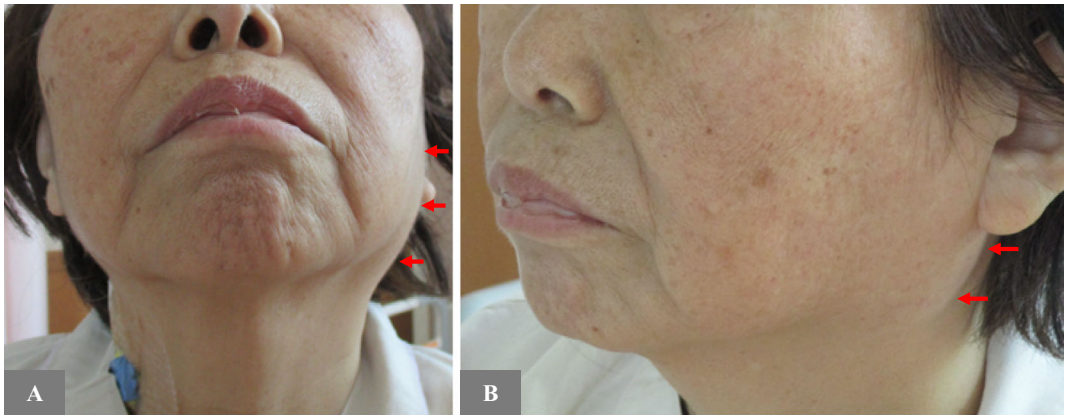

Figure 1. **Macroscopic findings of parotitis. (A) Frontal view. (B) Left lateral view. The left parotid region is swollen without redness.**

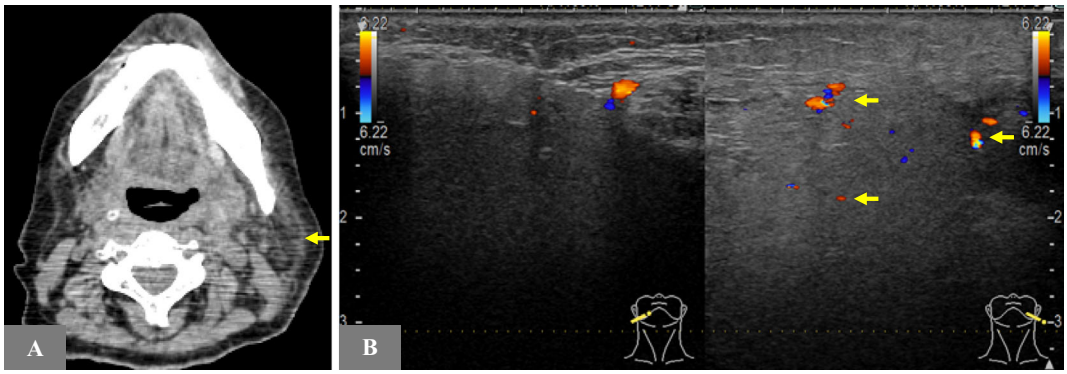

Figure 2. **Images of parotitis on computed tomography (A) and ultrasonography (B) before the fourth administration of L-asparaginase, on day 16. The enlarged left parotid gland is apparent on computed tomography (A). Thickening and increased blood flow of the left parotid gland are detected on ultrasonography (B).**

mor, and no findings of pancreatitis were seen on computed tomography (CT) (Fig. 2A). Thickening and increased blood flow of the left parotid gland were detected by ultrasonography (Fig. 2B). L-asparaginase was not administered on days 16 or 18 due to suspicion of L-asparaginase-induced parotitis. No additional treatment for parotitis was administered aside from ceasing L-asparaginase.

Her symptoms were relieved on day 18, and the serum amylase concentration decreased to 153 U/L by day 20 (Fig. 3). L-asparaginase was again administered on day 20 in accordance with the protocol, with no recurrence of parotitis observed. On day 16, mumps antibody titers (enzyme immunoassay) were as follows: immunoglobulin (Ig)M, 0.07; IgG, 2.7; and negative results of tests for autoimmune diseases such as Sjögren's syndrome, anti-neutrophil cytoplasmic antibody-associated vasculitis and IgG4-related disease. Ptyaloliths or parotid tumor were excluded by CT and ultrasonography. Finally, L-asparaginase-induced parotitis was diagnosed by excluding the differential diagnosis of parotid gland inflammation and based on symptom improvement after the cessation of L-asparaginase.

ALL showed a complete response (CR) after induction chemotherapy. The patient received bone marrow transplantation (BMT) from an HLA-matched sibling donor at the first remission and has maintained a CR since BMT. Re-administration of L-asparaginase was therefore only performed the once, on day 20 of induction chemotherapy.

Discussion

The present patient developed L-asparaginase-induced parotitis. Symptoms were relieved within 5 days after the cessation of L-asparaginase, and no recurrence of parotitis was observed with a single re-administration of L-asparaginase. Parotitis is a very rare adverse event of L-asparaginase, and its incidence and pathogenesis have not been clarified. The parotid glands are exocrine glands, like the pancreas, so a shared pathogenesis between parotitis and pancreatitis has been suggested. A review of drug-induced parotitis identified cases involving L-asparaginase (7 cases in 4 reports), clozapine (13 case reports) and phenylbutazone (13 cases) (2). Nine cases of L-asparaginase-induced parotitis, including another case report and the present case, are summarized in Table (3-7). Each of these nine cases developed parotitis during induction chemotherapy for ALL. The response to induction chemotherapy against leukemia was not clearly de-

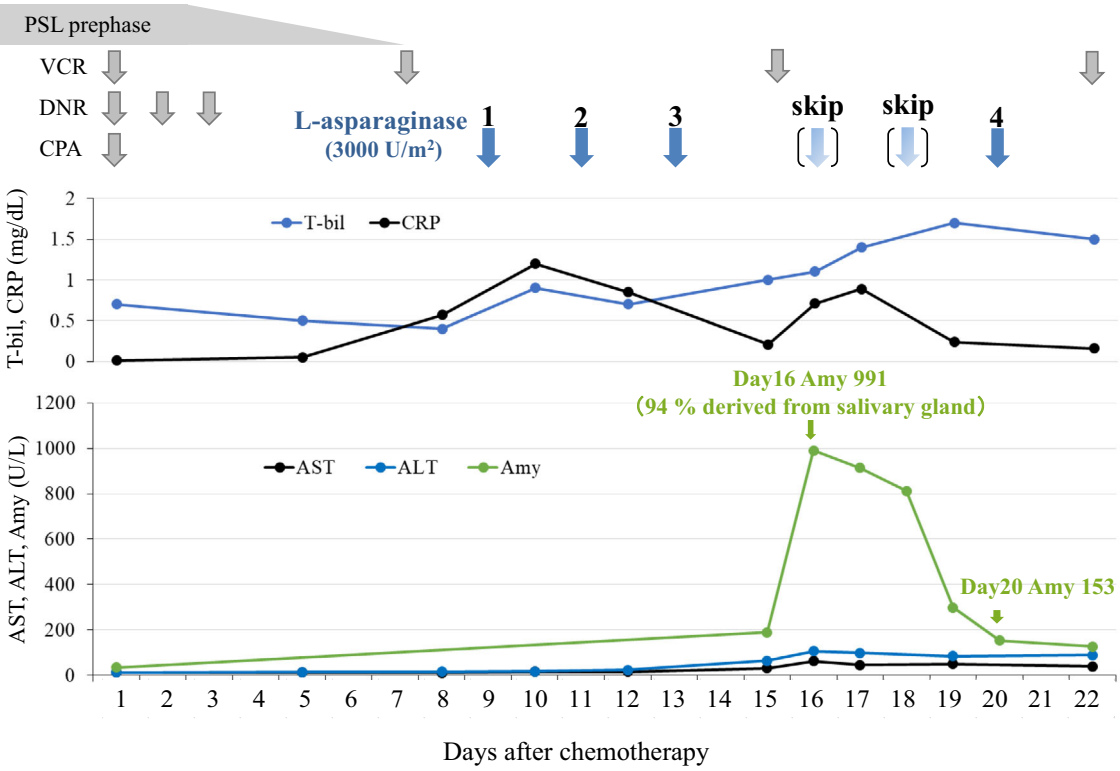

Figure 3. **Clinical course from the start of chemotherapy and development of parotitis. AST: aspartate aminotransferase, ALT: alanine aminotransferase, Amy: serum amylase, T-bil: total bilirubin, CRP: C-reactive protein, CPA: cyclophosphamide, DNR: daunorubicin, VCR: vincristine, PSL: prednisolone**

Table. **Summary of Reported Cases of L-asparaginase-induced Parotitis.**

Reference	Age/Sex	Disease	L-asparaginase (U/m^2×doses)	Bilateral/ Unilateral	Onset	Improvement	Rechallenge
3	14 y/ M	ALL	6,000×1	Unilateral	3 hours	Yes (4 days)	No
4	17 y/ M	NHL	10,000×4	Bilateral	18 days	Yes (a week)	No
5	15 y/ M	ALL	NR	Bilateral	15 days	Yes (2 days)	No
6	4 children	ALL, NHL	>10,000×>6	NR	NR	NR	NR
7	7 y/ M	ALL	NR	Bilateral	NR	Yes (a week)	NR
Our case	67 y/ F	ALL	3,000×3	Unilateral	8 days	Yes (4 days)	Yes

ALL: acute lymphoblastic leukemia, NHL: non-Hodgkin lymphoma, NR: not reported

scribed in any of the reported cases. The asparaginase formulation applied was obtained from *E. coli* in two of the nine cases and from *Erwinia carotovora* in one of the nine cases. The type of asparaginase formulation was not described in the other six cases. The onset of parotitis was variable, developing within 3 hours in the earliest case and 2-3 weeks after starting L-asparaginase administration in the other cases. Cumulative doses of L-asparaginase ranged from 6,000 U/m^2 to more than 60,000 U/m^2 prior to the development of parotitis. The development of parotitis might thus be unrelated to the cumulative dose. Only 1 in every 10 cases developed parotitis with pancreatitis at the same time. While the timing of the onset and cumulative doses of L-asparaginase have been variable, all cases showed improvement within a week after ceasing L-asparaginase. Re-administration in the present case showed no recurrence of parotitis. However, re-administration of L-asparaginase after parotitis should be performed with great caution due to the lack of established safety.

L-asparaginase is a key drug in the treatment of ALL, but unusual adverse effects of L-asparaginase often act as an obstacle to the continuation of ALL treatment. This rare adverse event should be recognized as improving within one week after the cessation of L-asparaginase.

The authors state that they have no Conflict of Interest (COI).

References

1. Sakura T, Hayakawa F, Sugiura I, et al. High-dose methotrexate therapy significantly improved survival of adult acute lymphoblastic leukemia: a phase III study by JALSG. Leukemia **32**: 626-632,

2018.

2. Brooks KG, Thompson DF. A review and assessment of drug-induced parotitis. Ann Pharmacother **46**: 1688-1699, 2012.

3. Sica S, Pagano L, Salutari P, et al. Acute parotitis during induction therapy including L-asparaginase in acute lymphoblastic leukemia. Ann Hematol **68**: 91-92, 1994.

4. Uysal K, Uguz A, Olgun N, Sarialioglu F, Büyükgebiz A. Hyperglycemia and acute parotitis related to L-asparaginase therapy. J Pediatr Endocrinol Metab **9**: 627-629, 1996.

5. Nakamura CT, Wilkinson R, Woodruff K. Pancreatitis and parotitis following therapy with L-asparaginase. Int Pediatrics **14**: 25-27, 1999.

6. Chan GC, Chiang AK, Ha SY, Lau YL, Ong JB, Lee AC. Asparaginase-induced acute parotitis: an uncommon and self-limiting complication. Med Pediatr Oncol **39**: 73-74, 2002.

7. Kathwate J, Mundada S, Patil P. L-asparaginase induced acute parotitis during intensification therapy of acute lymphoblastic leukemia. Indian J Cancer **51**: 537, 2014.