

Photophobia and Lingual Ulceration in a Child with Acute Promyelocytic Leukemia Using All-Trans Retinoic Acid (ATRA): ATRA-Related or Not?

Akut Promyelositik Lösemi Tanısı Konmuş ve All-Trans Retinoik Asit (ATRA) Kullanan Bir Çocukta Fotofobi ve Dil Ülserasyonu: ATRA ile İlişkili mi, Değil mi?

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To the Editor,

All-trans retinoic acid (ATRA) is an important component of induction therapy in acute promyelocytic leukemia (APL). Although common toxicities such as differentiation syndrome, hyperleukocytosis, and pseudotumor cerebri are widely known, rare mucocutaneous and ophthalmic side effects may be ignored, especially in young patients. Here, we present a child with APL who developed headaches, photophobia, and an isolated ulcerative tongue lesion, all of which are thought to be related to ATRA therapy.

A 5-year-old child was admitted for pancytopenia and disseminated intravascular coagulation. Bone marrow examination and flow cytometry confirmed APL. The patient's initial leukocyte count was $<10 \times 10^9/L$, indicating standard risk. The AML-MRC-15 protocol was used for induction treatment, which included ATRA at 45 mg/m²/day.

During the first course of ATRA therapy, the patient had headaches and a strong sensitivity to light. According to his parents, he could not keep his eyes open in strong light and regularly covered them. Cranial magnetic resonance imaging, normal intracranial pressure, and a fundoscopic examination all indicated no abnormalities. Thus, pseudotumor cerebri was ruled out. ATRA-related toxicity was suspected and so the ATRA dose was reduced by half, resulting in rapid improvement of the symptoms within a few days. Following the first course of the protocol, hematological improvement was detected and a bone marrow examination confirmed complete remission (CR).

In the second course of the protocol, while ATRA was administered at half the dose, a painful ulcerative lesion with a yellowish-white covering developed on the dorsum of the tongue (Figure

1A). At the same time, the patient was neutropenic (absolute neutrophil count: $0.1 \times 10^9/L$), afebrile, and clinically stable. No other oral mucosal lesions or widespread mucositis were found. Bacterial and fungal cultures collected from the lesion were negative. The serum galactomannan assay was negative. Viral testing was also done, and polymerase chain reaction (PCR) performed for the herpes simplex virus (HSV) with a sample from the lesion was negative. Empirical teicoplanin and fluconazole therapy was started but no clinical improvement was seen. Although chemotherapy-related oral mucositis is common during neutropenia, the lesion's isolated location, the absence of widespread oral involvement, the negative microbiological results, and the lack of response to antimicrobial therapy all pointed to a non-infectious cause. Thus, ATRA-induced tongue

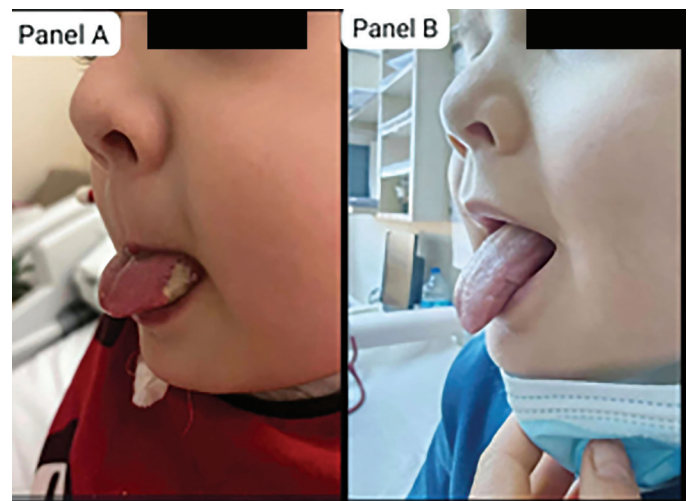


Figure 1. All-trans retinoic acid (ATRA)-associated lingual ulceration in a child with acute promyelocytic leukemia. A) Painful ulcerative lesion with a yellowish-white coating on the dorsum of the tongue during ATRA therapy. B) Complete resolution of the tongue lesion 7 days after discontinuation of ATRA.

ulceration was suspected. Despite continued neutropenia, the lesion significantly improved within 4 days of stopping ATRA and completely disappeared by day 7 (Figure 1B). According to the AML-MRC-15 protocol, if a patient has entered CR and has received ATRA for at least two courses, ATRA should not be used in subsequent courses. Thus, we did not use ATRA for the remainder of the protocol.

Headaches, photophobia, and mouth ulcers have been reported rarely in adult patients using ATRA [1,2]. Although ATRA-related cutaneous symptoms are common, they are typically manifested as scrotal dermatitis and ulceration. Focal lingual ulceration is extremely rare and may be misinterpreted as chemotherapy-related mucositis or an opportunistic infection in neutropenic patients [3,4,5]. In our case, the absence of extensive oral mucosal involvement, negative microbiological test results including HSV PCR, a lack of response to empirical antibiotic therapy, and the lesion's quick recovery following ATRA withdrawal all supported a causative relationship with ATRA.

Our experience with this case suggests that early detection of such unusual adverse effects in pediatric APL patients is therapeutically significant, as it may reduce unnecessary diagnostic tests and prolonged antimicrobial exposure, while also enabling safe management through temporary dose reduction or discontinuation of ATRA treatment.

Keywords: Acute promyelocytic leukemia, All-trans retinoic acid, Ulceration, Photophobia

Anahtar Sözcükler: Akut promiyelositik lösemi, All-trans retinoik asit, Ülserasyon, Fotofobi

Ethics

Informed Consent: Informed consent was obtained from parents.

Footnotes

Authorship Contributions

Concept: E.Y.O., E.Ç., S.K.K., Ü.K.; Design: E.Y.O., Z.K., E.Ç., S.K.K.; Data Collection or Processing: E.Y.O., Z.K., E.Ç., Ü.K.; Analysis or Interpretation: E.Y.O., Z.K., S.K.K., Ü.K.; Literature Search: E.Y.O., Z.K., E.Ç., S.K.K., Ü.K.; Writing: E.Y.O., Z.K., S.K.K.

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