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Ocular Symptom Can Be the First Presentation of Differentiation Syndrome in Acute Promyelocytic Leukemia

Dear Editor,

Acute promyelocytic leukemia (APL) is a subtype of acute myelocytic leukemia, characterized by the chromosomal abnormality t(15:17) coding a PML/RAR alpha fusion protein that affects differentiation of the promyelocyte cell in bone marrow. All-trans retinoic acid (ATRA), a key treatment for APL, acts as a differentiating agent in combination with other induction chemotherapy. Differentiation syndrome (DS) is a complication in APL patients undergoing induction chemotherapy with ATRA or arsenic trioxide [1]. The pathophysiology of DS is not understood precisely; however, it appears to be associated with a large pool of leukemic blasts, massive tissue infiltration of cells, cytokine increase, and systemic capillary leak syndrome, clinically presenting as dyspnea, fever, peripheral edema, weight gain, pleural, pericardial effusion, and acute kidney injury [2,3]. We present the case of a 66-year-old woman experiencing visual discomfort after starting ATRA treatment. This case highlights that visual symptoms can arise earlier than other well-known life-threatening symptoms of DS.

A 66-year-old female patient presented with a four-month history of headaches, nausea, and vomiting. Blood tests revealed pancytopenia, and bone marrow examination confirmed PML/RARA gene positive. She was diagnosed with APL for the first time and was admitted to the Department of Hematology and Medical Oncology at Ewha Womans University Mokdong Hospital for induction chemotherapy, where she received cytarabine, idarubicin, and ATRA as her induction chemotherapy treatment. Five days after ATRA treatment, she was referred for visual dimness and peripheral blurred vision. Her medical history included hypertension and branched retinal vein occlusion in her left eye, which had been treated with intravitreal injections three times two years prior. Her corrected visual acuity was 20 / 40 in the right eye and 20 / 32 in the left eye. Anterior segment finding was normal except for mild nuclear sclerosis in both eyes. Funduscopic examination revealed multiple retinal hemorrhages on the posterior pole in both eyes and Roth's spot appearance in the left eye. Spectral-domain optical coherence tomography showed subretinal fluid (SRF) in the macula area of the right eye (Fig. 1A). Two days after ocular symptoms appeared, systemic DS symptoms, such as fever, weight gain, and dyspnea appeared, and pulmonary edema was evident in her chest x-ray. As a DS treatment protocol, intravenous dexamethasone was administered for 12 days. Two weeks later after the diagnosis of DS, SRF in macula became more aggravated, with involvement of the fellow eye, while ocular symptoms persisted. Twenty days after DS diagnosis, bilateral serous retinal detachment (SRD) was observed. However, fluorescein angiography showed no significant abnormality, with the exception of a previous branch retinal vein occlusion lesion in her left eye (Fig. 1B); the anterior segment was not remarkable. Her symptoms continued for about 1 month under ATRA treatment and slowly regressed with visual recovery in parallel with discontinuing ATRA (Fig. 1C). Two days after discontinuing ATRA, minimal SRF remained on her right eye. Two weeks later, her corrected visual acuity was 20 / 20 in the right eye and 20 / 25 in the left eye. She achieved complete remission of SRD with improvement in visual symptoms (Fig. 1D).

We report the case of DS with ocular manifestation as a first symptom. Ocular manifestation of DS has been reported several times in previous case reports, involving retinal hemorrhage, SRD with intraretinal fluid, choroidal effusion, pseudotumor cerebri, and optic disc edema [2,4,5]. SRD can also appear in ocular infection, inflammatory disease, retinal vascular disease, malignancy, and leukemic retinopathy. Therefore, differential diagnosis should be considered. However, in this patient, the ocular symptom had developed after using the differentiating agent, ATRA. Systemic symptom appeared later. Anterior segments and fluorescein angiography findings were unre-

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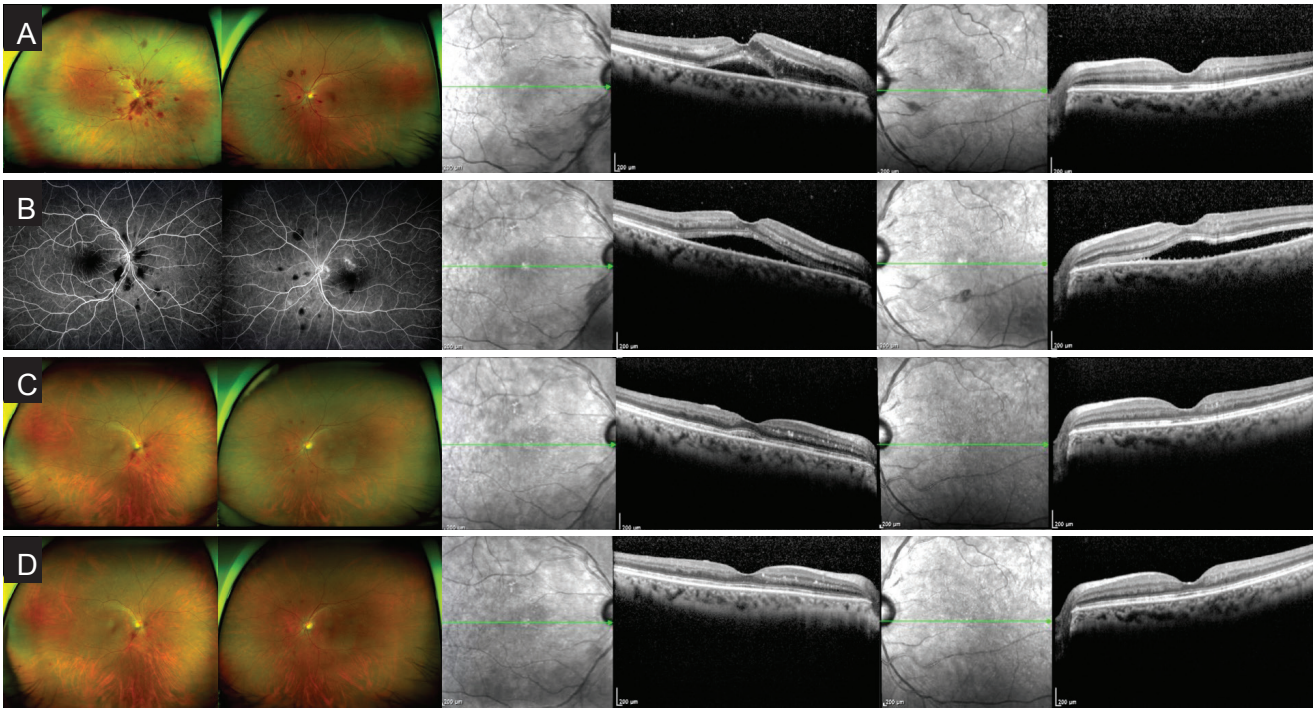

Fig. 1. Serial fundus photograph, spectral-domain optical coherence tomography, and fluorescein angiography images from a 66-year-old female acute promyelocytic leukemia patient. (A) Initial examination showed multiple retinal hemorrhages in fundus photography. The right eye showed more severe retinal hemorrhage in the posterior pole, with macular edema and mild vitreous hemorrhage. Spectral-domain optical coherence tomography showed subretinal fluid in the right eye only, not in left eye. (B) Fluorescein angiography showed no definite leak point in either eye. An old branch retinal vein occlusion lesion was observed in the left eye. Three weeks later, her serous retinal detachment became aggravated, involving the fellow eye. (C) After discontinuing all-trans retinoic acid medication, serous retinal detachment regressed with visual symptom recovery. (D) Ten days later after discontinuing all-trans retinoic acid, complete serous retinal detachment remission was observed. Informed consent for publication of the clinical images was obtained from the patient.

markable to consider other differential diagnoses. After ceasing ATRA, bilateral SRD on optical coherence tomography was regressed, and the patient's symptom was also relieved.

In conclusion, patients receiving ATRA treatment may first present with acute visual symptoms, followed by life-threatening complications such as fever, dyspnea, peripheral edema, and weight gain. Thus, careful observation of ocular symptoms in APL patients is of the utmost importance if the patient is undergoing ATRA treatment.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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