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Fundus white spots associated with graft-versus-host disease in the remission phase of acute myeloid leukemia

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ABSTRACT

Purpose: To report a case of fundus white spots associated with graft-versus-host disease (GVHD) during the remission phase of acute myelogenous leukemia (AML).

Observations: A 60-year-old woman was diagnosed with AML 7 months earlier, and after 3 months of chemotherapy, she underwent bone marrow transplantation 2 months earlier and was in remission. When she first came to our department with the chief complaint of persistent bilateral floaters before she developed AML, she had a skin rash caused by GVHD that had been diagnosed 4 days earlier, and the fundi of both eyes showed multiple white spots in the deep retinal layers. One month later, the GVHD skin rash had resolved with topical steroid treatment, and the fundus white spots had mostly disappeared. Fifteen months after the initial visit, the fundus white spots had completely disappeared, with remaining hypofluorescent dots on fundus autofluorescence. Her best-corrected visual acuity was 1.2 in each eye at the first visit and remained at 1.0 in the right eye and 1.2 in the left eye at the final visit 15 months later.

Conclusions and importance: Fundus white spots may occur in the early phase of GVHD, causing focal retinal pigment epithelium atrophy after resolution.

1. Introduction

Retinal hemorrhage and exudates are well-known retinal findings associated with leukemia. Leukemia-associated papilledema, iridocyclitis, and orbital and lid tumors are also common features. However, leukemic pigment epitheliopathy is a rare entity that has mainly been reported in association with leukemia in children.

On the other hand, graft-versus-host disease (GVHD) after bone marrow transplantation (BMT) may result in dry eye, cataract, blepharitis, ocular hypertension, and keratitis filamentosa, but fundus abnormalities have rarely been documented.

A case of bilateral fundus white spots that likely occurred due to an abnormality of retinal pigment epithelium (RPE) associated with GVHD during the remission phase of acute myelogenous leukemia (AML) is reported.

2. Case report

A 60-year-old woman complained of photopsia and floaters in both eyes 7 months earlier and visited an eye clinic. At the first consultation, cotton wool patches and spindle retinal hemorrhages around the optic discs were found in both eyes (Fig. 1). She had no history of hypertension, diabetes mellitus, or renal dysfunction and was referred to an internist for a thorough systemic examination. A complete blood cell count showed pancytopenia with hemoglobin of 6.4 g/dl, white blood cell count of 900/μl, and platelet count of 43,000/μl. Bone marrow biopsy showed 63% myeloblasts, and leukemia cells were negative for myeloperoxidase. Flow-cytometric analysis showed expression of CD13, CD34, CD117, and HLA-DR on the surface of leukemia cells. Based on the above, she was diagnosed with AML of the M0 subtype of the French-American-British classification. She underwent chemotherapy in the Department of Hematology, Osaka City University Hospital, for three months, followed one month later by HLA-matched unrelated BMT. One month after transplantation, the AML went into remission. Although she had skin rashes on the arms and legs diagnosed as a sign of GVHD four days earlier, her general condition was good; she was then referred to our department for consultation regarding bilateral floaters that had persisted since before the onset of AML.

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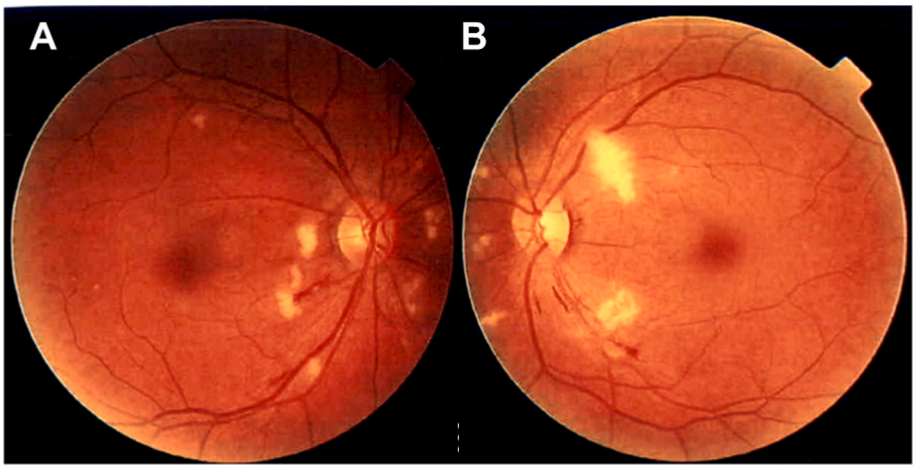

Fig. 1. Fundus photographs of the right eye (A) and the left eye (B) from the first ophthalmic examination at the previous eye clinic show cotton wool spots and spindle retinal hemorrhages around the optic discs.

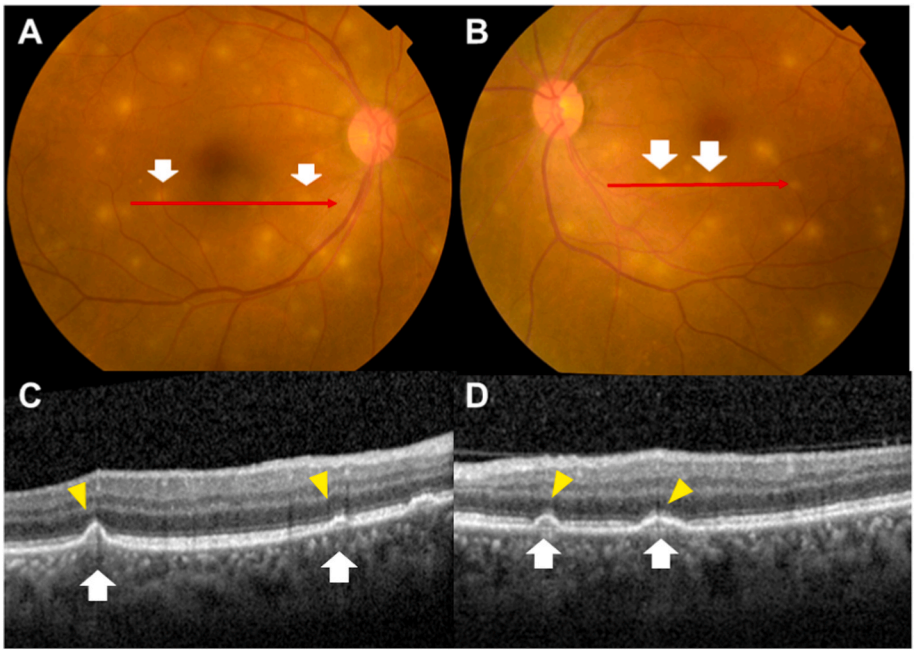

Fig. 2. Multiple subretinal white spots (arrows) are seen in both eyes (A, B). Optical coherence tomography shows some protrusions (arrows) of RPE and overlaid hyperreflective foci (arrow heads) in the deeper retina, identical to white spots (C, D).

Her best-corrected visual acuity (BCVA) was 1.2 in either eye with the Landolt C chart. The anterior segment and optic media findings were normal, but the fundus examination showed multiple subretinal white spots and a few peripheral retinal dot hemorrhages in both eyes. No apparent abnormality was seen in the retinal vessels, and cotton wool spots found on the first ophthalmic examination at the previous eye clinic were not present. Optical coherence tomography (OCT) showed some protrusions of RPE and overlaid hyperreflective foci in the deeper retina identical to white spots (Fig. 2). The macula looked normal in shape in both eyes. Fundus autofluorescence (FAF) showed focal hyperfluorescence with a central hypofluorescent dot at the sites of white spots (Fig. 3). Hyperfluorescent dots were found on fluorescein angiography, and hypocyanescent spots were seen on indocyanine-green angiography, which were identical to white spots (Fig. 4). A month later, her skin rash had improved with a topical steroid, and the fundus white spots were regressing.

Eight months after BMT, hepatic impairment and oral inflammation due to GVHD occurred, and she was started on oral prednisolone (25 mg). The dose of prednisolone was tapered with an improvement of hepatic function and terminated by 2 months. No recurrence of fundus white spots was observed during this period. Twelve months after BMT, a hematopoietic blood transfusion was performed for suspected recurrence of AML at the molecular level because of the gradual elevation of a tumor marker (WT-1) from 6 months after transplantation, though no recurrence was indicated on bone marrow biopsy examination. Fifteen months after BMT, the white spots had disappeared completely, and no hyperfluorescence was seen on FAF. However, hypofluorescent dots remained and increased slightly in size from our first examination (Fig. 5). The BCVA remained at 1.0 in the right eye and 1.2 in the left eye without recurrence of white spots.

3. Discussion

A case of bilateral fundus white spots during early GVHD after BMT

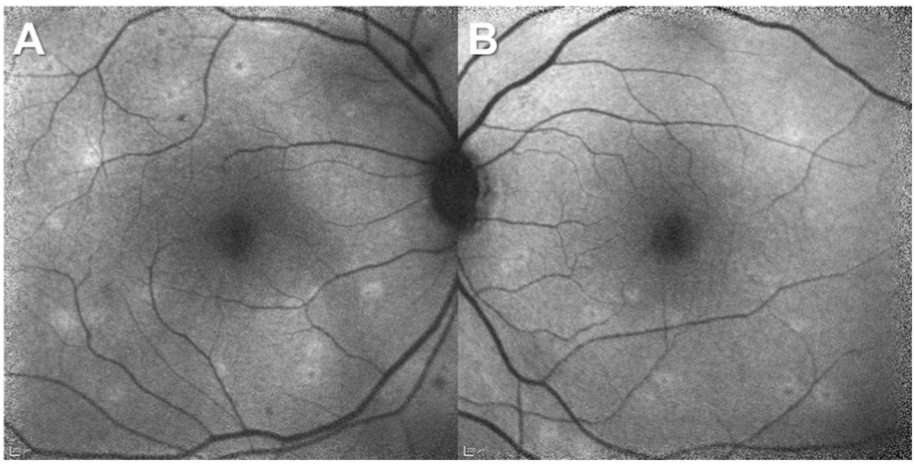

Fig. 3. Fundus autofluorescence of the right eye (A) and the left eye (B) shows focal hyperfluorescence with central hypofluorescent dots (arrow heads) at the sites of white spots.

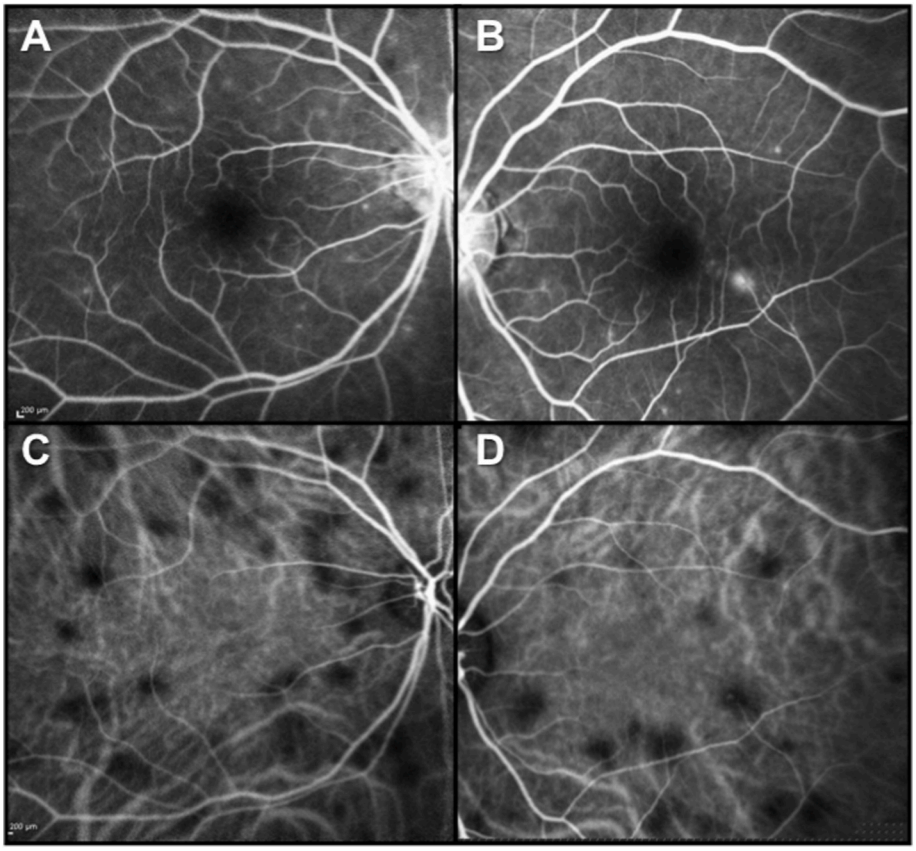

Fig. 4. Hyperfluorescent dots are found on fluorescein angiography (A, B). Filling defects of the choriocapillaris are seen on indocyanine-green angiography, identical to the white spots (C, D).

in the remission phase of AML was presented. Based on multimodal imaging of the fundus, we hypothesized that the white spots at the fundus suggested a disturbance of choroidal circulation and concurrent RPE damage.

As an ocular complication of leukemia, retinal pigment epitheliopathy was reported in a pediatric case, but it is rare in adults. Verbraak et al. reported retinal pigment epitheliopathy with a reticular pattern of yellow-white lesions in remission phase of acute lymphoblastic leukemia, and the reticular pattern became more defined with time and remained.[1] In autopsy cases, infiltration of leukemia cells to the choroid and RPE layer was frequently reported,[2] which suggested RPE dysfunction caused by direct invasion of tumor cells or secondary ischemia following infiltration of leukemia cells into the choriocapillaris. Such complications usually occur when a disease is clinically and hematologically active, but a case of acute lymphocytic leukemia was reported to show RPE dysfunction accompanied by serous retinal detachment ahead of the recurrence of leukemia that occurred a few months later.[3] Although the white spots in this case were not very similar to that reticular pattern, disappeared over time, and no hematological recurrence of leukemia was observed throughout the follow-up

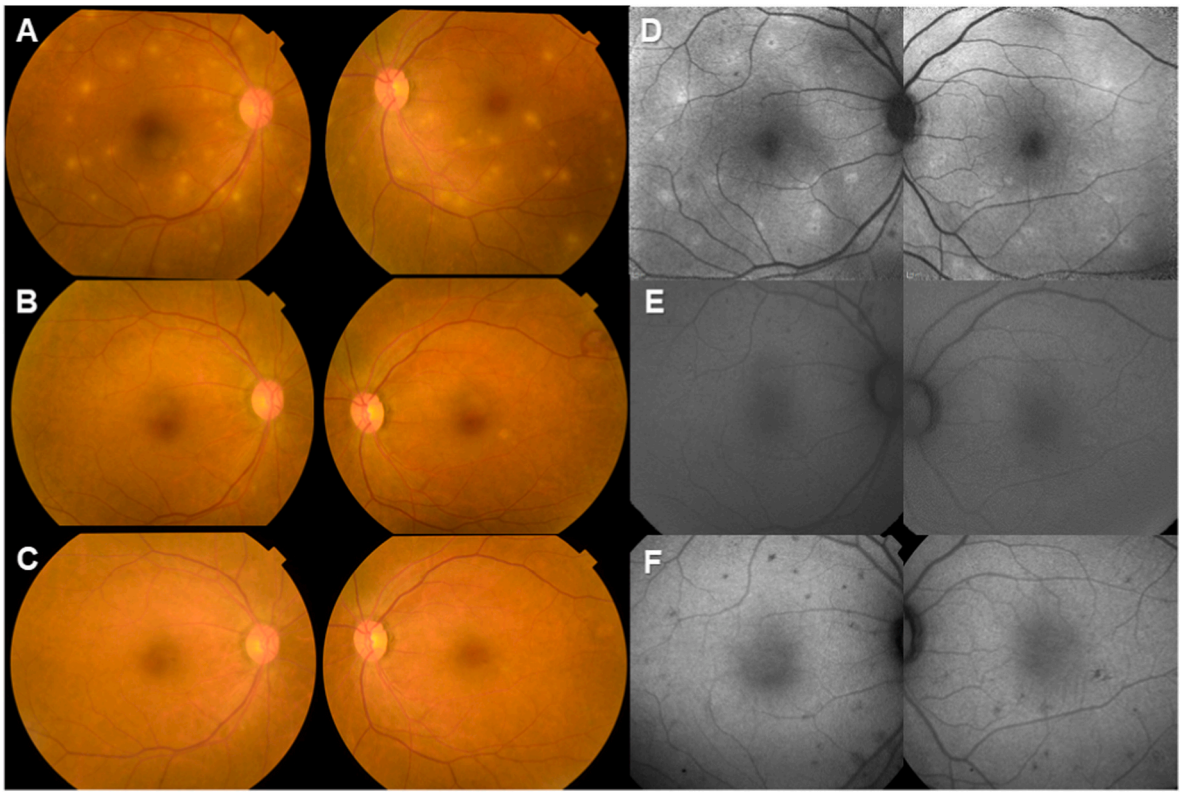

Fig. 5. Color fundus photograph and fundus autofluorescence at the first visit to our department (A, D). The fundus white spots have regressed over time. In the next month, the white spots have mostly disappeared (B), and no hyperfluorescence is seen on fundus autofluorescence (E). Fifteen months later, hypofluorescent dots remain and are slightly increased in size from the first visit to our department (F). Color fundus photograph at A: First visit, B: 1 month later, and C: 15 months later. FAF at D: first visit, E: 1 month later, and F: 15 months later. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

period, fundus white spots appeared 5 months before the recurrence at the molecular level. In addition, it is possible that the fundus white spots were the residue of retinal abnormalities due to direct infiltration of tumor cells found before BMT, since no ophthalmic examination was performed between the first visit to the eye clinic and our examination. However, white spots were found in the period of complete remission of AML a month after BMT and when a sign of stage 2 GVHD appeared on her skin indicating acute GVHD. Ocular complications of GVHD occur mostly in the anterior segment, lacrimal glands, Meibomian glands, and cornea, causing dry eye, keratoconjunctivitis sicca, and corneal ulcers, whereas fundus abnormalities have rarely been reported, including serous retinal detachment in a case of acute GVHD[4] and bilateral panuveitis with serous retinal detachment in a case of chronic GVHD.[5] GVHD is a disturbance of host cells induced by donor immunity that causes lymphocytic infiltration to organs such as the skin. After the recovery phase, an autoimmune mechanism may occur that induces choroidal inflammation and vascular hyperpermeability due to lymphocytic infiltration to the choroid. Similar findings are observed in the early phase of primary ocular malignant lymphoma, which shows multiple yellow-whitish lesions at the fundus due to sub-RPE lymphocytic infiltration.[6] For all of these reasons, the findings in the present case might suggest lymphocytic infiltration to the sub-RPE space caused by an immune response due to GVHD. However, it was not clear why the fundus white spots did not recur with the second GVHD.

In addition, the deep retinal white spots seen in the present case were similar to those seen in multiple evanescent white dot syndrome (MEWDS). MEWDS causes relatively sudden visual field and vision impairment, photopsia, and other symptoms, usually with multiple white spots in the middle to deep layers of the retina in one eye, which often resolve spontaneously within 1–2 months. Although the etiology of MEWDS remains unknown, some entities are associated with viral prodromes, suggesting a potential viral or infectious etiology. As with most autoimmune conditions, unknown triggers are thought to cause inflammation or autoimmune processes in the posterior eye.[7] In the present case, the white spots were bilateral, and the only subjective symptom was persistent nonspecific floaters, but it remains possible that the cause is not only direct leukocyte infiltration or lymphocyte infiltration, but also an autoimmune mechanism or secondary inflammation of the outer retina similar to MEWDS caused by such cellular infiltration.

The findings appeared to resolve with improvement of GVHD by steroid treatment, but it might be a resolution of the initial retinal complication of AML over time. More cases will need to be examined to clarify this point.

In conclusion, fundus white spots may occur in the early phase of GVHD, causing focal RPE atrophy after resolution.

Patient consent

Written, informed consent was obtained from the patient for the publication of the details of the case.

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Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Declaration of competing interest

The following authors have no financial disclosures: AK, MY, YN, TK, SH.

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