Journal of clinical and experimental hematopathology
Vol. 58 No.4, 180-183, 2018

Letter to the Editor

Intraocular lymphoma as relapse after chemotherapy for primary breast diffuse large B-cell lymphoma

Keywords: Intraocular lymphoma, breast lymphoma, vitrectomy, diffuse large B-cell lymphoma, intrathecal methotrexate

TO THE EDITOR

A 68-year-old woman developed right breast pain and visited a hospital. A 2-cm mass was palpable in the areola at 9 o'clock and was visualized as a well-defined tumor shadow on ultrasound examination. Needle biopsy revealed large abnormal lymphoid cells in a diffuse pattern (Fig. 1A), which were positive for CD20 and CD5, and negative for CD3, CD10, and cyclin D1. The Ki67-labeling index was high at 60%. The pathological diagnosis was primary breast diffuse large B-cell lymphoma. Whole-body 2-[^{18}F]fluoro-2-deoxy-D-glucose positron emission tomography (PET) was normal except for high uptake in the right breast (SUVmax=19.26) and a 1-cm area in the axillary lymph node on the right side (SUVmax=2.01). She was in stage IA with a single risk factor (age) using the international prognostic index. Over 3 months, she underwent 6 courses of R-CHOP chemotherapy (rituximab: 375 mg/m^2, cyclophosphamide: 750 mg/m^2, doxorubicin: 50 mg/m^2, vincristine: 1.4 mg/m^2, and prednisolone: 100 mg x 5 doses), combined with intrathecal injection of methotrexate (10 mg) and cytarabine (40 mg). She achieved complete remission. One year and 4 months later, she developed blurred vision in the right eye and visited an eye doctor. The best-corrected visual acuity was 0.6 in the right eye and 1.0 in the left eye. The intraocular pressure was 23 mmHg in the right eye and 17 mmHg in the left eye. She had previously undergone cataract surgery with intraocular lens implantation in both eyes. The right eye had no aqueous inflammatory cells but had vitreous opacity with several yellowish thickened retinal lesions in the right eye (Fig. 2A, 2B, 2C). The left eye was normal. PET demonstrated no abnormal uptake. She underwent vitrectomy with

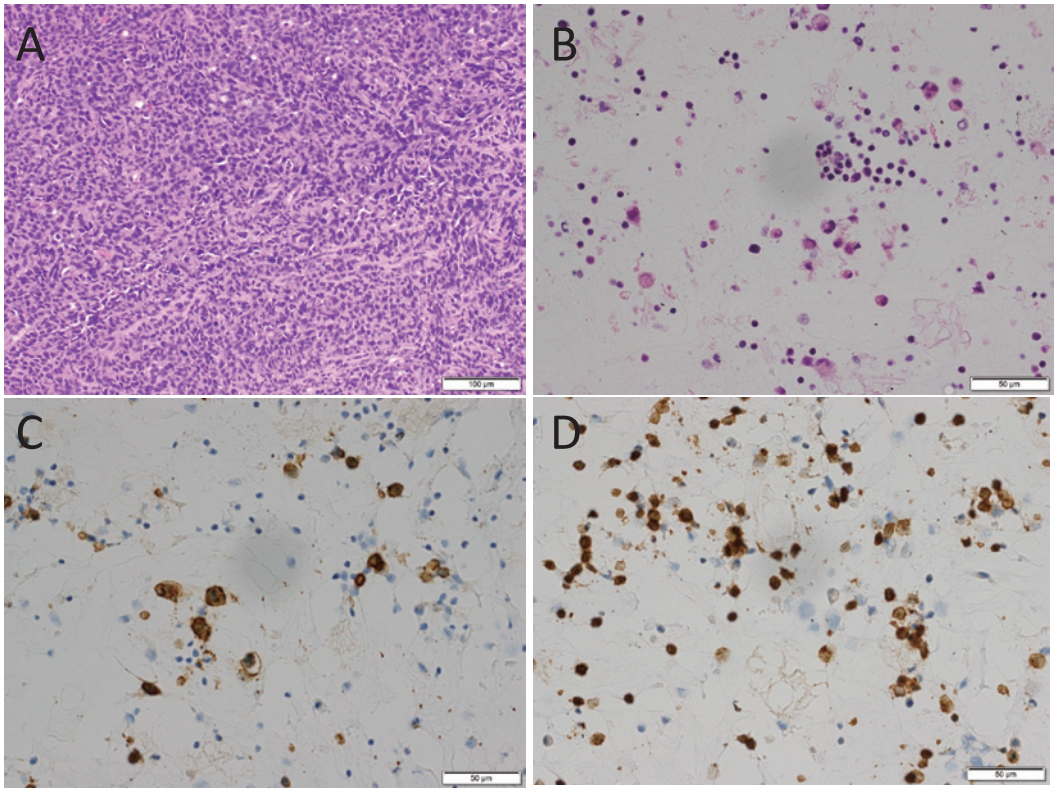

Fig. 1. ***A***. Hematoxylin-eosin staining of right breast needle biopsy specimen at the initial visit. Note the diffuse infiltration of large cells with irregular nuclei. ***B-D***. Hematoxylin-eosin and immunostaining of paraffin-embedded sections of vitrectomy cell block from the right eye. Note the large cells positive for CD20 (***C***) admixed with small lymphocytes positive for CD3 (***D***). Bar = 100 μm in ***A***, and bar = 50 μm in ***B-D***.

laser photocoagulation applied to the retinal area with capillary non-perfusion in the entire mid-peripheral fundus (Fig. 2E, 2F). A paraffin-embedded cell block was prepared by centrifugal pelleting of the vitrectomy specimen. Hematoxylin-eosin (Fig. 1B) and immunostaining of sections revealed CD20-positive large cells (Fig. 1C) admixed with dominant CD3-positive small lymphocytes (Fig. 1D), leading to the pathological diagnosis of intraocular relapse of large B-cell lymphoma. CD5 staining in the large cells was unclear. She was referred to an oncologist.

In the following 3 months, she underwent 4 courses of systemic chemotherapy with high-dose methotrexate (1000 mg/m^2) and cytarabine (2000 mg/m^2 x 4 doses), together with rituximab (375 mg/m^2). Then, she received external irradiation to the right eye at a total dose of 30 Gy (2 Gy in 15 fractions). The retinal lesions resulted in degeneration and

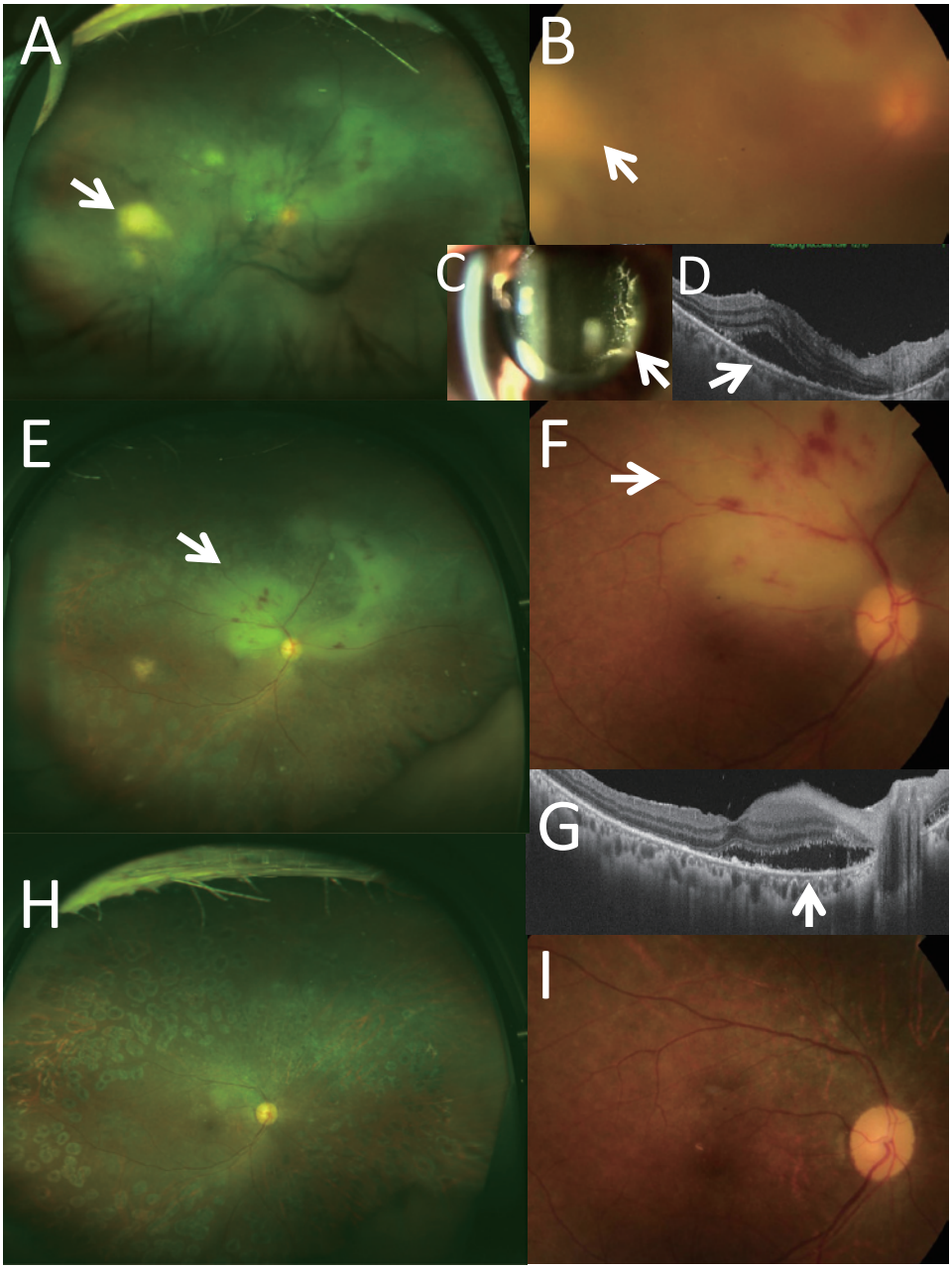

Fig. 2. Wide-view fundus photograph (***A***), fundus photograph (***B***), slit-lamp biomicroscopic image (***C***), and horizontal section of optical coherence tomography (***D***) in the right eye of a 70-year-old woman. Note the vitreous opacity (***A***, ***B***, ***C***, arrow in ***C***) and yellowish subretinal lesion temporal to the macula (arrows, ***A***, ***B***), and subretinal fluid (arrow, ***D***). Wide-view fundus photograph (***E***), fundus photograph (***F***), and horizontal section of optical coherence tomography (***G***) 2 weeks after vitrectomy. Note the yellowish large thick subretinal lesion superior to the optic disc (arrows, ***E***, ***F***) and subretinal fluid (arrow, ***G***). Wide-view fundus photograph (***H***) and fundus photograph (***I***) after systemic methotrexate and cytarabine, followed by total eye irradiation at 30 Gy. Note the resolution of retinal infiltrates and degeneration. Spotty retinal degeneration appeared after retinal laser photocoagulation on vitrectomy.

complete response (Fig. 2H, 2I). The best-corrected visual acuity was 0.7 in the right eye and 1.0 in the left eye. The left eye was normal. She used no medication or eye drops. She abruptly developed amnesia, and irregularly shaped masses with contrast enhancement along the inferior horn of the lateral ventricles on both sides and the caudal side of the anterior horn of the lateral ventricle on the left side were observed on magnetic resonance imaging. Under a diagnosis of central nervous system relapse, she underwent systemic chemotherapy with high-dose methotrexate (3500 mg/m^2) and total brain irradiation at a dose of 30 Gy. She developed facial nerve palsy on the left side, likely due to meningeal infiltration, and underwent intrathecal administration of methotrexate at 15 mg and cytarabine at 40 mg four times weekly. She is stable and on palliative care.

Intraocular lymphoma clinically manifests as vitreous opacity or yellowish subretinal pigment epithelial infiltration or their combination,[1] and presents as a diagnostic challenge for eye doctors to differentially diagnose from intraocular inflammatory diseases such as uveitis. In general, a diagnosis of intraocular lymphoma is made with immunostaining of sections of paraffin-embedded cell blocks prepared from pellets of vitrectomy fluid by centrifugation.[2,3] Primary intraocular lymphoma is rare and most often associated with primary central nervous system lymphoma. The lesion in the eye precedes or follows the brain lesion, or both lesions occur at the same time. More rarely, secondary intraocular infiltration with lymphoma can occur following the development of lymphoma in other parts of the body excluding the central nervous system. In this letter, we report a patient who was confirmed to have secondary intraocular infiltration of primary breast diffuse large B-cell lymphoma. To the best of our knowledge, there has been only one case report of intraocular involvement as vitreous opacity in a patient with primary breast lymphoma.[4]

As the initial treatment for primary breast diffuse large B-cell lymphoma, intrathecal administration of methotrexate and cytarabine was combined with the standard R-CHOP regimen for systemic chemotherapy. Intrathecal prophylactic drug administration is based on CD5-positive lymphoma, as in this patient, having a propensity for central nervous system infiltration. A poor prognostic factor in primary breast diffuse large B-cell lymphoma is central nervous system involvement.[5-8] It should be noted that the large B-cell lymphoma in our patient relapsed in the eye and the brain after intrathecal drug administration.

The retina is part of the central nervous system, and the optic nerve sheath has subarachnoid space communicating with the cerebrospinal fluid. Further communication of the subarachnoid space of the optic nerve with the vitreous has been clinically demonstrated by reports of subarachnoid hemorrhage leading to vitreous hemorrhage.[9] Clinically, vitreous hemorrhage associated with subarachnoid hemorrhage is called Terson syndrome.[9] Intrathecally injected methotrexate and cytarabine may diffuse into the vitreous via the subarachnoid space of the optic nerve, although at an unknown concentration. In this patient, the intrathecal administration did not prevent lymphoma from relapsing in the subretinal pigment epithelial area or the vitreous, suggesting the concentration of drugs in the vitreous to be low. Lymphoma cells may have escaped the systemic chemotherapy by prophylactic intrathecal administration and survived in the intraocular space, which is immunologically protected and isolated from the body by the blood-ocular or blood-retinal barrier.

The relapse of primary breast diffuse large B-cell lymphoma in this patient manifested as vitreous opacity and subretinal pigment epithelial thick lesions, which are the hallmark of intraocular lymphoma. A small number of CD20-positive large cells was admixed with a larger number of CD3-positive small lymphocytes on immunostaining using paraffin sections of a cell block created from the vitrectomy specimen. The subretinal pigment epithelial lesions in the right eye resolved after systemic chemotherapy with high-dose methotrexate, cytarabine, and rituximab. The therapeutic outcome in this patient further supports that the intraocular lesions were indeed the manifestation of lymphoma infiltration.

High-dose methotrexate combined with cytarabine and rituximab was selected for this patient as the systemic chemotherapy regimen at the relapse of the intraocular lesions. The regimen is the standard for primary central nervous system lymphoma because these drugs are known to cross the blood-brain barrier. As intraocular relapse may be a preceding sign of central nervous system relapse, this regimen was chosen considering the presumed subclinical central nervous system involvement. Total eye irradiation at the median dose of 30 Gy was performed as consolidation therapy. Intravitreous methotrexate injection[10,11] was not used for the present patient because total eye irradiation was more reliable. Even with these measures, central nervous system relapse was not prevented in this patient.

CONFLICT OF INTEREST

The authors declare no conflict of interest in this study.

REFERENCES

1 Matsuo T, Yamaoka A, Shiraga F, Matsuo N. Two types of initial ocular manifestations in intraocular-central nervous system lymphoma. Retina. 1998; 18 : 301-307.
2 Matsuo T, Ichimura K, Ichikawa T, *et al.* Positron emission tomography/computed tomography after immunocytochemical and clonal diagnosis of intraocular lymphoma with vitrectomy cell blocks. J Clin Exp Hematop. 2009; 49 : 77-87.
3 Matsuo T, Ichimura K. Immunocytochemical diagnosis as inflammation by vitrectomy cell blocks in patients with vitreous opacity. Ophthalmology. 2012; 119 : 827-837.
4 Ohta K, Sano K, Hirano T, Sugimoto T, Kikuchi T. B cell monoclonality of intraocular lymphoma and breast lymphoma. Br J Ophthalmol. 2008; 92 : 296-297.
5 Jeanneret-Sozzi W, Taghian A, Epelbaum R, *et al.* Primary breast lymphoma: patient profile, outcome and prognostic

factors. A multicentre Rare Cancer Network study. BMC Cancer. 2008; 8 : 86.
6 Radkani P, Joshi D, Paramo JC, Mesko TW. Primary breast lymphoma: 30 years of experience with diagnosis and treatment at a single medical center. JAMA Surg. 2014; 149 : 91-93.
7 Jabbour G, El-Mabrok G, Al-Thani H, *et al.* Primary breast lymphoma in a woman: a case report and review of the literature. Am J Case Rep. 2016; 17 : 97-103.
8 Mohamed KEH, Ali RAE. Primary breast lymphoma: a case report and review of the literature. Clin Pract. 2017; 7 : 939.
9 Kuhn F, Morris R, Witherspoon CD, Mester V. Terson syndrome. Results of vitrectomy and the significance of vitreous hemorrhage in patients with subarachnoid hemorrhage. Ophthalmology. 1998; 105 : 472-477.
10 Smith J, Rosenbaum JT, Wilson DJ, *et al.* Role of intravitreal methotrexate in the management of primary central nervous system lymphoma with ocular involvement. Ophthalmology. 2002; 109 : 1709-1716.
11 Frenkel S, Hendler K, Siegal T, Shalom E, Pe'er J. Intravitreal methotrexate for treating vitreoretinal lymphoma: 10 years of experience. Br J Ophthalmol. 2008; 92 : 383-388.

Toshihiko Matsuo,[1)] Takehiro Tanaka,[2)] Tomofumi Yano[3)]
[1)]Ophthalmology, Okayama University Hospital, Okayama City, Japan, [2)]Pathology, Okayama University Hospital, Okayama City, Japan, [3)]Hematology and Oncology, Okayama Rosai Hospital, Okayama City, Japan
Corresponding author: Toshihiko Matsuo, MD, PhD, Ophthalmology, Okayama University Medical School and Graduate School of Interdisciplinary Science and Engineering in Health Systems, 2-5-1 Shikata-cho, Okayama City 700-8558, Japan.
E-mail: matsuot@cc.okayama-u.ac.jp

Received: July 18, 2018.
Revised: September 24, 2018.
Accepted: October 2, 2018.
J-STAGE Advance Published: November 9, 2018
DOI:10.3960/jslrt.18026