

Case Study

Intraocular Relapse with Hypopyon and Retinal Infiltrates after Chemotherapy and Peripheral Blood Stem Cell Transplantation for Extranodal NK/T-Cell Lymphoma

Toshihiko Matsuo,¹⁾ Takehiro Tanaka,²⁾ Kouichi Ichimura,²⁾ and Yusuke Meguri³⁾

We report a case of intraocular relapse of extranodal NK/T-cell lymphoma with anterior chamber hypopyon and retinal infiltrates. A 55-year-old man developed fever, malaise, anorexia, and hepatosplenomegaly, and was diagnosed with NK/T-cell lymphoma by liver biopsy. He underwent 2 courses of SMILE (dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide) chemotherapy, followed by myeloablative peripheral blood stem cell transplantation, donated by his brother. Two months later, he developed high-grade fever, hepatosplenomegaly, and peritoneal lymphadenopathy, and the relapse with hemophagocytic syndrome was diagnosed by bone marrow biopsy. He underwent 2 courses of SMILE salvage chemotherapy, followed by non-myeloablative peripheral blood stem cell transplantation, donated by his son. Two months later, he noticed blurred vision in both eyes. The right eye had aqueous cells and keratic precipitates, but no retinal lesions. The left eye had hypopyon in the anterior chamber with numerous aqueous cells, and retinal white infiltrates with retinal hemorrhages. The aqueous cells, obtained by anterior chamber paracentesis, were positive for CD3, CD56, and Epstein-Barr virus-encoded RNA, but negative for CD20 by immunocytochemical staining. Head magnetic resonance imaging demonstrated white matter lesions in the anterior to parietal lobes on the right side. The patient underwent intrathecal methotrexate injection and external beam radiation at 40 Gy, covering the entire brain and both eyes. The retinal lesions and hypopyon disappeared. Two months later, the patient died of renal failure, and autopsy demonstrated multi-organ involvement of lymphoma cells. In conclusion, we report a case of NK/T-cell lymphoma relapse with intraocular lesions, after combined chemotherapy and hematopoietic stem cell transplantation. [J Clin Exp Hematop 55(3) : 157-161, 2015]

Keywords: extranodal NK/T-cell lymphoma, hypopyon, aqueous, retinal infiltrates, hematopoietic (peripheral blood) stem cell transplantation

INTRODUCTION

Hypopyon is the accumulation of white blood cells in the lower portion of the anterior chamber of the eye, and is a sign of intraocular inflammation, called uveitis, which includes iritis and iridocyclitis. Hypopyon, also known as pseudo-hypopyon, as well as vitreous opacity, are two major manifestations of intraocular involvement with lymphoma¹⁻⁴ or leukemia.⁵⁻⁷

Nasal-type extranodal NK/T-cell lymphoma is a type of malignant lymphoma defined in the 2008 version of the

World Health Organization (WHO) Classification of Tumors of Hematopoietic and Lymphoid Tissues.⁸⁻¹⁰ The course of the disease is aggressive, and the treatment requires intensive chemotherapy¹¹ and hematopoietic stem cell transplantation.¹²⁻¹⁴ In this report, we present a patient with pseudo-hypopyon and retinal infiltrates as a manifestation of intraocular relapse of extranodal NK/T-cell lymphoma after two rounds of allogeneic peripheral blood stem cell transplantation.

CASE REPORT

A 55-year-old man presented with fever, general malaise, and anorexia mid-May of 2010. Ultrasonography revealed hepatosplenomegaly, and blood tests showed higher levels of serum aspartate aminotransferase and alanine aminotransferase, as well as elevation of serum soluble interleukin-2 receptor. Abdominal computed tomography revealed perihepatic and paraaortic lymphadenopathy, suggestive of lymphoma (Fig. 1A). At the beginning of June, liver biopsy demon-

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Departments of ¹Ophthalmology, ²Pathology, and ³Hematology/Oncology, Okayama University Hospital and Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, Okayama City, Japan

Corresponding author: Toshihiko Matsuo, M.D., Ph.D., Department of Ophthalmology, Okayama University Medical School and Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, Shikata-cho 2-5-1, Okayama City 700-8558, Japan.

E-mail: matsuo@cc.okayama-u.ac.jp

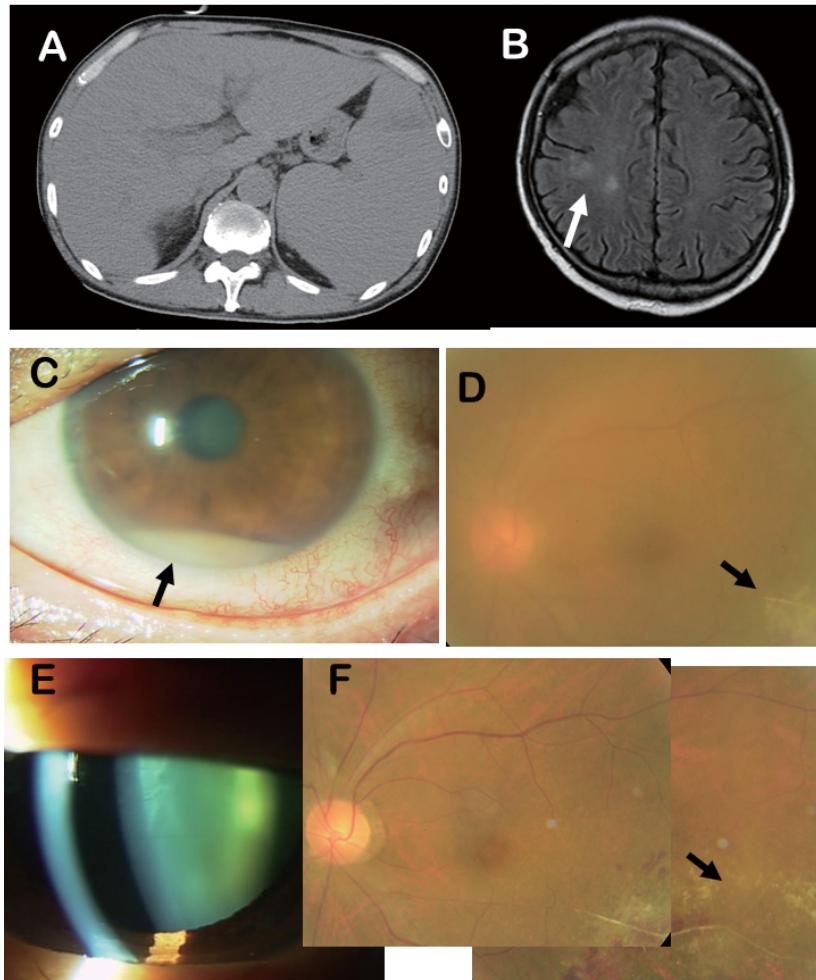


Fig. 1. Hepatosplenomegaly in a 55-year-old man (1A) on a computed tomographic scan in June 2010, before SMILE chemotherapy with dexamethasone (steroid), methotrexate, ifosfamide, L-asparaginase, and etoposide. White matter lesions (arrow in 1B) in the right parietal lobe on magnetic resonance imaging with T2-weighted fluid attenuation inversion recovery (FLAIR) in April 2011. Anterior chamber hypopyon (arrow in 1C) and retinal infiltrates (arrow in 1D) with vitreous opacity (1D) in the left eye in April 2011. The hypopyon has disappeared (1E), as have the vitreous opacity (1F) and retinal infiltrates (arrow in 1F) in May 2011, after external beam radiation.

strated extranodal NK/T-cell lymphoma. Medium-sized cells in the perivascular infiltration were positive for CD3 (cytoplasmic), CD56, EBER (Epstein-Barr virus-encoded RNA), and TIA1, but negative for CD20, CD4, CD5, and CD8 (Fig. 2). *In situ* hybridization (ISH) for EBER was performed with an oligonucleotide probe (Bond ISH Probe, EBER Probe, Leica Microsystems, Newcastle Upon Tyne, UK) by an automated ISH stainer (LEICA BOND-MAX, Leica Microsystems).¹⁵⁻¹⁷

In mid-June, the patient developed peritonitis caused by sigmoid colon perforation, as a sequela of diverticulitis, and underwent emergency surgery for resection of the perforated colon and construction of an artificial anus. Pathological examinations of the resected colon did not demonstrate involvement with lymphoma.

By the end of June, of the B symptoms, the patient still had fever and night sweats, but no weight loss. His general health performance status was 2 by the WHO scale. Bone marrow tap detected no apparent involvement of lymphoma cells. Blood examination showed a white blood cell count of $4.28 \times 10^3/\mu\text{L}$ (with differential of 76% segmented neutro-

phils, 4% stab neutrophils, 15% lymphocytes, 1% monocytes, 1% basophils, 1% atypical lymphocytes, 1% metamyelocytes, and 1% myelocytes), red blood cell count of $3.93 \times 10^6/\mu\text{L}$, platelets $79 \times 10^3/\mu\text{L}$, hemoglobin 11.3 g/dL, serum lactate dehydrogenase 504 IU/L, serum C-reactive protein 2.46 mg/dL, serum soluble interleukin-2 receptor 3,551 U/mL, and serum total bilirubin 2.44 mg/dL. Renal function was normal. He underwent two courses of SMILE chemotherapy,¹¹ consisting of dexamethasone (steroid), methotrexate, ifosfamide, L-asparaginase, and etoposide. In September, he underwent allogeneic peripheral blood stem cell transplantation, from an HLA-identical donor (younger brother), after myeloablative pretreatment with fludarabine and busulfan, followed by cyclosporine A and methotrexate for graft-versus-host disease prophylaxis. In October, he developed systemic skin redness, suggesting graft-versus-host disease. In November, he developed high-grade fever, anorexia, and general malaise, and abdominal computed tomography revealed hepatosplenomegaly and peritoneal lymphadenopathy. He also showed thrombocytopenia and elevated levels of serum lactate dehydrogenase and ferritin. Bone

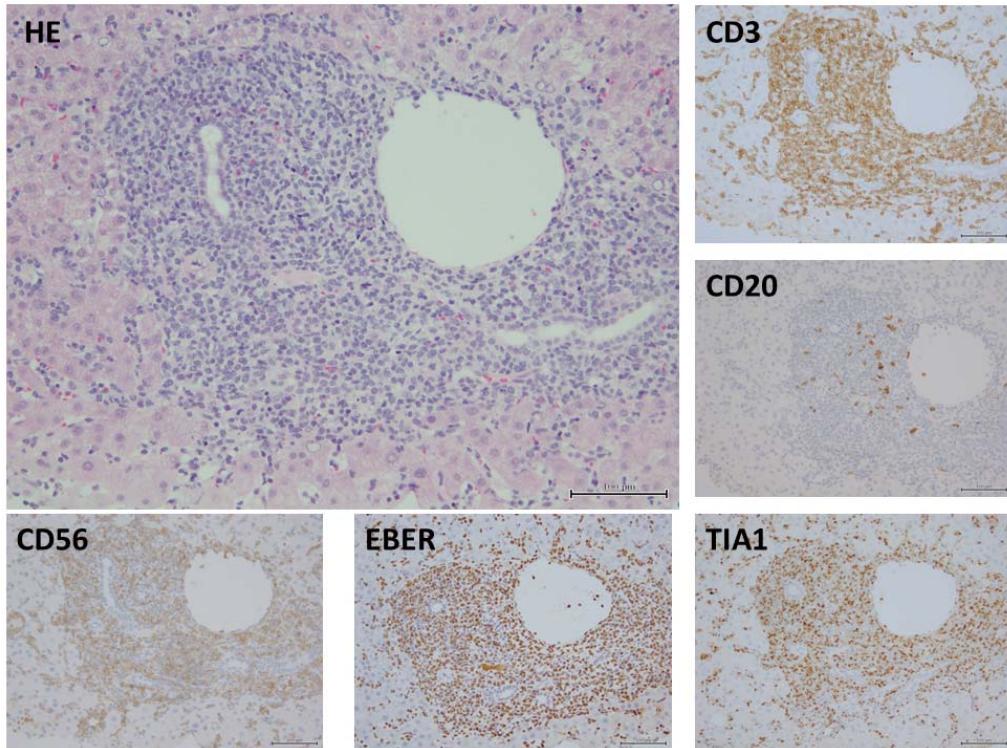


Fig. 2. Liver biopsy in a 55-year-old man at the initial visit in May 2010. Perivasculair infiltration with medium-sized cells with irregularly-shaped nuclei (H&E stain), which are positive for CD3 (cytoplasmic), CD56, EBER (Epstein-Barr virus-encoded RNA), and TIA1, but negative for CD20. Original magnification, $\times 20$. Bar = 100 μm .

marrow biopsy revealed phagocytosis of trilineage hematopoietic cells, and an increase of CD56-positive cells to 82.8%, leading to the diagnosis of lymphoma relapse and lymphoma-associated hemophagocytic syndrome. The lymphoma cells were also positive for EBER (Fig. 3). He underwent corticosteroid pulse therapy with 1 g daily intravenous methylprednisolone, combined with intravenous immunoglobulin administration.

The patient underwent salvage SMILE chemotherapy twice in November and December 2010. In February 2011, he underwent non-myeloablative ‘mini’ peripheral blood stem cell transplantation, supplied by a haplo-identical donor (son), after non-myeloablative pretreatment. In March, he developed diarrhea as a symptom of graft-versus-host disease and was administered 80 mg prednisolone daily.

In April, he noticed blurred vision in both eyes. Best-corrected visual acuity was 1.2 in the right eye and 0.4 in the left eye. Intraocular pressure was 16 mmHg in the right eye and 42 mmHg in the left eye. The right eye showed 2+ aqueous cells with 1+ mutton-fat keratic precipitates, while the left eye showed massive aqueous cells with hypopyon (Fig. 1C) and 3+ mutton-fat keratic precipitates. The retina was normal and the vitreous had no opacity in the right eye, while the left eye had a yellowish retinal lesion with retinal

hemorrhages inferotemporal to the macular area, and vitreous opacity (Fig. 1D). Anterior chamber paracentesis showed lymphoma cells in both eyes, which were positive for EBER, CD56, and CD3 (cytoplasmic), but negative for CD20 (Fig. 3). Aqueous fluid obtained by aqueous tap, was placed on glass slides, dried, fixed with 4% paraformaldehyde, and stained as described above.

The patient was administered 0.1% betamethasone and latanoprost eye drops for both eyes to control the aqueous inflammation and intraocular pressure, respectively. T2-weighted fluid attenuation inversion recovery (FLAIR) magnetic resonance imaging revealed regions with high signals within the white matter of the border between the right frontal and parietal lobe (Fig. 1B). He was administered 15 mg intrathecal methotrexate twice, and underwent external beam radiotherapy at a total dose of 40 Gy over 20 fractions, covering the entire brain and both eyes, because he had no other apparent relapsing foci. Following radiotherapy, the aqueous cells in both eyes and hypopyon in the left eye disappeared (Fig. 1E), as did the retinal lesions (Fig. 1F). The best-corrected visual acuity was 1.2 in both eyes. The patient died of renal failure and respiratory failure in June. Autopsy revealed multi-organ involvement with lymphoma cells.

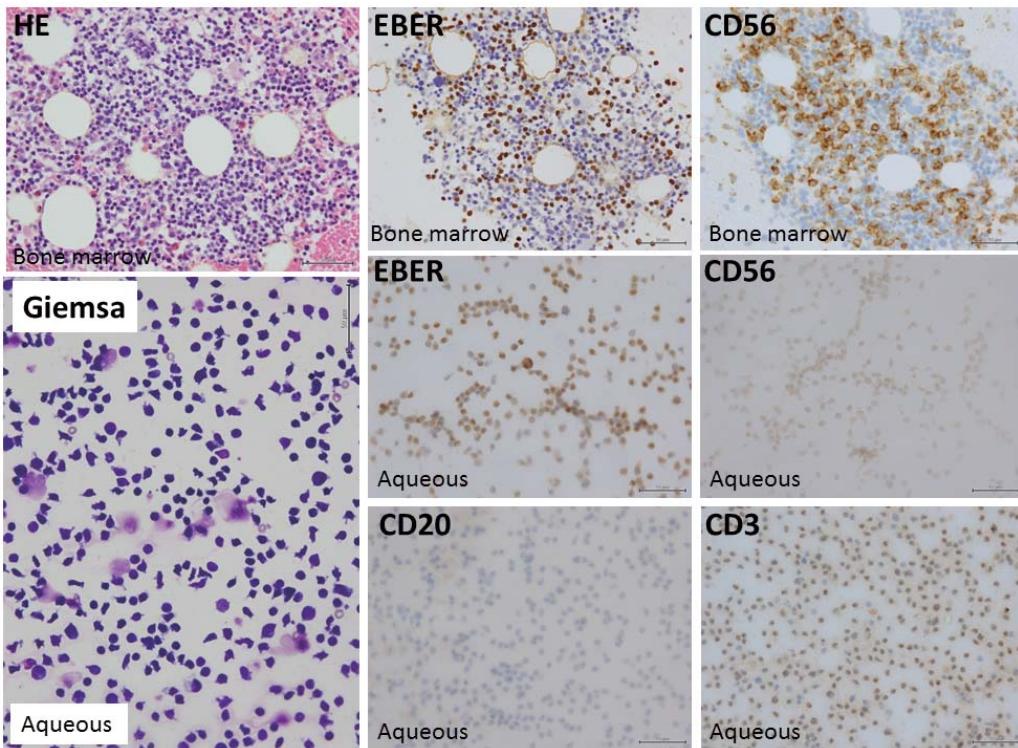


Fig. 3. Bone marrow biopsy (*top row*) in November 2010. Predominance of medium-sized monotonous cells (H&E stain), which are positive for EBER (Epstein-Barr virus-encoded RNA) and CD56. Aqueous tap (*middle and bottom row*) in the left eye in April 2011. Medium-sized cells with irregularly-shaped nuclei (Giemsa stain), which are positive for EBER, CD56, and CD3 (cytoplasmic), but negative for CD20. Original magnification, $\times 40$. Bar = 50 μm .

DISCUSSION

Nasal-type extranodal NK/T-cell lymphoma is a common type of malignant lymphoma in Asian populations, and can occasionally develop without nasal or paranasal involvement. The present patient showed hepatosplenomegaly with abdominal lymphadenopathy, but had no upper airway involvement, and was diagnosed with extranasal, or non-nasal type, at the initial presentation. The intraocular and central nervous system relapse at the final stage may have arisen from lymphoma cells that survived the combined chemotherapy and allogeneic peripheral blood stem cell transplantation.

NK/T-cell lymphoma has been reported to cause orbital infiltration,^{18,19} and intraocular infiltration, including aqueous cells^{18,20} and vitreous opacity,^{21,22} as rare manifestations. The present patient showed aqueous cells in the right eye, and vitreous opacity, anterior chamber hypopyon, and retinal infiltrates in the left eye. Immunocytochemical staining revealed the aqueous cells to be NK/T-cell lymphoma cells. Furthermore, these intraocular manifestations were resolved after external beam radiation, suggesting the hypopyon and retinal infiltrates had been due to intraocular infiltration by NK/T-cell lymphoma. The intraocular infiltration showed

good response to radiation, leading to improved vision; however the patient died of renal failure and respiratory failure in multi-organ relapse of lymphoma.

Intraocular infiltration by lymphoma cells after chemotherapy may be a poor prognostic sign due to likely concurrent infiltration of the central nervous system.²³ The eyes and central nervous system are protected from the immune system in a similar fashion: the eyes by the blood-aqueous barrier and blood-retinal barrier, and the central nervous system by the blood-brain barrier. The present patient showed central nervous system lesions at the time he developed the hypopyon and retinal infiltrates. Treatment options include radiation to the brain and eyes, or intrathecal or intravitreous methotrexate injection.^{24,25} Intravitreous methotrexate injection was not performed in this patient because he had shown marked response to external beam radiation.

CONFLICT OF INTEREST: The authors declare that they have no conflict of interest.

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