Case of Primary Intraocular Lymphoma with Extraocular Extension

Maki Kuro^a Kayako Matsuyama^a Masato Matsuoka^a Ryo Kosaki^d
Nobuaki Shikata^b Tetsuya Nishimura^a Kanji Takahashi^c

^aDepartment of Ophthalmology and ^bDivision of Diagnostic Cytopathology and Histopathology, Takii Hospital, Kansai Medical University, Moriguchi, ^cDepartment of Ophthalmology, Hirakata Hospital, Kansai Medical University, Hirakata, and ^dKozaki Eye Clinic, Osaka, Japan

Key Words

Primary intraocular lymphoma · Diffuse large B-cell lymphoma · Extraocular extension · Secondary glaucoma

Abstract

Purpose: To describe a case of primary intraocular lymphoma (PIOL) with an extension through the sclera that was confirmed to be part of the PIOL by histopathological examinations. **Case:** An 89-year-old woman was referred to a local clinic with a 1-year history of persistent blurred vision in her left eye. After 2 years without aggressive treatments, she had a marked reduction of vision and pain in her left eye. The clinical diagnosis was panophthalmitis, and the eye was enucleated and submitted for histopathological study. **Results:** Light microscope examination showed that atypical lymphocytic cells had infiltrated into both the intraocular and extraocular areas. The anterior chamber angle was blocked by infiltrating tumor cells, which were also detected around the optic nerve. The tumor cells destroyed Bruch's membrane and infiltrated around the perineural and perivascular areas within the sclera. Immunohistochemistry showed that the tumor cells were positive for B-lymphocyte surface antigen (CD20), B-cell antigen receptor complex-associated protein alpha chain (CD79-alpha), and had a high positive rate

for anti-Ki-67 antibody. **Conclusion:** The finding in our case indicates that early diagnosis and treatment are important for eyes with PIOL because the tumor can spread and penetrate the sclera and invade extraocular tissues.

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Introduction

Lymphomas of the eye constitute <1% of all lymphomas, and intraocular lymphomas are rarer than orbital lymphomas [1]. A primary intraocular lymphoma (PIOL) is a subtype of non-Hodgkin's lymphoma of the central nervous system (NHL-CNS) and it can spread into the vitreous, retina, retinal pigment epithelium, Bruch's membrane, and optic nerve [1, 2]. Of the patients with NHL-CNS, 20–25% have ocular involvements [1, 3]. The tumors typically consist of large B-cell lymphomas, which are an intermediate to high-grade malignancy [1]. However, little has been reported on cases of PIOL with extraocular extensions [4–8].

We report a case of PIOL that penetrated through the sclera, leading to a direct invasion into periocular tissues. The extension was confirmed to be part of the PIOL by histopathological examinations.

Fig. 1. Photograph of the anterior segment and ultrasonogram of the eye with PIOL. **a** Slit-lamp photograph of the left eye in April 2013. A proliferative membrane with hemorrhage can be seen in the pupillary zone (arrow). **b** Ultrasonographic image obtained in July 2013. Total retinal detachment (arrows) with a large mass under the detached retina, and a thickening of the posterior wall of the eye can be seen.

Case Report

An 89-year-old woman was referred to a local clinic in April 2011 because of a 1-year history of persistent blurred vision in her left eye. Her best-corrected visual acuity was 20/100 in her left eye, and dense opacities were present in the vitreous. Topical corticosteroid therapy was started, but she was not compliant with her follow-up examination because she could not travel to the clinic repeatedly due to her senility. She had a further decrease in vision in April 2013, and although her visual acuity was light perception and the pupil was blocked by proliferative tissues (fig. 1a), she did not return for follow-up examinations. After 3 months, she had severe pain, lid swelling, conjunctival injection, and chemosis. She was diagnosed with endophthalmitis and referred to the Takii Hospital, Kansai Medical University, Moriguchi, Japan, in July 2013.

At initial examination, she had no light perception in her left eye, and the intraocular pressure was 36 mm Hg. The anterior chamber was severely inflamed, and the left pupil was blocked by proliferative tissues that obstructed the view of the fundus. Ultrasound biomicroscopy showed total retinal detachment with adhesions that resembled a long-standing retinal detachment (fig. 1b). The patient was diagnosed with panophthalmitis, and because of the severe pain, we enucleated the left eye after receiving informed consent from the patient.

Intraoperative Findings

The orbital connective tissue adhered strongly to the eye globe and bled excessively from any incision. The enucleated eye had a solid mass adjacent to the optic nerve.

Tissue Processing

The enucleated eye was cut in the horizontal plane and fixed in 4% neutral buffered formalin. The tissues were embedded in paraffin and cut at 3 μ m. The sections were stained with hematoxylin and eosin (HE) or prepared for immunohistochemical studies.

Immunohistochemical Methods

Immunohistochemical staining was done by the amino acid polymer method using Simple Stain MAX-PO (MULTI; Nichirei Biosciences, Tokyo, Japan). The reaction products were made visible by 3,3'-diaminobenzidine (DAB). Antibodies to the following markers were used: B-lymphocyte surface antigen (CD20; clone, L26; Nichirei Biosciences) and B-cell antigen receptor complex-

Fig. 2. Gross findings of a slice of the enucleated eye (HE; scale bar = 5 mm). The iris (arrowhead) and ciliary body (arrow) are diffusely and densely infiltrated by atypical lymphoid cells. The retina is detached. Marked choroidal thickening (asterisk), scleral invasion, and extraocular extension (double asterisk) of the tumor can be seen.

associated protein alpha chain (CD79-alpha; clone, JCB117; Nichirei Biosciences) as B-cell markers, CD3 (clone, PS1; Nichirei Biosciences) and CD45Ro (clone, UCHL-1; Nichirei Biosciences) as T-cell markers, and Ki-67 (clone, MIB-1; Dako, Glostrup, Denmark) as proliferation marker.

Histopathological Findings

Gross examination showed that the posterior part of the eye had extensive plate-like thickening of the choroid. The thickening was 4.8 mm with a 2.4 mm white mass on the vitreous side and an extraocular whitish 8.4 mm prominence in the corresponding part.

The HE sections showed that the intraocular iris, ciliary body, subretina, choroid, sclera, and extraocular areas were diffusely and densely infiltrated by atypical cells (fig. 2). The atypical cell contained oval-shaped nuclei that were twice the size of the nuclei of macrophages. They had conspicuous nucleoli and basophilic cytoplasm. In addition, mitotic figures were occasionally seen (fig. 3a). The iris was infiltrated by tumor cells, and the anterior chamber angle was blocked by infiltrating tumor cells (fig. 4a, b). Tumor cells

Fig. 3. Histopathological and immunohistological sections of PIOL. **a** The atypical lymphocytes can be seen in the subretinal space. The atypical cells have oval-shaped nuclei that are twice the size of the nuclei of macrophages. They have conspicuous nucleoli and basophilic cytoplasm. Mitotic figures can be seen (arrows; HE; scale bar = 50 μ m). **b, c** Tumor cells are positive for CD20 (**b**) and for CD79-alpha (**c**), which are both B-cell markers (scale bar = 50 μ m). **d** The high Ki-67 positive rate (average >90%) indicates extensive proliferation (scale bar = 50 μ m).

were also scattered in the vitreous cavity. Although the retina was detached and had necrotic changes, it was not infiltrated by tumor cells. Numerous tumor cells and clusters of necrotic cells were detected in the subretinal space (fig. 2). Tumor cells were also detected around the optic nerve and had invaded the sclera (fig. 4d–f). The tumor cells destroyed Bruch's membrane and infiltrated around the perineural and perivascular areas within the sclera (fig. 4e).

Immunohistochemistry showed that the tumor cells were positive for CD20 (fig. 3b), CD79-alpha (fig. 3c), and a large number (average >90%) were Ki-67 positive, indicating intense proliferation (fig. 3d). In contrast, the cells were negative for CD3 and CD45Ro.

Clinical Course

The patient was diagnosed with PIOL, and the tissue type was diffuse large B-cell lymphoma (DLBCL). The blood chemistry tests showed high levels of soluble interleukin-2 receptor (582 U/ml). Computed tomography (CT) of the whole body showed a high-density lesion in her left orbit, but no other lesion was found. The patient received irradiation therapy (total dose, 40 Gy), and the size of the lymphoma was reduced. Chemotherapy was not performed because of her advanced age. After the irradiation therapy, the patient was transferred to a rehabilitation hospital for long-term care.

Discussion

The findings showed an extension of a PIOL through the sclera to invade not only the intraocular and extraocular areas but also the perivascular and perineural areas

within the sclera (fig. 4d, e). In addition, the tissue type of the intraocular tumors and that of the periocular tumors were the same, namely DLBCL (fig. 3).

Several cases of PIOL with extraocular extensions have been reported. Noda et al. [4], Neudorfer et al. [5], and Sasaki et al. [6] reported cases of PIOL with choroidal and periocular involvement. However, they did not confirm that the extraocular tumor was an extension of the intraocular tumor by histopathology. In the case described by Noda et al. [4], vitreous, chorioretinal, and orbital biopsies were performed, but the diagnosis of a malignant lymphoma was made only by the orbital specimen. Neudorfer et al. [5] and Sasaki et al. [6] detected intraocular and orbital lymphomas by color Doppler [5], ultrasonography, CT, and magnetic resonance [5, 6], but they examined only the periocular tumors by histopathological examinations [5, 6]. Raju and Green [7] and Cursiefen et al. [8] reported some cases of PIOL with extraocular extensions after cataract surgery and vitrectomy. Although they did confirm the correspondence of the intra- and extraocular tumors by histopathological examinations, the extraocular extensions were caused by sclerotomy and not by spontaneous growth [7, 8].

There were four major histopathological findings in our case. First, the tissue type of both the intraocular and periocular tumor was DLBCL (fig. 3). DLBCL is one of the NHL-CNS, constitutes the majority of intraocular

Fig. 4. Histopathological section of the eye with PIOL. **a** Secondary angle closure due to atypical cell infiltration of the angle and iris root (arrow). The tumor cells have infiltrated from the ciliary body into the sclera (arrowhead; HE; scale bar = 500 μ m). **b** The iris is infiltrated by tumor cells that spread into the pupillary area (arrow; HE; scale bar = 500 μ m). **c** Tumor cells have spread from the ciliary body into the sclera (area enclosed by arrowheads). **d** Tumor cells have infiltrated into the posterior part of the eye. Tumor cells have infiltrated into the subretinal space (asterisk) and passed out of the sclera (double asterisk). Infiltration into the sclera (arrows) and optic disc (arrowhead) can be seen. **e** Tumor cells have infiltrated around a penetrating nerve (asterisk) in the sclera. **f** Tumor cells have infiltrated into the sclera (asterisk: tumor cells; arrowhead: scleral collagenous fiber; **c-f** HE; scale bar = 100 μ m).

lymphomas [9], and is known to be a high-grade malignancy. For this reason, the vitreous, retina, and optic nerve can be involved [1]. In contrast, mucosa-associated lymphoid tissue-type lymphomas constitute the majority of periocular lymphomas, which are a low-grade malignancy and slowly growing tumors with fewer metastases or less invasion into surrounding tissues [10]. In our case, the DLBCL cells invaded the perivascular and perineural tissues, indicating that the lymphoma cells primarily developed in the intraocular space.

Second, the tumor cells invaded from the intraocular area to the periocular area through the sclera (fig. 4c, d, f). Anatomically, the sclera is penetrated by fine channels, the scleral emissaria, which contain penetrating vessels from the uvea, the ciliary vessels, and the vortex veins as well as branches of the ciliary nerves. Because these channels provide passages for extraocular extensions of intra-

ocular tumors, tumors can grow into the posterior orbital space [11]. In our case, the tumor cells were detected not only in the sclera itself (fig. 4c, d, f) but also in the perineural and perivascular areas within the sclera (fig. 4e). These findings indicate that the intraocular tumor had a potential of extending into the extraocular area through the sclera.

Third, the lymphoma cells also invaded the anterior chamber (fig. 4a). Secondary angle closure glaucoma caused by an intraocular tumor has been reported, and malignant melanomas are the most common cause of the glaucoma [12]. In contrast, little has been reported on the angle closure glaucoma caused by a PIOL [13], probably because iris invasion by lymphomas is rare [10, 13]. Of the 13 cases with iris invasion by lymphomas reported by Mashayekhi et al. [13], only 2 had secondary glaucoma caused by a PIOL. In our case, the lymphoma cells invad-

ed the angle, which resulted in secondary angle closure, high intraocular pressure, and severe eye pain.

Fourth, the DLBCL cells invaded multiple tissues within and outside the eye (fig. 2), and the type and number of cells indicated an extensive proliferative reaction according to immunohistochemical examinations (fig. 3d). Recent lifetime prognosis of PIOL is poor with a 5-year survival rate of about 60% [14, 15]. Kimura et al. [15] reported that the most common symptom of PIOL was blurred or reduced vision, and the average interval between the occurrence of subjective symptoms and the definitive diagnosis as a PIOL was 10.9 months (range, 2 weeks–9 years). In our case, the duration of blurred vision was estimated to be at least 3 years according to the clinical history. We suggest that the long-standing tumor without aggressive treatment caused the extraocular extension of the PIOL. The lymphoma cells had grown slowly in the vitreous space in the early phase. Thereafter, the cell proliferation progressed and began invading multiple parts of the eye.

There is a limitation to this report. Although magnetic resonance and positron-emission tomography are useful in examining systemic and CNS lymphomas, our patient was not examined by these tests because of her advanced age and mental status. However, we assumed that she had

no systemic or CNS lymphomas for the following reasons. First, CT and blood tests did not indicate the existence of systemic or CNS lymphomas, and second, the patient had a quite long-standing clinical course without aggressive treatments. If she had had a systemic lymphoma or CNS involvement, she would have had systemic or neurological symptoms.

In summary, we report a case of PIOL with extraocular extension, which was confirmed to be the same tumor by histopathological examinations. The findings in our case indicate that early diagnosis and treatment are needed to treat eyes with PIOL because the tumor can invade extraocular areas through the sclera.

Statement of Ethics

Written informed consent was obtained from the patient for the purpose of publication.

Disclosure Statement

The authors have no financial interest in any materials or methods presented in this paper.

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