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CASE REPORT

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Multiple choroidal granulomas in lymphomatoid granulomatosis: a case report

Ryo Taguchi[1*], Yoshiaki Tanaka[1], Machiko Shimmura[1], Hiroko Takano[1], Akihiro Kakehashi[1] and Toshikatsu Kaburaki[1,2]

Abstract

Background Lymphomatoid granulomatosis (LYG) is a rare B-cell lymphoproliferative disorder predominantly affecting middle-aged men. The disease occurs primarily in the lungs; however, reports of lesions in intraocular regions are scarce. Herein, we report a case of choroidal granulomas in a patient with LYG.

Case presentation A 55-year-old male patient presented to a respiratory specialist with pneumonia of unknown cause. His serum-soluble IL-2 receptor level was highly elevated, and transbronchial lung biopsies revealed granulomatous lesions. Sarcoidosis was suspected, and an ophthalmological examination was performed. The best-corrected visual acuity was 1.2 in both eyes. Although no cells were present in the anterior chambers or anterior vitreous in either eye, multiple large yellowish-white exudates on the fundus of the right eye and soft exudates around the optic disc in the left eye were observed. Optical coherence tomography revealed choroidal granulomas consistent with the yellowish-white lesions in the right eye. Fluorescein angiography revealed tissue staining in the right eye consistent with granulomatous choroidal lesions. Both eyes showed capillaritis, mainly in the nasal retina. Subsequently, a thoracoscopic left lung biopsy led to a pathological diagnosis of LYG, and chemotherapy was initiated. Thereafter, the yellowish-white exudates gradually scarred, and the choroidal granulomas and soft exudates disappeared; thus, a vitreous biopsy was not performed. After autologous hematopoietic stem cell transplantation, the LYG was in remission. No ocular lesion recurrence was observed in the subsequent 18 months.

Conclusions LYG may cause multiple large choroidal granulomas.

Keywords Lymphomatoid granulomatosis, B-cell lymphoproliferative disorder, Lung, Choroidal granulomas, Case report

*Correspondence:
Ryo Taguchi
ryo0616tag.jichi@gmail.com
[1]Department of Ophthalmology, Saitama Medical Center, Jichi Medical University, 1-847 Amanuma-cho, Omiya-ku, Saitama-shi, Saitama 330-8503, Japan
[2]Department of Ophthalmology, Jichi Medical University, 3311-1 Yakushiji, Shimotsuke, Tochigi 330-8503, Japan

Background

Lymphomatoid granulomatosis (LYG), first described by Liebow et al. in 1972, is a rare B-cell lymphoproliferative disease characterized by extranodal, angiocentric, and vasodepleting features [1]. Many normal T cells and a small number of atypical B cells are involved [1]. Recently, the Epstein–Barr virus has been implicated in the etiology and pathogenesis of the disease [1]. The disease is relatively common in middle-aged men in their 40s to 60s [2]. The male-to-female patient ratio is 2:1 [2]. The lungs (100%) are the primary site of disease, with extrapulmonary lesions commonly seen in the central nervous system (CNS) (40%), skin (34%), kidney (19%), and liver (17%) [2, 3]; however, conjunctival, lacrimal gland, and intraocular lesions have been reported very rarely [2–5]. Herein, we report a case of choroidal involvement in LYG.

Case presentation

A 55-year-old male patient with no medical history experienced cough and dyspnea while walking. Two weeks later, he was admitted to the Department of Respiratory Medicine, Saitama Medical Center, Jichi Medical University, for close examination and treatment of pneumonia of unknown cause.

A blood test revealed a high soluble interleukin-2 receptor (sIL-2R) level of 5410 U/ml. Abdominal computed tomography (CT) revealed swollen intra-abdominal lymph nodes, leading to suspicion of malignant lymphoma. Bone marrow puncture and biopsy were performed, but no lymphoma cell infiltration was observed.

Bronchoalveolar lavage (BAL) and transbronchial lung biopsy were performed. BAL showed a granuloma lesion with intravenous infiltration of lymphocytes. The patient was referred to the Department of Ophthalmology, Jichi Medical University Saitama Medical Center, for ophthalmic examination on suspicion of sarcoidosis.

At the initial visit, the binocular best-corrected visual acuity (BCVA) was 1.2. The intraocular pressure was 16 mmHg in the right eye and 19 mmHg in the left eye, and no inflammatory finding was noted in the anterior or intermediate translucent zones of both eyes. Fundus examination revealed multiple large yellowish-white infiltrating lesions in the right eye and soft exudates around the disc, predominantly in the left eye (Fig. 1). Optical coherence tomography revealed choroidal granulomas consistent with the yellow-white lesions in the right eye. The left eye showed swelling of the nerve fiber layer, which was consistent with soft exudates (Fig. 2). Vitreous opacities were scant in both eyes. Scattered iris processes were observed at the corner angles in both eyes; however, no peripheral anterior synechiae or nodules were observed. Fluorescein angiography (FA) showed tissue staining in the right eye, which was consistent with choroidal granulomatous lesions, periphlebitis, and capillaritis. Both eyes exhibited multiple hyperfluorescence dots, mainly in the nasal retina. Indocyanine green angiography showed hypofluorescence in the early phase and mild hyperfluorescence in the late phase of the right eye, consistent with choroidal granulomas, and multiple dark spots in both eyes (Fig. 3).

Systemic investigations showed a high sIL-2R level of 3280 U/ml, but ACE and lysozyme were normal. Rapid plasma regain (RPR) and Treponema pallidum (TP), and Toxoplasma IgM, IgG antibodies were negative. And interferon-gamma release assay (IGRA) was not performed, but the mantoux test was negative (5 × 4 mm). anterior chamber aqueous humor polymerase chain

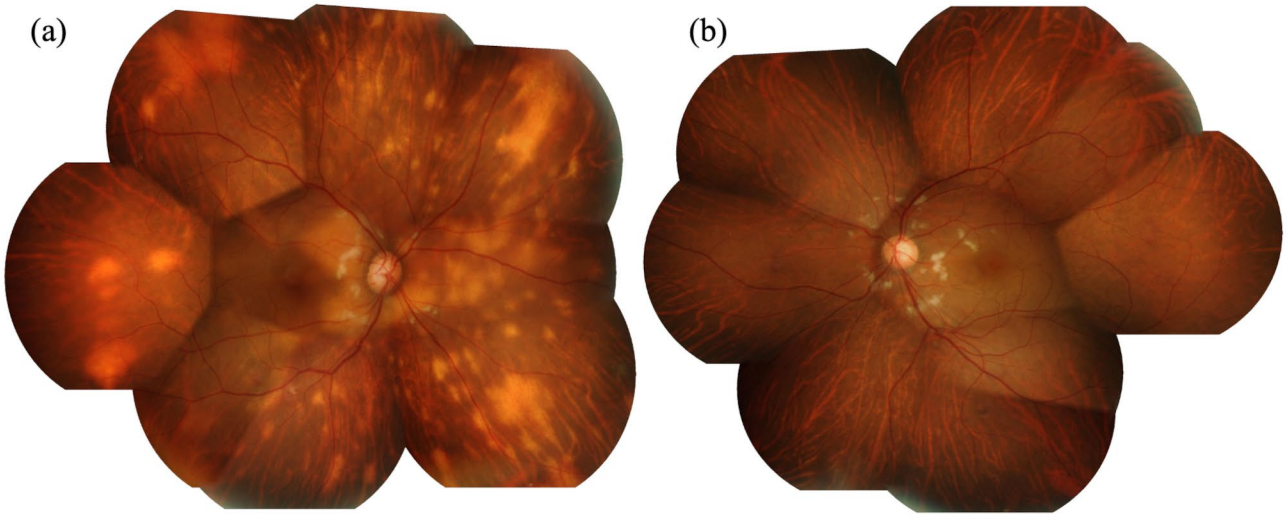

Fig. 1 Fundus photographs of both eyes at the initial examination. (**a**) Right eye. Multiple large yellowish-white infiltrate lesions are observed. (**b**) Left eye. Soft exudates predominantly around the optic disc are observed

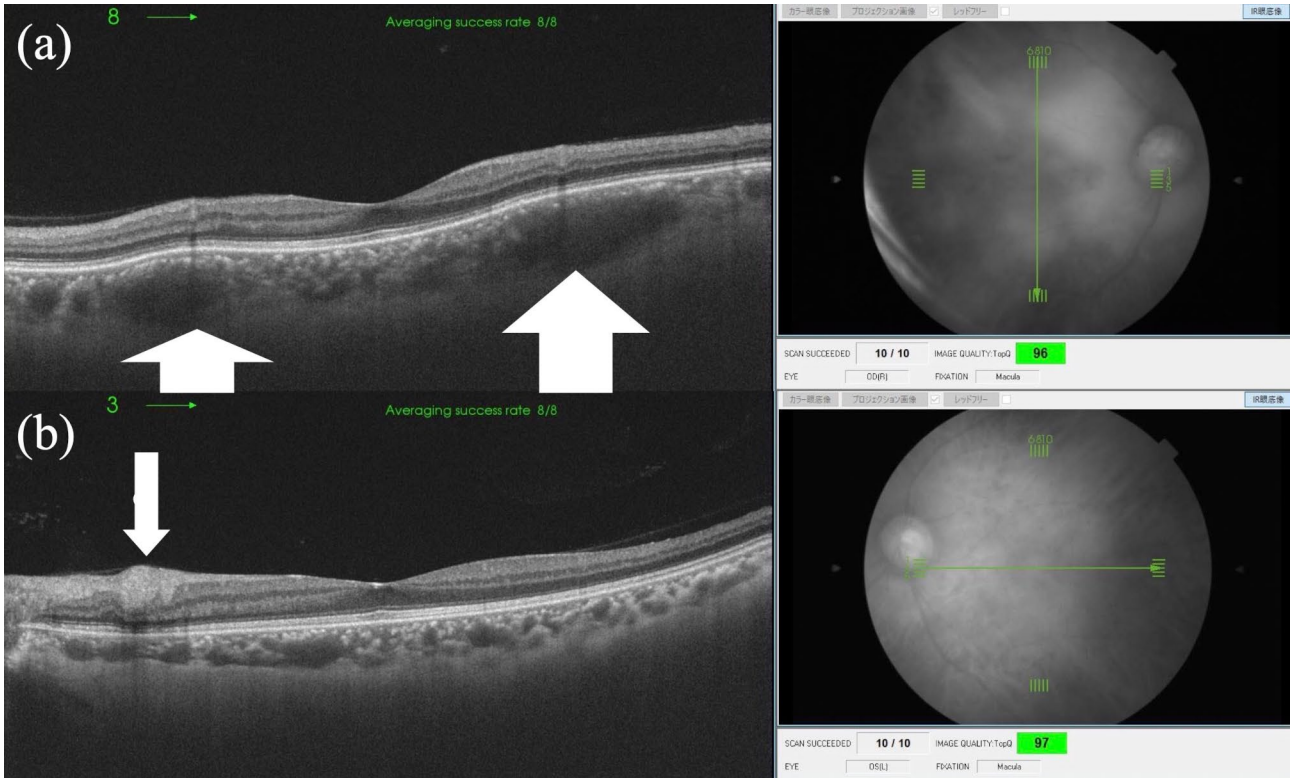

Fig. 2 Optical coherence tomography of both eyes at the initial examination. (**a**) Right eye. Choroidal granulomas (arrow) consistent with yellowish-white infiltrative lesions are observed. (**b**) Left eye. Swelling of the nerve fiber layer (thin arrow) consistent with soft exudates is observed

reaction (PCR) testing was not performed because there was no inflammation in the anterior chamber.

Simple chest CT revealed an infiltrative shadow predominantly in the left lower lung field but no bilateral hilar mediastinal lymphadenopathy, thus not meeting the clinical diagnostic criteria for sarcoidosis. At this point, the patient was started on prednisolone 30 mg/day for lung lesions by the Respiratory Medicine Department, and we monitored its effectiveness for the eye lesions.

One week later, thoracoscopic left lung biopsy was performed by a respiratory physician. Pathological examination revealed partial nodular necrotic lesions with lymphocytic infiltration around and within the vessels. Immunostaining showed scattered CD20-positive large cells and a few EBV-encoded small RNA1-positive cells (Fig. 4). The patient was diagnosed with LYG grade 1 based on the LYG histological classification (Table 1). Systemic chemotherapy was initiated for LYG by the hematology department according to the treatment for diffuse large B-cell lymphoma: six courses of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) and two courses of high-dose methotrexate. However, 5 months after chemotherapy, chest CT revealed infiltrative shadows in the right middle lobe and left lower lobe, along with new mass-like consolidations under the interlobar pleura of the upper and lower lobes of the left lung, suggesting relapse in both lungs. Therefore, the patient was treated with four courses of rituximab, gemcitabine, dexamethasone, and cisplatin (R-GDP regimen). Finally, autologous peripheral blood stem cell transplantation was performed 5 months later, and the systemic LYG lesions subsided. Since then, there has been no recurrence of the systemic lesions.

Regarding the ocular lesions, since the start of systemic chemotherapy, the yellow-white lesion in the right eye scarred over and reduced in area, and the choroidal granuloma and soft exudates in the left eye disappeared within 2 months. Subsequently, the ocular lesions subsided. At the last observation, 25 months after the initial visit, BCVA was 1.2 in both eyes. No recurrences of the ocular lesions were observed (Fig. 5). The patient reported no issues with his eyes or overall condition after the treatment. Vitreous biopsy was not performed because the vitreous opacity was minimal in both eyes, and the retinochoroidal lesions resolved with systemic chemotherapy.

Discussion and conclusions

LYG is classified as a mature B-cell tumor in the 2017 WHO classification [6]. The life prognosis is generally poor. Katzenstein et al. reported a mortality rate of 63.5% and a median survival of 14 months in a retrospective

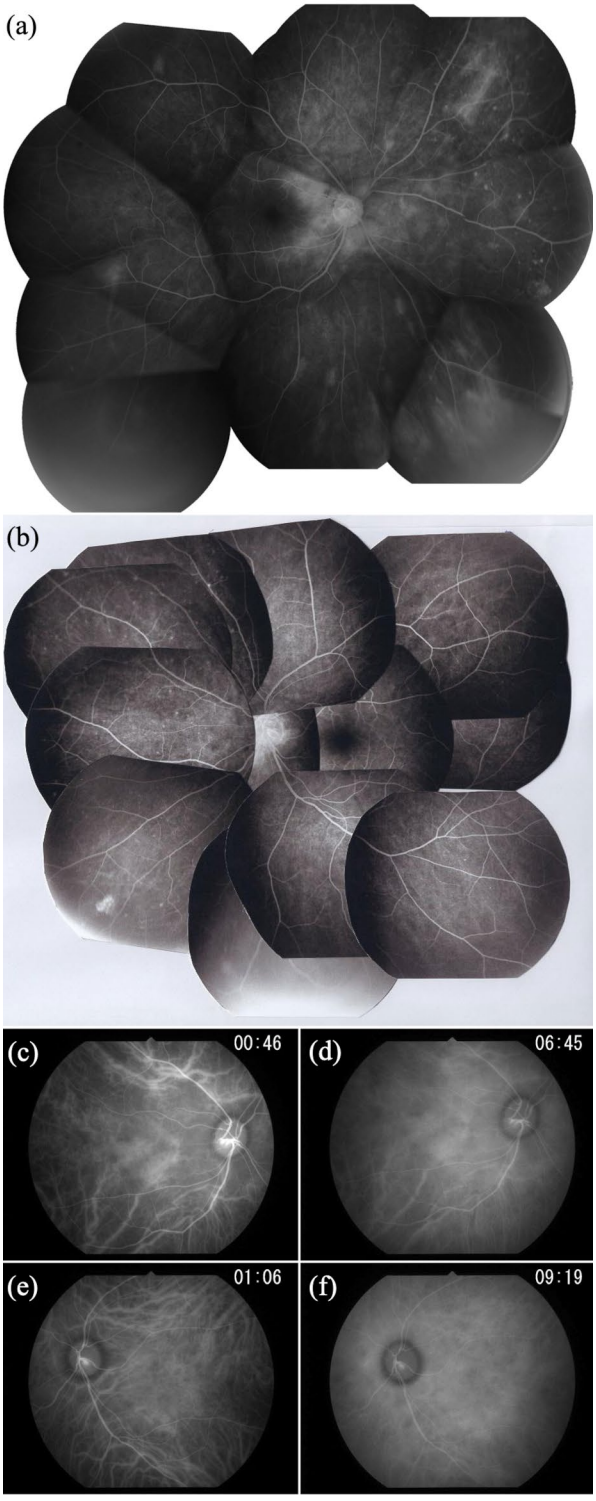

Fig. 3 Fluorescein angiography (FA) and indocyanine green angiography (IA) of both eyes at initial examination. (**a**) Right eye. FA image reveals tissue staining consistent with choroidal granulomas lesions, periphlebitis, and capillaritis. (**a**, **b**) Both eyes. FA image reveals multiple hyperfluorescence dots, mainly in the nasal retina. (**c**, **d**) Right eye. IA image reveals hypofluorescence in the early phase and mild hyperfluorescence in the late phase, consistent with choroidal granulomas. (**c**–**f**) Both eyes. IA image reveals multiple dark spots

study of 152 LYG cases [1, 6, 7]. No standard treatment has been established [1]. Low-grade LYG (grade 1 or grade 2) treated with oral corticosteroids, single-agent chemotherapy, and IFN-α2b has been reported successful. High-grade LYG (grade 3) was treated with high-dose corticosteroids and combination chemotherapy (R-CHOP). Patients with refractory or relapsed conditions were treated with hematopoietic stem cell transplantation [2].

Dunleavy et al. reported the current progression-free survival (PFS) for LYG. At a median follow-up time of 5 years, the PFS of patients with grade 1–2 LYG was 56%, with a median time to remission of 9 months. In contrast, all patients with grade 3 needed dose-adjusted etoposide, prednisolone, vincristine, cyclophosphamide, doxorubicin, and rituximab chemotherapy. In 24 patients with grade 3 LYG, many of whom had received prior therapy, the PFS was 40%, with a median follow-up of 28 months, and 66% achieved complete remission [3].

Pradeep et al. reviewed 18 cases of previously reported LYG [8]. Of the 18 cases (9 male and 9 female, mean age 43.9 (7–75 years), 6 cases presented with ocular symptoms at the initial presentation, while the other cases initially presented with respiratory or CNS symptoms. The ocular findings included eyelid abnormalities such as ptosis in six cases; diplopia, nystagmus, and pupillary disturbances in five cases; scleral and conjunctival findings in four cases; choroidal infiltrates in four cases; retinal findings such as retinal vasculitis and serous retinal detachment in four cases; optic nerve papilla findings in three cases; lacrimal gland swelling in three cases; and orbital infiltrate findings in three cases. Five patients with orbital and conjunctival involvement were successfully treated using radiotherapy. The remaining patients were treated with corticosteroids or immunosuppressive agents, and ocular symptoms improved in all cases, except for optic neuropathy. Eight of the seventeen patients died, with a median survival of 6 months (range, 6 weeks to 2 years). Ocular manifestations of LYG described in literature are varied, although some have been reported to resemble those of granulomatosis with polyangiitis. Multiple tissue biopsies have thus often been required for a definitive diagnosis of LYG [8]. In the present case, LYG was definitely diagnosed by lung biopsy.

Forman et al. reported a 41-year-old Caucasian female patient with optic neuritis associated with LYG [9]. She suffered optic disc edema in the left eye with a visual disturbance (BCVA of 0.2), color blindness, and ocular pain with eye movement. In addition, brain magnetic resonance imaging revealed high signal intensity in the left optic nerve and optic nerve sheath. Seven weeks later, her visual acuity decreased to no light perception, and she died of respiratory failure 10 days later. Pathological examination revealed diffuse necrosis of the optic nerve,

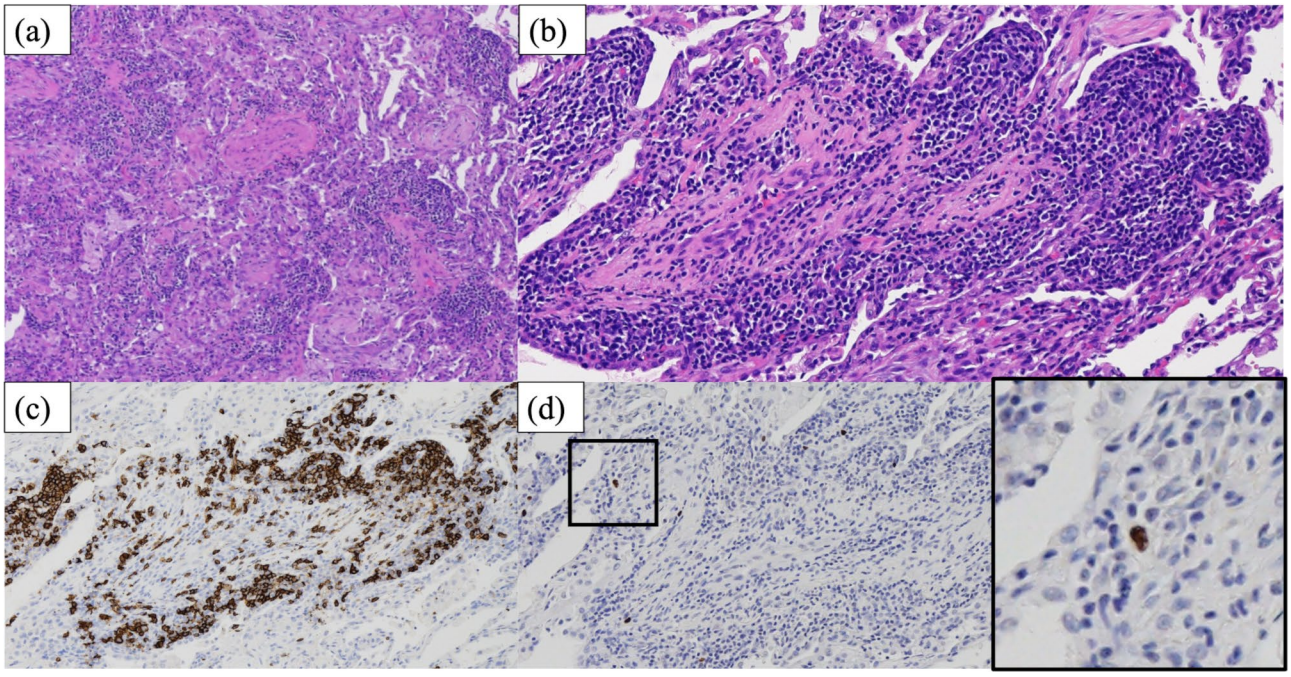

Fig. 4 Pathology photographs of thoracoscopic left lung biopsy. (**a**) Photomicrograph of the transbronchial biopsy demonstrates partial nodular necrosis. (hematoxylin-eosin, original magnification ×40). (**b**) Higher magnification shows a vaso-centric spread of lymphocytes and infiltration of the vascular lumen (hematoxylin-eosin, original magnification ×100). (**c**) Immunohistochemistry reveals that the scattered CD20-positive large cells. (CD20 immunohistochemical stain, original magnification ×100). (**d**) Immunohistochemistry revealing a few EBER1-positive cells (EBER-ISH, original magnification ×100)

Table 1 Histological classification of LYG (See ref. [2, 12])

Grade	Infiltration	Large atypical cells	Necrosis	EBV-positive cells/HPF*
Grade 1	Polymorphous lymphocytic infiltration	none to rare	None to partial	< 5
Grade 2	Pleomorphic lymphocytic infiltrate with few large cells or fibroblasts	Scattered to small clusters	Scattered	5–20 (occasionally > 50)
Grade 3	Partial pleomorphic lymphocytic infiltrate with large atypical cells	small to large clusters (sometimes with Hodgkin cells)	Extensive	> 50 and often > 100 cells

*HPF, high power field

Grade 1: Variable lymphocyte proliferation without cellular atypia; necrotic lesions are usually absent or very partial; fewer than five EBV-positive cells are present at high magnification. Grade 2: Large cells are mixed in a diverse inflammatory background, but not the cellular atypia of a tumor; CD20-positive B cells are seen sporadically and may be in small clusters; EBV-positive cells are present at high magnification, less than five in number. Necrotic lesions are more frequent than those in grade 1, with 5–20 EBV-positive cells at high magnification. Grade 3: Inflammatory background, but with many large atypical B cells, forming larger clusters than in grade 2; Hodgkin-like multinucleated cells may also be present; and EBV-positive cells are numerous and often exceed 50 at high magnification

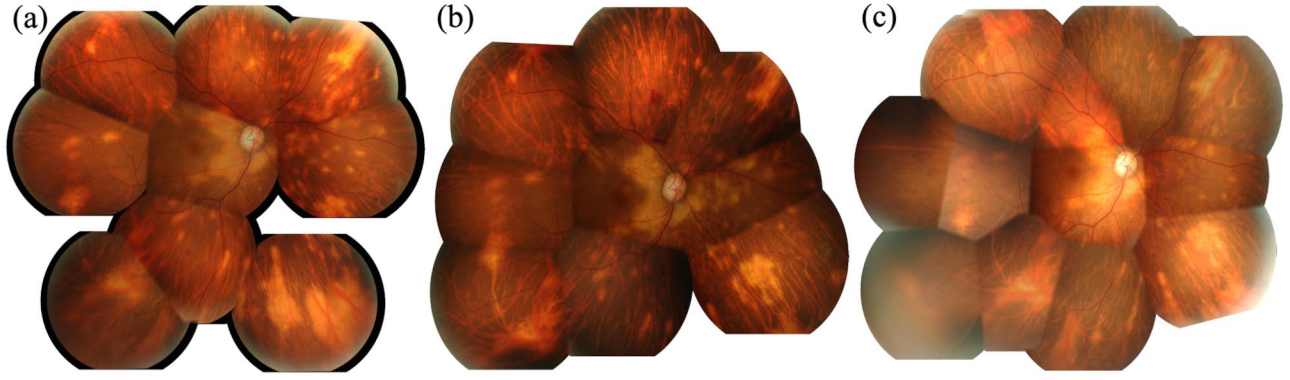

Fig. 5 Fundus photographs of the right eye after the start of systemic chemotherapy. (**a**) 1 month, (**b**) 12 months, and (**c**) 25 months. The yellowish-white lesions in the right eye are seen to be scarred and reduced in area, and the choroidal granulomas have finally disappeared

thickening of the nerve sheath, and infiltration of small mature and large atypical lymphocytes [9]. Conversely, Tse et al. reported a case of a 29-year-old South American male patient with retinal vasculitis associated with LYG [4]. The patient's binocular uncorrected visual acuity was 1.0 at the initial visit. The fundus showed binocular sheathing and whitening of the retinal vessels in the peripheral retina, predominantly in the right eye, with moderate numbers of vitreous cells. FA showed an avascular area and leakage from the retinal arteries and veins superotemporally in both eyes [4]. Corticosteroid treatment improved vasculitis and vitreous opacity, but his general condition worsened with infiltration of the lungs, cerebellum, kidneys, and skin; the patient died 5 months after the onset of the disease and 2 months after the start of treatment [4].

In a report of four cases of LYG with choroidal involvement, three had no choroidal granulomas, but one case showed multiple hyperfluorescence on FA, consistent with choroidal infiltrations [4]. We believe that this case is similar to our case with choroidal granulomas.

Cameron et al. reported a case of a 39-year-old man who developed bilateral exudative macula detachments 16 years following onset of LYG [10]. At the time of his initial ophthalmological examination, he was taking 20 mg of prednisolone daily to control the pulmonary symptoms of LYG. His visual acuities were 20/60 OD and 20/40 OS. Fundus examination revealed bilateral dome-shaped smooth elevations of the macula with subretinal fluid visible, consistent with exudative retinal detachments. FA demonstrated bilateral multifocal pinpoint leakage throughout the macula and extensive subretinal fluid. The patient's dose of prednisolone was increased to 60 mg daily. Within 4 weeks, visual acuities had returned to 20/20 OU. Fundus examination revealed complete resolution of the subretinal fluid. The dose of prednisolone was thereafter reduced back at 20 mg, no recurrence of the subretinal fluid. At the last observation, 2 years after the initial visit, no recurrences of the ocular lesions were observed [10].

Cao et al. reported a case of a 74-year-old white patient with retinal vasculitis in LYG with concurrent cytomegalovirus retinitis [11]. At the initial visit, the BCVA in the right eye was 0.8. Slit-lamp examination revealed large keratic precipitates, quiet anterior chamber, with 1 + anterior vitreous cell and 1 + haze in the righ eye. Fundus examination revealed vitritis with a focal area of retinal whitening in the temporal periphery in the rifht eye. FA of the right eye showed optic disc leakage and temporal peripheral nonperfusion. The patient was started on topical difluprednate 0.05% four times daily in both eyes for presumed inflammation secondary to LYG. Three days later, his right BCVA decreased to 0.5. Examination showed diffuse KP in the right eye, 3 + AC cell in the right eye, and worsened retinal whitening temporally. Aqueous fluid was CMV positive, and he was promptly treated with antivirals and showed improvement of area of retinal whitening temporally with inactive-appearing border after receiving a total of 6 intravitreal foscarnet injections. Cao et al. concluded that despite medical history, it is important to consider infectious etiologies when assessing a patient with intraocular inflammation [11]. In the present case, anterior chamber aqueous humor PCR testing was not performed because there was no inflammation in the anterior chamber, but RPR and TP, and Toxoplasma IgM, IgG antibodies were negative. And IGRA was not performed, but the mantoux test was negative (5 × 4 mm). Based on these findings, syphilitic uveitis, toxoplasmic retinopathy, and tuberculous uveitis were ruled out.

Intraocular lesions of LYG are quite rare and have seldom been reported, especially those showing clinical features of choroidal involvement, that is, multiple large choroidal granulomas, as in the present case. When encountering a case of multiple choroidal granulomas, LYG should be considered as a possible differential diagnosis for sarcoidosis.

Abbreviations

LYG	Lymphomatoid granulomatosis
CNS	Central nervous system
sIL-2R	Soluble interleukin-2 receptor
CT	Computed tomography
BAL	Bronchoalveolar lavage
BCVA	Best-corrected visual acuity
FA	Fluorescein angiography
RPR	Rapid plasma regain
TP	Treponema pallidum
IGRA	Interferon-gamma release assay
PCR	Polymerase chain reaction
R-CHOP	Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone
R-GDP regimen	Rituximab, gemcitabine, dexamethasone, and cisplatin
PFS	Progression-free survival

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Author contributions
RT wrote the main manuscript text. TK revised the grammar and spelling. All authors read and approved the final manuscript.

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Data availability
Data is provided within the manuscript.

Declarations

Ethics approval and consent to participate
The study was approved by the review board of Saitama Medical Center, Jichi Medical University. Written informed consent was obtained from the patient.

Consent for publication
Written informed consent was obtained from the patient.

Competing interests
The authors declare no competing interests.

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