

Unique and progressive retinal degeneration in a patient with cancer associated retinopathy

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ABSTRACT

Purpose: To report clinical course of a patient with cancer-associated retinopathy (CAR) medicated by steroid therapy, focusing on retinal degeneration progression.

Observations: A 67 years-old female patient, who had a surgical history of endometrial carcinoma with adjuvant chemotherapy, was referred to our hospitals for the complaints of sudden reduced visual acuity and visual field constriction in the right eye. Best corrected visual acuity (BCVA) was 0.4 and 1.0 in right and left eyes, respectively. Funduscopy showed almost normal appearance in both eyes. Fluorescein angiography showed slight fluorescein leakage from the optic disc in both eyes and an inferior arcade vessel in the right eye. Optical coherence tomography (OCT) images showed loss of ellipsoid zone (EZ) and thinning of outer retinal layers at the nasal area of the fovea in both eyes. Goldmann perimetry (GP) demonstrated several paracentral absolute scotomas with peripheral visual field constriction in the right eye, and a paracentral relative scotoma with preserved peripheral visual field in the left eye. Ten months after the first visit, retinopathy progressed in both eyes. Funduscopy indicated mild retinal degeneration along with arcade veins with white sheathing of retinal arteries. Slightly visible EZ at the fovea and loss of EZ and interdigitation zone and thinning of outer retinal layers at other areas were observed in OCT images from both eyes. GP showed no response in both eyes. Oral prednisolone therapy was started and gradually tapered over a 3-month period. Twelve and fifteen months after the first visit, BCVA, EZ at the fovea in OCT images, and visual field gradually improved, whereas retinal degeneration along arcade veins became apparent.

Conclusions and Importance: We reported a patient with CAR who exhibited progressive retinal degeneration and good response to oral prednisolone therapy. This case expands the clinical spectrum of CAR.

1. Introduction

Cancer-associated retinopathy (CAR), which is firstly reported by Sawyer et al., in 1976, is one form of autoimmune retinopathy and proposed to be an immunological retinopathy associated with anti-retinal autoantibodies (ARAs).^{1,2} It is hypothesized that autoantibodies against tumor antigens cross-react with proteins expressed in

retinal photoreceptor cells, and this cross-reactivity promotes initiation of apoptosis and subsequently leads to retinal degeneration.^{3,4} Despite the number of identified ARAs, patients with CAR exhibit common clinical features such as sudden and acquired onset, unremarkable fundus appearance in the early stage, progressive retinal degeneration, severely decreased responses in electroretinography (ERG), and central and peripheral visual field defects in the advanced stage.⁵ Previous

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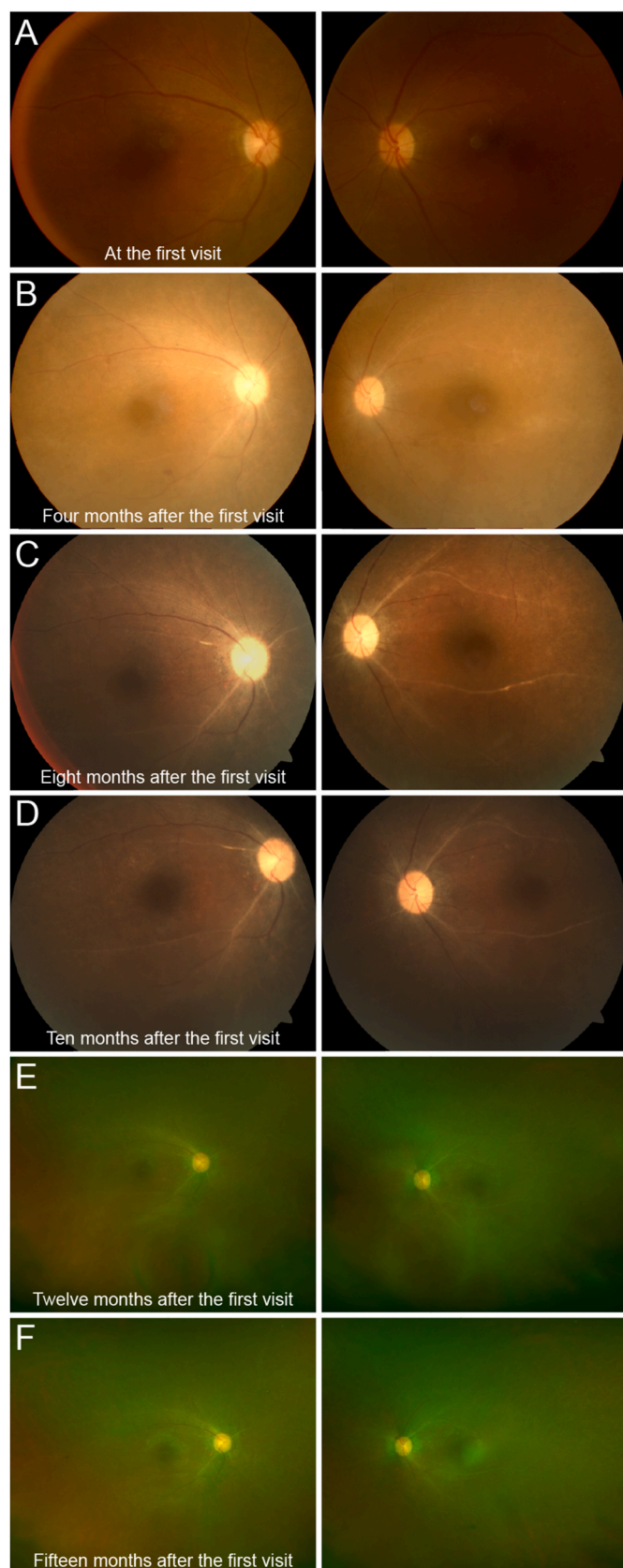
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Fig. 1. Clinical course of fundus photograph.

(A) At the first visit, funduscopy shows almost normal appearance in both eyes. (B) Four months after the first visit, funduscopy shows white sheathing of retinal arteries and mild retinal degeneration around arcade veins in both eyes. remarkable change in left eye.(C) Eight months after the first visit, funduscopy shows deterioration of white sheathing of retinal arteries and retinal degeneration around arcade veins in both eyes compared with that after four months after the first visit. (D) Ten months after the first visit, funduscopy shows no remarkable change in both eyes compared with that after 8 months after the first visit. (E) Twelve months after the first visit, funduscopy shows retinal degeneration along with arcade veins without retinal pigment epithelium (RPE) clumping in both eyes. (F) Fifteen months after the first visit, funduscopy shows apparently retinal degeneration along with arcade veins without RPE clumping in both eyes.

studies using optical coherence tomography (OCT) have clarified thinning of outer retinal layers and ellipsoid zone (EZ) abnormalities at the macular, indicating that photoreceptor cell death occurs in patients with CAR.⁶⁻⁸ Although the management of CAR is challenging, immunosuppression therapies with and without cancer therapies have been attempted, and some patients have achieved improvement of visual function.^{5,9-13} However, most previous studies focused on identifications of ARAs, type of cancer, and therapeutic outcomes,^{5,14,15} whereas few studies focused on the pattern of retinal degeneration progression.

Here, we report one patient with CAR whose retinal dysfunction was improved with oral prednisolone therapy, focusing on retinal degeneration progression.

1.1. Case report

A 67-year-old female patient was referred to Fujiyoshida Municipal Medical Center with complaints of suddenly reduced visual acuity and visual field constriction in the right eye. She had no ophthalmic and autoimmune disease history. The surgical history included abdominal total hysterectomy and bilateral salpingo-oophorectomy for endometrial carcinoma at 66 years old. The patient had received adjuvant chemotherapy comprising docetaxel and carboplatin. Metastasis to lymph nodes was found by computed tomography at postoperative 12 months, which was the same time as the first ophthalmic examination.

At the first ophthalmic examination, best corrected visual acuity (BCVA) was 0.4 [spherical -3.50 diopter (D), cylinder -0.50 D, axis 180°] in the right eye and 1.0 (spherical -5.00 D, cylinder -0.50 D, axis 170°) in the left eye. Slit lamp examinations showed no abnormalities in the anterior segment and media. Fundus examination showed almost normal appearance in both eyes (Fig. 1A). Fluorescein angiography (FA) showed slight fluorescein leakage around the optic disc in both eyes and an inferior arcade veins in the right eye (Fig. 2A). OCT (Carl Zeiss Meditec AG, Dublin, CA, USA) showed thinning of outer retinal layers and loss of EZ at the nasal area of the fovea, whereas the interdigitation zone (IZ) was visible in both eyes (Fig. 3A). Visual field testing using Goldmann perimetry (GP; Haag-Streit, Bern, Switzerland) showed several paracentral scotomas of V-4e isopter with peripheral visual field constriction of I-4e isopter in the right eye and paracentral scotomas of I-4e and V-4e isopters with preserved peripheral visual field in the left eye (Fig. 4A).

Four months after the first visit, she noticed aggravation of her symptoms. Funduscopy showed white sheathing of retinal arteries and mild retinal degeneration around arcade vessels in both eyes (Fig. 1B). FA showed further fluorescein leakage around the optic disc and partial arcade vessels in the right eye, with no remarkable change in the left eye (Fig. 2B). GP showed severe visual field constriction with a few peripheral visual islands in both eyes (Fig. 4B). Flash electroretinogram (ERG), using a light-emitting diode with a built-in electrode (LE-4000, Tomey, Nagoya, Japan), was performed with a stronger flash under dark-adapted (DA) conditions to record DA 200 (cd s/m²) ERG. DA 200

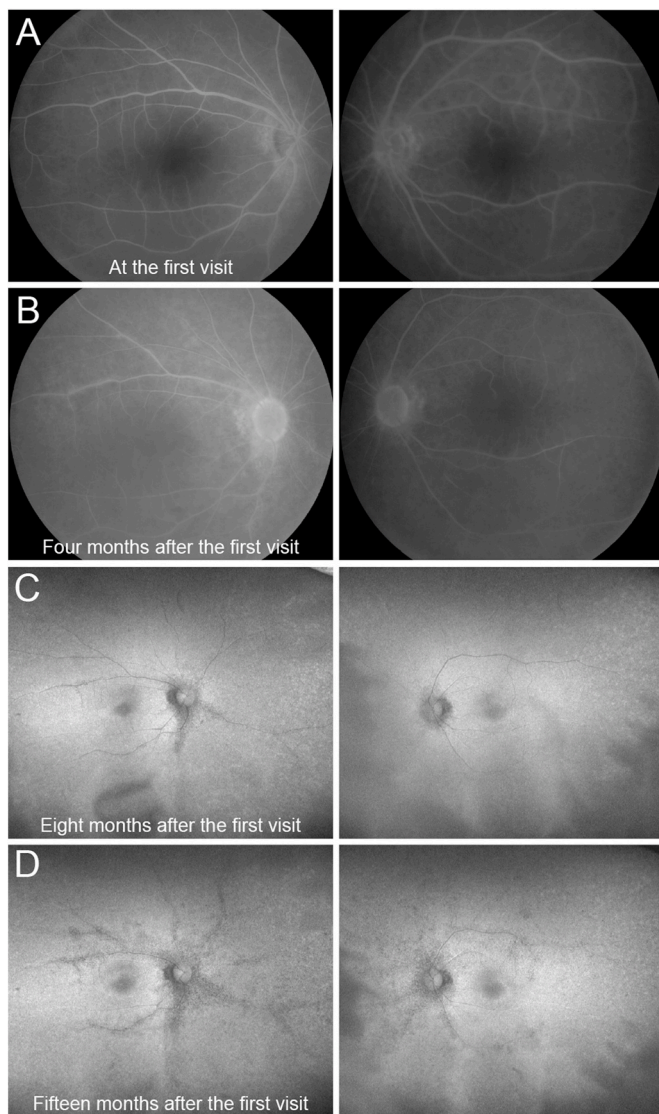


Fig. 2. Clinical course of fluorescein angiography (FA) and fundus autofluorescence (FAF) images.

(A) At the first visit, FA shows slight fluorescein leakage around the optic disc in both eyes and inferior arcade veins in right eye. (B) Four months after the first visit, FA shows further leakage around the optic disc and partial arcade veins in right eye, and no remarkable change in left eye. (C) Eight months after the first visit, FAF shows hypo-autofluorescence (AF) around the optic disc in both eyes and partial inferior arcade veins in right eye. (D) Fifteen months after the first visit, FAF shows hypo-AF area along with arcade veins in both eyes.

ERG showed severely decreased a- and b-wave responses.

Six months after the first visit, new metastasis to lymph nodes was detected by computed tomography. Adjuvant chemotherapy comprising docetaxel and carboplatin was changed to doxorubicin.

Eight months after the first visit, she was referred to the Jikei University School of Medicine Hospital for examination and treatment of retinal dysfunction. BCVA was 0.6 in the right eye and 0.7 in the left eye. Funduscopy showed deterioration of white sheathing of retinal arteries and retinal degeneration around arcade vessels in both eyes (Fig. 1C) compared with imaging results obtained four months after the first visit. Fundus autofluorescence imaging (FAF; Optos 200Tx, Ultra-Wide Field Retinal Imaging System, Optos, Dunfermline, UK) showed hypo-autofluorescence (AF) around the optic disc in both eyes and partial inferior arcade vessels in the right eye (Fig. 2C). OCT showed loss of EZ/IZ and thinning of the outer retina throughout the macular except for

blurred EZ at the fovea in both eyes (Fig. 3B). GP showed deterioration of visual fields defects in both eyes (Fig. 4C).

Blood testing did not detect any apparent systemic disorders, however, C-reactive protein (0.35 mg/dl; normal range, 0–0.3), anti-nuclear antibody (47; normal range, 0–19.9), herpes simplex virus antibody (16×; normal range, 0–3), cytomegalovirus antibody (8×; normal range, 0–3), and Toxoplasma gondii IgG antibody (12 IU/ml; normal range, 0–5) were elevated. Some of these positive findings might be related to endometrial carcinoma and associated therapy. There were no signs of systemic and ocular infection and inflammation. In addition, anti-recoverin antibody, assessed using western blot analysis and performed as previously described,¹⁶ was negative.

Ten months after the first visit, the patient noticed further aggravation of reduced visual acuity. BCVA was light perception in both eyes. Although funduscopy showed no remarkable change (Fig. 1D), OCT showed a faintly visible EZ at the fovea and loss of EZ and thinning of outer retinal layers at other areas in both eyes (Fig. 3C). GP showed complete loss of visual fields in both eyes (Fig. 4D). Oral prednisolone therapy (60 mg/day) was started and gradually tapered over a 3-month period. Adjuvant chemotherapy comprising doxorubicin was subsequently changed to irinotecan.

Twelve months after the first visit, BCVA was surprisingly improved to 0.2 in the right and 0.3 in the left eyes. Funduscopy showed retinal degeneration along with arcade veins without retinal pigment epithelium (RPE) clumping in both eyes (Fig. 1E). OCT revealed that EZ at the fovea became more visible compared with the finding 10 months after the first visit, whereas loss of EZ and thinning of outer retinal layers in other areas were unchanged in both eyes (Fig. 3D). GP also showed partial restoration of central visual fields in both eyes and peripheral visual field of an island limited to the inferior area in the right eye (Fig. 4E).

Fifteen months after the first visit, BCVA was 0.2 in the right eye and further improved to 0.7 in the left eye. Funduscopy showed apparent retinal degeneration along with arcade veins without RPE clumping in both eyes (Fig. 1F). FAF also showed a hypo-AF area along with arcade veins in both eyes (Fig. 2D). OCT showed more distinct and visible EZ at the fovea in both eyes, whereas findings of other areas were not changed (Fig. 3E). GP showed further restoration of central visual fields in both eyes and peripheral visual field in the right eye (Fig. 4F). Anticancer effects of irinotecan remained unclear. The patient died at 69 years old.

2. Discussion

Here, we reported a patient with CAR who exhibited progressive retinal degeneration along with retinal veins within several months and the recovery of retinal structure and function by oral prednisolone therapy.

To date, most previous studies focused on how retinal degeneration progresses at the macular in patients with CAR.^{6,7} However, little is known about the findings of progressive retinal degeneration at the midperipheral or peripheral retina in patients with CAR. We considered that the reason why the unique finding of retinal degeneration along with retinal veins exhibited in our patient might be related to the presence of retinal vasculitis. In fact, active retinal vasculitis in Behçet's disease was known to develop into paravenous retinal degeneration in some patients, who exhibited hypo-AF along with retinal veins on ultra-wide FAF.¹⁷ In our patient, FA findings showed leakage around the optic disc and inferior arcade veins in the acute phase, indicating the presence of retinal vasculitis. Finally, FAF findings revealed hypo-AF along with retinal veins in the chronic phase, indicating retinal degeneration. Generally, clinical characteristics of retinal degeneration along with retinal veins accompanied by RPE clumping are classified into pigmented paravenous retinochoroidal atrophy (PPRCA).¹⁸ The finding of retinal degeneration along with retinal veins in our patient was similar finding to characteristics of PPRCA. However, our patient exhibited mild retinal degeneration without RPE clumping, which was

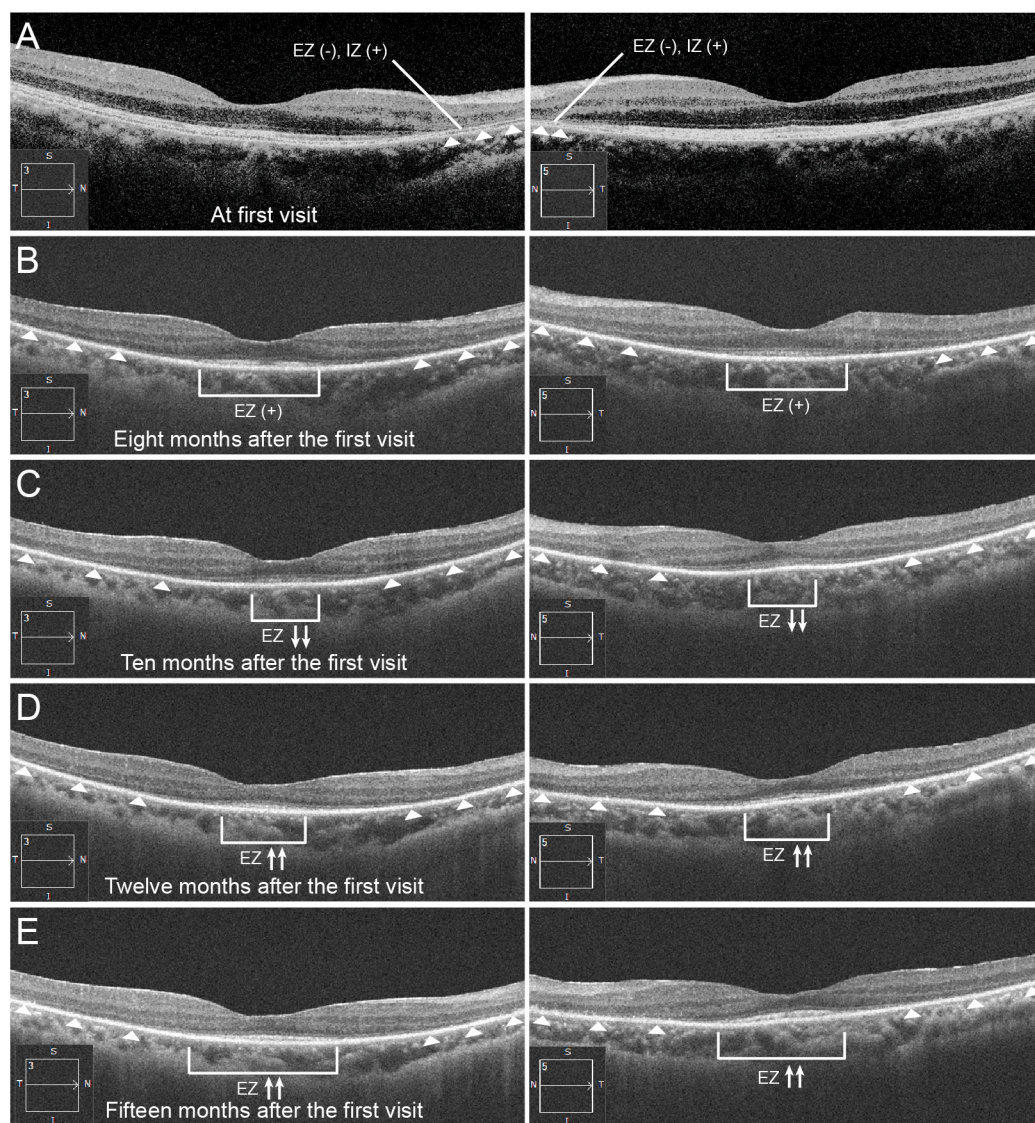


Fig. 3. Clinical course of optical coherence tomography (OCT) images. (A) At the first visit, OCT shows thinning of outer retinal layers, loss of ellipsoid zone (EZ) at nasal areas (arrow heads), but interdigitation zone (IZ) is visible in both eyes. (B) Eight months after the first visit, OCT shows loss of EZ/IZ and outer retina throughout the macula (arrow heads) except for blurred EZ at the fovea in both eyes. (C) Ten months after the first visit, OCT shows faintly visible EZ at fovea, and loss of EZ and thinning of outer retinal layers at other areas (arrow heads) in both eyes. (D) Twelve months after the first visit, OCT reveals that the fovea becomes more visible compared with the finding 10 months after the first visit, whereas loss of EZ and thinning of the outer retinal layers at other areas (arrow heads) were not restored in both eyes. (E) Fifteen months after the first visit, OCT shows more distinct and visible EZ at the fovea in both eyes whereas the findings of other areas (arrow heads) were not changed.

not typical clinical characteristics of PPRCA. Although the lack of identification of anti-recoverin antibody was a negative finding for the diagnosis of CAR, the characteristics of fast progression, severe functional deterioration, and notable white sheathing were not consistent with PPRCA but instead were consistent with CAR. Furthermore, endometrial carcinoma has been reported as one of the major causes of CAR,^{14,19} which also supported the evidence of CAR. In summary, our patient with CAR exhibited unique findings of progressive retinal degeneration along with retinal veins without RPE clumping.

The mechanism underlying CAR is considered to involve cross-reactivity between autoantibodies against tumor antigens and retinal photoreceptor cells.^{3,4} Therefore, immunosuppression therapies with and without cancer therapies are the reasonable medical option for CAR,^{15,20,21} although there are no established guidelines. Immunosuppression therapies for CAR have resulted in various outcomes from improvement including structural improvement in OCT images^{12,13} and cessation of disease progression¹¹ to continued progression.²² Our patient was treated with oral prednisolone therapy, which resulted in improvement of BCVA, visual field, and EZ in OCT images.

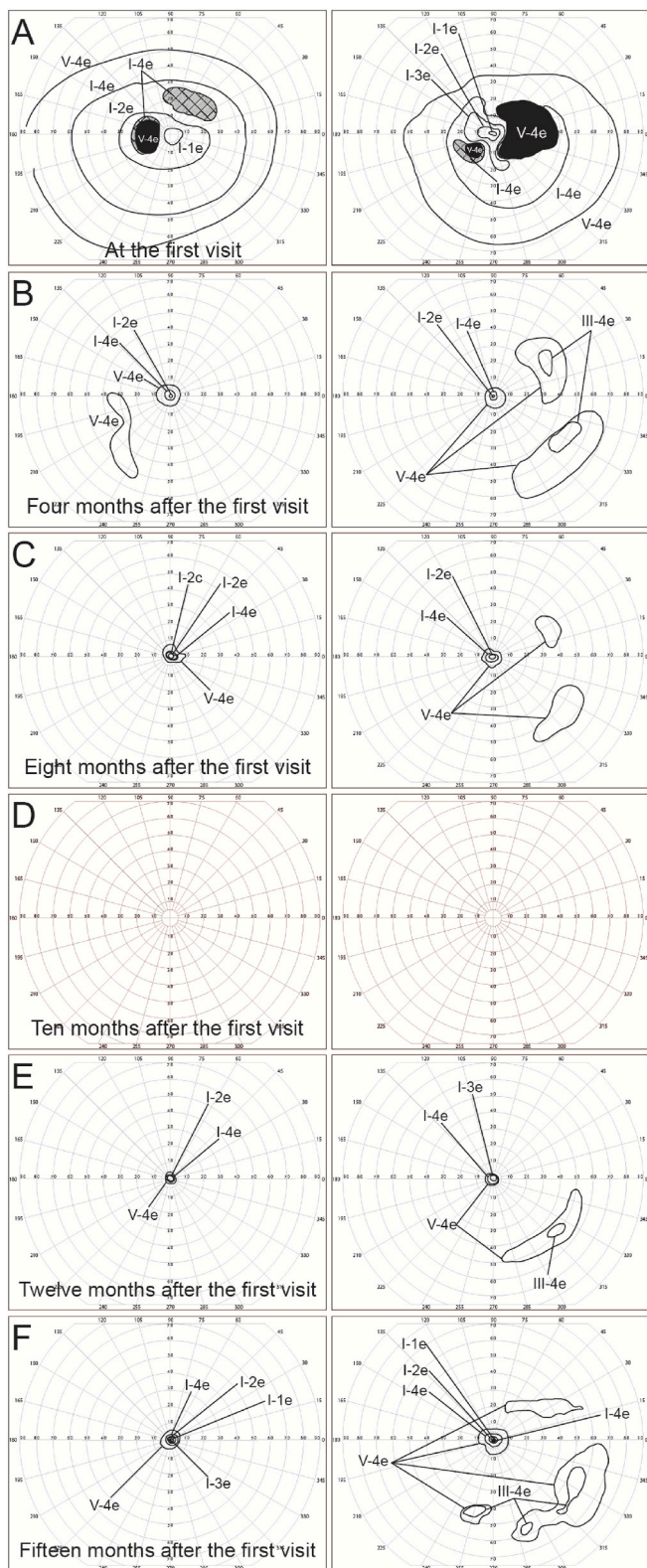
Although the conditions responsible for immunosuppression therapies have not been clarified, Huynh et al. suggested that suppression of secondary inflammation and apoptosis of photoreceptor cells may result in good therapeutic outcomes.¹² Another study suggests the

immunosuppression therapy should be performed soon and for long time as possible.²⁰ Furthermore, we reported another patient with thymoma-associated retinopathy who showed good visual prognosis including improvement of reduced rod-mediated ERG responses following immunosuppression therapy and thymectomy.²³ We considered that appropriately timed immunosuppression therapy might inhibit further immune responses and/or inflammation by suppressing phagocytes and inflammatory cytokines in some patients with CAR, resulting in recovery of dying photoreceptor cells and suppression of further photoreceptor cell death. In this patient, outer retinal layers and visual field showed improvement because we initiated immunosuppression therapy as soon as aggravation of retinal structure and function was revealed. These results indicated that early treatment and long-term therapy are important for visual prognosis in patients with CAR.

In conclusion, we reported a patient with CAR who exhibited progressive retinal degeneration along with retinal veins and good response to oral prednisolone therapy for improvement of retinal function. This case expands the clinical spectrum of CAR.

Patient consent

Written informed consent was obtained from patient for publication of this case report and any accompanying images.



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Fig. 4. Clinical course of visual fields.

(A) At the first visit, Goldmann perimetry (GP) shows several paracentral scotomas of V-4e isopters with constriction of peripheral visual fields of I-4e isopters in the right eye and paracentral relative scotomas of I-4e and V-4e isopters with preserved peripheral visual fields in the left eye. (B) Four months after the first visit, GP shows severe constriction of visual fields with a few peripheral visual islands in both eyes. (C) Eight months after the first visit, GP shows deterioration of visual fields defects in both eyes. (D) Ten months after the first visit, GP shows complete loss of visual fields in both eyes. (E) Twelve months after the first visit, GP shows partial restoration of central visual fields in both eyes and peripheral visual fields of an island limited to the inferior area in the right eye. (F) Fifteen months after the first visit, GP shows further restoration of central visual field in both eyes and peripheral visual fields in right eye.

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Authorship

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

Declaration of competing interest

The authors declare that there are no conflicts of interest regarding this paper.

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