Intravenous rituximab and oral cyclophosphamide for the treatment of cancer-associated retinopathy in a patient with epithelial ovarian cancer: A case report

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Abstract. Cancer-associated retinopathy (CAR) is a rare paraneoplastic disorder mediated by auto-antibodies that cross-react with retinal antigens leading to gradual visual defects. Early diagnosis and initiation of treatment is crucial to avoid permanent visual loss. Although most patients with CAR respond to intravenous steroids and intravenous immunoglobulin (IVIG), there are some cases refractory to the aforementioned treatment strategies. The present study describes a case of CAR in a patient with ovarian cancer that was initially resistant to most treatment regimens (chemotherapy, steroids, IVIG). Treatment with rituximab at 375 mg/m^2 and oral cyclophosphamide was administered and the patient showed marked improvement of visual acuity. Electroretinogram showed a 40 and 10% improvement in scotopic and photopic vision, respectively. Notably, at the most recent follow up, the patient was still in remission. In conclusion, treatment with intravenous rituximab and oral cyclophosphamide is a promising treatment option for those cases of CAR that do not respond to steroids, immunomodulatory agents and IVIG.

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Introduction

Cancer-associated retinopathy (CAR) is a rare paraneoplastic disorder causing diffuse retinal degeneration that was first described by Sawyer *et al* in 1976 (1). In CAR, retinal degeneration occurs in the presence of autoantibodies that cross-react with tumor antigens homologous to retinal-tissue components. CAR is most commonly associated with small cell lung carcinoma, although it has also been reported in breast cancer and gynecological malignancies (ovarian, cervical, endometrial) (2). In up to 50% of cases, visual loss from CAR may occur even before the diagnosis of cancer (2). The clinical triad of 'photosensitivity, ring scotomatous visual field loss, and attenuated retinal arteriole caliber' should always raise suspicion for underlying malignancy, as highlighted by Jacobson *et al* (3).

Early diagnosis and initiation of treatment is crucial for the preservation of vision. Even after the administration of immunosuppressive treatment, prognosis remains poor, leading to permanent visual loss often reaching no light perception. Although systemic treatment for the primary malignancy induces a significant decline in circulating autoantibodies, treatment of the ocular disease is necessary. There is no established treatment protocol for CAR. Systemic or intraocular steroids, immunomodulatory agents (azathioprine, cyclosporine, mycophenolate mofetil) and plasmapheresis have been used with variable results. Guy and colleagues first used IVIG (intravenous immunoglobulin) in CAR and reported improvement even from the third day of administration (4). Since then, IVIG has been administered either alone or in combination with steroids offering improvement or stabilization of visual symptoms (5). When the aforementioned agents fail, prognosis of CAR is poor gradually leading to visual loss.

Herein, we report a case of CAR in a patient with ovarian cancer that was initially resistant to most treatment regimens (chemotherapy, steroids, IVIG) presenting persistent nyctalopia even during disease remission and who was eventually treated with rituximab and oral cyclophosphamide. Despite

the initial poor results to steroids and IVIG, treatment with intravenous rituximab and oral cyclophosphamide offered marked improvement of visual acuity and previous reported nyctalopia.

Case report

A 67-year-old Caucasian woman originally presented at the Oncology Department of Alexandra University Hospital with a recent diagnosis of ovarian cancer. She had undergone primary cytoreductive surgery with total hysterectomy with bilateral salpingo-oophorectomy in June 2015 for high-grade serous carcinoma of the left ovary FIGO stage IIIA that resulted in debulking to no residual tumor. The patient subsequently received six cycles of adjuvant platinum-based chemotherapy with paclitaxel and carboplatin (July 2015-October 2015). The patient remained disease-free until January 2019 that presented with progressive, bilateral visual impairment at night (nyctalopia) gradually developing over the past 6 months. Her past ocular history included bilateral cataract surgery that had been performed three years before without any complications, as well as high myopia. Follow-up revealed an elevation in serum CA-125 levels and a left paraaortic lymph node enlargement close to left renal pelvis. On ophthalmologic examination, anterior segment examination and intraocular pressure were normal in both eyes. There was no relative afferent pupillary defect. Best-corrected visual acuity was 20/25 in the right eye and 20/32 in the left eye. Dilated fundoscopy demonstrated narrowed retinal arteries and attenuation of retinal vessels bilaterally, while diffuse retinal pigment epithelium abnormalities were found in fundus autofluorescence (FAF) (6). Fluorescein angiography was normal, while optical coherence tomography (OCT) showed outer retinal layers' thinning with absence of photoreceptor layer parafoveally in both eyes (6). Visual field showed reduced sensitivity and constriction of visual field. Electroretinogram (ERG) showed markedly reduced retinal sensitivity affecting the rod system by 70% and the cone system in a lesser extent (40%) in both eyes, as it has been previously published by our team (6). The ocular examination was indicative of a paraneoplastic syndrome and the diagnosis of CAR was highly suspected. On this basis, western blot analysis was performed for anti-retinal antibodies that revealed the presence of anti-enolase antibodies (Fig. S1). Consequently, the diagnosis of CAR was confirmed.

After consultation with the ophthalmologists, we initiated systemic therapy for the underlying malignancy. The patient received chemotherapy with twelve cycles of gemcitabine and carboplatin in combination with bevacizumab from February 2019 to August 2019 and then stayed on maintenance treatment with bevacizumab until October 2019. The treatment resulted in partial response of the disease in computerized tomography (CT) scans and a reduction in CA-125 serum levels.

Despite the radiographic and biochemical disease response to treatment, the vision remained impaired especially at night. The patient's nyctalopia gradually deteriorated over the next months although repeat CT scans revealed no disease progression. In addition, the photopic function was also impaired at this time and the patient reported blurred daytime vision. The ophthalmologic examination was repeated on October 2021 and the new ERG showed persistent abnormalities in a- and b-waves with further deterioration of the rod system. Best-corrected visual acuity was also reduced to 20/32 in the right eye and 20/40 in the left eye. Fundoscopy showed deterioration of white sheathing of retinal arteries and retinal degeneration around arcade vessels in both eyes.

Given the absence of disease recurrence on sequential CT scans, the patient was initiated on treatment with intravenous steroids in October 2021, although the treatment was unsuccessful. Since the treatment with intravenous steroids failed, the treatment plan was switched to IVIG (intravenous immunoglobulin) at a dose of 400 mg/kg per day for five days. However, the visual function showed no improvement. Upon consultation of ophthalmologists, we decided to administer intravenous rituximab in combination with oral immunosuppressive treatment with cyclophosphamide. The patient received intravenous rituximab at a dose of 375 mg/m^2 weekly for a total of six cycles along with oral cyclophosphamide 100 mg/m^2 twice daily in June 2022.

Three months after treatment, both daytime and night vision were remarkably improved. Best-corrected visual acuity was increased to 20/25 in the right eye and 20/32 in the left eye. The new ERG showed improved scotopic vision by 40% and photopic vision by 10% in both eyes (Fig. 1). These findings are consistent with the clinical improvement reported by the patient. Of note, the patient remains still in remission at the last disease assessment that was performed in July 2022. A written informed consent was obtained from the patient for the publication of this data.

Discussion

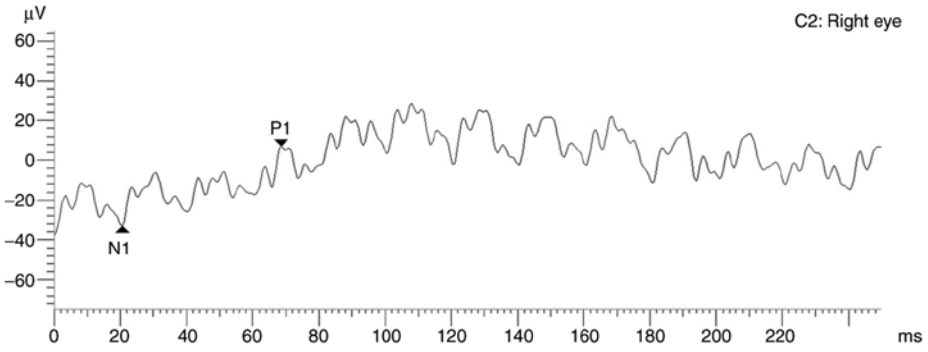
CAR is a member of the broad spectrum of autoimmune retinopathy (AIR) diseases (7). Autoimmune retinopathy is generally separated in paraneoplastic (pAIR) and non-paraneoplastic (npAIR) in the absence of malignancy. CAR is an immune-mediated retinal degeneration characterized by progressive painless diminution of vision, abnormal ERG findings and the presence of anti-retinal antibodies. Ocular manifestations typically include nyctalopia, photopsia, constricted visual fields, uveitis, optic or chorioretinal atrophy (8,9). The time interval from cancer diagnosis to the onset of retinopathy can vary from weeks to months (lymphoma and lung cancer) to even years in other malignancies (breast and prostate cancer). Early diagnosis and treatment is crucial to prevent irreversible retinal damage and permanent visual loss.

Molecular mimicry is considered as the driving force behind CAR pathogenesis. CAR is a result of a cross-reactivity between tumor antigens and components of retinal photoreceptors leading to an antigen-antibody reaction (Fig. 2). The antigenic protein that was first described was a 23 kDa retinal protein in patients with small cell carcinoma of the lung and CAR and was observed by Thirkill *et al* in 1987 (10). This 23 kDa protein identified as the CAR-antigen was named as 'recoverin-like protein'. Recoverin is a Ca^{2+}-dependent activator of photoreceptor guanylate cyclase involved in light and dark adaptation of photoreceptors (11). Autoantibodies against recoverin attack photoreceptors and bipolar retinal cells causing their death by caspase-mediated apoptosis. Several retinal

1.Step: Rod Resp.
Meas. range: ±1 mV
Sample freq.: 2 kHz (500 µs)
Meas. filter: 1 Hz-300 Hz

Background: dark
Stimulator: int.LED 2 cd/m^2 white
Avg's/Artef.: 3/3

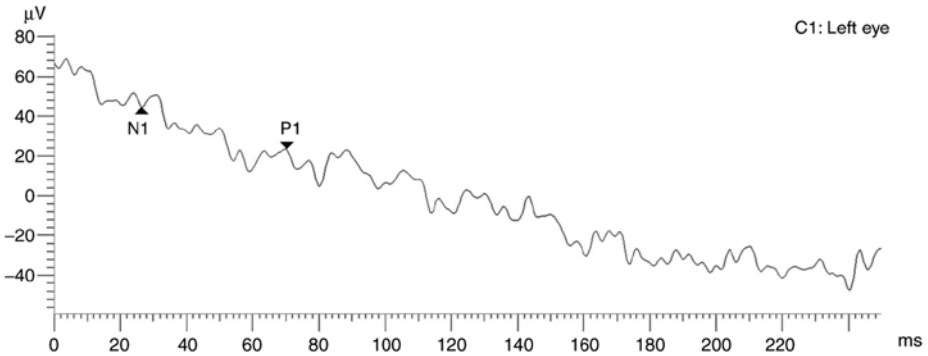
Marker N1: 20.5 ms –33.0 µV
Marker P1: 68.5 ms 40.2 µV



Meas. range: ±1 mV
Sample freq.: 2 kHz (500 µs)
Meas. filter: 1 Hz-300 Hz

Background: dark
Stimulator: int.LED 2 cd/m^2 white
Avg's/Artef.: 3/3

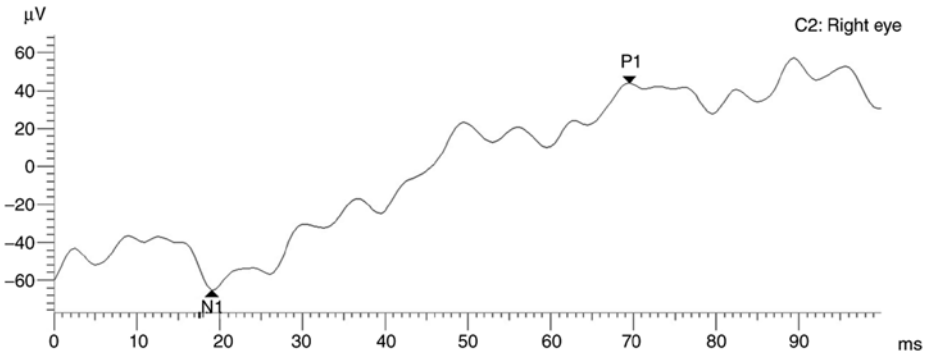
Marker N1: 26.5 ms 44.6 µV
Marker P1: 70.2 ms 21.0 µV



2.Step: Max Resp.
Meas. range: ±1 mV
Sample freq.: 2 kHz (500 µs)
Meas. filter: 1 Hz-300 Hz

Impedance: (+) 4 KΩ (–) 1 KΩ
Background: dark
Stimulator: int.LED 2 cd/m^2 white
Avg's/Artef.: 3/2

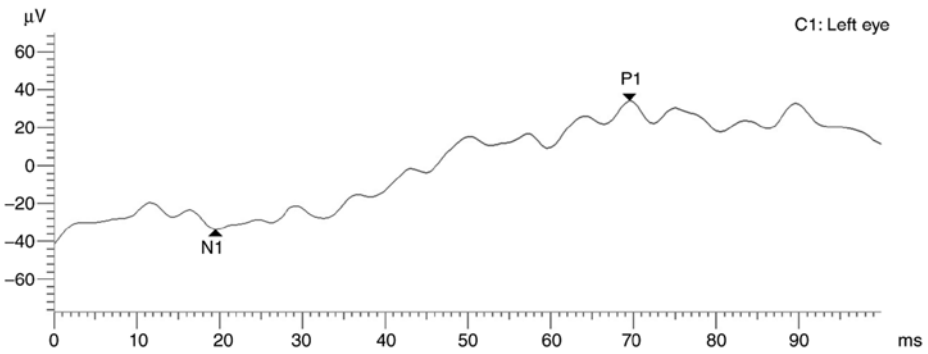
Marker N1: 19.0 ms –65.2 µV
Marker P1: 69.5 ms 109.0 µV



Meas. range: ±1 mV
Sample freq.: 2 kHz (500 µs)
Meas. filter: 1 Hz-300 Hz

Impedance: (+) 5 KΩ (–) 5 KΩ
Background: dark
Stimulator: int.LED 2 cd/m^2 white
Avg's/Artef.: 3/2

Marker N1: 19.5 ms –33.8 µV
Marker P1: 69.5 ms 67.9 µV



3.Step: Scotopic 10
Meas. range: ±1 mV
Sample freq.: 2 kHz (500 µs)
Meas. filter: 1 Hz-300 Hz

Impedance: (+) 2 KΩ (–) 1 KΩ
Background: dark
Stimulator: int.LED 10 cd/m^2 white
Avg's/Artef.: 1/1

Marker N1: 28.5 ms –78.1 µV
Marker P1: 65.5 ms 108.7 µV

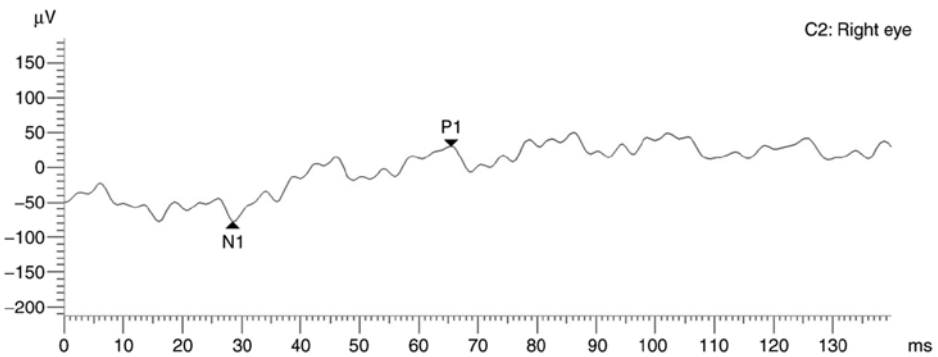


Figure 1. Continued.

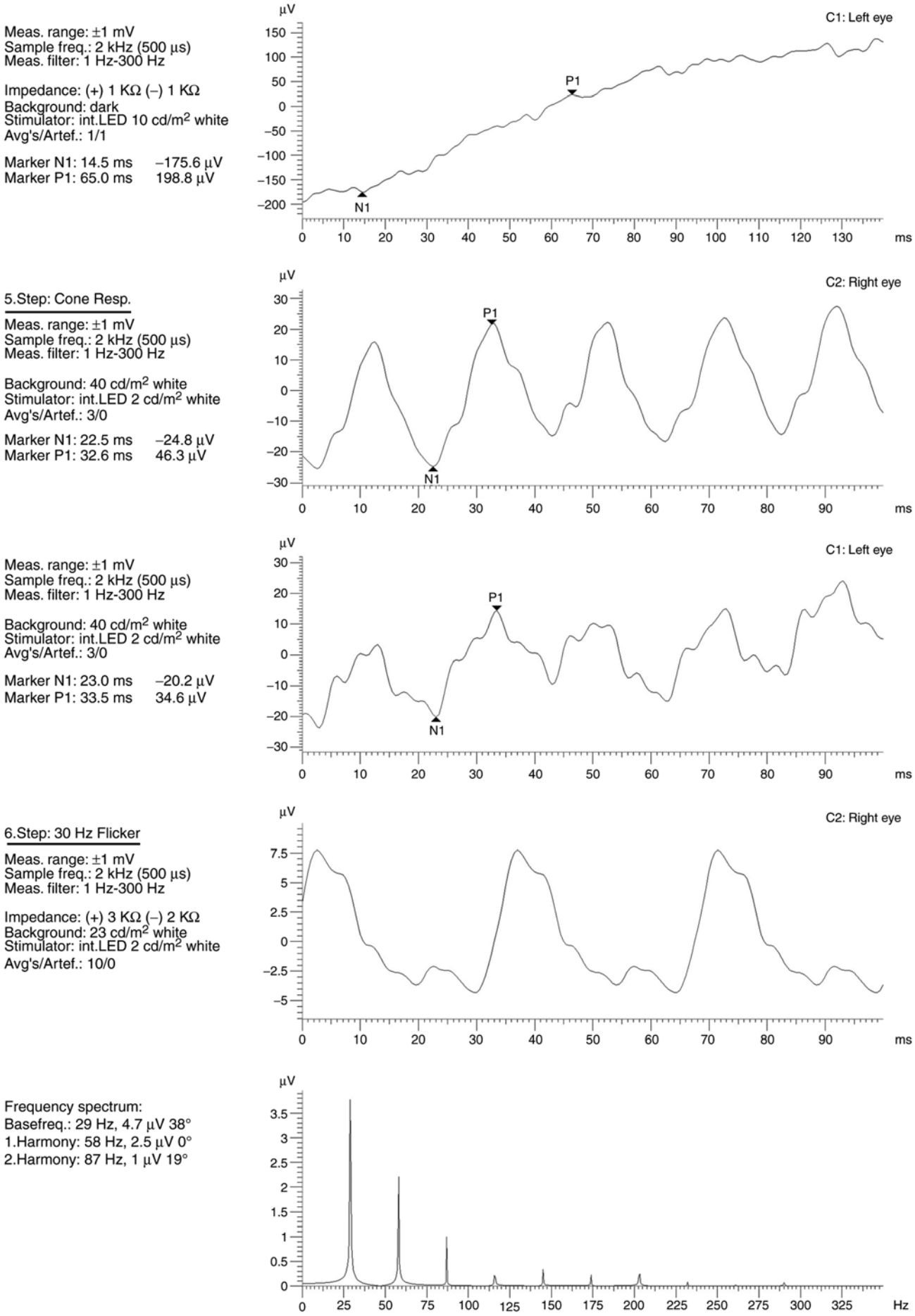


Figure 1. Full-field electroretinogram showing the improvement of the amplitudes of a- and b-waves in under both scotopic and photopic conditions.

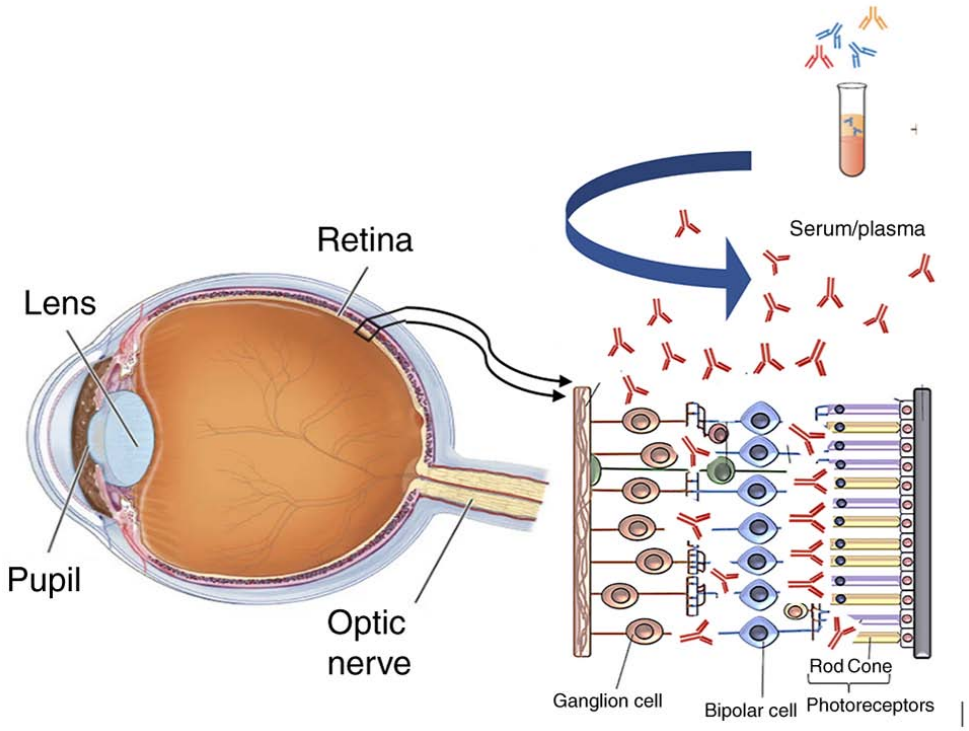


Figure 2. Pathogenesis of cancer-associated retinopathy in the ocular microenvironment.

autoantibodies that cross-react with components of ocular receptors have been reported. Although recoverin (23 kDa) is the most common antibody identified, other antibodies include α-enolase (46 kDa), arrestin (48 kDa), transducing-a (40 kDa) and b (35 kDa), heat shock cognate protein (HSC 70) (65 kDa), anti-carbonic anhydrase II (30 kDa), photoreceptor cell-specific nuclear receptor (PNR) (46.5 kDa), interphotoreceptor retinoid-binding protein (145 kDa), and tubby-like protein-1 (TULP1) (78 kDa) (12). Anti-retinal antibodies can be detected via Western Blot analysis, enzyme-linked immunosorbent assay (ELISA) or immunohistochemistry (IHC) in the patient's serum, although serological testing for antibodies is negative in up to 45% of cases. In our patient, α-enolase antibodies were detected. Enolase is a glycolytic enzyme found in rods, cones, ganglion cells, and Müller cells. Three different isoforms of enolase have been described, but the α-isoform have mostly been reported in CAR (13). The presence of anti-enolase antibodies in the serum of patients with CAR was first described by Adamus *et al* (14). Typically, anti-α-enolase antibodies increase as the tumor burden grows, which partly explains why these antibodies are usually detected after tumor diagnosis. Unlike recoverin, α-enolase-targeting antibodies predominantly affect the ganglion cells and inner retina (15). Visual impairment in enolase-associated retinopathy is thought to be less severe than recoverin-associated retinopathy that is characterized by acute onset and fast progression (2). However, CAR with anti-α-enolase antibodies may be more difficult to control as in our case, even with intravenous immunoglobulin therapy. Of note, anti-retinal antibodies can be found in the 42% of healthy people or patients with autoimmune disorders (16).

The diagnosis of CAR typically involves a complete ophthalmologic examination with visual fields, FAF, OCT and ERG. Fundus examination may be initially normal, although periphlebitis or mild vitritis can be detected. Later, there is arteriolar narrowing, a salt-and-pepper appearance, and optic atrophy. OCT typically shows significant thinning of the photoreceptor layer and loss of the inner reflective layer, while it can also reveal cystic spaces or occasionally mild schisis-like changes, which are relatively diagnostic for pathologic anti-retinal antibodies. ERG is necessary for the diagnosis of CAR, being usually abnormal with severely diminished or extinguished a- and b-waves involving rods and cones, and is considered to be more sensitive than OCT or FAF (2).

The target of therapy in CAR is to diminish circulating auto-antibodies to prevent the progression of retinal degeneration and stabilize current disease condition. No standard protocol exists for the treatment of CAR and the rapid progression makes it often a challenging condition. Treatment of the primary malignancy is thought to induce a significant decline in the number of circulating antibodies. The most widely reported therapy includes oral corticosteroids at doses as high as 1 to 2 mg/kg/day (prednisone 60-80 mg/day) or intravenous steroids such as methylprednisolone (500 mg/day for three days) (2,5). In some cases, periocular/intravitreal steroids can be used, although there could be a rise in intraocular pressure. Steroids usually bear transient improvement in visual acuity and visual fields. Other valuable options include plasmapheresis or immunomodulatory agents such as azathioprine (100 mg/day), cyclosporine (100 mg/day) or mycophenolate mofetil (2 g/day) (2,17). In some cases, IVIG proved to be of clinical benefit at a dose of 400 mg/kg/per day for five days) as administered in our patient (4). Ramos-Ruperto *et al* reported that 9 out of 12 patients with CAR treated with IVIG showed visual stabilization although only four of them showed improvement (5). IVIG has been administered mostly in

combination with steroids or other agents, including plasmapheresis or rituximab (5). Whatever the treatment combination, IVIG proved to be effective when administered early after CAR onset, usually within the first 4 weeks (5).

Recently, rituximab is becoming more popular in the treatment of CAR (18-24). The recommended dose is 375 mg/m^2 once a week for four weeks or 1,000 mg twice a week for 2 doses in combination with immunosuppressive agents (such as prednisone, cyclophosphamide, azathioprine, infliximab, cyclosporine, and mycophenolate) (18-23). Rituximab is a chimeric monoclonal antibody targeting the B-cell surface antigen CD20 and was originally developed for the treatment of non-Hodgkin B-cell lymphoma. However, rituximab has been effectively used for the treatment of autoimmune diseases, including rheumatoid arthritis, systemic lupus erythematosus (SLE) and Graves' disease. Since CAR is an autoimmune condition caused by anti-retinal autoantibodies, inducing memory B-cell depletion with rituximab could be a reasonable treatment option. Treatment with rituximab could reprogram memory B cells so that they cannot recognize the retinal antigen. Davoudi *et al* reported 16 patients with paraneoplastic and nonparaneoplastic autoimmune retinopathy resistant to prior immunosuppressive treatment that were treated with rituximab either as monotherapy or in combination with other agents (cyclophosphamide, mycophenolate mofetil, IVIG, intravitreal triamcinolone (IVT), periocular triamcinolone and bortezomib) (21). In this study, visual improvement was profound in 14% of the cases, while stabilization of the visual impairment was achieved in 63%. Of note, patients who experienced visual improvement were those treated within 4 and 7 months from symptom onset and before severe loss of function on ERG was detected (21). Our results and those of others indicate that rituximab in combination with oral cyclophosphamide is a valuable treatment alternative in heavily pretreated CAR (18-24).

In conclusion, treatment of aggressive CAR, that is refractory to steroids and IVIG, with intravenous rituximab and oral cyclophosphamide could bear substantial improvement. We report the case of a patient with ovarian cancer-related CAR and gradually deteriorating visual symptoms that showed no benefit from intravenous steroids and IVIG, while eventually responded to rituximab and oral cyclophosphamide administration.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

AAnd and KK confirm the authenticity of all the raw data. FZ, MAD, GT and KK conceptualized the study. AAnd, IC, PT and AAna collected all the data required. AAna, IC, KK, PT, JT, AAna performed the study investigation. ZF, MAD and TG are responsible for the project administration. ZZ, MAD, TG, IC, KK supervised the writing of the manuscript. AAnd, KK, PT, JT and AAna wrote the original draft. AAnd, JT, IC and KK reviewed and edited the original draft. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

The patient provided written informed consent for this case study to be published.

Competing interests

KK has received honoraria by Roche, BMS, MSD and IPSEN. MAD has received honoraria from participation in advisory boards from Amgen, Bristol-Myers-Squibb, Celgene, Janssen, Takeda. FZ has received honoraria for lectures and has served in an advisory role for Astra-Zeneca, Daiichi, Eli-Lilly, Merck, Novartis, Pfizer, and Roche. The remaining authors declare no conflict of interest.

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