Case Reports in Oncology

Case Rep Oncol 2023;16:785–790
DOI: 10.1159/000531624
Received: February 10, 2023
Accepted: June 13, 2023
Published online: September 4, 2023

Case Report

Case Report of Seronegative Cancer-Associated Retinopathy in a Patient with Small Cell Lung Carcinoma

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Keywords
Cancer-associated retinopathy · Small cell lung cancer · Paraneoplastic syndrome

Abstract
Cancer-associated retinopathy (CAR) is a rare paraneoplastic syndrome characterized by autoimmune destruction of photoreceptor cells. It is associated with several tumor types, including small cell lung carcinoma (SCLC). Corticosteroids have been the mainstay treatment for CAR, although no therapeutic standard has truly been established. A 66-year-old female with significant smoking history and age-related macular degeneration (ARMD) presented with rapidly declining bilateral visual acuity. Ophthalmologic examination findings appeared consistent with the known diagnosis of ARMD but did not otherwise present a clear alternative etiology. Imaging with a computed tomography (CT) scan revealed a right hilar mass which was confirmed to be limited stage SCLC based on a subsequent biopsy and further imaging with a positron emission tomography/computed tomography (PET/CT) scan. Antibody testing was negative for anti-recoverin antibodies. The patient experienced a complete response to chemoradiation with cisplatin and etoposide; however, her ocular symptoms did not respond to a combined treatment approach with corticosteroids, plasmapheresis, and intravenous immunoglobulin (IVIG). While CAR represents a rare condition in SCLC, cases that are seronegative for anti-recoverin are even less common. Further, the diagnosis of CAR by ophthalmologic examination may be more challenging in patients with pre-existing ocular diseases, such as macular degeneration. Clinicians should have suspicion for paraneoplastic blindness in patients with known risk factors for malignancy, whose ocular symptoms are inconsistent with exam findings.

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Introduction

Cancer-associated retinopathy (CAR) is a rare paraneoplastic syndrome that occurs in several tumor types including small cell lung carcinoma (SCLC) [1–3]. It was first described by Sawyer in 1976 through a case series of three women who developed photoreceptor degradation in the setting of anaplastic tumors [4]. Destruction of photoreceptor cells in CAR is mediated through an autoimmune mechanism, in which tumor cells generate anti-retinal antibodies [1]. Several antigenic targets are implicated in lung cancer-associated CAR, including recoverin, alpha-enolase, hsc70, retinal S antigen, PNR, TRMP1, and potentially other unidentified retinal antigens [2, 5]. Roughly 70% of CAR cases are positive for anti-recoverin antibodies [3, 5]. Recoverin is a calcium-binding protein found in retinal photoreceptor cells that regulates phosphorylation of rhodopsin. Tumor-generated anti-recoverin antibodies have been shown to alter rhodopsin phosphorylation, triggering caspase-dependent pro-apoptotic pathways in photoreceptor cells [6]. However, a small subset of patients is seronegative for anti-recoverin antibodies [5].

In patients with CAR, visual disturbances can present months in advance of the identification of malignancy [7]. As such, clinical manifestations of paraneoplastic retinopathy are important for clinicians to recognize. Visual function may decline rapidly over the course of weeks to months, presenting with reductions in visual acuity and color vision, photosensitivity, scotoma, prolonged dark adaptation, and night blindness [1, 6, 7]. The combination of photosensitivity, ring scotoma, and attenuated retinal arteries on fundoscopy should raise suspicion for CAR, especially in older patients whose visual symptoms are inconsistent with the examination's findings [1, 3]. A reduced or flattened response on electroretinogram (ERG) and immunohistochemical detection of anti-retinal antibodies are crucial for the diagnosis of CAR [3, 8, 9]. Unfortunately, the visual prognosis of patients with CAR tends to be poor [8].

Immunosuppressive therapy with oral and intravenous corticosteroids has shown mixed results based on other case reports with some patients experiencing modest improvement in visual acuity at best [1, 3, 8, 10]. Initiating immunosuppressive therapy prior to diffuse photoreceptor damage may yield better clinical outcomes [1, 3, 10]. A case report of 3 patients treated with intravenous immunoglobulin (IVIG) showed mixed results, with 1 patient experiencing improved visual acuity and visual fields, 1 patient with improved visual fields, and another with no change in vision [8]. CAR being a relatively rare paraneoplastic syndrome, no randomized trials exist clarifying best practices in treating the condition. In this setting, case studies documenting clinician and patient experiences treating the condition are of critical importance.

Case Presentation

Here, we present a case of a 66-year-old female with a past medical history notable for a 22.5-pack-year smoking history, chronic obstructive pulmonary disease, and age-related macular degeneration (ARMD), who presented to ophthalmology with a 5-day history of floaters and flashes present in both eyes. During this visit, she received a vascular endothelial growth factor (VEGF) inhibitor injection for treatment of her ARMD. Her vision continued to progressively worsen over the following days. She went to the emergency department for further evaluation. At the time of presentation to the emergency department, she was only able to distinguish shapes, describing her vision as a "dark blur." It was noted that she had also lost roughly 25 pounds over the past year, which she indicated was a planned weight loss. A computed tomography (CT) scan of the head and brain revealed multiple calcified

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atherosclerotic plaques and mild focal stenosis of the right internal carotid artery origin but was otherwise unremarkable. The patient declined an MRI at that time and opted to follow up with ophthalmology as an outpatient.

Optical coherence tomography performed during her outpatient ophthalmology evaluation showed signs were consistent with the patient's underlying history of ARMD, demonstrating a previously identified area of choroidal neovascularization and no active subretinal fibrosis. Dense central scotomas were identified on Humphrey visual field testing. The patient declined to complete Goldmann size V testing during the visit. Given these results, no clear etiology presented itself to explain her recent, rapid decline in vision. Recommendations were made by ophthalmology to rule out paraneoplastic syndrome secondary to malignancy.

A chest CT scan revealed a right hilar mass which was confirmed to be limited-stage small cell lung carcinoma (SCLC) based on a subsequent biopsy and further imaging with a positron emission tomography/computed tomography (PET/CT) scan. At the time of her initial consultation with oncology, the patient was nearly blind and, as a result, had experienced a significant decrease in quality of life and ability to perform activities of daily living. A brief ocular examination revealed that she was able to distinguish colors and rough morphology of objects. Anti-recoverin autoantibody testing was negative.

Given the patient's medical history and ocular findings, progression of her ARMD represented a possible explanation for her symptoms. However, with the rapidity of decline in her vision and the juxtaposition of the patient's ocular symptoms with the diagnosis of SCLC, a paraneoplastic syndrome seemed to be a more likely explanation. There are several ocular-involving paraneoplastic syndromes associated with lung cancer, including CAR, cancer-associated cone dysfunction, bilateral diffuse uveal melanocytic proliferation, and paraneoplastic optic neuritis [6]. Of these, CAR seemed the most likely based on the clinical presentation and its strong association with SCLC [1].

The patient initiated chemoradiation with cisplatin and etoposide and 60 Gy intensity-modulated radiation therapy (IMRT). She ultimately completed 4 cycles of chemoradiation, followed by prophylactic cranial radiation. Concomitant with chemoradiation, she was treated with a taper of prednisone starting at 1 mg/kg and plasmapheresis for her presumed paraneoplastic blindness. The patient completed 5 cycles of plasmapheresis; however, her vision loss continued to progress and by the time of her second cycle of chemotherapy, she was only able to distinguish bright colors. Plasmapheresis and corticosteroids were discontinued, in part due to the patient's continued visual decline but also due to concerns that plasmapheresis might decrease the efficacy of the chemotherapy agents which are highly protein-bound [11]. After completing chemoradiation, she received 3 cycles of IVIG for treatment of paraneoplastic blindness.

This patient achieved a complete response regarding her limited stage SCLC. At the time of writing this manuscript, the patient is 3.5 years out from her SCLC diagnosis with no evidence of disease. Unfortunately, the patient's vision and associated quality of life continued to decline. At a follow-up visit with oncology occurring roughly 5 months after discontinuing chemoradiation, initiating immunosuppressive therapy with rituximab was discussed but was ultimately declined by the patient due to concerns over its side effects.

Discussion

Here, we report a case of a female patient with SCLC and CAR, treated with corticosteroids, plasmapheresis, and IVIG, along with chemoradiation and prophylactic cranial radiation. Ultimately, the patient achieved a complete response in terms of her SCLC but had no improvement in her ocular symptoms. SCLC typically carries a poor prognosis, with roughly a 7% 5-year survival [9]. It has been hypothesized that autoimmune mechanisms

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underlying ocular paraneoplastic syndromes may be associated with better cancer outcomes and that rare cases of spontaneous regression of SCLC in patients with CAR may be in part due to recoverin-specific cytotoxic T-lymphocyte response [3, 12].

Prior case reports of CAR have highlighted the importance of early disease recognition and treatment initiation, which appears to be a critical factor in modifying the otherwise rapid progression of visual decline [1, 3, 9, 10, 13]. Patients with paraneoplastic blindness often experience visual disturbances which may be the first symptoms that initiate the diagnostic steps resulting in their cancer diagnosis [7, 9]. This case highlights the challenges of recognizing clinical manifestations of CAR in the setting of pre-existing ocular disease such as ARMD. In patients with advanced macular degeneration, providers need to maintain a broad differential, particularly when sudden onset visual changes occur.

Treatment options for CAR are somewhat limited. While there is no definitive therapy regimen, early treatment with corticosteroids has shown to halt if not improve visual function and disease process for some patients [1, 3, 9, 10, 13]. Combination therapies with corticosteroids, IVIG, plasmapheresis, and other immunosuppressive agents such as rituximab have also been documented [8, 14, 15]. However, many patients will have continued progression of retinopathy despite treatment [1, 2, 8]. Additionally, treatments may be further limited by contraindications to immunosuppression or patient preferences.

Previous literature has highlighted the importance of detecting anti-retinal antibodies in the diagnosis of CAR [8, 9, 15]. However, a small percentage of patients with CAR are negative for anti-recoverin antibodies [2, 5, 10, 15]. In this patient's case, the identification of other antigenic targets implicated in lung CAR was limited by logistic and transportation-related challenges given her impaired vision and the COVID-19 pandemic. Previous case reports have demonstrated that CAR can be identified and treated based on clinical presentation even when anti-recoverin antibodies are not found [10]. However, this task may be complicated based on the presence of pre-existing ocular disease. As such, clinicians should have suspicion for paraneoplastic blindness in patients with known risk factors for malignancy, whose ocular symptoms are inconsistent with ophthalmologic exam findings. In our experience, autoantibody panels can take several days, if not longer to result. In these scenarios, physicians may be faced with the decision of whether a patient's clinical history and presentation in the context of a recent cancer diagnosis warrants treatment for CAR in the absence of autoantibody panels. The same could be said for patients whose antibody panels are negative for anti-recoverin but who otherwise meet the clinical presentation for CAR.

We would like to conclude by sharing some of this patient's own words and thoughts as they pertain to her condition. Her sentiments highlight the profound hardships faced by patients suffering from CAR and are a reminder of how much we have yet to learn in treating this rare condition.

> "I remember when it all started. I woke up and felt like a curtain was coming down over my eyes. I can still see a little bit, but not very well. My vision feels like I'm fifteen feet at the bottom of a swimming pool, looking back up at the surface. That shimmering light you see at the surface, that's how everything looks now. Everything has become hard. I can't drive. That was one of the worst parts. I used to be able to drive large trucks, farm equipment, anything. I had no transportation. The American Cancer Society had been giving me rides, but during COVID a lot of my transportation options were shut down. I've always said that death doesn't scare me but being blind scares me. That's just what it is. I told this to my doctor: I'm not worried about this cancer; I'm worried about having to go on living blind."

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The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000531624).

Statement of Ethics

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. This retrospective review of patient data did not require ethical approval in accordance with local/national guidelines.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

No outside funding sources were used or solicited in producing this case report.

Author Contributions

Joshua Morales is the hematologist/oncologist who cared for this patient. He selected, revised, and approved this case report. John Benfield is the medical resident who aided in acquiring and interpreting chart data, literature review, and revising this case report. Miles Thomas is the medical student responsible for reviewing and acquiring chart data, literature review, and drafting this case report.

Data Availability Statement

All data underlying the results are available as part of the article and no additional source data are required. Further inquiries can be directed to the corresponding author.

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