CASE REPORT

Cancer-associated retinopathy as the leading symptom in colon cancer

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Introduction

Paraneoplastic syndromes are a heterogeneous group of clinical disorders that arise due to an underlying neoplasm. By definition, these clinical symptoms are not directly related to physical effects of the neoplasm or its accompanying metastases, but are rather triggered by an alteration of the immune system (cross-reactivity) or by secretion of functional hormones from the tumor. Symptoms therefore show a broad variety ranging from endocrine to neurologic, but may also involve any other system of the body.

Among paraneoplastic syndromes, visual disorders are extremely rare. Cancer-associated retinopathy (CAR) (Table 1) is a paraneoplastic syndrome mediated by autoantibody formation against proteins in retinal photoreceptor cells [1]. The disease was first described in 1976. Recently, extraocular cancer was identified as the source of autoantibody formation in patients with CAR. The autoimmune reaction itself leads to retinal photoreceptor cell death [2–4]. No specific test exists to confirm CAR what makes its diagnosis quite difficult. Typically, loss of vision develops over months and can precede the diagnosis of the underlying malignancy. The percentage of patients presenting with visual symptoms prior to cancer diagnosis seems to be relatively unclear.

Key clinical message

Cancer-associated retinopathy (CAR) is a rare paraneoplastic visual syndrome. Its early detection may lead to the diagnosis of the causative malignancy. As many different types of malignancies are known to be associated with CAR, it is important that clinicians are aware of the phenomenon of CAR.

Keywords

Cancer, cancer associated retinopathy, colon, colorectal.

In one study of Adamus et al. [6], only eight of 209 patients had visual symptoms before cancer diagnosis, whereas Rahimy and Sarraf reported preceding symptoms in almost half of patients with CAR [8]. The diagnosis of CAR is established if a combination of different characteristic features is present. Often visual field defects, abnormal electrotinograms and serum autoantibodies can be found [5]. Different autoantibodies have been investigated and identified in patients with CAR. Only about 65% of CAR patients present antiretinal antibodies and the most frequently detected are – in descending order – against α-enolase (~30% of patients), transducin (~17%), carbonic anhydrase II (~14%), and recoverin (~10%) [6]. Because CAR is such a rare disease, there are no statistical data on its incidence or prevalence. According to the work by Adamus et al. [6], average age of presenting symptoms is 65 years and the disease affects more women than men with a ratio of 2:1. Since the first review in 2003, which included 55 cases, the number of CAR has significantly increased [7]. The vast majority of tumors associated with CAR are small-cell lung cancer and gynecological malignancies [6, 10]. Case reports exist for other solid tumors including non-small-cell lung, bladder, prostate, pancreatic, small bowel, thymus, and thyroid cancer [8]. The association of CAR with colon cancer has also been described, but seems to be extremely rare. In the current
## Table 1. Overview: Cancer types, autoantibodies detected, treatment and outcomes for CAR.

| Author            | Year   | Malignancy                  | Symptoms                                                                 | Autoantibodies          | Therapy                                    | Course                           |
|-------------------|--------|-----------------------------|--------------------------------------------------------------------------|--------------------------|--------------------------------------------|----------------------------------|
| Thirkill CE       | 1989   | Small-cell lung cancer      | Progressive loss of vision in both eyes 20/50 OD                         | No AB reported          | Plasmapheresis                             | No improvement                   |
|                   |        |                             | 20/100 OS                                                                 |                          |                                            |                                  |
| Ohnishi Y         | 1993   | Small-cell lung cancer      | Right eye with ring scotomas                                             | Recoverin Arresin       | Prednisone                                 | Mild improved vision             |
| Adamus G.         | 1998   | Endometrial cancer          | Loss of color vision in OS and blurring vision in OD. Visual acuity was 20/70 OD and counting fingers OS | Recoverin               | Methylprednisolone and immunomodulator drug | Visual acuity stabilized at hand motions |
| Whitcup SM        | 1998   | Benign Warthin tumor        | Progressive vision loss in both eyes                                      | Recoverin               | Systemic prednisone treatment             | Visual acuity diminished to no light perception |
|                   |        | of the left parotid gland   |                                                                          |                          |                                            |                                  |
| Yoon YH           | 1999   | Ovarian cancer              | Sense of darkness in both eyes 20/25 OD 20/30 OS                        | 3-enolase               | Prednisone p.o.                            | Visual acuity diminished to movement perception |
| Guy J             | 1999   | Pat. 1 Adenocarcinoma of the lung | Pat. 1 Rapid progressive visual loss Pat. 2 Blindness Pat. 3 Loss of vision in the right eye | Pat. 1 enolase Pat. 2 recoverin Pat. 3 enolase | Immunoglobulin i.v. | Pat. 1 Marked visual field improvement, visual acuity maintained at 20/50 OD and 20/40 OS. Pat. 2 No improvements Pat. 3 Improvements in visual field defects Improved retinal function |
|                   |        | Pat. 2 Adenocarcinoma of the cervix | Pat. 2 adenocarcinoma of the cervix Pat. 3 Adenocarcinoma of the pancreas |                          |                                            |                                  |
| Jacobsen D        | 2000   | Adenocarcinoma of the sigmoid colon | Progressive visual glare in both eyes                                  | No anti-retinal antibodies | No CAR-specific therapy | Visual acuity in follow up 20/50 OD, 20/40 OS |
| Raghunath A       | 2010   | Neuroendocrine carcinoma of the fallopian tube | Progressive worsening of vision in both eyes. Best visual acuity 20/25 OD, 20/60 OS Dimmed vision in both eyes with best corrected visual acuity 20/150 in both eyes | Carbonic anhydrase II 3-enolase No AB reported | No CAR-specific therapy | Vision deteriorated to light perception only |
| Cybulksa P        | 2011   | Clear cell carcinoma of the endometrium | Decreased vision, photopsias and nyctalopia in both eyes Progressive bilateral constriction of visual fields | 3-enolase 3-transducin | Serial intravitreal injections of triamcinolone | Vision preserved at 20/40 OD and 20/32 OS |
| Huynh N           | 2012   | Poorly differentiated squamous cell carcinoma of the lung | Decreased vision, photopsias and nyctalopia in both eyes Progressive bilateral constriction of visual fields | 3-enolase | Serial intravitreal injections of triamcinolone | No CAR-specific therapy |
| Chao D            | 2013   | Colon adenocarcinoma        | Decreased vision, photopsias and nyctalopia in both eyes Progressive bilateral constriction of visual fields | 3-enolase 3-transducin | Serial intravitreal injections of triamcinolone | No CAR-specific therapy |
| Author     | Year | Malignancy                        | Symptoms                                                                 | Autoantibodies       | Therapy                                           | Course                                                                 |
|------------|------|----------------------------------|--------------------------------------------------------------------------|----------------------|--------------------------------------------------|------------------------------------------------------------------------|
| Ogra S     | 2013 [22] | Carcinoid tumor of the small bowel | Progressive blurring of vision and nyctalopia in both eyes               | Carbonic anhydrase   | Prednisolone oral                                | Visual acuity improved 20/30 OS 20/25 OS Pat. died 1 month after diagnosis of CAR from small bowel obstruction |
| Michiyuki S | 2014 [23] | Small-cell lung carcinoma        | Progressive central vision loss OD and bilateral neuroretinitis         | Recoverin 3-enolase  | Optic disk swelling disappeared                   | Each eye with improvement in color vision                              |
| Turaka K   | 2014 [24] | Immature teratoma of the ovary   | Diminished vision in both eyes                                          | Arrestin             | Methylprednisolone i.v. along with i.v. immunoglobulins and rituximab, followed by systemic prednisolone and bivweekly intravenous immunoglobulins and rituximab for 3 months |                                                          |
| Nakamura T | 2015 [25] | Large cell neuroendocrine carcinoma of the lung | Rapid visual disorder in the dark, photophobia and impaired visual field. Visual acuities for both eyes 20/20 | No anti-retinal antibodies | No CAR-specific therapy                           | Visual function was stable                                             |
| Javaid Z   | 2015 [26] | Cervical intraepithelial neoplasia | Unilateral blurred vision, disturbance in color and night vision and central sparing with residual VF islands of OS | No AB reported      | Periodic steroid injections                       | Visual acuity remained stable                                           |
literature, there are only two reported cases of colon cancer patients suffering from CAR. These two reports have certain interesting similarities with the patient we are reporting [9, 10].

**Case Presentation**

We present the case of a 76-year-old man who experienced progressive loss of vision of both eyes over a time period of 18 months. The patient was otherwise healthy, had no regular medication and is a nonsmoker. The family history for retinal disorders was negative. During the 18 months period, the patient was sent to several ophthalmologists, but no definitive diagnosis could be established. Magnetic resonance imaging of the head did not reveal retrobulbar tumor and all the intraorbital structures as well as the chiasma opticum appeared to be normal. Finally, ophthalmologic evaluation at our institution was highly suspicious for CAR. The best corrected visual acuity was 0.8 for oculus dexter (−0.25/−0.75/176°) and 0.4 for oculus sinister (−1.25/150°). Full-field electroretinogram (ERG) did not show any amplitudes in A- and B-waves. Multifocal ERG revealed markedly attenuated bilateral responses in the central and paracentral region. Visually evoked potentials (VEP) showed substantially delayed amplitude and latency periods for both eyes and in Flicker 30 Hz ERG responses were also substantially reduced. Examination of the field of vision for both eyes showed central scotomas. The patient had no other eye or neurological symptoms. Empiric steroid therapy was instituted with 20 mg prednisone per day and antiretinal antibody analysis was performed (Oregon Health and Science University, Portland, OR, United States and MVZ Labor Volkmann, Karlsruhe, Germany). Western blot was negative for recoverin, α-enolase, transducin, and carbonic anhydrase II antibodies. Subsequent positron emission tomography–computed tomography (PET-CT) revealed a tumor mass in the ascending colon (Figs 1A and B). Colonoscopy showed an ulcerated adenocarcinoma occluding one-third of the bowels circumference, with a carcinoembryonic antigen (CEA) in normal range. The patient reported no weight loss, changes in bowel habits, melena, or hematochezia. In addition, family history for colon cancer was negative. Laparoscopic right-sided hemicolecotomy was performed and histological diagnosis confirmed an adenocarcinoma pT1, pN0 (0/12). On postoperative day two, emergency laparotomy was necessary due to an acute abdomen. Intraoperatively complete ischemia of the remaining colon was detected and subtotal colectomy with creation of an ileostomy had to be performed. Immediately after operation, CT scan angiography was carried out to exclude thrombotic events elsewhere. Tests for other diseases combined with coagulation disorders like systemic lupus erythematous and anti-phospholipid antibody syndrome were negative. Histology demonstrated acute ischemic enterocolitis on the basis of thrombosis of the arteries. Further recovery was uneventful. Finally, empiric steroid therapy was continued with 50 mg/day. Despite this therapy, the loss of vision was progressive. Three months after

![Figure 1](image-url). Yellow arrow: Mass in the ascending colon, diameter of 3.5 cm, with significantly increased glucose metabolism of SUVmax 8.9.
operation best corrected visual acuity was 0.6 for oculus dexter and 0.4 for oculus sinister. Full-field ERG showed no photopic or scotopic response. Multifocal ERG did not show any answer. Examination of the field of vision for the right eye showed an absolute scotoma central, infero-nasal and superior, and for the left eye, a concentric absolute scotoma, meaning that the patient has lost almost all his visual acuity.

**Discussion**

The current literature reveals only two other reports about CAR in association with colon cancer. These two patients presented with similar characteristics [9, 10]. As in these two cases, our patient neither had any gastrointestinal complaints nor colon cancer was diagnosed prior to CAR. Moreover, anti-retinal antibodies could not be detected with western blot, a finding also described by Jacobsen et al. They instead detected antibodies with immunocytochemical analysis, a method not available on a commercial basis in Europe. The patient’s serum in the report by Chao et al. was positive for α-enolase and transducin, but not for recoverin. One should be aware that patients with CAR tend to have a broad spectrum of anti-retinal antibodies often with up to six different antibodies in western blot [11]. Furthermore, we have to take into account that in up to 35% of CAR patients-specific antibodies cannot be detected [6, 9]. Our patient was diagnosed with stage I colon cancer and therefore no adjuvant treatment was necessary. Chao et al. and Jacobsen et al. reported a stage II and Duke C adenocarcinoma of the sigmoid colon, respectively. Both patients did receive adjuvant chemotherapy. Eight months after treatment anti-retinal antibodies could not be detected neither by western blot nor by immunocytochemistry in the patient reported by Jacobsen et al. and visual symptoms almost completely resolved. Chao et al. do not state if cancer treatment could improve visual symptoms and if the level of anti-retinal antibodies decreased after operation. Whether treatment of the causative cancer may delay or even stop progressive loss of vision is unclear.

Adamus et al. reported a case of a patient suffering from small-cell lung cancer in whom cancer treatment decreased the amount of antibodies, probably as a result of radiation therapy. As soon as the host’s immune system did recover, antibody levels again began to raise. The authors therefore speculate that cancer treatment itself does not improve vision [12].

Heckenlively and Ferreyra reported that prednisone can stabilize loss of vision in CAR patients, but has to be administered over a period of at least 1 year [11]. In the review by Rahimy and Sarraf, the authors described different treatment attempts showing mixed results. They reported on cases in which a combination of systemic corticosteroids either with plasmapheresis, intravenous immunoglobulin administration, or immunomodulatory therapies was used [8]. These sometimes promising results have to be taken with caution because the sample size varies between one and six patients, all suffering from different types of malignancies. It should be clearly stated that currently no evidence for the management of CAR is existing. Immunosuppressive therapy is the main element in treatment of CAR but visual prognosis remains poor and loss of vision might be inevitable [8].

In summary, early detection of paraneoplastic visual syndromes may lead to the diagnosis of the causative malignancy. Therefore, in case of unusual visual disorders, suspicion of an underlying malignancy should arise. Due to the simple fact that malignancies can occur in different organs, we strongly encourage that every clinician should be aware of the phenomenon of cancer-related retinopathy.

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**Conflict of Interest**

The authors declare no conflict of interest.

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