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CASE REPORT

Cancer-associated retinopathy as the leading symptom in colon cancer

Benjamin Weixler, Daniel Oertli & Christian Andreas Nebiker

Department of Surgery, University Hospital Basel, Basel, Switzerland

Correspondence
Christian Andreas Nebiker, Department of Surgery, University Hospital Basel, Spitalstrasse 21, 4031 Basel, Switzerland. Tel: +41 61 265 25 25; Fax: +41 61 265 73 56; E-mail: christian.nebiker@usb.ch

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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.

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 autoimmune antibodies directed against proteins in retinal photoreceptor cells [1]. The disease was first described in 1976. Recently, extraocular cancer was identified as the source of autoimmune antibody 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. 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 electroretinograms 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 [13]	Small-cell lung cancer	Progressive loss of vision in both eyes 20/50 OD 20/100 OS	No AB reported	Plasmapheresis	No improvement
Ohnishi Y 1993 [14]	Small-cell lung cancer	Right eye with ring scotomas	Recoverin Arrestin	Prednisone	Mild improved vision
Adamus G. 1998 [15]	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 [16]	Benign Warthin tumor of the left parotid gland	Progressive vision loss in both eyes	Recoverin	Systemic prednisone treatment	Visual acuity diminished to no light perception
Yoon YH 1999 [17]	Ovarian cancer	Sense of darkness in both eyes 20/25 OD 20/30 OS	α-enolase	Prednisolone p.o.	Visual acuity diminished to movement perception
Guy J 1999 [18]	Pat. 1 Adenocarcinoma of the lung Pat. 2 Adenocarcinoma of the cervix Pat. 3 Adenocarcinoma of the pancreas	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
Jacobsen D 2000 [9]	Adenocarcinoma of the sigmoid colon	Progressive visual glare in both eyes	No anti-retinal antibodies	No CAR-specific therapy	Improved retinal function
Raghunath A 2010 [19]	Neuroendocrine carcinoma of the fallopian tube	Progressive worsening of vision in both eyes. Best visual acuity 20/25 OD, 20/60 OS	Carbonic anhydrase II α-enolase	No CAR-specific therapy	Visual acuity in follow up 20/30 OD, 20/40 OS
Cybulska P 2011 [20]	Clear cell carcinoma of the endometrium	Dimmed vision in both eyes with best corrected visual acuity 20/150 in both eyes	No AB reported	Five sessions plasmapheresis and intravenous immunoglobulin plus intravitreal triamcinolone acetonide injection OS	Vision deteriorated to light perception only
Huynh N 2012 [21]	Poorly differentiated squamous cell carcinoma of the lung	Decreased vision, photopsias and nyctalopia in both eyes	α-enolase	Serial intravitreal injections of triamcinolone	Vision preserved at 20/40 OD and 20/32 OS
Chao D 2013 [10]	Colon adenocarcinoma	Progressive bilateral constriction of visual fields	α-enolase α-transducin	No CAR-specific therapy	

Table 1. Continued.

Author Year	Malignancy	Symptoms	Autoantibodies	Therapy	Course
		20/60 OD 20/25 OS			Visual acuity improved 20/30 OS 20/25 OS
Ogra S 2013 [22]	Carcinoid tumor of the small bowel	Progressive blurring of vision and nyctalopia in both eyes	Carbonic anhydrase II α-enolase	n/a	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 neuroretinits	Recoverin α-enolase CRMP-5	Prednisolone oral	Optic disk swelling disappeared
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 biweekly i ntravenous immunoglobulins and rituximab for 3 months	Each eye with improvement in color vision
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	Periocular 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 andydrase 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 hemicolectomy 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 erythematosus 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

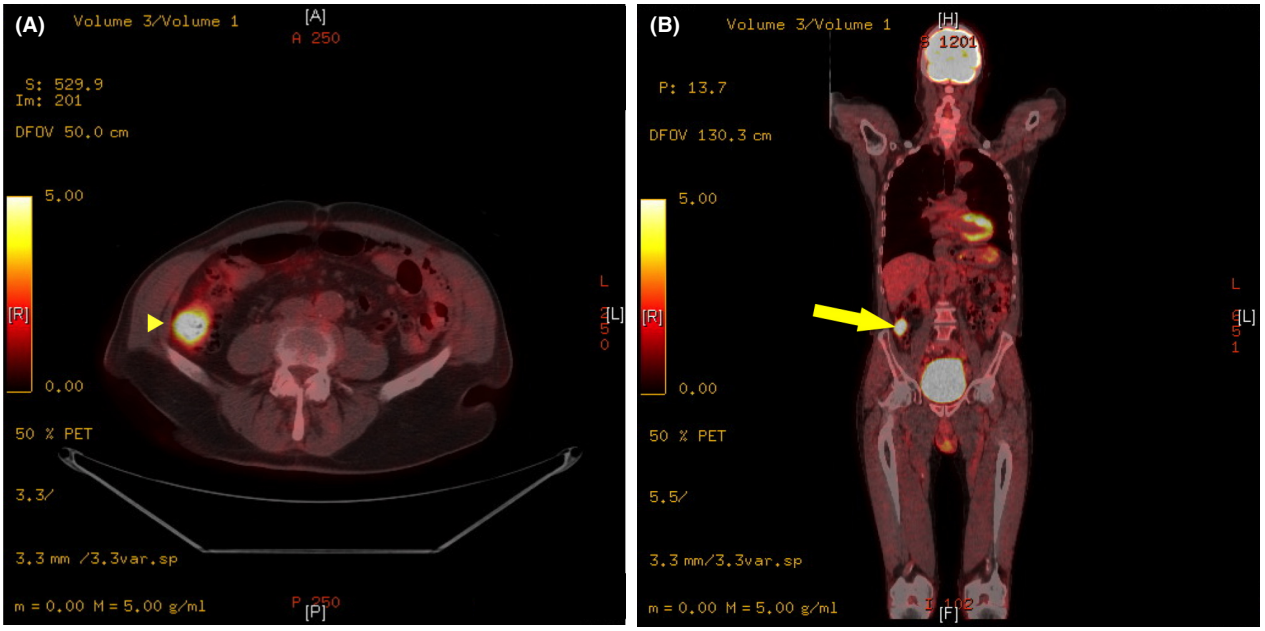

Figure 1. Yellow arrow: Mass in the ascending colon, diameter of 3.5 cm, with significantly increased glucose metabolism of SUVmax 8.9.

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.

All three authors contributed equally to conception, design, writing, revising, and final approval of the article.

Conflict of Interest

The authors declare no conflict of interest.

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