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Cancer associated retinopathy

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Cancer associated retinopathy (CAR) is one of the paraneoplastic syndromes. An important factor of its pathogenesis is the cross-reaction between the autoantibodies and retinal proteins such as recoverin. Recoverin, a calcium binding protein found in cones and rods, is responsible for the adaptation to light and darkness. Expression of recoverin in cancerous tissues stimulates the production of antirecoverin antibodies, which penetrate into retinal photoreceptor cells and cause misregulation of the phototransduction pathway and induction of apoptotic death. The triad of characteristic CAR symptoms includes photosensitivity, ring scotomatous visual field loss and attenuated arteriolae caliber. CAR may usually be observed before the diagnosis of cancer, but it is possible to recognize it after primary malignancy detection. Ophthalmologic examination, Goldmann perimetry, ERG, MERG, and antirecoverin titers are recommended in the course of diagnosis. CAR therapy includes not only primary carcinoma treatment, but also methods typically applied in autoimmune disorders, such as: systemic corticosteroid therapy, plasmapharesis and intravenous immunoglobulin.

Retinopatia paranowotworowa

Retinopatia paranowotworowa (CAR) zaliczana jest do zespołów paraneoplazmatycznych. Główną rolę w jej patogenezie odgrywa reakcja krzyżowa pomiędzy antygenami siatkówki, (jak rekoweryna), a przeciwciałami przeciw nim skierowanymi. Rekoweryna, proteina wiążąca wapń, jest komponentą czopków i pręcików. Odgrywa kluczową rolę w adaptacji do światła i ciemności. Ekspresja rekoweryny przez tkanki nowotworowe stymuluje produkcję przeciwciał anty-rekowerynowych. Przeciwciała te penetrują przez barierę krew-siatkówka i docierają do warstwy komórek światłoczułych, powodując zaburzenia procesu fototransdukcji i indukcję apoptozy. Nadwrażliwość na światło, mroczki pierścieniowe w polu widzenia, zwężenie naczyń tętniczych dna oka stanowi charakterystyczną triadę objawów CAR. Retinopatia paranowotworowa zwykle jest obserwowana przed wykryciem nowotworu, lecz znane są również doniesienia rozwinięcia objawów CAR jako następstwa pierwotnego procesu złośliwego. Bardzo pomocnymi i zalecanymi narzędziami diagnostycznym są: badanie okulistyczne, perymetria Goldmana, ERG (elektroretinografia), MERG (wieloogniskowa elektroretinografia), oznaczanie poziomu przeciwciał anty-rekowerynowych. Leczenie CAR zakłada nie tylko leczenie pierwotnego procesu nowotworowego, lecz również włączenie terapii stosowanych w leczeniu chorób autoimmunologicznych, czyli sterydoterapii ogólnej, plazmafarezy i wlewów dożylnych immunoglobulin.

Key words: cancer associated retinopathy, recoverin, anti-recoverin antibodies, retinal degeneration
Słowa klucze: retinopatia paranowotworowa, rekoweryna, przeciwciała anty-rekowerynowe, degeneracja siatkówki

Cancer associated retinopathy (CAR) belongs to paraneoplastic syndromes resulting in progressive loss of vision and clinical signs of retinal degeneration. The syndrome was first described by Sawyer and associates in 1976, and since that time many cases have been reported in association with various systemic malignances such as: small cell lung cancer, non-small cell lung cancer, breast cancer, invasive thymoma, uterine cervical cancer, endometrial cancer, lymphoma [1-11].

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The conjectural pathogenesis of cancer- associated retinopathy has been confirmed by *in vitro* and *in vivo* experiments using rat models [12,13]. CAR is considered to be an autoimmune disorder that involves cross-reaction between autoantibodies and retinal proteins such as recoverin. Recoverin is a 23 kD calcium binding protein found in rods and cones which plays a critical role in the visual sensory response. It plays a major role in light and dark adaptation by regulating rhodopsin phosphorylation and dephosphorylation in a calcium dependent manner. Recoverin gene was mapped to the human chromosome 17 by Murakami and associates in 1992 and localized by Mc Ginns and associates at position 17p13.1, which is a region containing a number of cancers related loci [14,15]. Production of antirecoverin antibodies

is stimulated by expression of recoverin in cancerous tissues. There is a hypothesis that single mutational event inactivates a copy of the p53 suppressor gene, which turns on the synthesis of recoverin protein. 23 kD epitopes synthesized outside the eye evoke production of circulating antibodies [15]. The antirecoverin antibodies penetrate into the retina's photoreceptor cells through the peripheral circulation and block recoverin function, causing misregulation of the phototransduction pathway, and induction of apoptotic death. It is proved that antirecoverin antibodies are the inducers of retinal cell apoptosis via the caspase 9- and caspase 3- dependent way [16]. However, it has to be noticed that not only antirecoverin antibodies can be detected in serum of patients with CAR but also antibodies against enolase, 34 kD, 46 kD, 60 kD, 65 kD or 70 kD protein [7,10,17-19].

The main manifestation of CAR is rapid, progressive bilateral visual loss, although some patients initially present with only one affected eye. Complaints refer to both rod and cone dysfunction. Clinical problems associated with cone dysfunction include photosensitivity, abnormal visual acuity, color vision abnormalities as well as central scotomas, and an abnormal cone- mediate electroretinogram (ERG). Clinical problems associated with rod dysfunction include nyctalopia, prolonged dark adaptation, peripheral or ring scotomas and an abnormal rod-mediated ERG [4, 20].

The results of ophthalmologic examination often show a triad of symptoms: photosensitivity, ring scotomatous visual field loss and attenuated retinal arteriole calibre [22]. Fundus finding in-patients are not specific, and could reveal normal fundus examination, optic disc pallor, narrowing of the retinal arterioles and the retinal pigment epithelium changes [4,18, 20, 22].

Fluorescein angiography may demonstrate progressive diminution of peripheral retinal blood flow, slow perfusion and staining of venules [3]. Electrooculography presents reduced light peak/dark trough ratio [23]. Electroretinography (ERG), which is helpful in most cases, shows reduction of amplitudes in cone and rod-mediated response. Multifocal electroretinography (MERG) may be useful in cases where the visual field loss is localized. In some cases MERG was used to quantitative the loss of electrical activity and to correlate this to Goldmann perimetry. Laboratory investigation to detect antirecoverin antibodies in serum is recommended to establish diagnosis [6].

Patients with CAR require treatment for primary carcinoma. However, it is not uncommon for CAR patients to develop visual loss before detecting malignancy. Rising antibody titers may be considered as indication for therapy. A gold standard for treatment does not exist. Typical treatment used in autoimmune disorders such as: systemic corticosteroid therapy, plasmapheresis, and intravenous immunoglobulin (IVIG) is recommended [18, 24-26]. More than half of the patients respond with visual improvement and antibody titers reduced to normal after Prednisone. Combined therapy with oral corticosteroids and plasmapheresis may result in a recovery of vision, as well as IVIG, which appear to provide beneficial effects. Patients with CAR treated both with Prednisone and plasmapheresis without response had a dramatic response to IVIG [26]. The effective methods of treatments are still a subject of many researches.

CAR is being increasingly recognized over the last 27 years, since Sawyer's discovery. Similar to other paraneoplastic disorders, cancer- associated retinopathy is most often associated with underlying small-cell carcinoma of the lung although it has been report to accompany a number of other malignancies.

CAR is usually observed before the diagnosis of cancer, as was reported in most cases of small-sell lung carcinoma, invasive thymoma, and uterine cervical cancer [1-3, 7, 11]. In a few cases it has been recognized after the detection of the primary malignancy. A good example of cancer-associated retinopathy developing after carcinoma detection is offered by the case of a 65- year-old man who underwent resection of adenocarcinoma of the lung. Ten months later he complained of deterioration of vision [4]. A similar situation was reported in two patients with breast cancer – both presenting with paraneoplastic retinopathy. However, in these cases immunology tests showed antiretinal antibodies, which failed to react with the 23 kD retinal antigen recoverin [5]. Sometimes CAR detection in breast cancer can be more complicated. Sadowski et al. report the case of an 84-year-old patient with breast and colon cancer, who complained of a decrease in visual acuity after treatment with low-dose antiestrogens. Side effects of tamoxifene were suspected, but after fundus and visual field examination and ERG & MERG the paraneoplastic syndrome was diagnosed [6].

CAR should focus not only the attention of the ophthalmologists, but also that of the oncologist. If a patient with cancer complains of "dimming" of vision with missing areas of the visual field, central and cecocentral scotomas, hemeralopia, photopsias, night blindness, loss of color vision and/or photosensitivity CAR must always be considered. Laboratory examination for CAR is necessary in all such cases. By way of analogy in-patients presenting ocular CAR-like symptoms ought to be diagnosed for cancer.

Detecting and monitoring antiretina titers can be useful in patient management, especially in order to estimate retinal function. Reducing the antibody response carries a potential risk of increasing cancer mortality, however those are only suspicions, and not clinically documented examples.

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