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LETTER TO THE EDITOR

A new anti-outer plexiform layer antibody in autoimmune retinopathy?

Un nouvel anticorps dirigé contre la couche plexiforme externe dans la rétinopathie auto-immune?

Introduction

Paraneoplastic syndromes (PNS) are a diverse group of clinical conditions that can occur in cancer patients. These syndromes arise from mechanisms unrelated to metastasis, nutritional deficiencies, infections, blood clotting disorders, or cancer treatment side effects. Symptoms can manifest in various systems, including the endocrine, neuromuscular, cardiovascular, skin, blood, gastrointestinal, kidney, and other organs. Most PNS are triggered by immune responses elicited by proteins expressed by the tumor. These immune responses are often mediated by antibodies that react with both the tumor and the nervous system, including the retina [1]. Autoimmune retinopathy (AIR) and cancer-associated retinopathy (CAR) are two sides of the same coin. They both are classified under the broad spectrum of autoimmune retinopathy, but AIR may be either paraneoplastic (CAR) or non-paraneoplastic (npAIR) [2]. The diagnostic of such a syndrome may be difficult, and often late. The diagnostic approach is mainly based on the clinical presentation, the presence of personal or familial history of cancer and autoimmune diseases, the results of electrophysiology.

Two types of retinopathy are linked to cancer: cancer-associated retinopathy (CAR) and melanoma-associated retinopathy (MAR). CAR, first described in 1976, is relatively rare with fewer than 100 reported cases [3]. MAR, first described in 1988, is even less common. CAR is most often associated with small-cell lung cancer but can also occur with other cancers like breast and endometrial. MAR is exclusively linked to cutaneous malignant melanoma [4]. Unlike CAR, which often precedes cancer diagnosis, MAR typically presents after melanoma diagnosis, often at a metastatic stage. Both CAR and MAR share similar clinical presentations, including bilateral vision loss, light flashes, night blindness, and light sensitivity. Eye exams may reveal abnormal visual fields and normal-appearing fundi in early stages, along with color vision impairment and prolonged dark adaptation.

The historical and first discovery of antiretinal antibody was the 23 kDa antibodies against RECOVERIN protein [5]. Autoimmune studies characterized further anti-retina antibodies (anti-carbonic anhydrase II, anti-GAPDH, etc.) [6]. All known antibodies target the outer layers of the retina, either the whole outer layer or specifically the outer nuclear layer. The only antibodies marking the outer plexiform layer in AIR are anti-recoverin antibodies; however, they also target the outer nuclear layer. So far, none of the well-known antibodies target specifically the outer plexiform layer [6].

It is within this context that we present, to our knowledge, the first case of autoimmune retinopathy with a specific antibody targeting the outer plexiform layer.

Case presentation

Clinical presentation

A 64-year-old woman complained of a vision decrease over the last nine months. She had a personal history of high blood pressure, severe erosive rheumatoid arthritis diagnosed in 2009 without treatment for eight years (by choice of the patient), and suspicion of autoimmune hepatitis. In her family history, her two sisters, her mother, and her mother's niece had breast cancer at the age of 50. Her main complaint was bilateral visual haze, both nearby and far away, painless and without nyctalopia. The patient described photophobia and some photopsia, especially when she woke up. Previous follow-ups failed to find an explanation.

Ophthalmological examination was considered normal and cerebral MRI was unremarkable with no lesion on the optic nerves in the chiasmatic part or further posterior visual pathways. She was then referred to our neuro-ophthalmology unit. At this time, the best corrected visual acuity was finger counting at 1 m. Both eyes had a correct intraocular pressure. The fundus examination did not reveal any abnormality. There were no retinal or papillary abnormalities (Figs. 1B and 1D). Spectral-domain OCT pointed out an abnormal thinning of the outer nuclear layer (Fig. 1A). Usually, the nuclear layer is thicker than the plexiform layer, but here the ratio is reversed. Multiple hypocyanescent dots were revealed on retinal angiography (Fig. 1C). On visual evoked potentials (ISCEV method with METROVISION device), both flash and checkerboard patterns did not have any detectable response. Global electroretinogram (ISCEV method with METROVISION device) pointed out an extinguished response of both sides: A and B waves were severely reduced in rod, mixed, cone, and flickers responses (Fig. 1E). So far, we could conclude with an advanced and bilateral rod-cone dystrophy.

Immunological study

In front of subacute retinopathy in a woman, in her sixties, without other signs of retinitis pigmentosa, it was reasonable to extend the research. The extension assessment including a whole body tomodensitometry, a whole-body PET

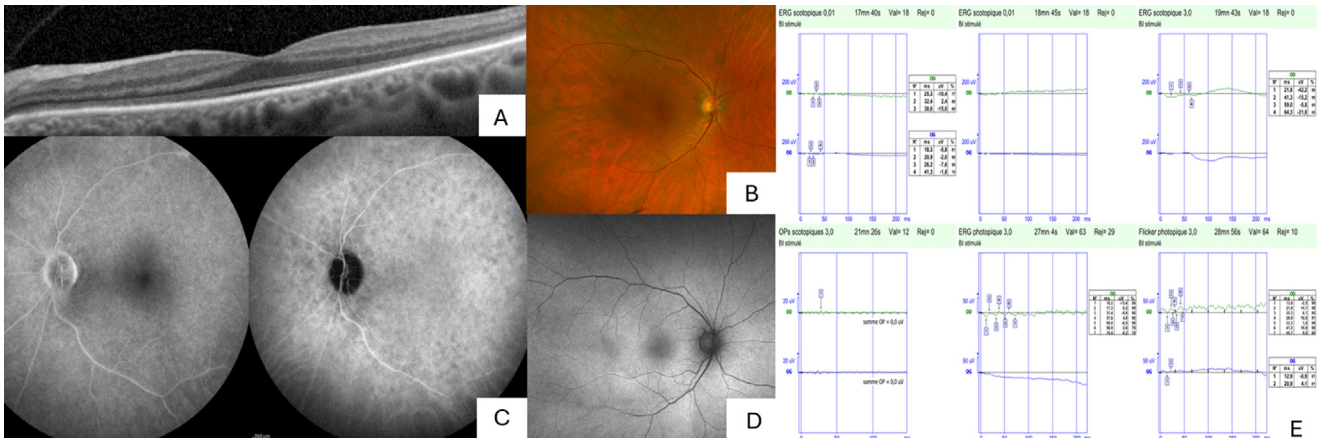

Figure 1. A: spectral domain OCT; B: fundus examination in retinal photography without anomaly, showing a normocolored and sharp optic disc; C: angiography including a fluorescein image on the left and an indocyanine image on the right after 15 minutes of injection; D: autofluorescence retinal photography; E: electroretinogram: scotopic conditions in the first four traces, photopic conditions in the last two traces.

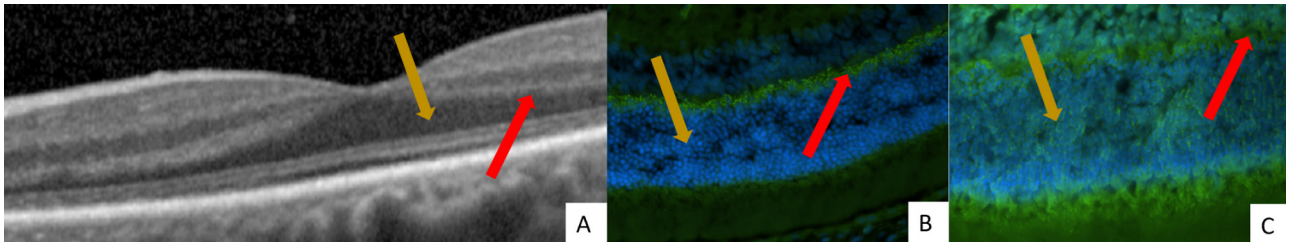

Figure 2. A: spectral-domain OCT showing a reduction of the outer nuclear layer. The yellow arrow indicates the inner nuclear layer, while the red arrow points to the inner plexiform layer; B: patient's serum applied to monkey retina using indirect immunofluorescence with a DAPI staining protocol, showing specific fixation of the outer plexiform layer (red arrow). Only the plexiform layer exhibits immunofluorescent labeling; C: recoverin antibodies detected via indirect immunofluorescence on monkey retina with DAPI staining. There is non-specific binding involving both the inner nuclear and inner plexiform layers.

tomodensitometry, an abdominal ultrasound and a mammography, did not find any suspect lesion. Blood immunoglobulin electrophoresis had an abnormal elevation of total IgG (140%) due to an abnormal IgG4 spike. Infectious serology, including HIV, hepatitis C, and hepatitis B, were negative. Lumbar puncture was blood contaminated and showed 28 white cells (38% lymphocytes, 67% neutrophils), 15,000 red cells, elevated protein level of 1.23 g/l with normal glycorrhachia. CSF analysis revealed an IgG4 spike concordant with serum. There was no suspect cell and a large infectious screening (bioFire film array) was negative. So did antineuronal antibodies panels (including anti-Hu, anti-CV2, anti-Ri, anti-GAD, and anti-recoverin antibodies) in serum and cerebrospinal fluid (CSF). However, the patient's serum and CSF were studied by indirect immunofluorescence on the rat's eyes and monkey's retina. The patterns were atypical with an intense and specific labeling of the outer plexiform layer (Fig. 2).

Discussion

The anti-recoverin antibody, a major cause of autoimmune retinopathy, targets all the outer retinal layers indiscriminately in indirect immunofluorescence [7]. The second most well known antibody, targeting alpha-enolase, in turn targets ganglion cells as well as Müller's cells and photoreceptors [8]. In our patient, the IgG4 marking is intense and specific to this axonal and dendritic layer, without anti-recoverin antibodies. Up to date, no antibodies are as specific. This suggests the presence of an unknown antibody exclusively targeting, for the first time, the outer plexiform layer.

MAR was not considered in this case based on multiple arguments. Apart from the fact that no melanoma was detected, the electroretinogram responses do not correspond to this pathology (the usual preservation of the a-wave in MAR). The antibodies found typically target bipolar cells [9].

No cancer has been diagnosed; however, few results highlight that autoimmune retinopathy occurs far before the diagnosis of cancer, up to five or six years [10]. Some cancers are keener than others in causing autoimmune retinopathy. Non-small cell lung carcinoma and breast cancer seem to be implicated, like in most paraneoplastic syndromes. It may explain that in our patient, no cancer has been found so far.

Conclusion

To conclude, this 64-year-old patient presented with many criteria to suspect an autoimmune retinopathy with atypical antibodies targeting only the outer plexiform layer. Some arguments head towards the cancer-associated form: an important familial history and an active smoking history. However, the autoimmune form may be suspected by

the presence of atypical IgG4 and the presence of previous autoimmune diseases such as severe rheumatoid arthritis and autoimmune hepatitis. The medical team decided, after a multidisciplinary discussion, to treat the patient with rituximab, targeting both rheumatoid arthritis and autoimmune retinopathy. Her follow-up will probably help us to specify her pathology, but after several months, her retinopathy seems to be stabilized and no neoplasia was found.

Disclosure of interest

The authors declare that they have no competing interest.

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