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Significance of Anti-retinal Autoantibodies in Cancer-associated Retinopathy with Gynecological Cancers

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Abstract

Background: The presence of autoantibodies (AAbs) is the primary serological indicator of autoimmunity. Cancer-associated retinopathy (CAR) is associated with AAbs and different types of cancer. The goal of the study was to examine the profile of serum autoantibodies in women with gynecological cancers with and without paraneoplastic visual manifestation.

Methods: Retrospective studies of a cohort of 46 women with symptoms of CAR and gynecological tumors, including endometrial, cervical, ovarian, and fallopian tubes, 111 women with similar tumors without symptoms of CAR, and 60 age-matched healthy controls. Presence of serum AAbs and the identity of targeted antigens were performed by western blotting and their significance was evaluated using an Fisher's exact test.

Results: The patients with gynecological CAR had the highest proportion of seropositivity (80%), followed by patients with gynecological cancers without CAR (61%) and healthy controls (58%). Differences in recognition frequencies were found for 17 antigens and 5 retinal antigens were frequently targeted: enolase, aldolase C, carbonic anhydrase II, recoverin and GAPDH. The occurrence of anti-glycolytic enzymes was 2-3 times more frequent in CAR and cancer patients than healthy controls. Anti-recoverin AAbs were prevalent in endometrial CAR. Anti-CAII antibodies were not significantly different between groups of women. In this cohort, cancer was diagnosed before the onset of retinopathy with latency from 2 months to 30 years. The discovery of the ovarian and endometrial cancers and manifestation of visual problems often coincided but Fallopian tube carcinoma was found after visual onset.

Conclusion: New retinal targets were identified for gynecological CAR. Each gynecological-CAR has its own autoantibody profile different from non-CAR profile, implying that a complex autoantibody signature may be more predictable for diagnosis than a singular AAb. Specific anti-retinal AAbs were most prevalent in women with CAR but their profiles were not fully distinguished from cancer controls.

Keywords: Autoantibodies; Autoimmune retinopathy; Cancer; Autoantigen; Antibody profiling; Retina; Paraneoplastic

Abbreviations: AAbs: Autoantibodies; CAR: Cancer Associated Retinopathy; GAPDH: Glyceraldehyde 3-Phosphate Dehydrogenase; CAII: Carbonic Anhydrase II

Introduction

Visual paraneoplastic syndromes associated with gynecologic malignancies include cancer-associated retinopathy (CAR) and diffuse uveal melanocytic proliferation (BDUMP) [1]. Both syndromes related to gynecological malignancies are rare. It has been hypothesized that in CAR visual loss occurs due to the presence of autoantibodies (AAbs) specific to tumor antigens that cross-react with certain proteins existing in retinal photoreceptor cells [2]. The published case reports on gynecological cancers associated with retinopathy, including an endometroid ovarian carcinoma, endometrial adenocarcinoma, undifferentiated cervical reserve cell carcinoma, ovarian papillary serous cystadenocarcinoma, primary epithelial ovarian cancers, except fallopian tube carcinoma have not reported on associated autoantibodies [3-5]. One case of CAR associated with primary ovarian carcinoma was linked with serum AAbs against anti-carbonic anhydrase II [6]. However, the presence of AAbs is the primary serological indicator of autoimmunity and should be studied to fully understand autoimmune-mediated pathogenic process in those diseases.

The presence of serum AAbs is thought to be the consequence of breakdown of immunological tolerance however AAbs are not exclusive of CAR syndrome. AAbs generated against self-antigens are also found in cancer during massive tissue damage but then of importance, they are also produced in healthy subjects without cancer or CAR and in the complete absence of known external antigenic stimulation [7]. The potential roles of those natural antibodies could be prognostic and diagnostic in the monitoring of levels of natural IgM antibodies to specific apoptosis-associated antigens to better predict future clinical manifestations [8]. However, their role in initiation of autoimmunity is unclear [9].

Anti-retinal AAbs that have been reported in CAR are diverse, cross-react with cancer antigens and often represent cytoplasmic proteins, including the 23-kDa recoverin and the 46-kDa α-enolase proteins [10]. In neurological paraneoplastic syndromes, the humoral response against CNS intracellular proteins was usually correlated with poor prognosis, while AAbs reactive with membrane components

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appeared to have a better prognosis [11]. Moreover, the repertoire of AAbs found in cancer patients partly coincides with diverse repertoire of AAbs found in autoimmune diseases [12]. Some cancer patients develop AAbs that recognize new antigens whose expression is restricted to tumor cells, at the same time most tumor-associated AAbs can also be detected in CAR patients, e.g. recoverin [13].

Retinal autoantigens associated with gynecological-CAR have not been studied because this is an uncommon syndrome. AAbs are likely made as the initial body defense against the growing tumor, and when they cross-react with retinal antigens this may lead to CAR. Taking into consideration the presence of anti-retinal AAbs in both health and disease, the goal of this study was to examine the repertoire of serum anti-retinal AAbs and identify distinct autoantibody biomarkers in CAR patients with different types of gynecological malignancies in comparison to healthy women and to patients with similar cancers but without visual symptoms of CAR at the time of testing. We hypothesized that AAbs found in CAR patients might have unique disease-specific profiles that allow distinguishing between controls and cancer patients.

Methods

Patients

Sera were obtained from repositories of the MD Anderson Cancer Center and Oregon Health and Science University (OHSU). The studies were approved by the IRB from OHSU and MD Anderson Cancer Center and our research adhered to the tenets of the Declaration of Helsinki and is in accordance with HIPAA regulations. The inclusion criteria for CAR diagnosis were unexplained and progressive visual loss, present photopsia, nyctalopia, abnormal ERG, progressive worsening of visual acuity and visual fields, ring scotomas, suspected or diagnosed cancer. Patients that have known genetic (familial) causes, ocular infection, ocular trauma, intraocular surgery (other than cataract surgery), drug toxicity, retinal detachment, and typical age-related macular degeneration were excluded from the studies. The subjects with symptoms of CAR represented 45 Caucasian women and 1 Asian woman of an average age of 59±12.5 ranging from 25 to 89 years old and gynecological cancers, including endometrial, uterine, cervical, ovarian, and fallopian tubes cancers. Table 1 presents demographics of our cohort. Women with signs of CAR presented with progressive loss of vision with photopsia (4 patients), reduced to undetectable responses in ERG (19 patients), reduced visual acuity from 20/50 to complete loss (22 patients), color impairment (10 patients), constriction of visual fields, ring or central scotomas (17 patients), and night blindness (7 patients). In the ovarian cancer-CAR group, diffuse bilateral melanocytic proliferation (BDUMP) was found in 2 patients and another 2 patients had melanoma after ovarian cancer was detected. Ocular inflammatory processes like uveitis, vitritis, cells in the vitreous and vasculitis were associated with CAR in 9 patients. Also sera from 111 patients with related uterine and ovarian cancers without symptoms of CAR and 60 sera from age-matched healthy women were included for comparison.

Cancer	CAR patients n=46, average age 59.4±16.1	Cancer patients n=111, average age 60	Healthy subjects n=60, average age 60.4 ± 7.4
	Patients with anti-retinal autoantibodies to total subjects		
Endometrial	6/6	18/30	n/a
Uterine	6/9	0	n/a
Cervical	11/14	20/30	n/a
Ovarian	12/15	18/30	n/a
Fallopian tube	2/2	12/21	n/a
Total Seropositive	37/46 (80%)	68/111 (61%)	35/60 (58%)

N/A not applicable.

Table 1: Seropositivity in study groups.

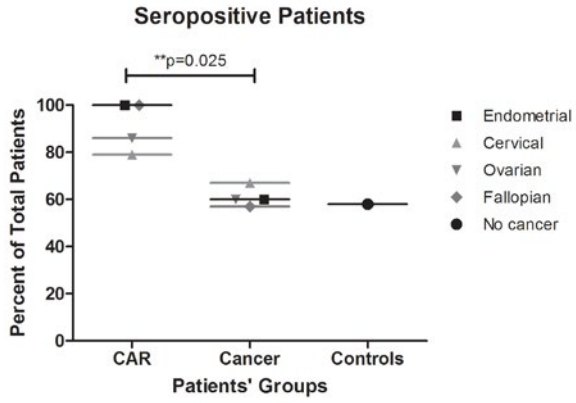

Figure 1: Incidence of anti-retinal autoantibodies in 3 groups of patients: CAR group - patients with symptoms of cancer associated retinopathy, Cancer group - patients with gynecological cancers without visual problems, Control group - healthy subjects. The presence of autoantibodies against human retinal proteins was investigated in the following gynecological cancers: endometrial, cervical, ovarian, and fallopian tube. The graph represents percent of seropositive patients within each group compared to controls.

Western blotting

Sera were tested for the presence of anti-retinal autoantibodies by western blotting as published before [10]. Briefly, human retinal protein extract was separated by SDS-gel electrophoresis using 10% Criterion gels (Bio-Rad) followed by transfer to a PVDF membrane using semi-dry apparatus. Individual blots were then immunostained with 1:25 diluted patient's serum followed by incubation with anti-human IgG (H and L chain) conjugated to alkaline phosphatase (Invitrogen). The immune reaction was then developed using AP substrate (Invitrogen). As positive controls we used human anti-enolase reference serum (1:100), rat anti-enolase Enol-1 MAb (1:2000), and rabbit anti-recoverin antiserum (1:50,000). A negative control contained secondary antibodies only.

Statistical analysis

The P value was calculated from an Fisher's exact test. The differences in presence of antigens between the group with and without symptoms of CAR were tested by the Fisher's exact test. All computations were computed using the R project for Statistical Computing (http://www.r-project.org).

Results

To investigate the occurrence of anti-retinal AAbs in gynecological CAR we analyzed serum samples from three groups for comparison: (i) CAR group - women with cancer presented with ocular symptoms of CAR, n=46; (ii) non-CAR group - women with cancer without clinical symptoms of CAR, n=111; and (iii) control group -age-matched healthy women subjects, n=60. CAR was diagnosed in patients with gynecological cancers, such as uterine, endometrial, cervical, ovarian, and fallopian tube and sera of those patients were tested for the presence of autoantibodies against human retinal proteins. Then the identity of antibody reactive proteins was confirmed by additional western blotting using purified targeted proteins on the blot. Our results showed that specific anti-retinal AAbs occurred in CAR patients as well as in

cancer patients without the visual symptoms of CAR but at a different percentage. As is presented in Figure 1 and Table 1 the patients with gynecological malignancies associated with CAR had the highest proportion of seropositivity (80%) than patients with gynecological cancers without CAR (61%) and healthy female subjects (58%). The analysis using the exact Fisher test revealed the statistical significance between CAR and non-CAR groups (p=0.025) and CAR and control groups (p=0.021).

All three groups of patients showed heterogeneity in their retinal protein recognition for 17 antigens but were focused on 5 proteins: enolase (46-kDa), aldolase C (40-kDa), carbonic anhydrase II (30-kDa), recoverin (23-kDa) and GAPDH (36-kDa) as more frequently targeted than other retinal proteins (Figure 2). While AAbs against those retinal proteins were present in each of gynecological cancer groups their prevalence was different. As demonstrated in Figure 2 an overlap occurs among specific AAbs between groups of patients but their incidence varied. For example, the incidence of AAbs specific to enolase, aldolase, and GAPDH in controls subjects was significantly lower than in patients with cancer (Figure 3). Anti-α-enolase AAbs were detected in 35% cancer patients and 13% control subjects (p=0.006, Fisher's exact test). Anti-GAPDH antibodies were significantly higher in patients with CAR (13%) compared to 3% patients without retinopathy (p=0.028, Fisher exact test). Overall anti-carbonic anhydrase II (CAII) AAbs were not significantly different between groups (p=0.682, exact Fisher's test) and were detected in 13% CAR patients, 14% cancer patients and 18% healthy women and but there were greater differences within the individual cancer groups (Figure 2). Two patients with bilateral diffuse uveal melanocytic proliferation (BDUMP) had AAbs against 35-kDa and 46-kDa proteins (one patient) and 30-kDa, 50-kDa and 70-kDa proteins (second patient).

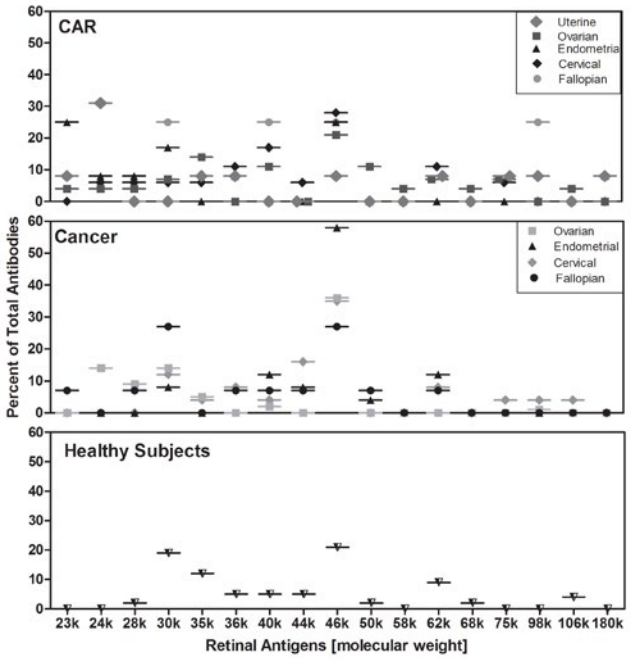

Figure 2: Distribution of specific retinal autoantibodies according to the retinal proteins targeted by autoantibodies within each group of patients. X-axis shows retinal proteins marked by their molecular weight (k=1000). Graph represents the percent of antibodies reacting with each protein within a group.

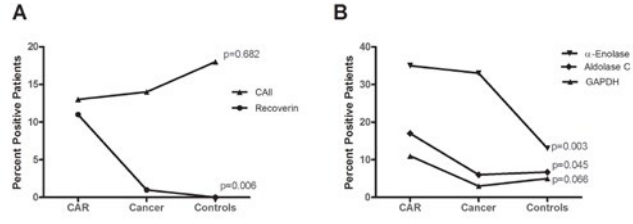

Figure 3: Trends in autoantibody recognition of five retinal proteins in three groups of patients. (A) Comparison of anti-recoverin antibodies to anti-carbonic anhydrase II protein (CAII) shows an increase in anti-recoverin antibodies in CAR patients compared to controls and no significant change in anti-CAII AAbs between groups. (B) Comparison of autoantibodies against glycolytic proteins, including α-enolase, aldolase C and glyceraldehyde 3-phosphate dehydrogenase (GAPDH) in three groups shows a significant increase in those antibodies in CAR patients. P values were calculated by the Fisher's exact test.

We observed a trend in the AAb incidence between the groups tested. Our analysis showed that AAbs against glycolytic enzymes such as enolase, aldolase, GAPDH occurred almost 3 times more frequent in CAR patients than healthy individuals (Figure 3). Figure 4 shows anti-retinal AAbs profiles in CAR and cancer without signs of CAR at the time of testing. Remarkably, AAbs against glycolytic enzymes were common, suggesting that they were generated in response to the upregulation of those proteins during intensive glycolysis in carcinogenesis, which in effect triggered abnormal antibody production [14]. It has been reported that the increased expression of α-enolase (ENO1) on tumor cells is strictly related with the malignancy of those cells and their high metastatic ability [15,16]. It is important to point out that in this cohort, all endometrial-CAR patients had metastatic tumor and had significantly increased AAbs against enolase (p=0.00038) as well as recoverin (p= 0.00014), which make this a distinct antibody signature from non-CAR profile.

Although we observed an overlap in retinal protein recognition in all groups among different autoantibodies each gynecological CAR had its own antibody signature (Figure 4). The striking difference occurred in anti-recoverin AAbs that were present in CAR and almost completely absent in non-CAR women (p=0.00014, Fisher's exact test). Anti-recoverin AAbs were present in 50% of endometrial-CAR, 11% uterus-CAR and 7% ovarian-CAR in contrast to none present in healthy subject sera. In the cancer group, only one woman with neuroendocrine fallopian tube cancer out of 21 subjects had anti-recoverin AAbs (4.7%). This retinal calcium-binding protein has been recognized as a CAR antigen, which its aberrant expression is capable of triggering the generation of specific AAbs in patients with malignant tumors and the subsequent development of the paraneoplastic syndrome, cancer-associated retinopathy [10,17,18]. In the case of fallopian tube cancer without retinopathy, 12 out of 21 patients were seropositive with 19% of anti-enolase and 38% of anti-CAII AAbs. Because we had only 2 patients with this rare fallopian-CAR it is not possible to conclude about the incidence of AAbs in CAR in comparison to other groups. By combining antigens to a set of biomarkers, specificity and sensitivity of a disease signature increase. The maximum observed sensitivities with one marker were 0.4, 0.5 and 0.38 for ovarian, endometrium and cervix cancer, respectively. The sensitivities were 0.53 with 2 makers (30-kDa and 46-kDa), 1.00 with 3 markers (23-kDa, 30-kDa, 46-kDa), and 0.64 with 4 markers (30-kDa, 35-kDa, 40-kDa, and 45-kDa) for each cancer.

To determine whether the manifestation of visual symptoms is correlated with the time of cancer diagnosis, we examined the latency time from the cancer diagnosis to the discovery of CAR and the related antibodies. In this cohort, cancer was diagnosed in these women before

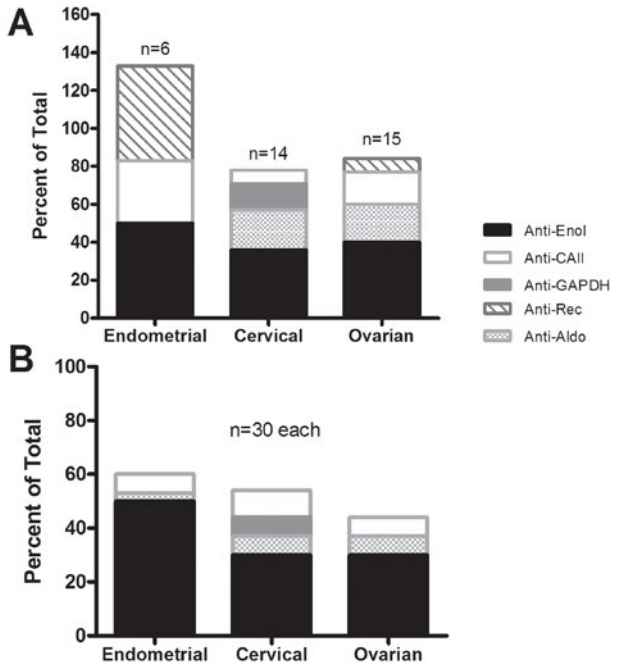

Figure 4: Antibody signatures for five distinct retinal proteins in sera of two groups of patients: (A) CAR group - patients with symptoms of cancer associated retinopathy and (B) Cancer group - patients with gynecological cancers without visual problems divided by the cancer type (endometrial, cervical, and ovarian). Stocked bars show the percent of positive AAbs within each group.

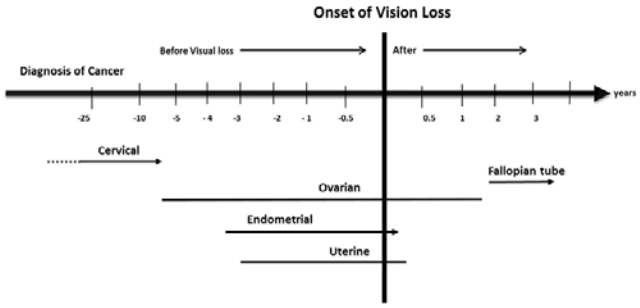

Figure 5: Latency time of finding cancer, onset of visual loss, and detection of anti-retinal autoantibodies in patients with CAR associated with different gynecological cancers. Note that cancer was often diagnosed before diagnosis of retinopathy with latency from 2 months to 30 years with the longest interval in cervical malignancies (on average 21 years). The diagnosis of the ovarian and endometrial cancers and retinopathy often coincided and visual symptoms preceded diagnosis of the fallopian tube cancer.

diagnosis CAR with latency time from 2 months to 30 years with the longest interval in cervical malignancies (on average 21 years). Such a long interval between the diagnoses of primary cancer in women with cervical cancers suggests that sudden manifestation of visual problems about 20 years later could be related to other problems although undiagnosed malignant tumor cannot be excluded. On the other hand, the diagnosis of the ovarian and endometrial cancers and findings of CAR and autoantibodies often closely coincided in those patients and in some cases preceded the diagnosis of cancer by few months (Figure 5). In addition, the ocular symptoms preceded the diagnosis fallopian tube carcinoma by 2-3 years in both of our patients.

Discussion

Our studies showed that anti-retinal AAbs were present in women with gynecologic malignancies with and without clinical symptoms of CAR as well as in healthy women controls however women with gynecologic-CAR had a higher proportion of seropositivity. Five retinal proteins were targeted by AAbs in CAR more frequently and these were: carbonic anhydrase II, recoverin, α-enolase, aldolase C, and GAPDH. A high incidence of AAbs specific to α-enolase and other glycolytic enzymes in our patients suggests their causal relationship to CAR. The production of some of those autoantibodies may be related to metabolism of cancer cells that up-regulate a number of different pathways to keep up with demands for rapidly dividing cells [16]. Glycolysis is one such pathway, which is up-regulated in transformed cells regardless of the presence or absence of oxygen. Studies showed that the overexpression of aldolase C by tumor cells was an indication of human endometrial cancer, like other tumor types, this cancer survival depends on glycolysis for its energy supply [19]. Other studies suggested that enolase might be a useful target for the therapy of cancer through the development of anti-enolase antibody-based therapy. However, an increased presence of anti-enolase antibodies could be harmful to the retina and could result in retinal degeneration [20,21]. It has been demonstrated that all of these glycolytic enzymes (NSE, NNE, aldolase C, Pyruvate kinase M1) are also membrane bound and expressed on the surface of neuronal cells [22,23]. Enolase existsas a monomer and also as dimers, including both α-γ enolase dimer on the membrane surface [24]. These are multifunctional proteins that are all expressed intracellularly and on the cell surface and such accessibility to these proteins on the membrane can stimulate the production of AAbs [25].

Some patients with CAR have AAbs against a single retinal protein, e.g. recoverin, and such AAbs are considered to be specific for this entity. However, our current study shows that more than one antibody specificities may exist in a single cancer patient and even in healthy subject in a lower level. The antibody profile may be a potential signature of specific malignancy and among other factors can be considered as a diagnostic tool of CAR syndrome. Of note, in some patients, visual symptoms of CAR may be present without the finding of anti-retinal autoantibodies, possible because AAbs can have also tumor suppressing effects through the generation of immune complexes thus they may not be detected in the serum [26]. Overall CAR sera had higher incidence of AAbs and each gynecological CAR had anti-retinal autoantibodies against more than one antigen, suggesting a trend towards an antibody signature associated with a specific gynecologic tumor. Unfortunately, we do not have large enough numbers to make definitive statements about this. Usefulness of anti-retinal AAbs in recognition of the underlying tumor is also important, e.g. anti-recoverin AAbs were frequent in endometrial CAR but absent in healthy subjects. The sensitivity can be improved by combining antigens to a set of biomarkers to increase specificity and sensitivity of a disease signature. For example, the maximum observed sensitivities with one marker were 0.4, 0.5 and 0.38 for ovarian, endometrium and cervix cancer, respectively. Other proteins such as glycolytic enzymes that showed increased seroreactivity in cancer also showed reactivity in healthy individuals but in lower incidence. The fact that many of the antigens reacting with sera from cancer patients are also reactive with sera from patients without cancer diseases emphasizes the importance of combining different antigens to a set of biomarkers to increase specificity and sensitivity of a disease signature. The sensitivities can

be enhanced to 0.53 with 2 makers (30-kDa and 46-kDa), 1.00 with 3 markers (23-kDa, 30-kDa, 46-kDa), and 0.64 with 4 markers (30-kDa, 35-kDa, 40-kDa, and 45-kDa) for each cancer.

Also, antibody isotypes and titers may help in the diagnostic value of these autoantibodies as IgGs seem more pathogenic then IgMs (found in normal subjects), and high concentrations of AAbs are usually found in patients with cancer and CAR. The value of a biomarker depends not only on its occurrence in a given disease, but also in their specific use for early diagnosis, monitoring or prognosis [27]. Thus our findings suggest that anti-recoverin AAbs testing should only be performed in the context of ocular presentation relevant to CAR that has a reasonable likelihood of having the disease for which the testing is appropriate. If not, the predictive value of a positive test maybe too low. It is worth to mention that the incidence and titer of autoantibodies in healthy individuals increases with age [28]. Our subjects' average age is ~60 years old that predispose them to generation of various AAbs. In addition, molecular mimicry and autoimmune cross-reactivity of autoantibodies has been suggested as a possible pathogenic mechanism in post-streptococcal disease [25]. The etiology of CAR remains to be fully characterized but autoimmunity may occur when tumor antigens that mimic retinal proteins induce the immune system to lose tolerance for these self-proteins and accidentally begin targeting the retina. Also, healthy people have natural antibodies that are involved in maintaining homeostasis by removing cell-debris or tumor cells, or by preventing inflammation by binding and neutralizing cytokines [29]. Therefore, it is important to consider that many AAbs are found at low levels in healthy subjects and that AAbs against retinal targets can be present years before disease onset and remain non-pathogenic if the blood-retina barrier is not breached [30].

Conclusions

Recent studies from the cancer field show that autoantibody signatures seem to be particularly relevant for detection of cancer at different stages because during cancer growth the immune system elicit serum autoantibodies that can be considered as relevant cancer biomarkers [27]. Our studies identified new retinal targets for gynecological CAR. Novel autoantibody profiling will help to detect CAR for each cancer that may manifest months to years after the initial malignancy diagnosis and also before the cancer diagnosis. Each gynecological-CAR has an own autoantibody profile different from non-CAR antibodies, which suggests that the complex autoantibody signatures may be more predictable than singular AAb (Figure 4). The diagnosis of these paraneoplastic syndromes associated with gynecologic malignancies is essential as they can be occasionally life-threatening. An additional benefit from our studies is that in some paraneoplastic manifestations anti-retinal AAbs can be also used as markers of the underlying malignancy and aid in diagnosis of the primary cancer.

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