

Cancer-Associated Retinopathy in Patients with Newly Diagnosed Breast Tumor

Ceyhun SAYMAN¹ , Hülya TİRELİ¹ , Günay Meryem GÜRLEYİK² 

¹Department of Neurology, Health Sciences University, Haydarpaşa Numune Education and Research Hospital, İstanbul, Turkey

²Department of General Surgery, Health Sciences University, Haydarpaşa Numune Education and Research Hospital, İstanbul, Turkey

ABSTRACT

Introduction: Paraneoplastic neurological syndromes (PNS) are rare neurological conditions and they are mostly triggered by autoimmune mechanisms. Cancer-related retinopathies (CAR) are even rarer and commonly related with breast tumor in woman. This limits our knowledge about pathophysiology of CAR. In this study, we question the association between histopathological findings and onconeural antibodies in breast cancer.

Method: Thirty-two patients with newly diagnosed breast cancer admitted to the oncology outpatient clinic were included in the study. None of the participants have visual complaints. After the neurological examination of the patients, two tubes of 5 cc venous blood were obtained by screening onconeural antibodies. Samples were investigated in ASDETAE (İstanbul University Experimental Medicine Research Institute).

Results: Patients included in the study included one patient (3.1%)

with grade 1, 14 patients (43.8%) with grade 2 and 17 patients (53.1%) with grade 3 invasive breast cancer. Perineural invasion was detected in 5 (15.6%) patients. Progesterone receptor positivity was found in 26 (81.2%) patients and estrogen receptor positivity was found in 27 (84.4%) patients. In 7 (21.9%) patients, CERBB2 was positive and in 25 (78.1%) patients, Ki 67 was positive. A total of 12 (37.5%) patients had onconeural antibody positivity. Antibody positivity was significantly higher in patients with high grade tumor ($p=0.008$).

Conclusion: There may be a relationship between tumor grade and the presence of onconeural antibodies in breast cancer patients. By the detection of new biochemical markers, significant contribution can be made to the early diagnosis and treatment of underlying cancer.

Keywords: Paraneoplastic disorders, cancer-associated retinopathy, recoverin antibody, breast tumor

Cite this article as: Sayman C, Tireli H, Gürleyik MG. Cancer-Associated Retinopathy in Patients with Newly Diagnosed Breast Tumor. Arch Neuropsychiatry 2021;58:278–282.

INTRODUCTION

Paraneoplastic neurological syndromes (PNS) are rare neurological conditions in cancer patients. They may affect one or more parts of the nervous system and are thought to be independent of the local or direct effect of the underlying malignancy. PNS cannot be explained by the underlying cancer-related metastasis, opportunistic infections and side effects of cancer treatment as these are triggered by autoimmune mechanisms (1–4).

PNS may occur between 1/1000 and 1/10,000 of cancer patients. Syndromes are often associated with small cell lung cancer (SCLC), ovarian cancer, breast cancer, thymoma and lymphoma (2, 5). PNS usually occurs before a cancer is diagnosed so it is very important to recognize the syndromes early to control of symptoms and treatment of underlying cancer (1, 6).

On the other hand, Cancer-related retinopathies (CAR) are so rare within PNS and are associated with various types of cancer such as SCLC, non-SCLC, breast cancer, endometrial cancer, nasopharyngeal cancer, invasive thymoma, lymphoma and others (7–9). Breast cancer is the second most cause observed in women death and PNS is frequently seen with breast cancer in women (10). There is a relation between PNS and onconeural antibodies. They are positive in 60–70% of breast cancer related PNS.

Although the presence of antibodies is helpful in diagnosis of PNS, their absence do not exclude the possibility of PNS (11).

The target structure in CAR is the antigens found in photoreceptors (7, 13). The first and most common antibody found is the recoverin protein. 15 other types of antigen proteins have also been identified in addition to the recoverin antibody. Patients typically complaint of light sensitivity, visual acuity and color vision abnormalities, as well as symptoms such as night blindness, prolonged dark adaptation, and scotoma (12). Patients without neurological symptoms usually have low levels of antibodies, but in some cases patients were observed still having high levels of antibodies in the nervous system without any signs or symptoms. Therefore, we find that the relationship between antibodies and cancer is robust but the relationship between neurological symptoms and onconeural antibodies is more ambiguous (14, 15).

The development of new treatment modalities improved the survival of cancer patients, which in turn may increase cancer-related neurological problems that may be seen in time. Despite recent advances in cancer treatment, CAR pathophysiology is still unknown. We also don't have enough information about the effect of lymph node metastasis, receptor type, histologic subtype and paraneoplastic processes in breast cancer. The

aim of this study is to identify the association between histopathological findings and onconeural antibodies in breast cancer.

METHODS

32 newly diagnosed breast cancer patients admitted to the oncology outpatient clinic were randomly investigated. All patients had examined by senior neurologist after their blood tests were performed. None of the patients had visual complaints but only two patients had sensory complaints on the lower limbs. No toxic substances or drugs uses that could have otherwise explained neurological findings were found.

Two 5 cc tubes of venous blood were obtained by screening onconeural antibodies. After 20 minutes at room temperature, the blood was centrifuged at 2000 rpm for 10 minutes and the supernatant (serum) was transferred to Eppendorf tubes in 500 cc aliquots and stored in an 80 degree freezer. Samples were sent to the ASDETAE (Istanbul University Experimental Medicine Research Institute) Department of Neuroscience following the cold chain rules. Immunoblot sticks containing recombinant proteins of target paraneoplastic antigens from Hu, Yo, Ri, Ma2, CV2, amphiphysin, Tr, Zic4, Sox1, titin, recoverin, GAD IgG antibodies were compared with samples which were considered positive when reacting with recombinant protein of appropriate kD weight.

Data were collected after the purpose of the research was explained to the volunteer patients and their written consent were obtained. Ethical approval of the study was obtained from the local ethics committee at Haydarpaşa Research and Training Hospital (Date: 30.01.2018).

Statistical Analysis

Data were analyzed with IBM Statistical Package for Social Sciences (SPSS) 21 package program. Descriptive statistics provided for categorical data are in frequency (n) and percentage (%) and continuous data are described by mean and standard deviation of the sample population. Chi-square test was used for the statistical analysis of categorical variables and when the chi-square test assumptions were not met, Fisher's exact test was used, 0.05 p-value.

Table 1. Demographic and immunohistochemical features of the cases

Age (mean ± standard deviation)	4.5±9.08
Gender (n (%))	
Female	32 (100%)
Male	0
Invasive ductal breast cancer (n (%))	
Grade 1	1 (3.1%)
Grade 2	14 (43.8%)
Grade 3	17 (53.1%)
Perineuronal invasion (n (%))	
+	5 (15.6%)
-	27 (84.4%)
Progesterone receptor (n (%))	
(+)	26 (81.2%)
(-)	6 (18.8%)
Oestrogen receptor (n (%))	
(+)	27 (84.4%)
(-)	5 (15.6%)
CERBB2 (n (%))	
(+)	7 (21.9%)
(-)	25 (78.1%)
KI 67 (n (%))	
(+)	25 (78.1%)
(-)	7 (21.9%)

RESULTS

Clinical Features and Laboratory Results of Cases

The clinical and demographic characteristics of the patients are detailed in Table 1. All patients were women and aged between 30–65 years. In the pathological staging of patients with invasive breast cancer; 1 (3.1%) was grade 1, 14 (43.8%) were grade 2, 17 (53.1%) were grade 3. According to the pathology report results, 5 (15.6%) patients had perineural invasion. Progesterone receptor positivity was found in 26 (81.2%) patients and oestrogen receptor positivity was found in 27 (84.4%) patients. 7 (21.9%) patients had CERBB2 and 25 (78.1%) patients had Ki 67 positivity. Only 2 (6.2%) patients had sensory neuropathy that was confirmed by the electromyography.

Onconeural Antibody Results of Cases

Onconeural antibody positivity was observed in 12 (37.5%) of the patients included in the study. Antibody positivity is detailed in Table 2.

The Relationship between the Presence of Immunohistochemical Findings and Antibody Positivity

Onconeural antibody positivity was detected in 11 (40.7%) oestrogen

Table 2. Onconeural antibody results of the cases

Antibody	
(+)	12 (37.5%)
(-)	20 (62.5%)
Amphiphysin	
(+)	2 (6.2%)
(-)	30 (93.8%)
CV2	
(+)	4 (12.5%)
(-)	28 (87.5%)
Ma2Ta	
(+)	0
(-)	32 (100%)
Ri	
(+)	0
(-)	32 (100%)
Yo	
(+)	2 (6.2%)
(-)	30 (93.8%)
Hu	
(+)	2 (6.2%)
(-)	30 (93.8%)
Recoverin	
(+)	9 (28.1%)
(-)	23 (71.9%)
SOX1	
(+)	0
(-)	32 (100%)
Titin	
(+)	4 (12.5%)
(-)	28 (87.5%)
Zic4	
(+)	0
(-)	32 (100%)
GAD65	
(+)	0
(-)	32 (100%)
TrDNER	
(+)	0
(-)	32 (100%)

Table 3. Comparison of presence of oestrogen receptor and antibody positivity

Oestrogen receptor	Antibody (-)	Antibody (+)	Total	p value
(+)	16 (59.3%)	11 (40.7%)	27 (100%)	0.62*
(-)	4 (80%)	1 (20%)	5 (100%)	

* Fisher's exact test.

Table 4. Comparison of presence of progesterone receptor and antibody positivity

Progesterone receptor	Antibody (-)	Antibody (+)	Total	p value
(+)	15 (57.7%)	11 (42.3%)	26 (100%)	0.37*
(-)	5 (83.3%)	1 (16.7%)	5 (100%)	

* Fisher's exact test

Table 5. Comparison of C-erbB-2 and antibody positivity

C-erbB-2	Antibody (-)	Antibody (+)	Total	p value
(+)	5 (71.4%)	2 (28.6%)	7 (100%)	0.68*
(-)	15 (60%)	10 (40%)	25 (100%)	

* Fisher's exact test.

Table 6. Comparison of Ki-67 and antibody positivity

Ki-67	Antibody (-)	Antibody (+)	Total	p value
(+)	17 (68.0%)	8 (32%)	25 (100%)	0.37*
(-)	3 (42.9%)	4 (57.1%)	7 (100%)	

* Fisher's exact test.

Table 7. Comparison of perineural invasion and antibody positivity

Perineural invasion	Antibody (-)	Antibody (+)	Total	p value
(+)	2 (40.0%)	3 (60%)	5 (100%)	0.35*
(-)	17 (65.4%)	9 (34.6%)	26 (100%)	

* Fisher's exact test.

Table 8. Comparison of tumor grade and antibody positivity

Tumor grade	Antibody (-)	Antibody (+)	Total	p value
Grade 1–2	13 (86.7%)	2 (13.3%)	15 (100%)	0.008*
Grade 3	7 (41.2%)	10 (58.8%)	17 (100%)	

* Pearson chi-square test.

Table 9. Comparison of tumor grade and recoverin positivity

Tumor grade	Antibody (-)	Antibody (+)	Total	p value
Grade 1–2	13 (86.7%)	2 (13.3%)	15 (100%)	0.08*
Grade 3	10 (58.8%)	7 (41.2%)	17 (100%)	

* Pearson chi-square test.

receptor positive cases and 16 (59.3%) oestrogen receptor positive cases were found to be antibody negative. There was no significant relationship between the presence of oestrogen receptor and antibody positivity ($P=0.62$) (Table 3).

Antibody positivity was detected in 11 (42.3%) cases positive for progesterone receptor, while antibody positivity was detected in 15 (57.7%) cases positive for progesterone receptor. No significant correlation was found between the presence of progesterone receptor and antibody positivity ($P=0.37$) (Table 4).

Antibody positivity was detected in 2 (28.6%) cases positive for C-erbB-2, while antibody positivity was found in 5 (1.4%) cases positive for C-erbB-2. There was no significant relationship between C-erbB-2 positivity and antibody positivity in the subjects ($p=0.68$) (Table 5).

Antibody positivity was found in 8 (32%) patients who were positive for Ki-67, while antibody negativity was found in 17 (68.0%) patients who were positive for Ki-67. There was no significant relationship between ki-67 positivity and antibody positivity in the subjects included in the study ($P=0.37$) (Table 6).

Antibody positivity was detected in 3 (40.0%) cases with perineural invasion, while antibody negativity was detected in 2 (40%) cases with perineural invasion. There was no significant relationship between the presence of perineural invasion and antibody positivity ($P=0.35$) (Table 7).

Relationship between Tumor Grade and Antibody Positivity

In the pathological staging of patients with invasive breast cancer; 1 (3.1%) was grade 1, 14 (43.8%) were grade 2, 17 (53.1%) were grade 3. The correlation between tumor grade and antibody positivity was evaluated and grade 1 and 2 tumors were evaluated together. Tumor grade was grade 1–2 in 2 (13.3%) patients with antibody positivity and grade 3 in 10 (58.8%) patients with antibody positivity. A statistically significant correlation was found between antibody positivity and tumor grade. Antibody positivity was significantly higher in patients with high grade tumors ($p=0.008$) (Table 8).

Relationship between Tumor Degree and Recoverin Antibody Positivity

In the pathological staging of patients with invasive breast cancer; 1 (3.1%) was grade 1, 14 (43.8%) were grade 2, 17 (53.1%) were grade 3. The correlation between tumor grade and recoverin antibody positivity was evaluated and grade 1 and 2 tumors were evaluated together. Tumor grade was grade 1–2 in 2 (13.3%) patients with antibody positivity and grade 3 in 7 (41.2%) patients with antibody positivity. There was no significant relationship between the presence of perineural invasion and antibody positivity ($p=0.08$) (Table 9).

DISCUSSION

Ocular findings related with cancer occur due to tumor, metastasis and distant effect. Of these, ocular findings caused by distant effects are generally referred to as ocular paraneoplastic syndrome (OPS). OPSs are grouped under three broad categories: CAR, melanoma-associated retinopathy (MAR) and bilateral diffuse uveal melanocytic proliferation affecting the retina and/or choroid. Patients typically complain of light sensitivity, visual acuity and color vision abnormalities, as well as symptoms such as night blindness, prolonged dark adaptation, and scotoma (12).

Antigens were observed to behave differently in these OPSs. For example, the target structure in CAR is the antigens found in photoreceptors, and recoverin antibody (23–48 kD) is the most common and one of the many

CAR related antibodies. On the other hand, the target structure in MAR is retinal bipolar cells and the target antigens present in these cells have not yet been fully identified. There are 15 other types of antigen proteins have also been identified in addition to the recoverin antibody (7, 13).

CAR symptoms may be observed before the diagnosis of cancer as it has also been recognized after detecting a primary malignancy. Therefore, early discovery of paraneoplastic visual disorders should raise suspicion of an underlying malignancy, which may also support its conclusion. CAR symptoms are most observed in SCLC but can also be seen in gynaecological, breast and endocrine cancers (16, 17).

It is known that 60–70% of PNSs developed in breast cancer patients have Onconeural antibodies. The antibody rate was 53.6% in a recent study of 56 patients with PNS due to breast cancer (18). In our study, antibody positivity was observed in 37.5% of the cases. And the ratio of recoverin antibody was 15%, much more than our expectations. as the recoverin antibody was only observed in 4.5% of breast cancer related retinopathies in the literature (19).

Onconeural antibodies can be detected without paraneoplastic neurological symptoms even at low titers (eg 1:1000). For example, patients with no paraneoplastic syndrome in SCLC have anti-Hu positivity of 15% (20). It is already known in the literature that, more than one Onconeural antibody may coexist with a tumor while anti-Yo positivity is usually found on its own (15). Our results complement these conclusions in the literature by finding new antigen coexistence. In our study, CV2 and recoverin antibody were positive in two of the three patients and amphiphysin and recoverin antibody were positive in the other.

We couldn't find a significant relationship between the hormone receptors (progesterone, estrogen), immunohistochemical markers such as Cerb2, Ki67, and perineural invasion which may be associated with pathogenesis and prognosis of breast cancer patients. There is a correlation between antibody level and tumor grade.

Although PNSs like cerebellar degeneration, sensorimotor neuropathy, and opsoclonus/myoclonus syndrome are seen more frequently than CAR in breast tumor patients, CAR should be questioned in detail whether patients have visual complaints and if necessary, detailed ophthalmologic evaluation should be performed. Identifying and controlling for the presence of recoverin antibodies and their titers in parallel with neurological and ophthalmic examinations can be valuable in managing and understanding the relationship between cancer and the development of ophthalmic symptoms.

Onconeural antibodies are produced as an immune response to a tumor that ectopically expresses a neuronal antigen. These antibodies are then directed to antigens in the central and/or peripheral nervous systems. There is no evidence to support the general use of onconeural antibodies as potential cancer markers in individuals without neurological symptoms. In clinical practice, it would be more beneficial to have antibody analysis limited to the patients with neurological symptoms suspected of PNS.

In conclusion, this study showed that there may be a relationship between tumor grade and the presence of onconeural antibodies in breast cancer patients. It should be kept in mind that the response to treatment after PNS develops is limited. Therefore, the presence of new biochemical markers may contribute to the early diagnosis and treatment of the underlying cancer.

It can be beneficial for the survival of the patients and increase the quality of life with the new studies. We should expand awareness of clinicians as well as PNS and CAR in breast tumor patients.

Ethics Committee Approval: Ethical approval of the study was obtained from the local ethics committee at Haydarpaşa Research and Training Hospital (Date: 30.01.2018, No: HNEAH-KAEK 2017/KK/157).

Informed Consent: Data were collected after the purpose of the research was explained to the volunteer patients and their written consent were obtained.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept- CS; Design- HT; Supervision- HT; Resource- GMG; Materials- CS; Data Collection and/or Processing- HT, CS; Analysis and/or Interpretation- HT, CS; Literature Search- CS; Writing- CS; Critical Reviews- HT, GMG.

Conflict of Interest: The authors declared that there is no conflict of interest.

Financial Disclosure: No disclosure.

REFERENCES

- Höftberger R, Rosenfeld MR, Dalmau J. Update on neurological paraneoplastic syndromes. *Curr Opin Oncol* 2015;27:489. (Crossref)
- Tüzün E, Dalmau J. Limbic encephalitis and variants: classification, diagnosis and treatment. *Neurologist* 2007;13:261–271. (Crossref)
- Leypoldt F, Wandinger KP. Paraneoplastic neurological syndromes. *Clin Exp Immunol* 2014;175:336–348. (Crossref)
- Graus F, Dalmau J. Paraneoplastic neurological syndromes: diagnosis and treatment. *Curr Opin Neurol* 2007;20:732–737. (Crossref)
- Kanikannan MA, Sirisha Y, Uppin MS, Jabeen SA, Kandadai RM, Sundaram C, Raghunadharao D, Borgohain R. Incidence and spectrum of paraneoplastic neurological syndromes: single center study. *J Neurooncol* 2015;125:197–206. (Crossref)
- Vedeler CA, Antoine JC, Giometto B, Graus F, Grisold W, Hart IK, Honnorat J, Sillevs Smitt PA, Verschuuren JJ, Voltz R; Paraneoplastic Neurological Syndrome Euronetwork. Management of paraneoplastic neurological syndromes: report of an EFNS Task Force. *Eur J Neurol* 2006;13:682–690. (Crossref)
- Keltner JL, Thirkill CE, Yip PT. Clinical and immunologic characteristics of melanoma-associated retinopathy syndrome: eleven new cases and a review of 51 previously published cases. *J Neuroophthalmol* 2001;21:173–187. (Crossref)
- Misiuk-Hojo M, Jurowska-Liput J, Gorczyca W. Cancer associated retinopathy. *Nowotwory J Oncol* 2004;54:584–586.
- Mohamed Q, Harper CA. Acute optical coherence tomographic findings in cancer-associated retinopathy. *Arch Ophthalmol* 2007;125:1132–1133. (Crossref)
- Koçak S, Çelik L, Özbaş S, Sak SD, Tükün A, Yalçın B. Meme kanserinde risk faktörleri, riskin değerlendirilmesi ve prevansiyon: İstanbul 2010 Konsensus Raporu. *Meme Sağlığı Derg* 2011;7:47–67.
- Fanous I, Dillon P. Paraneoplastic neurological complications of breast cancer. *Exp Hematol Oncol* 2015;5:29. (Crossref)
- Tateiwa H, Gotoh N, Ichikawa M, Kikuchi T, Yoshimura N. Molecular cloning and characterization of human PTB-like protein: a possible retinal autoantigen of cancer-associated retinopathy. *J Neuroimmunol* 2001;120:161–169. (Crossref)
- Adamus G, Ren G, Weleber RG. Autoantibodies against retinal proteins in paraneoplastic and autoimmune retinopathy. *BMC Ophthalmol* 2004;4:5. (Crossref)
- Storstein A, Monstad SE, Haugen M, Mazengia K, Veltman D, Lohndal E, Aarseth J, Vedeler C. Onconeural antibodies: improved detection and clinical correlations. *J Neuroimmunol* 2011;232:166–170. (Crossref)
- Pittock SJ, Kryzer TJ, Lennon VA. Paraneoplastic antibodies coexist and predict cancer, not neurological syndrome. *Ann Neurol* 2004;56:715–719. (Crossref)
- De Potter D. Ocular manifestation of cancer. *Curr Opin Ophthalmol* 1998;9:100–104. (Crossref)
- Katsuta H, Okada M, Nakauchi T, Takahashi Y, Yamao S, Uchida S. Cancer-associated retinopathy with invasive thymoma. *Am J Ophthalmol* 2002;134:383–389. (Crossref)
- Murphy BL, Zalewski NL, Degnim AC, McKeon A, Flanagan EP, Pittock SJ, Habermann EB. Breast cancer-related paraneoplastic neurologic disease. *Breast Cancer Res Treat* 2018;167:771–778. (Crossref)
- Adamus G, Karren L. Autoimmunity against carbonic anhydrase II affects retinal cell functions in autoimmune retinopathy. *J Autoimmun* 2009;32:133–139. (Crossref)
- Titulaer MJ, Klooster R, Potman M, Sabater L, Graus F, Hegeman IM, Thijssen PE, Wirtz PW, Twijnstra A, Smitt PA, van der Maarel SM, Verschuuren JJ. SOX antibodies in small-cell lung cancer and Lambert-Eaton myasthenic syndrome: frequency and relation with survival. *J Clin Oncol* 2009;27:4260–4267. (Crossref)