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Immunotherapy-induced retinopathy mimicking cancer associated retinopathy

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ABSTRACT

Purpose: To report a patient who developed a cancer associated retinopathy (CAR) like syndrome in the setting of pembrolizumab and lenvatinib combination therapy for metastatic endometrial carcinoma. Symptoms resolved with normalization of objective functional tests following cessation of medications.

Observations: A 52-year-old female with history of endometrial carcinoma, managed with pembrolizumab infusions and daily oral lenvatinib treatment for 18 months, presented to a tertiary eye center with complaints of nyctalopia, photosensitivity and photopsia. Further investigations revealed a reduction in b-wave amplitude on full field ERG (ffERG), a mild color vision deficit, and positive antiretinal antibodies against carbonic anhydrase II, enolase and arrestin. A preliminary diagnosis of CAR was made. One month following diagnosis, the patient discontinued both lenvatinib and pembrolizumab and subsequently reported significant improvement in her eye symptoms and vision. Repeat ffERG had normalized with a robust b-wave, with an improvement noted on repeat color vision testing. A presumed diagnosis of immunotherapy-induced retinopathy was made, with clinical findings mimicking CAR.

Conclusions and importance: Pembrolizumab and lenvatinib treatment may be associated with a reversible retinopathy, with presentation very similar to CAR.

1. Introduction

Autoimmune retinopathy (AIR) is a rare immune-mediated disease characterized by progressive, painless vision loss, visual field defects and photoreceptor dysfunction in the presence of antiretinal antibodies (ARAs). AIR can be categorized as paraneoplastic AIR (pAIR), which involves cancer associated retinopathy (CAR) and melanoma-associated retinopathy (MAR), or non-paraneoplastic AIR (npAIR).[1]

CAR is a paraneoplastic syndrome which is usually diagnosed in the setting of visual symptoms such as vision loss, positive visual phenomena (photopsia, flickering), nyctalopia and light sensitivity, normal retinal exam, electrophysiological changes, presence of ARAs, and evidence of systemic malignancy.[2] CAR is commonly associated with lung and breast malignancies. However, endometrial cancer has also been associated with CAR.[2,3] Anti enolase and recoverin antibodies (Abs) have been frequently associated with CAR, but reports on their frequencies are variable.[2,4] On the other hand, a study has demonstrated that around 50% of cases with presumed CAR tested negative for ARAs.[5] The mere presence ARAs alone does not establish the diagnosis of AIR as it can be present in the normal population and in different inflammatory ocular conditions.[1,6] The role of ARAs has yet to be fully elucidated.

Cytotoxic T-lymphocyte-associated protein 4 (CTLA4), programmed death-1 (PD-1) and their respective ligands are well-known physiological pathways that inhibit T cells, representing immune "checkpoints". Checkpoint inhibitors (CPIs) act by antagonizing immune checkpoints, thus increasing T cell activity and the host's ability to fight tumor cells. However, this immune dysregulation results in a unique set of autoimmune reactions called immune-related adverse events (irAEs).[7] irAEs can occur in up to 70% of patients receiving anti–PD-1 agents and up to 90% of patients receiving anti–CTLA4 agents.[8] In addition, studies have shown that patients with preexisting autoimmune diseases may experience an increased frequency of flares of their autoimmune condition when taking CPIs.[9] Pembrolizumab is an FDA-approved CPI used to treat a variety of advanced malignancies.

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We report a patient who developed a CAR-like syndrome in the setting of pembrolizumab and lenvatinib, a multiple kinase inhibitor, combination therapy for metastatic endometrial carcinoma. Cessation of both drugs resulted in resolution of symptoms and normalization of objective findings.

2. Case presentation

A 52-year-old female presented to a tertiary eye center with complaints of nyctalopia, photosensitivity and photopsia for 3 weeks. Her past medical history was remarkable for stage IV metastatic endometrial carcinoma, which was managed surgically with a total hysterosalpingo-oophorectomy with pelvic and para-aortic lymph node dissection two years prior to presentation. She subsequently underwent radiotherapy and chemotherapy (6 cycles of carboplatin + paclitaxel) followed by pembrolizumab infusions (CPI) every three weeks and daily oral lenvatinib (protein tyrosine kinase inhibitor) to control her liver and lymph node metastasis. The treatment lasted for 18 months, after which her eye symptoms developed. At her initial ophthalmology visit, best corrected visual acuity was 20/20 and intraocular pressure was with in normal limits OU. Her ophthalmic examination was unremarkable except for trace nuclear sclerosis in both eyes (OU). Funduscopic examination and ancillary tests including optical coherence tomography and fundus autofluorescence were within normal limits OU (Fig. 1). Given the history of malignancy, CAR was suspected, and various examinations including but not limited to electrophysiological tests, color vision test and serologic tests for ARAs were performed.

Combined rod-cone response in full field ERG (ffERG) demonstrated b-wave reduction, and a relatively preserved a-wave with a b:a ratio near 1, compared with normal values of around 2 (Fig. 2-C). Overall, ffERG showed diffuse dysfunction mainly affecting the rods, with minimal cone dysfunction (Fig. 2-A&E). Multifocal electroretinography did not show significant macular dysfunction. Farnsworth D15 Color Vision testing in both eyes revealed mild color vision deficit with mild tritan axis and dark adaptometry showed impaired dark adaptation. ARAs panel was positive for antibodies against carbonic anhydrase II (CA II), enolase and arrestin. Anti-optic nerve antibody panel was positive for anti 45-kDa Abs. A preliminary diagnosis of CAR was made.

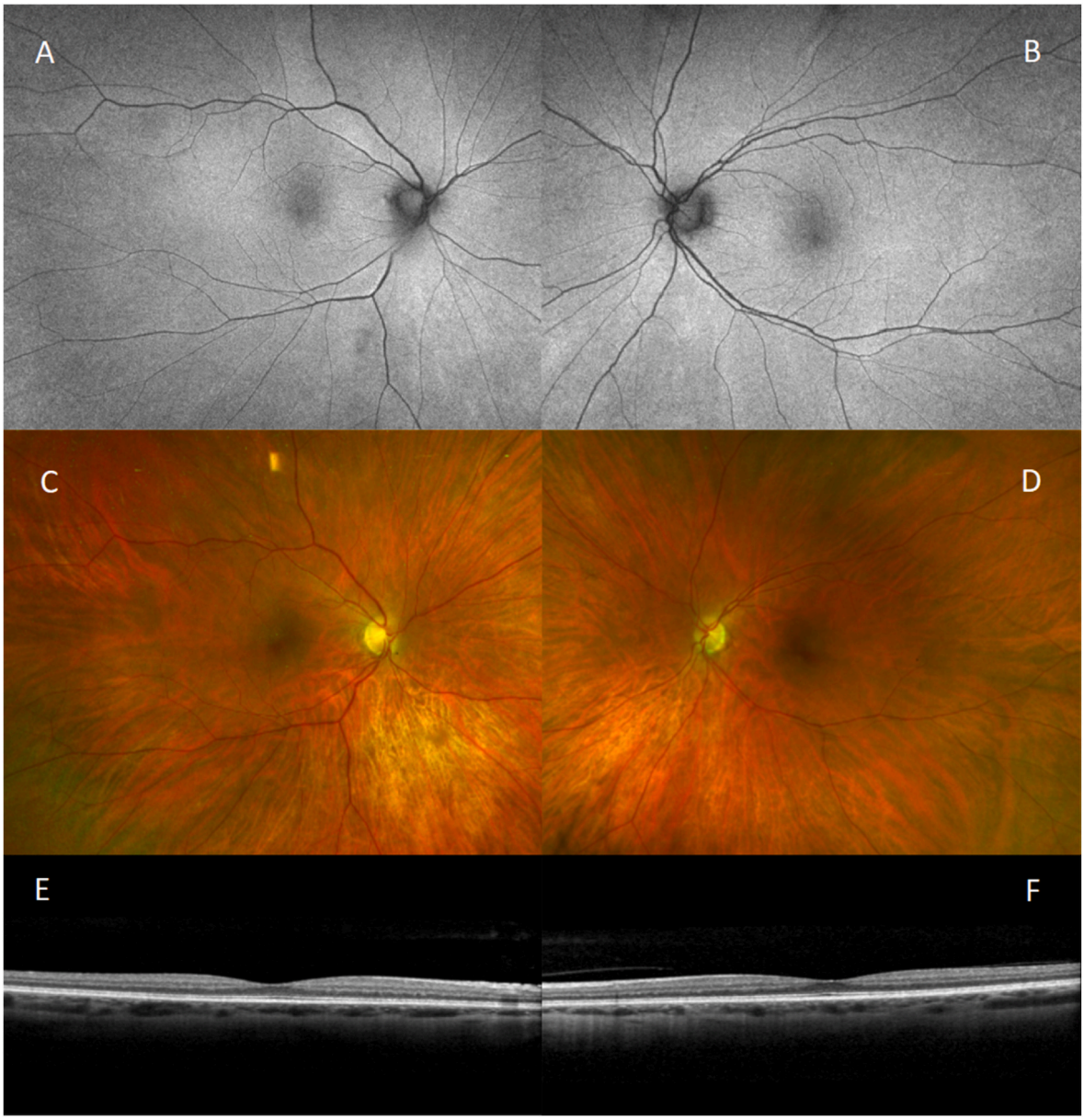

Fig. 1. Unremarkable autofluorescence (A&B), fundus photos (C&D) and optical coherence tomography (E&F) of both eyes at the initial ophthalmology visit.

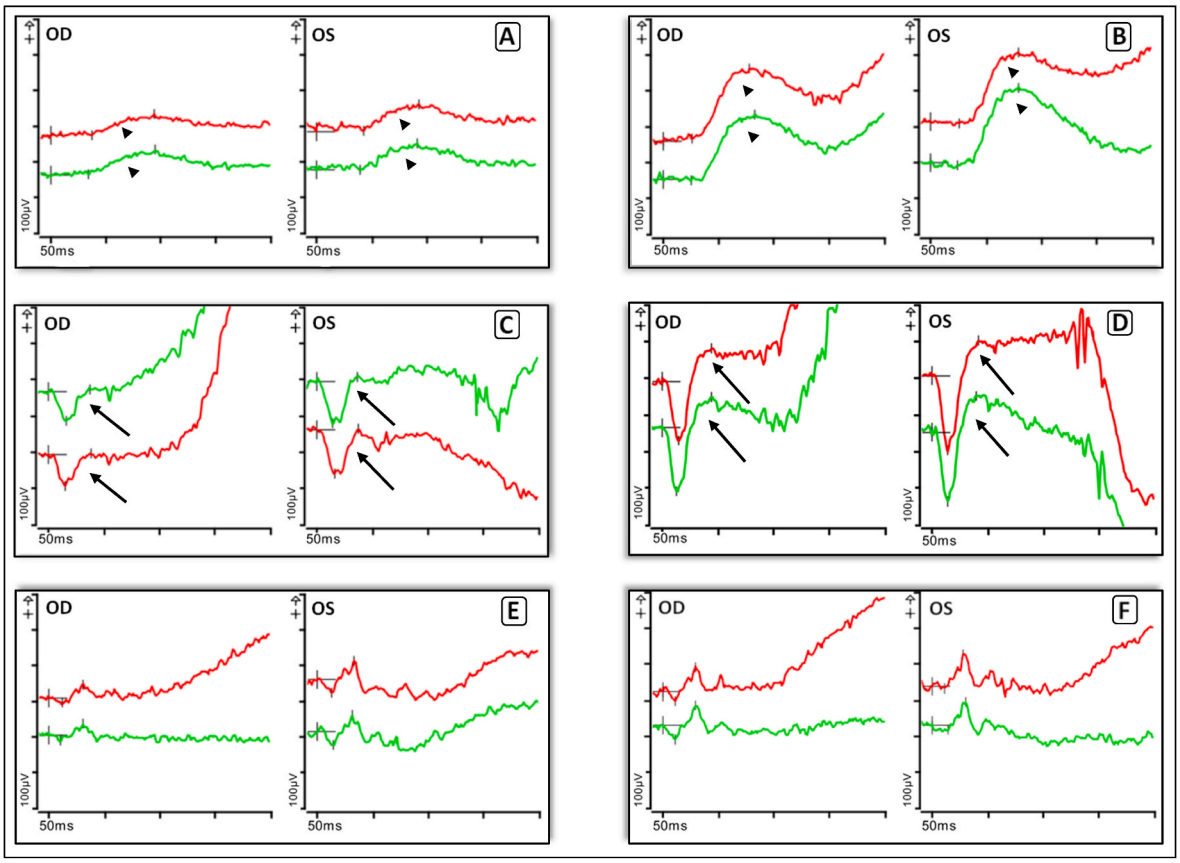

Fig. 2. A: Scotopic 0.01 b wave (rod) response during therapy showing almost distinguished b wave (arrow heads). B: Scotopic 0.01 b wave (rod) response 2 months following discontinuation of lenvatinib/pembrolizumab therapy showing robust b wave (arrow heads). C: Mixed rod and cone scotopic 3.0 response showing depressed b wave (arrows). D: Mixed rod and cone scotopic 3.0 response 2 months following discontinuation of lenvatinib/pembrolizumab therapy showing robust b wave (arrows). E: Photopic cone response during therapy showing intact cone function. F: Photopic cone response 2 months following discontinuation of lenvatinib/pembrolizumab therapy showing minimal changes. OD: right eye. OS: Left eye. Red and green waves represent two measurements of the same eye done in the same session. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

After one month before receiving any treatment for the eyes, the patient discontinued both lenvatinib and pembrolizumab, with lenvatinib stopped 5 days prior to the last dose of pembrolizumab. Both drugs were discontinued as the patient had developed systemic adverse events including arrythmia, electrolyte imbalance, hypothyroidism and severe diarrhea. In addition, the managing team suspected that the eye symptoms might be secondary to the immunotherapy, thus a drug holiday was warranted. Five days following cessation of pembrolizumab (10 days from the last dose of lenvatinib), the patient reported significant improvement in her eye symptoms and vision, with full recovery noted after an additional 10 days.

Six weeks after discontinuation of her lenvatinib/pembrolizumab therapy, the patient denied recurrence of her visual symptoms. Her ophthalmological examination remained stable from the previous visit. Repeat ffERG had normalized with a robust b-wave (Fig. 2-B, D & E). Repeat color vision testing improved with few symmetrical errors. A repeat ARAs test was not done due to financial considerations. The patient was seen again after 4 months (around 6 months from discontinuing the medications) and did not have symptom recurrence. Given these findings along with her history, a presumed diagnosis of immunotherapy-induced retinopathy was made, with clinical findings mimicking CAR.

3. Discussion

PD-1 inhibitors, e.g. pembrolizumab, are known to be associated with ocular adverse events including Vogt-Koyanagi-Harada syndrome, exudative retinal detachment, central retinal artery occlusion, anterior uveitis, posterior uveitis, neuroretinitis, scleritis and periocular edema.[10] Lenvatinib is a multiple receptor tyrosine kinase inhibitor that targets vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF) and platelet derived growth factor receptors.[11] To the best of our knowledge, it has not been associated with significant ocular side effects. The combination of pembrolizumab and lenvatinib has been approved by the FDA, and is currently used, for the treatment of advanced endometrial carcinoma.[11]

In the index case, the patient developed CAR-like symptoms that were first believed to be paraneoplastic secondary to her metastatic endometrial cancer and later confirmed by ffERG. However, all of the patient's subjective symptoms and functional tests normalized after stopping the pembrolizumab and lenvatinib combination therapy.

Based on the Naranjo Adverse Drug Reaction Probability Scale,[12] it is possible/probable that the reported ocular adverse events were secondary to either pembrolizumab, lenvatinib or both. This is supported by the rapid subjective and objective improvement after cessation of immunotherapy. However, as they were discontinued at essentially the same time, we cannot discern which medication, pembrolizumab or lenvatinib, was associated with the observed visual compromise.

Few reports have associated AIR-like symptoms with checkpoint inhibitors. Reddy et al. reported a case linking CAR-like symptoms to nivolumab, which is a PD-1 inhibitor.[13] In their report, the authors described a 64-year-old female with stage IV lung adenocarcinoma who developed photopsia and color vision abnormalities shortly after starting nivolumab therapy. ffERG revealed moderate to severe dysfunction

of rods and cones in OD only. ARA panel was negative for Abs against both enolase and recoverin, but positive for Abs against CA-II, GADPH, PKM2 and 112-kDa proteins. Shortly after stopping nivolumab and starting oral steroids, the patient reported improvement of her photopsia in OU. Repeat OCT after 3 months showed no change, but the authors did not repeat ERG testing and concluded that these findings are more likely to represent nivolumab toxicity rather than CAR.[13]

Shahzad et al. also described a case of MAR in a monocular patient whose fellow eye was exenterated due to metastatic uveal melanoma.[14] Shortly after the first cycle of immunotherapy with nivolumab and ipilimumab (a checkpoint inhibitor that inhibits CTLA4), the patient developed severe photopsia. Following 9 weeks of treatment (3 cycles), the patient developed severe pneumonitis which was treated with oral prednisone and discontinuation of CPI therapy. The authors reported that the ERG was compatible with MAR and visual symptoms partially improved with systemic and intravitreal steroids. No ARAs panel or repeat ERG testing was done.[14] Young et al. also reported a case of CAR associated with nivolumab and ipilimumab therapy for cervical cancer. However, details including presence of ARAs or abnormal ERG features were not described.[10]

The present case differs from the aforementioned cases in several aspects. To our knowledge, this is the first report to document reversal of ERGfindings following discontinuation of immunotherapy, which supports the notion that the ocular symptoms and findings were more likely caused by drug toxicity than by CAR. In addition, the visual symptoms developed more than 1 year following initiation of immunotherapy, which is different from previous cases in which symptoms developed shortly after starting the immunotherapy. Moreover, our patient did not receive any treatment for her eye symptoms but only cessation of immunotherapy, which contrasts with the previously reported cases.

Another interesting finding in our case is the selective depression of the b-wave on ffERG to a near electronegative degree which is commonly associated with MAR (although also reported with CAR).[15] In addition, MAR has been commonly associated with the presence of anti-enolase, anti-arrestin and anti-CA-II Abs,[4] all of which were present in our case. It is unclear why our patient had both ARAs and ffERG profiles common in MAR.

Several explanations could be postulated to explain our patient's findings. Most ARAs can be detected in healthy asymptomatic individuals with minimal to no effect,[4] but they may induce retinal damage in the setting of ocular inflammation or cancer therapy.[16] Interestingly, ARAs have also been shown to induce MAR-like ERG changes in otherwise healthy animal retinas in an experimental setting.[16,17] Moreover, ARAs can be generated secondary to non-immune mediated retinal damage, which may exacerbate ongoing damage to retinal cells.[16] Hence, it is possible that our patient had pre-existing ARAs which may have exacerbated the cytotoxic effect on the retina induced by the chronic immunotherapy, leading to the CAR-like ocular symptoms and ERG changes observed. Stopping the immunotherapy may have halted the damaging effect on the retina, which would have prevented further damage by ARAs, explaining the rapid symptom reversal. Another possibility is that the positive result of ARAs was just false positive.

Our patient experienced visual improvement spontaneously just 5 and 10 days after the last dose of pembrolizumab and lenvatinib, respectively. The fact that the patient used to administer pembrolizumab every 3 weeks might lead to question whether the patient symptoms were secondary to pembrolizumab, as its half-life is estimated to be between 14 and 27 days.[18] Lenvatinib, on the other hand, has a half-life of 28 hours.[19] Should pembrolizumab be the causative agent, improvement of symptoms should have occurred throughout her treatment with pembrolizumab. The cessation of lenvatinib 10 days prior to her visual improvement may support a more causative role of lenvatinib in the development of her visual symptoms. However, this remains to be elucidated as lenvatinib has never been previously associated with significant ocular adverse reactions.

4. Conclusion

Herein, we present an interesting case of CAR-like syndrome in a patient with history of endometrial carcinoma treated with pembrolizumab and lenvatinib, who was met with rapid subjective and objective visual improvement following cessation of pembrolizumab and lenvatinib. Given the rapid visual recovery, it could be postulated that the patient's visual compromise may have been associated with pembrolizumab or lenvatinib use, rather than a possible CAR. Further studies are required to fully elucidate this association.

Patient consent

Consent to publish this case report has been obtained from the patient.

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Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Declaration of competing interest

None of the authors has any conflicts of interest to disclose.

References

1. Dutta Majumder P, Marchese A, Pichi F, Garg I, Agarwal A. An update on autoimmune retinopathy. *Indian J Ophthalmol. Sep*. 2020;68(9):1829–1837. https://doi.org/10.4103/ijo.IJO_786_20.
2. Shildkrot Y, Sobrin L, Gragoudas ES. Cancer-associated retinopathy: update on pathogenesis and therapy. *Semin Ophthalmol*. Jul-Sep 2011;26(4-5):321–328. https://doi.org/10.3109/08820538.2011.588657.
3. Sekiguchi I, Suzuki M, Sato I, Ohkawa T, Kawashima H, Tsuchida S. Rare case of small-cell carcinoma arising from the endometrium with paraneoplastic retinopathy. *Gynecol Oncol. Dec*. 1998;71(3):454–457. https://doi.org/10.1006/gyno.1998.5049.
4. Adamus G, Champaigne R, Yang S. Occurrence of major anti-retinal autoantibodies associated with paraneoplastic autoimmune retinopathy. *Clin Immunol. Jan*. 2020; 210:108317. https://doi.org/10.1016/j.clim.2019.108317.
5. Adamus G, Ren G, Weleber RG. Autoantibodies against retinal proteins in paraneoplastic and autoimmune retinopathy. *BMC Ophthalmol*. Jun 4 2004;4:5. https://doi.org/10.1186/1471-2415-4-5.
6. Ten Berge JC, Schreurs MW, Vermeer J, Meester-Smoor MA, Rothova A. Prevalence and clinical impact of antiretinal antibodies in uveitis. *Acta Ophthalmol*. May 2016; 94(3):282–288. https://doi.org/10.1111/aos.12939.
7. Calabrese L, Velcheti V. Checkpoint immunotherapy: good for cancer therapy, bad for rheumatic diseases. *Ann Rheum Dis. Jan*. 2017;76(1):1–3. https://doi.org/10.1136/annrheumdis-2016-209782.
8. Kostine M, Chiche L, Lazaro E, et al. Opportunistic autoimmunity secondary to cancer immunotherapy (OASI): an emerging challenge. *Rev Med Interne. Aug*. 2017; 38(8):513–525. https://doi.org/10.1016/j.revmed.2017.01.004.
9. Tison A, Quere G, Misery L, et al. Safety and efficacy of immune checkpoint inhibitors in patients with cancer and preexisting autoimmune disease: a nationwide, multicenter cohort study. *Arthritis Rheumatol. Dec*. 2019;71(12): 2100–2111. https://doi.org/10.1002/art.41068.
10. Young L, Finnigan S, Streicher H, et al. Ocular adverse events in PD-1 and PD-L1 inhibitors. *J Immunother Cancer*. Jul 2021;9(7). https://doi.org/10.1136/jitc-2020-002119.
11. Makker V, Taylor MH, Aghajanian C, et al. Lenvatinib plus pembrolizumab in patients with advanced endometrial cancer. *J Clin Oncol. Sep 10*. 2020;38(26): 2981–2992. https://doi.org/10.1200/JCO.19.02627.
12. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther. Aug*. 1981;30(2):239–245. https://doi.org/10.1038/clpt.1981.154.
13. Reddy M, Chen JJ, Kalevar A, Terribilini R, Agarwal A. Immune retinopathy associated with nivolumab administration for metastatic non-small cell lung cancer. *Retin Cases Brief Rep. Spring*. 2020;14(2):120–126. https://doi.org/10.1097/ICB.0000000000000675.
14. Shahzad O, Thompson N, Clare G, Welsh S, Damato E, Corrie P. Ocular adverse events associated with immune checkpoint inhibitors: a novel multidisciplinary management algorithm. *Ther Adv Med Oncol*. 2021;13. https://doi.org/10.1177/1758835921992989, 1758835921992989.

15. Goetgebuer G, Kestelyn-Stevens AM, De Laey JJ, Kestelyn P, Leroy BP. Cancer-associated retinopathy (CAR) with electronegative ERG: a case report. *Doc Ophthalmol. Jan.* 2008;116(1):49–55. https://doi.org/10.1007/s10633-007-9074-9.
16. Adamus G. Are anti-retinal autoantibodies a cause or a consequence of retinal degeneration in autoimmune retinopathies? *Front Immunol.* 2018;9:765. https://doi.org/10.3389/fimmu.2018.00765.
17. Lei B, Bush RA, Milam AH, Sieving PA. Human melanoma-associated retinopathy (MAR) antibodies alter the retinal ON-response of the monkey ERG in vivo. *Invest Ophthalmol Vis Sci. Jan.* 2000;41(1):262–266.
18. Centanni M, Moes D, Troconiz IF, Ciccolini J, van Hasselt JGC. Clinical pharmacokinetics and pharmacodynamics of immune checkpoint inhibitors. *Clin Pharmacokinet. Jul.* 2019;58(7):835–857. https://doi.org/10.1007/s40262-019-00748-2.
19. Aust Lenvatinib. *Prescr. Dec.* 2017;40(6):242–243. https://doi.org/10.18773/austprescr.2017.070.