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Bilateral exudative retinal detachment in the macula a few hours after oral administration of melanoma drugs — binimetinib and encorafenib: a case report

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ABSTRACT

Mitogen-activated extracellular signal-regulated kinase (MEK) inhibitor-associated retinopathy (MEKAR) is observed in oncological patients undergoing MEK inhibitor therapy, such as binimetinib and encorafenib. It is characterized by self-limiting accumulation of the subretinal fluid. MEKAR typically presents bilaterally, involving the fovea, and reveals characteristic optical coherence tomography (OCT) features compared to central serous chorioretinopathy (CSR), which may clinically resemble. Recent studies highlight that MEKAR often resolves without discontinuing the inhibitors. We report a case of a 55-year-old female with metastatic melanoma who developed MEKAR a few hours after administering binimetinib and encorafenib treatment. Progress in the development of oncological diseases' pharmacological treatment, and consequently increased use of MEK inhibitors, should raise awareness among ophthalmologists regarding the management of patients with MEKAR and the importance of collaboration with oncologists.

KEY WORDS: MEK inhibitor-associated retinopathy (MEKAR); BRAF 6V00E mutation; binimetinib; encorafenib; central serous chorioretinopathy (CSR)

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INTRODUCTION

BRAF is a component of the RAS/RAF/MEK/ERK signaling pathway (MAPK), whose continuous activation leads to increased proliferation, survival, invasion, and metastasis of cancer cells.

Mutations in *BRAF* are prevalent in many types of cancers, including melanoma, papillary thyroid carcinoma, and colorectal cancer. A frequently occurring mutation in melanoma is *BRAF V600E*. It is associated with metastases and poorer prognosis [1].

Advances in genetic diagnostics and drug development have resulted in the creation of molecules targeted against the mutated BRAF kinase (e.g. encorafenib) and against the mitogen-activated extracellular signal-regulated kinase (MEK) directly activated by *BRAF* (binimetinib).

These molecules have proven their effectiveness in the treatment of melanoma and have led to a significant improvement in the prognosis of patients with metastatic melanoma with the *BRAF V600E* mutation [2].

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Drugs used in cancer chemotherapy are characterized by multiple side effects. Among the adverse effects of drugs targeting mutated BRAF and MEK kinases is retinopathy of the serous retinal detachment type, clinically similar to central serous chorioretinopathy (CSR) [3]. Due to the widespread occurrence of such side effects observed in multiple scientific studies, especially with the use of MEK inhibitors, the term MEKAR has been proposed to describe serous retinopathy associated with the use of MEK inhibitors [4].

MEKAR is classically described as the occurrence of self-limiting subretinal fluid accumulations that often resolve even without discontinuation of MEK and BRAF inhibitors.

The high effectiveness of BRAF and MEK inhibitors and the improved prognosis for melanoma patients have resulted in an increase in the popularity of this type of treatment and the creation of drug programs containing their various combinations also in the treatment of other cancers [2].

This resulted in an increased incidence of MEKARs, which a more significant number of ophthalmologists may encounter in clinical practice.

We present the case of a patient with metastatic melanoma of unknown origin, treated with binimetinib in combination with encorafenib, in whom only a few hours after taking oral tablets containing these substances bilateral macular serous retinopathy with accompanying visual disturbances occurred.

CASE PRESENTATION

A 55-year-old female patient was admitted to the Ophthalmology Department of the University Clinical Hospital in Opole with symptoms of blurred vision in both eyes, which occurred a few hours after being administered binimetinib (Mektovi) and encorafenib (braftovi) prescribed for melanoma metastases to the skin.

The diagnosis of melanoma of unknown primary origin was made a few months earlier at the Oncology Department of the Opole Oncology Centre based on genetic tests of material taken from the right axillary lymph nodes, which revealed the presence of a *BRAF V600E* gene mutation.

In January 2021, the patient developed an enlarging mass in the right axillary region. In June 2021, a core needle biopsy of the axillary lymph nodes revealed positive S100+ expression, and suspicion of metastatic malignant melanoma in the lymph nodes was raised. Imaging studies, including a contrast-enhanced computed tomography (CT) scan of the chest and abdomen performed in July 2021, showed right axillary lymphadenopathy, multiple liver metastases, small metastatic lesions in both lungs and osteolytic changes in the iliac bone. A molecular study using real-time polymerase chain reaction (PCR) of the material taken from the axillary lymph node revealed activating mutations in codons V600E, V600K, V600R, and V600D of the *BRAF* gene, confirming the diagnosis of malignant melanoma. In August 2021, magnetic resonance imaging (MRI) of the head was also performed. It did not reveal any signs of tumor growth or metastases.

A positron emission tomography-computed tomography (PET-CT) scan revealed pathological uptake in the iliac bone, liver, lung tumors, right axillary lymph nodes, a nodule in the right breast, and the left infraspinatus muscle. The primary site could not be determined despite numerous imaging and physical examinations.

The patient's oncological status was classified according to the Tumor–Node–Metastasis (TNM) staging system as cTxNxM1-IV. Medical interview revealed chronic nicotine use — 30 pack-years.

The patient was chronically treated only for hypertension with nebivolol 2.5 mg. Due to pain in the right axillary region, pain medications, including transdermal buprenorphine 35 μg/h, pregabalin 75 mg, and oral morphine 20 mg as needed, were used. The patient was qualified for treatment under the anti-BRAF/MEK drug program with encorafenib 450 mg/day (total 12,600 mg) and binimetinib 90 mg/day in two doses of 45 mg each (total 2520 mg) for 28 days.

Due to disease progression, pembrolizumab 200 mg intravenously was added (June 10, 2022). During the use of the aforementioned medications, monitoring occurred before and after the administration of pembrolizumab while continuing encorafenib.

Optical coherence tomography (OCT) examinations did not show pathological changes, suggesting that MEK inhibitors were the only cause of MEKAR. The patient, besides having hyperopia corrected with glasses [oculus dexter (OD; right eye) +6.5 Dsph, oculus sinister (OS, left eye) +5.5 Dsph], had no prior ophthalmic treatment.

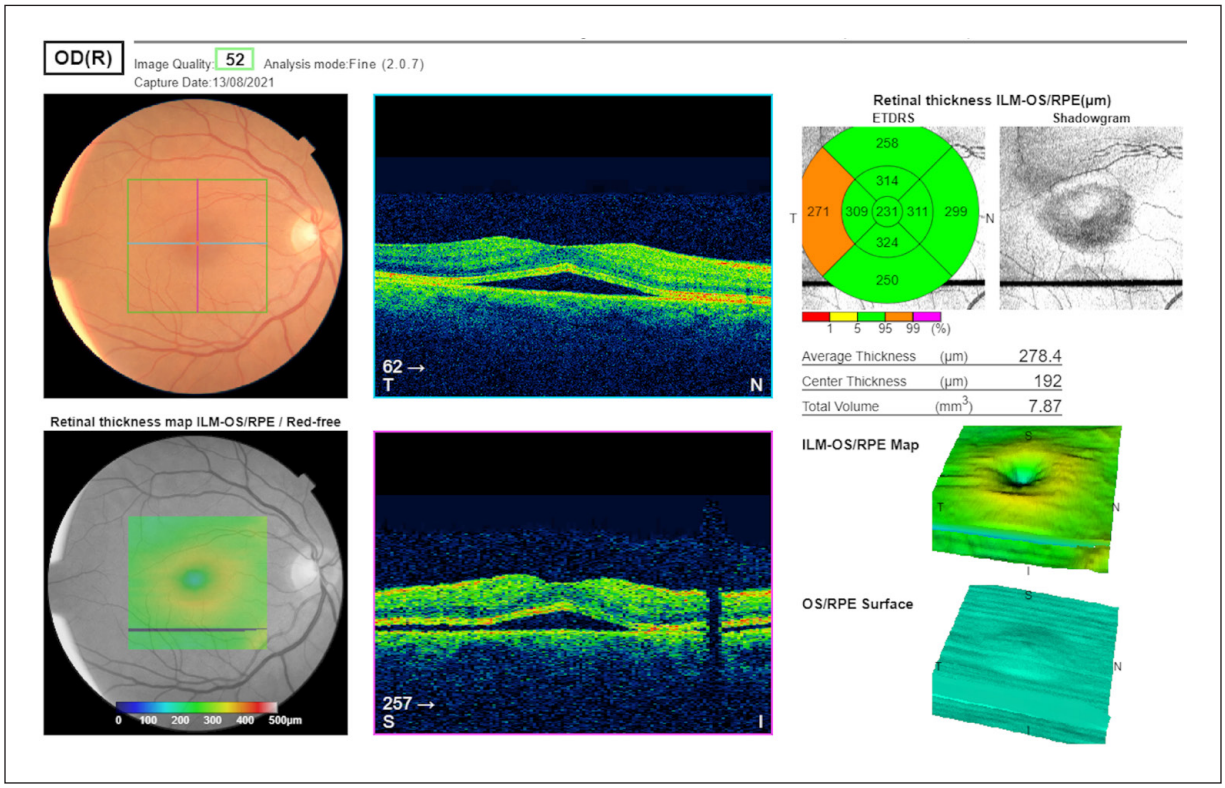

FIGURE 1. Optical coherence tomography (OCT) imaging showing retinal detachment in the macula of the right eye (OD) at the time of the patient's presentation to the Ophthalmology Department

On the day of presentation, visual acuity was decreased, with the OD at 20/35 and the OS at 20/32. The patient reported the following symptoms: blurred vision at both distance and near and metamorphopsia, including color changes with a dominance of yellow hues, missing contours of objects, and difficulty recognizing her reflection in the mirror.

Upon examination, bilateral changes were noted. A hyporeflective space was observed in the macula between the retinal pigment epithelium (RPE) and the outer segment of the photoreceptors (interdigitation zone — IZ), encompassing the fovea with a thickness of 352 µm in the OD and 329 µm in the OS (Fig. 1, 2). No deviations were found in the retinal nerve fiber layer (RNFL).

After an ophthalmological consultation, the oncologists discontinued binimetinib. The patient continued treatment with encorafenib.

During a follow-up examination one and a half months later, both eyes improved in visual acuity to 20/20, and macular changes were resolved in both eyes as observed in OCT (Fig. 3, 4).

In the follow-up after 12 months, there were no macular deviations in the OCT examination.

DISCUSSION

Initially, the authors classified observed ophthalmic adverse effects following MEK inhibitor use as serous retinal detachments, either CSR or CSR-like.

However, recent studies published in 2017 by Francis et al. from MSK Cancer Center in New York present clinical and morphological features distinguishing MEKAR from CSR. According to Francis et al., the median time from the initiation of therapy to the onset of symptoms was 14 days [3]. Authors reported that in a group of 25 patients treated with MEK inhibitors, 80% showed retinal changes visible on OCT, 92% were bilateral, 83.3% involved the fovea, and 73.8% had a domed shape. In all cases in this study, fluid leakage was located between the RPE and the IZ. The decrease in visual acuity did not exceed two Snellen lines [2].

According to the literature, the frequency of bilateral occurrence in the typical course of CSR is

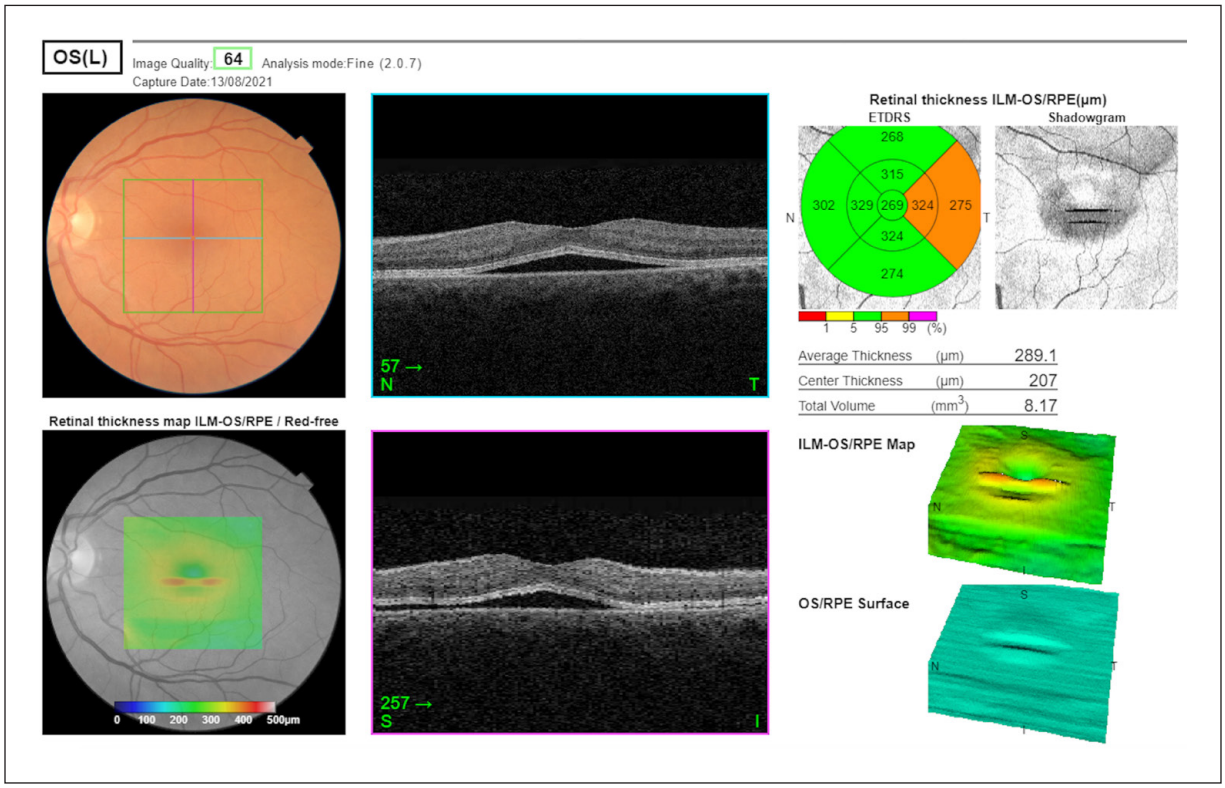

FIGURE 2. Optical coherence tomography (OCT) imaging showing retinal detachment in the macula of the left eye (OS) at the time of the patient's presentation to the Ophthalmology Department

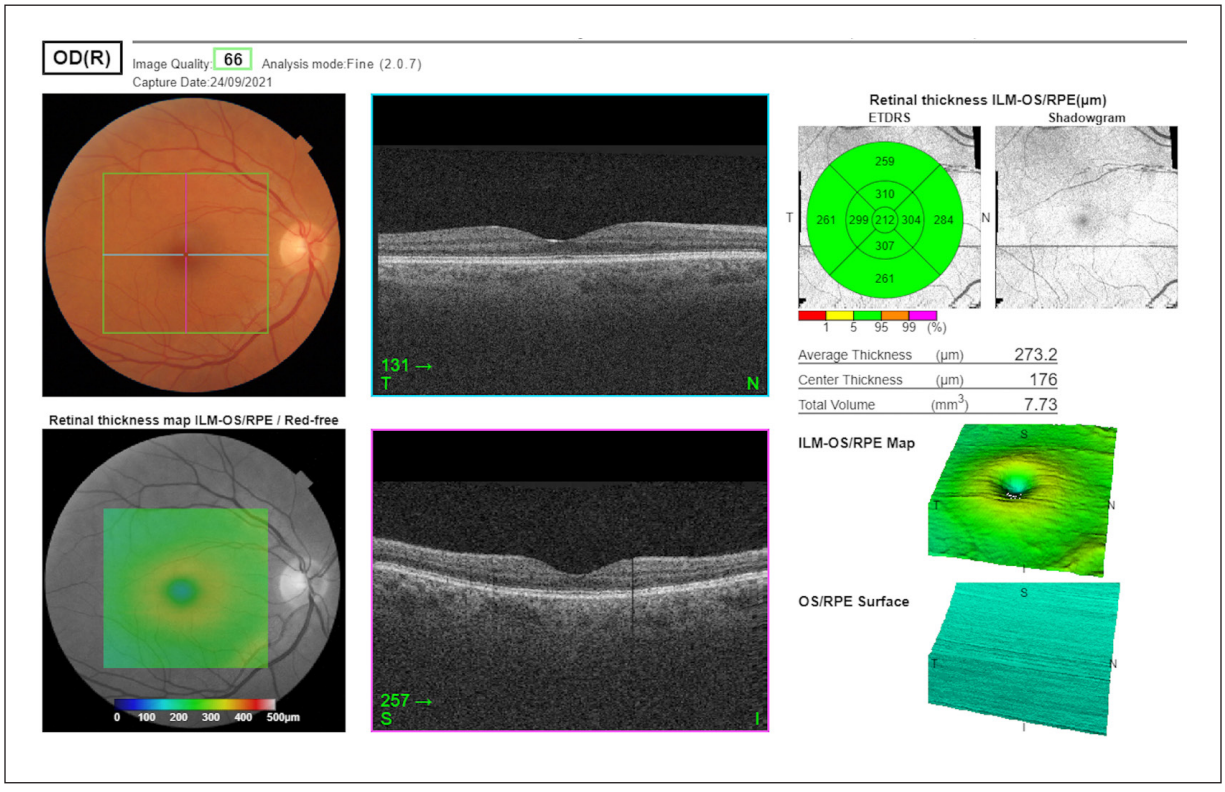

FIGURE 3. Optical coherence tomography (OCT) imaging showing the resolution of macular changes in the right eye (OD)

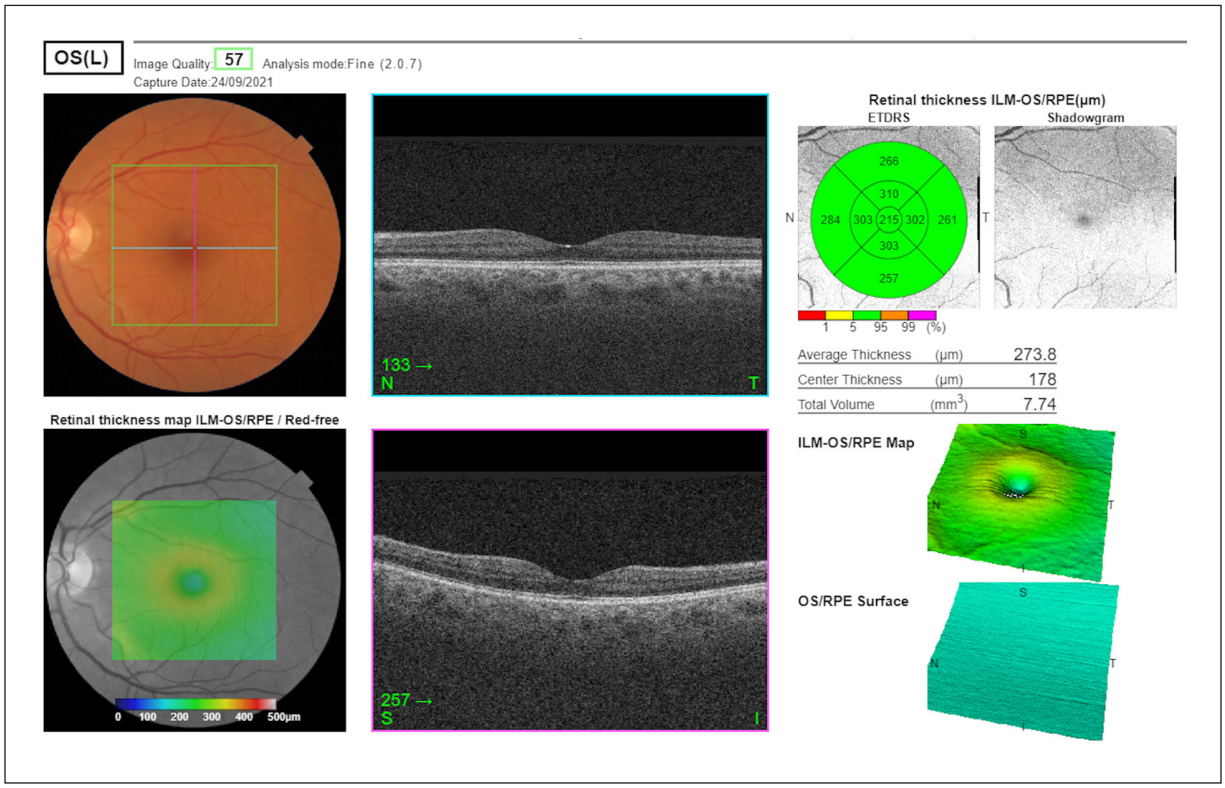

FIGURE 4. Optical coherence tomography (OCT) imaging showing the resolution of macular changes in the left eye (OS)

estimated at 5–18% [5]. Additionally, CSR changes in OCT tend to show the gravitational movement of subretinal fluid 6, which was not observed in our patient.

These findings indicate that our patient has experienced MEKAR rather than CSR. Differential diagnosis should also consider vitelliform degeneration, which can occur in melanoma.

The authors emphasize the self-limiting and time-resolving nature of MEKAR despite the continued use of MEK inhibitors. The time to resolve the changes depended on the number of therapy cycles, and the average was 32 days (a mean of 21 days with a single cycle and an average of 54 days after more than 5 cycles). However, the literature describes a case where MEKAR-like changes induced by the administration of lacnotuzumab did not resolve for 266 days (until the patient's death) [7].

CONCLUSIONS

The case we presented, while not isolated since it concerns most patients treated with MEK inhibitors, appears controversial due to the surprisingly short time from drug administration to the onset of symptoms — just a few hours [3]. In the above discussion, we undertook differential diagnosis with vitelliform degeneration, which can occur in the course of melanoma, and similarly presenting CSR, which we can likely exclude: correlation with drug use, bilateral location in the fovea, typical domed shape, minimal decrease in visual acuity, and resolution of symptoms after drug discontinuation, without recurrence, are consistent with the clinical and morphological features described in the study by Francis et al. [3].

Due to the high frequency of vision disturbances, patients treated with MEK inhibitors should receive special ophthalmic care. The decision to discontinue anticancer drugs in case of their occurrence should not be hasty but made in consultation with oncologists. It is advisable to search for risk factors or the impact of previously coexisting ophthalmic conditions such as diabetic retinopathy, diabetic macular edema (DME), or exudative age-related macular degeneration (AMD).

In the era of developing cancer treatments with monoclonal antibodies and the popularization of drug programs, including MEK inhibitors such as binimetinib, it seems appropriate to expand ophthalmologists' knowledge in this area and foster interdisciplinary collaboration between ophthal-

mologists and oncologists to ensure optimal care for oncological patients.

Ethics statement
Not applicable to this study.

Consent to participate
Not applicable to this study.

Author contributions
M.G. designed the case report. M.G., D.T., M.K. and A.L. contributed to writing and editing of this manuscript. All authors read and approved the final version.

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Conflict of interest
The authors declare no competing interests with the content of this manuscript.

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REFERENCES

1. Zaleśna I, Hartman ML, Czyż M. [BRAF mutation in progression and therapy of melanoma, papillary thyroid carcinoma and colorectal adenocarcinoma]. Postepy Hig Med Dosw (Online). 2016; 70: 471–488, doi: 10.5604/17322693.1201719, indexed in Pubmed: 27180965.
2. Potocki LP, Potocki PM, Wysocki PJ. BRAF — a new therapeutic target in colorectal cancer. Oncol Clin Pract. 2018; 14(2): 86–95, doi: 10.5603/OCP.2018.0013.
3. Francis JH, Habib LA, Abramson DH, et al. Clinical and Morphologic Characteristics of MEK Inhibitor-Associated Retinopathy: Differences from Central Serous Chorioretinopathy. Ophthalmology. 2017; 124(12): 1788–1798, doi: 10.1016/j.ophtha.2017.05.038, indexed in Pubmed: 28709702.
4. Groselli S, Heinrich D, Lohmann CP, et al. MEK-Inhibitor-assoziierte Retinopathie unter Binimetinib-Therapie bei kutanem malignem Melanom. Der Ophthalmologe. 2020; 118(2): 169–174, doi: 10.1007/s00347-020-01089-3.
5. Zhang X, Lim CZ, Chhablani J, et al. Central serous chorioretinopathy: updates in the pathogenesis, diagnosis and therapeutic strategies. Eye Vis (Lond). 2023; 10(1): 33, doi: 10.1186/s40662-023-00349-y, indexed in Pubmed: 37430344.
6. Zarnegar A, Ong J, Matsyaraja T, et al. Pathomechanisms in central serous chorioretinopathy: A recent update. Int J Retina Vitreous. 2023; 9(1): 3, doi: 10.1186/s40942-023-00443-2, indexed in Pubmed: 36670451.
7. Chancellor JR, Kilgore DA, Sallam AB, et al. A Case of Non-Resolving MEK Inhibitor-Associated Retinopathy. Case Rep Ophthalmol. 2019; 10(3): 334–338, doi: 10.1159/000503414, indexed in Pubmed: 31762764.