Comparing Tamoxifen Retinopathy and Macular Telangiectasia Type 2 with Two Cases

Fundanur Karakuş[1], Pınar Kaya[2], Berrak Şekeryapan Gediz[3]

ABSTRACT

Summary: Tamoxifen is an anti-estrogenic agent commonly used as adjuvant therapy in hormone receptor-positive breast cancer cases. Among its reported ocular toxicities, retinopathy is the most frequently observed manifestation. Macular telangiectasia type 2, on the other hand, is an idiopathic, bilateral, and asymmetrically progressive retinal vasculopathy that closely resembles Tamoxifen retinopathy in terms of clinical findings. The aim of this article is to provide a comparative evaluation of these two clinically similar pathologies.

Key Words: Mac-Tel type 2, macular telangiectasia type 2, Tamoxifen maculopathy, tamoxifen retinopathy.

INTRODUCTION

Tamoxifen is a non-steroidal selective estrogen receptor modulator used as adjuvant endocrine therapy in patients with estrogen receptor-positive breast cancer. It has been shown to reduce the risk of recurrence and mortality following surgery in operable breast cancer, and to decrease the incidence of contralateral breast cancer in high-risk patients.[1,2] The toxic effects of Tamoxifen on the eye were first described in 1978.[3,4] The reported incidence of ocular side effects in the literature ranges from 0.9% to 11%, including keratopathy, cataract, optic neuritis, crystalline retinopathy with or without macular edema, and pseudocystic foveal cavitation.[5,6]

Macular telangiectasia type 2, also known as idiopathic perifoveal telangiectasia, juxtafoveolar retinal telangiectasia type 2A, or Mac-Tel 2, is an acquired, bilateral, neurodegenerative macular disease. It typically develops between the fourth and sixth decades of life and is characterized by minimal dilation of parafoveal capillaries, graying of the affected retinal area, right-angled retinal venules, refractile deposits in the superficial retina, hyperplasia of the retinal pigment epithelium, foveal atrophy, and subretinal neovascularization.[7]

In this study, we aim to compare Tamoxifen retinopathy (TR) and Mac-Tel 2, two diseases with overlapping clinical features through our cases and to discuss their differential diagnosis.

CASE REPORTS

CASE 1

A 38-year-old female patient presented to our outpatient clinic with complaints of decreased vision in both eyes persisting for several months. Best-corrected visual acuity was measured as 0.8 in the right eye and 0.2 in the left eye. Anterior segment examination revealed no pathology, and

1. MD, Ankara Etlik City Hospital, Opthalmology Department, Ankara, Türkiye
2. MD, Assoc. Prof., Ankara Etlik City Hospital, Opthalmology Department, Ankara, Türkiye
3. MD, Prof., Ankara Etlik City Hospital, Opthalmology Department, Ankara, Türkiye

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Correspondence author:
Fundanur Karakuş
Email: fundanurkarakus@gmail.com

intraocular pressures were within normal limits. Fundus examination showed a reduction in the foveal reflex in both eyes and crystalline-like deposits in the parafoveal region. Optical coherence tomography (OCT) was performed, which revealed minimal foveal cavitation with loss in the outer retinal layers and interdigitation zone in the right eye, and cyst formation in the inner retinal layers with a full-thickness macular hole covered by the internal limiting membrane in the left eye **(Figure 1)**. Optical coherence tomography angiography (OCTA) revealed no abnormalities in either the deep or superficial vascular plexuses **(Figure 2).** An initial diagnosis of Mac-Tel type 2 was considered. However, upon further anamnesis, it was learned that the patient had undergone breast cancer surgery 5 years earlier and had been started on adjuvant Tamoxifen therapy thereafter. Consequently, the clinical picture was attributed to Tamoxifen-induced retinopathy, and discontinuation of the medication was recommended.

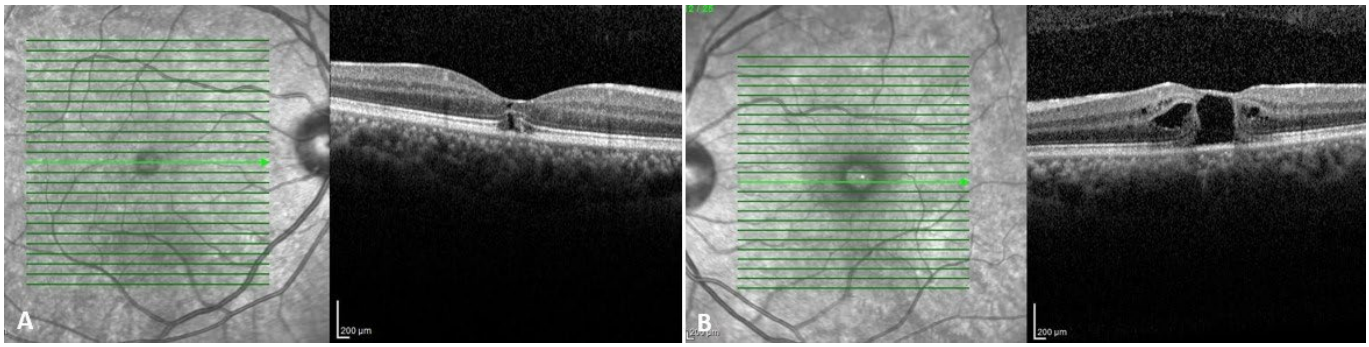

Figure 1. *In the optical coherence tomography imaging of the first case, (A) the right eye demonstrated minimal foveal cavitation in the outer retinal layers accompanied by loss in the interdigitation zone, while (B) the left eye showed cyst formation in the inner retinal layers and a full-thickness macular hole covered by the internal limiting membrane.*

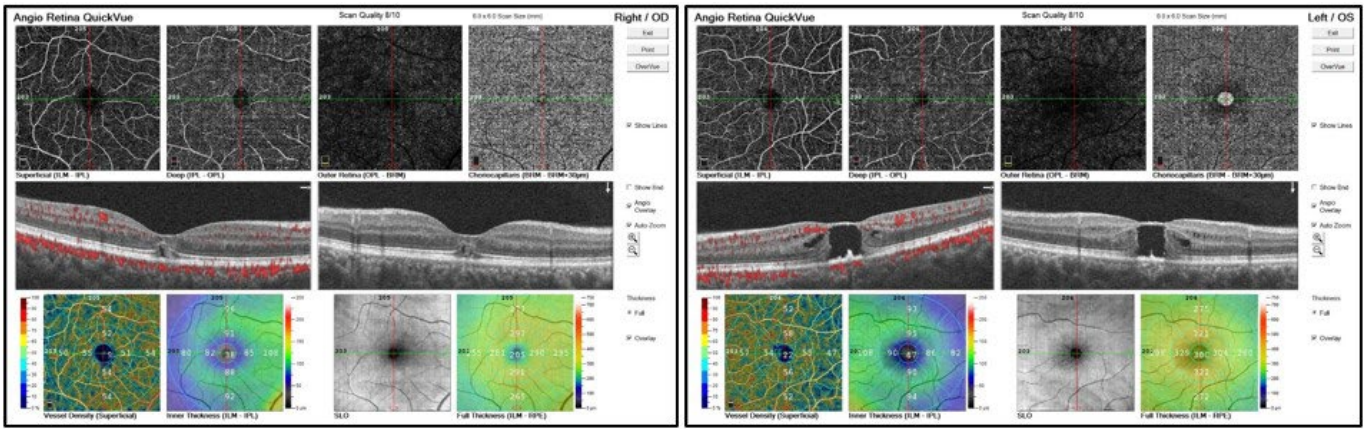

Figure 2. *In the optical coherence tomography angiography of the first case, no pathology was observed in either the deep or superficial vascular plexuses.*

CASE 2

A 54-year-old female patient presented to our outpatient clinic with complaints of decreased vision in both eyes for the past 2 years. Best-corrected visual acuity was 0.9 in the right eye and 0.6 in the left eye. Anterior segment examination revealed no pathology, and intraocular pressures were within normal limits. Fundus examination demonstrated a reduction in the foveal reflex in both eyes. Optical coherence tomography (OCT) showed normal findings in the right eye, while in the left eye minimal foveal cavitation was observed in both the inner and outer retinal layers, accompanied by loss in the ellipsoid zone (EZ) and interdigitation zone. Fundus autofluorescence (FAF) imaging revealed no abnormalities **(Figure 3).** Optical coherence tomography angiography (OCTA) also showed no pathology in either the deep or superficial vascular plexuses **(Figure 4)**. Medical history revealed that the patient had undergone breast cancer surgery 5 years earlier and was started on adjuvant Tamoxifen therapy, which was discontinued after 4 years due to the development of Tamoxifen retinopathy (TR). She reported not having used Tamoxifen for the past 1.5 years and was placed under follow-up in our clinic.

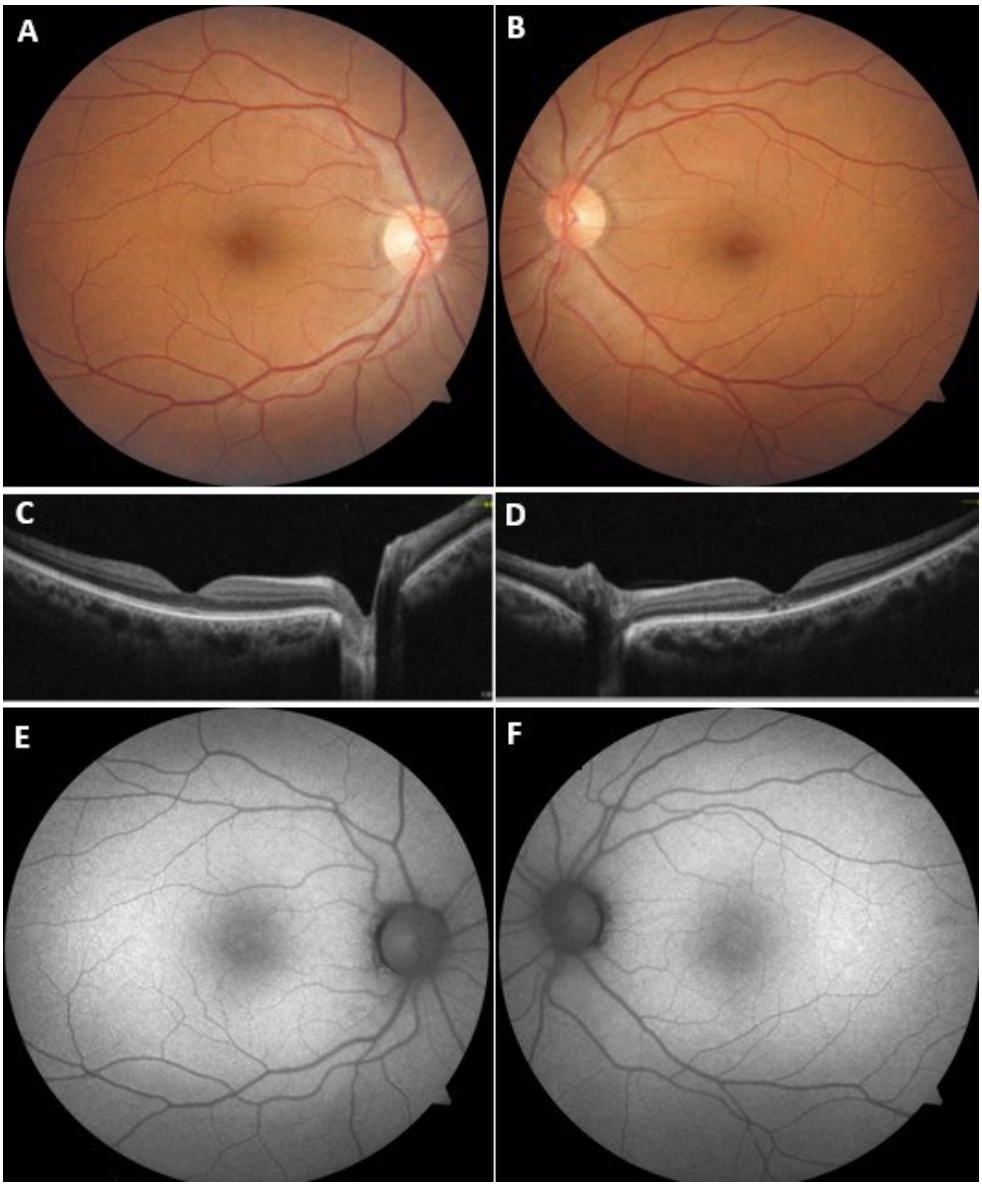

Figure 3. *In the color fundus photographs of the second case, a decrease in the foveal reflex was observed in the right (A) and left (B) eyes. Optical coherence tomography showed normal findings in the right eye (C), while in the left eye (D) minimal foveal cavitation in both the inner and outer retinal layers was detected, accompanied by loss in the ellipsoid and interdigitation zones. Fundus autofluorescence imaging revealed no pathology in either the right (E) or left (F) eye.*

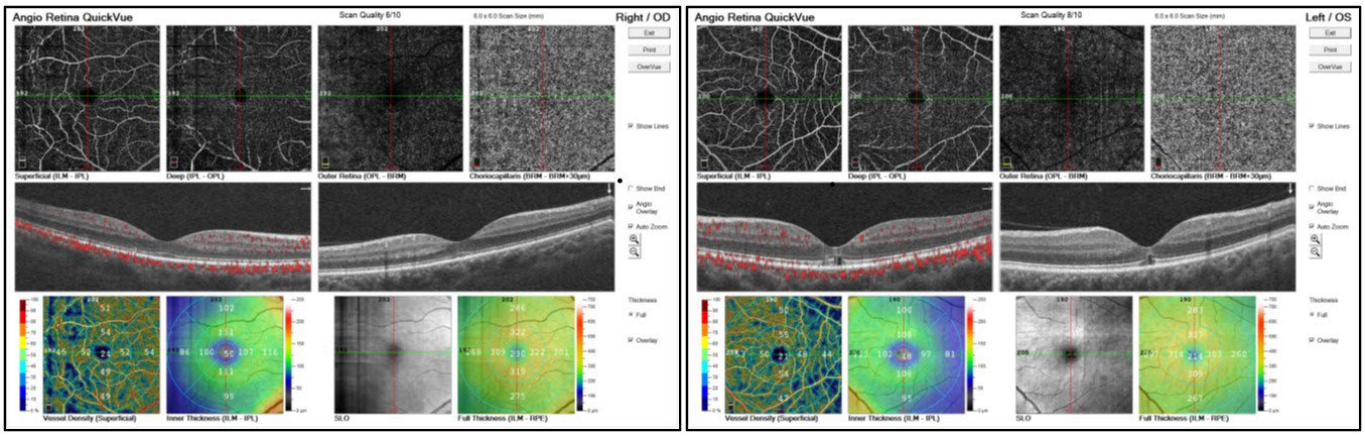

Figure 4. *In the optical coherence tomography angiography of the second case, no pathology was detected in either the deep or superficial vascular plexuses.*

DISCUSSION

Although Tamoxifen retinopathy and Mac-Tel 2 are two retinal disorders with similar symptoms and clinical findings, their treatment and prognosis differ; therefore, making a differential diagnosis is of great importance. In this article, we discuss the similarities and differences between these two entities in light of the literature, based on two presented cases.

Tamoxifen retinopathy was first reported in the literature in association with high-dose use of the drug, after which the recommended dosage was reduced and the mechanisms underlying ocular toxicity began to be investigated.[3,4] A cumulative dose exceeding 100 g has been suggested as a possible contributing factor.[8] Subsequently, it has been reported that maculopathy may develop even at low doses (10–20 mg/day) and can be detected in asymptomatic patients as well.[8-10] The current standard Tamoxifen regimen for breast cancer is 5 consecutive years; however, the global Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) trial demonstrated that extending treatment to 10 years significantly reduces the risk of recurrence and mortality in breast cancer.[11] Therefore, longer treatment durations with Tamoxifen may be adopted, and routine ophthalmologic consultations should be considered in order to monitor for ocular toxicity.

Mac-Tel 2 is most commonly observed bilaterally, whereas there is no statistically definitive information regarding whether TR occurs unilaterally or bilaterally.[12] TR and Mac-Tel 2 demonstrate similar structural changes on optical coherence tomography (OCT). Clinically, crystalline deposits may be observed on fundus examination, while OCT findings may include focal disruption of the photoreceptor layer and hyporeflective foveal cavitations.[13-15] In TR, early stages on OCT typically show foveal cyst formation due to disruption of the photoreceptor layer, while advanced stages may reveal cystoid macular edema and full-thickness macular holes confined by the internal limiting membrane.[16] The crystalline deposits observed in Mac-Tel 2, however, correspond to cystic spaces within the inner retinal layers on OCT. Another multimodal imaging method, fundus autofluorescence (FAF), is particularly important in diagnosis, as it demonstrates increased autofluorescence in the fovea of Mac-Tel 2 patients.[15,17,18] In our second case, the absence of pathological findings on FAF supported the diagnosis of TR.

In serial observations of Mac-Tel 2 patients, it has been shown that neurodegenerative and neurovascular changes progress simultaneously.[19,20] In a study by Park et al.[21] comparing OCT and OCTA findings at diagnosis and one year later in patients with Mac-Tel 2 and TR, intraretinal cavitations, ellipsoid zone (EZ) loss, and telangiectasia in the capillary plexuses were observed in both groups. While EZ disruption in Mac-Tel 2 predominantly affected the temporal region, in TR it remained confined to the foveal center. OCTA analysis demonstrated that vascular density was significantly reduced in the deep temporal parafovea in Mac-Tel 2 eyes and in the superficial

fovea in TR eyes. At the one-year follow-up, Mac-Tel 2 patients exhibited progression of EZ loss accompanied by proliferative vascular remodeling, whereas in TR patients one year after drug discontinuation, capillary rarefaction and telangiectasia remained unchanged, but partial EZ recovery was noted in some areas. This improvement in the EZ layer can be observed even in advanced TR following discontinuation of Tamoxifen, suggesting microvascular improvement. Therefore, although the clinical findings of these two entities are similar, their prognoses differ, making differential diagnosis essential.

Fundus fluorescein angiography (FFA) is considered the gold standard in the diagnosis of Mac-Tel 2. In particular, the presence of telangiectatic capillaries temporal to the fovea observed in the early phase, followed by diffuse late-phase leakage, is diagnostic.[22] In TR patients, however, despite the cystoid macular edema appearance on OCT, no leakage is observed on FFA.[12] Although the absence of FFA imaging in our cases represents a limitation, the history of Tamoxifen therapy, the characteristic OCT findings of the lesions, and the absence of typical Mac-Tel 2 changes on OCTA enabled a diagnosis of TR to be established even without FFA examination.

In the pathogenesis of both diseases, defects in Müller cells—which provide nutritional and regulatory support to retinal neurons and vascular structures—are implicated. The glutamate-aspartate transporter produced by Müller cells plays a key role in removing glutamate, which exerts toxic effects on the retina.[23,24] Tamoxifen inhibits glutamate uptake in Müller cells, leading to glutamate-induced toxicity, Müller cell dysfunction, and subsequent apoptosis. This process contributes to vascular remodeling and neurodegeneration of the retinal layers.[24,25] Moreover, Müller cell ablation alters the expression and regulation of vascular endothelial growth factor-A, disrupting the balance between angiogenic and anti-angiogenic factors, which in turn leads to vascular telangiectasia and neovascularization in the deep retinal layers.[26] To prevent this progressive degeneration, early detection of TR and discontinuation of Tamoxifen therapy are essential. In our second case, discontinuation of the drug following the detection of changes during routine ophthalmic examination allowed relative preservation of visual acuity.

CONCLUSION

Since Tamoxifen retinopathy and Mac-Tel type 2 present with similar clinical findings, obtaining a detailed medical history and identifying medications used by the patient are of great importance. While one of these retinal pathologies is idiopathic, the other develops as a drug-related adverse effect; therefore, confirming the diagnosis is crucial for prognosis, as discontinuation of Tamoxifen may be required. In the differential diagnosis, multimodal imaging techniques should be employed to investigate and evaluate the characteristic features of each disease.

The ocular complications of Tamoxifen therapy reported in the literature are largely based on anecdotal observations. Routine ophthalmologic examinations for patients receiving Tamoxifen therapy should be integrated into multidisciplinary practice, as this is highly important for preventing potential complications.

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