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Tamoxifen Retinopathy. An Uncommon but Serious Complication: Case Report

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Abstract: Tamoxifen is a selective estrogen receptor modulator most widely used in the treatment of hormone-dependent breast cancer. We describe a case of a 51-year-old woman treated with tamoxifen for 4 years who had gradual diminution of vision in both eyes of three months duration. On examination, visual acuity was 20/40 in the right eye and 20/50 in the left eye. A fundus examination revealed bilateral symmetric crystalline deposits in the macula. There were characteristic structural changes on spectral domain-optical coherence tomography, including abnormalities of the ellipsoid zone and outer nuclear layer. Subsequently, tamoxifen was switched to anastrozole. Despite cessation of tamoxifen, her vision did not improve. The clinical presentation of tamoxifen retinopathy is discussed, along with the importance of regular ophthalmic examination for individuals receiving tamoxifen, even in low doses.

Keywords: Tamoxifen; Retinopathy; Ocular toxicity; Maculopathy.

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1. Introduction

Breast cancer is the most common cancer diagnosed in women and the second leading cause of worldwide cancer-related mortality, of which 67–81% are estrogen receptor-positive. Tamoxifen is an oral selective estrogen modulator that acts to competitively inhibit the binding of endogenous estrogens. It is widely used to treat and prevent the recurrence of hormone receptor-positive breast cancer. The drug has been approved for use in reducing the incidence and mortality of breast cancer among patients at moderate to high risk of breast cancer. Tamoxifen also has many off-labeled uses and may require additional data. Like many cancer drugs, tamoxifen is associated with numerous adverse effects. The most common systemic side effects include hot flashes, nausea, vomiting irregularly, rash, deep venous thrombosis and pulmonary embolism. Although tamoxifen is usually well-tolerated in low doses, ocular complications have been reported in patients who use it daily [1].

Ocular toxicity of tamoxifen has been described since 1978 and includes conjunctivitis, keratopathy, cataract, glaucoma, optic neuritis, retinopathy and ophthalmic vein thrombosis [2-5]. Of these, the pathologies of the retina appear to be the most frequent and of the greatest clinical significance. Since then, many more cases have been described, and patterns are beginning to be identified. The standard treatment with tamoxifen for breast cancer prevention after completion of chemotherapy is 20-40mg/day for 5 to 10 consecutive years depending on the patient's menopausal and individual factors. There-

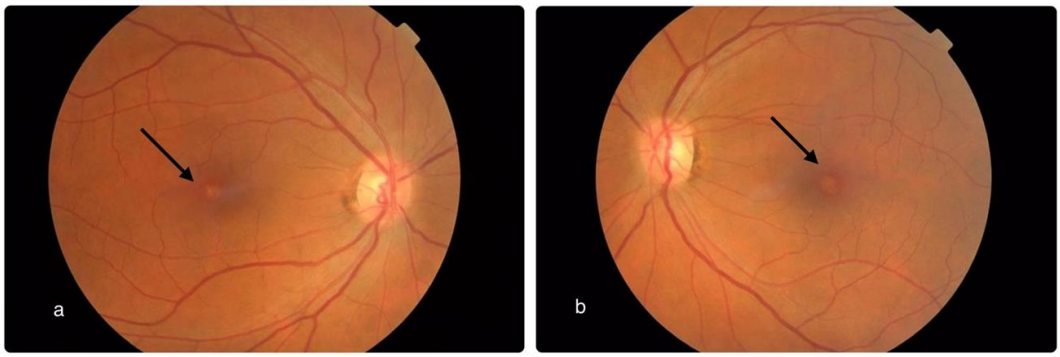
fore, patients with poorer prognosis disease and its toxicity on eyes should be more concerned. It has been suggested that periodic ocular evaluations be done to detect these complications before visual deterioration occurs [3, 4].

Noureddin et al [3] found that eight of 65 women using standard doses of tamoxifen developed corneal, retinal, or optic nerve head changes, and, in some cases, two types of change. Furthermore, they suggested that the development of toxicity was related significantly to the duration of drug use. Alterations in the retina appears to occur in as many as 12% of patients taking a daily dose of 20 mg of tamoxifen for at least 2 years, including crystalline deposits, telangiectasia, macular edema, hyperreflective deposits in the retinal layers, and pseudocystic foveal cavitation. Of the patients affected, fewer than half developed symptomatic changes in visual acuity [5]. Tamoxifen retinopathy (TR), though rare, causes irreversible retinal degeneration. So, early detection helps in prevention of visual loss. Patients with high body mass index and dyslipidemia are at higher risk of developing TR [3, 5, 6]. Here we describe a case of TR documented by fundus photography and spectral-domain optical coherence tomography (SD-OCT), emphasizing the importance of considering advances in ophthalmic images modalities for screening and greater characterization of this toxicity.

2. Case Report

A 51-year-old female presented to our clinic with progressive bilateral visual loss of vision for the last 3 months. She had been diagnosed with breast cancer and had undergone a radical mastectomy 4 years ago. Since then, she had been receiving oral tamoxifen at a dosage of 20 mg/day with a cumulative dose of 35.2g. Chemotherapy with doxorubicin and cyclophosphamide for breast invasive ductal carcinoma was used for five months after mastectomy. On presentation, the Snellen best corrected visual acuity (BCVA) was 20/40 in the right eye (OD) and 20/50 in the left eye (OS). Her BVCA had been 20/20 bilaterally in the past. Intraocular pressure was normal and anterior segment examination was unremarkable. Pupils were reactive with no afferent pupillary defect, and ocular motility was normal in both eyes (OU). The color vision measure Ishihara chart was normal. Fundus examination revealed bilateral symmetric crystalline deposits in the macula (Figure 1).

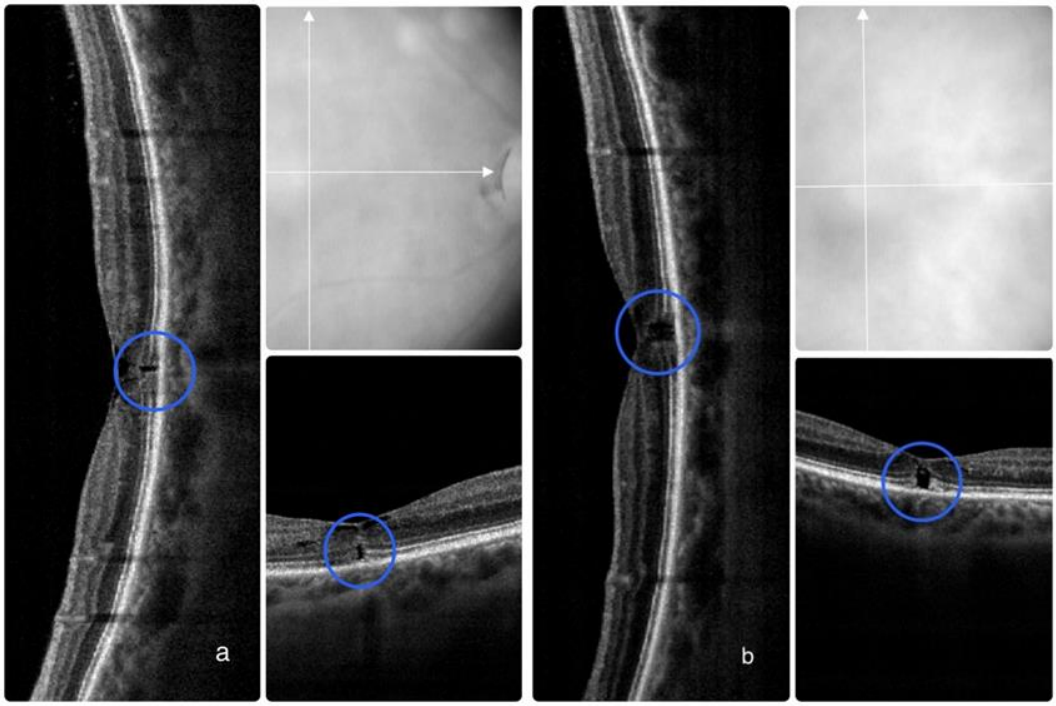
Figure 1. Fundus photograph of the right (a) and left (b) eyes with fine yellow white refractile deposits in perifoveal area (arrows). These deposits may be related to axonal degeneration as suggested by Kaiser-Kupfer et al. [2].



The 24 -2 octopus perimetry (Haag Streit, Switzerland) revealed only a mild sensitivity depression within the central 10º field. SD-OCT scan showed outer retinal loss with foveal cavitation, cysts, refractile crystals deposits in the inner retinal layers and ellipsoid zone disruption in OU (Figure 2). Based on this history and the clinical and imaging findings, the diagnosis of TR was made. Tamoxifen was discontinued after discussion with

the oncologist, and the unfavorable prognosis was explained. Instead of tamoxifen, treatment with anastrozole (1mg/day) was started. After 6-month follow-up, results of BCVA, fundoscopic examination and SD-OCT imaging remained stable with neither progression nor regression.

Figure 2. Spectral-domain optical coherence tomography (SD-OCT) showing hyporeflective spaces in the retinal layers and disruption of the ellipsoid zone of the right (a) and left (b) eyes (blue circles). The ellipsoid zone represents the inner portion of the photoreceptor layer that is densely packed with mitochondria, and has unique, clinically useful functional significance.



3. Discussion

Despite reports of the successful use of tamoxifen in reducing breast cancer recurrence and mortality, potential ocular complications have emerged, particularly those affecting the macula. TR is characterized by crystalline deposits and pseudocystic cavitation in the central macula, with or without macular edema [2, 5, 7]. Previous reports have found the prevalence of TR varying from 1.5% to 11,8% in patients being treated for breast cancer [8,9]. However, recent studies have reported higher prevalence rates, which might be partly explained by use of SD-OCT as a diagnostic tool in detecting earliest retinal changes, such as crystalline deposits, intraretinal pseudocysts and alterations of the photoreceptor layer in tamoxifen users [6, 10, 11]. Most previous studies were based only on the fundus examination.

The mechanism of retinal changes associated with tamoxifen is still unclear. Tamoxifen inhibits the glutamate-aspartate transporter, leading to excessive intracellular accumulation of glutamate in Müller cells, that are vital in maintaining retinal cell integrity and homeostasis of the retinal layers. It may cause intraretinal cystic foveal cavitation, sharing common features with Macular Telangiectasia type 2 (MacTel2) [7]. In 1978, Kaiser-Kupfer and coworker suggested that crystalline retinal deposits formation in tamoxifen users can be related to axonal degeneration in the nerve fiber and inner plexiform layers of the retina, as demonstrated by SD-OCT imaging [2]. It has been also postulated that tamoxifen binds with polar lipids, inhibiting normal catabolism in the lysosomes and

inducing cell damage through oxidative stress. [11]. Moreover, the pathogenesis of Tamoxifen-related macular edema presumably involves vascular endothelial damage, increased vascular permeability and elevated vascular endothelial growth factor [12].

Retinal lesions similar in appearance to those associated with tamoxifen may also occur with inherited metabolic disorders such as oxalosis, nephropathic cystinosis, Bietti's crystalline retinopathy, Sjogren-Larsson syndrome, Kjellin syndrome, Alport's syndrome, talc retinopathy, calcified drusen and parafoveal telangiectasis [5]. Ocular toxicity is more evident with cumulative dosing greater than 100g. Our patient was taking 20mg daily, which is the recommended dose. Koulisis et al [13] showed maculopathy ocurring at low dose (20mg daily) and much lower cumulative doses (0.42g). Our patient was presented with decreased visual acuity and fundoscopy showed crystal deposits without macular edema. SD-OCT revealed diffused disruption of the ellipsoid zone and interdigitation zone, and intraretinal cavitation in both eyes, which was correspond to the complaint of decreased visual acuity, which also agrees with the findings presented in previous studies [5-7,13].

Patients with MacTel2 and TR showed intraretinal cavitation, ellipsoid zone (EZ) loss, and capillary telangiectasia in the superficial and deep plexuses. Most findings in patients with TR were limited mainly to the foveal center, whereas changes in patients with MacTel2 were present throughout a slightly larger region, mainly temporal to the foveal center [14]. TR is currently managed by discontinuing tamoxifen therapy with the approval of the patient and the prescribing medical physician; however, no significant recovery of visual acuity has been noted in most cases. Intravitreal injections of triamcinolone acetonide or antivascular endothelial growth factor therapy have been performed, like treatments employed for MacTel2 or in cases with macular edema [5,12]. We have withdrawn tamoxifen and started on anastrozole in our patient. The importance of screening is well-recognized for patients taking tamoxifen. However, there is no consensus on the frequency and modalities to detect the development of TR. A common recommendation is to conduct regular screenings including OCT and fundoscopy, perhaps every 6 months, particularly for patients who have been on tamoxifen therapy for at least 2 years [5, 15].

4. Conclusion

Interprofessional teamwork and communication provides increased likelihood of success for all patients. Because TR is irreversible, it is of great value to detect earlier signs of retinal changes. So, patients undergoing tamoxifen therapy should be examined by the ophthalmologist before drug initiation and screened for ocular toxicity periodically improving the chance of visual preservation. Retinography, fluorescein angiography and SD-OCT provide valuable information for identifying structural changes and evaluating ocular findings in patients receiving tamoxifen therapy. We recommend SD-OCT, a non-invasive, accurate, and reproducible method, for the follow-up of patients using tamoxifen, regardless of duration of treatment.

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Research Ethics Committee Approval: We declare that the patient approved the study by signing an informed consent form and the study followed the ethical guidelines established by the Declaration of Helsinki.

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Conflicts of Interest: The authors declare no conflicts of interest.

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