Tamoxifen Retinopathy: Retinal Cavitation without Crystalline Deposits

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Abstract

Tamoxifen is a selective estrogen receptor modulator that is commonly used to treat and prevent the recurrence of estrogen receptor-positive breast cancer. Even at low doses, adverse effects have been reported, such as pseudo cystic foveal cavitation, refractile crystalline deposits, and photoreceptor disruption. With the advent of modern imaging technology such as optical coherence tomography, the prevalence of tamoxifen retinopathy has been found to be greater than previously believed. We report a case of tamoxifen retinopathy that manifested without typical crystalline retinal deposits and a normal fundus exam, with a diagnosis based on clinical findings, risk factors, and multimodal imaging. A comprehensive review of the condition is also presented, including pathophysiology, treatment, and multimodal imaging results.

KEY WORDS:
tamoxifen; retinopathy; crystals; cavitation

INTRODUCTION

Historically presenting as crystalline retinopathy, tamoxifen retinopathy is secondary to high or chronic low doses of tamoxifen, an anti-estrogen drug used in the treatment and prevention of estrogen receptor breast cancer.[1-3] This condition was thought to be rare. However, with the introduction of multimodal imaging, an earlier diagnosis can be made with or without the presence of retinal deposits.[4,5] In addition to crystalline deposits, typical signs as revealed by optical coherence tomography (OCT) can include pseudo-cystic cavitation, or more rarely, macular edema or macular holes.[5] The differential diagnosis includes other conditions that can result in retinal crystal deposition; however, the main differential is macular telangiectasia type 2.[6-10] This is in accordance with a likely analogous underlying pathology, Müller cell involvement, which results in similar clinical presentation.[5] Treatment options are limited to extreme presentations, and communication with the underlying prescriber is key as patients may require an alternative to tamoxifen.[6,11] This case report details a presentation of tamoxifen retinopathy, pseudo cystic cavitation without crystalline deposits, that was diagnosed with the aid of multimodal imaging.

CASE REPORT

A 57-year-old African American female presented for a comprehensive eye exam with longstanding but stable complaints of dry eyes OU. The patient's medical history was remarkable for essential hypertension, type two diabetes mellitus, high cholesterol, and a history of breast cancer. The patient's last HbA1c was unknown and the last fasting blood sugar measurement was 379 mg/dL. Current systemic medications included nebivolol, losartan, sitagliptin, glipizide, and tamoxifen. She also used artificial tears as needed in both eyes for her dry eyes. The breast cancer was diagnosed 5 years prior and was subsequently treated with radiation therapy and tamoxifen at 20mg once daily since that time. The patient did not have any known medical or drug allergies. Her body mass index (BMI) was measured at 34.3 kg/m^2. Her family history was remarkable for paternal glaucoma, maternal diabetes mellitus, and hypertension in the patient's brother. The patient was also an everyday smoker of ½ pack a day for over 10 years. Her last eye exam was 2 years prior, and noted dry eyes OU, grade 1 nuclear sclerotic cataracts OU, and no diabetic retinopathy in either eye.

Best corrected visual acuity through a prescription of -2.50-2.25x160 OD and -2.75-1.75x010 OS was 20/30-2 in each eye. There was no improvement with pinhole. Best corrected acuities at the previous exam, through a similar prescription, -2.50-2.00x160 OD and -2.50-1.50x010 OS, were 20/20 OD and OS. Pupils, confrontation fields, and extraocular motilities were normal. The slit lamp examination was remarkable for mild meibomian gland dysfunction and grade 1 nuclear sclerotic cataracts OU. Intraocular pressures were 15 mmHg OD and OS. Fundus examination revealed small cup-to-disc ratios of 0.15 horizontally and vertically in both eyes. The macula and retinal periphery were unremarkable OU (Figure 1). As the patient had a mild reduction in acuity with a history of tamoxifen usage, baseline OCTs were obtained (Cirrus; Zeiss Inc, Dublin, CA). The 5-line raster OCT results revealed small pseudo cystic cavitation at the fovea with sparing of the RPE (Figure 2). There was no evidence of any crystalline deposits or macular edema in the 5-line raster scans or on the macular cube scans. Due to the presence of central cavitation OD and OS, a baseline 10-2 visual field was performed (Humphrey Field Analyzer 3; Zeiss Inc, Dublin, CA). Field testing showed a mild defect (P<2%) inferior to fixation OD and mild defect at fixation OS (Figure 3). Additional imaging was also obtained with optical coherence tomography angiography (OCT-A, Cirrus; Zeiss Inc, Dublin, CA). Testing was unremarkable for the superficial and deep capillary plexus scans, as no saccular capillary telangiectasia of the retinal vessels was noted OD or OS (Figure 4). In addition, there were no signs of a grayish perifoveal sheen, right-angled veins, pigmented plaques, or macular neovascularization in either eye (Figures 1,3,4). Fundus autofluorescence (FAF)(California; Optos Inc., Marlborough, MA) was unremarkable and revealed normal autofluorescence of both eyes (Figure 5). No abnormal hyper or hypo auto fluorescence was noted.

Figure 1: *Optos widefield fundus imaging was unremarkable for obvious crystalline tamoxifen-related changes OD (A) and OS (B).*

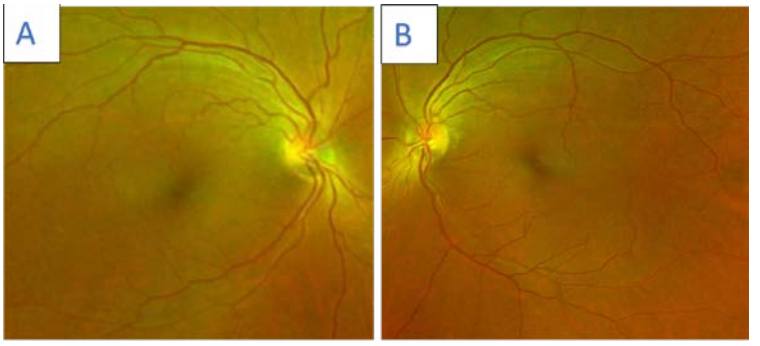


Figure 2: *Baseline optical coherence tomography scans of the macula (high-definition 5-line raster) revealed bilateral retinal cavitation of the fovea OD (top) and OS (bottom).*

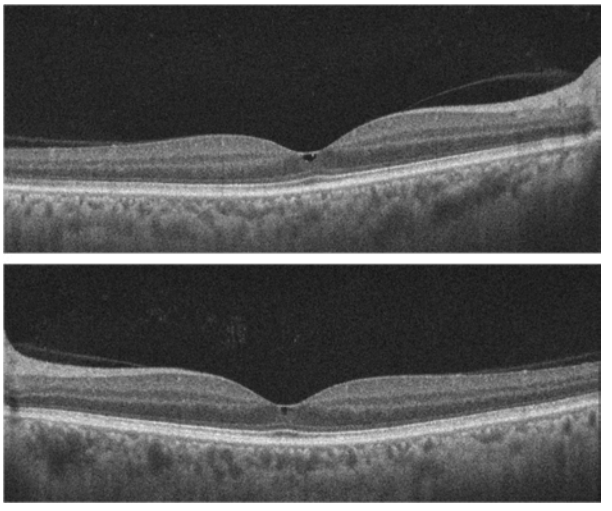


Figure 3: *Baseline central visual field testing, 10-2, revealed a mild defect inferior to fixation OD (left side) and a mild defect at fixation OS (right side)*

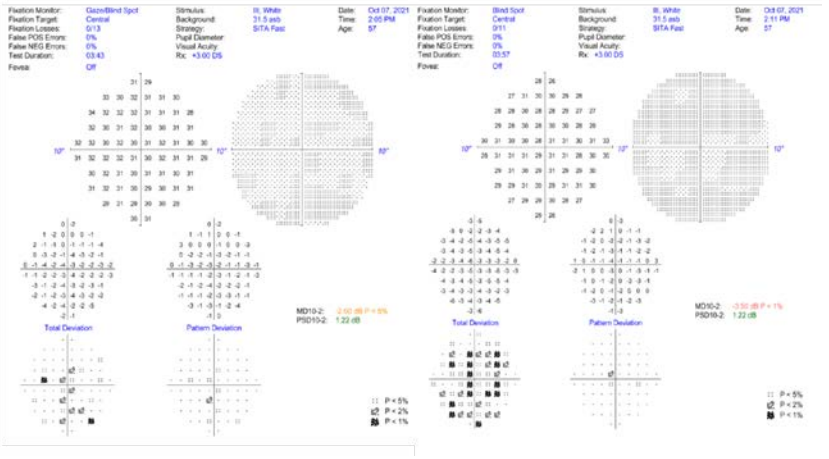


Figure 4: *FAF OD (A) and OS (B) showing normal foveal hypo-autofluorescence with no evidence of any abnormal hyper or hypo autofluorescence.*

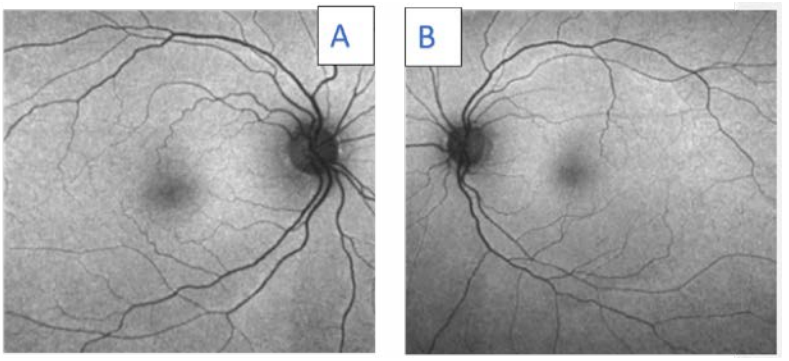
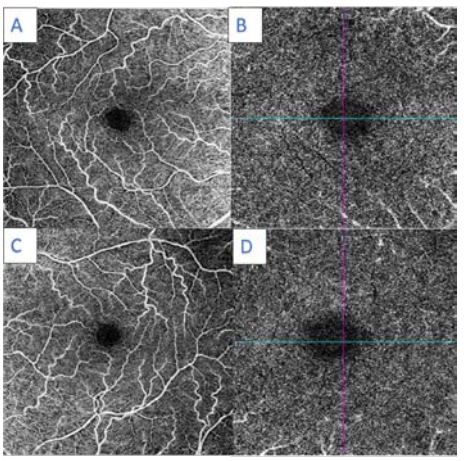


Figure 5: *OCT-A of the right eye and left eyes. Top: Superficial (A) and deep (B) capillary plexus scans OD. Bottom: Superficial (C) and deep (D) capillary plexus scans OS. No telangiectatic vessels were observed for either eye for each of the scans.*



As the patient was currently taking tamoxifen, based on her clinical presentation, differentials included:

- Talc retinopathy: This condition usually occurs in patients with a history of intravenous drug abuse resulting in the deposition of talc in the retina.[8] No crystalline deposits were observed in our patient and she denied any illicit drug use.

- Canthaxanthine retinopathy: Canthaxanthine is a naturally occurring carotenoid that is used for food coloring and as an oral tanning agent. Large doses can also result in crystalline retinopathy.[8] Again, no crystalline retinopathy was appreciated in our patient, who also denied using canthaxanthine.

- Methoxyflurane retinopathy: Methoxyflurane is an inhaled anesthetic that can result in crystalline deposits in the retina.[8] The patient denied any use or exposure to methoxyflurane.

Clinicians should note that these conditions are related to a similar fundus appearance, specifically retinal crystalline deposits, which our patient did not have. Hence, the leading differentials should be conditions that present with outer retinal cystic foveal cavitation:

- Vitreo-macular traction (VMT): persistent anterior-posterior VMT may cause intraretinal cavitation which is best seen on OCT. No VMT was seen at the fovea OD or OS on OCT.

- Macular telangiectasia type 2 (MacTel2): This condition is considered to be the main differential for tamoxifen retinopathy due to a similar pathology and clinical presentation, namely foveal cavitation.[5] MacTel2 was also considered as a differential due to the bilateral presentation in this patient. Risk factors for MacTel2, including middle to old age, hypertension, and diabetes mellitus, were also noted in our case.[12,13] Telangiectatic vessels, which can be seen with MacTel2, were not visible upon OCT-A. Other findings such as loss of retinal transparency and blunted venules and proliferative stage findings, such as retinal pigment hyperplasia and neovascular complexes, were also not observed.[14-16]

Tamoxifen retinopathy was the final diagnosis due to the presence of central intraretinal hypo reflective cavitations visible on OCT, reduction of visual acuity, and long-term tamoxifen usage with matching risk factors including increased BMI (obese category based on her BMI) and dyslipidemia.[4] The patient's oncologist was contacted and recommended discontinuation of tamoxifen. Alternatives were to be discussed at a follow-up visit with them. Unfortunately, the patient was lost to follow up.

DISCUSSION

Tamoxifen, a selective estrogen receptor modulator, is indicated in the treatment of breast cancer as an adjunct treatment option for those who have already undergone surgery and radiation treatment for breast cancer, and for females with ductal carcinoma in situ. Off-label indications include but are not limited to treatment of desmoid tumors, advanced or recurrent ovarian cancers, meningiomas, and bladder cancer.[17] Unfortunately, this drug can result in a retinopathy that typically manifests as crystalline retinopathy with pseudo cystic foveal cavitation. While this was initially thought to occur when tamoxifen was used at high doses,[7] regular low-dose usage (20mg daily), which is the standard of care at this time, has also been reported to result in retinopathy,[18,19] with a prevalence of 1.5% to 11.8% in various studies.[19-21] However, many of these studies were performed without the use of OCT. Therefore, the actual values are likely underestimated. In a recent study by Kim et al., in which OCT imaging was performed on all patients, the prevalence was found to be 12%, and another study reported a prevalence of 12.2%.[22]

Ocular toxicity from tamoxifen can include whorl keratopathy, cataracts, and, albeit rarely, optic neuritis.[23] However, the most common and classic finding has always been retinopathy, namely crystalline deposits.[5] The crystals have been isolated to the inner retina, specifically the nerve fiber layer and the inner plexiform layer. The crystals themselves are a benign finding alone and do not interfere with vision. Other findings can include pseudo-cystic cavitation on OCT. This can occur in and around the fovea, which can result in subtle or severe vision loss, with or without subjective visual complaints. [5] Recently, studies have shown that retinopathy can present without crystals, namely pseudo cystic cavitation.[4,5] This was noted in our patient, as no crystalline deposits were noted upon fundus examination or on OCT scans. As traditional thinking has associated tamoxifen with crystalline retinopathy, these studies underscore the need for baseline and follow-up OCT scans to detect possible retinal cavitation. Other rare findings can include the formation of macular holes and macular edema.[9,24]

Therefore, based on the presenting signs, patients can be asymptomatic, or show central vision loss and metamorphopsia. While the onset of retinopathy takes 2-3 years on low doses, higher doses can result in more immediate manifestations.[4,19] A recent study has helped identify risk factors for tamoxifen retinopathy. Those researchers concluded that increased BMI and hyperlipidemia were significantly linked with increased chances of tamoxifen retinopathy.[4] Our patient had both of these conditions. Other risk factors such as diabetes, hypertension, and cardiovascular problems were not associated with an increased risk of retinopathy. Interestingly, those researchers also found that the stage of breast cancer treated, the type of chemotherapeutic agent used, the menopausal status, and a history of hormone replacement therapy were also not associated with an increased risk of retinopathy.[4]

The presence of increased BMI and increased lipid levels may correlate with possible ocular pathophysiology associated with tamoxifen. Tamoxifen is a cationic and amphiphilic agent and is more likely to bind to lipids (hyperlipidemia) resulting in a tamoxifen-lipid compound that accumulates in lysosomes.[5] This is likely the main mechanism associated with the corneal deposition of tamoxifen.[25] The compound has also been linked to oxidative damage in the retina and the retinal pigment epithelium.[4,5] Another possible or secondary mechanism involves tamoxifen and its interactions with glutamate. Tamoxifen results in elevated levels of glutamate in the retina, specifically in Müller cells. Müller cells have multiple functions including glutamate metabolism. Tamoxifen inhibits glutamate aspartate transport in these Müller cells, leading to retinal/neuronal apoptosis and vascular remodeling.[5]

The retinal findings noted with tamoxifen retinopathy are strikingly similar to those of its main differential diagnosis, MacTel2. Studies on MacTel2 patients have shown hypo reflective cavities of the inner and outer retina, photoreceptor disruption, crystalline-like deposits, and full-thickness macular holes upon OCT imaging.[23,26] This suggests a possible underlying pathology, namely Müller cell involvement and atrophy.[18] Other multimodal testing has also shown similar findings in the two conditions. Parallel vascular changes using OCT-A have been noted. Lee et al., in their study using OCT-A on tamoxifen retinopathy patients, showed saccular capillary telangiectasia in the deep capillary plexus of the area temporal to the fovea. These capillaries also demonstrated diffuse hyper fluorescence in the late stages of fluorescein angiography. These are similar findings that are also seen with MacTel2. Although fluorescein angiography was not performed in this case, the previous finding suggests a need for further research into a possible vascular component to tamoxifen retinopathy.[18] In the same study, the authors also noted right-angled venules in the deep capillary plexus.[18] Right-angled venules are an established finding in MacTel2.[27] Fundus autofluorescence findings were also shown to be similar in the same study, with results showing an increase in autofluorescence at the fovea in early cases of tamoxifen retinopathy with progression to a mixed pattern of hyper and hypo autofluorescence in later stages.[18]

Although differentiating the two conditions can be difficult at times, even with the aid of multimodal imaging, clinicians can look for other possible subtle findings to help make a final diagnosis. Chief among them is the use of tamoxifen. The presence of the aforementioned signs without the use of tamoxifen suggests a diagnosis of MacTel2. Recently, Park et al. evaluated patients with MacTel2 and compared them to patients who had been diagnosed with tamoxifen retinopathy 1 year prior and who had also discontinued tamoxifen use at that time.[28] They found that, while both sets of patients had photoreceptor disruption, the MacTel2 group was more likely to have this finding temporal to the fovea than the tamoxifen retinopathy group, which had a foveal center location. The vascular density as measured by OCT-A was also similar at baseline in the two groups. However, one year later, the MacTel2 group showed decreased vascular density and further photoreceptor loss while the tamoxifen retinopathy group maintained findings consistent with their baseline scans.[28] Age of onset/diagnosis could help to differentiate the conditions. While MacTel2 is most likely to occur in patients between the ages of 50 and 69, tamoxifen retinopathy tends to occur in patients in their 40's and 50's.[4,29] Caution should be taken when evaluating these studies as many of them are retrospective with smaller sample sizes. Clinicians should also be cognizant that, although rare, some patients with tamoxifen retinopathy could possibly have concurrent MacTel2 or vice versa.[4,23]

Once a formal diagnosis is reached, possible treatment can be guided by the degree and amount of retinal pathology noted. Retinal crystals do not lead to disrupted visual acuity, so discontinuation of the medication is not needed. However, with the discontinuation of tamoxifen, the crystalline deposits tend to resolve, although full resolution may not be seen.[1] When complications such as pseudo-cystic cavitation at the fovea or photoreceptor disruption are detected, the oncologist can consider switching to another medication. Alternative medications can include aromatase inhibitors such as anastrozole or another selective estrogen receptor modulator, raloxifene. Aromatase inhibitors are typically indicated for post-menopausal women who are diagnosed with estrogen receptor-positive breast cancer. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis of trials looked at aromatase inhibitors versus

tamoxifen in postmenopausal women with early-stage estrogen receptor-positive breast cancer. The analysis revealed that aromatase inhibitors reduce recurrence rates by 30% compared with tamoxifen over a 5-year treatment period.[6] A more recent study looked at aromatase inhibitors in pre-menopausal women with estrogen receptor-positive breast cancer. The meta-analysis revealed that the use of an aromatase inhibitor rather than tamoxifen, in addition to suppressing ovarian function in premenopausal women, reduced the absolute risk of recurrence by 3% at 5 and 10 years.[11] Raloxifene is another option for patients, however when compared to tamoxifen, it was found to be 76% as effective in reducing the risk of invasive breast cancer over almost 7 years.[26] Although outside the scope of eyecare, eye physicians should be aware of possible alternatives to tamoxifen for their patients. Each of these alternative options comes with certain indications and contra-indications along with side effects.[2,3,6,11] The ultimate alternative option should be decided upon through discussions between the patient and their oncologist.

Rarer complications such as macular edema and macular holes have been noted. The macular holes are thought to arise from extended damage to Müller cells and not from a traditional tractional vitreo-retinal pathology. Hence, treatment with vitrectomy and internal limiting membrane peel may not be justified as case reports have shown poor visual outcomes.[9] Macular edema has also been noted in select case reports. These patients were ultimately taken off tamoxifen and improvement was noted with anti-VEGF injections.[24,30,31] Thus, referral to a retinal specialist may be warranted if edema is detected. While discontinuation of the drug may result in the resolution of retinal crystals and some macular edema, the retinopathy can still progress. Case reports have shown degenerative retinal changes that progress after withdrawal of the drug, including increased foveal thinning, enlargement of foveal cavitation, and increased foveal hyper autofluorescence as seen on FAF.[10,18]

As alluded to earlier, the tamoxifen dosage was 120 mg daily, which resulted in an increased chance of retinopathy.[23] Since that time, standard dosing is usually 20mg daily for 5 years.[2] However, many clinicians may be unaware that patients may be on tamoxifen for an extended duration; 10 years or more. This practice is mainly due to the results of the Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) trial. In this study, almost 13,000 women with early breast cancer who had already completed 5 years of treatment with tamoxifen were randomly assigned to either continue tamoxifen for an additional 5 years or discontinue tamoxifen after 5 years. The study showed that 10 years of adjuvant tamoxifen was superior to 5 years of tamoxifen at reducing the risk of breast cancer recurrence or death.[2] These findings were also seen in a similar study, the Adjuvant Tamoxifen-To Offer More? (aTTom) trial.[3] Based on the recommendations from these landmark studies, clinicians should be aware of the increased probability of retinopathy for patients.

CONCLUSION

With the results of the ATLAS and aTTom studies proving that a longer duration of tamoxifen treatment is beneficial in treating breast cancer and preventing relapses, the incidence of tamoxifen retinopathy is likely to increase. Although various clinical signs can be present, clinicians should be aware that tamoxifen retinopathy can present solely with pseudo cystic cavitation and without crystalline deposits. If OCT scanning is not performed, some patients and their visual complaints may be dismissed or attributed to other lesser pathologies such as cataracts.[5] Therefore, the importance of annual screening with OCT is vital. Vigilant surveillance, with baseline scanning and repeat scans as needed, of patients on long-term low-dose tamoxifen therapy is advised in hopes of early detection and prevention of vision loss. ●

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