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Case report

The tipping point: Tamoxifen toxicity, central serous chorioretinopathy, and the role of estrogen and its receptors

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ABSTRACT

Purpose: To describe a case of tamoxifen toxicity superimposed on central serous chorioretinopathy (CSCR). We review the role of estrogen and the effect of tamoxifen on ocular tissues.

Observations: A 32-year-old Hispanic female with infiltrating ductal carcinoma of the left breast (T2N1M0, triple-positive), status post chemotherapy and bilateral mastectomy, presented with complaint of a floater and decreased central vision of the right eye (OD). Symptoms began three weeks after initiating tamoxifen and five months after the last cycle of chemotherapy and dexamethasone. Visual acuity (VA) was 20/30 OD at presentation. Clinical examination and multimodal imaging revealed subretinal fluid (SRF) and pigment epithelial detachment (PED) suggestive of CSCR. After one month of monitoring, VA improved to 20/20; there was SRF resolution, small PED, and focal ellipsoid zone (EZ) band loss. Two weeks later, after undergoing surgery and starting a topical steroid, she returned with count fingers (CF) VA and large SRF OD. Steroid cessation improved SRF after one month, but VA was unchanged. Tamoxifen was discontinued, and VA improved to 20/100 with near-complete resolution of SRF at three weeks, and significant reduction in choroidal thickness at two months. At final follow-up, VA was 20/200, and there was focal EZ band loss sub-foveally, minimal SRF, and small PED.

Conclusions and Importance: Treatment with tamoxifen may lead to ocular toxicity and can complicate the recovery course of patients affected with CSCR. Variations in levels of the estrogen receptor-alpha (ER-α) and treatment with tamoxifen (ER-α partial agonist) may lead to loss of the protective effect of estrogen in the retinal pigment epithelial cells in premenopausal women. Furthermore, tamoxifen toxicity can lead to focal photoreceptor loss. Treatment in these cases should be coordinated together with the oncologist.

1. Introduction

Tamoxifen is an important, potentially life-saving medicine used in the treatment of patients with hormone-receptor positive breast cancer.[1] It is a selective estrogen receptor modulator that is usually well tolerated. Common systemic side effects include nausea, vomiting, rash, hot flashes, and mood changes, but more severe systemic and ocular side effects are rare. When ocular toxicity results, vision loss can be greatly disturbing to the patient, and may result from crystalline retinopathy, macular edema, or optic neuritis amongst other toxicities.[2] Advances in ophthalmic imaging modalities have allowed for greater characterization and understanding of this toxicity. Here we describe a case of tamoxifen toxicity with a novel presentation, which posed a clinical dilemma.

2. Case Report

A 32-year-old Hispanic, premenopausal female with history of infiltrating ductal carcinoma of the left breast (T2N1M0, ER/PR/HER2 positive), status post chemotherapy, bilateral mastectomy, and reconstruction surgery, presented with complaint of a floater and decreased central vision of the right eye (OD), which started the prior evening. She characterized the deficit as a small, dark area

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involving only the center of her vision. She denied flashes of light, diplopia, ocular pain, and other ocular symptoms. She noted no changes in her left eye. She reported no previous ocular problems or trauma. She denied fever, chills, headaches, nausea, vomiting, rashes, tinnitus, and joint pain. She provided written consent to include her medical information in this report.

Five months prior, the patient had completed six cycles over fifteen weeks of neoadjuvant chemotherapy with docetaxel (125 mg), carboplatin (900 mg), trastuzumab (540 mg), and pertuzumab (840 mg) administered intravenously at each cycle. Included in this peri-chemotherapy regimen was daily dexamethasone (8 mg oral), monthly leuprolide (7.5 mg intramuscular), and pegfilgrastim (6 mg subcutaneous) injected once per chemotherapy cycle. She suffered one episode of neutropenic fever, but otherwise her course was well tolerated. Next, she underwent left modified radical mastectomy and right prophylactic mastectomy with immediate reconstruction bilaterally, and she declined radiation therapy. Her surgical history and past medical history were otherwise unremarkable; she denied obstructive sleep apnea and family history of ocular disease or cancer. She denied tobacco or drug use, and drank limited alcohol socially. She also denied the use of steroids, inhalers, and energy drinks within the past five months.

At the time of ophthalmic evaluation, five months had passed since her last cycle of chemotherapy and dexamethasone, and her only active medications were low-dose, oral tamoxifen (20 mg daily; initiated three weeks prior) and intravenous trastuzumab (540 mg every three weeks; initiated eight months prior). Best-corrected visual acuity (BCVA) was 20/30 OD and 20/25 in the left eye (OS). Intraocular pressure was 19 in both eyes (OU). Pupils were round and reactive with no afferent pupillary defect. Extraocular movements were full OU. Confrontation visual fields were full. Amsler grid was normal, and Ishihara color plates were 8 of 8 in each eye. Slit lamp and dilated fundus exam were normal, except for vitreous syneresis OU and macular edema OD (Fig. 1A&D; Optos, Marlborough, MA).

Spectral domain optical coherence tomography (SD-OCT; Cirrus 5000, Carl Zeiss Meditec, Inc., Dublin, CA) revealed a large amount of subretinal fluid (SRF) and detachment of the neurosensory retina, resulting in disruption of the foveal contour and two underlying retinal pigment epithelial detachments (PED) OD. Also noted were few, small, hyperreflective foci in the outer plexiform layer (OPL; Fig. 1B–C). SD-OCT macula OS was normal (Fig. 1E–F). Fluorescein angiography revealed small foci of hyperfluorescence inferior to the fovea, which began early during the arterial phase and increased slightly in intensity and size on later phases, localizing to the PED, consistent with an expansile dot pattern (Fig. 2; Optos). She was counseled that she had clinical findings suggestive of central serous chorioretinopathy. We recommended steroid avoidance, stress reduction if possible, and decided to monitor closely.

She returned one month later with subjective improvement in vision, as well as improvement in BCVA to 20/20 OU. We noted marked reduction of SRF with a small PED remaining, and focal, granular hyperreflectivity and loss of the EZ band subfoveally, above the PED OD (Fig. 3A; Spectralis, Heidelberg, Germany). We opted to continue to monitor. As she continued to do well, she cancelled her follow-up appointment. During that time, she underwent revision of her reconstructive breast surgery and concurrently developed a rash above her eyebrows, which she self-treated with an over-the-counter, topical hydrocortisone 1% cream.

She presented two weeks later with sudden and severe worsening of her vision to count fingers OD and with extensive SRF OD, more severe than on initial presentation (Figs. 3B and 4A; Spectralis). Autofluorescence OS was normal (Fig. 4B). Her choroidal thickness OD and OS measured an average of 443 ± 44.3 μm (491 μm subfoveally) and 405 ± 43.1 μm (432 μm subfoveally), respectively (Fig. 5A–B). We counseled her to stop the hydrocortisone cream, discussed various treatment options, and after discussion of the risks and benefits, we decided to monitor closely and follow-up in one month. At this next visit, after cessation of topical steroid, her vision had not improved despite a reduction in SRF. Given these findings, after discussion with her oncologist, we asked her to discontinue the tamoxifen, five months after its initiation.

Three weeks later, vision improved to 20/200 OD with near-complete resolution of SRF but with persistent PED and focal loss of the EZ band subfoveally on OCT (Fig. 3C). One month later, we noted a statistically significant reduction in choroidal thickness OD ($p < 0.01$; compare Fig. 5A and C), with no difference in OS ($p = 0.35$; compare Fig. 5B and D; DRI OCT-1, Topcon Medical Systems, Oakland, NJ). Four months after cessation of tamoxifen,

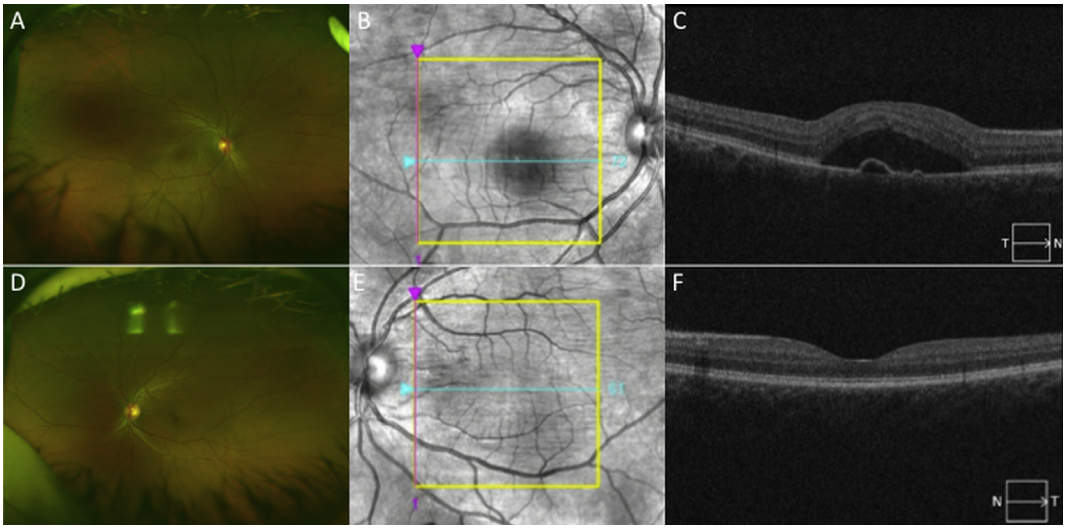

Fig. 1. A. Wide-field color photograph revealing normal appearance of the optic nerve, vessels, and periphery, but significant edema in the macula OD. B-C. Fundus overlay and spectral domain optical coherence tomography (SD-OCT) of the macula OD revealing an enlarged foveal avascular zone corresponding to a large amount of subretinal fluid (SRF) with disruption of the foveal contour and a retinal pigment epithelial detachment. There are foci of hyperreflectivity within the outer plexiform layer. D. Wide-field color photograph revealing normal appearance of the optic nerve, macula, vessels, and periphery OS. E–F. Fundus overlay and SD-OCT of the macula OS, which is normal in appearance.