Tamoxifen side effects, age-related macular degeneration (AMD) or cancer associated retinopathy (CAR)?

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INTRODUCTION

Tamoxifen retinopathy is an adverse effect of high-dose tamoxifen treatment. This non-steroidal oral antiestrogen binds to estrogen receptor proteins in the cytoplasm. Antiestrogens are beneficial in the treatment of metastatic breast cancer and are used as adjuvant therapy in the early stages of the disease to delay relapses (1, 2). Side effects in the eye, retinopathy and corneal changes, have been reported, especially in patients treated with high doses (60 or 100 mg/m²/day) for at least a year (3). The changes consist of macular edema, refractile macular and para-macular, whirl-like subepithelial corneal opacities, and decreased visual acuity (4). Low doses (20 or 30 mg/day) may also damage the eye and cause papillary edema and superficial retinal hemorrhages (5), corneal and retinal alterations (4, 6), only retinal changes (7-9) or bilateral optic neuritis (10). Differential diagnosis of other macular alterations such as drusen and age-related macular degeneration can be difficult (11), especially if the patient is elderly and needs tamoxifen or other antiestrogens. Senile macular degeneration is characterised by disturbances of the retinal pig-
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ment epithelium within the macular area and a de-
crease in visual acuity (12). A decrease of central vi-
sion in the elderly can also be due to mostly bilater-
al lesions, called drusen, which are deposits of ab-
normal material in Bruch’s membrane, deriving from
the retinal pigment epithelium (13-15).

Calcification may occur around drusen; their appearance
then changes from yellowish to refractile, with a crys-
talline look mostly due to cholesterol, which makes
differential diagnosis even more difficult (16). How-
ever, cancer itself can also cause retinopathy (CAR =
cancer-associated retinopathy) and has to be con-
sidered another possible diagnosis (17).

Here we present the ophthalmological findings of
a patient treated with tamoxifen for about ten
months, to illustrate the difficulty of differential di-
agnosis.

METHODS

The patient underwent an extensive ophthalmolog-
ical examination, which included measurement of vi-
sual acuity, neuro-ophthalmological investigation,
slit-lamp examination, dilated pupil funduscopy, fun-
dus photography, perimetry (Tübingen hand perim-
eter), a flash electroretinogram (flash-ERG) according
to the ISCEV standard (18) and multifocal elec-
troretinogram (m-ERG, 19). For the m-ERG, ampli-
tude and peak time responses were grouped by ec-
centricity (group 1 – foveal response, group 2 – mac-
ular response: 1.8 – 7°, group 3: 5 – 13°, group 4:
10.5 – 22°, group 5: 17– 30.5°).

RESULTS

An 84-year-old woman presented at our low vision
clinic to obtain a reading device because of inabili-
ty to read newspaper print. Two years earlier, breast
cancer had been diagnosed and treatment had start-
ed with antiestrogens. One year before the exami-
nation, the patient had been operated for a metasta-
tic colon carcinoma; no further diseases were known.
The patient never had problems with her eyes until
one year before, when she noticed a decrease in vi-
sual acuity.

At the time of ophthalmological examination she was
taking antiestrogens (anastrozol) and vitamins. Two
years before the examination the patient had been

treated with tamoxifen for ten months (30 mg/d), fol-

dowed by Lentaron (formestan) for six months and Arim-
dex (anastrozol) for nine months. The total tamoxifen
dosage was about 900 mg in ten months.

Fig. 1 - Macula in the right and left eyes of the patient with crystalline drusen and pigmentary atrophy.
Ophthalmological data

Visual acuity was 1/50 (+2.0 sph –0.5 cyl / 90°) right eye and 0.3 (+1.0 sph –0.5 cyl / 80°) left eye. Age-related signs in the anterior segments had been observed, with slight lens opacities and arcus senilis. The funduscopy showed regular optic discs and the crystalline deposits in the maculae. The right eye had a large area of retinal pigment epithelial geographic atrophy (Fig. 1). Extensive central scotomas extending to the left peripheral visual field were seen in perimetry (10°, 1000 asb stimulus, Tübingen perimeter). Electroretinographic findings (flash-ERG) included rod, cone and oscillatory potential amplitudes in the lower normal range (± 2 SD); all peak times were slightly prolonged in the multifocal ERG (mf-ERG) foveal responses (group 1) of the left eye and macular responses of the right eye (group 1-2) were undetectable. Peripherally to these areas, amplitudes increased with eccentricity, but failed to reach normal levels even in the outermost ring (group 5). Peak times were slightly delayed in groups 2 and 3, but within the normal range in the outer rings (groups 4 and 5).

DISCUSSION

The patient's advanced age and her medical conditions under treatment complicated and limited the investigations needed to ascertain the diagnosis, a frequent clinical situation. The patient refused further examination, such as dark adaptation, fluorescein angiography and magnetic resonance tomography (MRT) or cranial computer tomography (CCT). The patient suffered from colon and breast cancer and had therefore been treated with tamoxifen and other antiestrogens for long periods. She had noticed a decrease of visual acuity, and the ophthalmological investigation also showed visual field scotomata and abnormal flash and multifocal electroretinograms. These problems could have been caused by various mechanisms or diseases which would have different implications for monitoring and therapeutic strategies.

Because of her age, however, the most likely retinal disease is age-related maculopathy, other diagnoses being rare.

The deposits in the macula did not include all retinal layers. The macula showed atrophic areas with pigment alterations and drusen in their typical location, the Bruch's membrane (13, 15), which looked glittering if calcium was also present. Von Ruckmann et al (20) found no fundus autofluorescence of age-related drusen. However, Holz and Pauleikhoff (16) mention the possibility of cholesterol-containing drusen which have a crystalline appearance. This can confound the diagnosis of tamoxifen retinopathy, which would be distributed in all retinal layers.

In the literature, the intake of tamoxifen followed by retinopathy ranges from 6.0 g to 81.0 g for patients with retinopathy to less than 1 g for a patient with optic neuropathy. Heier et al (9) reviewed high- and low-dose therapy with tamoxifen, its side-effects and possibility of recovery. They conclude that the main difference between high- and low-dose toxicity is the reversibility after discontinuation of treatment. They did not find toxicity in patients with a total dosage of less than 10 g. Vinding and Nielsen (4) never diagnosed tamoxifen retinopathy below a total dosage of 8.1 g. This is contrary to Tang et al (21) who put the lower limit of antiestrogen-induced retinopathy at 23.7 g. Lazzaroni et al (11) confirm the possibility of low-dose tamoxifen retinopathy, but none of their patients had visual symptoms.

The total tamoxifen intake by our patient (about 900 mg) renders the diagnosis of toxic retinopathy unlikely. She had been treated with different antiestrogens: anastrozol, formestan and tamoxifen dihydrogen citrate. Even if all those therapeutics are antiestrogens, ocular side effects are described only for tamoxifen and consist of retinopathy and corneal changes. If discovered in time, the retinal and corneal lesions are potentially reversible, with a fair visual prognosis, challenging the ophthalmologist to be aware of ocular tamoxifen side effects and to keep the differential diagnosis in mind.

Another diagnosis to be considered is CAR. Patients with CAR show clinical and electrophysiological evidence of both cone and rod dysfunction (14, 22). The slightly prolonged implicit times in the flash-ERG of our patient and the effect on the peripheral visual field shown in the mf-ERG traces, indicate that retinal function loss was not confined to the macular area. Consideration of this patient's history, with this finding, could implicate CAR.

Bietti's crystalline retinopathy also causes reduced scotopic and photopic ERG responses (23, 24). However, this inherited disease is usually diagnosed in
young or middle-aged adults and, besides glittering crystals in the macula, limbal crystalline dystrophy of the cornea is one of the main features and an important diagnostic criteria. Because of the widespread possibilities of differential diagnoses, screening and monitoring of patients is necessary. As Ah Song and Sasco (25) suggested, the m-ERG should be part of the screening examinations. With its high resolution the m-ERG can detect small areas of retinopathy and is therefore a sensitive tool for the detection and monitoring of early macular alterations (26).

REFERENCES