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A rare case and literature review of leopard spot chorioretinopathy associated with ovarian carcinoma: Indicating progression?

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Abstract

Introduction: To report a case with leopard spot retinopathy secondary to bilateral diffuse uveal melanocytic proliferation (BDUMP) treated with steroidal eye drops.

Case Presentation: Observational case report. A 62-year-old woman with previous diagnosis of ovarian carcinoma presented with BDUMP accompanied by leopard spot retinopathy. Based on the imaging, the diagnosis was confirmed and treated with prednisolonacetate eye drops six times a day, which was tapered off over 6 weeks. Optical coherence tomography was conducted every several times during follow up and showed a slight regression of bilateral subretinal fluid. Visual acuity had increased to 0.2 logMAR in both eyes. Cataract surgery was performed due to visual deterioration caused by fast-proceeding cataracts and the patient achieved a visual acuity of 0.2 logMAR again. A reevaluation of ovarian cancer was initiated, which revealed tumor progress.

Conclusions: Steroidal eye drops improved the patients' visual acuity and resulted in regression of bilateral subretinal fluid, which may serve as initial therapy in patients with BDUMP. An early diagnosis as well as screening for systemic malignancy is of utmost importance.

Keywords: Bilateral diffuse uveal melanocytic proliferation; leopard spot chorioretinopathy; ovarian carcinoma; paraneoplastic intraocular syndrome; bilateral subretinal fluid.

Introduction

Bilateral diffuse uveal melanocytic proliferation (BDUMP) as a rare paraneoplastic intraocular syndrome is one of the few disorders, which can cause leopard spot retinopathy. This intraocular syndrome is characterized by multiple round or oval red spots at the level of the retinal pigment epithelium (RPE), multifocal hyperfluorescences corresponding with these fundus lesions, serous retinal detachment, diffuse choroidal thickening with focal nodules and fast-proceeding cataracts [1].

Patients with BDUMP most commonly present with painless, bilateral visual deterioration and median age has been reported at 65 years with a range from 34 to 89 years [2]. This condition is associated with a variety of systemic malignancies, but most frequently with female urogenital and male lung carcinomas. However, the incidence and pathogenesis is unknown due to its low incidence [2]. Herein, we report a patient with BDUMP accompanied by leopard spot retinopathy with ovarian carcinoma in medical history.

Case Presentation

A 62-year-old woman presented at our department with visual impairment in both eyes and visual blurring particularly in the right eye. In her prior medical history, metastatic adenocarcinoma of the ovary was diagnosed in the gynecologic department of our hospital two years earlier. Histology revealed a poorly differentiated clear cell entity. Primary debulking surgery was performed and chemotherapy was indicated. The adjuvant therapy regimen consisted of three cycles 175 mg/m2 paclitaxel (taxol®, Bristol-Myers Squibb Company, USA) combined with 10 mg/ml carboplatin (carboplatin AUC-5®, Accord Healthcare Limited, UK). Afterwards, chemotherapeutic treatment was replaced by six cycles 2 mg/ml doxorubicin (Caelyx pegylated liposomal, Janssen Pharmaceutica NV, Belgium) due to tumor progression. This therapeutic regimen was stopped and changed to three cycles 0.05 mg/ml trabect-

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edin (Yondelis, Pharma Mar S.A., Spain) for the same reason. The most recent abdominal computer tomography (CT) scan was conducted one month before initial presentation, which showed abdominal wall metastasis located in the lower left quadrant.

Best corrected visual acuity was 0.5 logMAR in both eyes at her initial presentation to our clinic. Slit-lamp examination revealed bilateral incipient corticonuclear cataract. Applanation tonometry was unremarkable in both eyes. Funduscopic findings in mydriasis included numerous bilateral red spots with subretinal detachment and a paracentral hyperpigmented lesion in the left eye. These red spots were round shaped with subtle borders distributed in the posterior pole resembling leopard spot pattern, which is shown in (Figure 1). In fundus autofluorescence (FAF, Heidelberg Engineering Inc., Heidelberg, Germany), hypoautofluorescent subretinal red patches were registered (Figure 1). Fundus fluorescein angiography (FFA, Heidelberg Engineering Inc., Heidelberg, Germany) showed multifocal hyperfluorescences in corresponding lesions, which is distinctive of BDUMP. Furthermore, exudative retinal detachment appeared in the later phases of FFA (Figure 2). Optical coherence tomography (OCT, Heidelberg Engineering Inc., Heidelberg, Germany) showed RPE atrophy, interspersed with increased retinal thickness, hyperreflective subretinal areas as a result of deposition of lipofuscin within the RPE and subretinal fluid with neurosensory detachment in both eyes (Figure 3). No specific abnormalities were observed in full-field electroretinogram (ERG, Metrovision, Pérenchies, France) as well as flicker ERG concerning the reduction of scotopic and photopic a- and b-wave amplitude associated with the syndrome. To rule out systemic disease, a thoracic x-ray was performed one day later, which showed a moderate pleural effusion. In abdominal ultrasound examination, preexisting abdominal wall metastasis was stable in size with no evidence of progression compared to the previous CT scan conducted one month before initial presentation. Active infectious diseases causing exudative retinal detachment were excluded by blood work.

Due to refusal of a recommended intravitreal injection of 4 mg triamcinolon acetonide (Volon A®, mibe GmbH Arzneimittel, Germany), the patient was instructed to use 10 mg/ml prednisolonacetate eye drops (Prednifluid®, mibe GmbH Arzneimittel, Germany) 6 times a day for one week in both eyes. Following treatment, visual acuity in both eyes had increased to 0.2 logMAR and OCT showed a slight regression of bilateral subretinal fluid. Local steroidal therapy with prednisolonacetate eye drops was tapered off over 6 weeks. 3 months after initial presentation a re-examination was done due to visual deterioration and blurring in both eyes. Slit-lamp examination revealed bilateral corticonuclear and posterior subcapsular cataract and best corrected visual acuity was 0.6 logMAR. Hence, the patient underwent bilateral cataract surgery resulting in an improvement of visual acuity to 0.2 logMAR. Moreover, the patient was referred to the oncological department for a re-evaluation of the ovarian cancer. A CT scan revealed a size progression of the abdominal wall metastasis. Due to tumor progression despite of 3 different chemotherapeutic regimes, predictive molecular biomarkers were tested and showed a gene alteration (MET-amplification). Based on this gene alteration, an individual therapeutic trial with Crizotinib was planned in the following tumorboard discussion. 7 months after initial presentation visual acuity was 0.2 logMAR and OCT showed a resolution of bilateral subretinal fluid.

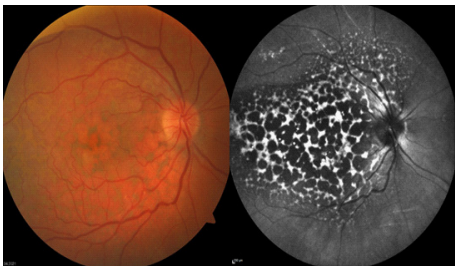

Figure 1: *Fundus photography and fundus autofluorescence in the right eye; Fundus photography (left) shows multiple round or oval red spots. Fundus autofluorescence imaging (right) demonstrates hyperfluorescent areas surrounded by zones of hypoautofluorescence in a leopard spot pattern.*

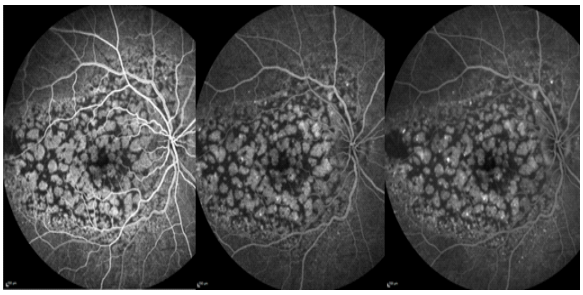

Figure 2: *Fluorescein angiography demonstrates multiple round or oval hyperfluorescent areas surrounded by hypofluorescent lesions in a leopard spot pattern (inverse fundus autofluorescence pattern) in early and late phases.*

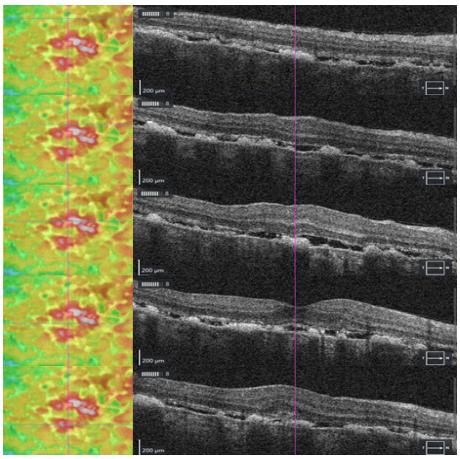

Figure 3: *Spectral domain optical coherence tomography in the right eye obtained within the parafoveal area shows serous retinal detachment, subretinal fluid, irregularities of the retinal pigment epithelium, hyperreflective subretinal deposits and choroidal thickening.*

Discussion

BDUMP is a rare paraneoplastic syndrome, whose underlying malignancy typically implies a poor prognosis with a low 5-year survival rate. Ocular symptoms include bilateral visual deterioration without clear etiology and often occur prior to systemic issues. Therefore, ophthalmologists may influence patients' morbidity and mortality by early detection and diagnosis. A screening for underlying systemic neoplasia is indicated, even though detection of metastatic spread after years

of tumor remission is challenging. Hence, clinicians should be sensitized to the importance of long-term follow up examinations in patients with ovarian cancer [3]. BDUMP is defined as an abnormally increased proliferation of primarily benign uveal melanocytes [2]. It is controversially discussed whether BDUMP has enough malignant cells to justify the diagnosis of malignant melanoma. Many cases presented in previous reports include a co-existing malignant melanoma, which, however, showed a highly aggressive behavior without typical leopard spot lesions [4-6]. Klicken oder tippen Sie hier, um Text einzugeben. Bilateral uveal nevi can be a differential diagnosis, but do not show the extensive infiltration of melanocytes [7]. In our case, the increased proliferation of uveal melanocytes was only verified by one hyperpigmented lesion in the left eye, but the typical association with ovarian carcinomas, the bilateral presence and the fast-proceeding cataracts confirmed the suspected diagnosis. One cardinal sign of BDUMP is serous retinal detachment in both eyes, whose pathogenesis is still unclear. We consider a breakdown in the blood-retinal barrier and a poor functioning in RPE as coexisting mechanisms. Another characteristic of BDUMP are fast-proceeding cataracts, whereas the pathogenesis of accelerated lens opacification is also unclear [8]. As typical characterization of BDUMP, it goes in line with the medical history of our patient, but we could not exclude rapid cataract formation secondary to local steroidal therapy.

There is still no successful concept for treating BDUMP. Basically, the focus has to be aimed at addressing the neoplasia. Plasmapheresis has shown some success to eliminate antibodies in BDUMP syndrome and stabilize visual deterioration. This effect might be explained by the removal of a certain IgG factor in the serum, which selectively stimulates melanocytes [9]. Nonetheless, not all patients benefit from this treatment and it carries potential risks associated with immunosuppression [3, 10]. Some authors report, that BDUMP was treated by local or systemic steroids, which showed variable results. In one case, application of systemic steroids improved visual acuity temporarily [11] and in another case, periocular injection of triamcinolone acetonide resulted in resolution of subretinal fluid. [12] To the best of our knowledge, our patient is the first one to be reported with improved visual acuity and regression of serous detachment after topical application of steroidal.

In 2017, Klemp and colleagues reviewed that 44 percent of 59 reported cases of BDUMP were diagnosed with an occult malignancy after the presentation of visual deterioration. Therefore, BDUMP has the propensity to herald the onset of a systemic neoplasia, requiring careful screening for several malignant entities. The prognosis after diagnosing BDUMP remains poor as most patients succumb to their life-threatening tumor. Overall mean survival has been reported at 15.7 months [2]. The importance of recognizing the clinical signs to enable an early diagnosis of this rare entity should be emphasized. Moreover, screening and intervening for systemic malignancy, if this is not already been recorded in the medical history, is of utmost importance. Further research is required to fully understand the genesis and pathologic mechanism of BDUMP. Thus, a systematic treatment guideline can be developed for this disabling ocular condition to improve the prognosis of affected patients.

Statements and Declarations

None of the authors has a financial interest in any of products, devices or drugs mentioned in this manuscript. No funding was received for this work. This study has been in accordance with the ethical standards laid down in the Declaration of Helsinki 1964 with actual revisions. The person gave the written informed consent prior to the inclusion in the study according to the guidelines in SOP06 V1.0. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study. All authors read and approved the final manuscript.

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