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ONCOLOGY

Ocular diseases in metastatic cutaneous melanoma: review of 108 consecutive patients in two German tertiary centers

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Abstract
Purpose To analyze the incidence and spectrum of ocular disease in patients with metastatic cutaneous melanoma.
Methods One hundred and eight consecutive patients with metastatic cutaneous melanoma were screened for ocular diseases using standardized eye examination, including measurement of visual acuity and intraocular pressure, slit-lamp examination, funduscopy in mydriasis, and spectral-domain optical coherence tomography (SDOCT) of the retina. Selected cases with atypical findings underwent electrophysiological studies. One patient was examined for hypercortisolism by a dexamethasone suppression test.
Results Ocular diseases were found in 65 out of 108 patients (60 %) with metastatic cutaneous melanoma, significantly more often in older patients (p=0.004). Cataract was present in 27 patients (25 %), pseudophakia in 22 patients (20 %), macular disease in 29 patients (28 %), diabetic retinopathy in ten patients (9 %), hypertensive retinal disease in 14 patients (13 %), retinal venous and arterial occlusive disease in three patients (3 %), optic neuropathy in four patients (4 %), and uveitis in one patient (1 %). Eight patients (8 %) had choroidal or iridal nevi, one patient (1 %) choroidal hemangioma, and one patient (1 %) choroidal metastasis. No patient had periocular neoplastic lesions. Paraneoplastic retinopathy manifesting as acute exudative polymorphous vitelliform maculopathy (AEPVM)-like disease was diagnosed in two patients (2 %) with multifocal central serous chorioretinopathy and development of vitelliform or fibrin-like subretinal deposits in one patient.
Conclusions Patients with metastatic cutaneous melanoma reveal ocular diseases with a spectrum similar to the normal population of this age range. Very rarely, uveal metastasis as well as paraneoplastic retinopathy can occur.

Keywords Oncology · Cutaneous melanoma · Ocular diseases · Paraneoplastic retinopathy

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Introduction

The incidence of cutaneous malignant melanoma is increasing faster than for any other cancer [1, 2]. In Germany, the incidence is rising, with almost the same numbers for men (7,340 patients in 2007 versus 8,910 in 2008 per 100,000 persons) and women (7,740 patients in 2007 versus 8,890 in 2008 per 100,000 persons), according to the register of cancer of the German Robert-Koch-Institute (RKI). Therefore, it may increasingly become a source for metastasis into the eye. In both our melanoma centers, at the Universities of Cologne and Erlangen, we generally see approximately 500 patients with cutaneous melanoma per year, about 20 % of them with metastases. The most important risk factors for cutaneous melanoma are a positive family history of melanoma, multiple normal and atypical nevi, and an exposure to ultraviolet radiation (UVR). Light-skinned people seem to be more susceptible to get melanoma, and this is attributed to the reduced production of protective melanin in the skin. Malignant melanoma of the skin accounts for approximately 80 % of deaths

from skin cancer [3]. The rate of metastasis is dependent on the size of the tumor and the depth of invasion (Clark level). Both lymphatic and hematogenic dissemination leads to tumor spread, and there is no preferential site for metastases. Often, metastases are found in the draining lymph nodes, lung, liver, skin, brain, and bone, but potentially every organ, including the eye, can be involved. The precise molecular mechanisms of metastasis in melanoma are under intense investigation [4].

The eye can be affected by cutaneous melanoma and be under the influence of the associated risk factors and treatment modalities in a variety of ways. Metastasis into the eye and orbit from cutaneous melanoma probably accounts for less than 5 % of all metastases. Usually the eye becomes affected in the setting of wide-spread metastasis in melanoma. The most common site for the primary tumor was reported to be the skin of the trunk (39 %), the upper (24 %) and lower (21 %) extremities, and least frequently (5 %) the head and neck [1]. As in cutaneous melanoma, increased exposure to ultraviolet (UV) radiation is a risk factor for some eye diseases such as pterygium of the conjunctiva [5], eyelid malignancies (basal cell carcinoma and squamous cell carcinoma), photokeratitis, climatic droplet keratopathy (CDK), and cortical cataract [6]. The role of UV exposure for the risk to develop age-related macular degeneration (AMD) remains controversial as it is probably related to visible light, particularly blue light [7]. Paraneoplastic retinal eye disease manifestations have been described as vitelliform retinal lesions [8, 9] and acute exudative polymorphous vitelliform maculopathy [10–12]. Also, systemic changes that accompany tumor progression, for example ectopic production of hormones such as steroids and adreno-corticotropic hormone, ACTH [13–15], could potentially affect the eyes. Complications of the tumor treatment regimen (radiation, toxicity of chemotherapy) can lead to secondary eye pathology, including cataract formation and retinopathy due to therapeutic radiation [16] and macular edema due to chemotherapy [17].

To the best of our knowledge, this is the first study to analyze the incidence and spectrum of ocular diseases in a consecutive series of patients with metastatic cutaneous melanoma.

Patients and methods

Between April 1, 2009, and April 1, 2013, 108 consecutive patients (64 women and 44 men), mean age 64±8 years (range, 29–88 years) at the time of eye examination (Table 1), with metastatic cutaneous melanoma were screened for ocular diseases at the Department of Ophthalmology, University of Cologne, Cologne, Germany, and the Department of Ophthalmology, University of Erlangen-Nuremberg, Erlangen, Germany. Inclusion criterion was presence of metastatic cutaneous melanoma without specific exclusion criteria. This retrospective, nonrandomized, clinical study was carried out in conformance with the tenets of the Declaration of Helsinki. Institutional review board or ethics committee was not required in this instance. Written informed consent was obtained from all patients.

According to the 2009 TNM classification system for cutaneous melanoma, 21 patients (19 %) were classified as M1a (distant skin, subcutaneous or nodal metastases), 29 patients (27 %) were classified as M1b (lung metastases), and 58 patients (54 %) were classified as M1c (all other visceral metastases, any distant metastasis with elevated lactate dehydrogenase) at the time of ophthalmic screening. The World Health Organization (WHO) performance status was scored 0 (asymptomatic: fully active, able to carry on all predisease activities without restriction) in 51 patients (47 %), 1 (symptomatic but completely ambulatory: restricted in physically stenuous activity, but ambulatory and able to carry out work of a light or sedentary nature; for example, light housework, office work) in 47 patients (44 %), 2 (symptomatic, <50 % in bed during the day: ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50 % of waking hours) in seven patients (6 %), and 3 (symptomatic, >50 % in bed, but not bedbound: capable of only limited self-care, confined to bed or chair 50 % or more of waking hours) in three patients (3 %). Mean period of time with metastases was 5±4 months (range, 1–22 months). At the time of eye examination, 76 patients (70 %) had no current treatment, two patients (2 %) were under immunotherapy, 15 patients (14 %) were under vaccine therapy, and 15 patients (14 %) were under kinase inhibitor therapy. Previous treatment for metastatic disease (completed at least 6 weeks prior to eye examination) included immunotherapy in 50 patients (46 %) and kinase inhibitor therapy in two patients (2 %).

Ophthalmic screening included a standardized eye examination with measurement of Snellen uncorrected visual acuity and best spectacle-corrected visual acuity, Hertel exophthalmometry, slit-lamp examination, tonometry, funduscopy in mydriasis, and spectral-domain optical coherence tomography (SDOCT) of the retina. Selected cases with atypical findings underwent fluorescein and indocyanine green angiography, electrophysiological studies including electroretinography and electrooculography, as well as standardized ophthalmic echography. Specifically, we considered the thickness (>2 mm), presence of subretinal fluid, symptoms and orange pigment, and whether the margin touched the optic disc to classify the fundus lesions and to differentiate nevi from choroidal melanoma. One patient (case 1, Fig. 1) was examined for hypercortisolism by a dexamethasone suppression test to exclude ectopic paraneoplastic adrenocorticotropic hormone (ACTH) production, and had a genetic testing for the BEST1-gene to exclude Morbus Best.

Table 1 Clinical characteristics of 108 patients with metastatic cutaneous melanoma

	Total (n=108)	Ocular manifestations	
		Present (n=65)	Absent (n=43)
Age at eye examination (years)			
Mean ± SD (range)	64±8 (29–88)	65±8 (39–88)	61±8 (29–77)
Gender			
Male, *n* (%)	69 (59 %)	38 (58 %)	26 (60 %)
Female, *n* (%)	44 (42 %)	27 (42 %)	17 (40 %)
Metastatic stage at eye examination[a]			
M1a, *n* (%)	21 (19 %)	13 (20 %)	8 (19 %)
M1b, *n* (%)	29 (27 %)	19 (29 %)	10 (23 %)
M1c, *n* (%)	58 (54 %)	33 (51 %)	25 (58 %)
Period of time with metastases (months)			
Mean ± SD (range)	5±4 (1–22)	5±4 (1–19)	5±5 (1–22)
WHO performance status at eye examination			
0, *n* (%)	51 (47 %)	30 (46 %)	21 (49 %)
1, *n* (%)	47 (44 %)	28 (43 %)	19 (44 %)
2, *n* (%)	7 (6 %)	5 (8 %)	2 (5 %)
3, *n* (%)	3 (3 %)	2(3 %)	1 (2 %)
Treatment at eye examination			
Immunotherapy, *n* (%)	2 (2 %)	2 (3 %)	–
Chemotherapy, *n* (%)	–	–	–
Radiotherapy, *n* (%)	–	–	–
Vaccine therapy, *n* (%)	15 (14 %)	8 (12 %)	7 (16 %)
Kinase inhibitor therapy, *n* (%)	15 (14 %)	9 (14 %)	6 (40 %)
No therapy, *n* (%)	76 (70 %)	46 (71 %)	30 (70 %)
Previous treatment (≥6 weeks prior to eye examination)			
Immunotherapy, *n* (%)	50 (46 %)	29 (45 %)	21 (49 %)
Chemotherapy, *n* (%)	–	–	–
Radiotherapy, *n* (%)	–	–	–
Vaccine therapy, *n* (%)	–	–	–
Kinase inhibitor therapy, *n* (%)	2 (2 %)	1 (2 %)	1 (2 %)
No therapy, *n* (%)	56 (52 %)	35 (54 %)	21 (49 %)

SD standard deviation, *WHO* World Health Organization

Retrospective review of the charts of patients with metastatic cutaneous melanoma that were screened for eye diseases. Age, gender, metastatic stage at eye examination, period of time with metastases, WHO performance status and treatment at or ≥6 weeks prior to eye examination

[a] According to 2009 TNM classification system for cutaneous melanoma

Main outcome measures included the frequency and spectrum of ocular diseases. Commercial software (SPSS version 19.0 for Windows; SPSS, Inc., Chicago, IL, USA) was used for all statistical analyses. Comparisons between the presence and absence of ocular diseases were performed using the nonparametric Mann–Whitney *U* test, Fisher's exact test and Pearson's chi-square test. A p value of less than 0.05 was considered statistically significant.

Results

Ocular disorders were present in 65 (60 %) out of 108 patients with metastatic cutaneous melanoma (Table 2). Patients with ocular diseases were significantly older than those without ocular disorders (p=0.004). No significant association was observed with gender (p=0.488), metastatic stage (p=0.729), period of time with metastases (p=0.787), WHO performance status (p=0.926), current treatment (p=0.655), and previous treatment (p=0.856).

Using slit-lamp biomicroscopy, cataract was found in 27 patients (25 %), pseudophakia in 22 patients (20 %), pseudoexfoliation syndrome in three patients (3 %), and Fuchs' endothelial dystrophy in one patient (1 %). Retinal fundus revealed non-proliferative diabetic retinopathy in eight patients (7 %), proliferative diabetic retinopathy in one patient (1 %), diabetic macular edema in one patient (1 %), non-ischemic branch retinal vein occlusion in one patient (1 %), ischemic central retinal vein occlusion in one patient (1 %), branch retinal artery occlusion in one patient (1 %), hypertensive retinal disease grade 1 in ten patients (9 %), and hypertensive retinal disease grade 2 in

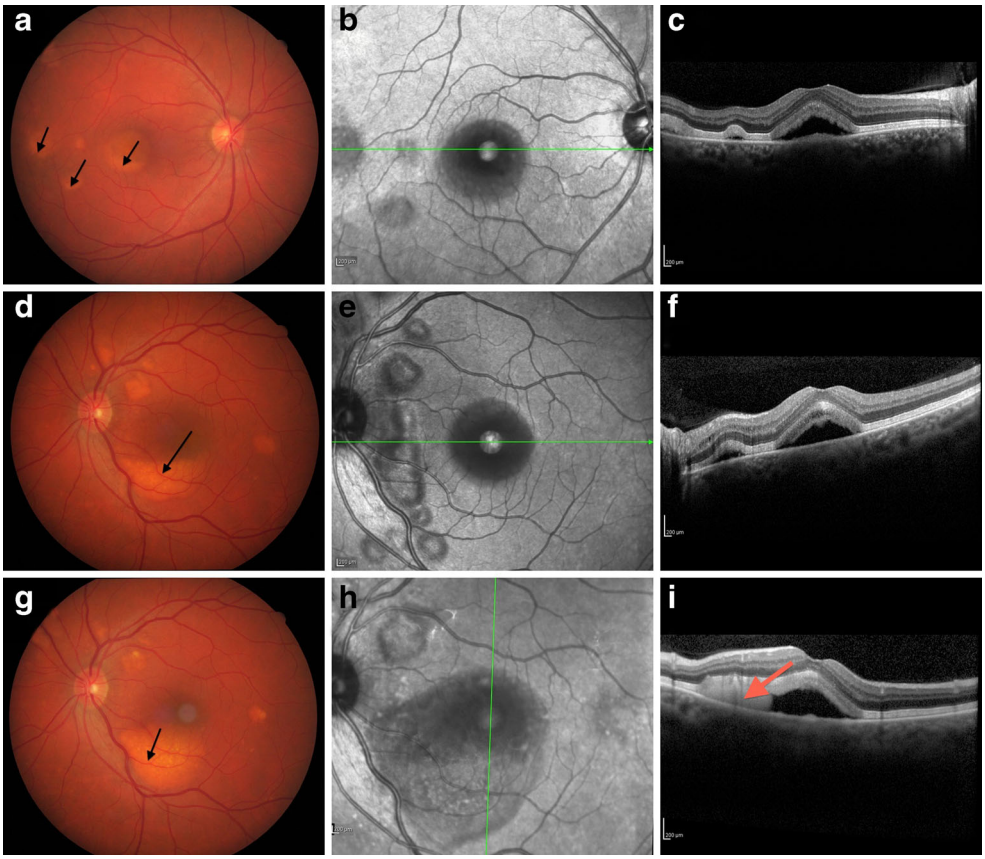

Fig. 1 Patient 1 with multifocal polymorphous serous retinal detachments and yellowish subretinal deposits. Fundus photographs (**a**, **d**, and **g**), level of OCT examination (**b**, **e**, and **h**) and corresponding SD-OCT layer (**c**, **f**, and **i**). Multiple polymorphous flat lesions with yellowish deposits (indicated by *black arrows*), concentrated in the lower parts are visible by funduscopy (**a**, **d**, and **g**). SDOCT was performed in different layers to demonstrate serous detachments of the lesions (**c**, **f**, and **i**) and the accumulation of the deposits (indicated by a *red arrow*) in the lower subretinal parts of the lesions (**i**). Figures **g**, **h**, and were performed 8 months after **a**–**f**, which were performed at the initial visit. Note the enlargement of the central macular lesion of the left eye with increase of the vitelliform material

four patients (4 %). Funduscopy and SDOCT of the macula revealed non-exudative age-related macular degeneration in 20 patients (19 %), exudative age-related macular degeneration in four patients (4 %), macular hole in one patient (1 %), epiretinal membrane in one patient (1 %), and cystoid macular edema in three patients (3 %). Uveal tumors were clinically diagnosed as choroidal nevi in five patients (5 %), iridal nevi in three patients (3 %), choroidal hemangioma in one patient (1 %), and choroidal metastasis in one patient (1 %). None of the patients showed evidence for an uveal melanoma. Glaucomatous optic neuropathy was found in four patients (4 %). One patient had an intermediate uveitis (1 %). No patient presented with periocular neoplastic diseases such as neoplasias of the ocular surface, the eyelids and the orbit (0 %).

Interestingly, two patients (2 %) presented with multifocal bilateral retinal lesions comprised of serous detachments and yellowish vitelliform-like subretinal deposits. Case 1 (Fig. 1) was a 60-year-old male with cutaneous melanoma (metastatic stage M1a and WHO performance status 0) that was diagnosed 3 years before ophthalmic evaluation. The best spectacle-corrected visual acuity (standard Snellen test) was 20/32 in the right eye (RE) and 20/25 in the left eye (LE). The anterior segment of both eyes was unremarkable. Funduscopic evaluation revealed multiple oval and curvilinear lesions confined to the posterior pole, which had accumulation of a yellowish vitelliform or fibrin-like material in their inferior part (Fig. 1a, d, and g). SDOCT (scan levels in Fig. 1b, e, and h) revealed this material to be located in the subretinal space (Fig. 1h) of the inferior part of the lesion, whereas the upper parts of the lesion showed no deposits (Fig. 1c and f). Furthermore, the lesions were accompanied by serous retinal detachment corresponding to the lesional area. The amount of the yellowish depostits in the LE increased 8 months after the initial visit (compare Fig. 1d and e to g and h), but visual acuity remained stable at this time-point and decreased from 20/25 to 20/32 in the LE, 3 months later. This patient underwent dendritic cell based tumor-vaccination therapy 1 month before the first visual symptoms that he described as central relative scotoma. The patient was tested for presence of the BEST1-gene to exclude Morbus Best, with negative result. Also, a dexamethasone suppression test to exclude ectopic paraneoplastic steroid or ACTH production, revealed normal parameters. Case 2 was a very similar case, but without the fibrin-like deposition within the lesions. A 42-year-old female, was diagnosed with cutaneous melanoma (metastatic stage M1a and WHO performance status 0) 2 years before manifestation of the eye disease (Fig. 2). The best spectacle-corrected visual acuity (standard Snellen test) was 20/20 in the right eye (RE) and 20/40 in the left eye (LE). Multifocal electroretinography (mfERG) revealed a normal result (not shown). Funduscopy showed extensive and round flat lesions in the macular

Table 2 Ocular manifestations of 108 patients with metastatic cutaneous melanoma

	Total (n=108)
Diabetic retinopathy	
Non-proliferative diabetic retinopathy, n (%)	8 (7 %)
Proliferative diabetic retinopathy, n (%)	1 (1 %)
Diabetic macular edema, n (%)	1 (1 %)
Retinal venous occlusive disease	
Non-ischemic branch retinal vein occlusion, n (%)	1 (1 %)
Ischemic branch retinal vein occlusion, n (%)	–
Non-ischemic central retinal vein occlusion, n (%)	–
Ischemic central retinal vein occlusion, n (%)	1 (1 %)
Retinal arterial occlusive disease	
Branch retinal artery occlusion, n (%)	1 (1 %)
Central retinal artery occlusion, n (%)	–
Amaurosis fugax, n (%)	–
Hypertensive retinal disease	
Grade 1, n (%)	10 (9 %)
Grade 2, n (%)	4 (4 %)
Grade 3, n (%)	–
Grade 4, n (%)	–
Macular disease	
Non-exudative age-related macular degeneration, n (%)	20 (19 %)
Exudative age-related macular degeneration, n (%)	4 (4 %)
Macular hole, n (%)	1 (1 %)
Epiretinal membrane, n (%)	1 (1 %)
Cystoid macular edema, n (%)	3 (3 %)
Central serous chorioretinopathy, n (%)	–
Paraneoplastic retinopathy	
Melanoma-associated retinopathy, n (%)	–
Acute exudative polymorphous vitelliform maculopathy-like disease, n (%)	2 (2 %)
Uveal tumors	
Choroidal nevus, n (%)	5 (5 %)
Choroidal melanoma, n (%)	–
Choroidal metastasis, n (%)	1 (1 %)
Choroidal hemangioma, n (%)	1 (1 %)
Iridal nevus, n (%)	3 (3 %)
Ciliary body melanoma, n (%)	–
Ciliary body metastasis, n (%)	–
Optic neuropathies	
Papillitis, n (%)	–
Ischemic optic neuropathy, n (%)	–
Glaucomatous optic neuropathy, n (%)	4 (4 %)
Uveitis	
Uveitis anterior, n (%)	–
Uveitis intermedia, n (%)	1 (1 %)
Uveitis posterior, n (%)	–
Panuveitis, n (%)	–
Periocular diseases	
Ocular surface neoplasms, n (%)	0 (0 %)
Eyelid non-melanoma neoplasms, n (%)	0 (0 %)
Orbital neoplasms, n (%)	0 (0 %)
Other diseases	
Cataract, n (%)	27 (25 %)
Pseudophacia, n (%)	22 (20 %)
Pseudoexfoliation syndrome, n (%)	3 (3 %)
Fuchs' endothelial dystrophy, n (%)	1 (1 %)

All patients had a basic ophthalmic examination with visual acuity and intraocular pressure, slit-lamp examination and funduscopy in mydriasis, and an optical coherence tomography (OCT) of the retina. Some patients had electroretinogram (ERG) and electrooculogram (EOG) testing. One patient was screened for hypercortisolism by a dexamethasone suppression test

region (Fig. 2a, d), that corresponded to serous retinal detachments (Fig. 2c, f). Early, mid-phase, and late frames (Fig. 2g, h and i) in the fluorescein angiography showed a mild hypofluorescence within the macular lesions, similar to case 1 (not shown). This patient was treated with interferon-α-2b (IFN-α-2b) at the time of eye examination. However, 50 (46 %) out of the 108 patients in our study have been also treated with this kind of immunotherapy (Table 1).

Discussion

Up-to-date information regarding the significance of ocular diseases in patients with metastatic cutaneous melanoma is largely based on a collection of case report series [1]. The present study performed, to the best of our knowledge for the first time, a comprehensive ophthalmic examination including SDOCT of the retina in consecutive patients. Specifically, a complete ophthalmic status was determined, including diseases that are not related to the melanoma. Due to the highly specialized departments in our eye clinics, to avoid bias, we compared these data with results from extensive epidemiological studies [18–22]. Our data suggest that patients with metastatic cutaneous melanoma reveal a spectrum of ocular diseases similar to the normal population of this age range. Ocular diseases that are associated with increased exposure to UV radiation were not found at higher rates compared to the normal population, as we did not find any periocular neoplastic disease in patients with metastatic cutaneous melanoma. Taken together, these results on a small consecutive patient sample from two German tertiary centers neither indicate nor suggest a relation of the ocular findings to metastatic melanoma, except for three cases, one with uveal metastasis of melanoma and two with paraneoplastic retinopathy that is very rarely seen in melanoma. The diagnosis of the patient with an uveal metastasis of cutaneous melanoma was based on

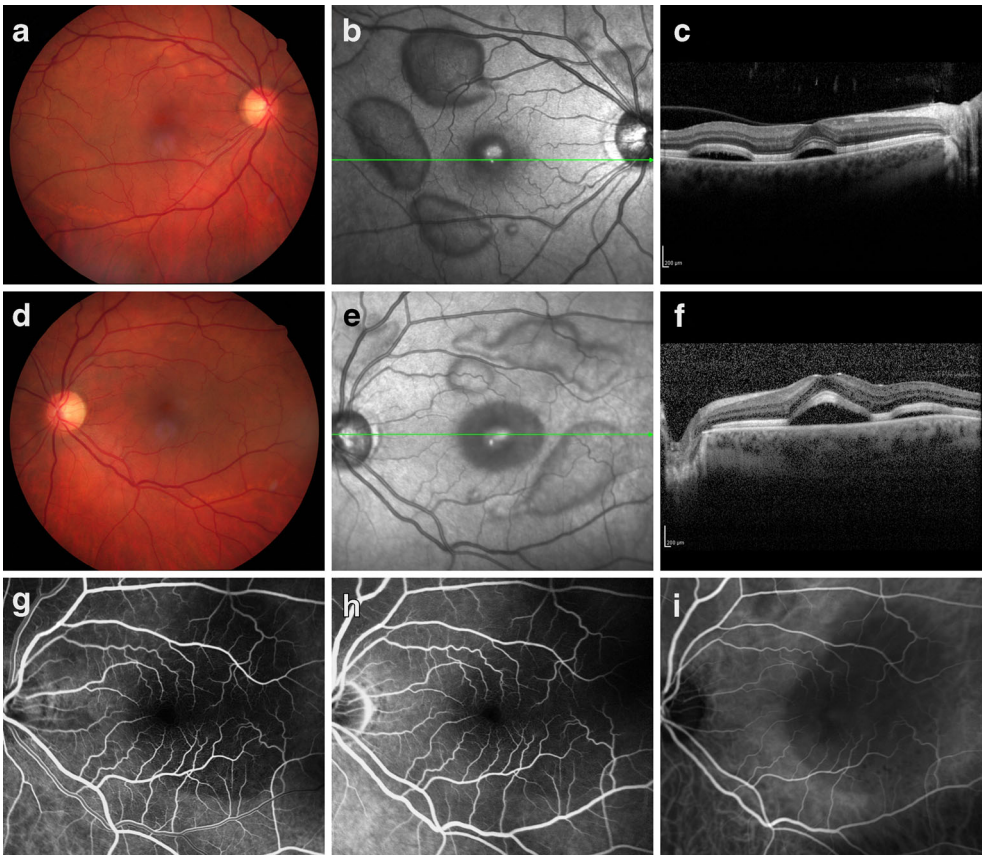

Fig. 2 Patient 2 with multifocal polymorphous serous retinal detachments. Fundus photographs (**a**, **d**), level of OCT examination (**b**, **e**) and corresponding layer (**c**, **f**). **g**–**i** shows fluorescein angiography frames of the early- (**g**), mid- (**h**) and late-phase (**i**). In this case, the visible funduscopic changes comprise of a flat round lesion spanning almost the complete macular region that do not correspond to the lesions that were found in the SDOCT or angiography. SDOCT demonstrates multiple serous detachments without subretinal deposits (**c**, **f**, and **i**). Similarly to case 1 (not shown), fluorescein angiography shows a mild hypofluorescence at the posterior pole in all frames (early- (**g**), mid- (**h**) and late-phase (**i**)

the clinical setting (widespread metastasis of cutaneous melanoma, stage M1c and WHO performance status 3), the funduscopic appearance and echographic features, as described in "Patients and methods". The lesion had irregular borders, was only slightly pigmented, and had intermediate internal echographic reflectivity. Therefore, and in summary, we considered this fundus lesion to represent a metastatic focus and not a primary uveal melanoma. Nevertheless, based on our observations and previous studies, uveal metastasis of cutaneous melanoma appears to be extremely rare [1] and occurring rather in progressed metastatic melanoma. In addition, within the 108 examined patients we found two that had retinal findings similar to some cases that were previously described as a part of the melanoma-associated retinopathy (MAR) spectrum [8, 9]. In both patients, the SDOCT findings appeared similar to multifocal central serous chorioretinopathy (CSC). In line with this, the yellowish pseudovitelliform lesions would represent fibrin-like material. Subretinal deposition of a fibrin-like material in central serous chorioretinopathy (CSC) has been described previously [23, 24]. Although CSC is a disease of unknown etiology, it has been reported that elevated serum levels of corticosteroids have a negative effect on the clinical course [25]. In patients with cutaneous melanoma, there have been many reports about ectopic paraneoplastic production of the adreno-corticotropic hormone (ACTH) that can lead to increased serum levels of cortisol [13, 15]. We speculated that the features that were similar to CSC in the two patients may represent the consequences of ectopic paraneoplastic ACTH production. Therefore, a dexamethasone suppression test was performed in one patient (case 1, Fig. 1) to look for endogenous hypercortisolism. We found all endocrinological parameters within the normal range, virtually excluding ectopic ACTH-production at the time of testing. However, because this test was performed 4 years after manifestation of the CSC-like lesions, it is not possible to exclude previous episodes of ectopic ACTH-production in this patient. Other features, such as the yellowish deposits in case 1, resembled aspects of Morbus Best. However, this patient had normal electrophysiological findings including ERG and EOG, and was negative for the gene BEST1. On the other hand, the fluorescence angiography findings of both patients showed a mild hypofluorescence in all frames without any leakage, compatible with findings similar to Morbus Best but not representative of CSC. Taken together, this constellation most likely represents a variant of "acute exudative polymorphous vitelliform maculopathy" (AEPVM)-like disease that has been reported in patients in the context of melanoma or carcinoma, but also as idiopathic [10–12]. However, case 2 does not completely fulfill the definition of AEPVM, as it lacks the vitelliform deposits. Similar findings have also been reported in a previous case report [26], but in the context of MAR. However, we did not see any findings that would support our

cases to be a part of the MAR spectrum, as the patients had normal electrophysiological findings. Possibly, both disease manifestations may be found in some patients. In summary, we found a normal range of ocular diseases in patients with cutaneous melanoma except for two unusual cases of acute exudative polymorphous vitelliform maculopathy. In conclusion, patients with metastatic cutaneous melanoma reveal ocular diseases with a spectrum similar to the normal population of this age range. Very rarely, uveal metastasis as well as paraneoplastic retinopathies such as AEPVM-like disease can occur. A large multicentric epidemiological study would be necessary to confirm these data.

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