

Conjunctival Melanoma and BRAF Inhibitor Therapy

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Abstract

Background: BRAF is a proto-oncogene that encodes the protein B-Raf. This is a serine/threonine kinase and part of the mitogen-activated protein kinase (MAPK) pathway. Vemurafenib is a potent inhibitor of the mutant BRAF. It is approved for cutaneous melanoma.

Patient/methods: A 80-year-old woman presented with irregular pigmented, hyperaemic upper and lower eye lid changes and alterations in the temporal conjunctiva of the right eye 03/2011. A conjunctival melanoma was detected with expression of BRAF Mutation on exon 15 (by PCR). For causal therapy the only primary surgical option was offered: exenteration of the right orbital. The patient refused this surgical intervention. To stabilize and prevent progression of the lesions, treatment with a BRAF inhibitor (vemurafenib) has been started over 16 month period of time.

Results: After successful tumour response and decreasing size complete resection was performed 08/2013. The therapy was terminated due to a controlled tumour situation and progressive deterioration of general condition 09/2013. The progression of conjunctival melanoma could be prevented by this therapy by now.

Discussion: To the best of our knowledge it is the first case to show the permanent recovery of a conjunctival melanoma after BRAF inhibitor therapy. Over the course of time there was a significant reduction of the patient's general condition including weight loss, vomiting, headaches. These side effects should be carefully evaluated in further studies.

Keywords: BRAF inhibitor; Vemurafenib; Conjunctival melanoma; Eyelid surgery

Introduction

The conjunctival malignant melanoma is a rare tumor arising from degenerated melanocytes of the conjunctiva. It may consist of a primary acquired melanosis (56%), from a naevus of the conjunctiva (26%) or de novo (18%). Mostly affected are the bulbar shares (92%), while additionally infestations of the palpebral shares, the fornix, the plicae semilunares or caruncula were demonstrated [1].

The conjunctival melanoma represented 2-5% of all ocular malignant tumors and 5-7% of all primary ocular melanomas [1-3]. It occurred more frequently in patients aged 60 years and over [4,5]. Mortality of 15-30% and local recurrence by nearly 60% of the patients with previous ocular treatment was reported [4]. The tumor cells would commonly spread using the lymphatic way to regional lymphatic nodes or more rarely take the haematogenous way and spread in the brain, the liver and the lung [4]. A sentinel node scintigraphy was therefore recommended.

In this case an 80-year-old woman presented with irregular pigmented, hyperaemic upper and lower eyelid changes and alterations in the temporal conjunctiva of the right eye 03/2011 (Figure 1). The left eye presented a primary acquired conjunctival melanosis without any atypia. Further ophthalmologic diagnosis of the patient were a bilateral brunescens cataract, age related macula dystrophy and a myopic fundus.

Visual function of the right eye was 20/40 and of the left eye 20/100 due to the age related macula degeneration at the first presentation.

The patient denied concomitant symptoms (fever, night sweats and weight loss).

Upper and lower eyelid excision plus conjunctival excision and subsequent plastic surgery showed a conjunctival and partly cutaneous melanoma 04/2011 (Figure 2); complete resection could not be performed.

Chest x-ray and abdominal ultrasonography showed no evidence of metastasis.

Histopathology

04/2011

Immunohistochemical evaluation of the pigmented tarsal lesions showed nests of atypical melanocytes in the epithelium layer and the

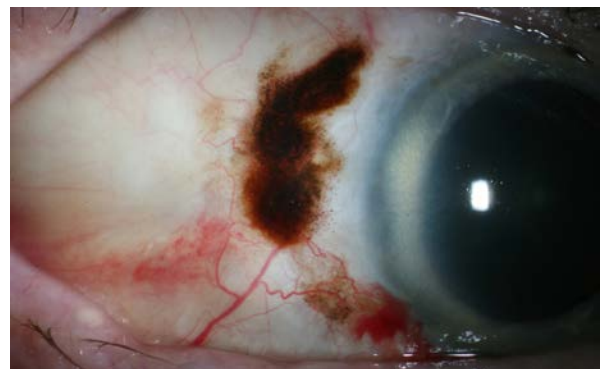


Figure 1: 03/2011 conjunctival melanoma right eye.

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Figure 2: 04/2011 local recurrence conjunctiva right eye.

lamina propria, enlarged nuclei, eosinophilic nucleoli and nuclear inclusions. The diagnosis of conjunctival melanoma was assessed; further immunophenotypical tests showed positive results for HMB45, Melan A, S-100, tyrosinase, with a high growth rate >50% in the melanocytic cells, further nuclear p63 negativity (Figure 5).

By PCR and pyrosequencing a mutation in exon 15 of the BRAF gene was detected.

Therapy and Outcome

The current gold standard states the complete surgical resection of a malignant melanoma. Also adjuvant therapy radiotherapy, brachytherapy or cryotherapy can be performed. Topical treatment of mitomycin C eye drops or interferon alpha as subconjunctival or topical injections can be complementarily supplied [6-8].

Additionally to primary excision a ruthenium applicator 1227 treatment was implemented on the conjunctival lesions in April 2011. In case of the local tumor recurrence another excision and lid surgery took place in July 2011 and in January 2012. In September 2012 the patient showed up with new alterations of the known melanoma and non insano resection took place in 10/2012 and 03/2013 (Figures 3 and 4).

For causal therapy the primary surgical option was offered: exenteration of the right orbital. However, the patient refused this surgical intervention several times as she started suffering from suicidal ideas and wanted to keep her visual function as this had a high impact on her quality of life in the age of 80 years.

To stabilize and prevent progression of the lesions, treatment with a BRAF inhibitor (vemurafenib) has been initiated, monitored by the Department of Dermatology Charite in March 2012.

The vemurafenib therapy was continued for a 16-month period of time. The treatment was administered orally every day and controlled by monthly monitoring both in Dermatological and Ophthalmological outpatient departments.

After successful tumor response and a decreasing in size complete surgical resection was performed in August 2013.

The therapy was terminated due to a controlled tumor situation and progressive deterioration of general condition in September 2013. Over the course of time there was a significant reduction of the patient's general condition including weight loss (8 kg in 6 months), nausea and vomiting, headaches.

Yet the progression of conjunctival melanoma could be prevented and the visual function restored over 3 years.

Discussion

The complicated situation of our patient was due to the tumor location; the melanoma was situated in different conjunctival and eyelid positions, so criteria of cutaneous and conjunctival melanoma were fulfilled. Furthermore we had to evaluate the patient's needs of obtaining visual function (oculus melior) as well as the risk of the metastatic tumor spreading. For causal therapy the primary surgical attempt was an exenteration of the orbita. The patient strongly refused this intervention of primary surgery. She was even considering suicide when imagining the surgical outcome. In the tumor board specialists of dermatology and ophthalmology decided to perform local tumor excisions to minimize tumor size and progression, so in the following months several local recurrence resections were carried out.

After the BRAF mutation was detected in conjunctival and cutaneous lid biopsies, BRAF inhibitor therapy was carried out as off label therapy in this special condition and in agreement of patient's consent.

In 22-50% of conjunctival melanomas a V599E (V600E sometimes called) BRAF mutation was detected [1,9,10]. Griewank et al. identified BRAF mutations in 23 of 78 (29%) conjunctival melanomas, demonstrating the majority of BRAF mutations ($n=21$; 91%) were V600E (T1799A) mutations [10]. BRAF mutations were significantly rising in tumors located at the caruncle (66% BRAF vs. 0% NRAS and 33% wild-type; $P=0.03$) as well as tumors originating from melanocytic nevi (65% BRAF vs. 27% NRAS and 9% wild-type; $P<0.001$) [10]. So a close relationship of conjunctival melanoma was suggested to cutaneous and mucosal melanoma and therefore therapeutic options of metastatic cutaneous and mucosal melanomas should be taken into consideration including clinical trials of novel agents for this patient's cohort [10].

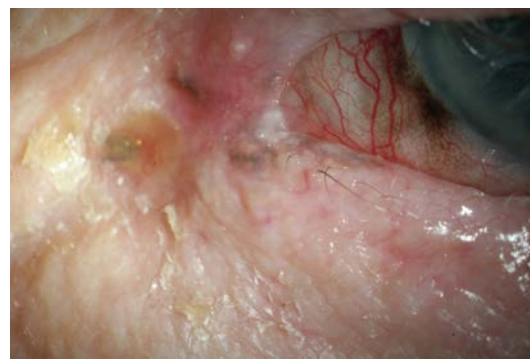


Figure 3: 10/2012 local recurrence right eye.



Figure 4: 03/2013 local recurrence right eye.

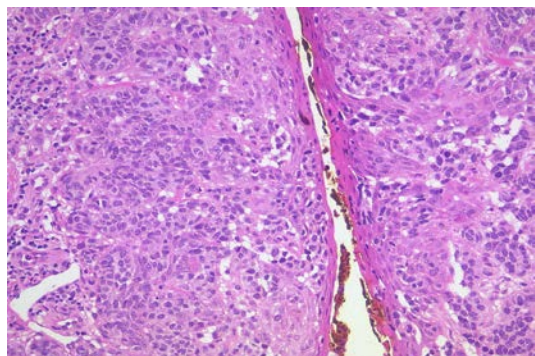


Figure 5: Histopathology: atypical melanoma cells on lower eye lid.

BRAF is a protooncogene encoding the protein B-RAF, which is a serine/threonine kinase and part of the mitogen-activated protein kinase (MAPK) pathway. On this pathway signals from cytokines, hormones and growth factors were forwarded on to growth receptors on the cell surface and then transcription factors were activated in the nucleus. In the nucleus the expression of genes was regulated, which have an influence on apoptosis, cell cycle progression and differentiation of the cell. Mutations of components of the pathway such as BRAF cause its constitutive activity followed by unregulated proliferation and growth of the mutant cells [11].

One of the most common mutations in the BRAF gene as mentioned earlier was the V599E mutation. In this case an exchange of thymidine by adenosine in nucleotide 1796 took place, whereby the amino acid valine was replaced by glutamate during translation [12]. This mutation of BRAF was partly responsible for the conversion of the malignant melanoma, papillary thyroid carcinoma and colorectal cancers [13].

Maldonado et al. reported about a cohort of 115 patients with primary invasive melanomas and showed a statistically significant increase in BRAF mutations of melanomas occurring on intermittent sun exposed skin (23/43, 54% specimens) compared to chronically sun exposed skin (1/12, 8%) and rarely sun exposed skin such as palms and soles (6/39, 15%) [14]. Clinical outcome or the presence of a melanocytic nevus was not associated to the BRAF mutation: Six (55%) of 11 nevus-associated melanomas and 15 (43%) of 35 unassociated melanomas had a BRAF mutation ($p=0.73$). An elevated copy number of the mutated allele could be demonstrated, thus implicating BRAF as an important factor driving selection for the frequent copy number increases of chromosome 7q in melanoma [14].

Trying to detect important risk circumstances the V600E BRAF mutation was identified in 14 of 28 (50%) conjunctival nevi, but in none of the 15 conjunctival primary acquired melanosis, with and without atypia. The V600E BRAF mutation was identified in two of the five (40%) conjunctival melanomas [15]. The detected mutation did not differentiate in conjunctival nevi in children or adults. The received observations suggesting that the oncogenic event leading to BRAF mutations affect only conjunctival nevi and not primary acquired melanosis [15].

After a successful Phase III Study the BRAF inhibitor PLX4023 (vemurafenib) was approved (U.S. since 08/2011 and Germany since 02/2012) for the treatment of cutaneous metastatic and unresectable malignant melanoma, provided that this mutation can be detected [16]. Vemurafenib was a potent inhibitor of the mutant BRAF, but had no effect on cells carrying the wild-type gene. The mean interval

to treatment response was 6.7 months. Compared to dacarbazine in metastatic melanoma the relative mortality was reduced by 63% and the risk of cancer progression by 74% [16].

In this first case report the rehabilitation therapy was performed as off label therapy in exceptional circumstances: In the patient's unmedicated status a primary healing strategy would have led to complete loss of visual function, stereoscopic perception and cosmetical deformation by surgery.

Further running of the disease will now show whether a permanent restoration in this case was possible.

It could be demonstrated that the vemurafenib therapy may also be successfully applied in conjunctival melanoma, especially if surgical intervention cannot be put into practice by different reasons (patient's agreement, difficult to access surgery). There have been promising indications to start therapy in advanced metastatic melanoma and local findings restricted to tumor surgery by difficult and multiple locations.

It must be mentioned that there were severe side effects of vemurafenib, so a careful selection of patients must be made before starting a long-term therapy.

Very common side effects were a squamous cell carcinoma of the skin, seborrheic keratosis, skin papilloma, headache, vomiting, myalgia and malaise [16,17].

Common side effects included the following: Basal cell carcinoma, new primary melanomas, paralysis of the facial nerve, uveitis, Palmar-plantar erythrodysesthesia syndrome, weight loss and QT time extension [16,17].

Weight loss, nausea and vomiting and headache were reported by the patient, so the extension of side effects should be observed during and after vemurafenib therapy. Positive and negative effects of vemurafenib therapy should be seriously re-evaluated at all times. By taking the skin alterations in concern dermatological prophylaxis was recommended during and after vemurafenib therapy: Our patient has fulfilled monthly dermatological checkups.

Furthermore a combination of vemurafenib therapy with other therapeutic options including immunotherapy could be used to establish tumor reduction therapy guidelines [18].

Limits of the report were the number of patients treated, so further investigations of vemurafenib therapy in conjunctival melanoma are needed before schematic therapy guidelines can be defined.

In conclusion this newly developed drug therapy can be considered for first-line therapy to reduce tumor size in locations difficult to access for surgery (Plica semilunaris tumor with difficult lacrimal duct reconstruction) after an increased number of patients has been studied or it could be considered as a therapeutic option to prevent tumor progression if primary surgery is refused by the patient.

To the best of our knowledge when conducting this research, no literature was found where vemurafenib therapy is combined with conjunctival melanoma.

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Competing Interests Statement

There are no competing interests.

Contributorship Statement

All our authors (Bertelmann E, Mai C, Pahlitzsch M) fulfilled substantial contributions to conception, acquisition of data and analysis.

Furthermore to drafting the article and revising it critically for important intellectual content; and finally took responsibility of the version to be published.

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