AMJ Australasian Medical Journal [AMJ 2017;10(7):571-574]

Metastatic cutaneous melanoma associated with vitreous seeding

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CASE STUDY

Please cite this paper as: Rocke JR, O'Day RFJ, Giudicatti LC, Clark JB. Metastatic cutaneous melanoma associated with vitreous seeding. AMJ 2017;10(7):571–574.
https://doi.org/10.21767/AMJ.2017.2959

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ABSTRACT

Background
Ocular metastases of cutaneous melanoma exclusive to the vitreous are a rare presentation and usually represent disseminated disease. Although traditionally associated with poor outcomes, recent developments in melanoma treatment have vastly improved prognosis.

Aims
To review new targeted therapies for metastatic-melanoma.

Methods
Literature review of current clinical guidelines, systematic reviews and case series surrounding current recommended targeted therapies for metastatic-melanoma.

Results
New targeted therapeutic agents offer improved treatment response, progression free survival, overall survival and have a better side-effect profile than traditional chemotherapy agents for metastatic melanoma.

Conclusion
Targeted agents for melanoma have improved patient prognosis and life expectancy, likely leading to reduced need for surgical intervention.

Key Words
Metastatic melanoma, targeted therapy, ocular metastases, BRAF, new treatments, cancer

Implications for Practice:

1. What is known about this subject?
Despite representing only 1 per cent of total skin cancers, melanoma remains the greatest cause of skin cancer deaths.

2. What new information is offered in this case study?
Targeted therapies are among several new advancements in treatment options for advanced melanoma (Stage III and IV) which have vastly improved prognosis.

3. What are the implications for research, policy, or practice?
New targeted agents have improved survival and prognosis for patients with advanced melanoma, leading to reduced need for medical intervention and an ongoing prioritisation of chronic disease management (e.g., glaucoma, diabetic retinopathy).

Background

Melanoma accounts for only 1 per of skin cancers, however, represents the highest rate of skin cancer-related deaths.[1] Traditionally, metastatic melanoma was associated with very poor survival rates of 10–15 per cent for Stage IV (widespread) disease.[2,3] There has been several recent developments in the therapies available for unresectable (Stage III and IV) melanoma, which have shown improvements in response rates, progression free survival and overall survival.[1] These medications include immunotherapy agents which work to enhance the patient's own immune-mediated response to the tumour, as well as therapies targeted to act on specific gene mutations, proteins or tissue environment involved in tumour growth and survival.[1] This case describes an unusual presentation of cutaneous melanoma metastasising to the vitreous humour which clinically resolved following treatment with modern targeted agents.

Case details

An 81-year-old male presented to the ophthalmology department with a 6-week history of painless visual loss and floaters in both eyes. Past medical history was significant for cutaneous melanomas, one excised from his back several years previously and another recently excised from his right cheek. On examination, his right visual acuity was hand movements and left was 6/9, intraocular pressures were normal. The conjunctiva and sclerae were not injected and there was no anterior chamber inflammation. He had bilateral large, dense anterior vitreous cells (Figure 1). No retinal or choroidal masses were present. The most likely diagnosis was felt to be primary intraocular lymphoma. To establish the diagnosis, a vitrectomy was performed on the right eye. Undiluted vitreous was sent for histopathology, flow cytometry and immunohistochemistry. Results showed abnormal cells containing brown cytoplasmic pigment that were S100 positive, consistent with a diagnosis of melanoma. Flow cytometry was negative for lymphoma. At 1-week follow up, the patient's right visual acuity had improved to 6/7.5, however intraocular pressure was elevated to 42mmHg. Gonioscopy showed a large collection of pigmented cells in the inferior angle (Figure 2) likely to be a collection of melanocytic cells. It was thought that the elevated pressure was the result of angle occlusion by the debris with a possible steroid response related to Prednefrin Forte (prednisolone 1 per cent/phenylephrine 0.12 per cent). This was weaned promptly and he was commenced on topical anti-glaucoma drops (brimonidine 0.2 per cent/timolol 0.5 per cent). Further cell typing found the melanoma to be a BRAF-mutant, amenable to combination therapy treatment with dabrafenib, a selective inhibitor of BRAF V600E kinase, and trametinib, a MEK-inhibitor. Oncological work up classified the patient as having stage-IVc disease (widespread). The patient underwent treatment with dabrafenib and trametinib. After sixth months of treatment the lesions had reduced in size with resolution of visual symptoms, normalisation of intraocular pressure off all topical therapy and clearance of the cells in the anterior chamber angle.

Discussion

We report the case of an 81 year-old man with cutaneous melanoma metastasising to the vitreous of both eyes. This was complicated by a high intraocular pressure, likely due to outflow obstruction, which resolved following treatment with a combination of dabrafenib and trametinib.

Cutaneous melanoma is highly prevalent in the Australian demographic, affecting 1 in 18 people by the age of 85 and with an overall incidence of 49 per 100,000 people.[4] Ocular metastasis is a rare but important manifestation of metastatic disease, and may be the first clue to diagnosis. An American systematic review of 93 patients found that 89 per cent of patients with ocular metastases had at least one other non-ocular metastasis present.[5] Melanoma most often metastasises to other skin/subcutaneous tissue sites, lymph nodes, lung, liver, brain, or bone with reports of ocular involvement ranging from 1 per cent, to 33 per cent in widespread terminal disease.[5] Ocular metastases typically present intraocularly two thirds of the time, extraocularly one third of the time and involve both sites 5 per cent of the time. Exclusive vitreous seeding has been found to be the presentation approximately 9 per cent of cases.[5]

After diagnosis, the decision regarding first-line treatment is guided by the suitability of targeted treatments, determined by the presence or absence of BRAF mutations. If positive, BRAF-inhibitors are often pursued and if negative, then further testing to identify mucosal, acrolentigenous or uveal primaries gives direction to appropriate therapeutic options.[4] If other targets are found, immunotherapy may be considered in the form of CTLA-4 or PD-1 T-cell checkpoint inhibitors. This modality of treatment has demonstrated very good efficacy.[3]

Traditionally, prognosis of metastatic melanoma has been dire, with 1-year survival rates as low as 33 per cent, 5-year survival rates of less than 20 per cent and a median overall survival (mOS) of 9-months.[3,6] Modern therapy with BRAF inhibitors has, however, revolutionised melanoma treatment by targeting BRAF-mutations and other points in the mitogen-activated protein kinase (MAPK) pathway.[6] Approximately half of cutaneous melanomas are BRAF-mutation positive and therefore amenable to treatment with agents such as dabrafenib and trametinib, which have been available for use in Australia since 2014.[7] Use in combination may result in more favourable outcomes than dabrafenib alone by overcoming acquired resistance in the MAPK pathway.[7] Furthermore, these inhibitors now form the backbone of systemic melanoma therapy therapy with a generally well tolerated side-effect profile and impressive response rate of 76 per cent with median progression-free-survival (mPFS) of 9.4 months and a mOS of 27.4-months.[3,7] Approximately 20 per cent of patients are now progression-free at 3-years.[8] This compares to previous conventional chemotherapeutic agents including dacarbazine, used either alone or in combination with interferon or interleukin-2, achieving response rates below 20 per cent with a mPFS of 4-months and a mOS of less than 9-months.[6]

For the ophthalmologist, the modern era of targeted

therapy may decrease the need for intra-ocular surgery or radioactive plaques in cases of melanoma with intra-ocular metastases. Improved survival also means that ongoing management of chronic diseases such as diabetic retinopathy and glaucoma remains important.

Conclusion

For the ophthalmologist, metastatic melanoma presenting as vitreous infiltrate is a very rare first presentation of metastatic disease, but needs to be considered in any unexplained vitreous cellular infiltrate. Its presence usually indicates widespread disease. Recent advancements in treatment with targeted chemotherapeutic agents have improved patient survival meaning that ongoing management of chronic diseases such as diabetic retinopathy and glaucoma remains important.

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ACKNOWLEDGEMENTS

We would like to thank Mr. Marcus J. Fernihough for his optimisation of the figures used in this manuscript.

PEER REVIEW

Not commissioned. Externally peer reviewed.

CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

FUNDING

No sources of funding to declare

PATIENT CONSENT

The authors, *Rocke JR O'Day RFJ, Giudicatti LC, Clark JB*, declare that:

1. They have obtained written, informed consent for the publication of the details relating to the patient(s) in this report.
2. All possible steps have been taken to safeguard the identity of the patient(s).
3. This submission is compliant with the requirements of local research ethics committees.

Figure 1: Large, dense anterior vitreal cells seen in the left eye, which appear suspicious for malignancy

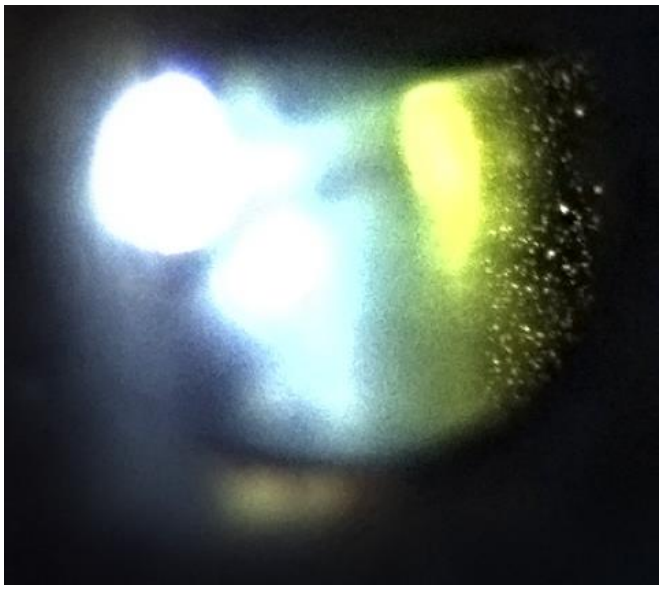

Figure 2: Gonioscopy of the right eye 1-week post vitrectomy showing pigmented debris in the inferior angle. This was associated with an intraocular pressure of 42mmHg and cleared after systemic treatment of melanoma