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Clearance of plasma cell free DNA in metastatic uveal melanoma with radiographic response to immune checkpoint inhibitors

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ABSTRACT

Purpose: To report a case of metastatic uveal melanoma treated with immune checkpoint inhibition in which serial circulating tumor DNA (ctDNA) was assessed throughout treatment.
Observations: A 33-year-old man was diagnosed with metastatic uveal melanoma and initially had progression of disease following hepatic embolization and nivolumab/ipilimumab. At the time, plasma ctDNA *GNA11* and *SF3B1* were measurable and repeat ctDNA showed increased variant allele frequency following further progression of disease on vorinostat. Following additional nivolumab/ipilimumab, radiographic response was noted and repeat ctDNA became undetectable and remained so at 27 months follow up.
Conclusions and importance: Clearance of cell free DNA in metastatic uveal melanoma may be associated with radiographic response to immune checkpoint inhibitors.

1. Introduction

Circulating tumor DNA (ctDNA) is a small component of cell free DNA (cfDNA), specifically sourced from apoptotic or necrotic tumors cells and can be detected in a number of bodily fluids including blood. Circulating tumor DNA has been used in diagnosing a variety of cancers, detecting minimal residual disease (MRD), and monitoring treatment responses.[1–3] Variant Allele Frequency (VAF) is a proxy for tumor burden. CtDNA levels can provide information regarding clinical burden and shifts in cfDNA levels may be associated with clinical response.[1–3] This has been shown in a number of cancers, specifically those with a wealth of published ctDNA studies, namely lung, renal, breast and cutaneous melanoma.[4–7] However, there is a dearth of information regarding ctDNA levels and clinical response in ocular tumors. Here we present a case of metastatic uveal melanoma with serial plasma ctDNA over the course of treatment; and we demonstrate that useful clinical information may be gleaned from this noninvasive blood test.

2. Case report

A 33-year-old man was diagnosed with uveal melanoma in the right eye (cT1aN0 Collaborative Ocular Melanoma Study small, gene expression profiling DecisionDx UM (Castle Biosciences) Class 1A) and treated with radioactive plaque by an outside physician. Subsequent outside treatment included transpupillary thermotherapy (TTT) for recurrence. When he presented to our group five years later, recurrent uveal melanoma (Supplementary Fig. 1) was noted and the patient underwent enucleation. Next generation sequencing (NGS) using the Memorial Sloan Kettering IMPACT assay revealed the following somatic tumor mutations: *GNA11* exon5 p.Q209L and *SF3B1* exon 14 p.R625C (wildtype for BAP1). Histopathology showed microscopic extraocular extension at a site of thinned sclera, presumed to be near the location of prior TTT. He underwent adjuvant external beam radiation to the orbit (3000 cGy/5 fractions) without incident. Abdominal Magnetic resonance imaging (MRI) surveillance did not reveal metastasis until 15 months later when liver biopsy confirmed metastatic melanoma with NGS showing *GNA11* exon5 p.Q209L and *SF3B1* exon 14 p.R625C. The patient did not possess HLA-A 02:01 and was not eligible for

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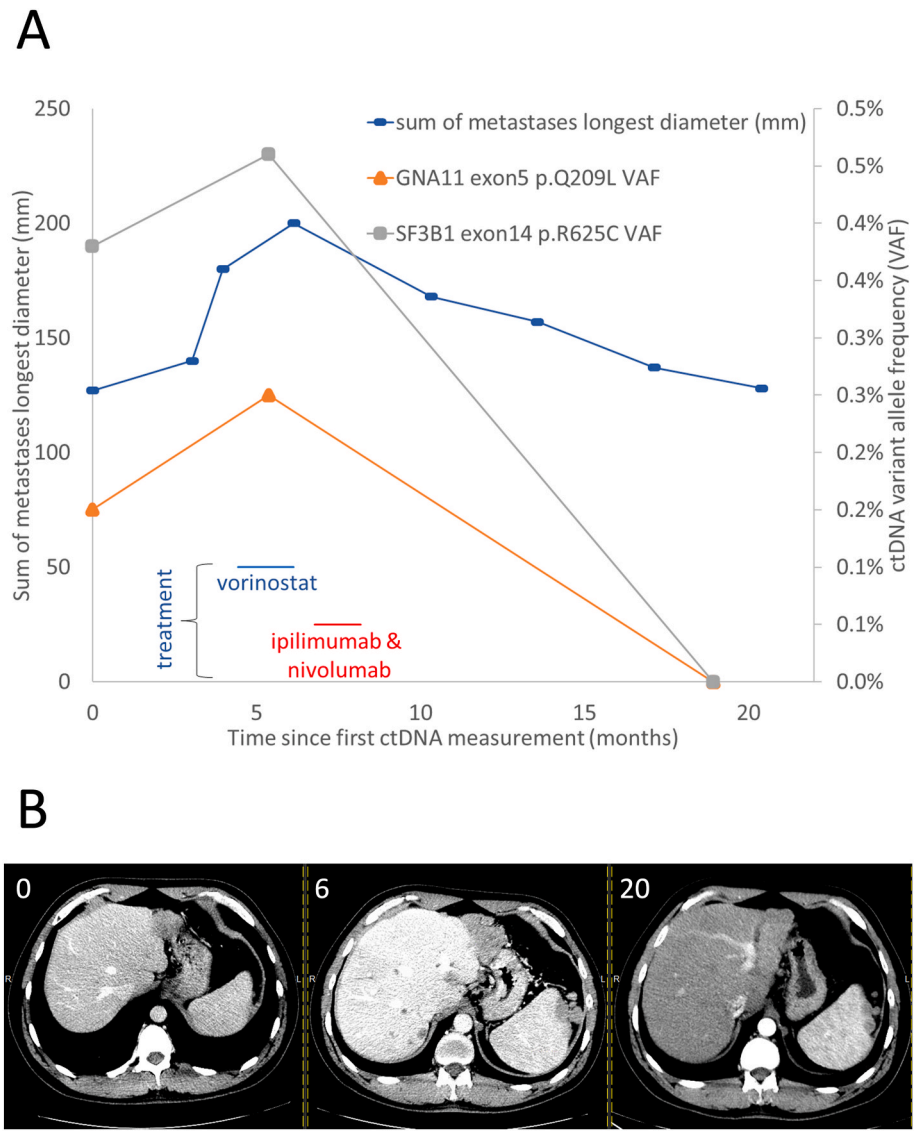

Fig. 1. A) Change in size of metastases and circulating tumor DNA (ctDNA) over time before and after treatment. The sum of metastasis diameters reflects the burden of metastatic disease and was highest 6 months after first ctDNA collection; this was also the time when the ctDNA variant allele frequency (VAF) was highest. The sum of metastasis diameters thereafter decreased following treatment with ipilimumab and nivolumab, and the ctDNA VAF decreased to an undetectable level. (B) Representative axial computed tomography (CT) images of the abdomen at time of first ctDNA collection (0), six months later during treatment with vorinostat, before treatment with ipilimumab and nivolumab (6), and twenty months later, following treatment with ipilimumab and nivolumab (20) demonstrating the presence of hepatic and peritoneal metastases that enlarged and progressed between 0 and 6 months, and thereafter decreased in size or resolved between 6 months and 20 months.

Tebantafusp. He was treated with six doses of monthly nivolumab 480mg and concurrent left hepatic embolization, until progression was noted in the right liver. He then received one dose of combination nivolumab 1mg/Kg and ipilimumab 3mg/Kg and concurrent right hepatic embolization. Progression of disease was noted one year later, at which time plasma cell free DNA was evaluated using MSK-ACCESS, an assay using deep sequencing and hybridization capture to detect very low frequency somatic alterations in 129 cancer related genes.[8] This revealed *GNA11* exon5 p.Q209L (VAF 0.15%) and *SF3B1* exon 14 p.R625C (VAF 0.38%). He was treated on a clinical trial with vorinostat 300mg twice daily with primary progression of disease noted at 8 weeks in liver, peritoneum, lung, lymph nodes, and bone. Repeat cfDNA at that time demonstrated a concordant rising VAF: *GNA11* (VAF 0.25%) and *SF3B1* (VAF 0.46%). Due to inadequate response to treatment, three cycles of combination nivolumab 1mg/Kg/ipilimumab 3mg/Kg were given, complicated by grade 1 hepatitis. Radiographic response of all metastatic sites was noted at 15 weeks. At 36 weeks, plasma circulating tumor DNA was undetectable for both *GNA11* exon5 p.Q209L and *SF3B1* exon 14 p.R625C and at the 65-week follow-up, the patient has exhibited sustained radiographic response. The treatment course with metastatic response, treatment, and ctDNA is graphically represented in Fig. 1.

Evaluating three lesions at random exhibited 31% tumor shrinkage versus baseline, which would correspond to a RECIST partial response. Additional immune checkpoint inhibition, including maintenance nivolumab was not administered given his history of drug-induced hepatitis. He has remained progression free for 27 months since his last treatment.

Over the course of his immune checkpoint inhibitor treatment, the patient developed cutaneous vitiligo with depigmentation of his skin and cilia, in addition to depigmentation of his fundus which has been described with immune checkpoint inhibition[9] (Fig. 2). No intraocular inflammation was noted throughout his treatment course and his vision in his remaining eye remains 20/20.

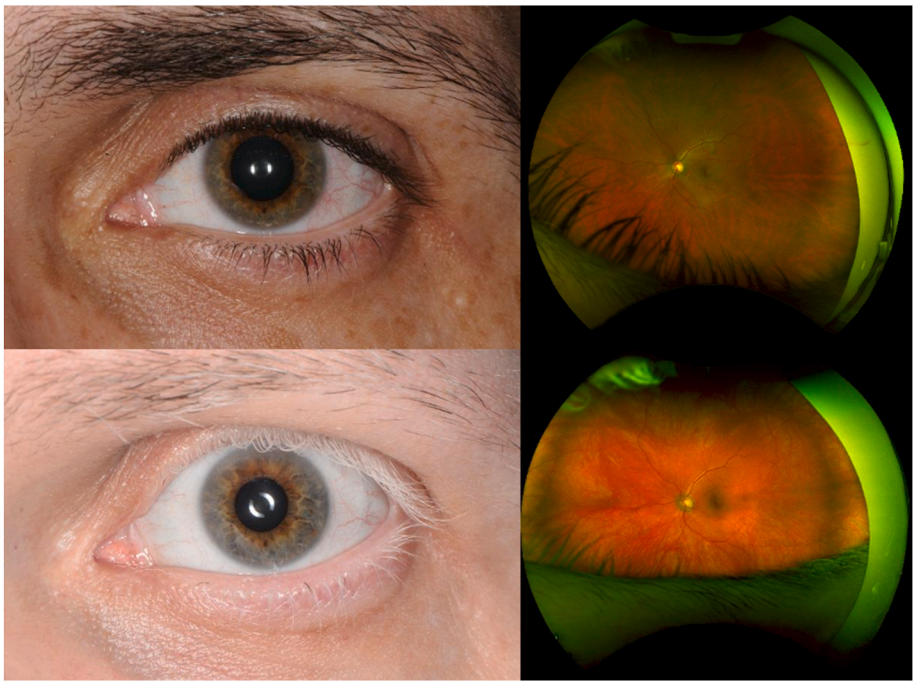

Fig. 2. Ocular adverse effect while on immune checkpoint inhibition External photo of left fellow eye prior to immune checkpoint inhibition (upper left), and following treatment, poliosis and vitiligo developed (lower left). Fundus photo of left fellow eye prior to immune checkpoint inhibition (upper right), and following treatment, fundus depigmentation (blonde fundus) developed (lower right).

3. Discussion

In some non-melanoma malignancies, it is known that changes in ctDNA levels during treatment can provide information about clinical disease in at least two ways. Elevations in ctDNA levels are associated with disease progression and may even be detected before rises in tumor markers or radiographic confirmation.[10,11] Furthermore, early decreases in ctDNA are associated with therapeutic response, and are being established as a predictive biomarker for response to treatment.[12] While these findings have been established in a number of the most common malignancies, there is minimal published information regarding the significance of ctDNA dynamics in rarer cancers such as uveal melanoma.

A small case series demonstrates metastatic uveal melanoma progression on treatment with protein kinase C is associated with rises in ctDNA[13]; and the phase 2 trial of tebentafusp included a small cohort of patients in which early reductions in ctDNA reflected clinical response to drug.[14] Uniquely we describe ctDNA clearance associated with therapeutic response of metastatic uveal melanoma to immune checkpoint inhibition. Specifically, sustained radiographic response of metastatic uveal melanoma coincided with clearance of uveal melanoma specific ctDNA (*GNA11* and *SF3B1*), over 15 months follow up– which is measurable given the mean survival of metastatic uveal melanoma is a mere 9 months.[15] It is worth noting that metastatic uveal melanoma with SF3B1 splicesome mutation is a distinct category with high neoantigen burden and likelihood of response to immune checkpoint inhibition.[16]

Unlike over half of their cutaneous counterparts,[17] it is predicted that only 10–15% of metastatic uveal melanoma patients will respond to immune checkpoint inhibition (ICI). Given ICI are more likely to respond to malignancies with a higher mutational burden, the mutational "blandness" of uveal melanoma is thought to render them less amenable to therapy. Early establishment of treatment response via a noninvasive blood test would be especially useful for metastatic uveal melanoma such that other therapeutic paths may be promptly considered.

Molecular assessment by ctDNA analysis may provide a more sensitive means of treatment response than standard radiographic imaging. In the context of treating with immune checkpoint inhibition, which has one of the most profound immune related toxicity profiles (ocular findings of which were demonstrated in our patient), earlier response results may be particularly helpful: either justifying continued therapy or potentially saving patients from unnecessary continued treatment in the context of unsatisfactory response and adverse events. Albeit one patient, our case offers an example for the utility of ctDNA analysis in the assessment of metastatic uveal melanoma response to immune checkpoint inhibition.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editor of this journal.

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Ethics approval and consent to participate

No ethical approval required.

Availability of data and materials

All data generated and analyzed during this study are included in this article.

CRediT authorship contribution statement

Jasmine H. Francis: Writing – original draft, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Christopher A. Barker:** Writing – review & editing, Investigation, Formal analysis. **Julia Canestraro:** Writing – review & editing, Data curation. **David H. Abramson:** Writing – review & editing, Investigation. **Alexander Shoushtari:** Writing – review & editing, Methodology, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: None of the authors have a proprietary interest in the material presented in this study. Disclosures include JHF: none. CAB: has received honoraria from Regeneron, his institution receives research funding for clinical trials from Regeneron, EMD Serono, Physical Sciences Incorporated, Amgen, Elekta, Melanoma and Skin Cancer Trials Limited, Merck, Alpha Tau Medical and the University of California San Francisco, and he has received support to attend meetings from the National Comprehensive Cancer Network, University of Washington, and the National Cancer Institute;. JC: none. AS: board for Bristol-Myers Squibb, Immunocore, Novartis, Erasca. Trial support to institution from Bristol-Myers Squibb, Immunocore, Novartis, Targovax, Polaris, Pfizer, Alkermes, Checkmate Pharmaceuticals, Foghorn Therapeutics, Linnaeus Therapeutics, Prelude Therapeutics. Iovance Therapeutics. DHA: none.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajoc.2024.102021.

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