Variable Results for Uveal Melanoma–Specific Gene Expression Profile Prognostic Test in Choroidal Metastasis

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New molecular technologies, including cytogenetic analysis, multiplex-ligation probe amplification (MLPA), and gene expression profiling (GEP), may provide prognostic information regarding the risk for metastasis in the setting of primary uveal melanoma. Patients with uveal melanoma want knowledge of metastatic prognosis regardless of the impact on medical management.

DecisionDx-UM GEP (Castle Biosciences) is a commercially available test that examines 15 genes (including 3 control genes) to generate prognostic subgroups (class 1: low metastatic risk and class 2: high metastatic risk) for uveal melanoma. Although the DecisionDx-UM test is not marketed as a diagnostic test, it is frequently used without cytopathology to confirm the diagnosis and may be used instead of cytopathology to determine the metastatic potential of a suspicious choroidal tumor. A tumor that is found to be class 1 might continue to be observed, whereas a tumor found to be class 2 might be promptly treated, despite the lack of evidence that treating a primary uveal melanoma alters a patient’s risk for metastasis.

We report 4 cases of choroidal metastatic tumors, for which the DecisionDx-UM GEP provided an irrelevant test result to illustrate that GEP testing alone may misdirect diagnosis in the absence of cytopathology or other melanoma-specific testing such as chromosome 3 status.

Report of Cases

This study, which was conducted from January 2012 to December 2014, was approved by the institutional review board of the University of California, Los Angeles. Written consent was obtained from all patients.

Case 1

A man in his 80s with a medical history of prostate cancer treated with external radiation and hormone therapy 11 years previously presented with blurry vision, pain, and photopsia in the left eye.

Distance best-corrected visual acuity (BCVA) in the affected left eye was 20/125. Dilated fundus examination (DFE) of the eye revealed a superotemporal choroidal tumor with serious retinal detachment (Figure, A and B). Ultrasoundography
findings revealed a dome-shaped lesion of 4.65 mm in height
and greatest basal diameter of 15.19 mm, with medium internal
reflectivity by A-scan.

The patient underwent iodine-125 brachytherapy with in-
traoperative fine-needle aspiration biopsy (FNAB). Gene ex-
pression profile testing revealed class 1A. Cytopathology re-
vealed findings consistent with metastatic prostate cancer.

Case 2
A woman in her 60s with a medical history of a benign
breast cyst presented with 3 weeks of distorted vision in the
right eye.

Best-corrected VA was 20/25 in the affected right eye.
Dilated fundus examination of the right eye revealed an el-
evated choroidal tumor involving the macula with serous reti-
nal detachment (Figure, C and D). Ultrasonography findings
revealed an irregularly shaped lesion of 3.25 mm in height and
greatest basal diameter of 12.60 mm, with medium reflectivi-
ties by A-scan.

The patient underwent iodine-125 brachytherapy with in-
traoperative FNAB. Gene expression profile testing revealed
class 1A. Cytopathology revealed numerous cells suggestive of
neoplasm but was nondiagnostic. Additional workup re-
vealed metastatic neuroendocrine lung cancer.

Case 3
A woman in her 70s with a medical history of lung cancer
presented with 3 weeks of distorted vision in the left eye.

Best-corrected VA was 20/70. Examination of the left eye revealed dilated inferior episcleral vessels. Di-
lated fundus examination of the left eye revealed an infero-
temporal peripheral choroidal tumor (Figure, E and F). Ultra-
sonography findings revealed a dome-shaped lesion of 7.56 mm
in height and greatest basal diameter of 16.54 mm, with low-
to-medium reflectivities by A-scan.

Additional systemic workup revealed stable findings
with no progression of the primary treated lung cancer.
From a systemic standpoint, the medical oncologist felt the
choroidal lesion was highly unlikely to represent a meta-
static lesion based on the systemic workup. The patient
underwent iodine-125 brachytherapy with intraoperative
FNAB. Gene expression profile testing reported class 1A.
Cytopathology revealed findings consistent with metastatic
small-cell lung carcinoma.

Case 4
A man in his 60s presented with shadowing and distortion of
vision in the left eye for 2 months. He had no history of sys-
temic cancer.

Best-corrected VA in the left eye was 20/40. Dilated fund-
us examination of the left eye revealed a choroidal tumor su-
perotemporal to the macula with serous retinal detachment
(Figure, G and H). Ultrasonography findings revealed a dome-
shaped lesion of 2.66 mm in height with greatest basal diam-
eter of 11.19 mm, with mostly medium internal reflectivities
by A-scan.

The patient underwent iodine-125 brachytherapy with in-
traoperative FNAB. Gene expression profile testing revealed
class 2, with a discriminant value of 0.02. Cytopathology was
consistent with metastatic lung cancer.

Discussion
We report the first case series, to our knowledge, of GEP test
results in choroidal metastatic tumors. Uveal melanoma-
specific GEP testing may provide both class 1A and class 2 re-
sults for nonuveal melanoma tissue. A single case report has
been previously published by Seider et al,9 which also demon-
strated that the DecisionDx-UM GEP test may errantly pro-
vide prognostic information on a solitary choroidal meta-
static lesion.

Choroidal metastatic tumors that are asymptomatic may
be observed.10 If vision is affected, the standard treatment
for these tumors may be external beam radiotherapy. In cases
of focal choroidal metastatic disease, iodine-125 brachy-
therapy may also be considered. Given that patients with
uveal melanoma may often have other malignancies,11,12 it is
not uncommon to find 2 separate malignancies in a given
patient. At our center and others, cases of choroidal meta-
static tumors may be treated with brachytherapy. Intraoper-
ative FNAB for tissue may be performed in such cases, particu-
larly if a tissue diagnosis is necessary for staging purposes.

DecisionDx-UM is a prognostic test that has been report-
edly validated in lesions clinically diagnosed as choroidal mela-
noma. However, the study that validated the DecisionDx-UM
test confirmed the diagnosis of uveal melanoma by cytopa-
thology in only 79.7% of tumor samples included in the
analysis.7 As our series indicated, DecisionDx-UM can
indeed provide class 1 and class 2 results when analyzing
nonuveal melanoma tissue; the test does not distinguish
between different choroidal lesions including choroidal
melanoma vs nonmelanoma vs choroidal nevus. The class 2
expression pattern for a uveal melanoma at high risk for metas-
stasis may be similar to the expression profile of dedif-
ferentiated metastatic cancer. It is surprising that 3 of the 4
cases in our series of choroidal metastasis revealed a class 1
result; this further emphasizes that the test has not been
validated to provide prognostic information in nonmela-
noma samples and underscores the importance of obtaining
a biopsy also for cytopathology for diagnostic confirmation, particularly in cases where additional molecular testing may be performed.

In situations where the diagnosis of choroidal melanoma is uncertain, alternative molecular tests are available that provide diagnostic and prognostic information of tissue samples. Multiplex ligation-dependent probe amplification,13 which is now commercially available for choroidal melanoma (Impact Genetics), provides information on tumor DNA rather than RNA, which is examined in the GEP test. Multiplex ligation-dependent probe amplification has the ability to detect aberrations in up to 45 chromosomal loci in a single assay. Tissue can also be sequenced for \textit{GNAQ} or \textit{GNA11} mutations,14 which may aid in ruling in a diagnosis of pri-
mary uveal melanoma when no chromosomal abnormalities are present with MLPA.

Conclusions

Care must be taken to properly and accurately interpret results to eliminate confounding data and diminish ocular misdiagnosis. One must proceed with caution when interpreting the result of any test beyond the clinical scenario for which it was validated. At our center, it is standard practice to submit biopsy material for cytopathology in addition to molecular prognostic testing. We feel that cytopathologic confirmation is requisite in any biopsy setting particularly when material is obtained for molecular prognostication. Continued studies are needed to investigate the weaknesses and strengths of evolving molecular prognostic tests that can potentially provide critical information to patients.

REFERENCES