ONCOLOGY

MD Roundtable: Choroidal Nevus or Melanoma?

MODERATED BY ARUN D. SINGH, MD,
WITH BERTIL E. DAMATO, MD, PHD, AND J. WILLIAM HARBOUR, MD

This article is part of an occasional series of MD Roundtables, in which a group of experts engage in discussion of a topic of interest in their field. This month, Arun D. Singh, MD, of the Cole Eye Institute at Cleveland Clinic, leads a roundtable on diagnosis and management of a patient with a pigmented choroidal mass; he is joined by Bertil E. Damato, MD, PhD, of the University of California, San Francisco, and J. William Harbour, MD, of Bascom Palmer Eye Institute.

*In this online version of the story, asterisks indicate responses where the speaker later edited or added commentary to the original material.

Case Study

(1A) Fundus photograph of the right eye showing a small juxtapapillary pigmented choroidal lesion. The lesion extends nasally up to the optic disc margin and temporally into the fovea. (1B) Overlying and dispersed orange pigmentation (lipofuscin) is autofluorescent.

Case Presentation

Dr. Singh: This is a case of a 44-year-old male who presented with reduced vision in the right eye for about six months. There's nothing unusual in the family, personal, or social history. His prior eye examination was about two-and-a-half years ago. At that time, the optometrist had noted some "leakage in the macula," without ancillary testing, but there was no diagnosis.

On examination, the patient's vision was actually very good: 20/30. He had normal pressure, normal anterior segment, blue irides; the left side was completely normal, and all the findings were limited to the right fundus. In Figure 1, we can see a pigmented choroidal mass mostly in the macular region, going from the disc margin temporally. It's about 6.5 by 5.0 mm at the base and is about 1.5 mm thick. Overlying the tumor are orange pigmentation and subretinal fluid tracking downward. The optic disc itself is normal, and the tumor is in proximity of the disc margin for about five clock hours, from 6 to 11 o'clock.

Preliminary Diagnosis

Dr. Singh: *First, what additional tests would you like to do, and what are the diagnostic considerations at this point even before we do a diagnostic test?*

Dr. Harbour: I don't see any other testing that needs to be done at this point. I think you presented the information I would need to make a clinical diagnosis, and that would be of a high-risk choroidal melanocytic tumor.

A Question of Risk. ***Dr. Singh:*** *What do you mean by high risk?*

***Dr. Harbour:** I believe that the lesion has some chance of being a melanoma at the present time, and a high risk for becoming a melanoma at some point in the future. None of us can tell for sure whether a given tumor is a melanoma or not based on clinical examination and testing, especially a small lesion like this. The only way to know for sure it's a melanoma is if it metastasizes, and we don't wait for that to happen before deciding on treatment. Therefore, we're always dealing with an element of uncertainty when making treatment decisions.

Dr. Singh: *Bertil, what do you think about this diagnosis, and how would you label this?*

Dr. Damato: I think that because of the large clumps of orange pigment and the serous detachment, and the way the tumor surrounds the disc, the

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chances are, on balance, that it is a malignant melanoma.

Biopsy: Methods and Concerns

Dr. Singh: *What testing would you like, Bertil, to help you confirm clinically that it is a melanoma?*

Dr. Damato: I would go straight to a biopsy, using a fine needle or vitreous cutter. That's the only way to confirm that this is a melanoma. I've removed several lesions like this, by endoresections, and done biopsies, and the majority have been melanomas, some even with epithelioid cells and aggressive histology

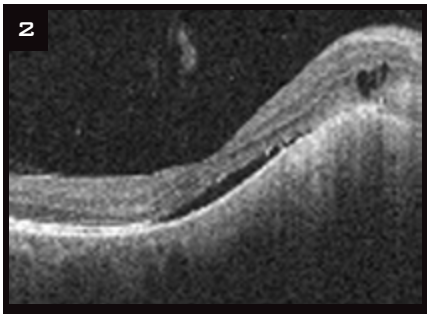
Dr. Singh: *If, on cytological assessment, it is a melanoma, then what would you do?*

Dr. Damato: I would give the patient the choice between proton beam radiotherapy and enucleation.

Age, Biopsy, and Treatment. ***Dr. Singh:*** *Bill, what diagnostic test would you order to substantiate your clinical diagnosis?*

***Dr. Harbour:** I don't think there are any more clinical tests that need to be done. I disagree that looking at cell morphology from a biopsy sample can confirm that this is a melanoma—the presence of epithelioid cells cannot distinguish a melanocytic tumor that can metastasize from one that cannot. Only molecular profiling of the biopsy can do that with acceptable accuracy. Epithelioid cells are more common in class 2 metastasizing tumors, but they can also be seen in nonmetastasizing class 1 tumors. I would do a biopsy for molecular testing if it would affect my treatment decision. Whether or not to treat depends a lot on the patient's age, tumor size, and location.

In this patient, the macular location would mean profound vision loss if treated by any modality. I would not recommend biopsy or treatment an older patient—let's say older than about 80—unless there was demonstrable growth of such a small tumor. This is because the metastatic process usually has a long latency period, as you have published on, and there is a low chance of metastasis within five to 10 years, even if the tumor has the aggressive class 2 profile and a *BAP1* mutation.



OPTICAL COHERENCE TOMOGRAPHY. Fovea is detached by shallow subretinal fluid.

However, in this particular patient, who is only 44 years old, I would recommend biopsy. If the molecular test result revealed a class 1 profile, I would have a long discussion with the patient about the risks and benefits of treatment, whereas if the tumor exhibited the class 2 profile, it would be an easy decision to recommend prompt treatment. [Note: These classes, based on a gene expression profiling test, are meant to predict the risk of metastasis within five years. Class 1 represents low risk, and class 2, high risk.

Dr. Singh: *Which approach would you take for the biopsy?*

Dr. Harbour: I would take a transvitreal approach with a 27-gauge needle, using indirect ophthalmoscopy for visualization.

Cytology vs. Gene Expression. ***Dr. Singh:*** *What's the likelihood that you would actually get a cytological confirmation?*

Dr. Harbour: Cytology is not helpful here. It will not tell you the difference between a melanoma and a nevus. The gene expression profiling is what I would be interested in to determine whether it's class 1 or 2. And the chance of getting an adequate sample for the gene expression profiling is about 97 percent.

Weighing the Risks

Dr. Singh: *So even for a thin tumor like this, which is possibly a nevus with some high-risk features, you would recommend biopsy of a macular tumor in a patient with 20/30 vision?*

***Dr. Harbour:** We are now pretty good at doing transvitreal biopsies on very small tumors in the macula with low risk of vision loss, so that would not cause me to hesitate. The decision regarding biopsy is based on whether it would affect the decision to treat. We recently showed that even if a choroidal melanocytic tumor is class 2, it is unlikely to metastasize within at five to 10 years if it is less than 12 mm in diameter and has not shown significant growth. Thus, in an elderly patient with this particular tumor, I would not be inclined to biopsy because I would recommend close observation rather than prompt treatment. On the other hand, this 44-year-old man would be expected to live many more years, and that risk is going to accumulate over time, especially for a class 2 tumor. So I would be more inclined to biopsy in helping to make a treatment decision.

Changing the Outcome. ***Dr. Singh:*** *So with this small melanoma—if it is truly a melanoma—you are implying that your therapy would change his outcome for survival.*

***Dr. Harbour:** If this were a small melanoma with the ability to spread, such as a tumor with a class 2 molecular profile, treatment could potentially improve survival by eradicating the tumor prior to metastasis.

However, it is important to point out that it has never been formally proved that any treatment for uveal melanoma changes the outcome for survival. It is also important to keep in mind that for every one small tumor like this that has the ability to metastasize, there are dozens if not hundreds of similar tumors that do have the ability to metastasize, and we do not want to needlessly treat all of those patients.

Dr. Singh: *And if it is class 1, you wouldn't treat them at all?*

***Dr. Harbour:** I would discuss the risks and benefits with patient, but I would be less insistent on treating such a small macular tumor if it were class 1 than if it were class 2. If this tumor were in the periphery, where the risk

of vision loss would be less, I would be more inclined to recommend treatment, regardless of molecular class, with either TTT [transpupillary thermotherapy] or plaque radiotherapy. But in this patient, I would weigh a number of competing risks: risk of vision loss, risk of metastasis, and so forth.

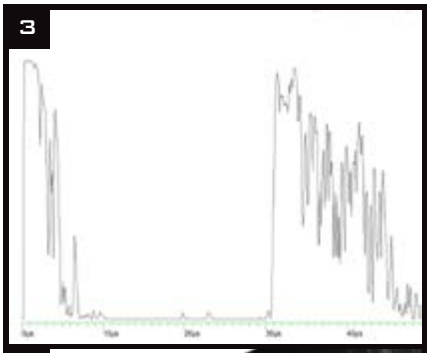
The overwhelming weight of evidence from the literature, imperfect as it may be, shows no significant increase in metastatic risk by initially managing such a small lesion by close observation for evidence of growth rather than prompt treatment.

Concerns About Growth? *Dr. Singh: So we know that this tumor has a high risk of growth, if it's not already growing, because of the risk factors. So if you don't treat, this tumor could possibly go down the optic nerve, increase the detachment, and reduce vision. Is that not a consideration?*

***Dr. Harbour:** Melanomas rarely go down the optic nerve, and when they do, it's not really clinically relevant, as it is in retinoblastoma. So I'm not too concerned about that. You can control serous macular detachment with low energy TTT without much damage to vision. What I am concerned about is treating a tumor that may have little or no risk for metastasis at the present time, when treatment would result in profound if not complete loss of vision. I would want to have molecular prognostic information in order to offer the patient the ability to make a more informed decision.

Counterpoint: Importance of Cytology. *Dr. Singh: Bertil, what would you do if it's class 1 versus class 2—or does that really matter?*

Dr. Damato: My views are totally different from my friend Bill, in that with regard to biopsy, I think that histology or cytology has a much better chance to distinguish between nevus and melanoma. And the reason is that nevi and many melanomas will be class 1, whereas with histology, you'd be able to see epithelioid cells and/or spindle cells with large nuclei and nucleoli and so on. So I think the two tests complement each other, and gene expression profiling isn't the only way of looking at the genetic type. There are other tests as well, and those will show other chromosomal abnormalities that will help to distinguish between the two conditions.



ULTRASOUND. Note high internal reflectivity (3) of small placoid choroidal tumor (4).

Dr. Singh: So if it is, let us say, nonmetastasizing melanoma versus metastasizing melanoma based upon the genetic testing, what would you do?

Dr. Damato: If it's got metastatic potential, I would definitely treat it. I've seen patients like this with a tumor of this size die of metastasis within six to seven years. So unless the patient is moribund, the patient should be given the opportunity to decide whether they want treatment.

With regard to class 1, we do not know how many of these develop into class 2 and when they do so. I have seen one case with very strong circumstantial evidence of malignant transformation while the patient was under observation, and the patient subsequently died. So, irrespective of the effect on vision, I would discuss with the patient the risks and benefits of biopsy and of the different forms of treatment and listen to what the patient has to say. I think the patient's attitude toward risk should really be taken into account.

Accuracy of Sampling. *Dr. Singh: In the absence of cytological confirmation, how do we know that what we are sampling is truly a representative of the tumor?*

***Dr. Harbour:** We never know for sure—whether we're looking at gene expression, chromosomes, or cytology—if we have sampled the tumor representatively. However, we've done a lot of research with gene expression profiling over the years to look at this question, and the likelihood of a biopsy not matching the gene expression of the tumor as a whole is extremely low, less than 10 percent, probably less than 5 percent.

*We have also shown convincingly in multiple peer-reviewed articles that cytologic and histologic prognostic factors such as epithelioid cells and large nucleoli cannot come close to the accuracy of gene expression profiling for distinguishing a nonmetastasizing nevus or melanoma from a metastasizing melanoma. In the modern era, such highly sophisticated molecular testing has replaced cytology for this purpose.

Dr. Singh: Is the rate of sampling error higher for small tumors?

***Dr. Harbour:** That's been claimed by one person, but I have not seen it myself in all of the research we have done on sampling error over the years. Proper surgical technique, placing the needle near the geometric center of the tumor, using the first needle pass for molecular testing, and proper handling of the sample are all critical, as we have published. With our technique, we've not seen much in the way of sampling error.

Follow-up on the Patient

Dr. Singh: I do have a follow-up on this patient, with whom I discussed the different options.

I told him that, clinically, I would say that this was a melanoma or had a very high chance of being a melanoma, and that doing nothing—in my mind—was not the right way forward. We could es-

tablish the diagnosis by cytology, by gene expression profiling, or by enucleation, wherein he would have both the diagnosis and the treatment all in one.

Dr. Harbour: I would not enucleate this patient. I would treat him either with a notched plaque and TTT or with protons.

Dr. Damato: I would leave it to the patient to decide. Most patients would opt for proton beam or plaque radiotherapy; but some are happier having the eye removed, and if you talk them out of it, the chances are they won't be happy with the results of radiotherapy. So it really depends on the patient's choice.

The Right Decision? ***Dr. Singh:*** *So, I did offer him radiation therapy with a clear understanding that his vision would not be very good. Even if we did nothing, over the long term he would lose vision; and after radiation, he would certainly lose vision; and if you did enucleation, of course, he would lose all vision. So the vision wasn't something to be saved here, except maybe some peripheral vision.*

After about a week, he came back with his wife, his mother, and the whole family, and they decided to go with enucleation, which was done. Histologically, it proved to be a mixed-cell-type melanoma, with about 90 percent spindle cells and 10 percent epithelioid. We also did a needle aspiration biopsy and sent it for gene expression profiling. And it came back as class 1 melanoma. So in retrospect, do you think it was the wrong thing to do?

Dr. Harbour: It was the right thing to do because you educated the patient, and he thought about it, he told you what he wanted, and that's what you did.

*Since it was class 1, its probability of metastasis in the next five to 10 years was very low, but it is possible that it could have evolved into a class 2 over time, and his risk would have accumulated over the years.

Terminology Issues

Dr. Harbour: However, I would modify one thing you said: Just because you see epithelioid cells cytologically does not mean it's a melanoma. In my mind a melanoma means it has metastatic potential, and you never know that until the patient metastasizes.

Dr. Singh: I don't think that's necessarily the case. For example, you can have locally aggressive tumors that are malignant, although they do not have metastatic potential.

Dr. Harbour: What does the term malignant mean?

Dr. Singh: In pathology, metastatic potential is only one attribute of a malignant tumor.

***Dr. Harbour:** The two attributes of a malignant tumor are invasion and metastasis. Invasion is rarely a factor in making a clinical decision in uveal melanoma. Therefore, in my opinion, metastatic potential is almost always the single most important attribute of malignancy in uveal melanoma.

The manner in which some physicians still use the terms malignant and benign derive from the work of [Rudolph] Virchow and other pathologists from the 1800s, where most specimens came from autopsies of individuals with metastatic cancer. That is a far cry from studying fine-needle biopsies on tiny eye tumors. Those words don't have the same meaning today. We're always dealing with a level of uncertainty about metastatic potential, especially with small tumors that we treat today but would never have been treated in Virchow's day.

We all have anecdotal cases like the one mentioned by Bertil in which a patient with a small tumor developed metastasis, but we can't let anecdotes blur our objectivity. Indeed, I've seen many patients with lesions like this that did not grow and did not metastasize. And I have patients who had extremely large tumors occupying the whole globe that were enucleated 15 or 20 years ago, were class 1 and they haven't metastasized. We need to be driven by data, not anecdotes.

Dr. Singh: So that's why I was saying metastasizing melanoma or nonmetastasizing melanoma, given that we still use nevus and melanoma as benign and malignant terminology.

Evolving Management

Dr. Singh: *I think we all agree that our management is evolving. We are moving away from pure clinical impressions to histologic or cytologic or molecular typing in deciding how we would approach some patients. Five years ago, nobody would have talked about a needle biopsy as the first-line diagnostic method for such tumors.*

Dr. Damato: I think that several of us were doing biopsy years ago to establish the diagnosis. It's becoming more a bit more widespread now, but it's not necessarily a new approach.

Dr. Singh: *For something small in the macula?*

Dr. Damato: Yes, something small. But in this patient, it is possible to get a good biopsy without affecting the vision. If you notice, the lesion is more inferior and is not necessarily going to affect the vision.

A Controversial Case. ***Dr. Singh:*** *I think we have covered all the controversy that we can come up with—anything to add?*

Dr. Harbour: I think this is one of the most controversial types of patients you could show because it isn't straightforward. There are a lot of competing risks, and it's a great case to illustrate where we are now.

Dr. Damato: I agree this is a very instructive case. My feeling is that this patient had the correct treatment, not only because it's what he wanted but also because if there are any patients with uveal melanoma where we save their life, this is the kind of case where the opportunities are created. ■

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