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Review

The hunt for the secrets of uveal melanoma

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Abstract

The many secrets of uveal melanoma are being uncovered. Information on host and environmental factors that predispose to uveal melanoma has been published. The most important factors include light eye colour, fair skin, inability to tan and chronic sun exposure. Clinical clues that are visible on ophthalmoscopy have been shown to be significant factors in predicting growth of small borderline tumours and allow for early detection of melanoma. These factors include thickness over 2 mm, subretinal fluid, symptoms, orange pigment overlying the tumour and tumour margin within 3 mm of the disc. Refined methods of cytogenetic analysis have identified several chromosomal mutations associated with uveal melanoma. Currently, the most important mutation proves to be chromosome 3 monosomy, an abnormality associated with greater risk for metastatic disease.

Key words: eye, genetics, melanoma, monosomy 3, prognosis.

Introduction

Some movies leave a lasting impression. Sergio Leone's 3-h Italian film entitled 'The Good, The Bad, and The Ugly' depicted the drama, violence and simplicity of the ageless Western. This story focused on three gunslingers during the Civil War period who were not particularly good friends, but, through their partnership, worked together in a treasure hunt for money. The plot had unexpected and adventurous twists and turns. They were lucky and unlucky. They faced good guys and bad guys. They were funny and serious. They were partners and competitors in their treasure hunt.

Fast-forward a century and one-half ahead and the hunt continues for the secrets of uveal melanoma. Explorers are identifying host and environmental causes for this devastating malignancy. Others are seeking clinical methods for earliest detection and management. Others are delving into the secrets behind the origin of melanoma. What goes wrong in the cell to cause this cancer? What chromosomal changes lead to uveal melanoma? Still others are working on protocols to treat metastatic melanoma, potentially when the disease is microscopic and before it is symptomatic. We are lucky and unlucky in our methods. We generate good ideas and bad ideas. Working together we slowly piece together the complicated melanoma puzzle.

Host and environmental factors that lead to melanoma

What host and environmental factors are associated with uveal melanoma? Numerous investigations of factors related to the development of uveal melanoma have been published, but recently two important meta-analyses of all published reports have summarized the findings.[1,2] In 2006, Weis *et al.* provided a meta-analysis of 132 published reports on host factors important in the development of uveal melanoma.[1] They found light eye colour, fair skin colour and inability to tan to be risks for the development of uveal melanoma. In comparison, similar factors have been found important in the development of cutaneous melanoma, and these include blond or red hair, fair skin colour, light eye colour, skin freckling, presence of cutaneous nevi and sensitivity to sunlight.[3] It is believed that these phenotypic findings predispose to an altered response to ultraviolet light, hence leading to an increased host risk for cutaneous melanoma.[4]

In 2005, Shah *et al.* provided a meta-analysis of 133 published reports on environmental factors for the development of uveal melanoma and found only arc welding to be a risk factor.[2] Geographic birth location was not a factor. They commented that patients exposed to intermittent intensive sunlight exposure such as vacationing at a tropical site was not a risk, but chronic sunlight exposure such as long-term outdoor employment was a borderline risk for uveal melanoma. In comparison, ultraviolet light exposure is the most important risk factor for cutaneous melanoma. More specifically, geographical birth location closer to the equator and at higher altitude is substantially associated with greater

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risk for cutaneous melanoma.[5] Intermittent intensive sunlight exposure such as tropical vacationing promotes a 70% increase in odds for skin melanoma, but chronic sunlight exposure with outdoor occupation is protective. These latter findings for cutaneous melanoma are quite different from those for uveal melanoma. Ultraviolet light plays a major role in the development of cutaneous melanoma and a minimal role in the development of uveal melanoma.[2]

Early detection of melanoma

How can we detect this malignancy earlier? There are volumes of publications on this subject and most have identified similar clinical factors relevant to the diagnosis of small melanoma, that is, melanoma 3 mm or less in thickness.[6–9] These factors include tumour **t**hickness over 2 mm, subretinal **f**luid, patient **s**ymptoms, **o**range pigment and tumour **m**argin within 3 mm of the disc. These features are remembered by the mnemonic To Find Small Ocular Melanoma (TFSOM).[7,8] Three or more features suggest 50% chance or greater for tumour growth. Tumours as thin as 1.0 mm have been found to develop metastatic disease.[7,8] Based on tumour doubling time, it is theorized that the average size of uveal melanoma at the time that it produces tumour metastasis is approximately 3.0 mm in basal dimension and 1.5 mm in thickness.[10,11] In fact, it is estimated that most metastases from uveal melanoma initiate approximately 5 years before the intraocular tumour is detected and treated.[10] So, it is important to scrutinize every choroidal nevus for risk factors for melanoma.[12,13] Early identification could be life-saving. However, keep in mind that a choroidal nevus without risk factors does carry a potential for transformation into melanoma, albeit low risk, so we advise that all choroidal nevi be followed lifelong.

Take a minute to reflect on the progress with cutaneous melanoma. Detection and treatment of cutaneous melanoma at an early stage is correlated with improved survival. Dermatologists use the mnemonic 'A, B, C, D' for Asymmetry, Border irregularity, Colour variation and Diameter larger than a pencil eraser to identify early skin melanoma.[14] Pigmented skin lesions with one or more of these features are excised. Cutaneous melanoma is currently detected at a mean thickness of 0.76 mm in thickness and the 10-year survival is 90%. The survival worsens on a continuum with increasing thickness.[15] Similarly, choroidal melanoma thickness correlates with prognosis and 5-year survival is 84% for small melanoma (under 4 mm thickness), 68% for medium melanoma (4–8 mm thickness) and 47% for large melanoma (over 8 mm thickness).[16] Using the mnemonic TFSOM, choroidal melanoma can be detected before obvious growth and treated promptly, hopefully with improved survival.

Already we are witnessing a slight trend towards earlier uveal melanoma detection. In the Collaborative Ocular Melanoma Study, tumour basal diameter greater than 15 mm declined over time from 30% of 1330 cases reported in the 1980s to 25% of 1397 cases reported in the 1990s.[17] In an analysis of 8000 patients with uveal melanoma managed at our centre over the past four decades, there has been a trend towards earlier referral of melanoma with thin tumours 3 mm or less representing about 20% of all cases in the 1980s and 30% of all cases in the 1990s (Thangappan A, Furuta M, Shields CL *et al*. Posterior uveal melanoma thickness at diagnosis correlates with tumour location. Analysis of 8000 consecutive patients. Presented as a poster at the American Academy of Ophthalmology, New Orleans, 12 November 2007). Based on these trends, ocular oncologists are more often faced with decisions regarding management and prognostic implications of small choroidal melanoma.

Cytogenetic abnormalities in melanoma

Cytogenetic abnormalities in uveal melanoma have been found on several chromosomes including 1, 3, 6, 8, 11 and 13.[18–23] Monosomy of chromosome 3 is currently believed to be the most important genetic abnormality predictive of systemic metastasis. Monosomy 3 is found in about 50% of eyes enucleated with melanoma and 30% of eyes treated conservatively with plaque radiotherapy.[20,24] Retrospective studies on patients with uveal melanoma demonstrating monosomy 3 following enucleation have revealed substantial increased risk for metastatic disease. In 1996, Prescher *et al.* reported on 54 eyes with uveal melanoma that were assessed for copy number of chromosome 3 by karyotype analysis, comparative genomic hybridization, or both and found 30 patients with monosomy 3, 50% of whom developed metastatic disease by 3 years.[20] Of the 24 patients with disomy 3, there were no metastasis. They commented that monosomy of chromosome 3 was a significant predictor of overall patient survival. Patel *et al.* showed the importance of loss of chromosome 3 and gain of chromosome 8q in patient survival.[25] They evaluated 33 samples in which 16 had chromosomal imbalances and 17 showed no imbalance. They found 10 of 16 with imbalance developed liver metastases whereas none of the 17 without imbalance had metastases ($P < 0.0001$).

More recently, refined gene expression has been used to obtain genetic information from uveal melanoma. In 2003, Tschentscher *et al.* explored gene expression levels in 20 uveal melanomas using oligonucleotide microarrays containing 12 500 probes and found two groups of melanomas that interestingly divided into two groups, those with disomy 3 and those with monosomy 3.[26] In 2004, Onken *et al.*, using gene expression profiling, confirmed the presence of two classes of uveal melanoma in which class 1 patients showed 95% survival and class 2 patients showed 31% survival at 8-year follow up.[23] From these results, it is postulated that genetic testing for uveal melanoma could allow for identification of high-risk patients and provide direction for individualized patient management with systemic therapies.[27,28]

The previous studies listed above employed genetic testing of enucleated eyes with melanoma using fresh tissue harvested from the globe.[18–23] Several published reports have indicated that genetic testing of non-enucleated eyes with melanoma is possible using fine needle aspiration

biopsy.[24,29–31] Using fine needle aspiration biopsy, only 10 or 20 cells are harvested in the needle tip and they are amplified and then studied with fluorescent *in situ* hybridization or microsatellite assay.[24,29–31] Midena *et al.* investigated this technique in eight eyes with medium size melanoma using a 30-gauge transscleral technique into the tumour base and found 88% yield.[29] Young *et al.* employed similar technique, sampling the tumour base in 18 cases and found 50% yield.[30] They commented that thin tumours offered the poorest yield. Shields *et al.* employed two different approaches for tissue sampling 140 cases.[24] They used a 27-gauge needle into the tumour apex through the pars plana for posterior melanoma and achieved 97% yield. For peripheral tumours, they used a 30-gauge needle transscleral into the tumour base and achieved 75% yield. They commented that thin peripheral tumours offered the least yield. Shields *et al.* further investigated genetic testing of small melanomas under 3 mm thickness.[31] They found monosomy 3 in 26% of small choroidal melanomas and this mutation was statistically correlated with documented tumour growth.[31] Patients with monosomy 3 are offered more intense systemic monitoring and potential therapeutic protocols.[28]

Correlation of cytogenetic abnormalities with histopathology of melanoma

Monosomy of chromosome 3 has been correlated to more aggressive histopathological features. Scholes *et al.* studied 105 patients with uveal melanoma and found that chromosome 3 monosomy correlated with epithelioid cells ($P < 0.001$), vascular loops ($P = 0.002$), largest basal diameter ($P = 0.002$), ciliary body involvement ($P = 0.008$) and metastasis-related death ($P = 0.0003$).[32] Damato *et al.* provided further investigation into prognostic factors in 356 patients with uveal melanoma and noted that the most significant factors for tumour-related death were larger basal tumour diameter ($P < 0.001$), monosomy 3 ($P < 0.001$) and epithelioid cell type ($P = 0.004$).[33] Tumours with monosomy 3 carried a 3.65 greater risk for metastatic death than those without this mutation. These aggressive histopathological features combined with the genetic abnormalities could contribute to the previously published worse patient survival. Further long-term studies on this cohort regarding life prognosis is anticipated.

Tumour regression correlation with cytogenetic findings of uveal melanoma

Following radiotherapy, previous observations from our group in the 1980s showed that rapid regression of choroidal melanoma following plaque radiotherapy implied an ominous systemic prognosis.[34] It was speculated that this association was due to more mitotically active tumours being more responsive to radiotherapy. Glynn *et al.* found that patients with rapidly declining melanoma height following proton beam radiotherapy showed higher rates of metastasis compared with those with slowly shrinking tumours in the first 2 years.[35] They speculated that the greater radiosensitivity of more malignant tumours, tendency for more rapidly regressing tumours to shed cells leading to metastasis, or failure of the immunological defence for rapidly regressing tumours accounted for the higher metastatic rate. Kaiserman *et al.* in 2004 indicated that both initial tumour height and post-radiotherapy tumour regression rate correlated with patient survival.[36] Tumours with eventual metastases displayed more rapid regression rate of 6.1% per month as compared with those that did not have metastatic disease with regression rate of 4.3% per month. They indicated that the post-radiotherapy regression rate could be useful in estimating the risk for metastatic spread and possible employment of preventive systemic therapy. We are currently investigating the relationship of chromosome 3 monosomy with tumour regression rate. As anticipated, tumours that display chromosome 3 monosomy have shown faster regression rates as compared with tumours with chromosome 3 disomy (Shields CL, Bianciotto C, Rudich D *et al*. Submitted for publication).

Systemic therapy for melanoma

Regarding systemic therapy, symptomatic metastatic melanoma typically offers poor survival of approximately 6 months.[37] However, improved outcome has been found with early detection of metastasis.[38–40] Newer approaches, based on results from cutaneous melanoma metastases, aim to treat asymptomatic micrometastases using novel chemotherapeutic agents, immune boosting medications, antivascular endothelial growth factors, multi-kinase inhibitors with antiproliferative and antiangiogenic effects, and antisense oligonucleotides.[40] Identification of high-risk patients relies predominantly on cytogenetic findings within the melanoma.

Conclusion

The secrets of uveal melanoma are gradually being uncovered. Now we better understand the host and environmental factors that predispose to this malignancy, the methods for early detection and cytogenetic abnormalities. There is still much more 'good, bad, and ugly' of melanoma to discover. Some day we will find the treasure and understand the origins, behaviour and best therapy for melanoma. Some day we will offer patients a better systemic outcome.

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