1) Germline mutations in BAP1 and the New Familial Melanoma Syndrome

BAP1 is a BRCA1 associated protein

Somatic mutations in the ubiquitin carboxyl-terminal hydrolase of BAP1 or deletions at 3p21 have been identified as key features of primary uveal melanoma tumors that metastasize

Now Germline mutations in BAP1 have been identified as the etiology of a new familial melanoma syndrome

Three families described thus far: 1 with atypical nevi with large epithelioid cell component in the dermis along with cutaneous and uveal melanoma 2) uveal melanoma and mesotheliomas 3) uveal melanoma and lung adenocarcinoma with meningiomas1-4.

Can also be seen in sporadic cases of atypical nevi with clone of large epithelioid cells often with spitzoid cytomorphic features in the dermis. These lesions do not have other features of Spitz such as epidermal hyperplasia, Kamino bodies or clefting4.

The tumors occur following loss of heterozygosity at 3p21 where BAP1 is located.

88% of the cases tests (37/42) also have BRAF mutation which is typically absent in conventional Spitz nevi4.

Often these nevi form large sheets of dermal epithelioid cells with atypia but again lack epidermal or other changes typical of Spitz nevi. Hence the BAP1 mutated/3p21 deleted lesion can result in one pattern of epithelioid Spitz tumor. Histologic features are distinct from atypical Spitz tumors with 11p gain or HRAS mutations which are large bulky lesions with deep dermal sclerosis and dispersion of nests to single cell units at the base4.

2) New somatic mutations in melanoma:

GNAQ and GNA11 newly described mutations in uveal melanomas occurring a mutually exclusive pattern. These genes have overlapping functions in melanocytic neoplasms and up regulate the Map kinase pathway.

GNAQ encodes the alpha subunit of heterotrimeric G proteins which couples
transmembrane receptors to intracellular signaling.

GNAQ also present in 54% of blue nevi while GNA11 in only 7%5,6.

GNAQ and GNA11 of no prognostic significance thus far but possible therapeutic importance as trials with MEK inhibitors in GNAQ and GNA11 mutated uveal melanoma underway.

3) Paradoxical Activation of Wild Type BRAF in Melanocytic Tumors From Patients Treated with Vemurafenib

In a phase 3 trial comparing vemurafenib (BRAF Kinase Inhibitor) to dacarbazine in metastatic melanoma patients, overall survival was 84% in vemurafenib treated group versus 64% in dacarbazine treated group. Vemurafenib was associated with a relative reduction of 63% in the risk of death and of 74% in the risk of either death or disease progression, as compared with dacarbazine (P<0.001 for both comparisons). Cutaneous side effects included rash, photosensitivity, alopecia as well as squamous cell carcinomas and keratoacanthomas7-9.

Dalle et al, also reported as part of the vemurafenib trials at their center (Université Claude Bernard Lyon 1, Pierre Bénite, France) that 4 patients developed 6 new pigmented lesions of which 5 were new primary melanomas and were all wild type for BRAF10.

We have also subsequently seen patients with dysplastic nevus syndrome at our center treated with vemurafenib who have shown dermoscopic evolution in their nevi concerning for malignant transformation directly after starting vemurafenib. In one patient, 3 nevi with regular reticulated dermoscopic pattern transformed to an inverse pigment pattern concerning for melanoma. On biopsy all were diagnosed as severely dysplastic nevi and were all wild type for BRAF.

Hence vemurafenib may cause paradoxical activation of wild type BRAF. Melanocytes with mutated BRAF do not have elevated RAS levels and hence do not tend to dimerize where as those with type BRAF tend to have elevated RAS levels causing dimerization of BRAF. Vemurafenib inhibition of one of the kinase domains in the BRAF dimer appears to cause transactivation of the other kinase domain and hence may cause paradoxical activation of the Map kinase pathway11-12. This maybe the source of the phenomenon observed in these few patients. Hence patients treated with vemurafenib and other BRAF kinase inhibitors should be monitored closely by dermatologists for the possibility of new second primary melanomas.
4) New Developments in Spitz Tumors and Molecular Diagnostics

Molecular techniques including comparative genomic hybridization and fluorescence in situ hybridization are emerging as important techniques in the diagnosis and classification of melanocytic tumors with ambiguous histologic features. However the true test of the value of these lesions is based on their ability to predict prognosis. An important consideration in evaluating this is the recent study from Ludgate et al showing that in their experience with 67 cases of atypical Spitz tumors with a minimum of 5 years follow up that up to 47% had sentinel node involvement without any subsequent adverse effect. Only one patient out of 67 died and this patient had a negative sentinel node. This study is important by further providing evidence that sentinel node involvement by an atypical Spitz tumor does not equate to a diagnosis of melanoma.

Overall there are few studies with a significant population of Spitz tumor cases with outcomes to evaluate the prognostic benefit of molecular studies to detect chromosomal aberrations. These include Gerami et al 2009 AJSP, Gaiser et al, Modern Pathology, Vergier et al Modern Pathology and Massi et al JAAD. All of these studies have some strengths and limitations but further studies are needed to look at ability of molecular studies to predict outcome in atypical Spitz tumors and these studies are underway.

Optimizing FISH for diagnosis of atypical Spitz tumors. New probe set recently developed includes 6p25, 11q13, 9p21 and 8q24. This probe set has significantly better sensitivity for spitzoid melanomas primarily because of inclusion of 9p21. In our experience the sensitivity of this assay for spitzoid melanomas is close to 90% while the older probe set including 6p25, 6q23, 11q13 and Cep6 was closer to 70% sensitive in spitzoid melanomas. Overall the newer assay has higher sensitivity at 94% and specificity of 98% in differentiating melanomas from benign nevi as compared to the older probe set.

FISH targeting 9p21 is a highly specific FISH marker for spitzoid melanoma when used to detect homozygous deletions at 9p21 while heterozygous deletions can be seen in Spitz nevi, dysplastic nevi, and atypical Spitz tumors.

5) Defining new subtypes of melanoma using FISH (the 8q24 melanoma)

In a case control prognostic study looking at melanomas with and without metastasis after 5 years follow up we found melanomas with 11q13 (CCND1) or 8q24 (MYC) gains to be highly associated with the metastatic group.
On further analysis we found that in addition to an aggressive clinical course, 8q24 positive melanomas have highly characteristic clinical and histologic features. These melanomas typically have an amelanotic clinical and histologic appearance, occur on areas of intermittently but not chronically sun damaged skin, have no associated precursor nevus, are often nodular or primary dermal and have highly irregular nuclear contours with coarse chromatin\textsuperscript{20}.

Furthermore we found a positive correlation between 8q24 copy number gains and elevated MYC protein expression, decreased MITF expression and decreased tyrosinase levels suggesting that the amelanotic clinical appearance maybe a direct result of down regulation of MITF by MYC.

Hence we suggest the 8q24 melanoma is a specific subtype of aggressive melanoma, with characteristic clinical and histologic features.

Reference List


