A Case for Performing Molecular Analysis on Challenging Melanocytic Lesions

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Introduction:

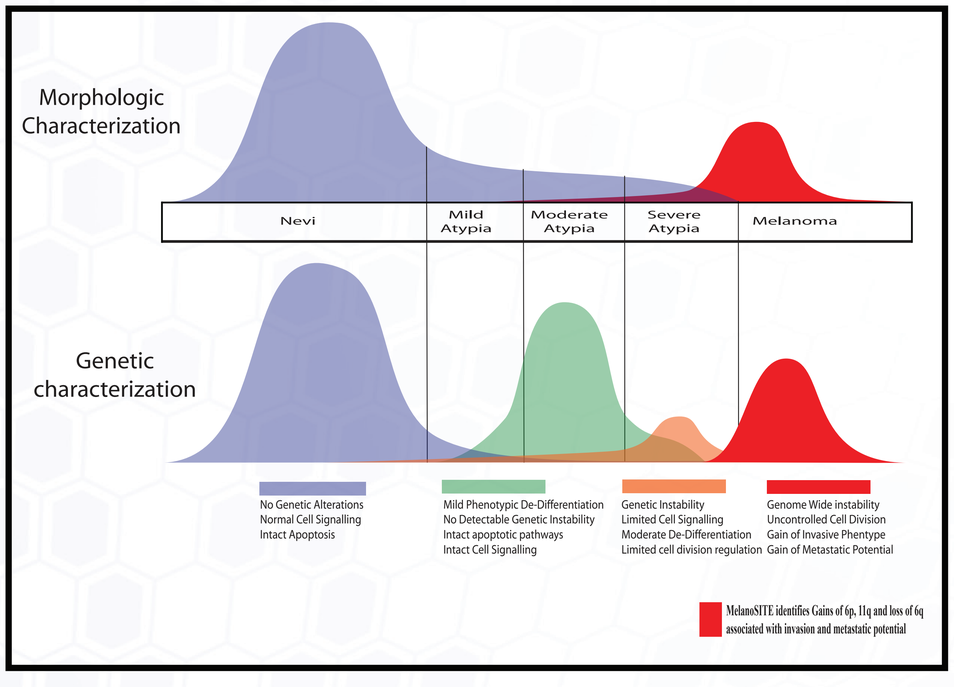
The characterization of melanocytic progression to melanoma presents specific challenges derived from the diverse phenotypic nature of the disease. While benign nevi contain few or no genetic alterations, melanoma are known to possess frequent gross genetic alterations. As such, there continues to be widespread discussion on the fundamental underlying biology of dysplastic nevi. Central to the argument is the contested proposition of the nature of melanocytic dysplasia; are a subset of dysplastic nevi premalignant lesions of melanoma, or are all dysplastic nevi fundamentally benign and genetically distinct from melanoma?

Recently, Fluorescent in situ hybridization (FISH) has been utilized to identify atypical melanocytic lesions with gross chromosomal aberrations, as a surrogate marker for progression to melanoma. Having utilized this assay in a clinical setting for several months, this review will provide a statistical overview of the first 200 clinical atypical melanocytic cases submitted for analysis (including a breakdown of samples by morphology and percent positivity by FISH), and highlight a subset of cases where the FISH result was clinically important in rendering a final diagnosis.

Discussion:

Progression from melanocyte through dysplasia to melanoma has been shown in several research studies to be an evolutionary process requiring multiple genetic events that subsequently affect several oncogenenic and tumor suppressor pathways which ultimately result in increasing dysplasia progression to invasion and metastatic potential. We developed a clinical assay using 4 FISH probes that identify gross genetic alterations in pathways known to be critical to invasion and metastatic potential in melanoma. We then analyzed 500 cases, comprised of 157 nevi, 167 dysplastic nevi, and 176 melanoma. The 4-probe FISH assay correctly identified 83.8% of melanomas, and 98.1% of all benign nevi. Clinically we have presented data from the last 200 cases. Based on the results of the validation and the initial clinical assay performance, the 4-probe FISH assay accurately identifies a molecular signature which is consistent with lesions that have invasive and metastatic potential. Lesions with these genetic qualities should be considered as possessing a genetics signature consistent with invasion and metastatic potential, even if this is not evident by morphology alone.

Scientific Background:



The progression of melanocytic nevi to melanoma can be characterized genetically by a defined initiating event, followed by a series of degenerative progressive genetic mutations, phenotypic de-differentiation, activation of tumor oncogenes, inhibition of tumor suppressor genes, until the cell reaches a state of de-differerentiation where invasion and metastatic potential is possible. FISH is a particularly useful tool for the diagnosis of cancer, as it is highly applicable for detecting the gross genetic changes characteristic of a cell with oncogenic potential. This is highly applicable in cases such as melanocytic lesions, where the differentiation of an atypical melanocytic lesion from a melanoma leads to a substantial difference in excision margins and follow-up treatment.

Clinical Validation:

	Total Cases	Positive by FISH	% Positive
Nevus			
Congenital	8	0	0.0%
Compound	37	0	0.0%
Intradermal	62	1	1.6%
Junctional	9	0	0.0%
Mild Atypia	32	2	6.3%
Blue	9	0	0.0%
Subtotal	157	***Percent Positive***	1.9%
Melanoma			
Superficial Spreading	71	57	80.3%
Spindle Cell	3	2	66.7%
Nodular	45	42	93.3%
In Situ	8	6	75.0%
Metastatic	40	33	82.5%
Subtotal	167	***Percent Positive***	83.8%
Dysplastic Nevus			
Moderate Atypia	60	4	6.7%
Severe Atypia	29	4	10.3%
Scalp	38	4	7.9%
Spitz	49	6	12.2%
Subtotal	176	***Percent Positive***	9.1%
		Percent Positive	***500***

Review of the benign lesions determined the assay identified genetic abnormalities in a total of 83.8% of melanomas, and 1.9% of nevus without atypia, while genetic abnormalities were identified in 6.3%, 6.7%, and 10.3% of nevus identified with mild, moderate and severe atypia, respectively.

Case Data:

Diagnosis on Requisition	Total Cases	Positive Result	% Positive
Atypical Melanocytic Lesion	37	5	14%
Atypical Melanocytic Lesion severe atypia	16	3	19%
Benign Neoplasm	40	4	10%
Melanoma	101	32	32%
Melanoma Rule Out (Melanoma ?)	35	8	23%
Neoplasm of Uncertain Behavior of other site	7	2	29%
Neoplasm of Uncertain Behavior of Skin	192	43	22%
Spindle Cell	5	2	40%
Spitz Nevus	25	6	24%
Spitz Tumor	9	1	11%
Unspecified Disorder of the skin	27	10	37%
BCC or SCC	5	3	60%
Other	21	2	10%
Total	**520**	**121**	**23%**

Total number of males	191
Total number of females	329
Total	**520**