Detection of Genetic Aberrations in the Assessment and Prognosis of Melanoma

Whitney A. High, MD, JD, MEng*

KEYWORDS

• Atypical nevus • Atypical Spitz nevus • Comparative genetic hybridization • Diagnosis
• Gene expression profiling • Fluorescent in situ hybridization • Melanoma • Prognosis

KEY POINTS

- Melanoma is an often subjective diagnosis made using light microscopy and H&E staining, and the dermatopathologic impression may be augmented by other means.
- Additional means for augmenting a histologic impression of melanoma include immunohistochemical (IHC) staining and/or genetic testing.
- In problematic lesions, IHC stains used to refine or refute the diagnosis of melanoma may include Melan-A/MART-1, S100, Ki67, p16, and HMB-45.
- In problematic lesions, adjunctive genetic assessment of melanoma used to refine or refute the diagnosis of melanoma include comparative genetic hybridization (CGH), fluorescent in situ hybridization (FISH), and gene expression profiling (GEP).
- There exist new genetic means to stratify risk and gauge prognosis in melanoma, and as additional adjunctive therapy expands, and surveillance protocols are further refined, growth in this area is anticipated.

INTRODUCTION

At present, the histologic diagnosis of skin cancer remains a critical step in the evaluation and management of skin disease. For the foreseeable future, and from a medicolegal standpoint in particular, a histologic report of cancer is requisite for additional intervention. For example, melanoma requires histologic staging information (eg, Breslow depth, presence/absence of ulceration, dermal mitotic activity) to select appropriate management. Even entrance into oncologic trials for melanoma, using new agents and new protocols, is affected by this histologic staging information.

In dermatopathology, the underlying practical means for rendering a cancer diagnosis has changed little in the last 140 years.[1] Each work day, dermatopathologists in the United States rely heavily on hematoxylin and eosin (H&E) staining and standard light microscopy to render most diagnoses. Moreover, even when a diagnosis is augmented by an adjunctive technique of some sort, H&E evaluation still remains a cornerstone or "back-bone" of the diagnostic schema.

Yet, reliance on simple histomorphologic assessment of tumors (ie, the physical appearance and arrangement of cancerous cells under the microscope) to predict genetic potential (ie,

University of Colorado School of Medicine, 12605 E 16th Avenue, Aurora, CO 80045, USA
* 12635 East Montview Boulevard, Suite 160, Aurora, CO 80045.
E-mail address: Whitney.High@ucdenver.edu

Dermatol Clin ■ (2017) ■–■
http://dx.doi.org/10.1016/j.det.2017.06.015

possession of genetic characteristics to become fatal metastatic disease) is not without consequence. Parenthetically, in the social sciences, reliance on outward appearances to predict behavior is considered an inefficient means of analysis (ie, so-called profiling)[2]; yet in dermatopathology, variations on this same type of pattern recognition are ubiquitously used.

In truth, particularly with regard to melanocytic neoplasia, there remain fundamental disagreements, even among dermatopathology experts, as to what represents melanoma.[3–7] Additionally, it has been demonstrated, repeatedly, that with regard to the histomorphologic assessment of melanoma, discrepancies among key histologic features exist.[7,8] It has been estimated by some experts that about 10% of pigmented lesions examined at expert tertiary melanoma centers may defy a singular confident diagnosis.[4]

Therefore, if specialty care providers in dermatology and dermatopathology desire to know what a skin neoplasm is capable of doing, at least in terms of yielding metastatic disease and patient demise, it is imperative that they develop and adopt means of genetic assessment, for it is precisely such genetic potential that is of concern in caring for patients.

This article focuses on available techniques used for the evaluation of melanocytic neoplasms. The reason for this focus is practical in nature: this is where the bulk of available adjunctive genetic techniques currently lie. At present, there are not significant and useful genetic techniques, in widespread use, for the evaluation of basal cell carcinoma or squamous cell carcinoma, although there is some interest in the latter. The evaluation of dermatofibrosarcoma protuberans, by means of a break-apart fluorescent in situ hybridization (FISH) probe that identifies a specific translocation, permeates clinical practice, yet this tumor is relatively rare.

Although cutaneous lymphoma may be the subject of genetic studies to demonstrate clonality, again as an adjunctive measure to light microscopy and immunohistochemistry (IHC) studies, clonality is not the equivalent of malignancy, nor is the absence of a detected clone exclusive of malignancy. Hence, given its lesser utility, and the fact this is a largely subspecialty concern, such a discussion is better reserved for an exclusive discourse on lymphoproliferative disorders.

DIAGNOSTIC MELANOMA ASSESSMENT

Lack of a Gold Standard

The assessment of melanoma is sometimes highly subjective. There are disagreements, even among experts, as to which challenging melanocytic neoplasms represent atypical/dysplastic/Clark nevi or melanoma, or which challenging spitzoid lesions represent classic Spitz nevi or atypical Spitz nevi/tumors or spitzoid melanoma. Complicating matters is that there is no singular gold standard, short of actual biologic behavior over time, which can prove something is, or is not, melanoma.

Moreover, where a tertiary care facility has overturned an assessment of melanoma rendered by an outside facility, or in the alternative, where a tertiary facility has rendered an assessment of melanoma, where an outside facility had not, there is bias to assume this second opinion is correct. Although perhaps a reasonable first assumption, given the expertise and depth of experience at a tertiary facility, in the absence of an adverse outcome experienced by the patient, there is no way to guarantee a second opinion is any more, or any less, correct than the first opinion rendered.

What if a person had melanoma, but it was treated as a severely atypical nevus, and the person simply survived? What if a person had a severely atypical nevus, but received treatment of melanoma that was unnecessary, but difficult to separate from melanoma survival?

In sum, the lack of a definitive gold standard, except in cases where an adverse outcome is experienced by the patient, poses a challenge to investigations of genetic diagnostic techniques[9]; this fact must be kept in mind in all of the discourse to follow.

Immunohistochemical Stains

Although the realm of H&E staining and light microscopy has changed little in the last century, the development and addition of IHC stains is a more recent development. The groundwork for modern IHC techniques was laid in the 1940s through 1960s, and widespread use of IHC began in earnest in the late 1980s.[10]

In brief, IHC represents a means to detect specific antigens in or on cells based on an antigen-antibody reaction that is recognized at the light microscopic level because of final application of a material that produces a visible color. Antigen retrieval is performed, and then a primary monoclonal antibody is applied. This antibody is directed against a specific tissue antigen. A secondary antibody is then applied that localizes to the first antibody. Conjugated to this secondary antibody are molecules of either horseradish peroxidase enzyme or alkaline phosphatase enzyme. Finally, a chromagen is applied that reacts with the conjugated enzyme to yield brown or red pigment deposition that is visualized under