Conceptual approach to early melanoma detection: models, tools, issues and challenges

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Practice points

- Benign melanocytic nevi and melanomas may develop from a common precursor along similar pathways, thus early stage melanomas may appear similar to their benign counterparts.
- Clinicians should strive to keep the threshold for early melanoma detection as low as possible without increasing the number of biopsies of benign lesions.
- The most critical step for early melanoma detection is the clinical total body skin examination.
- Dermoscopy provides greater pattern detail, allowing for the detection of more subtle features not apparent on the clinical examination. Confocal microscopy allows for even greater cellular and structural detail for lesions that remain challenging.
- Total body photography and follow-up imagery allow for the detection of change.
- Clinicians should approach the examination considering the 'smoking G.U.N.': lesions that are growing and unusual are worrisome, especially if dermoscopically nonuniform structures are present.

Identification and removal of melanoma early in its development remains the most effective treatment. However, identification of early melanoma remains challenging and may result in unnecessary morbidity due to the excess excision of benign melanocytic nevi. Herein, we present a conceptual model of benign and malignant melanocytic growths. The potential differences in the location of the cell of origin as well as considerations for neoplasm progression are also reviewed. Several of the clinical tools currently available, the integration of information from those different sources, and approaches to set an optimum biopsy threshold are discussed. While early detection remains a challenge, significant progress has been made. Insight into melanoma growth processes and appropriate use of available tools can result in the detection of thinner melanomas while also decreasing overall biopsy rates.

Background

Melanoma is a potentially fatal disease. Early identification is essential because survival decreases dramatically as the lesion depth increases [1]. However, early detection may be difficult as early melanomas may not have developed sufficient features to allow discrimination from benign melanocytic nevi. This challenge is further amplified by the fact that there are about 200,000 moles for every melanoma [2]. A physician's clinical insight into melanoma development along with the use of the appropriate clinical tools can optimize early detection.

The model we present is one that we have advanced and supported over the years. It provides a context in which it is easier to understand the early developmental changes when a melanoma

KEYWORDS

• confocal microscopy
• dermoscopy • dysplastic nevi • early detection
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crosses a threshold allowing detection with various approaches and technologies. We believe there is a place for integrating these concepts in the literature.

Conceptual modeling & framework for nevogenesis & melanomagenesis

The majority of melanomas develop *de novo* in normal appearing skin [3,4]. For the one-quarter of melanomas that appear to have developed in a nevus, less than half of those associated nevi are 'dysplastic' [2,5]. Thus an intermediate nevus stage does not appear to be required for melanoma development, and dysplasia does not necessarily predict degeneration [6,7]. How can this be explained? One straightforward explanation is that benign melanocytic nevi and melanomas develop from a common precursor (Figure 1). Thus a mutated precursor cell could give rise to either a benign melanocytic

nevus or a melanoma dependent on the complement of mutations present. Certainly a secondary mutation could also occur in a developing nevus resulting in the development of a coexistent melanoma. Differences in the type of mutations, precursor location, and the environment in which the neoplasms develop could give rise to the different patterns routinely seen in clinical practice [6,7].

• Precursor cell state & location

The state and location of the precursor cell can differ for the different melanocytic neoplasms (Figure 1) [6,7]. Melanocytic precursors migrate through the dermis and insert themselves into the epidermis during development. Once in the epidermal layer, most melanocytes differentiate but some persist in an immature state in the hair follicle or eccrine coils on volar skin [8–10]. A dermal perineural reservoir may exist for

Figure 1. Model for melanocytic neoplasm migration. Melanoma could develop in the epidermis or in the dermis. In the epidermal model, the cell of origin (A1) would exist in the epidermis and initial progression (A2) would occur there. Eventually the neoplasms would develop the ability to migrate into the dermis (A3) and eventually metastasize (A4). If the cell of origin is in the dermis and it has high epidermotropism (B1) it would be expected to marginally proliferate in the dermis and primarily (B2) migrate to the epidermis where in the context of epidermal cytokines it would continue to proliferate (B3). Excess cells may be extruded from the epidermis through the stratum corneum. Lymphatic involvement (B4) would be rare. If the cell of origin is in the dermis and has low epidermotropism (C1) it would be expected to proliferate in the dermis (C2) with only occasional cells migrating to the epidermis (C3). Excess cells may readily exit the skin and transverse the lymphatics (C4).

melanocytic precursor cells [7,11]. Further it is also possible that circulating cells could serve as precursors [12]. Thus there may be several different cell populations that could serve as a melanocytic neoplasm precursor. While dedifferentiation from a more mature precursor is also possible, in many ways it makes sense that the more immature cells serve as the cell of origin. These cells could remain in a quiescent state and acquire mutations over time, with the neoplasm not developing until the cell becomes stimulated. This could explain why early sunburns are correlated with melanoma later in life [13], which may happen when a mutated melanocytic precursor cell is activated to produce melanocytes. Due to the epidermotropic migratory characteristics, dermal cells could be the cell of origin even in neoplasms that appear to primarily be epidermal.

Data supporting skin origin

Clinical data and UV signature data support the concept that the majority of melanomas are unique lesions that develop directly in the skin [14,15]. However, it is also interesting that *BRAF* is not a UV signature mutation. The extent of UV mutations varies depending on neoplasm type, suggesting distinct mutagenic environments may drive the different melanoma subtypes [16,17].

Data supporting epidermal origin

Clinical and pathological findings of 'early' melanomas support the concept that melanomas first evolve in the epidermis. Clinically, early lesions are perceived to be flat with subsequent papule/nodule development presumably at the point the neoplasm begins to invade. Pathologically, the majority of melanomas appear to be in the epidermis or papillary dermis with few extending into the deeper dermis and fat, again suggesting progression from the epidermis to the deeper dermal structures. An epidermal origin seems particularly evident with lentigo maligna (melanoma *in situ*, type lentigo maligna). In these lesions, it seems likely that the keratinocytes create an environment to 'incubate' the neoplasm (possibly in a pre-existing solar lentigo). Clinical observation of lentigo maligna suggests a prolonged epidermal phase prior to dermal invasion. Interestingly even in these lesions occasional cells are identified in the superficial dermis by confocal microscopy [18]. For other melanoma types, definitive epidermal evolution is less clear. On review, 29% of *in situ*

melanomas were found to have a dermal component [19]. Thus it is possible that these '*in situ*' melanomas have a dermal origin with the bulk of the cells migrating into the epidermis, or that early invasion is common.

Data supporting dermal origin

All nevi and melanomas with a dermal component were either derived there or invaded from the epidermis or from some other source. Congenital melanocytic nevi appear to develop from neural crest cells migrating through the dermis towards the epidermis. Blue melanocytic nevi lack an epidermal component and likely develop from a dermal precursor. It is interesting that purely junctional nevi are seen in abundance in adulthood but are not present in young children, whereas the nevi identified in young children all appear to have a dermal component [20]. Nodular melanomas, or single lesions considered metastatic melanoma of unknown primary, may also have directly developed in the dermis. Murine melanoma models almost all develop melanomas from dermal melanocytic cells [21,22]. Recent studies have also suggested dermal melanocytic cells are commonly present in biopsies, even those of non-melanocytic origin [23]. Thus the development of melanocytic neoplasias from dermal cells is possible.

Data supporting origin in circulating cells

Circulating cells could also give rise to melanocytic neoplasms. Epidermotropic metastatic melanoma clearly can enter the epidermis. In fact, there are reports of melanoma metastases appearing entirely confined to the epidermis (*in situ*) [24]. Circulating benign melanocytic nevus cells have also been identified [25]. It is even possible that some melanocytic cells can pass directly through the lymph system [26]. Instances of patients with eruptive nevi may be better explained by circulating precursors than due to spontaneous mutations occurring at multiple different locations. Since bone marrow cells can be converted to melanocytes [27], it is rational to also consider the possibility of circulating cells giving rise to new melanocytic neoplasias [12]. This may also account for melanomas of unknown primary.

• Mutations & growth patterns

While precursor and location/environment are important, specific driving mutations are also critical to nevogenesis and melanomagenesis

(Figure 2). Different mutations likely give rise to different melanocytic growth patterns [28]. *GNAQ* mutations occur in 82.8% of blue nevi. *HRAS* mutations are almost exclusively seen in Spitz nevi. *NRAS* mutations are the most common mutation in congenital melanocytic nevi. *BRAF* mutations are most often associated with acquired melanocytic nevi [28]. However, there are still many nevus phenotypes for which the underlying driving mutation is not known.

Certain driving mutations may also give rise to specific growth patterns for melanoma. *GNAQ* primarily gives rise to ocular melanoma but may also be associated with darkly pigmented dermal melanomas [29]. *NRAS* is more commonly seen in nodular melanomas [28]. *BRAF* usually gives rise to superficial spreading melanomas. *KIT* mutations may be associated with a dark homogenous streaks pattern [30]. However, as

melanomas advance and mutations accumulate, discrete patterns are harder to discern, therefore these patterns may be most useful for early lesions.

Germline context

The melanocytic lesions on patients often match a specific pattern. This phenomenon allows for the clinical discrimination of lesions that do not match the patient's average nevus and the identification of lesions that appear similar to the patient's prior melanoma. This similarity of pattern is likely due to germline factors and their interaction with the neoplasm mutation(s). While entirely hypothetical, it could also be due to the neoplasms developing from a common circulating mutant stem cell population. Environmental factors, such as marked sunburns or other mutagenic agents, could also

Figure 2. Mutation driven melanocytic growth patterns. Melanocytic neoplasias grow with different patterns. There is still much work ahead to determine the relationships of the different mutations. It is interesting that some very specific mutations are associated with particular patterns of benign and malignant melanocytic neoplasms. *HRAS* Q61L is associated with benign Spitz neoplasms, *NRAS* Q61K/R is associated with large congenital melanocytic nevi and is increased in nodular melanomas. *BRAF* V600E/K is associated with acquired melanocytic nevi and especially superficial spreading melanoma. *KIT* mutations are associated with acral, mucosal, lentigo, and a dark streak pattern of cutaneous melanoma. *GNAQ* Q209L/P is associated with blue melanocytic nevi and ocular melanoma. These relationships are not 1:1 and remain complex but suggest that specific driving mutations are capable of creating neoplasms with certain identified patterns of growth.

have a modulating effect. It is interesting that neoplasms with different driving mutations appear to have evolved in different mutagenic environments, suggesting unique germline and environmental interactions for the various neoplasm types [16].

• Growth phases

There are different phases of melanocytic growth (Figure 3) [31–33]. Grossly three stages can be identified and include growth/proliferative, stable/senescent and involution/regression phases. However, transition between these stages may be more of a gradient than a switch. Trauma allows lesions that appeared stable to transiently re-enter a growth phase. This is often seen as a nevus recurrence in the base of a shave biopsy that was clinically clear. UV radiation and cytokines may also play a role in modulating change; thus it is not entirely clear if a stable nevus is fully senescent [33]. The involution or regression phase may be mediated by cell-specific cell-removal pathways (such as apoptosis) or by immune mechanisms. In melanoma, the proliferative driving mutation is complemented by at least one other mutation that damages cell cycle regulatory controls. Thus these lesions never fully stabilize and instead demonstrate progressive growth, often associated with genomic instability.

In both benign and malignant melanocytic neoplasias, an excess of melanocytic cells are produced during the proliferative phase. Some of these cells may be naturally extruded through the epidermis (pagetoid upward migration). Thus even a benign lesion can have some features worrisome for melanoma in its early growth phase. Therefore, it is important to be careful when interpreting these early lesions as melanoma. As the melanomas continue to grow and accumulate different genetic aberrations they become progressively more nonuniform and easier to detect [3].

• Genomic instability

A hallmark of melanoma is genomic instability. While some chromosomal arm changes are seen in Spitz nevi, losses and gains of entire chromosomes are largely confined to malignant lesions. The primary cause for the chromosomal instability is unknown but it could be related to the expression of germ cell meiotic proteins in melanoma that interfere with normal mitotic pathways (meiomitosis) [6]. Chromosomal instability

in melanoma appears to be an ongoing process with different metastases having differing complements of chromosomes [34,35]. It is this instability that creates subclones of melanoma cells with different pigmentary features and growth rates. Genomic instability is likely the primary cause of the nonuniform features that develop as melanoma cell populations expand, ultimately leading to the classical ABCDs seen with progressive melanoma growth.

• Integrating the concepts

While some melanomas may be lethal from the moment the neoplasm is initiated, most melanomas likely need time to evolve lethal potential. However, early identification of melanoma still requires a sufficient number of cells to allow for detection. The objective is to keep the threshold for melanoma detection as low as possible. One key point is to be familiar with normal growth and involution patterns for benign melanocytic nevi. A second is to recognize that inherent genetic and/or environmental factors cause patients to develop lesions of similar patterns. Most of the patterns will be benign, and lesions not matching the pattern of the other moles on the patient require further scrutiny. It is also important to note that a patient's subsequent melanomas may very well have a pattern similar to the prior melanoma [30,36–37]. The third and potentially most important issue is to pay attention to growth pattern, as differences will initially be subtle but will become more marked as the malignant lesions grow. Continued growth is very worrisome particularly if nonuniform features develop [3]. It is also important to note that some lesions may develop in the dermis and, therefore, may not be identified and removed in an *in situ* state.

• Early detection & tools

As melanomas grow they generally become more nonuniform and develop the traditional ABCD features, making the clinical diagnosis relatively straightforward. However, in the early stages these lesions may appear similar to their benign counterparts. This problem is compounded by the challenge of identifying a melanoma in the background of 200,000 benign melanocytic nevi [2]. In addition to the small early lesions, nodular, amelanotic and desmoplastic melanomas can also present difficulty as they may not have the traditional ABCDs. By combining knowledge of how the neoplasms

Figure 3. Benign versus malignant neoplasm progression. Benign melanocytic nevi and melanomas may initiate in a similar precursor cell. While both have mutations that drive proliferation, the melanoma may also include cell cycle regulatory defects. In the early growth stages, benign melanocytic nevi and early melanomas may appear clinically similar. In fact it is possible that the proliferative characteristics and possible epidermal discharge of excess cells from both at this stage could be interpreted as worrisome for early melanoma. As the lesions grow, the cell cycle regulatory system stabilizes the benign melanocytic nevus; while the melanoma continues to grow and begins to demonstrate genomic instability. With progression, the nonuniform features of the melanoma become more prominent while the benign melanocytic nevus may eventually involute/regress. Rarely a benign melanocytic nevus might also develop a secondary cell cycle mutation allowing for the co-existent development of a melanoma (gray arrow). Later stage melanoma detection is clinically more straightforward. Detection at earlier stages is helped with objective data on change and dermoscopic/confocal features.

grow and utilizing clinical tools (Figure 4), the thresholds for detecting these lesions earlier can be lowered.

• Overall clinical context

The clinical total body skin examination is the first critical step. A thorough, thoughtful skin examination will identify lesions that require a closer look. Benign lesions vastly outnumber malignant lesions. Because the malignant lesions include additional mutations, they tend to grow in a different pattern and become more prominent with continued growth. These lesions may simply be lighter or darker than the other lesions. They may also have a red hue due to increased blood flow and inflammation. Pink lesions also have to be evaluated carefully. Once these lesions have been identified on the clinical examination the next step is to look more closely with available tools.

• Dermoscopic context

Dermoscopy (surface microscopy) allows the clinician to visualize more pattern data,

allowing for the detection of subtle changes not apparent on the clinical examination. While this scope does allow for a more detailed examination, it is limited to the location where scope is placed. Dermoscopes can be used in polarized and nonpolarized modes. With a nonpolarized light, epidermal features are more prominent (i.e., milia-like cysts, comedo-like openings, and ridges). With polarized dermoscopy, deeper underlying structures are more clearly visualized. Dermoscopic features that are traditionally correlated with malignancy include atypical pigment network, pseudopods, blue-white veil, multiple colors and irregular dots/globules [3,38]. Dermoscopy may also allow the detection of nonuniform features, generally absent in benign lesions, but difficult to appreciate clinically. The presence of nonuniform features in a growing lesion is very worrisome for malignancy [3]. Optimally all lesions should be screened by dermoscopy [39]; however, a targeted approach toward the evaluation of outliers may also be used. The use of dermoscopy has been shown to

markedly increase the accuracy of melanoma detection [40].

• Confocal context

Even with dermoscopy, it is often difficult to determine if an early lesion is a melanoma [18,41]. This is especially challenging on sun damaged skin with lesions concerning for lentigo maligna versus benign lentigo (early melanocytic nevus, type lentigo simplex or flat seborrheic keratosis, type lentigo senilis). Small pink lesions are also particularly challenging clinically and dermoscopically. Confocal microscopy allows for visualization of cellular

and structural detail. The presence of sheets of dendrites, pagetoid cells and various architectural features may aid in the diagnosis of early melanoma. Confocal microscopy is best used on lesions with epidermal or very superficial dermal findings given its limited depth of penetration. It is generally only used on a few selected lesions as it can be time consuming and difficult to perform on specific areas, such as acral sites. Confocal microscopy can delineate melanoma from benign lesions that appear similar dermoscopically [18] and has been shown to significantly increase diagnostic accuracy [42].

Figure 4. Global clinical context versus focused cellular detail. There are multiple steps for early detection of melanoma. The first and most important step is a complete skin examination. This allows for the detection of unusual lesions. Change can also be determined by total body photography. The next step is to look closer with dermoscopy, allowing more detail to be visualized in the sampled areas. A final step for lesions that remain uncertain would be to use confocal microscopy, which provides discrimination of cellular detail, but only in the small regions of skin examined. A combination of these techniques allows for the detection of melanomas at very early stages. TBP: Total body photography.

• Detecting change

Total body photography

Total body photography (TBP) is a record of the entire body surface and functions as a tool to help identify lesions that are growing. True melanomas continue to grow but it is important to note that normal melanocytic nevi also have a growth phase, so growth alone is not a sufficient reason for removal. Unusual lesions that are growing should be considered high risk, and lesions that are also dermoscopically nonuniform are very worrisome for melanoma [3]. The combination of TBP and dermoscopy has been shown to detect melanomas at earlier stages and decrease biopsies of benign lesion resulting in very low benign to malignant ratios [4].

One of the challenges is determining who should be imaged. These individuals include those with numerous nevi, particularly dysplastic/atypical melanocytic nevi. Patients with a personal history of melanoma (especially if multiple), large congenital melanocytic nevi and genetic risk factors should also be considered for TBP.

Sequential dermoscopic imaging

For some lesions a benign diagnosis may be favored but malignancy cannot be fully ruled out and baseline photos may not be available to determine whether the lesion has changed. In these cases, dermoscopic follow-up is an option. Follow-up is generally limited to a certain number of lesions but this approach does allow for more detail than TBP. Most practitioners follow up the lesions initially at 3 months to determine if significant change has occurred [43]. If it has not, the lesion may continue to be followed in case it is an extremely slow growing melanoma. This approach helps prevent unnecessary biopsies while still identifying melanomas at early stages.

Sequential confocal imaging

For some lesions, sequential confocal imaging may be appropriate. One particular instance where this may play a role is in the follow-up of a lesion worrisome for recurrent lentigo maligna in the background of sun-damaged skin. Demonstration of an expanding focus of cells with confocal microscopy may drive early treatment (personal experience, unpublished data).

• Other technologies

Newer visualization tools such as optical coherence tomography and ultrasound are finding

their way into clinical practice and management. There are ongoing efforts to develop machines and tests that provide more objective data. Such devices include those based on multispectral imaging, electrical impedance, Raman spectroscopy and molecular tests aimed at diagnosis of melanoma or providing prognostic data [44–46]. Prognostic molecular tests may eventually replace sentinel node biopsies and allow us to determine which patients require treatment to prevent disease progression.

Other issues & challenges

• Screening

Anyone can develop a melanoma and ideally everyone should be screened. Data from Schleswig-Holstein and German studies supports this approach with a 49% and 47% reduction in mortality [47], respectively. However, from a cost-benefit perspective it also makes sense to focus efforts on the subpopulation of those most likely to develop melanoma. Risk for melanoma has been found to increase with the number of common melanocytic nevi [48], the number of atypical melanocytic nevi [49] and the degree of atypia of the nevi [50]. Increased size of dysplastic/atypical melanocytic nevi has also been associated with increased melanoma risk [51]. With congenital melanocytic nevi, increased size is also associated with increased melanoma risk [52]. Prior personal history increases relative risk approximately eightfold. Family history is a significant risk factor for melanoma, as 13% of melanoma patients have at least one first degree relative with melanoma [53]. Melanoma is twice as likely to develop if a parent is affected, three-times as likely if a sibling is affected and nine times as likely if both a parent and sibling are affected [54]. Intermittent sun exposure, history of sunburn [13], use of tanning beds [55], fair skin, red hair color and blue eye color are all associated with increased melanoma risk [56]. Certain genetic disorders such as xeroderma pigmentosum also predispose individuals to developing melanoma [57]. With advances in genetics, identification of the population at greatest risk will become more straightforward.

By screening these high risk individuals more closely, we can increase the likelihood of detecting potentially malignant lesions in their early stages and treating them successfully. These patients should be screened more frequently and presented with the option of TBP and other tools that can aid in early detection. Similarly,

patient education is paramount. Not only should patients be well versed on sun protection, but they should also be properly trained to perform periodic self-checks to identify changing moles.

• Excision approach

Careful examination will allow clinicians to target lesions at greatest risk for melanoma. If the clinical and dermoscopic are worrisome for melanoma, especially if nonuniform change is noted and/or confocal demonstrates worrisome features, the lesion should be excised with clear normal skin margins. This allows for a more complete examination by the dermatopathologist and reduces the need for re-excision of atypical lesions not meeting the dermatopathological criteria for melanoma. Shave excisions have a significant recurrence rate and are best avoided on lesions where there is concern for melanoma. However, the shave approach may be favored on large lesions where there is concern for lentigo maligna in order to provide the dermatopathologist a sufficient length of tissue to make the diagnosis. For excision of the lentigo maligna lesions, confocal microscopy may also be useful for defining the margins. The use of immunohistochemical, or in the future, multiple, simultaneous immunofluorescent markers may also help improve margin control.

Conclusion & future perspective

Whether originating in the dermis or epidermis, most melanomas develop in the skin and follow a predictable course. At early stages melanomas may not look that different from their benign counterparts. Due to additional mutations, a melanoma will often declare itself first by appearing unusual compared with the patient's general mole pattern. Tools such as dermoscopy, TBP and confocal microscopy have the capacity to increase our accuracy in identifying these lesions at earlier, more curable stages without increasing unnecessary

biopsies of benign lesions. Knowledge of change through baseline TBP or sequential images can play a very important role. A growing lesion that is unusual for the patient, particularly if it is growing in a nonuniform manner is very worrisome for malignancy (smoking G.U.N.).

Soon, molecular diagnostic tests will be able to better define these subsets of lesions and allow us to recalibrate detection approaches to target the removal of melanomas before they become lethal in a broad population. Developments in germline genetics may be critical in identifying patients at high risk but who lack outward phenotypic risk features for melanoma development. Technologies will also continue to improve and possibly the detection/diagnosis may be ultimately made by a total body scanner. While our understanding has increased dramatically, many questions remain unanswered. Applying the techniques we already have at hand will save lives, but continued efforts will save many more.

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