Malignant Melanoma

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INTRODUCTION

Malignant melanoma is an increasingly important public health problem in the US and worldwide. The incidence of melanoma has been increasing faster than that of any other cancer in the US and is now the fifth most common cancer in the US (1). It is estimated that 73,870 men and women were diagnosed with melanoma in 2015, and it is responsible for 1-2% of all cancer deaths and actually 9,940 men and women died with melanoma in 2015 (1). Incidence rates are higher in women than in men before age 50, but the incidence of melanoma increases significantly in men by age 65 or older (1). Although the incidence of, and mortality from, melanoma continues to increase, the rate of increase appears to be slowing. The factors contributing to this slowing are an increased public awareness and education, better prevention, and earlier detection (2).

Melanoma is the most common malignancy seen in the foot and the most common locations are the soles of the feet, thumb, or great toe. The term "acral lentiginous melanoma" refers to a melanoma of the hands and feet that account for 3-15% of all melanomas (3). Barnes et al reviewed the 1,018 patients prospectively who were seen for a primary cutaneous melanoma of the lower extremity over a period of 20 years and they found that melanomas of the foot were associated with a poorer prognosis for survival than melanomas of other parts of the lower extremity. They also mentioned that the specific location of the tumor on the foot was a significant factor in survival rate where the plantar and subungual lesions were associated with a poorer rate of survival than lesions of the dorsum (4). Fortin et al retrospectively reviewed patients who had a malignant melanoma of the foot or ankle over a period of 15 years, and reported the shorter survival rate for the patients who had a plantar or subungual lesion. They related that this might be the result of an initial misdiagnosis that noted to be the higher prevalence at the plantar and subungual sites (3). The most common misdiagnoses are benign nevus, subungual or traumatic hematoma, verruca, dermatofibroma, hallux paronychia, and pyogenic granuloma (3-5).

RISK FACTORS

Melanoma is primarily a disease of Caucasians with at least a 10-fold and a 7-fold increase in the incidence of melanoma compared with African American and American Hispanics, respectively (6). Phenotype plays a significant role in disease prevalence. Typically, fair-skinned individuals with red or blonde hair and blue eyes, or those who burn easily are more likely to develop a melanoma (1, 7).

Most melanomas arise de novo and therefore they are not the result of malignant transformation from existing skin lesion but melanoma occasionally can develop within certain precursor lesions, such as melanocytic nevi and dysplastic nevi (8, 9). The total number of nevi and its presence are important independent risk factors for the development of melanoma (10, 11). Studies have demonstrated that dysplastic nevi are reported in up to 34-56% of patients with melanoma (10), but the development of potential precursors to melanoma is inhibited by the regular use of sunscreen (12).

The sun exposure/UV radiation is closely linked to the development of melanomas and it is the most significant environmental factor contributing to melanoma (2). Multiple studies have demonstrated a significant correlation between tanning bed use and the risk of developing melanoma. The International Agency for Research on Cancer and the National Institutes of Health recognized the UV exposure from tanning beds as a carcinogenic risk (7, 13). The risk of melanoma increases substantially with each tanning bed use and inversely increases with age (13, 14). Westerdahl et al found a higher risk for developing a melanoma in individuals younger than age 36 years and the greater risk was associated with the use of commercial tanning devices and their use during the winter months (15, 16). This is an interesting observation because the skin of most individuals is known to be less adapted to UV radiation during the winter. In Australia, the country with the highest incidence of melanoma worldwide, legislation was been passed to ban tanning beds by the year 2014 (7).

Melanoma can be a familial disease and it has been estimated that up to 12% of cases of cutaneous melanoma are familial (2). A family history of melanoma increases an individual's risk of melanoma by a factor of 3-8 compared with individuals who have no family history (6).

DIAGNOSIS

Melanomas were often recognized only when they were large, ulcerated, and at more advanced stage because the distinction between a benign nevus and an early melanoma can be quite difficult (17). But early detection is key to reduce the risk and mortality that can be done by performing a through physical examination. The history should include assessment of the risk factors as described above.

The ABCD acronym (asymmetry, border irregularity, color variegation, diameter >6 mm) for melanoma screening (Figure 1) was devised in 1985 by professors at New York University Dermatology Department to provide the public and primary health care professionals with a useful and memorable mnemonic to aid in the early recognition of malignant melanoma. This was expanded to ABCDE, which includes a criterion for "evolving lesions" including any changes with respect to size, shape, symptoms (e.g., itching, tenderness), surface (e.g., bleeding), or shades of color (17, 18). Evidence has accumulated that the addition of "E" will substantially improve and enhance the ability of physicians and public to recognize melanomas at earlier stages (18).

Biopsy is the most accurate and confirmative diagnosis. The purpose of the biopsy is not only to confirm a diagnosis of melanoma but also to determine the maximum depth of penetration (7). There are 3 different types of technique: excisional, incisional, or shave biopsy (19). Excisional is to excise the lesion totally, with a 1 to 2 mm margin of clinically normal skin with the depth of the biopsy sample extending completely through the dermis and some subcutaneous fat. Incisional is a full-thickness biopsy that does not remove the entire lesion, but merely removes enough tissue to obtain a diagnosis. The simplest form of incisional biopsy is a punch biopsy and this is the preferable biopsy technique because it is simple and easy. The recommendation for the proper technique is to perform through the thickest area of the lesion and obtain multiple biopsy samples for large lesions to avoid a sampling error. This is performed with a disposable instrument; usually measuring 2-8 mm in diameter. A punch at least 4 mm in size should be performed to obtain an adequate tissue for accurate pathologic evaluation (2, 19).

Dermatoscopy is a useful technology that is easily used in the clinical setting. It uses a hand-held lighted magnifier to analyze skin lesions by observing subsurface structures (Figure 2). This instrument makes the epidermis essentially translucent and allows in vivo visualization of subsurface anatomic structures of the epidermis and papillary dermis that are otherwise not discernible to the unaided eye. Dermascopes usually facilitate a 10x magnification of the skin (20). Vestergaard et al reported that the diagnostic accuracy of dermoscopy in detecting melanoma improves the sensitivity and specificity of clinical diagnosis from 71% to 90% (21). However, the effectiveness of this technique depends on experience.
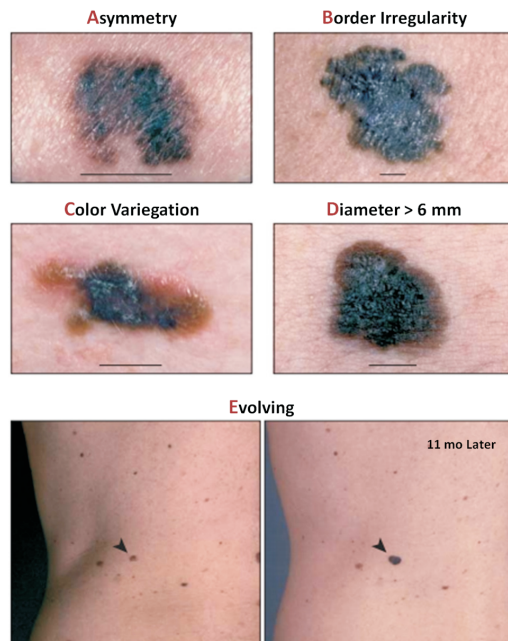

Figure 1. ABCDE of melanomas (from ref. 18).

Figure 2. A polarized light handheld dermascope.

PROGNOSIS

The prognosis of an individual patient can vary widely and depends largely on the stage of the melanoma at the time of diagnosis. In an effort to better predict survival in these patients, a number of variables have been found to influence survival. The single most important prognostic factor for overall survival is the status of the regional lymph nodes (7, 22, 23). Jansen et al reviewed 200 patients with a cutaneous melanoma who had undergone a sentinel node biopsy and found that the overall survival at 3 years was 93% if the sentinel node was negative and 67% if it was positive (24). The chance of mortality from melanoma increases substantially if there is metastasis to regional lymph nodes (7).

Another prognostic factor that consistently correlates with survival is Breslow thickness (2). This classification was described by Alexander Breslow in 1970, and recognized the depth of invasion as a vertical thickness of the melanoma in millimeters; the prognosis worsens as the thickness of the melanoma increases. Using Breslow thickness, melanomas are commonly considered to be thin (<1 mm), of intermediate thickness (>1-4 mm), or thick (>4 mm) (4). Diagnostic decisions are also based on the Breslow classification.

Clark level is a known classification system as well for the prognostic variable based on the level of invasion into the anatomic layers of the skin. Clark level 1 represents melanoma in situ, limited to the epidermis with no metastatic potential; level 2 is melanoma that extends into the papillary dermis; level 3 is filling the papillary dermis; level 4 is to the reticular dermis; and level 5 is invasion of the subcutaneous fat (2, 7, 24, 25).

Both Breslow thickness and Clark level are important prognostic variables but a recommendation from the American Joint Committee on Cancer (AJCC) is to use Breslow thickness solely and eliminate the Clark level from the melanoma staging protocol to simplify the staging system (25, 26). Breslow thickness actually has became the system of choice because many studies have been reported as showing that Breslow thickness retains its high level of prognostic significance and has been shown to be a more accurate method of predicting prognosis (4, 25, 26). Conversely, there are also many studies that show that both staging systems are high prognostic for melanomas (25).

Ulceration has been recognized as a very robust predictor of prognosis along with other variables (7, 26, 27). There is no clear reason but ulceration appears to be a phenotypic marker for worse tumor biology and greater propensity for invasion and metastasis. Patients with ulcerated melanomas have a worse prognosis than those with nonulcerated melanomas (26). Baade et al reviewed 28,654 patients who were diagnosed with a single invasive melanoma between 1995 and 2008 and found that survival is 7-fold higher with patients without ulceration (28).

Mitotic rate is recognized as an important and independent prognostic factor in the final version of the AJCC Melanoma Staging and Classification recommendations (26). Mitotic rate is the most recently validated prognostic factor and is very important to consider. A threshold of mitotic rate at least $1/mm^2$ is considered the most significant correlation with survival, and its rate declines as mitotic rate increases (26).

The AJCC has proposed an updated clinical and pathologic staging system in 2009 for cutaneous melanoma based on new data, which have accumulated in recent years (Figure 3). The original AJCC Staging Manual has included all the prognostic factors as discussed above but the newest version of staging system has references from an expanded sample size of the melanoma staging database and newly added mitotic rate.

TREATMENT

The standard treatment for melanoma is a surgical wide excision with margins if detected early. Noting the aggressive nature of melanoma recognized by William Norris in 1875, the recommendation is to remove the melanoma with appropriate margins (7). What constitutes adequate margins, when excising a melanoma, has been a point of contention for years. There are recommendations in the literature regarding the margins of excision for primary melanomas. The recent American Academy of Dermatology guidelines and others like the National Institutes of Health consensus group recommend 5 mm margins for in situ, 1 cm margins for lesions <2 mm thick, and 2 cm margins for lesions ≥2 mm thick (29, 30). In contrast to these groups, others have suggested that 1 cm margins are adequate for most lesions up to 2 mm in thickness and 2 cm margins for the greater thickness (2). According to many studies, 2 cm margins may be the adequate margin for the large thickness lesion whether they are >2 mm or ≥2 mm but interestingly retrospective analysis suggests that there is no advantage for margins wider than 2 cm (7). Nonetheless, performing wider margin excision will be appropriate for advanced melanomas when the surgeon decides it is needed due to the high risk of recurrence.

As mentioned previously, the status of the regional lymph node is the most important prognostic factor for survival. Therefore, the sentinel lymph node biopsy and following lymphadenectomy (LND) for a positive biopsy sample are essential. The questions arise as to what are the indications for sentinel lymph node biopsy. The literature has identified that ulceration and mitotic rate should be considered when deciding whether or not to perform sentinel lymph node

Classification	Thickness (mm)	Ulceration Status/Mitoses
T		
Tis	NA	NA
T1	≤ 1.00	a: Without ulceration and mitosis < 1/mm^2
		b: With ulceration or mitosis ≥ 1/mm^2
T2	1.01 – 2.00	a: Without ulceration
		b: With ulceration
T3	2.01 – 4.00	a: Without ulceration
		b: With ulceration
T4	> 4.00	a: Without ulceration
		b: With ulceration
N	**No. of Metastatic Nodes**	**Nodal Metastatic Burden**
N0	0	NA
N1	1	a: Micrometastasis*
		b: Macrometastasis†
N2	2 – 3	a: Micrometastasis*
		b: Macrometastasis†
		c: In transit metastases/satellites without metastatic nodes
N3	4+ metastatic nodes, or matted nodes, or in transit metastases/satellites with metastatic nodes	
M	**Site**	**Serum LDH**
M0	Mo distant metastases	NA
M1a	Distant skin, subcutaneous, or nodal metastases	Normal
M1b	Lung metastases	Normal
M1c	All other visceral metastases	Normal
	Any distant metastases	Elevated

Abbreviations: NA, not applicable; LDH, lactate dehydrogenase.
* Micrometastases are diagnosed after sentinel lymph node biopsy.
† Macrometastases are defined as clinically detectable nodal metastases confirmed pathologically.

Figure 3A. TNM staging categories for cutaneous melanoma (from ref. 26).

	Clinical Staging*				Pathologic Staging†		
	T	N	M		T	N	M
0	Tis	N0	M0	0	Tis	N0	M0
IA	T1a	N0	M0	IA	T1a	N0	M0
IB	T1b	N0	M0	IB	T1b	N0	M0
	T2a	N0	M0		T2a	N0	M0
IIA	T2b	N0	M0	IIA	T2b	N0	M0
	T3a	N0	M0		T3a	N0	M0
IIB	T3b	N0	M0	IIB	T3b	N0	M0
	T4a	N0	M0		T4a	N0	M0
IIC	T4b	N0	M0	IIC	T4b	N0	M0
III	Any T	N > N0	M0	IIIA	T1-4a	N1a	M0
					T1-4a	N2a	M0
				IIIB	T1-4b	N1a	M0
					T1-4b	N2a	M0
					T1-4a	N1b	M0
					T1-4a	N2b	M0
					T1-4a	N2c	M0
				IIIC	T1-4b	N1b	M0
					T1-4b	N2b	M0
					T1-4b	N2c	M0
					Any T	N3	M0
IV	Any T	Any N	M1	IV	Any T	Any N	M1

* Clinical staging includes microstaging of the primary melanoma and clinical/radiographic evaluation for metastases. By convention, it should be used after complete excision of the primary melanoma with clinical assessment for regional and distant metastases.

† Pathologic staging includes microstaging of the primary melanoma and pathologic information about the regional lymph nodes after partial (i.e. sentinel node biopsy) or complete lymphadenectomy. Pathologic stage 0 or stage IA patients are the exception; they do not require pathologic evaluation of their lymph nodes.

Figure 3B. Anatomic stage groupings for cutaneous melanoma (from ref. 26).

biopsy. Due to the powerful overall prognostic significance of ulceration, sentinel lymph node biopsy should be considered for all ulcerated melanomas, regardless of thickness (7). Likewise, a mitotic rate greater than 1/mm^2 is an indication for sentinel lymph node biopsy as it has been shown to be an important predictor of nodal metastasis (7, 26). Referring a patient to an appropriate surgeon for sentinel lymph node biopsy or LND is necessary after the full evaluation of the patient and its result if the pathology report of the lesion is available. To increase the reliability of the sentinel lymph node biopsy, it has been suggested that the definitive removal of the lesion should be done at the same time as the sentinel node biopsy, since extensive surgery and repair might disrupt the lymphatic drainage, making lymphoscintigraphy unreliable (2). Lastly, decision for an appropriate adjuvant therapy including systemic and/or radiation therapy will be determined in addition to the primary treatment (such as surgery) by an oncologist.

CASE REPORT

A 73-year-old female presented to the clinic with a history of a pigmented lesion in the plantar lateral aspect of the left foot of several months duration. On clinical examination, there was a 2.2 x 2 cm pigmented ulcerated lesion under the bottom of the lateral foot with irregular borders in the ulcer margins (Figure 4). A punch biopsy was taken from 2 different sites of the lesion and the histopathologic examination showed a malignant melanoma with a Breslow depth of 4.5 mm. The patient was immediately referred to a general surgeon and oncologist and a surgical wide excision of the tumor (4 cm margins) and sentinel lymph node biopsy were performed. Complete inguinal lymph node dissection was performed after the positive result of the sentinel lymph node biopsy. Fortunately, no metastasis to regional lymph nodes was found. Currently, the patient is receiving adjunctive therapy and is being closely monitored by the oncologist and general surgeon.

In conclusion, malignant melanoma is an increasingly important public health problem in the US and worldwide and its incidence continues to rise. A through history and physical examination performed by the clinician and an understanding of the risk factors associated with melanoma are crucial for making an appropriate diagnosis. A multidisciplinary approach focused on early detection and aggressive treatment may help to lower mortality from malignant melanoma.

Figure 4. Clinical appearance of the lesion.

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