REVIEW

Cutaneous Malignant Melanoma

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Skin cancer has become the most common neoplasm in the United States. With early diagnosis and appropriate management, most skin cancers have an overall 5-year survival rate of 95%. Cutaneous malignant melanoma (CMM), however, has a significantly higher morbidity and mortality, resulting in 65% of all skin cancer deaths. Although the long-term survival rate for patients with metastatic melanoma is only 5%, early detection of CMM carries an excellent prognosis, with surgical excision often being curative. Primary care physicians can play a critical role in reducing morbidity and mortality from CMM by recognizing patients at risk, encouraging the adoption of risk-reducing behaviors, and becoming adept at identifying suspicious lesions.

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CMM = cutaneous malignant melanoma; SLNB = sentinel lymph node biopsy; SPF = sun protection factor; UVR = UV irradiation

Outdoor activities have become an increasingly popular source of recreation in the United States. Unfortunately, the public has only recently recognized the dangers of prolonged skin exposure to sunlight, which include skin cancers. Skin cancer has become the most common neoplasm in the United States, with incidence reaching epidemic proportions. The American Cancer Society estimates that approximately 1 million new cases of basal cell or squamous cell carcinoma and approximately 54,200 new cases of malignant melanoma are diagnosed annually.[1] An estimated 1 in 5 Americans will develop skin cancer in their lifetime.[2] With early diagnosis and appropriate management, most skin cancers have an overall 5-year survival rate of 95%.[3] However, one type of skin cancer, cutaneous malignant melanoma (CMM), has a significantly higher morbidity and mortality. Although it is the third most common skin cancer, accounting for only 3% of all skin cancers, CMM accounts for 65% of all skin cancer deaths.[4]

Melanoma is the fifth most common cancer in men and the sixth in women in the United States.[1] From 1981 to 2002 the incidence of CMM has increased nearly 2.8-fold.[5] This increase is associated with an increased tendency to perform biopsies on pigmented lesions and has resulted in increased diagnosis of thin (<1 mm) CMM.[6] It is not entirely clear why we have failed to see a decrease in mortality with earlier detection.[7] One possible explanation is that there are certain subsets of the population, such as older men, who continue to present with thick lesions and therefore have a poor prognosis. According to one study, the median thickness of biopsy specimens of nodular melanomas did not change from 1988 to 1999 despite a 60% increase in the total number of melanomas diagnosed.[8] The incidence of melanoma in the United States is also increasing rapidly in children.[9] The annual incidence of melanoma in the United States from 1998 to 2002 was 17.2 per 100,000 population, a sharp increase from 5.7 per 100,000 population in 1973.[5,10] The projected lifetime risk of developing CMM for Americans has approached 1 in 63.[5] The annual cost of treating newly diagnosed CMM is estimated to exceed $550 million.[11]

Several likely reasons exist for the substantial increase in the incidence of melanoma, but accumulating evidence suggests that exposure to sunlight and other sources of UV irradiation (UVR) is a critical factor. Recreational exposure to UVR (including temporal patterns), exposure to sunlamps and tanning beds, sunburn history, and sunscreen use have become subjects of intense scrutiny in recent literature, as efforts to identify significant and potentially correctable risk factors continue.[12] In addition, the depletion of the earth's ozone layer may be an exacerbating factor in the worldwide increase in the incidence of melanoma as more intense UV light is permitted to reach the earth's surface.[13]

The importance of prevention and early detection of CMM cannot be overemphasized. Early detection of melanoma is crucial to long-term survival, because a direct and steep correlation exists between tumor thickness and mortality.[14] Although the long-term survival rate of patients with metastatic malignant melanoma is only 5%,[15] early disease carries an excellent prognosis, with surgical excision often being curative. Therefore, there has been considerable interest in improving public awareness of the risk factors (Table 1) and clinical manifestations of skin malignancy. Primary caregivers can play a critical role in disease management by recognizing patients at risk, encouraging

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TABLE 1. **Risk Factors for Cutaneous Malignant Melanoma**

History of melanoma or nonmelanoma skin cancer
Family history of cutaneous malignant melanoma
Atypical nevi or numerous nevi
History of severe (blistering) sunburns or intense intermittent sun exposures
Light skin, blond hair
Giant melanocytic nevus

the adoption of risk-reducing behaviors, and becoming adept at identifying lesions suggestive of melanoma.

CLINICAL CHARACTERISTICS

Melanoma is a malignant tumor derived from epidermal melanocytes and can occur in any tissue that contains these cells, including noncutaneous sites such as the oral mucosa, nasopharynx, paranasal sinuses, tracheobronchial tree, vulva, vagina, anus, urinary tract, central nervous system, and eye.[16] Fortunately, however, most melanomas arise on the skin surface and are therefore amenable to early detection.

Although clinical presentations may vary, the ABCD criteria highlight key characteristics suggestive of CMM in any atypical skin lesion: *a*symmetry, *b*order (and surface) irregularity, *c*olor variegation (especially black, red, blue, or white hues), and *d*iameter greater than 6 mm (the size of a pencil eraser).[17] Many lesions suggestive of melanoma will have some but not have all of these characteristics. For example, melanomas may be less than 6 mm in diameter, and thus it is important that even small skin lesions with atypical appearance be considered for biopsy.[18] The ABCD criteria have been expanded to ABCDE by many dermatologists to include the *e*volution of skin lesions.[19] Indeed, any change in a preexisting nevus, such as growth, pigmentary changes, pain, bleeding, or ulceration, is an indication for biopsy. In addition, the development of any new lesion is a reason for concern.

RISK FACTORS

Melanocytic Nevi

Roughly one third of CMMs arise from preexisting nevi (including both acquired and congenital types), whereas the remainder appear to arise de novo.[20] The presence of numerous melanocytic nevi, whether normal or atypical in appearance, confers risk of the development of cutaneous melanoma (Figure 1). The total number of moles on all body surfaces has been determined to be a critical risk factor for melanoma, conferring a relative risk of 7.6 for individuals with more than 100 moles compared with those with 10 or fewer moles.[21] However, it appears that the probability of malignant degeneration is proportional to the total surface area of melanocytic nevi rather than sheer number. This concept is exemplified by the rare giant congenital nevus, or bathing trunk nevus, which has a significantly increased risk of malignant degeneration.[22] Fortunately, most congenital nevi are small (<1.5 cm) and singular and pose substantially less threat.[23]

Inherited Factors

Some risk factors for CMM are clearly inherited. A family history of CMM can be documented in 6% to 12% of new cases.[23] Physicians should also be aware of the familial dysplastic nevus syndrome (or B-K mole syndrome), a disorder characterized by the development of numerous atypical nevi. Members of affected families share a 50% cumulative lifetime risk of developing a cutaneous melanoma.[24]

Phenotypic Characteristics

Regardless of family history, certain phenotypic characteristics are known to be predisposing factors for CMM. Light hair, skin, and eyes, especially when associated with Central or Northern European ancestry, are examples. These qualities, which are often associated with the inability to tan and the tendency to freckle or develop moles, underscore the importance of UVR in the development of cutaneous neoplasm.[25-27]

UVR Exposure

UV light appears to play a role in the etiology of malignant melanoma by harming the skin through DNA damage. Nowhere is this more clearly demonstrated than in patients with xeroderma pigmentosa, in whom the normal DNA

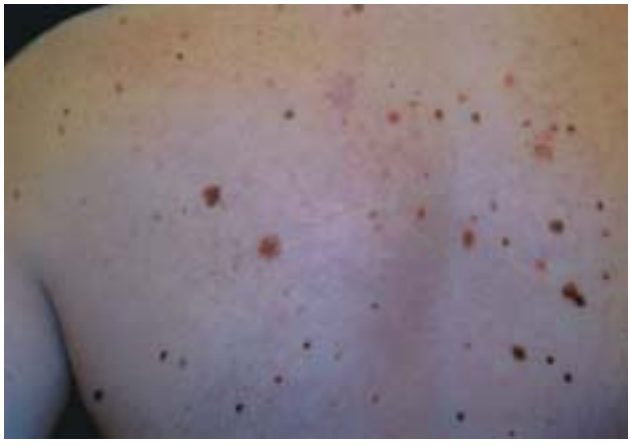

FIGURE 1. The presence of melanocytic nevi confers higher risk of the development of cutaneous melanoma. This adolescent boy had multiple variably pigmented and irregularly shaped acquired nevi on his upper back, chest, and face. From DermAtlas at: www.dermatlas.org, with permission.

repair machinery is faulty. Exposure to sunlight in these individuals leads to a high incidence of CMM and other cutaneous neoplasms.[28]

Furthermore, epidemiological evidence strongly supports the linkage between UVR exposure and development of cutaneous melanoma. Frequent sunburns, particularly in childhood[25,29,30] but also after the age of 19 years,[31] have been demonstrated to increase the risk of CMM.[32,33] Moreover, it is becoming clear that certain patterns of sun exposure are associated with different risks. For example, patients with long-term exposure to sunlight, such as farmers, show increased incidence of nonmelanoma skin cancer, such as basal cell and squamous cell carcinomas.[3] Meanwhile, for reasons yet to be elucidated, malignant melanoma risk is associated with intense intermittent episodes of sun exposure, especially those resulting in sunburns, such as resort sunbathing and exposure during hot, midday hours.[3,29,30,33,34] As a result, the increasingly popular use of sunlamps and tanning beds has come under scrutiny. Several states, including New York, Minnesota, Illinois, and Georgia, have introduced bills in 2005 proposing limitations on parlor tanning for those younger than 18 years. Although some studies have found no link between sunlamp and tanning bed use and CMM,[25,30] other studies have demonstrated an association, especially when exposure has resulted in sunburn.[35,36]

The type of UVR responsible for the induction of cutaneous neoplasms was originally believed to be primarily, if not exclusively, UV-B, which has long been known to induce both benign and malignant skin lesions in experimental animals through direct damage to genetic material. In recent years, however, it has become increasingly clear that exposure to UV-A, which was previously considered safer, may contribute to the development of CMM as well.[37] Indeed, UV-A can cause sunburn in humans and has been shown to induce epidermal tumors[38] and CMM in animal models.[39] In 1992, UV-A was reclassified as a 2A carcinogenic agent by the International Agency for Research on Cancer,[40] which may have important implications for people using tanning equipment. Tanning beds, which formerly emitted UV-B radiation, were modified in the early 1980s to emit primarily UV-A in an effort to reduce the risk of sunburns and benign and malignant skin lesions. Whether or not exposure to artificial tanning equipment will continue to confer risk of CMM is controversial. Although one study found no association between CMM and use of sunbeds after 1980, the authors point out that this may reflect the long latent period between UVR exposure and development of symptomatic disease.[35] Another study demonstrated a relatively high risk of developing CMM in patients younger than 30 years who had a history of more than 10 sunbed exposures per year, which presumably involved tanning equipment designed after 1980.[41] The authors of both studies advocate a prudent approach to tanning equipment until the relative risks are better defined.

SUN PROTECTION

The use of sunscreen products has long been advocated as an important strategy for reducing the risk of developing skin cancer. Since the introduction of para-aminobenzoic acid–based sunscreens in the 1920s, topical UV-absorbing products have been widely used for the prevention of sunburn and almost universally accepted as protection against the development of sun-associated neoplasms. Some evidence exists to support this. Sunscreen products certainly prevent sunburn,[42,43] and regular use can retard the development of age-associated skin changes.[38,44-47] Moreover, in several animal and in vitro models, sunscreens have been shown to protect against UV-induced tumor initiation and promotion.[47-49] Interestingly, however, scientific and epidemiological evidence that regular use of sunscreens can prevent the development of CMM is lacking.[50] Although CMM has been associated with sunburns, no consistent evidence exists that prevention of sunburn in the context of ongoing sun exposure confers protection against the development of CMM. Indeed, several countries, including the United States and Australia, in which sunscreen use was adopted readily and early, have shown paradoxical increases in the incidence of CMM despite sunscreen use.[51,52] Several studies have even suggested that the use of sunscreen itself is paradoxically associated with an increased risk of melanoma.[53-55]

These findings have raised concerns that rather than conferring protection against UV-induced CMM, sunscreen use may promote the development of CMM by delaying sunburn and encouraging prolonged sun exposure.[54,56] In a double-blind, randomized trial, 2 groups of vacationers assigned either sun protection factor (SPF) 30 or SPF 10 sunscreen were compared. Although the study was limited by a small sample size and an inability to ethically include a control group, a provocative finding was a greater mean daily and cumulative sun exposure in the group wearing SPF 30 sunscreen.[57] Furthermore, Stokes and Diffey[58] demonstrated that sunscreen users routinely apply less than the recommended amount of 2 mg/cm^2, achieving a mean of only 20% to 50% of the sun protection expected from the product's SPF. Coupled with increased exposure time, this observation may partially explain the findings of increased CMM in sunscreen users.

Several other possible explanations for these findings exist. First, most of these studies did not control for skin phenotype. A confounding variable may be fair-skinned

individuals who, as a result of their increased propensity to sunburn, are more likely to wear sunscreen regularly. These individuals are at a higher risk of developing cutaneous neoplasm because of their skin type. Furthermore, until 1989, most chemical sunscreens absorbed UV-B exclusively. The more recently recognized role of UV-A in UV photocarcinogenesis has led to the development of UV-A–absorbing products, which may enhance the protective effects of sunscreens. However, most products still block only a fraction of the UV-A spectrum[59] and may not block the deeply penetrating UV-A photons as effectively. A study by Wolf et al[50] showed that a combination UV-A/UV-B–absorbing sunscreen did not prevent the formation of CMM outgrowths in a mouse transplantation model, although it prevented sunburn. Alternatively, Garland et al[56] and Marks et al[60] have suggested that sunscreens might increase the risk of CMM by preventing the UVR-induced synthesis of vitamin D, which has been shown to suppress melanoma growth in vitro; however, no evidence exists of cutaneous vitamin D deficiency in sunscreen users.

Patients should be advised that the most effective methods of sun protection include sun avoidance (especially during peak hours from approximately 10 AM to 2 PM), use of shade, and use of sun-protective clothing such as hats and shirts. Although sunscreen with an SPF of 15 or greater is recommended, it has not been proved to be as effective as sun avoidance.

PATIENT SELF-SCREENING

Patients should be educated regarding the ABCDE's of melanoma and encouraged to check their skin on a monthly basis for any new or changing moles, because this practice is associated with detection of thinner melanomas.[61] Examination by a spouse greatly increases detection, particularly for male patients, and thus should be encouraged.[62] Although it is common for younger patients to develop new moles,[63] patients older than 40 years should have such lesions examined by a dermatologist. Additionally any patient with risk factors such as previous skin cancer, family history of melanoma, or a large number of moles should be followed up by a dermatologist for complete skin examinations.[64]

TYPES OF CMM

Four major types of CMM are currently recognized. Superficial spreading melanoma, which accounts for 70% of CMM,[65] arises in a preexisting dysplastic nevus more often than any other type.[20] It has a radial growth phase during which the lesion is confined to the epidermis and increases in diameter. This phase precedes a vertical growth phase in which the lesion extends downward into the dermis and exhibits increased metastatic potential. This type of melanoma affects men and women equally and most commonly appears on the trunk in men and the lower extremities in women. Most often diagnosed in the fourth and fifth decades, superficial spreading melanoma often evolves during a period of 1 to 7 years with varying shades of pigmentation[23] (Figures 2 and 3).

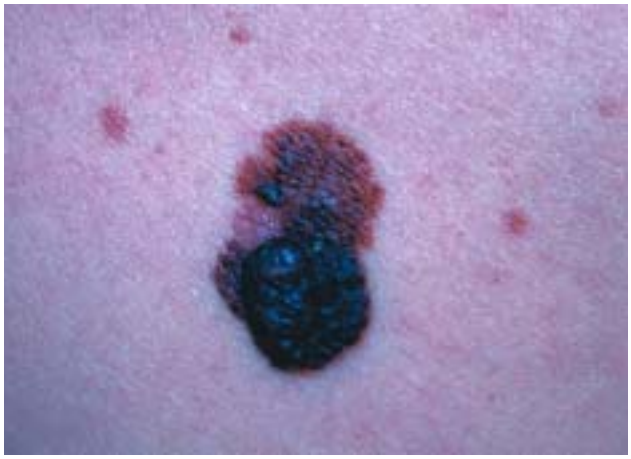

FIGURE 2. Superficial spreading melanoma: a 3-cm, brown plaque with variable pigmentation and a 1.5-cm, dark brown nodule arising from the inferior half of the lesion. From DermAtlas at: www.dermatlas.org, with permission.

Nodular melanoma, which accounts for 15% to 30% of CMM, is the most aggressive type of CMM, affecting predominantly men in their fifth decade of life.[65] Unlike superficial spreading melanoma, it often arises de novo, although it can also occur at the site of a preexisting nevus.

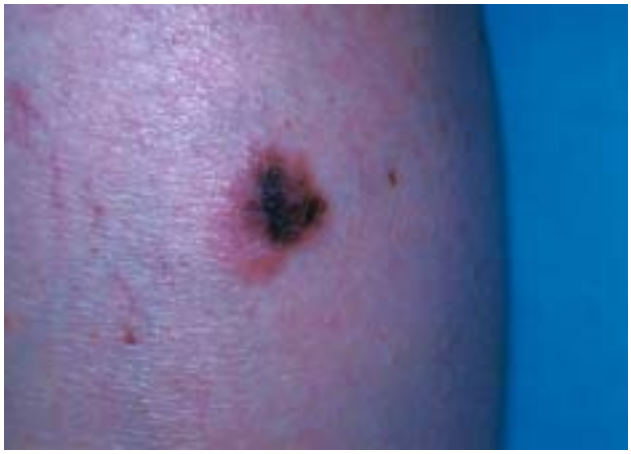

FIGURE 3. Superficial spreading melanoma: a 45-year-old woman noted darkening of a pigmented lesion on the left leg. The lesion was a 1-cm, irregular, brown plaque with a pinkish brown border. From DermAtlas at: www.dermatlas.org, with permission.

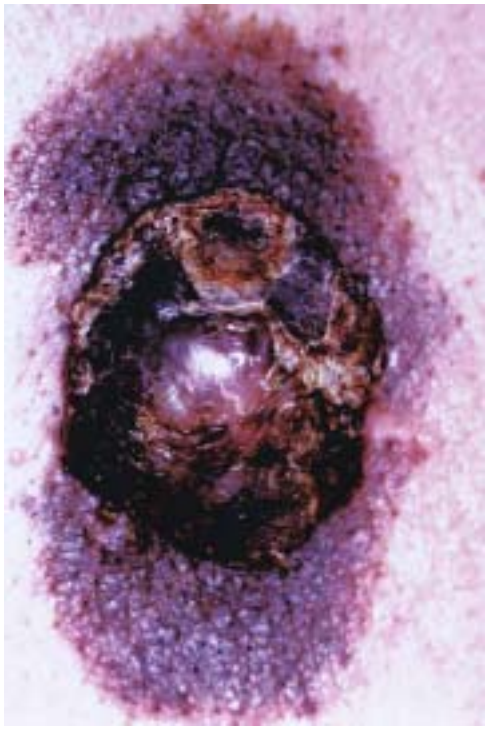

FIGURE 4. Nodular melanoma: round nodule on an oval, 3- by 5-cm, black patch. Ulceration and crusting are evident. From DermAtlas at: www.dermatlas.org, with permission.

Nodular melanoma lacks a significant radial growth phase and thus may have a small diameter. Since it has a predominantly vertical growth phase, nodular melanoma has a tendency toward greater depth of invasion and is associated with a worse prognosis than any other type. It tends to meet fewer ABCD criteria, and thus it may also be more difficult to recognize.[66] The lesion characteristically appears as a smooth, shiny, dome-shaped nodule of uniformly dark black or blue color and has a history of rapid growth[23] (Figure 4).

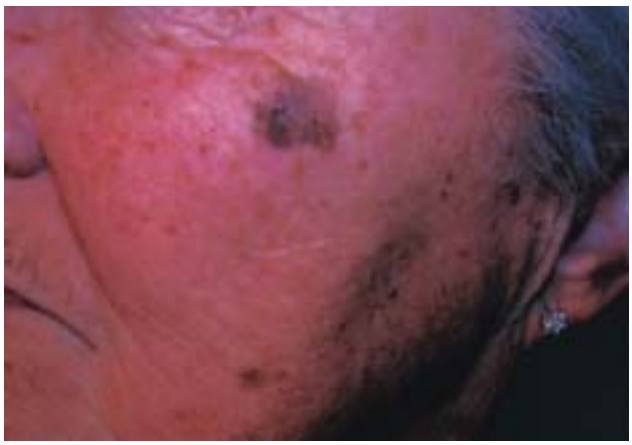

FIGURE 5. This elderly woman had a 5-year history of a slowly expanding pigmented patch with scalloped borders on the left cheek. A skin biopsy specimen showed lentigo maligna melanoma. From DermAtlas at: www.dermatlas.org, with permission.

Lentigo maligna melanoma, also known as melanoma in situ that occurs on extremely sun-damaged skin, is both the least aggressive and the least common type of CMM, accounting for less than 5% of CMM.[23] It primarily affects women in their seventh decade of life, arising almost exclusively on sun-damaged regions of the skin, such as the head, neck, and the dorsum of hands. Its benign precursor lesion, the lentigo maligna or Hutchinson freckle, is a large, tan macule that grows slowly for 3 to 15 years in a radial fashion, most often reaching 3 to 6 cm.[23] Lentigo maligna can be difficult to distinguish clinically from a solar lentigo, but areas of fine reticulate black pigmentation may be an early sign of evolving lentigo maligna. It is estimated that less than 5% of lentigo maligna will eventually display a component of vertical growth, thereby signaling the transition to lentigo maligna melanoma (Figure 5).

The acral lentiginous variety, although accounting for less than 5% of all CMM, accounts for 35% to 65% of CMM diagnosed in darkly pigmented individuals (African Americans, Asians, and Hispanics). It arises primarily on the palms, soles, nailbeds, and occasionally the mucous membranes, with the soles being the most common site.[23] The initial macular component on the palms and soles may be masked by thickened stratum corneum, and swabbing with alcohol may help delineate the lesion. Although darkened pigmentation of the fingernails or periungual region is often a normal finding, especially in African Americans, its presence should raise the possibility of acral-lentiginous melanoma (Figure 6). Features of linear nail pigmentation that should raise concern include pigment variegation, an irregular edge, or a single band greater than 3 mm in width. Not all melanomas fit neatly into this categorization. For example, 2% to 8% of melanomas are reportedly amelanotic (contain no pigment).[67] These melanomas often go clinically undiagnosed for long periods because of their uncharacteristic appearance. Desmoplastic melanoma is a rare melanoma variant with a firm texture that often is amelanotic and clinically may be mistaken for a scar. Compared with other melanomas, the desmoplastic variant is often deeper and demonstrates a greater frequency of local recurrence and a proclivity for tracking along nerves but is less likely to spread to lymph nodes.[68]

The course of progression from cutaneous lesions to metastasis varies with melanoma type. Nodular melanomas, with an early vertical growth phase, have the greatest tendency to metastasize early. More indolent types can be present for up to 15 years without distant spread. The protracted course that many CMMs exhibit underscores the

importance of early detection during a time when these malignancies are curable by surgical excision.

CLASSIFICATION

In 2000, the American Joint Commission on Cancer established an updated TNM staging system for CMM.[14,69,70] This system incorporates depth of tumor (absolute thickness in millimeters), ulceration, and metastases to lymph nodes, distant skin, and other organs. In this new staging system, ulceration upstages the lesion and worsens prognosis. The staging system also distinguishes between micrometastases and macrometastases. Macrometastases are clinically evident lymph node metastases, which are confirmed histologically, and these carry a worse prognosis than micrometastases, which are not clinically evident but are diagnosed with sentinel lymph node biopsy (SLNB) or elective lymph node biopsy.[71] The total number of positive lymph nodes continues to be a consideration, and patients with more than 3 positive lymph nodes are assigned a more advanced stage than those with fewer positive lymph nodes. Most patients diagnosed as having CMM (>80%) present with localized disease and are in American Joint Commission on Cancer stages I or II.

TREATMENT

Therapeutic options for cutaneous melanoma are determined by stage of disease at the time of presentation. Surgical excision is the only curative treatment and is the primary treatment of early (localized) disease. Melanoma in situ, wherein the tumor is limited to the epidermis, is excised with 5-mm borders. Invasive melanoma that extends into the dermis or deeper is excised with margins of 1 to 2 cm, determined by tumor thickness.[72] Success rates are high for thin tumors (<1.5 mm), approaching 90% survival at 5 years.[73] For thick or ulcerated tumors, which demonstrate an increased risk of metastatic disease, prognosis is less encouraging.

Often SLNB is performed for staging of disease, but it remains controversial because evidence does not support a therapeutic benefit. If sentinel lymph nodes are positive, a complete lymph node dissection is typically performed. The SLNB procedure has been proved to provide prognostic value and to accurately identify micrometastases.[74,75] A current multicenter trial with 2000 patients has shown that false-negative SLNB results are low as measured by nodal recurrence in a tumor-negative dissected sentinel node basin.[76] However, in thin melanomas (<1 mm), positive lymph nodes are rare, and SLNB is probably not warranted.[77] For thicker melanomas, performing a SLNB provides the patient with a reliable estimate of prognosis and may also help to risk stratify patients who are entered into adjuvant therapy trials.[78] However, data do not suggest that a survival benefit is associated with SLNB.[79,80] Moreover, currently no effective adjuvant therapies exist that could benefit sentinel node–positive patients.[80] Multicenter studies are currently in progress to further evaluate the effect of SLNB on morbidity and mortality.[76,78]

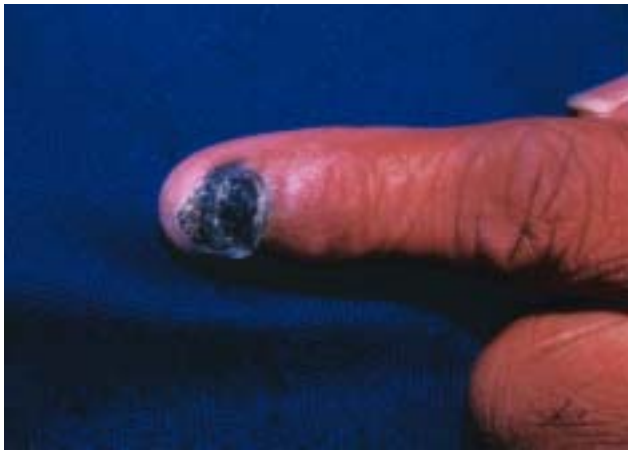

FIGURE 6. Acral lentiginous melanoma: black discoloration of the nailbed with spread of pigment into the cuticle and periungual skin. From DermAtlas at: www.dermatlas.org, with permission.

Chemotherapy and radiation therapy are of limited efficacy. The only adjuvant therapy shown to increase relapse-free survival in patients with thick lesions is interferon alfa 2, although it is not clear that it increases total survival and toxic effects are significant.[78,81] Distant metastatic melanoma (stage IV disease) carries a dismal prognosis, with a median survival of 6 to 8 months after diagnosis.[15] Treatment goals are primarily palliative and may include dacarbazine, the only chemotherapeutic agent approved for therapy of advanced melanoma.[81] The well-known antigenic properties of malignant melanoma have led to interest in the development of tumor vaccines, and other promising forms of immunotherapy are currently being investigated.

Finally, patients diagnosed as having CMM are at increased risk of a second primary melanoma and, therefore, will need lifelong dermatologic follow-up. Such follow-up includes complete physical examinations every 3 to 12 months, with more frequent visits for patients with multiple primary melanomas, multiple atypical nevi, and a family history of melanoma.[81,82] Patients should perform monthly self-examinations of the skin and avoid sun exposure.

CONCLUSION

The persistent increase in the incidence of CMM despite heightened public awareness of the risks of sun exposure and advancements in the early detection of the disease

raises questions about the effectiveness of current sun protective strategies. Most people accept that certain phenotypic characteristics, such as fair skin, light hair, and a tendency to burn, as well as certain patterns of exposure, in particular the intermittent high-intensity UVR exposures experienced by resort sunbathers and those who use tanning equipment, confer a higher risk of developing CMM. Less well recognized is the risk of complacency associated with the use of chemical sunscreens. UV-B– and even UV-A–absorbing sunscreens may be insufficient to prevent CMM if their antierythemogenic properties encourage prolonged sun exposure. Until the role of sunscreens is better defined, sun-safe strategies should emphasize sun avoidance, especially for individuals at risk and particularly between the hours of 10 AM and 3 PM during peak UV light exposure. Use of protective clothing and sunglasses when outdoors is recommended. Use of a sunscreen with an SPF of 15 or greater continues to be recommended by the American Cancer Society,[83] although, with insufficient clinical evidence, sole reliance on sunscreen protection should be discouraged. Finally, primary care physicians should be vigilant in the identification of skin lesions suggestive of melanoma and refer high-risk patients for prompt evaluation by a dermatologist.

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