Primary Cutaneous Malignant Melanoma

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History

A 60-yr-old male commercial pilot with more than 5000 h of flight time presented for a renewal of his first-class medical certificate in May, 2003. Because of his history of melanoma, his application was deferred to the Aerospace Medical Certification Division (AMCD). During a flight physical in February 1999, an enlarging mole on the right medial calf had been noted. According to the airman, the mole was enlarging but was not particularly suspicious. However, the lesion was biopsied and was confirmed to be a superficial spreading melanoma with a Breslow thickness of 0.92 mm and a Clark's level 3. The patient had undergone a wider skin excision at the biopsy site and sentinel node biopsies. The wider excision was cleared of any residual melanoma, and the biopsied nodes were negative for metastatic melanoma. He also underwent an adjuvant therapy with interferon. His recent CAT scans of brain, chest, abdomen, and pelvis were negative for any evidence of disease, and a brain MRI in 2003 was negative for metastasis. Presently, the applicant says he feels extremely well and has been quite active—flying and working. He denies any headaches, visual symptoms, cough, shortness of breath, chest pain or pressure, gastrointestinal or genitourinary symptoms. He has no new skin changes, nodularity, masses, or other concerns; his medical history is significant for seasonal allergy occasionally treated with loratadine, and gastroesophageal reflux treated with famotidine. His only previous surgery was a tonsillectomy. There is no family history of melanoma. He is allergic to aspirin. The airman denies alcohol and tobacco abuse and illicit drug use.

Physical Exam

The airman appeared well, alert, and oriented. Blood pressure was 130/88, pulse 70, weight 230 lbs., HEENT was unremarkable. Lungs were clear bilaterally without rales, rhonchi, or rubs. Heart had normal S1, S2 without murmurs; no S3, S4. The abdomen was benign without evidence of organomegaly, masses, or pain. The extremities were negative for edema or cyanosis. Neurologically, the patient was intact. A complete skin exam showed several areas of moles, all of which appeared to be slightly atypical but nothing of concern. There was no new suspicious lesion at the incision site on the right calf. CAT scans of brain, chest, abdomen, and pelvis, and brain MRI were all unremarkable.

Aeromedical Disposition

According to Federal Aviation Administration medical guidance, malignant melanoma warrants denial or deferral to the AMCD. **Table I** outlines the AMCD certification policy on airmen with melanoma with the use of brain MRI to rule out CNS metastasis.

Case outcome: The airman was granted Special Issuance for 1 yr. The next evaluation for melanoma with an MRI of the brain will be his last one, since he will have 5 yr of disease-free status.

Diagnosis and Prognosis

Suspected lesions must be properly biopsied for accurate diagnosis and histologic microstaging. Narrow excisional biopsy with 2 to 3 mm margins around the visible borders of the lesion and into the subcutaneous fat should be performed when possible. Wider margins (> 1-2 cm) may disrupt afferent cutaneous lymphatic flow

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MALIGNANT MELANOMA

Epidemiology

The incidence of melanoma shows substantial variations worldwide with an increased incidence of melanoma in fair skin individuals living near the equator. In the United States, it was estimated that over 53,000 adult Caucasians would develop melanoma in 2002, and 7400 people would die from metastatic disease within 2003 (4,9). The estimated lifetime risk for melanoma in Americans is currently 1 in 71 and is expected to increase to 1 in 50 by the year 2010 (9). However, the trends in mortality have been slowing (2). In one study of 10,211 Nordic airline pilots, there was a significant increase in the standardized incidence ratios ("SIRs"- ratios of observed over expected cases, based on national incidence rates) of skin cancers. In this study, the SIR for melanoma in Nordic pilots was 2.3 (95% CI 1.7-3.0) (7).

Etiology

The exact mechanism of carcinogenesis in melanocytes is not understood. Melanoma tends to occur in sites of intermittent, intense sun exposure (trunk and legs), rather than areas of cumulative sun damage (head, neck, and arms). Both ultraviolet A and B (UVA and UVB) have been implicated (9). Risk factors include:

1) changing nevus (noted by 80% of melanoma patients at time of diagnosis);
2) xeroderma pigmentosum (a condition of defective DNA repair postultraviolet exposure);
3) fair-skin phenotype;
4) excessive sun exposure;
5) familial atypical mole-melanoma (FAMM) syndrome;
6) atypical nevi;
7) prior melanoma;
8) melanoma in a first-degree relative.

It also has been documented recently in the U.S. of the increased risk of melanoma with systemic psoralin and ultraviolet A light (PUVA) therapy (9).

Clinical Presentation

Malignant melanoma (**Fig. 1**) may arise de novo or from a precursor melanotic nevus. In general, the clinical signs can be summarized as the ABCDs of melanoma:

Asymmetry (e.g., lesion is bisected and halves are not identical)
Border irregularity (uneven, ragged border)
Color variegation (presence of various shades of pigmentation)
Diameter of lesion (> 6mm)

The primary cutaneous melanomas can be further divided into four major clinical subtypes:

1. **Superficial spreading.** Accounts for 70% of all melanoma cases. Presents as a melanotic lesion with an irregular, asymmetric border; color variegation and a size from 6 to 8 mm on the upper back of both men and women and the lower extremities of women.
2. **Nodular.** Accounts for 15–30% of melanoma. Presents as a raised, dark brown to black papule or nodule. Ulceration and bleeding are common. The leg and trunk are the most common sites of involvement.
3. **Lentigo maligna.** Accounts for 4–15% of melanoma. Presents as tan or brown macule or patch with variation in pigment or areas of regression. Only 5–8% of lentigo malignas evolve into invasive melanoma. They are characterized by nodular development within the previously flat precursor.
4. **Acral lentiginous.** Accounts for 2–8% of melanoma in Caucasians and 29–72% in dark-complexioned individuals (African Americans, Asians, and Hispanics). It typically occurs on the palms, soles, or beneath the nail plate as an irregular, pigmented lesion (9).

and affect the ability to accurately identify the sentinel nodes in patients eligible for this procedure. For the same reason, orientation of the excisional biopsy should be parallel to lymphatic drainage, longitudinally on the extremities (9). In 2001, the American Joint Committee on Cancer (AJCC), after analyzing its previous staging system, revised the cutaneous melanoma staging system. The main changes were:

1) The Breslow depth is the most important prognostic factor in primary cutaneous melanoma with the new stratification cutoffs of < 1, 1.01-2, 2.01-4, and > 4 mm instead of previous cutoffs of 0.75, 1.5, and 4 mm;
2) Microscopic ulceration was found to be the next important adverse prognostic factor outside of thickness. It is classified as "a" for no ulceration and "b" for presence of ulceration (**Table II**). The presence of ulceration upstages the individuals to the next-worst prognostic level;
3) The number of regional lymph nodes involved is a more powerful predictor of survival than the extent of involvement of individual lymph nodes;
4) Sentinel lymph node status is the most important prognostic factor for recurrence and a powerful predictor for survival (1,5).

Laboratory testing and diagnostic imaging: Careful history and examination detect the majority of melanoma recurrences and direct further studies. Routine blood work and chest X-rays have limited value in follow-up of patients except for serum lactate dehydrogenase (LDH), which has been used to follow stage IV (disseminated) disease. Total body computed tomographic scans, as well as liver, brain, or bone imaging are not useful in detecting occult melanoma in asymptomatic patients. Whole-body positron emission tomography is currently being evaluated for detection of occult melanoma (6).

TABLE I. CERTIFICATION PROTOCOLS FOR MELANOMA (8).

Status	First Class, Second Class, Third Class
Breslow < 0.75 mm	Yearly Authorization for Special Issuance with status report AME-Issued Special Issuance Annual evaluation for 5 yr
Breslow > 0.75 mm	Special issuance w/ current status & brain MRI. Yearly for 1st - & 2nd-class; every 24 mo for 3rd-class Annual evaluation for 5 yr
Breslow > 0.75 mm & Local lymph node	Special issuance w/ current status & brain MRI. Yearly for 1st - & 2nd-class; every 24 mo for 3rd-class Annual evaluation for 5 yr
Metastatic (without CNS involvement)	Denial for **3** yr after treatment. Special Issuance w/current status & brain MRI every **6** mo for 5 yr (3rd-class requires MRI every 12 mo for 5 yr)
CNS metastasis	Denial for **5** yr after treatment. Special Issuance w/ current status& brain MRI every **3** mo for 5 yr. (3rd-class requires MRI every 6 mo for 5 yr) Follow-up frequency may be reduced after 5 yr. Off anticonvulsant medications for 2 yr, no history of seizures.

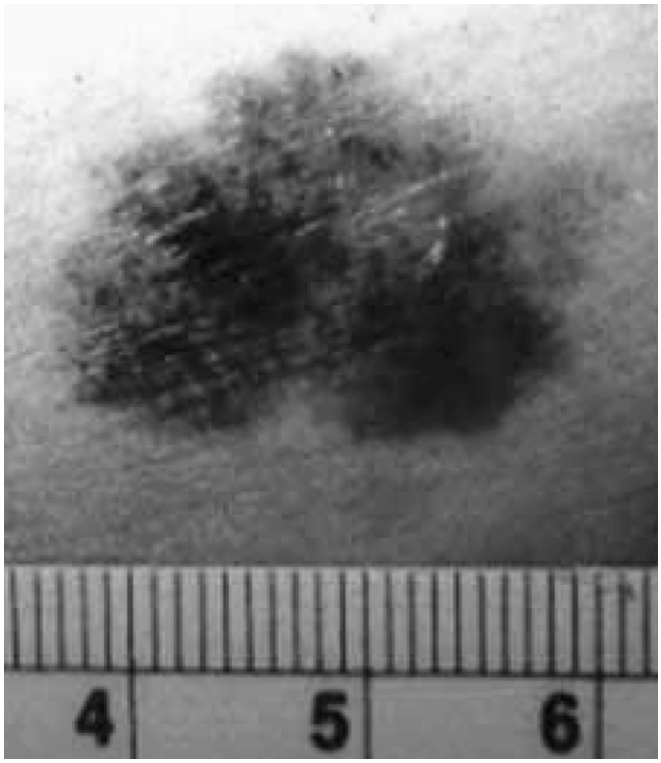

Fig. 1. Malignant melanoma. (Photo credit: James M. Grichnik MD, PhD, Duke Dermatology.)

Prevention: The best-known preventive measure is sun protection in early childhood and adolescence.

Treatment: The melanoma needs to be excised with clear margin. The World Health Organization (WHO) demonstrated that melanomas up to 2 mm in depth could safely be excised with a 1-cm margin with no detriment to patient survival (5). Lymph node dissection is recommended in all patients with enlarged lymph nodes. Elective lymph node dissection is still controversial. However, it is indicated with positive sentinel node. It may be considered in those with a primary melanoma that is between 1 and 4 mm thick (especially in patients $<$ 60 yr old). Adjuvant therapy with interferon alfa-2b (intron A) is considered controversial in patients with metastatic melanoma. It is approved by the FDA for AJCC stages IIb and III melanoma (3).

TABLE II. MELANOMA THICKNESS AND 5-YR SURVIVAL (1).

Thickness (mm)	5-Yr Survival (%) Without Ulceration	5-Yr Survival (%) With Ulceration
<1.0	90.9	95.3
1.01-2.0	77.40	89.0
2.01-4.0	63.0	78.7
>4.0	45.1	67.4

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