MELANOMA

Background

1. Definition:
   - Neoplasm originating from melanocytes (pigment producing cells) in skin, eyes, ears, leptomeninges, GI tract, oral and genital mucous membranes[1]
2. General Information:
   - Physical examination best source for early recognition
   - Suspected lesions should be carefully evaluated
   - Often overlooked due to time constraints during physical examination

Pathophysiology

1. Pathology of Disease:
   - Neoplastic transformation of melanocytes
   - 70% of cases believed to arrive de novo[1]
   - May develop from preexisting nevi of common, congenital, and atypical/dysplastic types[1]
   - Growth vertical and horizontal
   - May not be pigmented; amelanotic lesions diagnostically challenging and lethal if overlooked[2]
2. Incidence, Prevalence:
   - Estimated 40,010 New Cases in Men, 30,220 for Women[3]
   - Incidence lower among people of Maori, Pacific, and Asian ethnicities when compared to All European Populations[4]
3. Risk Factors[1]:
   - Intermittent, intense sun exposure with more occurrences increasing risk. Repeat exposure at younger age increases risk only because of the increased number of exposures
   - Genetic background
   - History of Sunburn and Blistering
   - History of atypical/dysplastic nevi
   - Family history of melanoma
4. Morbidity / Mortality[1]:
   - Melanoma is sixth leading cause of cancer
   - Accounts for 4% of skin cancers
   - Responsible for 73% of skin cancer deaths

Diagnostics

1. History:
   - New pigmented lesions
   - Change in color and size of chronic lesions
2. Physical Examination
   - Requires examination of entire body and lymph nodes with special attention to sun exposed areas
   - Itching, Bleeding, Ulceration

- Types of melanoma[2]:
  - **Superficial spreading** (70-80%)
    - Pigmented nevus that changes slowly over months to years Symmetrical, beads easily; may be amelanotic
    - Flat/ brown lesions-> discolored red, blue, change shape
    - Trunk (male); LE (female)
  - **Nodular Melanoma** (10-15%)
    - Dark brown/black papule/nodule, usually non-tender, round, hard, 1-2 cm (no prior lesion)
    - Symmetrical, beads easily; may be amelanotic
    - Legs, trunk; rapidly grow weeks/month
    - Aggressive vertical grow
  - **Lentigo Maligna Melanoma**(5-10%)
    - "Hutchinson Freckle" is precursor lesion medically known as Lentigo Maligna
    - >3cm flat tan/black macules or stains
    - May have hypopigmented areas
    - Sun exposed areas
  - **Acral Lentigenous** (7% Caucasians, 35-50% Dark Skinned)
    - Flat tan/brown stains, palms, hands, toes
    - Nails-discoloration, pigmented bands
    - Extremely aggressive
  - **Amelanotic Melanoma** (2%)

- Mnemonic: ABCDE[2]
  - **A**symmetry:
  - **B**orders: irregular nature
  - **C**olor: changes red, brown, white, blue
  - **Di**ameter: size greater than 6 mm
  - **E**volution: changes of lesion over time

3. Diagnostic Testing and Imaging
   - Biopsy
     - Full Thickness
     - Excisional
   - CXR
     - Staging for Stages I & II Disease
   - CT, MRI, Bone Scan
     - Staging > Stage II Disease
   - Baseline Labs
     - CBC, electrolytes, BUN/Cr, LDH, liver function tests
   - Serum S-100 Protein
4. Clinical Staging[7]
   - May be useful for estimating survival and possible treatment modalities
   - Stage 1A
     - Lesions ≤1mm thickness,
     - No ulceration or metastasis
     - 95% 5-Year Survival

- Stage 1B
  - Lesions ≤1mm thickness, with ulceration , but without lymph node involvement
  - Lesions between 1.01-2mm in thickness without ulceration or lymph node involvement
  - 91% 5-Year Survival
- Stage 2A
  - Lesions ≥1mm but ≤2 mm in thickness, with evidence of ulceration but no evidence of lymph node involvement
  - Lesions 2.01-4.0mm thickness without ulceration or lymph node involvement
  - 77-79% 5-Year Survival
- Stage 2B
  - Lesions 2.01-4.0mm thickness with ulceration but no lymph node involvement
  - Lesions ≥4.0mm without ulceration or lymph node involvement
  - 63-67% 5-Year Survival
- Stage 2C
  - Lesions ≥4.0mm with ulceration but no lymph node involvement
  - 45% 5-Year Survival
- Stage 3A
  - Patients with any depth of lesion with no ulceration and 1 positive lymph node (micrometastasis)
    - 70% 5-Year Survival
  - Patients with any depth of lesion with no ulceration and 2-3 positive lymph nodes (micrometastasis)
    - 63% 5-Year Survival
- Stage 3B
  - Patients with any depth of lesion with positive ulceration and 1 positive lymph node or 2-3 nodes positive (micrometastasis)
    - 50-53% 5-Year Survival
  - Patients with any depth of lesion with no ulceration and 1 lymph node positive or 2-3 positive lymph nodes (micrometastasis)
    - 46-59% 5-Year Survival
- Stage 3C
  - Patients with any depth of lesion with positive ulceration and 1 positive lymph node or 2-3 nodes positive (micrometastasis) or ≥4 positive metastatic lymph nodes, matted lymph nodes, or in-transit met(s)/satellite(s)
    - 24-29% 5-Year Survival
- Stage 4
  - Melanoma metastatic to skin, subcutaneous tissue, or lymph nodes with normal LDH level (M1a)
    - 19% 5-Year Survival
  - Melanoma metastatic to lungs with normal LDH (M1b)
    - 7% 5-Year Survival
  - Melanoma metastatic all to other visceral organs with normal LDH or any distant metastasis with elevated LDH (M1c)
    - 10% 5-Year Survival

Differential Diagnosis

1. Pigmented Actinic Keratosis
2. Dysplastic Nevus (Atypical Mole)
3. Basal Cell Carcinoma
4. Squamous Cell Carcinoma
5. Benign Nevus
6. Seborrheic Keratosis
7. Hemangioma
8. Solar Lentigo
9. Dermatofibroma
10. Traumatized Nevi of Skin Tag
11. Venous anomaly
12. Bowen's Disease

Therapeutics

1. Consultants as indicated
    - Dermatologist
    - Plastic Surgeon
    - Oncologist
    - Therapeutic Radiologist
2. Procedures
    - Excisional biopsy of lesions with wide margins preferred[2]
    - Local excision of malignant lesion
        - Recommended margins[7]
            - 5 mm margin for melanoma in situ
            - 1 cm margin for melanoma ≤ 2 mm thick
            - 2 cm margin for melanoma >2 mm thick
    - Prophylactic lymph node resection
        - Controversial
        - May be associated with improved survival in some patients
            - Patients <61 years old with melanoma 1-4mm
            - Patients <65 years old with melanoma at least 1.5mm
    - Sentinel lymph node biopsy
    - Lymph node dissection
3. Systemic Therapy
    - Chemotherapeutic agents
        - Include Dacarbazine, Cisplatin, Vinblastine,
            - Agents have not shown significant efficacy for metastatic cutaneous melanoma
    - Immunotherapeutic agents[6]
        - Interferon Alpha 2b (Intron A)
            - Inconsistent results
        - Peginterferon Alfa 2b (Sylatron)
            - Approved in March 2011 as adjuvant therapy following definitive surgical resection and complete lymphadenectomy
            - First adjuvant melanoma therapy approved by FDA in 15 years
        - Ipilimumab (Yervoy)
            - First new agent approved for melanoma in a decade

        - Remarkable promise in patients with metastatic melanoma
        - Approved by FDA in March 2011 for unresectable or metastatic melanoma
    - Interleukin 2 (Proleukin)
        - Only therapy known to cure advanced stage melanoma
    - Vemurafenib
        - Showed improved survival compared with Dacarbazine IV in patients with untreated metastatic melanoma and BRAF V600E mutation
- Vaccines
    - Gene Therapy still under evaluation.

Follow-Up

1. Based on staging of primary lesion[8]
    - Repeat visits scheduled by specialist handling either surgical removal or chemotherapeutics
    - Thinner lesions (<1 mm) require less follow-up
    - Follow up may be for months to years depending on the number of lesions and risk of recurrence
2. Must assess risk of recurrent lesions
    - Based on UV exposure
    - Based on patient health habits using sunscreen
    - Family history and ethnic background[2]
    - Patients with Confirmed lesions need skin exams every 6 months to one year for the rest of their life

Prognosis

1. Depends on stage
2. African Americans
    - Often have delayed diagnosis
3. More favorable
    - Females
    - Younger Patients
4. Amelanotic Melanoma
    - Often is missed or diagnosed in later stages

Prevention

1. Screening^[5]
    - Insufficient evidence to recommend for or against whole body skin exams by primary care physicians for early detection[5]
    - Insufficient evidence to support self examination for early detection of cutaneous melanoma, basal cell cancer, or squamous cell skin cancer in adults
    - Patients with suspicious lesions and intense sun exposure should be screened ^[5]
    - Fair skinned men and women age >65 with atypical moles and those with >50 moles constitute known groups at substantially increased risk of melanoma^[5]

2. Prevention[6]
    - Repeat intermittent intense sun exposure is a greater risk for melanoma than chronic sun exposure
    - Sunscreen blocking UV-A and UV-B light may have more effect than those only blocking UV-B
    - Sunscreen Studies have been inconclusive due to difficult standardization
    - Use of tanning beds and sun lamps increasing risk for melanoma? Data is unclear due to limited study designs and conflicting results from retrospective studies

Patient Education

1. Patient Education
    - Patients need to be educated on UV ray types
    - Risk Factor Education
        - Risk factors for exposure
        - Risk factors for recurrence
    - Prevention of Disease
        - Includes Proper Sunscreen application
        - Clothing
        - Reporting suspicious lesions to their primary care provider

References

1. Swetter, SM. Cutaneous Melanoma. Medscape Reference, 9 June 2011
2. Lane JE, Dalton RR, Sangueza OP. Cutaneous Melanoma: Detecting it earlier, weighing management options. Journal of Family Practice. Jan 2007;56 (1):18-28
3. Siegal R, Ward E, Brawly O, Ahmedin J. CA: A Cancer Journal for Clinicians. 2011;61:212-236
4. What Genetic or ethnic factors increase the risk of melanoma? Evidence-Based Practice. June 2011;6:1-2
5. U.S. Preventive Services Task Force. Screening for Skin Cancer. Topic Page. February 2009. http://www.uspreventiveservicestaskforce.org/uspstf/uspsskca.htm
6. Clancy CM, Tuckson RV, Henly DE. The Guide to Clinical Preventive Services. 2006;46-48
7. Edge SB, Byrd DR, Compton CC, Fritz AG, Green FL, Trotti A, et al. *Melanoma of the skin. AJCC Cancer Staging Manual*. 7th ed. New York, NY: Springer-Verlag; 2010
8. American Cancer Society http://www.cancer.org/acs/groups/cid/documents/webcontent/003120-pdf.pdf

Author: Alina Barrett, MD; Leland Dampier, MD; Peter Rives, MD, *Savannah FMRP, GA*

Editor: Robert Marshall, MD, MPH, MISM, CMIO, *Madigan Army Medical Center, Tacoma, WA*