Dermatologic Therapy, Vol. 21, 2008, 439–446
Printed in the United States · All rights reserved

DERMATOLOGIC THERAPY
ISSN 1396-0296

Lentigo maligna

GERT J. SMALBERGER*, DANIEL MARK SIEGEL† & AMOR KHACHEMOUNE†
**Department of Pathology, and †Department of Dermatology, SUNY Downstate, Brooklyn, New York*

ABSTRACT: Lentigo maligna (LM), a melanoma *in situ*, is a fairly common melanocytic lesion that usually develops on the chronically sun-exposed skin of the head and neck of Caucasians. It occurs mostly in people older than 40 years, with an incidence rate that increases with age and peaks in the seventh and eighth decades of life. Its diagnosis and treatment remain challenging. In this article, we review the history, epidemiology, clinical presentation, histology, and treatment of LM.

KEYWORDS: lentigo maligna meloma, lentigo maligna, melanoma *in situ*, treatment

Introduction

Lentigo maligna (LM) was first described by Hutchinson (Hutchinson's melanotic freckle) (1–5) and by Dubreuilh (*lentigo malin des vieillards*) over 100 years ago (6,7). Because of the slow and progressive growth of these lesions, Hutchinson considered these lesions to be infectious, and called them "infective senile freckles."

In 1894, Dubreuilh reported four cases of "lentigo malin des vieillards," meaning "malignant lentigo of the elderly" (6).

Through the years, LM has been known by many names, including lentigo melanosis, Hutchinson's melanotic freckle, senile freckle, lentigo malin des vieillards, precancerous non-nevoid melanocytoma, and circumscribed precancerous melanosis.

Today, the term "lentigo maligna" is commonly used by clinicians and pathologist to refer to melanoma *in situ* that occurs on sun-damaged skin (8). Most authors refer to this lesion as LM when it is confined to the epidermis, and as lentigo malignant melanoma (LMM) when it invades the dermis.

Malignant melanoma (MM) has historically been classified into 4 types: superficial spreading MM, lentigo maligna/lentigo maligna melanoma, nodular melanoma, and acral lentiginous melanoma (9–11). Once LM progresses to invasive melanoma (LMM), its prognosis is similar to that of the other types of melanoma when adjusted for tumor thickness (12–19).

Some authors question the prognostic significance of the subtyping MM into the four categories mentioned above. Maize and Ackerman believe that "LM" is a mere euphemism for *in situ* melanoma (11). Others argue that the subdivision is relevant, because LM tends to be poorly circumscribed and "standard" margins of excision may prove inadequate. Some suggest that LM should be called "melanoma *in situ*, lentigo maligna type" (8).

Address correspondence and reprint requests to: Amor Khachemoune, MD, 450 Clarkson Avenue Box 46, Brooklyn, NY 11203, or email: amorkh@pol.net.

Epidemiology

In the United States, the incidence of LM is the highest in Hawaii and lowest in the northern latitudes (20). The annual incidence of LM in Australia was estimated at 1.3 : 100,000 (21). These figures may be an underestimation, because many superficial and *in situ* melanomas treated in the outpatient setting are not reported.

LMM represents between 4% to 15% of all malignant melanomas (12,22–26) and between 10% and 26% of head and neck melanomas (14–16,27).

Little et al. found that the incidence of LM appears to be increasing (22). The increase has been attributed to increased UV radiation exposure; cumulative UVR is commonly accepted as the major risk factor for the development of LM (20,22,28–30). There is an association with light

skin color (30) and a history of severe sunburn (31). Foley et al. found that in Australia, LM occurs more frequently on the driver's side of the face and neck in men, and on the passenger's side in women. A plausible explanation for this phenomenon is that, according to the Australian road traffic accident database, most Australian drivers are men, and most front seat passengers are women (32).

O'Dell et al. postulate that there is impaired immune surveillance in sun-damaged skin, and therefore, the risk of skin cancer is greater (33).

LM occurs almost exclusively in Caucasians and rarely affects Asians (34). LM occurs mostly in people older than 40 years with a mean age of 65 years (35). LM rarely develops in 20- and 30-year olds (36,37). The incidence increases with age (22) and peaks in the seventh and eighth decades of life (12). Most large series of studies claim a slight female preponderance (24,35,37).

LM has been reported in association with several conditions, including porphyria cutanea tarda (38), Werner syndrome (39), tyrosinase-positive oculocutaneous albinism (40), and xeroderma pigmentosum (41,42). Cigarette smoking does not appear to be associated with the development of LM (43).

Clinical presentation

LM usually develops on chronically sun-exposed skin of the head and neck, with a predilection for the cheek (35,44). It presents as a slowly enlarging tan-to-brown macule with ill-defined borders (FIG. 1).

It is usually not associated with precursor melanocytic nevi (45). Other sites where LM occurs include the arm, leg, and trunk.

In 2002, Kroumpouzos et al. described four cases of perioral LM that spread into the oral mucosa. All four patients experienced significant long-term morbidity, and two never achieved remission (46). A high index of suspicion is required to diagnose these lesions, and it is important to examine the oral mucosa in all patients who present with atypical pigmented perioral lesions.

Rare cases of LM extending into the conjunctiva have been reported (2,47,48). Rare examples of amelanotic LM have been reported (49–58).

Clinically, the main differential diagnosis includes solar lentigo, pigmented actinic keratosis, and seborrheic keratosis (59).

The development of a papule or a nodule or a change in color within a LM may announce dermal invasion (LMM) (60,61). The risk of LM progressing to LMM is unknown, but it has been estimated that the lifetime risk of a 45-year-old who has a LM to develop LMM is approximately 5%, and that of a 65-year-old is approximately 2% (62)(FIG. 2).

Diagnosis

An excisional biopsy is the most accurate and ideal sampling method (63,64), but because LM tends to be large and poorly defined, it can rarely be performed. A full thickness incisional biopsy or multiple punch biopsies are acceptable, but may miss invasive foci (63). Punch biopsies are quick and easy and should be done in the most suspicious

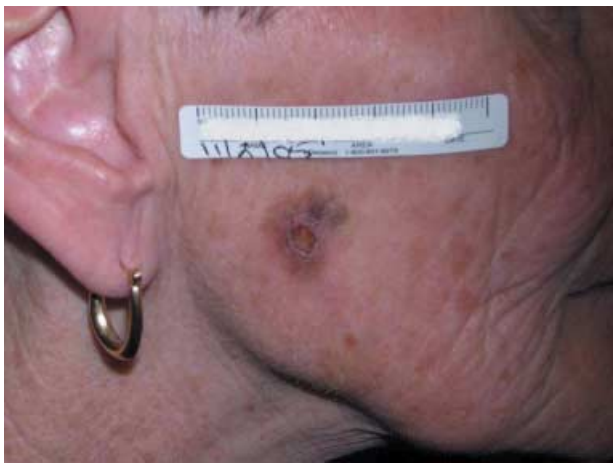

FIG. 1. A typical case of lentigo malignant on the cheek of a 73-year-old woman.

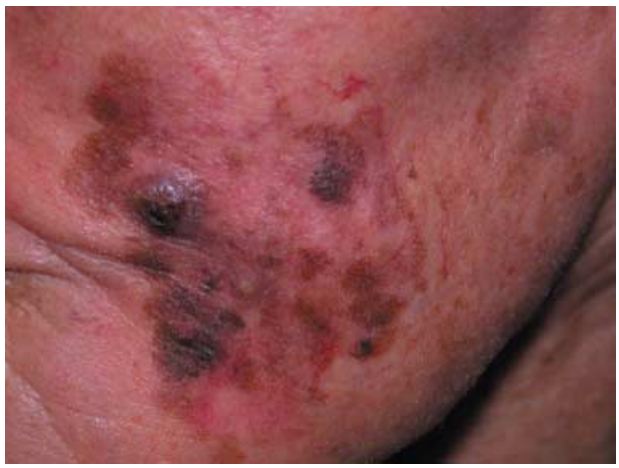

FIG. 2. Lentigo malignant melanoma: This figure shows the development of papules and nodules on a pre-existing lentigo maligna.

areas (i.e., palpable and darkly pigmented foci that may correspond with invasion) (63). A shave biopsy may compromise pathologic assessment (64), yet is frequently performed.

The biopsy should be read by a pathologist who is experienced in pigmented lesions; if the initial biopsy is inadequate to render a definite diagnosis, a rebiopsy should be considered (64).

Histopathology

Authors disagree about the histologic criteria of LM (65,66), and the histologic differential is broad (59). Some say that neither epidermal atrophy nor periadnexal extension is helpful in the diagnosis of LM (67). Others do not require solar elastosis for the diagnosis (29). However, Larsen and Grude, in a retrospective analysis of 669 cases of cutaneous melanoma, required atrophy, and solar elastosis for the diagnosis (68). Microscopically, a typical lesion shows effacement of rete ridges and confluent melanocytes along the dermal epidermal junction with adnexal extension. A lichenoid interface inflammatory infiltrate is sometimes present. The histopathologic features of LM are those of an intraepidermal (*in situ*) melanoma as described by Weyers, namely: (i) asymmetry in regard to the distribution of melanocytes, melanin, and infiltrates of lymphocytes; (ii) poor circumscription, (i.e., abnormal melanocytes disposed as solitary units present beyond the most peripheral discrete nest of melanocytes); (iii) an increased number of melanocytes arranged as solitary units within the epidermis and epithelial structures of adnexa and in some foci predominating over nests of melanocytes; (iv) a scatter of melanocytes disposed as solitary units and/or nests above the dermo-epidermal junction; and (v) nests of melanocytes that vary in size and shape, are not equidistant from one another, and tend to confluence. Signs of sun damage, namely, marked solar elastosis in the upper part of the dermis, are invariable (8).

The role of Woods light and dermoscopy/dermatoscopy. LM can extend far beyond the visual margins, which contributes to the high recurrence rate (35,69–72). Dermoscopy may be more accurate in diagnosing LM than visual inspection is (73–79). Robinson found that the visual margins were smaller than those defined by both Woods light and dermoscopy in all 26 cases reported by her (80). Because of the Woods light's ability to accentuate the differences in pigmentation, Paraskevas et al. say that the light is an "invaluable tool" to help delineate the borders of a LM (81).

Treatment options

The outcome of melanoma depends on the stage at presentation (82). LM is by definition a Stage 0 disease; it is a malignancy *in situ*. It has not ventured beyond the basement membrane into the dermis where lymphovascular invasion and subsequent metastases become possible. It is curable if completely excised. A most frustrating aspect of LM is its tendency to recur repeatedly following apparently adequate treatment (63).

Excisional surgery

When feasible, surgical excision remains the treatment of choice of LM (63,64). It offers the lowest recurrence rates (83)(FIGS. 3–5). In a review of 1351 histologically confirmed MIS cases, Zalaudek et al. found the 5-year recurrence rate for surgical excision was 6.8 ± 1.3% and 31.3 ± 8.5% for nonsurgical methods (84). Surgery is the only method that permits histologic confirmation.

Agarwal-Antal and colleagues found that the standard recommendation of 5 mm margins is adequate in less than 50% of cases of LM (85). Clinical margins greater than 5 mm may be necessary to achieve histologically negative margins for a large LM (64,85).

Mohs micrographic surgery (MMS). MMS, first described by Mohs (86) in 1941, offers intraoperative margin assessment. MMS for LM can be performed under local anesthesia (87).

MMS for LM may be performed as follows: the surgical site is prepped and draped in the usual way. The lesion, identified with the help of a Wood's light, and a 3-mm margin, is delineated. The lesion is excised. A 1-mm strip of this tissue will serve as the positive control during examination of the frozen sections of the margins. The remainder of the tissue is submitted for permanent sectioning. The first Mohs layer is now ready to be taken. Each peripheral incision should be beveled inward at approximately 45 degrees. The deep margin is cut parallel to the skin surface. Strips of 2 mm to 3 mm around the defect are excised (87,88). Care should be taken to preserve the orientation of tissue. The tissue is frozen, sectioned, and stained with hematoxylin–eosin (H&E) (+/− immunohistochemical stains). Additional layers are taken until all the margins are free of tumor. After assuring clear margins, the defect is repaired.

Large defects are often encountered, and consultation from plastic, head, and neck, or

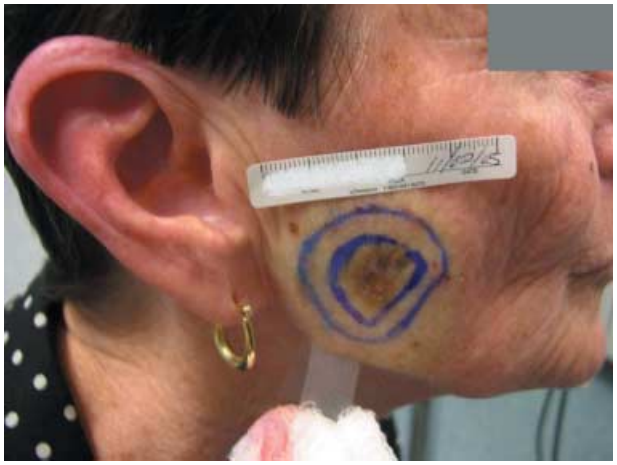

FIG. 3. The use of Woods light helped determining the margins of lentigo maligna.

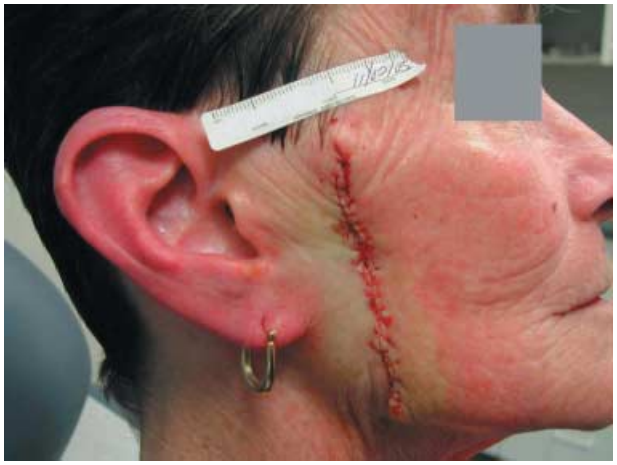

FIG. 4. Same patient in FIG. 3 – Excision of lentigo maligna and defect repair.

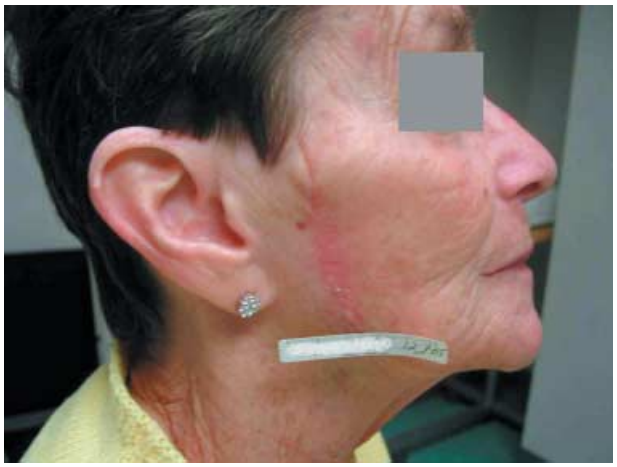

FIG. 5. One month post-surgery follow up.

oculoplastic surgeons may be needed in anticipation of reconstruction (87).

While the procedure may take several hours, MMS has the advantage that definite excision and closure can be achieved the same day. A drawback of MMS lies in the interpretation of frozen sectioned melanocytic lesions; keratinocytes may appear vacuolated (may resemble melanocytes), melanocytes may be altered during freezing, and inflammatory cells in the dermis may obscure invasive melanoma (89,90).

Two of the authors (DMS and AK) believe that MMS with light microscopy and routine stains (H&E or toluidine blue) is useful as long as one defines an endpoint at which confluent atypical-appearing melanocytes are no longer seen. In order to determine the patient's "normal" melanocyte density, a contralateral biopsy from a clinically normal-appearing skin area may be taken and the melanocyte density herein can be used as a reference. Permanent section evaluation (+/– immunostains) should be obtained on an additional thin margin to confirm the negative margin.

In addition to H&E, some recommend the use of immunohistochemistry to help identify melanocytes. A variety of immunohistochemical stains have been employed, including S-100, HMB-45, MART-1/Melan-A, and Mel-5 (87). Several authors have used MART-1/Melan-A to help identify melanocytes in frozen sections (91–96). Chronically photodamaged skin often has an increased number of melanocytes. These melanocytes will be highlighted with MART-1 and may, at the periphery of a LM, be incorrectly interpreted as LM. MART-1 cannot show if a melanocyte is malignant or not; it merely helps to identify melanocytes. Whether MART-1 will prove helpful in distinguishing MIS from melanocytic hyperplasia in sun-damaged skin remains to be seen.

Stevenson and Ahmed warn that while wide surgical excision or Mohs micrographic surgery is reported to have the highest cure rate for LM, it is often impractical because (i) of the constraints of extensive surgery in elderly patients, (ii) most lesions occur on the head and neck, (iii) of the difficulty in discerning the confines of the lesion histologically, and (iv) of the cost and time requirements (83).

Other treatment modalities

Surgery is sometimes not feasible because of potential aesthetic or functional impairment, comorbidity, or patient preference (97). The major

drawback of all non-surgical methods of treatment of LM is that the whole lesion cannot be submitted for histologic examination. Therefore, invasive malignancy may be missed, and clean margins cannot be verified (83).

A substitute to surgery should be effective to a depth of at least 3 mm to 5 mm below the skin surface to ensure treatment of periadnexal and subclinical invasive disease (97). Recurrence rates of superficially destructive modalities, such as cryosurgery, radiotherapy, electrodessication and curettage, laser surgery, topical 5-fluorouracil, and azelaic acid, vary widely (59,98).

Cryotherapy

Liquid nitrogen cryotherapy has mostly been used in the treatment of LM where surgery is technically difficult and cosmetically undesired (83). Cryotherapy is quick and easy and recommended for use in the elderly or infirm (83). While the 5-year recurrence has been reported to be as high as 34% (84), some have documented good success as long as the treatment time is sufficiently long (36,99–103). According to Gage et al. (104), cryotherapy destroys melanocytes and spares keratinocytes at –4 to –7 ºC. There are, however, no data to support that this also holds true for neoplastic melanocytes (83). There is, as yet, no standard treatment protocol for cryotherapy. Some authors (36,101) recommend a double freeze (30 to 60 s)–thaw cycle. Cryotherapy may be given with or without local anesthetic (83). Healing of cryosurgical wounds usually takes longer than excisional wounds do, and the cosmetic results may vary (59,101,105). The post-treatment area is often dyspigmented, and it may be difficult to know if the lesion was cured or if residual disease remains (63) and may necessitate a biopsy to exclude recurrence (106).

Laser therapy

A variety of lasers have been used as primary therapy for LM, but to date, no large series with long-term follow-up have been reported.

Radiation therapy

Radiation therapy is widely employed for the treatment of LM outside the USA (63). A German study, in which 42 patients with LM were primarily treated with radiotherapy, showed no recurrence (mean follow up of 23 months, median = 15 months). The cosmetic results were good to excellent in all cases (107). Longer follow up is needed, but radiotherapy may be a reasonable treatment option for LM in patients who are not suitable for surgery (63).

Azelaic acid

Treatment of LM with azelaic acid was first described by Nazzaro-Porro et al. in 1979 (108). Depending on the time needed to clear the lesion, a 15% to 20% cream is applied twice daily for 2 weeks to 12 months. Some report good to excellent results (108–113), others no response (44) while McLean described a case that progressed to LMM during treatment (114). One author (DMS) routinely places patients on topical azelaic acid 20% daily post-operatively ad infinitum and to date has had no recurrences in this patient group (personal observation, non-published data).

Immunotherapy

Recently there has been significant interest in the use of imiquimod for LM. Review of LM cases treated with imiquimod show a response rate that ranges from 66% to 100% and a mean clearance rate of 91% (97,115). A strong inflammatory reaction, characterized by weeping erosions, appears to be associated with a good response to imiquimod (115). In a case series, four of the six non-responders showed no inflammation (97). The frequency and duration of imiquimod application required to induce weeping erosions differ from patient to patient (115).

Imiquimod shows promise, but at the present, this treatment should be considered experimental due to the small number of patients studied, the uncontrolled trials, and the short follow up (97). Also, the dosing schedule, treatment periods, and the size and margins of lesions are variable or not specified. For these reasons, optimal treatment guidelines with imiquimod cannot be given (97). Invasive disease with satellite metastases during treatment with imiquimod has been reported (116).

Variable to poor results have been obtained with curettage and electrodessication (117–120). Cautery may compromise histologic interpretation and may delay healing (121).

Conclusion

LM is an *in situ* melanoma and cure should be the goal of treatment. The diagnosis and treatment of LM remain controversial. Surgical methods remain

the treatment of choice, but the standard 5 mm margin of excision may be inadequate. Other treatment modalities, including cryotherapy, laser, azelaic acid, cautery, curettage, electrodessication, radiation, laser, cryo- and immunotherapy, have been described. The challenge is to strike a balance between the risks and benefits of a given therapeutic approach. Age, health status, patient preference, and the size and location of the lesion should be taken into consideration. Knowledge of the different treatment options allows treatment to be tailored to the patient.

References

1. Hutchinson J. Notes on the cancerous process and on new growths in general. Arch Surg (London) 1890: **2**: 83–86.
2. Hutchinson J. On tissue dotage. Arch Surg (London) 1892: **3**: 315–322.
3. Hutchinson J. On cancer. Arch Surg (London) 1893: **4**: 61–63.
4. Hutchinson J. Lentigo-melanosis: a further report. Arch Surg (London) 1894: **5**: 253–256.
5. Hutchinson J. President's address at the Third International Congress of Dermatology. Arch Surg (London) 1896: **7**: 297–317.
6. Dubreuilh MW. Lentigo malin des vieillards. Ann Dermato1 Syphil (Paris) 1894: **5**: 1092–1099.
7. Dubreuilh MW. De la melanose circonscrite precanereuse. Ann Dermatol Syphil 1912: **3**: 129–151, 205–230.
8. Weyers W. Circumscribed precancerous melanosis of Dubreuilh. Dermatopathol Pract Concept 1997: **3**: 157–165.
9. Clark WH, From L, Bernadino EA, Mihm MC. The histogenesis and biologic behavior of primary malignant melanomas of the skin. Cancer Res 1969: **29**: 705–726.
10. Clark WH, Elder DE, Van Horn M. The biologic forms of malignant melanoma. Hum Pathol 1986: **17**: 443–450.
11. Maize JC, Ackerman AB. Malignant melanoma. In: Pigmented Lesions of the Skin. Philadelphia, PA: Lea & Febiger 1987, 165–224.
12. Koh HK, Michalik E, Sober AJ, et al. Lentigo maligna melanoma has no better prognosis than other types of melanoma. J Clin Oncol 1984: **2**: 994–1001.
13. Cascinelli N, van der Esch EP, Breslow A, et al. Stage I melanoma of the skin the problem of resection margins. Eur 5 Cancer 1980: **16**: 1079–1085.
14. Donnellan MJ, Seemayer T, Huvos AG, et al. Clinicopathologic study of cutaneous melanoma of the head and neck. Am J Surg 1972: **124**: 450–455.
15. Langford FPJ, Fisher SR, Molter DW, et al. Lentigo maligna melanoma of the head and neck. Laryngoscope 1993: **103**: 520–524.
16. Huvos AG, Mike V, Donnellan MJ, et al. Prognostic factors in cutaneous melanoma of the head and neck. Am J Pathol 1973: **71**: 33–45.
17. Balch CM, Murad TM, Soong S-J, et al. A multifactorial analysis of melanoma: prognostic histopathological features comparing Clark's and Breslow's staging methods. Ann Surg 1978: **188**: 732–742.
18. Drzewiecki KT, Andersen PK. Survival with malignant melanoma: a regression analysis of prognostic factors. Cancer 1982: **49**: 2414–2419.
19. Wanebo HJ, Cooper PH, Young DV, et al. Prognostic factors in head and neck melanoma. Cancer 1988: **62**: 831–837.
20. Newell GR, Sider JG, Bergfelt L, et al. Incidence of cutaneous melanoma in the United States by histology with special reference to the face. Cancer Res 1988: **48**: 5036–5041.
21. Holman CDJ, Mtioney CD, Armstrong BK. Epidemiology of pre-invasive and invasive malignant melanoma in Western Australia. Int J Cancer 1980: **25**: 317–323.
22. Little JH, Holt J, David N. Changing epidemiology of malignant melanoma in Queensland. Med J Aust 1980: **1**: 66–69.
23. Urist MM, Balch CM, Soong S, et al. The influence of surgical margins and prognostic factors predicting the risk of local recurrence in 3445 patients with primary cutaneous melanoma. Cancer 1985: **55**: 1398–1402.
24. McGovern VJ, Shaw HM, Milton GW, et al. Is malignant melanoma arising in a Hutchinson's melanotic freckle a separate disease entity? Histopathology 1980: **4**: 235–242.
25. Cascinelli N, Mombito A, Bufalino R, et al. Prognosis of stage I melanoma of the skin. Int J Cancer 1980: **26**: 733–739.
26. Popescu NA, Beard CM, Treaty PJ, et al. Cutaneous malignant melanoma in Rochester, Minnesota: trends in incidence and survivorship, 1950 through 1985. Mayo Clin Proc 1990: **65**: 1293–1302.
27. McGovern VJ. The classification of melanoma and its relationship with prognosis. Pathology 1970: **2**: 85–98.
28. Holman CDJ, Armstrong BK, Heenan PJ. A theory of the etiology and pathogenesis of human cutaneous malignant melanoma. J Natl Cancer Inst 1983: **71**: 651–656.
29. Holman CDJ, Armstrong BK. Cutaneous malignant melanoma and indicators of total accumulated exposure to the sun: an analysis separating histogenetic types. J Natl Cancer Inst 1984: **73**: 75–82.
30. Ellwood JM, Gallagher RP, Worth AJ, et al. Etiological differences between subtypes of cutaneous malignant melanoma: Western Canada melanoma study. J Natl Cancer Inst 1987: **78**: 37–44.
31. Holman CDJ, Armstrong BK, Heenan PJ. Relationship of cutaneous malignant melanoma to individual sunlight exposure habits. J Nat1 Cancer Inst 1986: **76**: 403–413.
32. Foley PA, Marks R, Dorevitch AP. Lentigo maligna is more common on the driver's side. Arch Dermatol 1993: **129**: 1211–1212.
33. O'Dell BL, Jessen RT, Becker LE, et al. Diminished immune response in sun-damaged skin. Arch Dermatol 1980: **116**: 559–561.
34. Mishima Y. Melanosis circumscripta praecancerosa (Dubreuilh): a non-nevoid premelanoma distinct from junction nevus. J Invest Dermatol 1960: **34**: 361–375.
35. Cohen LM, McCall MW, Hodge SJ, et al. Successful treatment of lentigo maligna and lentigo maligna melanoma with Mohs micrographic surgery aided by rush permanent sections. Cancer 1994: **73**: 2964–2970.
36. Kuflik EG, Gage AA. Cryosurgery for lentigo maligna. J Am Acad Dermatol 1994: **31**: 75–78.
37. Wayte DM, Helwig EB. Melanotic freckle of Hutchinson. Cancer 1968: **21**: 893–911.
38. Greenwald G. Lentigo maligna associated with porphyria cutanea tarda [Letter]. Arch Dermatol 1974: **110**: 298.
39. Barnett JH, Lee FG, Rinsky MJ. Acral lentiginous melanoma and lentigo maligna occurring in Werner's syndrome. Cutis 1983: **32**: 277–283.

40. Fukuro S, Yamaguchi J, Mamada A, et al. Xeroderma pigmentosum group D patient bearing lentigo maligna without neurological symptoms. Dermatologica 1990: **181**: 129–133.
41. Stall DB, Ruschak P, Kauh Y, et al. Lentigo maligna in a woman with oculocutaneous albinism. Arch Dermatol 1981: **117**: 360–361.
42. Ertle T, Wiskermann A, Janner M. Local treatment of lentigo maligna with azelaic acid. Arch Dermatol Res 1981: **271**: 197–203.
43. Holman CDJ, Armstrong BK. Hutchinson's melanotic freckle melanoma associated with non-permanent hair dyes. Br J Cancer 1983: **48**: 599–601.
44. Pitman GH, Kopf AW, Bart RS, et al. Treatment of lentigo maligna and lentigo maligna melanoma. J Dermatol Surg Oncol 1979: **5**: 727–737.
45. Gruber SB, Barnhill RL, Stenn KS. Nevomelanocytic proliferations in association with cutaneous malignant melanoma: a multivariate analysis. J Am Acad Dermatol 1989: **21**: 773–780.
46. Kroumpouzos G, Frank EW, Albertini JG, et al. Lentigo maligna with spread onto oral mucosa. Arch Dermatol 2002: **138**: 1216–1220.
47. Cohen LM, Zax RH. Recurrent lentigo maligna invading a skin graft successfully treated with Mohs micrographic surgery. Cutis 1996: **57**: 175–178.
48. Hicks C, Liu C, Hiranandani M, Garner A, Hungerford J. Conjunctival melanoma after excision of a lentigo maligna melanoma in the ipsilateral eyelid skin. Br J Ophthalmol 1994: **78**: 317–318.
49. Steigleder G-K. Pseudo-Paget des skrotums. Dermatologica 1958: **117**: 165–172.
50. Burket JM. Amelanotic lentigo maligna. Arch Dermatol 1979: **115**: 496.
51. Su WPD, Bradley RR. Amelanotic lentigo maligna. Arch Dermatol 1980: **116**: 82–83.
52. Paver K, Stewart M, Kossard S, et al. Amelanotic lentigo maligna. Aus J Dermatol 1981: **22**: 106–108.
53. Borkovic SP, Schwartz RA. Amelanotic lentigo maligna melanoma manifesting as a dermatitislike plaque. Arch Dermatol 1983: **119**: 423–425.
54. Pechman KJ, Bailin P. Recurrent amelanotic lentigo maligna melanoma: a case report. Cleve Clin Q 1983: **50**: 173–175.
55. Pichler E, Fritsch P. Macular amelanotic melanoma in situ. Dermatologica 1988: **177**: 313–316.
56. Herman KL, Shrager JD. Amelanotic lentigo maligna melanoma: a unique case and review of the literature. Cutis 1989: **44**: 45–48.
57. Kelly RI, Cook MG, Mortimer PS. Aggressive amelanotic lentigo maligna. Br J Dermatol 1994: **131**: 562–565.
58. Kaufmann R, Nikelski K, Weber L, et al. Amelanotic lentigo maligua melanoma. J Am Acad Dermatol 1995: **32**: 33–42.
59. Cohen LM. Lentigo maligna and lentigo maligna melanoma. J Am Acad Dermatol 1995: **33**: 923–936.
60. Odom RB, James WD, Berger TG. Melanocytic nevi and neoplasms. In: Odom RB, James WD, Berger TG, eds. Andrew's Diseases of the Skin, 9th ed. Philadelphia, PA: WB Saunders Co, 2000: 869–892.
61. Langley RGB, Mihm MC, Sober AJ. Clinical presentation: melanoma. In: Sober AJ, Haluska FG, eds. Skin Cancer. London: BC Decker Inc, 2001: 49–59.
62. Weinstock MA, Sober AJ. The risk of progression of lentigo maligna to lentigo maligna melanoma. Br J Dermatol 1987: **116**: 303–310.
63. McKenna JK, Florell SR, Goldman GD, Bowen GM. Lentigo maligna/lentigo maligna melanoma: current state of diagnosis and treatment. Dermatol Surg 2006: **32**: 493–504.
64. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology: Melanoma.v.2.2008. http://www.nccn.org/professionals/physician_gls/PDF/melanoma.pdf. Accessed August 22, 2008.
65. Larsen TE, Little JH, Grell SR, et al. International pathologists congruence survey on quantitation of malignant melanoma. Pathology 1980: **12**: 245–253.
66. Green A, Little JH, Weedon D. The diagnosis of Hutchinson's melanotic freckle (lentigo maligna) in Queensland. Pathology 1983: **15**: 33–35.
67. Tersteegen A, Steigleder GK. Is the involvement of the hair follicles and of the ducts of the sweat glands or the thickness of the epidermis a help in differential diagnosis between lentigo maligna melanoma (LMM) and superficial spreading melanoma in situ (SSM)? Z Hautkr 1990: **65**: 941–942.
68. Larsen TE, Grude TH. A retrospective histological study of 669 cases of primary cutaneous malignant melanoma in clinical stage I. Acta Patho1 Microbial Stand 1979: **87**: 255–260.
69. Lewis JE. Lentigo maligna presenting as an eczematous lesion. Cutis 1987: **40**: 357–359.
70. Grande DJ, Koranda FC, Whitaker DC. Surgery of extensive, subclinical lentigo maligna. J Dermatol Surg Oncol 1982: **8**: 493–496.
71. Michaelsen C, Breuninger H, Rassner G, et al. Der subklinische anteil im randbereich der lentigo maligna und des lentigo-maligna-melanoms. Hautarzt 1990: **41**: 142–145.
72. Dhawan SS, Wolf DJ, Rabinovitz HS, et al. Lentigo maligna: the use of rush permanent sections in therapy. Arch Dermatol 1990: **126**: 928–930.
73. Bafounta ML, Beauchet A, Aegerter P, Salag P. Is dermoscopy (epiluminescence microscopy) useful for the diagnosis of melanoma? Results of a metaanalysis using techniques adapted to the evaluation of diagnostic tests. Arch Dermatol 2001: **137**: 1343–1350.
74. Binder M, Schwartz M, Winkler A, et al. Epiluminescence microscopy: a useful tool for the diagnosis of pigmented skin lesions for formally trained dermatologists. Arch Dermatol 1995: **131**: 286–291.
75. Binder M, Puespoeck-Schwarz M, Steiner A, et al. Epiluminescence microscopy of small pigmented skin lesions: short-term formal training improves the diagnostic performance of dermatologists. J Am Acad Dermatol 1997: **36**: 197–202.
76. Kittler H, Pehamberger H, Wolff K, Binder M. Diagnostic accuracy of dermoscopy. Lancet Oncol 2002: **3**: 159–165.
77. MacKie RM. An aid to the preoperative assessment of pigmented lesions of the skin. Br J Dermatol 1971: **85**: 232–238.
78. Pehamberger H, Steiner A, Wolff K. In vivo epiluminescence microscopy of pigmented skin lesions, I: pattern analysis of pigmented skin lesions. J Am Acad Dermatol 1987: **17**: 571–583.
79. Soyer HP, Argenziano G, Talamini R, Chimenti S. Is dermoscopy useful for the diagnosis of melanoma? Arch Dermatol 2001: **137**: 1361–1363.
80. Robinson JK. Use of digital epiluminescence microscopy to help define the edge of lentigo maligna. Arch Dermatol 2004: **140**: 1095–1100.
81. Paraskevas LR, Halpern AC, Marghoob AA. Utility of the Wood's light: five cases from a pigmented lesion clinic. Br J Dermatol 2005: **152**: 1039–1044.

82. Balch CM, Soong SJ, Gershenwald JE, Thompson JF, et al. Prognostic factors analysis of 17,600 melanoma patients: validation of the American Joint Committee on Cancer melanoma staging system. Cancer Melanoma Staging System. J Clin Oncol 2001: **19**: 3622–3634.
83. Stevenson O, Ahmed I. Lentigo maligna: prognosis and treatment options. Am J Clin Dermatol 2005: **6**: 151–164.
84. Zalaudek I, Horn M, Richtig E. Local recurrence in melanoma in situ: influence of sex, age, site of involvement and therapeutic modalities. Br J Dermatol 2003: **148**: 703–708.
85. Agarwal-Antal N, Bowen GM, Gerwels JW. Histologic evaluation of lentigo maligna with permanent sections: implications regarding current guidelines. J Am Acad Dermatol 2002: **47**: 743–748.
86. Mohs FE. Chemosurgery: a microscopically controlled method of cancer excision. Arch Surg 1941: **42**: 279–295.
87. Clark GS, Pappas-Politis EC, Cherpelis BS, et al. Surgical management of melanoma in situ on chronically sun-damaged skin. Cancer Control 2008: **15**: 216–224.
88. Shriner DL, McCoy DK, Goldberg DJ, et al. Mohs micrographic surgery. J Am Acad Dermatol 1998: **39**: 79–97.
89. Braun M. Unreliability of frozen sections in the histologic evaluation of malignant melanoma [Abstract]. J Dermato1 Surg Oncol 1986: **12**: 641.
90. de Berker D. Lentigo maligna and Mohs [Letter]. Arch Dermatol 1991: **127**: 421.
91. Albertini JG, Elston DM, Libow LF, et al. Mohs micrographic surgery for melanoma: a case series, a comparative study of immunostains, an informative case report, and a unique mapping technique. Dermatol Surg 2002: **28**: 656–665.
92. Zalla MJ, Lim KK, Dicaudo DJ, et al. Mohs micrographic excision of melanoma using immunostains. Dermatol Surg 2000: **26**: 771–784.
93. Hendi A, Brodland DG, Zitelli JA. Melanocytes in long-standing sunexposed skin: quantitative analysis using the MART-1 immunostain. Arch Dermatol 2006: **142**: 871–876.
94. Bricca GM, Brodland DG, Zitelli JA. Immunostaining melanoma frozen sections: the 1-hour protocol. Dermatol Surg 2004: **30**: 403–408.
95. Kelley LC, Starkus L. Immunohistochemical staining of lentigo maligna during Mohs micrographic surgery using MART-1. J Am Acad Dermatol 2002: **46**: 78–84.
96. Davis DA, Kurtz KA, Robinson RA. Ultrarapid staining for cutaneous melanoma: study and protocol. Dermatol Surg 2005: **31**: 753–756.
97. Rajpar SF, Marsden JR. Imiquimod in the treatment of lentigo maligna. Br J Dermatol 2006: **155**: 653–656.
98. Johnson TM, Headington TJ, Barker SR. Usefulness of staged excision for lentigo maligna and lentigo maligna melanoma: the "square procedure". J Am Acad Dermatol 1997: **37**: 758–764.
99. Collins P, Rogers S, Goggin M, et al. Cryotherapy of lentigo maligna. Clin Exp Dermatol 1991: **16**: 433–435.
100. Lorenz E. Cryosurgery for lentigo maligna [short communication]. Dermatol Times 1983: **4**: 29.
101. Zacarian SA. In: Cryosurgery for Skin Cancer and Cutaneous Disorders. St Louis, MO: Mosby, 1985: 199–214.
102. Bohler-Sommeregger K, Schuller-Petrovic S, Neumann R, et al. Cryosurgery for lentigo maligna. Plast Reconstr Surg 1992: **90**: 436–440.
103. Dawber RPR, Wilkinson JD. Melanotic freckle of Hutchinson: treatment of macular and nodular phases with cryotherapy. Br J Dermatol 1979: **101**: 47–49.
104. Gage AA, Meenaghan MA, Natiella JR, et al. Sensitivity of pigmented mucosa and skin to freezing injury. Cryobiology 1979: **16**: 348–361.
105. Mahendran R, Newton-Bishop JA. Survey of UK current practice in the treatment of lentigo maligna. Br J Dermatol 2001: **144**: 71–76.
106. Bohler-Sommeregger K, Schuller-Petrovic S, Knobler R, et al. Reactive lentiginous hyperpigmentation after cryosurgery for lentigo maligna. J Am Acad Dermatol 1992: **27**: 523–526.
107. Schmid-Wendtner MH, Brunner B, Konz B. Fractionated radiotherapy of lentigo maligna and lentigo maligna melanoma in 64 patients. J Am Acad Dermatol 2000: **43**: 477–482.
108. Nazzaro-Porro M, Passi S, Balus L, et al. Effect of dicarboxylic acids on lentigo maligna. J Invest Dermatol 1979: **72**: 296–305.
109. Nazzaro-Porro M, Passi S, Zina G, et al. Effect of azelaic acid on human malignant melanoma. Lancet 1980: **1**: 1109–1111.
110. Nazzaro-Porno M, Passi S, Breathnach A, et al. Ten years observations on the effect of azelaic acid on lentigo maligna [Abstract]. J Invest Dermatol 1986: **87**: 438.
111. Nazzaro-Porro M, Passi S, Zina G, et al. Ten years experience of treating lentigo maligna with topical azelaic acid. Acta Derm Venereol Suppl 1989: **143**: 49–57.
112. Breathnach AS, Nazzaro-Porro M, Passi S. Azelaic acid. Br J Dermatol 1984: **111**: 115–120.
113. Prieto MAR, Lopez PM, Gonzalez IR, et al. Treatment of lentigo maligna with azelaic acid. Int J Dermatol 1993: **32**: 363–364.
114. McLean DI, Peter KK. Apparent progression of lentigo maligna to invasive melanoma during treatment with topical azelaic acid. Br J Dermatol 1986: **114**: 685–689.
115. Buettiker UV, Yawalkar NY, Braathen LR, Hunger RE. Imiquimod treatment of lentigo maligna: an open-label study of 34 primary lesions in 32 patients. Arch Dermatol 2008: **144**: 943–945.
116. Fisher GH, Lang PG. Treatment of melanoma in situ on sun-damaged skin with topical 5% imiquimod cream complicated by the development of invasive disease. Arch Dermatol 2003: **139**: 945–947.
117. Costello MJ, Fisher SB, DeFeo CP. Melanotic freckle. Arch Dermatol 1959: **80**: 753–771.
118. Coleman WP III, Davis RS, Reed RJ, et al. Treatment of lentigo maligna and lentigo maligna melanoma. J Dermato1 Surg Oncol 1980: **6**: 476–479.
119. Klauder JV, Beerman H. Melanotic freckle (Hutchinson), melanose circonscrite precancereuse (Dubreuilh). Arch Dermatol 1955: **71**: 2–10.
120. Miescher G. Uber klinik und therapie der melanome. Arch Dermatol Syphil 1955: **200**: 215–238.
121. Ackerman LV. Malignant melanoma of the skin. Tex State J Med 1949: **45**: 735–744.