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Review article

Challenge in diagnosis and management of lentigo maligna and lentigo maligna melanoma

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Abstract

Lentigo maligna (LM) is a subtype of melanoma in situ, which can evolve into lentigo maligna melanoma (LMM) if treated inadequately. LM and LMM are usually found on chronically sun damaged skin such as the face (cheek and nose) of the elderly on seventh or eight decade. Clinical manifestation of LM may be quite subtle, so early diagnosis is difficult to perform.The treatment of LM and LMM are challenging due to ill-defined clinical margin, predilection on the face with great size, and preponderance of the elderly, which are potential for recurrency and progressiveness from LM into LMM.

Keyword: Lentigo maligna, lentigo maligna melanoma

Introduction

Lentigo maligna melanoma (LMM) is one of the subtypes of invasive melanoma maligna (MM). Lentigo Maligna (LM) is known also as Hutchinson's melanotic freckle or pre-cancer melanosis circumscripta Dubreuilh which is considered as LMM in situ. LM is one of the subtype of MM which is on the radial/horizontal phase of growth, if there's no adequate management this condition will evolve into dermis and turn into LMM.[1-4] In United States the incidence of MM encompasses between 4-5% of skin cancer and MM contributes to 71-80% of all mortality caused by skin cancer.[5-8] LMM happened between 4-15% of all MM and encompases 10-26% of malignancy in head and neck area.[9] The incidence of LMM increase in last several decade and this is related to the increasing number of LM that developed into LMM during diagnosis period. Clinical picture of LM are similar with other benign lesion, which made high rate of mistake in early diagnosis of LM.[8,10]

The adequate management of LM is quiet difficult caused by the edge of LM is often amelanotic and not distinct. Visual observation is not adequate to determine the edge of the lesion. The inaccurate determination of lesion edge clinically or histopathologically may increase the rate of LM recurrence and the rate of LM to LMM transformation. [10]

This report includes many aspects such as epidemiology, etiopathogenesis, diagnosis and management of LM and LMM as two distinct entities which is in one spectrum evolution of a disease. Other subtypes of melanoma are not discussed in this report.

Epidemiology

According to data taken from *Surveillance, Epidemiology and End Results* (SEER) in 1990-2000, LM is one of the most common in situ melanoma (79-83%). The incidence of LMM in the year of 1990 encompases around 73% of all melanoma in-situ subtypes. There is a significant increase of LMM incidence in 1990 in which 8.4% of all invasive melanoma subtypes into 14% in the year of 2000. The increasing incidence was more prominent in elderly male. The most significant increase in incidence happened in male older than 65 years old in which the incidence were 20% in 1990 into 27% in 10 years.[11] Incidence of LM is the

highest in male in 70-79 years old age group (51.9 out of 100.000). This incidence increase from 2.2 out of 100.000 a year in 1970-1989 into 13.7 out of 100.000 per year in the year of 2004-2007.[12] A join research between Indonesian and Japanese hospitals that was conducted in dr. Cipto Mangunkusumo Hospital (RSCM), 1996-1999 found that the incidence of MM was around 7.9% (11 cases of MM out of 139 cases of skin cancer), LM was found in 2 out of 139 skin cancer patients in RSCM.[13]

Etiopathogenesis

LM and LMM were related to cumulative sun exposure, ageing, lightening of the skin, lentigo solaris, and actinic keratosis.[1] The number of melanocytic nevus had no association with the incidence of LM and LMM.[14] Each of the risk factor can trigger genetic mutation that cause the manifestation of MM.[15]

The development of MM consist of several stages, begins with a limited radial growth phase underwent to the epidermis (in situ) that may invade into other superficial dermis, without tumor mass (microinvasive). The next step is vertical growth phase or invasive tumorigenic growth phase. In this vertical growth phase, tumor experienced invasion into deep dermis.[16] Picture 1 describe that many biological and molecular MM transformation compared to other subtype of MM. LMM has no relationship with previous nevus.[14] Incidence of BRAF mutation in LMM is low, but the incidence of p53 mutation were higher in LMM compared to other subtypes of MM.[14]

International Agency for Research on Cancer (IARC) stated that the exposure of ultra-violet (UV) radiation from sunray and tanning product are the most common etiology for MM.[17,18] It is estimated that 86% of MM cases were linked with UV radiation from sunray or sunbed. UV radiation caused changes in pyrimidin dimer which is a transition of cytosine into tymine that may cause gene mutation. Chronic sun damage (CSD) which may cause solar elastosis and LMM. The predilections for CSD are head and neck area. The molecular changes of LMM happened because of sunray exposure, it is different compared with other subtypes of MM.[16] The largest genetic changes were observed from cyclin-dependent kinase 4 (CDK4) gene, cyclin-dependent kinase 2A (CDKN2A), CCND1 (gene that encodes D1 cyclin in 11q13) that includes other mutations of p53.[20-23] In 28% of LMM cases there's also mutation of KIT gene that encodes stem cells factor of tyrosine kinase.[16] Other subtypes of melanoma such as Superficial Spreading Melanoma (SSM) and nodular melanoma (NM) were caused by non-chronic sun damage (non-CSD) which are intermittent sun exposure. The predilection area of non-CSD is the trunk.[20,21] In melanoma non-CSD there is oncogene mutation of BRAF and NRAS. These are upstream regulator that is located higher compared to LMM and acral melanoma. In BRAF mutation, there are substitutions of thymidine into adenine. Mutation of BRAF was also commonly found in melanocytic nevus. So we can conclude that BRAF mutation does not happened in early melanogenesis.[25]

Research by Purdue et al in Australia 2005 found that melanoma has the highest expression of p53 gene. Many risk factors that had been identified are chronic sun exposure in the head and in neck chronic sun exposure and previous cumulative exposure, solar elastosis, freckle, history of skin cancer (non-melanoma). Melanoma with p53 gene expression that is located in the melanoma group with high number of nevus.[1]

Clinical manifestation

Clinical characteristic of LM and LMM were different from other types of melanoma. LM and LMM were more likely to appear in patients 70s or 80s, it is rarely seen in younger than 40 years old. LMM is considered as a distinct entity, because different epidemiology from other subtypes melanoma.[3]

LM usually shows longer radial growth because the appearance of LM was linked to several risk factors such as cummulative sun exposure or chronic sun exposure.[3] Predilection for the condition is the face (especially cheek and nose). In men the predilection area are in the neck, scalp, and ears.[22] Other location can often be found are hands, periocular area and conjungtiva.[1] The risk for transformation from LM to LMM are around 3-5%.[4,7]

LM lesion is usually patches that are similar to freckles with irregular shape. The color isbrownish or black. This lesion growth very slowly, it takes several months to years until central regression appeared. The periphery area will continue to expand. From time to time, there will be nodule in the central area that indicates transition from LM to vertical growth and change into LMM.[1]

Early complete diagnosis for MM is difficult. Research by Lipsker et al reported that delayed diagnosis is significant especially in MM that has

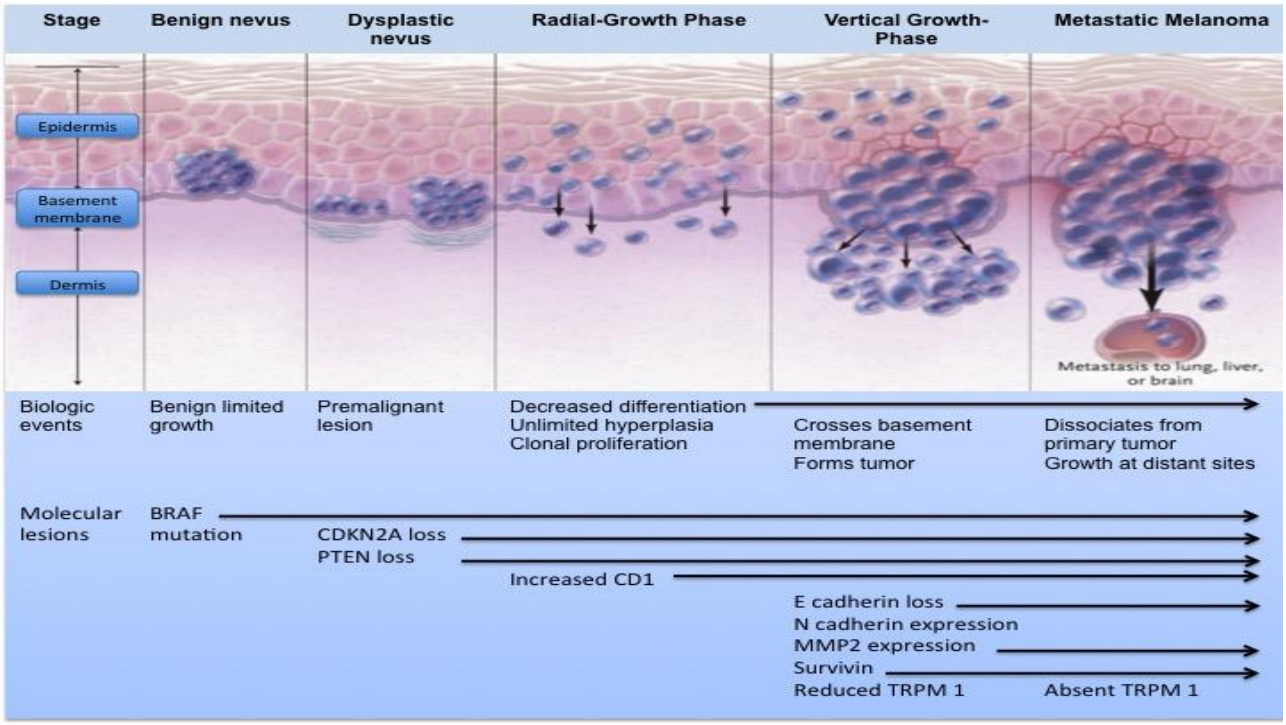

Figure 1. Biological and molecular changes in the process of melanoma maligna development.[15]

size more than 2 mm (mean delayed diagnosis of 25 months) compared to smaller than 1 mm (mean delayed diagnosis of 54 months).[27]

Early detection of MM lesion is very important to prevent the growth from LM into LMM.[7,27] American Academy of Dermatology showed the importance of ABCDE to detect early malignancy of melanoma which can be described as: A(asymmetry), B(border), C(color): changes of color of the lesion, D(diameter): larger than 6 milimeter, E(elevation/evolving): raised lesion or enlarging lesion.[3,13]

LMM lesion is generally larger compared to LM lesion. LMM lesion can be seen as nodule inside the macule. LM and LMM lesion is usually not distinct and usually are camouflaged by skin damage caused by solar effect such as lentigo, pigmented actinic keratosis, and freckle. This number caused the high number of reccurece on LM and LMM cases which is excised using standard measurement.[3]

Differential diagnosis

Differential diagnosis of LM and LMM are pigmented actinic keratosis, flat seborrheic keratosis[3], basal cell carcinoma with superficial pigmentation, in situ SSM, and dysplatic nevus.[1]

Pigmented Actinic Keratosis

Study found that LMM is quiet difficult to differentiate with pigmented actinic keratosis. Actinic keratosis which is also known as solar keratosis or keratinocytic is a pre-cancer stage. Skin that experienced photoaging may become actinic keratosis and may transform progressively into squamous cell carcinoma.[28] (table 1)

Solar Lentigo

Solar lentigo is a type of skin defect in which there is an irregular pigmentation that is difficult to differentiate with LM and LMM. The edge of solar lentigo tends to be more distinct and dark, raised and verucose. Macule lessions in LM are darker compared to lentigo solaris. Darker area usually are flat compared to others. LM lesion edges usually has indistinct border. Dermoscopy examination usually can differentiate LM and LMM. In solar lentigo there are some structure that differentiate this with other skin structures such as *brown-colored fingerprints*, m*oth-eaten borders, homogeny pigmentation* and *non-pigmented holes* that gave way *to pseudofollicular opening.*[31]*Annular granular pigmentation* and *grey pseudo network* that's usually found in LM and LMM can also be found in solaris lentigo.[30]

Table 1. Dermoscopy and histopathology appearance between pigmented actinic keratosis, lentigo maligna (LM), and lentigo maligna melanoma (LMM).

Pigmented actinic keratosis	LM	LMM
Precancer	Melanoma in situ	Melanoma
Dermoscopy		
Pigment looked brighter (*collision lesion)*	Blackish streak (97% specificity),black spots (100% spesificity)	
	Annular-granular pattern Hyperpigmented streak around the follicular area Dark rhomboid pattern	*Target like pattern* *Annular-granular pattern* or *peppering pattern* Increasing vascular density
Histopathology		
• Keratinocyte apoptosis in dermis or epidermis • Hyperkeratosis/parakeratosis • Melanofag in pars papilare dermis • Increasing melanin deposit	• Atypical *junctional* melanocytic hyperplasia • Expansion of melanosit to adnexal structure • *Photodamage* expansion: the increasing length of rete ridges, epidermis atrophy accompanied by elastosis histopathological appearance and dermis inflammation.	

Cited with modification from reference number 2

Dysplastic Nevus

Dysplastic nevus (atypical nevus) clinically and histologically can be similar to LM. Mistakes in diagnosis usually were made during incisional biopsy. It is recommended to do excisional biopsy to prevent misdiagnosis. Dysplastic nevus usually has irregular shaped border, asymmetric with diameter of 6-8 mm with varied color. Dysplastic nevus can appear sporadically or in patient with family history of MM. The predilection of dysplastic nevus is the trunk and it is rarely found in the face.[32]

Other types of melanoma

Each subtype of melanoma has several etiological characteristic. SSM are more commonly found in locations that has high number of sunray exposure, intermittent and young age. Nodular Melanoma (NM) are more commonly found in skins that had chronic sun exposure, in the elderly. Generally, NM lesion are thicker compared to other melanoma.[33]The incidence of LMM are 5-15% of cases, in which SSM are 70% of them, NM encompases 10-15% and acrallentigenous melanoma encompasses 5% of the cases.[3] (table 2)

Differentiating SSM in situ and LMM in situ are quiet difficult.[9] A research by Auslender et al reported that the LM predilection are 77% in the face, 24% of SSM happened in the face. The predilection of SSM are mostly in the trunk and lower extremity.[34]The radial growth of SSM in situ are considered shorter compared to LM. The age of onset usually younger compared to LM.[9]

Diagnosis and further examination

LM and LMM diagnosis were performed based on anamnesis, physical examination, and further workup. Gold standard for diagnosing LM and LMM are skin biopsy. [28]

Dermoscopy

In dermoscopy examination on LM and LMM we can find images of asymmetrical follicular opening, granular annular pigmentation, blackish rhomboid structure and follicular destruction.[31,36] LM and LMM amelanotic were found in lighter skin color, so it is quiet difficult to detect it only using the standard criteria.[36]

Histopathology

In histopathological examination of LM lesion, we found that there's an increase in the number of pleomorphic melanocyte atypical that congregates together and create basal epidermis layer that atrophied because of sunray. In LMM we found melanocyte longation that shaped like spindle from epidermis to the dermis layer.[3] It is quiet difficult to differentiate histopathologically between LM in the early stadium with melanocytic hyperplasia that changed because of sun exposure (solar melanocytosis) because the morphological changes are caused by subsequent process.[10]

Immunohistochemistry

Immunohistochemistry examination can be usefull to make diagnosis of LM and LMM. MART-1 is one of the monoclonal antibody that can be used in frozen section of LM and LMM. This examination is very sensitive to detect atypical melanocyte that

can be very difficult to see with hematoxylin and eosin stain. MART-1 is much faster, so it is appropriate for Mohs microscopic surgery (MMS).[37,38] Soluable adenylyl cyclase (sAC) marker is one of the various immunohistochemistry marker that can be used to differentiate benign and aggressive melanocyte proliferation. Sensitivity of sAC marker is 88% which enables us to detect the edge of LM and LMM (table 3).[39]

Table 2. Clinical and histological subtypes of melanoma characteristic.

	SSM	LM	NM
Clinical manifestations	Brown, grey, *violaceus,* pink	Brown, black and pigmented scar	Brownish, black or bluish brown
Borders	Clear and distinct borders. *Peninsula like protrusion*	Irregular borders	Papule or nodule without any pigmented lesion around it.
Shape	Nodule and papule	Flat, very rarely change into papule	Nodule or plaque with smooth surface and ulceration
Anatomical location Sun exposure	Body and trunk *Intermitent*	Face and neck Chronic	Body and extremity Chronic
Histopathology			
Intraepidermal melanocyte proliferation	Epitheloid-pagetoid cells that create cytoplasmic nest with amphophillic pigment, nucleolus	Many melanocyte in dermal-epidermal junction, many chromatic nucleus, many multinucleated cells and expanding into hair follicle	Only involing dermis, nested melanocyte proliferation (intraepidermal), not more than 3 rete ridges.
Epidermis Melanocyte proliferation	Hyperplasia Nest with various size. The tumor shapes like expansive nodule. Cytology similar to epidermis components.	Atrophy Nest containing many ephteloid and spindle cells. Similar to SSM and NM	Atrophy or hyperplasia Small nest and tumor cells that created expansive nodule.

SSM = superficial spreading melanoma, LM = lentigo maligna, NM= nodular melanoma.
Cited with modification from reference number 35.

Examination of sentinel lymph nodes

Examination of sentinel lymph nodes was done using radioisotope and blue dye coloring to detect micrometastasis in the KGB accurately. National Comprehensive Cancer Network (NCCN) guideliens recommended sentinel lymph nodes examination in primary melanoma with Breslow depth more than 1 mm.[40]

Staging

Staging LM and LMM according to *Guidelines American Joint Committee on Cancer* (AJCC) scored on the basis of primary tumor, lymph nodes involvement, and also the presence of distant metastasis.[41]

Management

In patients with clinical lesion that we think may be melanoma, narrow margin excisional biopsy must be done first to make diagnosis and detrermine the appropriate staging. Incisional biopsy can be done if the large melanocytic lesion in the face. Location for incisional biopsy can be chosen based on clinical examination and dermoscopy examination in the area with strong pigmentation, irregular or places with thickening skin.[1,3]

The mainstay for management of LM and LMM is surgical techniques that can evaluate tumor-free edge such as MMS, slow MMS, geometric staged excision, and the sphaghetti technique. In LM with extended lesion in the head and neck which is quiet difficult to reconstruct, the therapy of choice are

imiquimod, radiotherapy, cryo surgery, and laser therapy.[42] Further management of LM and LMM according to it's stage followed the algorthym (figure 2).[43]

Table 3. Melanoma immunohistochemistry marker.[28]

Marker	Identification
Pmel 17 (antiboy HMB-45)	Melanocytic tumor
MART-1 (antibodyanti MART-1)	Melanocytic tumor (less specific, can be found ini benign nevus)
Gp75 (antibodi Mel-5)	Epidermal melanocytic in nevus and melanoma
S-100 (antibody antiS-100)	Melanocytic tumor (can be found inihistioma, schwannoma, neurofibroma, clear cell sarcoma)
sAC (antibody R21)	LM/LMM (combined with MART-1 to determine tumor free edge in the lesion without distinct border)

Research by Carpenter et al in 2008 showed that 478 MM patients were divided into two groups. The first group have smaller interval between biopsy with definitive surgery (wide local excision) ≤ 28 days in 55% of the case and >28 days in 45% of the cases. In the second group ≤ 56 days in 92% of all cases and >56 days in 8% of the cases. We can find that the mean interval time between biopsy and definitive surgical techniques (wide local excision) are 30.5 days. There are no difference between disease free survival and overall survival in 10 years between first group with the group with ≤ 28 days interval and > 28 days interval. This finding can also be observed in the interval ≤56 days and > 56 days.[44] Mc-Kenna et al assessed the interval time between excisional biopsy and definitive operation of wide local excision in 986 patients with skin melanoma in Scotland. The patients were divided into 5 groups according to surgery interval: ≤ 14 days, 15-28 days, 29-24 days and 43-91 days and ≥ 92 days. The research results shows that survival outcome and recurrence of the melanoma do not have association with interval time between excisional diagnostic biopsy and wide local excision from melanoma.[45]

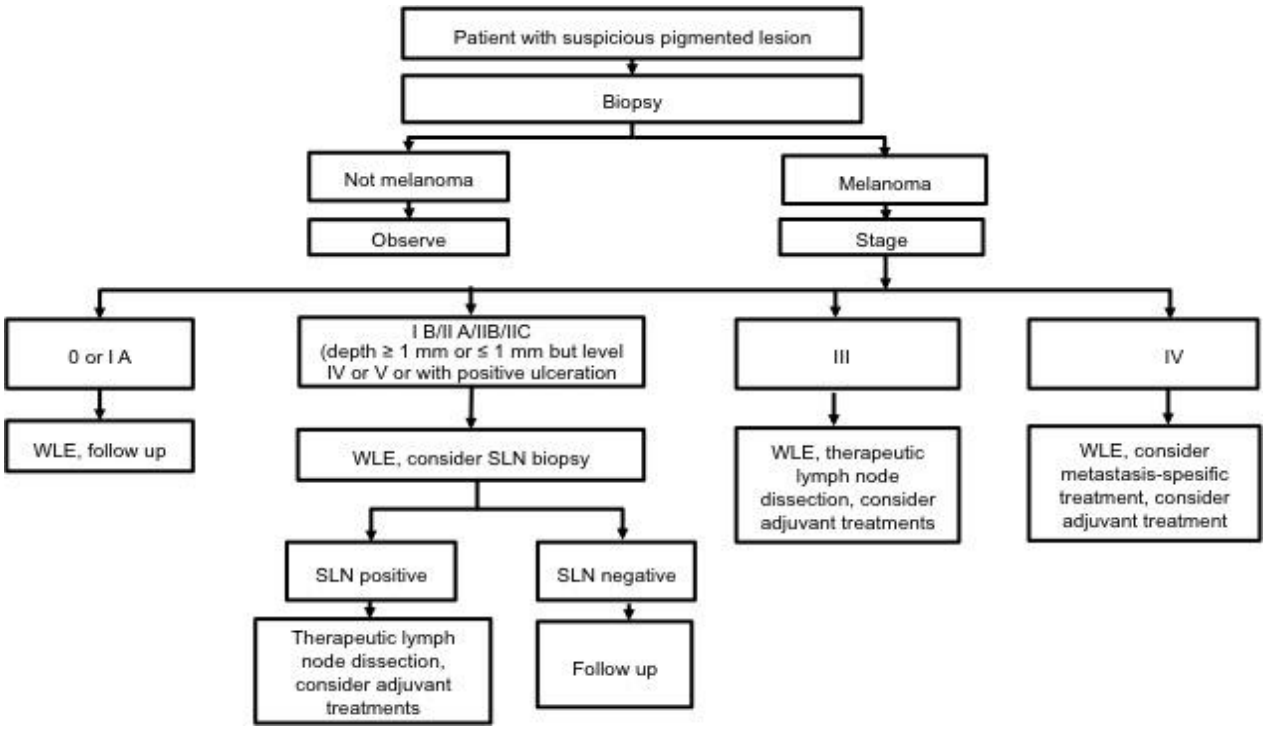

Figure 2. Management algorithm of pigmented lesion that may be melanoma.[40]
SLN= *sentinel lymph node biopsy*. WLE = *wide local excision*.

After the diagnosis of LM and LMM, further management choices are wide local excision. *Guidelines of Care for Primary Cutaneous Melanoma* recommends excisional limits for MM lesion generally based on tumor depth: 5 mm in in-situ lesion, 1 cm in lesion that is less than 2 mm and 2 cm in lesion that is more than 2 mm. In LM we needs higher than normal excisional limits because of the undefinitive border. Recurence rate of LM and LMM with standard excision that is recommended are 8-20%. MMS and progressive excision can reduce recurrence by 0-5% (table 4).[1,7,47]

Adjuvant systemic therapy

Adjuvant systemic therapy was usually given in patients with high risk of relapse after excisional surgery. Adjuvant therapy of interferon-alpha 2b were considered after MM stage I B and stage II with sentinel lymph nodes examination that were positive, stage III and stage IV.[43]

Combinational chemoteraphy

Combinational chemotherapy in the form of CVD (cisplastin, vinblastine and dacarbazine) were given to MM advanced stage that experienced metastasis.[43]

Imiquimod

Topical imiquimod is one of the alternative therapies for LM. A recent systematic review published in the year of 2015 showed that 347 cases of LM that were given imiquimod for 5 times a week for 3 months has high rate for histological cure (76.2%) and high rate for clinical cure (78.3%). The incidence for clinical recurrence were 2.3% with follow up of 34.2 ± 11.8 months.[48]

Frozen sectional surgery

Cold sectional surgery is one of the effective therapies for LM. This fact is due to sensitivity of melanocyte to cold. With the help of Wood's lamp, we can determine the edge of LM lesion. Cold sectional surgery can be done 5 mm from the edge of the lesion. Frozen section techniques that can be done are two freeze thaw cycle with two thawing periods.

Table 4. Reccurency number between LM and LMM in different surgical techniques.[47]

	Standard excision	MMS	MMS followed by rush permanent sections	Slow MMS	Square procedure	Staged,vertical edge excision with rush permanent sections
Angle of excision	90^0	45^0 atau 90^0	45^0	45^0	90^0	90^0
Margin size	2-10 mm	2-3 mm (plus 3-mm initial margin excised with central tumor)	4-6 mm	2-5 mm	5-10 mm	2-3 mm
Tissue mapping technique	Varies; none to orientation to face of clock	Standard MMS mapping	Standard MMS mapping	Standard MMS mapping	Tissue "strips" oriented and mapped	Oriented and mapped to face of clock
Tissue fixation method	Permanent	Frozen	Permanent and frozen	Permanent	Permanent	Permanent
Reader of margin histologic findings	Pathologist	MMS surgeon	MMS surgeon and pathologist	Pathologist	Pathologist	Pathologist
Sectioning orientation	Bread loaf	En face (horizontal or vertical)	En face (horizontal)	En face (horizontal)	En face (vertical)	Radial
Duration of follow up	3-3½ years, 42 months	5 years	58 months	22 months	Not reported	57 months
Recurrence rate	6/68 (8.8%), 16/81 (20%)	1/184 (0.5%)	1/38 (2,6%)	3/106 (2.8%)	0/35	3/62 (4.8%)

MMS = Mohs micrographic surgery, LM = lentigo maligna, LMM = lentigo maligna melanoma.

The gold standard target therapy for melanocyte is hair follicle. According to Smaniego which review LM, the recurrence of LM that were managed with frozen section technique are varied
between 0-50%. This may be caused by different technique and freezing parameter. The advantage of frozen sectional method is the relative easy difficulty in the excecution. The weakness for this methods are the extensive time needed for the recover (more than 3 months), and usually therewil be no total destruction that may cause recurrence or progressivity into LMM.[49]

Prognosis

LM has long radial growth phase, so the growth of this subtype is relatively slow, however if there are invasion to the deep skin the prognosis is similar to other subtype of MM. The prognosis parameter of LM and LMM are based on staging that includes tumor depth, mitosis speed, ulceration and LDH serum level. The prognosis parameter that is most important in tumor evaluation are tumor depth. There are two classifications for tumor depth: Breslow classification and Clark classification. Breslow classification scored prognosis into several level. Level I: depth of≤0.75 mm, level II: 0.76-1.50 mm, level III: 1.51-4.0 mm, level IV: ≥ 4.0 mm. Clark classification was based on the depth of invasion. Level I: invaded into the epidermis, level II: invasion into pars papilaris dermis, level III: invasion invaded location between dermis pars papilaris and parsreticularis. Level IV: invasion reached subcutaneous.[42] Detection and early therapy may increase survial rate. According to the research in Japan from 1987-201, survival rate of LMM in 10 years are 69%.[51]

Prevention

Preventing skin exposure against chronic sun ray and the appearance of sunburn are the prevention for LM and LMM. Regarding this we can use sun protector and hat to cover our face. Early detection with self-examination and vigilant with many skin disease especially signs and symptoms of melanoma may be important.[3]

Conclusion

LM is the in situ phase of LMM which is important in the recurrency and mortality of the patients if it's not treated adequately. By knowing the etiopathogenesis and epidemiology of LM and LMM, better education to the society may be given. Early diagnosis and management of this case may increase life expectancy and reduce disease burdent and recurrent rate.

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