VOLUME 1

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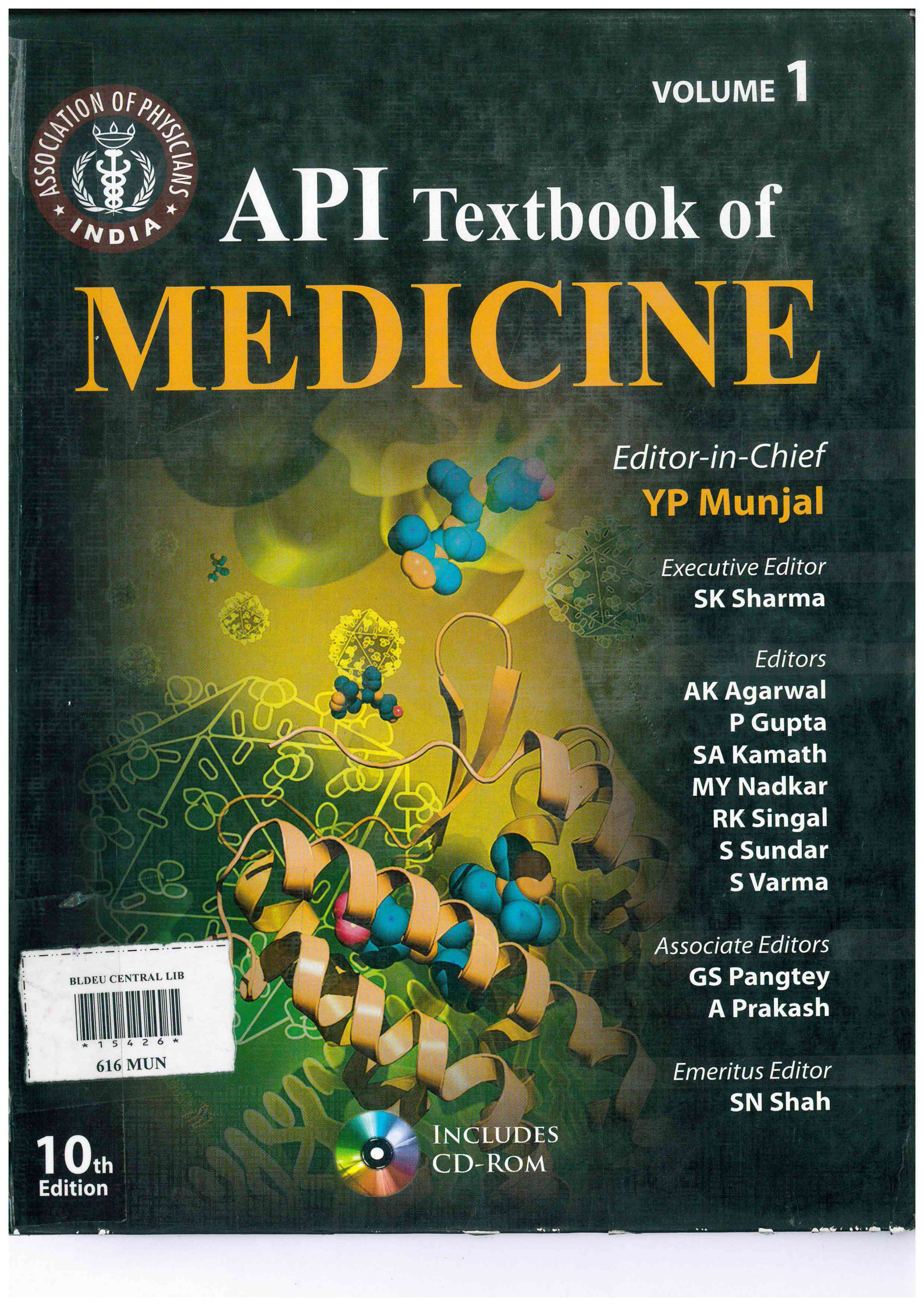

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Editor-in-Chief
Yash Pal Munjal

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10 Pre-malignant Conditions and Malignant Tumours of the Skin

Arun C Inamadar and Aparna Palit

INTRODUCTION

Pre-malignant and malignant skin lesions are more common amongst white races. Malignancies like primary cutaneous melanoma are extremely rare amongst Indians.

Exposure to solar and artificial ultraviolet rays (UVRs) and contact with carcinogenic chemicals are some of the predisposing factors for the development of cutaneous malignancies.

Genetic susceptibility to the development of skin malignancies is well known. High-frequency, low-penetrant genes are responsible for sporadic occurrence of skin cancers, whereas rare, low-frequency, high-penetrant genes are associated with familial cancer predisposition syndromes. Immunosuppressed state (organ-transplant recipients and human immunodeficiency virus [HIV] infection) confers a susceptibility to non-melanoma skin cancers.

Common pre-malignant skin lesions are actinic keratosis and leukoplakia.

ACTINIC KERATOSIS

These are hyperkeratotic lesions with malignant potential occurring on photodamaged skin of elderly individuals.

Fair-skinned outdoor workers are common sufferers, and occurrence is directly related to the degree of UVRs exposure. The common sites are scalp, face and dorsum of hands. The lesions are multiple, asymptomatic, brownish macules or papules (1 mm to >2 cm) with a rough, scaly surface. There may be pain and traumatic bleeding.

Histopathologically, there are features of dysplasia. Many lesions may undergo spontaneous resolution or may progress (<0.1%) to invasive squamous cell carcinoma (SCC). Management includes restricting outdoor activities, use of sunscreen, and destruction of existing lesions with 5-fluorouracil (5-FU) cream, cryotherapy or photodynamic therapy.

LEUKOPLAKIA

Leukoplakia is a white patch or plaque on the mucous membrane (**Figure 1**) which is not removable by rubbing, cannot be attributed to any specific underlying cause by its morphology, and requires a diagnosis by exclusion (World Health Organization [WHO]). Some leukoplakias have pre-malignant potential and may slowly progress to malignancy (2% to 5%) over several years.

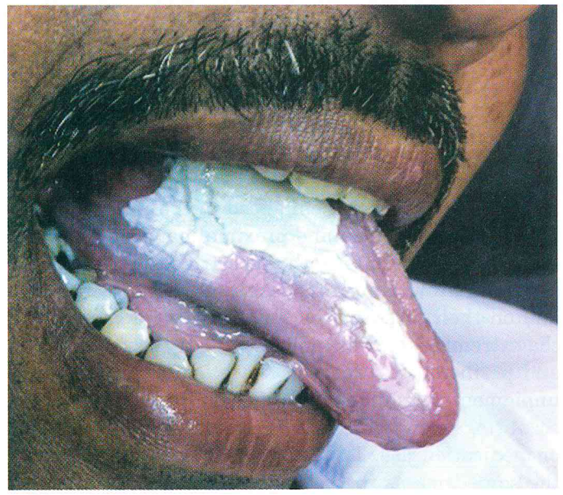

Figure 1: White plaque of leukoplakia on the mucous membrane

Various causes of leukoplakia have been presented in **Table 1**. It is common in elderly with an incidence rate of about 1%. Oral mucosa is the most common site, involving the palate, tongue or floor of the mouth. Clinically the lesions are asymptomatic diffuse, speckled or striated, or fixed white plaques with or without reddish reticulation on the surface (erythroplakia).

All lesions should have a biopsy to rule-out dysplasia. Moderate to severe dysplasia indicate higher risk for malignancy. Such lesions should be managed by topical bleomycin (0.5%), surgical excision, or laser ablation. Risk factors must be avoided.

MALIGNANT EPIDERMAL TUMOURS

Common malignancies of epidermal origin are SCC, basal cell carcinoma (BCC) and primary cutaneous melanoma. These skin tumours constitute part of some of the genodermatoses like Bloom's syndrome, Xeroderma pigmentosum (XP), Gorlin's syndrome, Muir-Torre syndrome, Bazex's syndrome, etc.

Table 1: Causes of Leukoplakia

Aetiology	Types	Risk of malignancy
Infective origin	Chronic candidal leukoplakia	Increased risk but malignancy uncommon
	Syphilitic leukoplakia (tertiary stage)	Rare condition, high malignant potential
	Oral hairy leukoplakia (Epstein-Barr virus)	Malignancy not recorded
	Leukoplakia associated with chronic renal failure (Epstein-Barr virus)	Slow progression to SCC over decades
	Proliferative verrucous leukoplakia (Human papilloma virus)	
Chronic irritation	Smoking	Higher risk, but rare
	Tobacco chewing	
	Chewing of betel leaves and areca nut	
	Snuff-dipping	
Idiopathic	—	—
Paraneoplastic (in association with internal malignancy)	May occur in association with visceral malignancies, specially those of upper aerodigestive tract	—
In association with genetic disorders	Dyskeratosis congenita Olmsted syndrome	—

Squamous Cell Carcinoma

Cutaneous SCC is the malignant proliferation of the epidermal keratinocytes.

Aetiopathogenesis

Exogenous risk factors for SCC include chronic exposure to UVRs, carcinogenic chemicals like tar, arsenic, and physical agents like ionising and thermal radiation. Latent infection with human papilloma virus is a factor precipitating SCC.

Clinical Features

The sites of predilection are photodamaged areas of the face and neck, burn scars, keloid, non-healing ulcers, existing pre-malignant lesions, or any site with long-term infection (lupus vulgaris) or inflammation. It starts as indurated areas or irregular, raised, painless nodules on such lesions. It enlarges rapidly with variegated/ulcerated surface, bleeding easily. In the late stage, the lesion becomes cauliflower-like (**Figure 2**) and malodorous. There are regional and distant lymphadenopathies. Visceral metastasis occurs through lymphatics.

Clinical Variants

Intraepidermal, *in situ* SCC with a small potential for invasiveness, are Bowen's disease and erythroplasia of

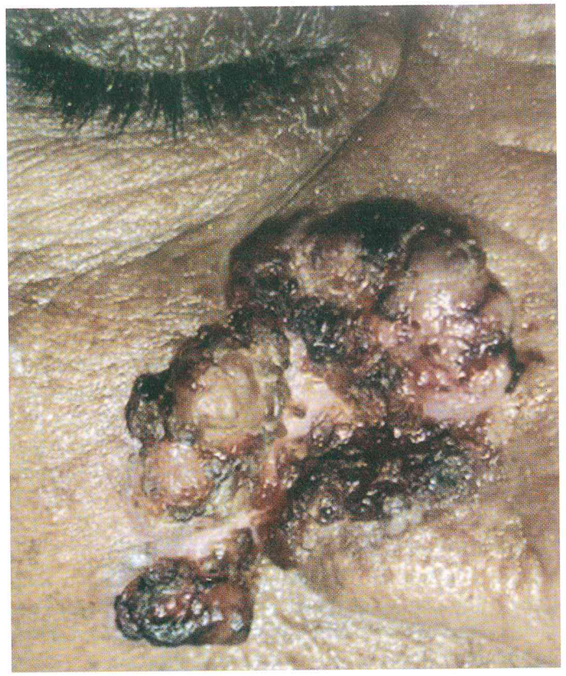

Figure 2: Cauliflower like fungating lesion of squamous cell carcinoma

Queyrat on genitalia. In India (Kashmir), prolonged contact with the *Khangri* (pot with coal fire) in the winter season is one of the precipitating factors causing SCC on the abdominal wall (*Khangri* cancer). Squamous cell carcinoma that arises from chronically scarred skin is known as Marjolin ulcer.

Diagnosis

Histopathologically, the lesions may be well-differentiated (individual cell keratinisation and horny pearls), or poorly differentiated (anaplastic keratinocytes invading the dermis; 'windblown' appearance).

Differential Diagnosis

Early lesions of SCC may be mistaken with actinic keratosis or BCC.

Treatment

Treatment includes the topical 5-FU, photodynamic therapy, Mohs micrographic surgery, surgical excision with wide margin (high-risk lesions <1 cm and any lesion >2 cm), radiotherapy, chemotherapy, or a combination of these.

Basal Cell Carcinoma

Basal cell carcinoma is the most common cutaneous malignancy worldwide, accounting for about 90% of

malignant tumours. Commonly known as rodent ulcer, it arises from the basal cells of the epidermis. It is locally invasive, and metastasises very rarely.

Aetiopathogenesis

Predisposing factors include exposure to UVRs (mostly ultraviolet B or medium wave [UVB]), occupational contact with tar or pitch, and ingestion of arsenic. The UV-induced mutations in the *TP53* tumour-suppressor gene (chromosome 17p) have been implicated in some cases of BCC. Multiple, early onset BCC may be seen in familial cancer syndromes.

Clinical Features

It occurs in the elderly and fair-skinned individuals, predominantly in the periorbital region (lower eyelid 70%, followed by inner canthus, upper eyelid and outer canthus). The initial lesion is a small, raised, translucent, pearly papule with or without pigmentation and prominent blood vessels. These are slow growing with a rolled-out border, gradually destroying the underlying tissue (**Figure 3**). Neglected, advanced lesions may invade the eye, underlying lacrimal duct and sinuses, facial and skull bones, and even the meninges, known as 'ulcus terebrans' (penetrating ulcer).

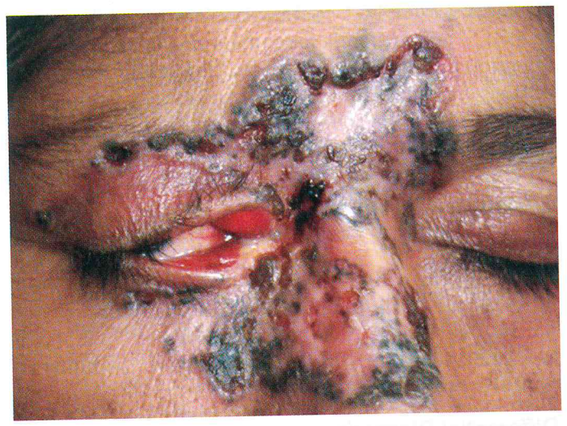

Figure 3: Large lesion of basal cell carcinoma with rolled-out border and distortion of inner canthus of eye

Clinical Variants

Various morphological patterns of BCC include:

1. Noduloulcerative (most common)
2. Cystic
3. Morphoeic (cicatricial)
4. Superficial spreading (multi-centric)
5. Pigmented.

Diagnosis

The histopathological picture includes islands of dark blue basal cells with peripheral palisading, invading the dermis. Mitotic figures and apoptotic bodies are seen in plenty.

Differential Diagnosis

The lesions have to be distinguished from keratoacanthoma, early SCC, seborrhoeic keratosis and melanoma.

Treatment

Different treatment modalities for BCC are topical imiquimod (5%) cream, 5-FU, interferon-α, surgical excision, Mohs' micrographic surgery, radiotherapy, cryotherapy, curettage, cautery, and photodynamic therapy. There are chances of recurrence or appearance of new lesions.

Cutaneous Malignant Melanoma

This is a malignant tumour of epidermal melanocytes resulting from UVRs exposure in genetically susceptible individuals. This malignancy occurs exclusively amongst white races. Primary cutaneous melanoma is extremely rare in Indian skin.

Aetiopathogenesis

Intermittent, unaccustomed or recreational solar exposures are the risk factors for cutaneous melanoma rather than chronic exposures. Other risk factors include positive family history (2%), presence of multiple benign melanocytic naevi, and a past history of melanoma. Mutation of the tumour suppressor gene *CDKN2A* (chromosome 9p21) is found in 10% to 30% patients, particularly in familial cases. Mutation of *CDK4,* melanocortin 1 receptor (*MC1R*) gene (chromosome 17) polymorphism, and the presence of oncogene BRAF are other susceptibility factors.

Clinical Variants

1. Superficial spreading melanoma (most common)
2. Nodular melanoma (rapid growth, poor prognosis)
3. Lentigo maligna melanoma (Hutchinson's lentigo)
4. Acral lentiginous melanoma (Darker races)
5. Subungual melanoma
6. Mucosal melanoma
7. Secondary melanoma without a detectable primary site.

Clinical Features

Common body sites involved are the trunk in men and lower legs in women. This malignancy affects younger people than other cutaneous carcinomas. Head and neck melanoma may result from cumulative solar exposure in older people.

In nodular melanoma, melanin pigment may be sparse. Lentigo maligna melanoma is very slow-growing, occurring on the face of elderly patients as brownish-black, irregular, flat lesions. Acral lentiginous melanoma occurs on the palms and soles as a central raised area surrounded by a pigmented macule. Subungual melanoma is commonly misdiagnosed as other benign conditions, and definitive diagnosis is usually late.

Diagnosis

A naevus with erratic behaviour (increased size, change in shape/colour) is suspicious. The 'ugly duckling' sign, as proposed by some French authors is that 'a naevus different from its "brother" naevi can be a melanoma'. Suspected lesions should have a biopsy with 1 mm to 2 mm of surrounding clinically normal skin. Histopathologically, invasion of the dermis by malignant melanocytes is the diagnostic feature.

There are systems to aid clinical diagnosis of melanoma; the American ABCDE (A = asymmetry, B = irregular border, C = irregular colour, D = diameter >1 cm, E = evolution), and the Glasgow seven-point check-list is the other common method.

Pathological prognostic guides include depth of invasion of tumour cells as expressed by the:

1. Breslow's tumour thickness (distance between granular layer and the deepest invasive area of primary lesion in mm).
2. Clark's levels (five levels, starting from *in situ* to invasion into fat, indicating extent of penetration of primary lesion).

Differential Diagnosis

Benign melanocytic naevi in young adults and seborrhoeic and actinic keratosis in the older age group are to be differentiated from melanoma.

Treatment

Tumour node metastasis staging system is followed to make decisions on treatment.

Management includes surgical excision, sentinel lymph node biopsy in case of thicker primary lesion, and adjuvant chemotherapy/radiotherapy in the advanced stage of the disease. Primary preventive measures include awareness campaigns regarding sun-protection and identification of early lesions.

Several vaccines for melanoma are in the process of development. These are used in affected melanoma patients instead of prophylactic use. Interferon α 2b and anticytoplasmic leukocyto antigen-4 antibody (iplimumab, ticlimumab) are under trial for the treatment of melanoma.

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