Skin Tumours

In a tropical and developing country like India, inflammatory dermatoses form the bulk of diseases encountered in a busy outpatient practice with fewer people seeking advice for indolent 'lumps' and 'bumps'. However, skin tumours are a challenging group of conditions that can be categorised into those that are commonly seen and easily recognised based on the characteristic site of presentation, size, colour, distribution and symptoms, the rarer ones and those that mimic other disorders and pose a diagnostic challenge. The latter group are diagnosed chiefly by histopathology, immunohistochemistry or other sophisticated diagnostic techniques. Skin tumours also form an important component of several genodermatoses.

Skin tumours develop as a result of proliferation of a single or multiple components of the skin.

They range from benign lesions that merely cause cosmetic concern to premalignant lesions and aggressive tumours. The vast majority of skin tumours are benign. Morphologically, they manifest as smooth papules, nodules, keratotic or cystic lesions that grow slowly. Multiplicity of lesions is a reliable clinical clue to the benign nature of the condition. Malignant tumours are usually solitary, irregular, rapidly growing plaques or nodules that may ulcerate. They may arise *de novo* but some may arise from a pre-existing benign tumour. Some tumours may metastasize.

Management is usually for cosmetic reasons and more often than not, diagnosis is made on excision biopsy, especially when patients present to a surgeon for a nodule. Some benign tumours may recur following incomplete excision. It is likely that many nodules that are excised are not examined histopathologically and those that are may be reported as benign skin tumours without further characterisation.

The diagnosis of a skin tumour is quite often made histopathologically but some tumours can be recognised with some certainty on clinical grounds. Multiplicity of lesions makes the diagnosis simpler than when there is a solitary papule or nodule.

Skin tumours are classified based on their primary site of origin [Table 1].

COMBINED TUMOURS

They exhibit bi- or multidirectional differentiation into two cell types i.e. they are composed of two different cell types, e.g. keratinocytes and melanocytes.[1] They also consist of cells demonstrating both features immunohistochemically (e.g. cytokeratin and S-100) and ultrastructurally (tonofilaments and compound melanosomes). These include combined SCC and melanoma or BCC and melanoma. They were first reported by Rosen *et al.* in 1984. They have to be distinguished from the following phenomena:

a. Tumour collision i.e. the juxtaposition of two originally separate and distinct neoplasms. The two lesions are sharply demarcated from each other: e.g. nevus and BCC, nevus and seborrheic keratosis, SCC and melanoma.
b. Melanocyte colonisation—This is the colonisation of epithelial neoplasms by non-neoplastic dendritic melanocytes. The melanocytes in such tumours are highly pigmented, have dendrites and lack cytologic atypia unlike the atypical melanocytes with no dendritic configuration and minimal pigmentation, as seen in combined tumours e.g. pigmented BCC or SCC, melanocytic matricoma, melanotrichoblastoma or pigmented eccrine porocarcinoma.
c. Antigen transfer, in which artefactual transfer of antigen from one cell line to the other occurs due to antigenic diffusion, leading to non-specific staining of the tumour cells. This differs from combined

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Table 1: Classification of skin tumours[1]

1. Keratinocytic tumours
They are derived from epidermal and adnexal keratinocytes
WHO has classified them into:
   a. Benign acanthomas
      i. Clear (pale) cell acanthoma
      ii. Epidermolytic acanthoma
      iii. Warty dyskeratoma (isolated keratosis follicularis)
      iv. Large cell acanthoma
      v. Seboacanthoma
      vi. Basosquamous acanthoma (Inverted follicular keratosis)
      vii. Lichen planus-like keratosis (lichenoid benign keratosis, lichenoid actinic keratosis, solitary lichen planus)
      viii. Picker's nodule
      ix. Seborrheic keratosis
      x. Keratoacanthoma (KA)
   b. Actinic keratosis including arsenical and PUVA keratosis
   c. Bowen's Disease and bowenoid papulosis
   d. Basal cell carcinoma
   e. Squamous cell carcinoma
2. Melanocytic tumours
3. Appendageal tumours
Tumours with apocrine and eccrine differentiation
   a. Malignant tumours
      Tubular carcinoma
      Microcystic adnexal carcinoma
      Porocarcinoma
      Spiradenocarcinoma
      Malignant mixed tumour
      Hidradenocarcinoma
      Mucinous carcinoma
      Digital papillary carcinoma
      Adenoid cystic carcinoma
      Paget disease of breast
      Extramammary Paget disease
   b. Benign tumours
      Hidrocystoma
      Syringoma
      Poroma
      Syringofibradenoma
      Hidradenoma
      Spiradenoma
      Cylindroma
      Tubular adenoma
      Tubular papillary adenoma
      Syringocystadenoma papilliferum
      Hidradenoma papilliferum
      Mixed tumour (chondroid syringoma)
Tumours with follicular differentiation
   a. Malignant tumours
      Pilomatrical carcinoma
      Proliferating tricholemmal tumour
   b. Benign tumours
      Trichoblastoma
      Pilomatricoma
      Tricholemmoma
      Multiple tricholemmomas
      Trichofolliculoma
      Fibrofolliculoma/trichodiscoma
Tumours with sebaceous differentiation
      Sebaceous carcinoma
      Sebaceous adenoma
      Sebaceoma
      Cystic sebaceous tumour
4. Soft tissue tumours
   a. Fibrous and fibrohistiocytic tumours
   b. Vascular tumours
   c. Smooth muscle tumours
   d. Skeletal muscle tumours
5. Neural tumours
6. Tumours of subcutaneous tissue

tumours in which 'appropriate' staining with regular distribution pattern is seen in the tumour cells.

Some tumours are an important clue for a genetic syndrome requiring appropriate management, e.g. sebaceous tumours in Muir-Torre syndrome, fibrofolliculomas, trichodiscomas, perifollicular fibromas in Birt-Hogg-Dube syndrome, trichoepithelioma, milia and cylindromas in Rasmussen syndrome, atrophoderma vermiculata, milia, hypotrichosis, trichoepithelioma, basal cell carcinoma and peripheral vasodilatation with cyanosis in Rombo syndrome or trichilemmomas in Cowden syndrome.[2-7] They may also be a marker for internal malignancy such as 'Sign of Lesser Trelat' with multiple seborrheic keratoses representing underlying visceral malignancy.[8]

OTHER DIAGNOSTIC TECHNIQUES FOR SKIN TUMOURS

Immunohistochemistry is an adjunct to conventional dermatopathology for assessing the tissue of origin or direction of differentiation of cells.[9] Immunohistochemistry involves application of antibodies directed towards the desired antigen followed by incubation with a peroxidase- labelled secondary antibody that is directed against the first antibody. Several markers are now available commercially to identify the lineage of cells and also differentiate primary from metastatic tumours, e.g. cytokeratins (low and high molecular weight) for various keratinocytic neoplasms, cytokeratins for tumours with follicular differentiation, simple epithelial keratins and carcinoembryonic antigen for tumours with ductal differentiation, epithelial membrane antigen for tumours with sebaceous differentiation. The antibodies directed against tissue antigen vary greatly in their specificity and binding affinity to the tissue. Hence, immunohistochemistry is not a 'magic bullet' and its result is not decisive at all times. Moreover, financial constraints also limit the use of this technique in a majority of cases.

Electron microscopy has been employed to identify subcellular structures indicating differentiation. However, this method is not used in every day practice and is largely a research procedure.[10]

Molecular techniques are also being developed to improve diagnostic precision of skin tumours.[11] Some of these techniques include southern blot, interphase fluorescence *in situ* hybridisation (iFISH), comparative genomic hybridisation (CGH), PCR, etc. They are being used for melanocytic neoplasms, soft tissue tumours especially sarcomas like dermatofibrosarcoma protuberance and basal cell carcinoma.

Nonetheless, recognition of the histomorphology with standard haematoxylin-eosin stains remains the most reliable way to diagnose these tumours.

Non-invasive diagnostic techniques for skin tumours

These are simple, yet novel, *in vivo* non-invasive techniques for the early diagnosis and appropriate treatment of skin tumours. Some techniques can study the skin at nearly histological resolution. These techniques help in selecting lesions that require a biopsy, in determining appropriate therapeutic modalities, verifying treatment efficacy and deciding about appropriate surgical margins.

Dermascopy (Epiluminescence microscopy)

It is a simple and inexpensive technique to visualise certain morphological features in the skin lesions that are not visible to the naked eye.[12] The lesion is covered with mineral oil, alcohol or water to eliminate surface reflection, making the cornified layer translucent to better visualise the epidermal pigment, dermo-epidermal junction and superficial dermis. It is then visualised with a hand lens, hand-held scope called the dermascope, stereomicroscope or a digital imaging system at magnifications varying from 6× to 100×. New hand-held dermascopes with polarised light are now available by which use of surface fluid becomes unnecessary.

Ultrasound

Skin tumours can be evaluated by high frequency 20 MHz sonography with an axial resolution of 50 μm and lateral resolution of 350 μm.[13] Skin tumours appear as homogenously hypoechoic areas as compared to the surrounding hyperechoic dermis. Different tumours have been differentiated on the basis of internal echoes within the tumour, e.g. BCC presents weak, unevenly distributed reflecting spots (internal echoes) inside the echo-poor tumour because of the presence of collagen bundles within the tumour. Melanomas appear as homogenously hypoechoic lesions, melanocytic nevi show irregularly distributed internal echoes, seborrheic keratosis shows partially interrupted thick entry echo with attenuation or disappearance of the dorsal echo. A sharp border between the hypoechoic tumour and hyperechoic dermis at the tumour base is seen, that helps to determine the tumour thickness.[14]

Confocal scanning laser microscopy (SCLM)

It enables the *in vivo* study of skin at nearly histologic resolutions.[15] It can image the epidermis and dermis with cellular-level resolution (0.5–1 μm in lateral dimension and 4–5 μm in axial ones) to a depth of 500 μm, producing images representing horizontal planes of the skin. It employs a diode laser at 830 nm with a power, less than 35 mW. A point source of light illuminates a point inside the object. High contrast images are obtained by imaging a single in-focus section and rejecting light from out-of-focus portions of the object by a filter. The contrast is provided by the difference in refractive index of organelles and other microstructures that appear bright and contrast with the background, e.g. acquired melanocytic nevus shows bright, highly refractile round to oval cells, located between the epidermis and dermo-epidermal junction or clustered into nests in the papillary dermis, in melanoma, there is a disarray of epidermal pattern leading to disappearance of the normal honeycomb pattern. The malignant cells are polymorphic. Also, branching dendritic-like cells are seen mainly in the basal layer and spreading upwards, suggesting a pagetoid pattern. In BCC, the peripheral palisading pattern, cystic spaces within the tumour and peritumoural lacunae can be recognised.[16]

Treatment of skin tumours varies from simple surgical excision for solitary lesions or multiple tumours unresponsive to other modalities, to Moh's micrographic surgery for lesions over critical anatomic locations or for large lesions, physical destructive modalities like scissor and shave excision, curettage with electrodessication, dermabrasion, chemical destruction with caustics like trichloroacetic acid or salicylic acid, radiotherapy, laser surgery and cryotherapy, medical modalities like intralesional chemotherapy with 5-FU, bleomycin, methotrexate, interferon α–2a and triamcinolone, topical agents such as 5% imiquimod cream, 3% diclofenac sodium in 2.5% hyaluronic acid gel[17] or photodynamic therapy with 5-aminolevulinic acid.[17-20]

Skin tumours represent a challenging group of dermatoses. A thorough clinical examination supplemented by histopathologic correlation is required to make a diagnosis in a majority of cases.

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