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Original Article

Pathology Section

Histomorphological Study of Skin Epithelial Tumours with Immunohistochemical Evaluation of p53 Expression in Malignant Tumours

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ABSTRACT

Introduction: Skin is the largest organ in the body. A variety of hyperplastic growths, benign and malignant tumours are encountered in clinical practice. Although skin tumours constitute <1% in India, the prevalence has been progressively increasing over the last few decades. However, limited studies have been conducted in Indian subcontinent to study skin tumours. Reportedly, pathogenesis of skin tumours in Indians is notably distinct than that observed in white-skinned people. This highlights the high demand for studying skin tumours on a larger scale in Indian subcontinent. Moreover, genetic mutations in tumours are crucial aspects of which p53 gene mutations are predominantly involved in the development of 50% of all tumours. The expression rate and positivity of p53 has been reported to vary between white- and dark-skinned individuals, mainly Indians however, this hypothesis remains to be validated on an extensive scale.

Aim: To analyse the histomorphology of skin epithelial tumors and subsequent p53 expression in malignant epithelial skin tumours.

Materials and methods: A two-year observational study from July 2014-June 2016 observational study was conducted in the Pathology Department of a tertiary care hospital and included 50 biopsy specimens of benign and malignant epithelial skin tumours.

All the specimens were histopathologically evaluated using haematoxylin and eosin staining technique. Moreover, the paraffin sections of specimens of malignant epithelial tumours were according to reference 12 used for analysis as mentioned in material methods. It is a semi-quantitative method. Positive and negative controls were run with each batch of slides.

Results: Of all the 50 specimens, 32 (64%) and 18 (36%) were obtained from males and females, respectively. Twenty-one (42%) specimens were malignant epithelial tumours, with Squamous Cell Carcinoma (SCC) (52.4%) and Basal Cell Carcinoma (BCC) (28.6%) being the most common types, whereas 26 (52%) were benign epidermal tumours, with nevi (46.15%) and seborrheic keratosis (34.61%) being the most common types. Remaining three (6%) specimens exhibited Bowen's disease. For SCC, percentage positivity of p53 for well, moderately and poorly differentiated tumours was 38.5%, 38.3% and 45%, respectively. For BCC, malignant melanoma and verrucous carcinoma % positivity was 68.33%, 55% and 15%, respectively.

Conclusion: Knowledge of histopathological patterns of skin lesions is a must, considering the distinct clinical manifestations. Such knowledge can be useful in understanding the disease prognosis and planning effective therapeutic strategies. In the present study, SCC followed by BCC was highly prevalent NMSCs, whereas melanocytic nevi and seborrheic keratosis were highly prevalent benign tumours. p53 expression is lower in Indians than white-skinned people.

Keywords: Bowen's disease, Carcinoma, Eosin, Haematoxylin, Melanoma, Mutation, p53 genes, Skin neoplasms

INTRODUCTION

The prevalence of epithelial skin tumours is intensifying worldwide. Nearly, 2-3 million non-melanoma skin cancers (NMSCs) and 132,000 melanoma skin cancers are diagnosed annually [1,2]. NMSCs, i.e., squamous cell carcinoma (SCC) and basal cell carcinoma (BCC), and malignant melanoma constitute the most prevalent primary skin tumours [1]. Compared to light-skinned people, skin tumours are less prevalent in dark-skinned people due to the protective effect exerted by eumelanin to withstand ultraviolet (UV)-induced skin damage [3]. Consequently in India, skin tumours constitute <1% of all tumours, and the prevalence is relatively low compared to that in Western countries. However, considering the substantially large population of India, the estimate of absolute number of patients with skin tumour is alarming. Although there is paucity of national and cross-country research for studying skin tumours in India, recent studies accentuate the increasing prevalence of NMSCs in the country [1,3]. Moreover, pathogenesis of tumour in Asians, mainly Indians, is remarkably different than that in Westerners. In Western-European countries, BCC is the most common cutaneous malignancy, whereas in India SCC is highly prevalent [1].

For the pathogenesis of tumours, genetic mutations are crucial aspects of which p53 gene mutations are predominantly involved in the development of 50% of all tumours. p53 mutations, resulting mainly from the exposure to UV radiation, are foremost in the development of skin tumours [4]. Immunohistochemistry of p53 is an affordable reproducible convenient method of mutational evaluation for diagnosing carcinomas. On immunohistochemistry testing, p53-positive tumours-presenting >10% of positively stained cancer cell nuclei-exhibit malignant features and more lymph node and liver metastases than p53-negative tumours [5]. These p53 mutations are reportedly higher in Westerners than in Asians, mainly Indians however, not many studies have validated this hypothesis. While existing skin tumour-oriented research revolves around Western countries, limited research has been conducted in India, suggesting a tremendous need for comprehensive research on a larger scale to avail current Indian perspective [6].

Considering the cross-cultural lifestyle, multiple atypical forms of skin tumours have been reported in Indian subcontinent, suggesting that causes and pathophysiology of skin tumours in India are different from that reported for Western countries [3]. In India, sparse research has evaluated risk factors, prognosis and histopathologic-clinicopathologic classifications of skin tumours [7,8]. Additionally, benign and malignant formsare remarkably similar in gross appearance, rendering reliable diagnosis challenging. Thus

in such cases, histomorphology of excised skin lesions is highly promising [9]. This study aimed at evaluating the histomorphology of and subsequent p53 expression in epithelial skin tumours in India.

MATERIALS AND METHODS

This was a two-year observational study from July 2014-June 2016 observational study conducted in the Pathology Department of MS Ramaiah Medical College and Hospital. The study included 50 resection specimens of epithelial skin tumours in the later stages, which were received for histopathological evaluation. The study was conducted in accordance with the Helsinki Declaration of 1975. Prior to conducting, the study was approved by the Institutional Ethics Committee of MS Ramaiah Medical College (registration number: STD-I/EC/0400/2014). Written informed consent was obtained from all the patients whose biopsy/surgical specimens were included in the study.

The inclusion criteria included benign and malignant epithelial skin tumours, whereas exclusion criteria included metastatic and highly necrotic tumours. The sample size of 50 was calculated considering a relative precision of 10% and desired confidence level of 95% [10].

Nearly ≤3-mm-thick biopsy specimens were subjected to direct processing, whereas 4-6-mm-and ≥7-mm-thick specimens were cut into 2-3-mm-thick slices prior to processing. For wide local excision, 2-4-mm-thick sections from lesional area and surgical margins, including deep resected margin, were submitted. After conventional processing, 5-µm-thick paraffin sections of specimens were stained by haematoxylin and eosin (H&E) stains for histopathological study. Additionally, for malignant epithelial tumours, 4-µm-thick sections were cut from the paraffin sections of specimens for quantitative immunohistochemistry to detect p53 expression. Immunohistochemistry was performed as described by Kim et al., (2016) [11]. Positive control was tissue block of infiltrating duct carcinoma of breast, and negative control was the same tissue without primary antibody added; these were run with each batch of slides. The slides were scored according to the percentage positivity as 0 (no staining), 1+ (0-5% staining), 2+ (5-50% staining) and 3+ (>50% staining) [12].

STATISTICAL ANALYSIS

Data were analysed using statistical software R studio 3.5.3. All continuous parameters were expressed as mean±standard deviation. Descriptive statistics of histopathological parameters were analysed as proportion and expressed as percentage.

RESULTS

Of all the 50 specimens, 32 (64%) and 18 (36%) were obtained from males and females, respectively. [Table/Fig-1] depicts the classification of specimens based on the age of patients. For the age groups, mean±SD was reported to be 48.54±20.71 years. Of the 50 specimens, 26 (52%), 21 (42%) and 3 (6%) exhibited benign, malignant and premalignant (Bowen's disease) tumours, respectively [Table/Fig-2].

Age group (years) of patients	No. of specimens, N=50, n (%)
<20	5 (10)
20-30	8 (16)
31-40	3 (6)
41-50	6 (12)
51-60	13 (26)
61-70	7 (14)
71-80	8 (16)

[Table/Fig-1]: Study specimens according to the age of patients.

Types of tumour	Subtype of tumour	No. of specimens, N=50, n (%)
Malignant epithelial tumour (N=21)	Squamous cell carcinoma	11 (52.4)
	Verrucous carcinoma	2 (9.5)
	Basal cell carcinoma	6 (28.6)
	Malignant melanoma	2 (9.5)
Benign epidermal tumour (N=26)	Verruca vulgaris	3 (11.5)
	Seborrheic keratosis	9 (34.61)
	Squamous papilloma	2 (7.69)
	Nevi	12 (46.15)

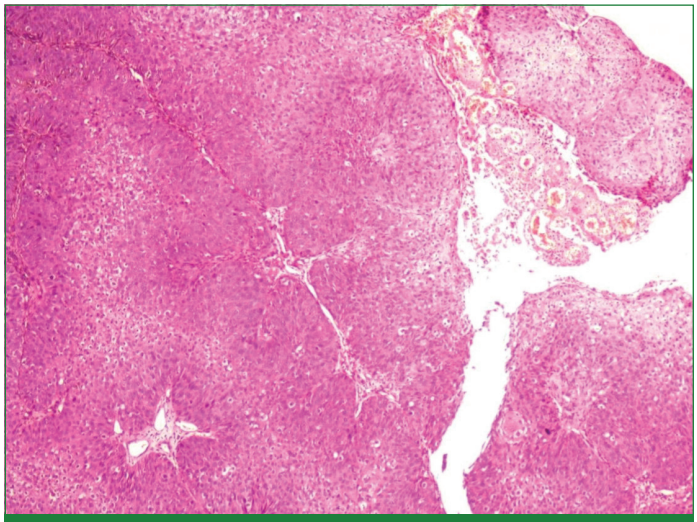
[Table/Fig-2]: Classification of specimens according the type of tumour.

Immunohistochemical findings

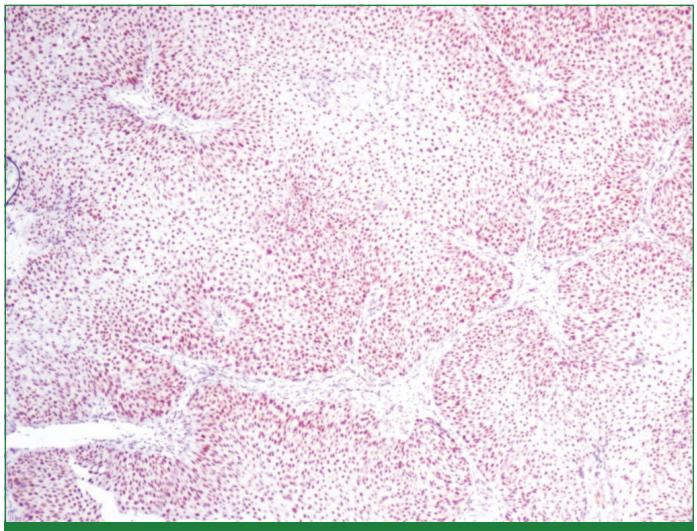
Malignant Epithelial Tumours

Squamous Cell Carcinoma

Presentation: These tumour cells were present as nests, sheets and singly in varying proportions. Well-differentiated tumours presented as keratin pearls. Cytoplasm was eosinophilic moderate-abundant with vesicular to hyperchromatic nuclei [Table/Fig-3-4]. According to the conventional grading of SCC, 7 (63.63%), 3 (27.27%) and 1 (9.09%) specimens were well differentiated, moderately differentiated and poorly differentiated, respectively.



[Table/Fig-3]: Moderately differentiated squamous cell carcinoma (H and E, ×400).



[Table/Fig-4]: Moderately differentiated squamous cell carcinoma (p53 staining, IHC,×20).

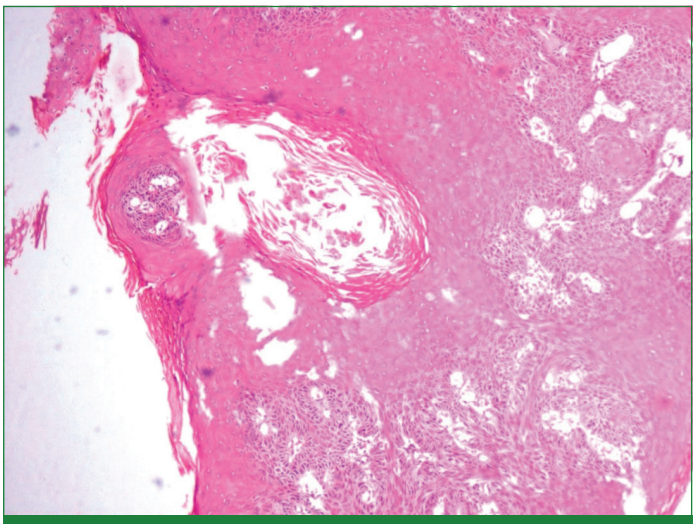
Age: Of the 11 (52.4%) specimens of SCC, 8 (72.72%) belonged to males, whereas 3 (27.27%) belonged to females. The incidence of age ranged from 22-78 years. With mean±SD of 53.63±16 years, 1 (9.1%), 2 (18.2%), 5 (45.5%), 1 (9.1%) and 2 (18.2%) specimens

belonged to patients who were in the age range of 21-30, 41-50, 51-60, 61-70 and 71-80 years, respectively.

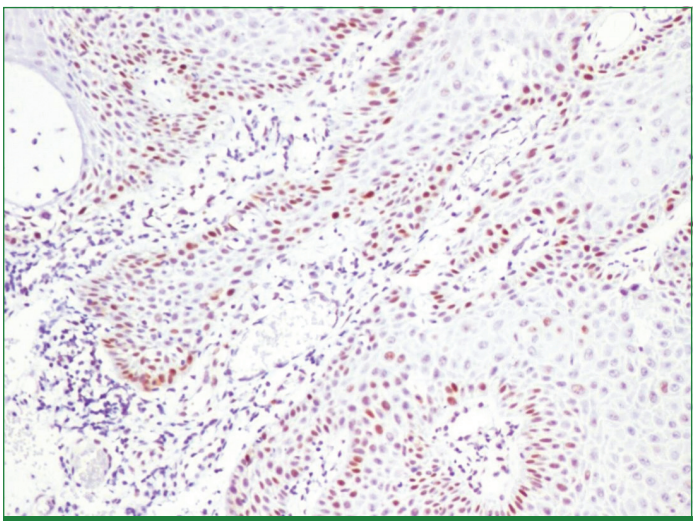
Location: In 4 (36.36%) patients,the tumour was present in the head and neck regions, i.e., one each in the right alar region, right neck, right cheek and scalp. In 3 (27.27%) patients, it was present in the genitalia (penile region); for 2 (18.18%), it was present in the extremities (in the thigh and fourth interdigital space) and for remaining 2 (18.18%), it was present in the chest wall and buttock each.

Verrucous carcinoma

Presentation: In the 2 (9.5%) specimens of verrucous carcinoma, the epithelium exhibited an asymmetric exophytic and endophytic growth patterns with pushing margins. Tumour cells showed glassy eosinophilic cytoplasm and exhibited minimal atypia and remarkably low mitotic activity [Table/Fig-5-6].



[Table/Fig-5]: Verrucous Carcinoma (H and E, ×400).



[Table/Fig-6]: Verrucous Carcinoma (p53 staining,IHC, ×10).

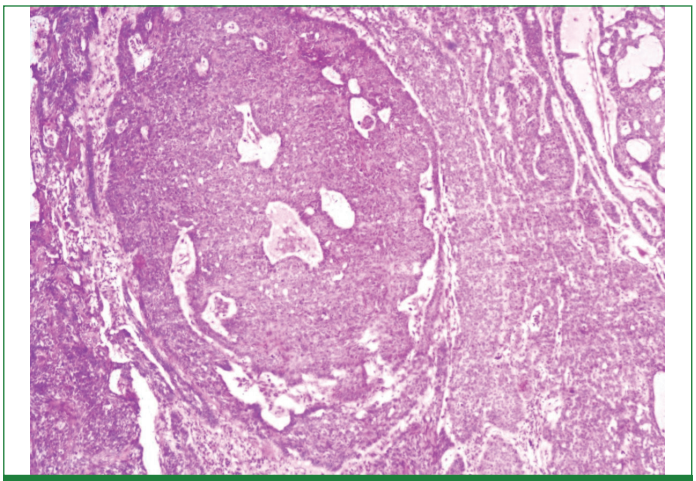
Age: Male-to-female ratio was 1:1. Of the two, one specimen each belonged to a 51- and 70-year-old patients.

Location: In 1 (50%) patient, the tumour was located on the edge of the lips, whereas in another (50%) patient, it was located in the external genitalia (penile region).

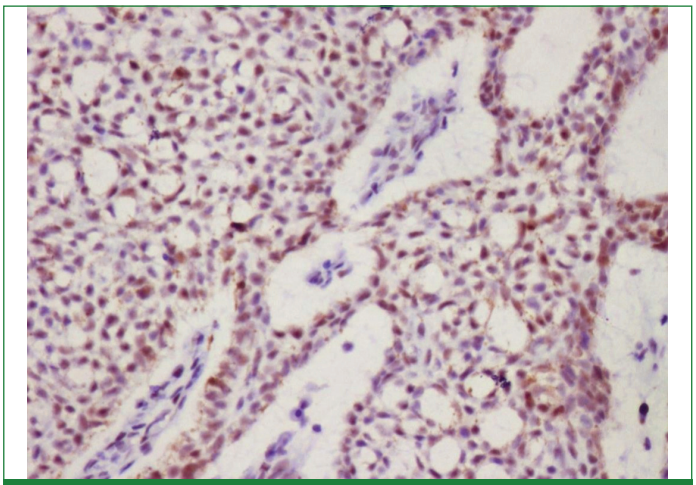
Basal cell carcinoma

Presentation: The tumour cells were composed of basaloid cells arranged in nests, islands and cribriform patterns and sheets, exhibiting peripheral palisading and retraction clefts [Table/Fig-7-11]. Moreover, based on the histomorphological variants of BCC, it was noted that pigmented, nodular, solid and basosquamous types accounted for 33.33%, 50%, 33.33% and 16.6% of all BCC, respectively.

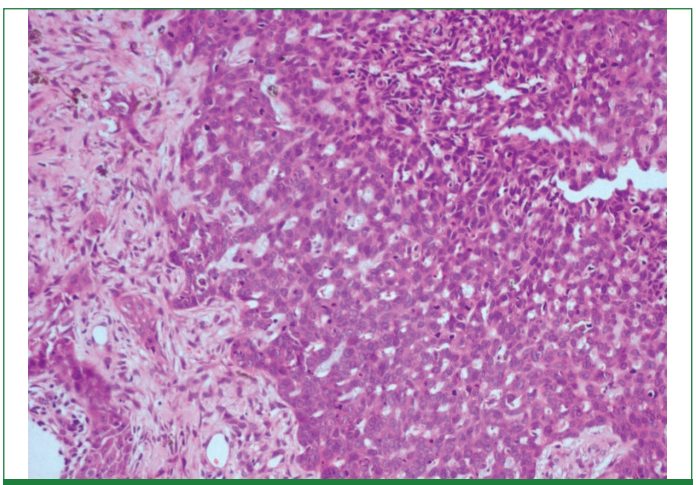
[Table/Fig-7]: Basal Cell Carcinoma (Gross specimen-postauricular region).



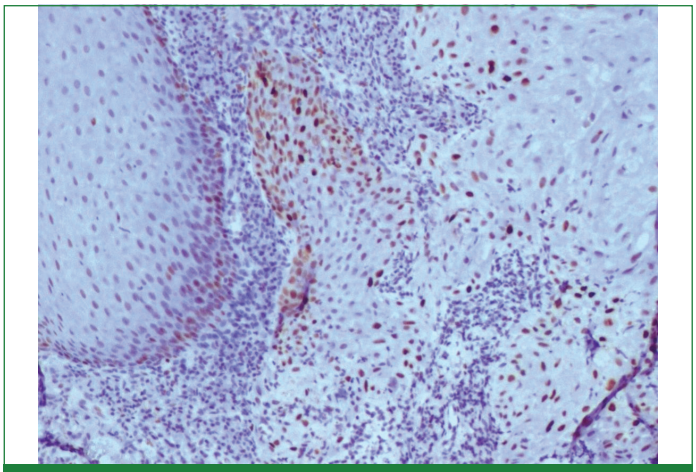
[Table/Fig-8]: Basal cell Carcinoma (H and E, ×400).



[Table/Fig-9]: Basal cell carcinoma (p53 staining, IHC, ×20).



[Table/Fig-10]: Basosquamous Carcinoma (H and E, ×100).



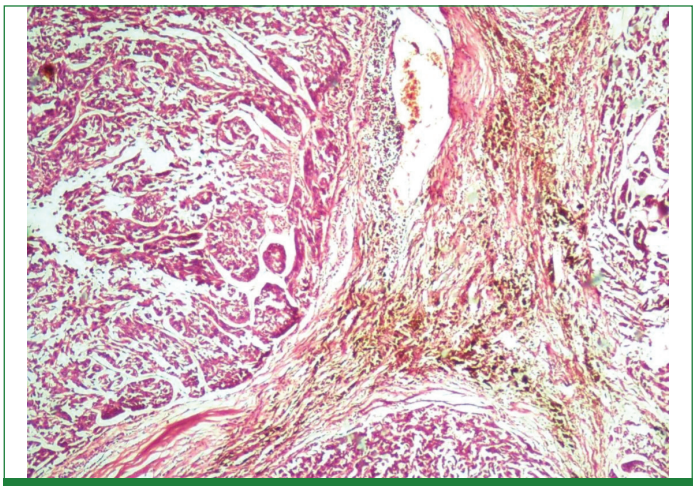
[Table/Fig-11]: Basosquamous Carcinoma (p53 staining,IHC, ×200).

Age: Of the 6 (28.6%) specimens of BCC, 4 (66.66%) belonged to females and 2 (33.33%) belonged to males. With mean±SD of 64.66±6.12 years, 1 (16.66%), 3 (50%) and 2 (33.33%) specimens belonged to patients who were 51-60, 61-70 and 71-80 years old, respectively.

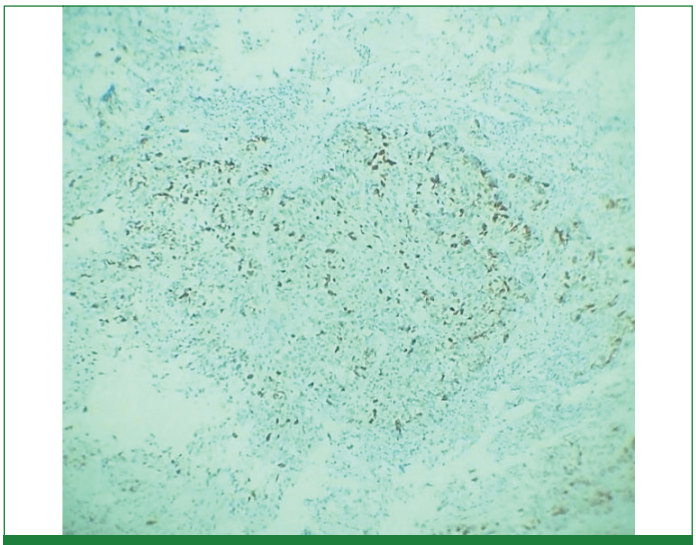
Location: The tumour was present in the head and neck region, i.e., one each in the right lower eye lid, right cheek, scalp, left forehead, left lateral canthus and postauricular region.

Malignant melanoma

Presentation: These cells, arranged in nests and sheets, appeared large with large nuclei with irregular contours, chromatin clumped at the periphery of nuclear membrane, prominent eosinophilic nucleoli and cytoplasm with fine melanin pigment granules [Table/Fig-12-13].



[Table/Fig-12]: Malignant melanoma (H and E, ×400).



[Table/Fig-13]: Malignant melanoma (p53 staining,IHC, ×200).

Age: Male-to-female ratio was 1:1. Of the 2 (2.95%), one specimen each belonged to a 51- and 70-year-old patients.

Location: In 1 (50%) patient, the tumour was located in the perianal region, whereas in the other (50%) patient, it was located in the 4th-5th interdigital space of the left foot.

Benign Epidermal Tumours

Verruca vulgaris (non-melanocytic)

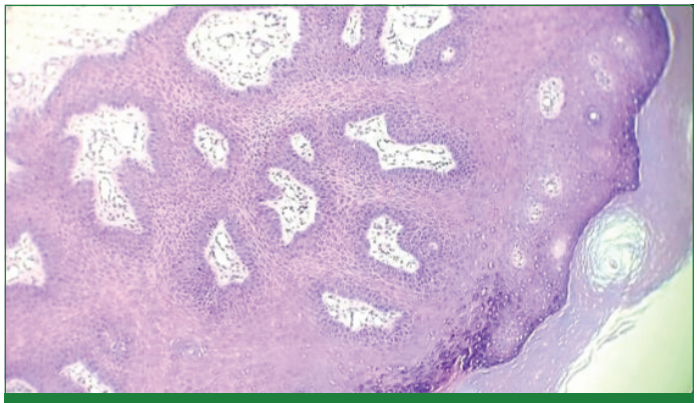
Presentation: Of all 26 benign tumours, 3 (11.5%) specimens presented palmo-plantar wart or verruca vulgaris exhibiting acanthosis, hyperkeratosis and some degree of papillomatosis with koilocytic changes.

Age: All three specimens belonged to patients who were in the age range of 8-27 years. Male-to-female ratio was 2:1.

Location: The tumour was located on the left finger in 2 (66.66%) and the left sole in 1 (33.33%).

Seborrheic keratosis (non-melanocytic)

Presentation: All 9 (34.61%) specimens of seborrheic keratosis exhibited acanthosis and hyperkeratosis. Papillomatosis and horn cysts were observed to a certain degree [Table/Fig-14]. Eight (88.88%) specimens were of the acanthotic type, whereas 1 (11.11%) specimen was a pigmented variant.



[Table/Fig-14]: Seborrheic keratosis (H and E, ×100).

Age: Five (55.55%) specimens belonged to males, whereas 4 (44.44%) specimens belonged to females. Age of the patients ranged from 38-71 years.

Location: In 2 (22.22%), 1 (11.11%), 1 (11.11%), 1 (11.11%), 1 (11.11%) and 3 (33.33%) patients, the tumour was located on the back, anterior abdominal wall, chest wall, breast, eyelid and face (including one on the postauricular region), respectively.

Squamous papilloma (non-melanocytic)

Presentation: These 2 (7.69%) specimens showed hyperkeratosis, parakeratosis, acanthosis and papillomatosis.

Age: Both the lesions were seen in male patients.

Location: Of the two patientswith squamous papilloma, the tumour was situated on the nape of the neck in 1 (50%) patient and the toe in another (50%) patient.

Nevi (melanocytic)

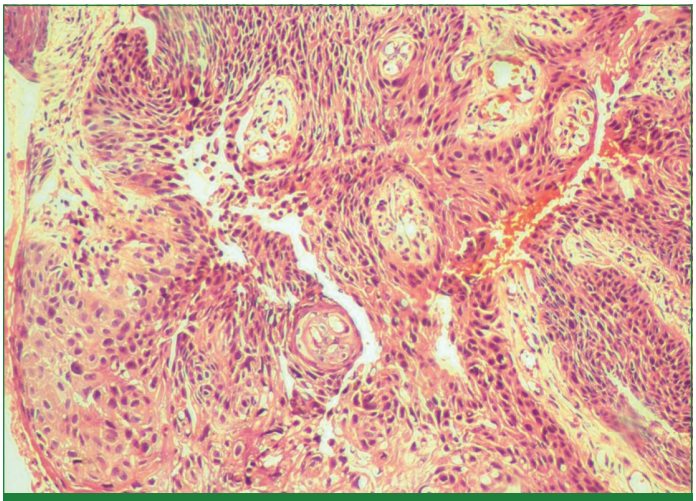
Presentation: Of the 12 (46.15%) melanocytic nevi, 4 (33.33%) were junctional; 5 (41.66%), compound nevi and 3 (25%), intradermal nevi. Nevus cell nests with coarse golden brown, intracytoplasmic granular pigment were located at the dermoepidermal junction in the dermis. As the nevus cells migrated to the dermis, they grew smaller in sise and appeared as cords and single cells.

Age: Male-to-female ratio was 3:1. All 12 (46.15%) specimens belonged to patients who were in the age range of 13-59 years.

Location: In 7 (58.33%), 3 (25%) and 2 (16.66%) patients, the tumour was located on the face, trunk and extremities, respectively.

Bowen's disease (non-melanocytic)

Presentation: In the 3 (6%) specimens presenting Bowens's disease, the tumour cells appeared as atypical squamous cells exhibiting mild to moderate pleomorphism without any infiltration and an intact basement membrane [Table/Fig-15].



[Table/Fig-15]: Bowen's disease (H and E, ×200).

Age: All three specimens belonged to patients who were in the age range of 53-75 years. Male-to-female ratio was 2:1.

Location: In all three patients, the tumour was located in the upper extremities.

p53 expression

For malignant epithelial tumours, p53 expression was evaluated as reported in [Table/Fig-16]. For SCC, % positivity for well-differentiated, moderately differentiated and poorly differentiated carcinomas was 38.5%, 38.3% and 45%, respectively. For BCC, malignant melanoma and verrucous carcinoma, % positivity was 68.33%, 55% and 15%, respectively.

DISCUSSION

Considering the rising prevalence of skin tumours in India, the present study aimed to evaluate the histomorphology and subsequent p53 expression in skin epithelial tumours. Skin tumours are more prevalent in white-skinned individuals, with BCC being the most common skin malignancy [3]. The prevalence is low in dark-skinned individuals, including Indians, mainly due to the protective effects of eumelanin against UV radiation [13]. Reportedly, in line with the literature, the present study reports that in dark-skinned individuals, mainly Indians, SCC is more common and aggressive than BCC and highly prevalent in males [3,9,14-16]. According to the American Cancer Society, the incidence of SCC in nearly thrice as higher in males than females owing to high occupational-recreational exposure to the sun with less UV-protection in males [17]. Similarly, BCC is also more prevalent in males [3]. However in the present study, BCC was more common in females, which was as reported by Asad et al (2014) [13]. In terms of NMSCs, SCC occurs more predominantly in white-skinned >50-year-old people, whereas BCC is known to be more common in teenagers and adults both [18,19]. In the present study, SCC was more commonly reported in younger age group than BCC. This altogether hypothesises that varying cross-cultural, gender-based and occupational differences and distinct geographical-epidemiological conditions or factors other than UV radiation are the influencing factors for skin tumours in India [3]. Moreover, the present study reported Bowen's disease-an early non-invasive stage of SCC-in 53-75-year-old patients, and it is highly prevalent in ≥60-year-old adults [20]. Bowen's disease is an in-situ SCC that occurs on any site of the body, more commonly in the upper extremities that are often exposed to the sun, as observed in the present study [21].

Available limited research in India mentions few atypical variants of NMSCs that are different from those reported in Western countries [3,22,23]. NMSCs exhibit same morphology with distinct architectural patterns [24]. Distinction between benign and malignant lesions may thus be difficult even for highly skilled dermatopathologists [25]. Thus although distinct morphological findings were not reported in the present study, the study highly recommends histomorphological evaluation and differentiation of skin lesions, considering their changing clinical manifestations reported in various Indian studies [22-24]. Such evaluations would contribute substantially to cancer research in India for better understanding of oncologists and more effective treatment measures for improved patient welfare.

In the present study, benign tumours were more common, mainly in younger patients (8-17 years), as compared to malignant forms (in 22-80-year-old patients). The present study also reports that benign forms are more prevalent in males than females [9]. This finding is concurrent with the literature, suggesting that benign tumours are more common than malignant ones and observed mainly in younger people, whereas prevalence of malignancies increases with age. This could be due to longer exposure of older individuals to harmful UV radiation that eventually strongly associates with malignant tumours [26]. Contrastingly, predominance of malignant skin tumours over benign forms has been reported in the literature [27,28]. The observed inconsistency is attributed to geographical variation [26]. Melanocytic benign skin tumours consist extensively of intradermal nevi presenting with unique clinical-morphological-genetic features [12,26]. Concurrent with the literature, the present study reports that nevi are common in <60-year-old people [13]. In the present study, second most common benign tumour was seborrheic kerastosis, which is a common benign form highly prevalent in middle-aged individuals [29-31]. Congruent with the literature, the present study observed common histopathological features of seborrheic kerastosis as papillomatosis, pigmentation, horn cysts, acanthosis and hyperkeratosis [29].

As observed in the present study, skin tumours primarily occur on head, neck and extremities-body sites highly exposed to maximum sunlight and UV radiation [9,16,26,32].

In terms of genetic mutations, the expression rate and positivity of p53 reportedly varies between white- and dark-skinned individuals, mainly Indians [6]. In the present study, p53 overexpression was notably low. Contrastingly, studies focusing on Western population have reported p53 activity of nearly 65-100% and 84-100% in SCCs and BCCs, respectively [10,33-35]. Compared to Western research, a study conducted by Malhotra et al (2011) in North Indian population reported p53 expression rate as low as 17.6% for BCC [8,10]. Reportedly, p53 expression and effects of UV radiations are interconnected in skin tumours in that UV-induced skin tumours inactivate p53, whereas high concentration of UV-protective eumelanin in the dark skin mitigates p53 mutations [36,37]. The present study hypothesises that in terms of skin carcinomas, observed low p53 activity in Indians is due to the effect of eumelanin in dark-skinned individuals. Nevertheless, this hypothesis needs to be validated by future studies.

p53 positivity scoring and percentage, N=21	Squamous cell carcinoma, N=11, n (%)	Basal cell carcinoma, N=6, n (%)	Verrucous carcinoma, N=2, n (%)	Malignant melanoma, N=2, n (%)
2+=5-50%	8 (72.72)	1 (16.66)	2 (100)	1 (50)
3+=>50%	3 (27.27)	5 (83.33)	0	1 (50)

[Table/Fig-16]: p53 expression in malignant tumours.

Limitation(s)

Because there was no direct contact with patients in the present study, socio-demographic parameters, including family history, social background, occupation and comorbidities, could not be evaluated, which otherwise would have helped better understand the risk factors and origin of skin tumours for a more comprehensive analysis. The sample size of 50 specimens is too less to extrapolate the findings to general population. Thus, future studies with larger sample sise should be conducted to validate the proposed hypothesis and comprehensively study the role of eumelanin in skin tumour. The increasing burden of skin tumour in India highlights the growing demand of introducing national diagnostic programs for early screening purposes and subsequent effective therapeutic intervention. This would substantially decrease cosmetic and functional morbidity and mortality and medical costs. Future studies can also be conducted to evaluate gender-based differences in various aspects of skin tumours in India. The study suggests to promote awareness among oncologists, clinicians and general population regarding growing preponderance of skin tumours in India. The present study provides a basis for future research for developing diagnostic, educational and preventive strategies for dealing with evolving variants of skin tumours.

CONCLUSION(S)

Histomorphological and immunohistochemical evaluation of skin lesions would contribute substantially to the comprehensive diagnosis of skin tumours and development of effective therapies and pharmaceutical drugs for improved patient management and outcomes. The knowledge of the frequency of histopathological patterns can help in viewing the prognostic outlook for patients. In this study, SCC was the most common skin malignancy, followed by BCC, and melanocytic nevus was the most common benign skin tumourfollowed by seborrheic keratosis. In this study, in malignant epithelial skin tumours, p53 expression rate varied in the degree of positivity. The present study hypothesises that p53 expression rate is relatively lower in Indians than that in white-skinned people.

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