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Review Article

Clinical Characteristics of Basal Cell Carcinomas of the Scrotum: An Institutional Retrospective Review

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Objective. To analyse the clinical and pathologic features, discuss therapeutic strategies, and possibly cause and identify prognostic factors of scrotal basal cell carcinoma (BCC) in Chinese patients. *Materials and Methods*. Between January 2012 and December 2022, 12 patients with scrotal BCC were diagnosed and treated at our institution. A review was conducted based on the clinical characteristics, pathology slides, and tissues of these patients. *Results*. The median patient age was 69.26 ± 11.23 years. The skin lesions presented as red papules, blue-grey polypoid nodules, erythematous patches, brownish plaques, and so on. All patients were treated using wide excision, but the margins varied from 0.5 cm to 2 cm. HPV infection was checked in all lesions, with 4 out of 12 testing positive for P16 and 1 for HPV16 DNA. We found mottled positive expression of P16 in the cytoplasm and membrane. One patient developed left inguinal lymph node metastasis and was successfully treated using bilateral inguinal lymphadenectomy. The rest recovered well without relapse. *Conclusions*. BCC of the scrotum is rare, but long-term surveillance is recommended for BCC patients, and whether genital HPV infection is a noteworthy feature for these patients remains under investigation.

1. Introduction

Basal cell carcinoma (BCC) is the most common malignancy worldwide. It is slow-growing, rarely metastasizes, and mainly occurs in areas frequently exposed to sunlight, such as the face, neck, and arms. BCC rarely affects the genitals (0.1–0.27% of all BCCs) [1] Scrotal BCC is rare in the Chinese population [2]. BCCs are unusual on sun-protected skin, but BCC cases involving the scrotum are more likely to metastasize [3]. And other etiologic factors must be considered. So we admitted 12 patients with scrotal BCC, and the overall details were recorded.

2. Methods and Materials

Between January 2012 and December 2022, 166 malignant scrotal neoplasms were diagnosed and treated in our urology and dermatology ward. Twelve cases were BCC. We reviewed the clinical records and pathologic slides of these patients with scrotal BCC. Formalin-fixed biopsy and resection specimens were routinely processed, embedded in paraffin, and stained with haematoxylin and eosin. DNA was extracted from the tissues either immediately or the tissues were frozen at −70 C until DNA extraction. The human papillomavirus nucleic acid detection kit (biochip method) is used with the nucleic acid chip detector (model BHF-VI) produced by Bohui Company. Several variables were analysed, including age at diagnosis, clinical presentation, tumour size, predisposing factors, histologic subtype, section intervals, and therapy choice.

Two experienced dermatopathologists reviewed all pathologic slides independently and grouped them into different variants according to the histopathology of BCC in the World Health Organization classification.

3. Results

The clinical data and demographics of all BCC cases are presented in Table 1. Our 12 patients came from four different provinces in China. The median patient age was

Table 1: The clinical data and demographics of all cases.

Case	Age	Clinical presentation	Lesion dimension (cm)	Duration (before diagnosis)	Depth of invasion	Treatment	Follow-up, months	Subtype	Excision margin (cm)	HPV (P16)	Outcome
1	72	Brownish plaque and nodule	3.0 * 3.0	2 m		Excision	88	Nodular	2	–	Complete remission
2	62	Brownish plaque and nodule with ulcer	5.0 * 3.0	5 Y	Lymph nodes	Excision and lymphadenectomy	84	Nodular and infiltrating	2	–	Complete remission
3	73	Dark red to brownish plaque	3.0 * 2.5	2 Y		Excision	86	Nodular and infiltrating	0.5	–	Complete remission
4	77	Brownish plaque and nodule	3.0 * 2.5	6 M		Excision	76	Nodular	0.5	–	Complete remission
5	82	Red to brown nodule with surface ulceration	3.0 * 2.5	5 Y		Excision	76	Nodular	0.5	–	Complete remission
6	43	Brownish plaque and nodule	2.0 * 2.0	6 M		Excision	55	Nodular and infiltrating	1	+	Complete remission
7	62	Indurated poorly defined plaque and nodule	4.0 * 3.0	30 Y	Muscular	Excision	55	Superficial and micronodular	2	+	Complete remission
8	71	Hyperpigmented infiltrated plaque with dotted ulcer	3.0 * 2.0	20 Y		Excision	44	Nodular and infiltrating	0.5	–	Complete remission
9	87	Brownish plaque and nodule	4.0 * 2.0	1 Y	Dermis layer	Excision	24	Nodular, keratotic	0.5		Complete remission
10	57	Brownish plaque and nodule	2.0 * 2.0	10 Y	Dermis layer	Excision	13	Superficial and micronodular	0.5	+	Complete remission
11	58	Pinkish dome-shaped, exophytic nodule	4.0 * 3.0	2 Y	Dermis layer	Excision	10	Nodular	0.5	–	Complete remission
12	63	Brownish plaque and nodule	2.0 * 2.0	6 M	Dermis layer	Excision	6	Superficial and micronodular	0.5	+	Complete remission

69.26 ± 11.23(range 43–87). None of the patients had a previous history of malignant tumours or other cutaneous diseases.

The skin lesions presented as red papules, blue-grey polypoid nodules, erythematous patches, brownish plaques, or several cauliflower-like lesions, with or without ulceration, varying in size from 2.0 to 4.0 cm in diameter (3.42 ± 0.91) (Figures 1(a) and 1(b)).

All patients received a histopathologic diagnosis after the first incisional biopsy. Microscopic examination revealed that the basaloid cell nests were of various shapes and sizes under the epidermis of the mass. The tumour nests, which were composed of basaloid cells, were of different shapes and sizes and located under the epidermis of the group, peripheral palisading, and peritumoural slits in which amyloid deposits were found (Figure 2(a)). At higher magnification, the basaloid cells had large nuclei, scant cytoplasm, hyperchromatic nuclei, and numerous mitotic figures (Figure 2(b)).

During the histological examination, we could determine some subtypes including nodular: 75% (12% had cystic degeneration and 40% had an infiltrative component); superficial: 10%; infiltrative: 8%; and micronodular: 7%. No morpheaform, metatypical (basosquamous carcinoma), and adenocystic variants were found.

Moreover, the masses of the lesions were diagnosed with HPV infection. We tested all 12 patients with P16 immunostaining, and only 4 of them had positive results. Reverse dot hybridization using biochip probes indicated that one of these cases tested positive for HPV16. (Figures 3 and 4).

Skin biopsy enables exact BCC subtype identification, while B-ultrasound and magnetic resonance imaging can play pivotal roles in the diagnosis of bony, vascular, or major nerve invasion [4]. All of the patients underwent ultrasound examination and MRI to screen for metastasis. We found a hypoechoic mass within the basement membrane and with localized thickening. (Figures 5 and 6)

The duration from the appearance of signs and symptoms to the diagnosis of BCC ranged from 2 months to 40 years (18.96 ± 10.62). Seven patients had never smoked; the remaining five patients were smokers at the time of diagnosis and had smoked longer.

Those patients were treated using wide surgical excision, and the margin varied between 0.5 cm and 2 cm. The first 2 in our studies used a standard 2 cm margin, while the margin in the rest varied depending on the recurrence risk profile. One patient had inguinal lymph node metastasis that was successfully treated using radical surgical resection.

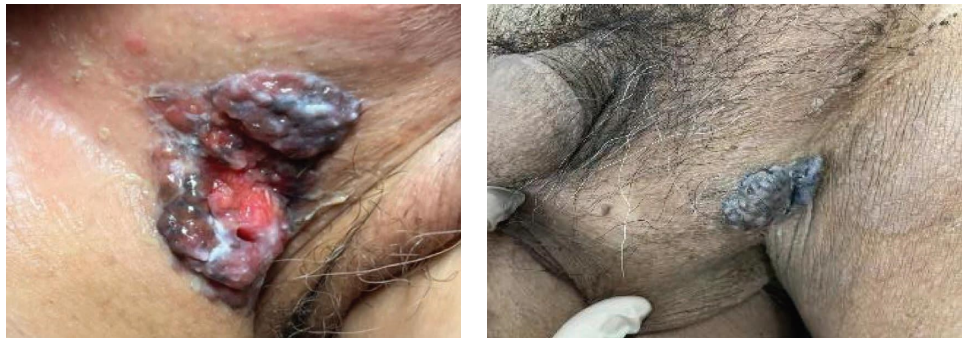
4. Discussion

BCCs account for 80% of all nonmelanoma skin cancers in the world and are more likely to occur in patients with a fair complexion, and their worldwide incidence has been continuously increasing [5]. It is most frequently seen after 50 years of age, but some patients develop BCC at an earlier age (<40 years) [6]. In our panel, there are three patients aged less than 60 years. Genital BCCs have significantly increased rates of metastasis compared to extragenital BCCs, accounting for 7% of all metastatic BCCs [7]. This emphasizes the importance of early detection and definitive surgical treatment of genital BCCs [8].

The pathogenesis of BCC is affected by a complex interaction between environmental, phenotypic, and genetic factors; due to its high incidence, many advances have also been made in the study of its molecular genetic background. The PTCH1 gene, as the key mutated gene for Gorlin syndrome (GS, also called basal cell nevus syndrome, which is characterised by the development of multiple BCCs), encodes a receptor that leads to the activation of the sonic hedgehog (SHH) pathway, which plays a vital role in the pathogenesis of BCC [9]. Consequently, this results in the decreased suppression of intracellular signalling by the G-protein-coupled receptor SMO, which leads to the direct upregulation of target gene transcription [10]. Xie's study showed marked enrichment in the cell cycle and p53 signalling pathway. FGF20, KIF23, and NCAPG were identified as diagnostic markers of BCC recurrence [11].

Ultraviolet radiation is the most significant risk factor for BCC development, including incredibly intense and intermittent sun exposure/sunburns in childhood and adolescence. Given that the external genitalia are not commonly exposed to sunlight, BCC rarely occurs in this anatomical region. Exposure to ultraviolet light is not always a predisposing factor in the development of BCC; other aetiologic factors should be considered when BCC appears in nonsun-exposed skin, such as radiotherapy, injury, dust exposure, ionising radiation, local chronic skin irritation, nonvenereal infection, chronic immunosuppression, photosensitizing drugs, carcinogenic chemical exposure, and smoking. Our patients all denied a history of injury and possible radiation.

It has also been proposed that genital papillomavirus (HPV) infection might stimulate the growth of scrotal BCCs [12]. The most common HPV-associated PeINs (penile intraepithelial neoplasias) included as "subtypes" are the basaloid subtype and warty subtype. Basaloid PeIN is recognised based on the presence of a rather monomorphic population of small immature cells (basaloid appearing) with high N : C ratios, numerous mitoses, and prominent apoptosis [13]. There are many different explanations for why P16 is positive in BCC. In 2004, Santos et al. [14] included 10 BCCs in their series of precancerous and malignant vulvar epithelial lesions and reported that 6 of 10 BCCs were P16 positive. In this series, positive was defined as >25% of cells stained and weakly stained. The degree of cell staining will decide whether P16 is positive. de Koning et al. [15] suggested that strong positive P16 immunostaining is a sensitive and specific marker for HPV-positive genital carcinoma and can help in subclassifying tumours with mixed or overlapping histologic features or in further exploring the relationship between HPV and BCC. It has also been noted that the positive expression of P16 was 75.0%, 88.8%, and 100.0% in superficial, nodal, and infiltrative histological subtypes, respectively. Bartoš [16] suggested that P16 expression may be associated with the aggressiveness and infiltrative nature of the tumour, with more vital positivity for P16 indicating a high likelihood of infiltration.



(a) (b)

Figure 1: (a) A grey, pink, and ulcerated nodule covered in greyish-white discharge on the right scrotum (5 × 3 cm). (b) A grey-blue, irregularly shaped nodule on the left scrotum (2 × 3 cm).

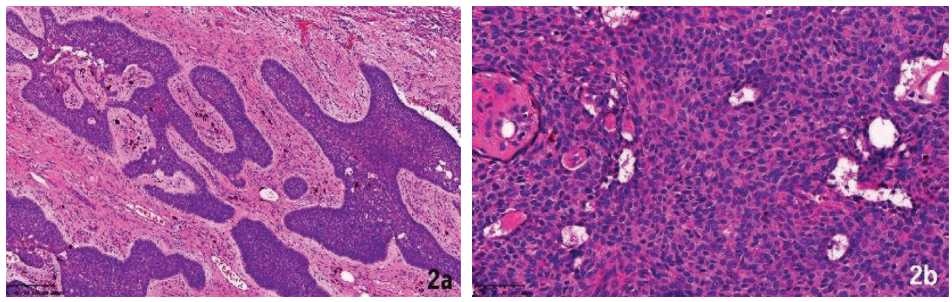
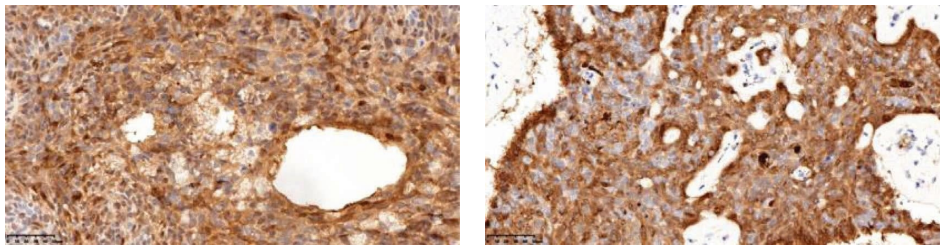
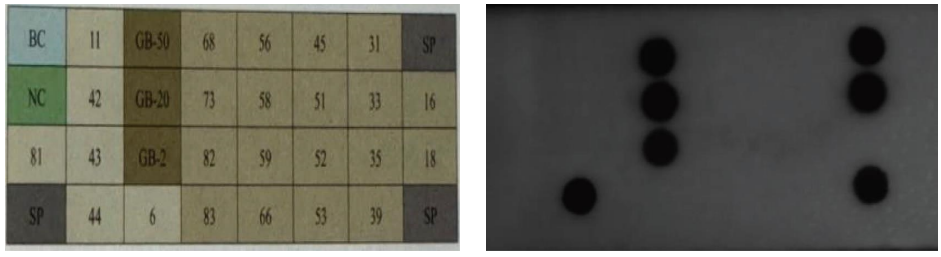


Figure 2: (a) Basaloid cell nests were of various shapes and sizes, showing infiltrative growth under the epidermis of the mass. (b) The basaloid cells had large nuclei, scant cytoplasm, hyperchromatic nuclei, and numerous mitotic figures.



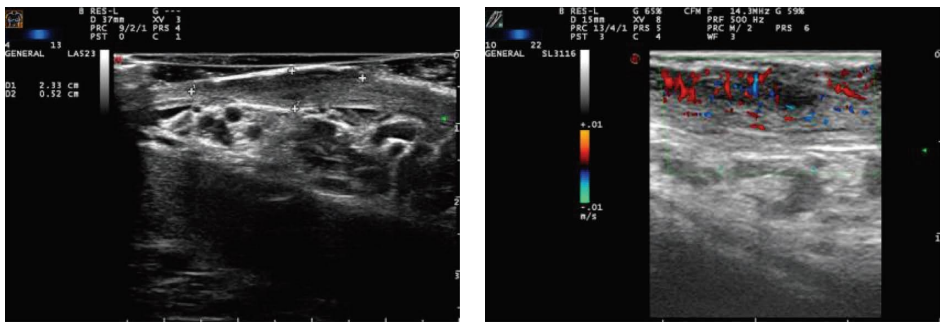
(a) (b)

Figure 3: Tumour cells had mottled positive P16 expression (tan staining) in the cytoplasm and membrane (a). The typical basaloid cells with tan staining in the cytoplasm (b).



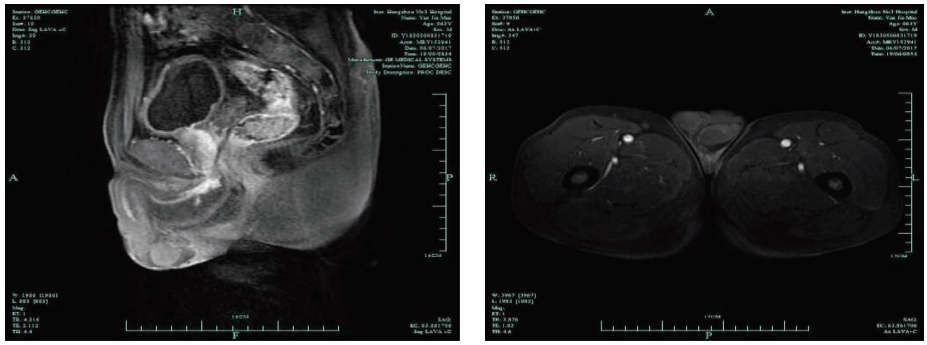
(a) (b)

Figure 4: Introduction to the hybrid film sample on the chip: different HPV probes: a quality control probe, an internal control probe, a positive control probe, and a negative control probe (a). Reverse dot blot hybridization shows HPV type-16 positive (b).



(a) (b)

Figure 5: (a) The basement membrane zone and dermis were indistinct and hypoechoic, approximately 23.3 ∗ 5.2 mm in extent. (b) CDFI shows abundant blood flow signals.



(a) (b)

Figure 6: In median sagittal section: with enhancement, localized thickening of the scrotal skin could be found (a). In transverse section: with enhancement, cross-sectional area and deep part of scrotum mass could be measured (b).

Elwood et al. [17] concluded that although genital BCC may indeed show patchy P16 staining, with up to 50% of tumour cells often showing enhanced peripheral P16 expression, the type of staining is markedly different from the diffuse intense P16 expression observed in actual high-risk HPV-associated lesions. Interestingly, although in situ hybridization for BCC has been reported in the scattered literature to show HPV positivity, PCR testing for HPV DNA has hardly been reported to be positive in the literature. The PCR testing of three BCC tissues by Nahass et al. [18] did not reveal the HPV gene, and in situ hybridization of four genital BCC tissues by Nehal et al. [19] did not reveal DNA of HPV types 6, 11, 16, 18, 30, 31, 33, 35, 45, 51, and 52. Gibson and Ahmed [20] also did not detect in situ hybridization in five genital BCC tissues for pan-HPV and for serotypes 6, 11, 16, 18, 31, 33, and 51. Wang et al. [21] tested all 33 genital BCC cases negative for HPV but unfortunately did not shed further light on the possible pathogenesis of genital BCC. Meibodi et al. [22] performed the first PCR test for HPV DNA in Asian BCC and still did not obtain a positive result.

We tested all 12 patients with P16 immunostaining and reverse dot blot hybridization; only 4 had P16 positive results. We found mottled positive expression of P16 in the cytoplasm and membrane. By biochip screening 24 types of HPV DNA, we only got one positive impact for HPV 16 DNA. Due to our relatively small cases and the retrospective nature of the analysis, it will be hard to determine whether HPV is associated with scrotum BCC; further cases and possibly other testing will add to this knowledge.

Therefore, further testing for other relevant specific markers of HPV in BCC biopsy tissues is needed as a reference. Further studies to compare HPV DNA in BCC using paraffin-embedded blocks, fresh tissues, and snap frozen punch biopsy, as well as alternative PCR methods such as real-time PCR and nested PCR using more primers that are more sensitive than conventional PCR, are recommended to detect HPV DNA in samples.

The goal of BCC treatment is to remove the tumours altogether and maximally preserve functions and aesthetics at the site of treatment. Current guidelines suggest a range of peripheral margins between 2 mm and 5 mm for low-risk tumours and between 5 mm and 15 mm for high-risk lesions [23]. For primary morphoeic BCC, an extended margin greater than or equal to 13 to 15 mm is recommended according to the BAD guidelines. Regarding deep lesions, deep margins should extend to the level of the fascia, perichondrium, or periosteum, while some recommended extending to the level of subcutaneous fat [24, 25]. Despite different biopsy habits between urologists and dermatologists (urologists prefer to punch and resect, while dermatologists prefer to shave instead), the final margin for our patients was decided by frozen confirmation, recovered well

without metastasis, and received no radiotherapy or chemotherapy after surgery. No metastasis was detected; we will continue to follow up with those patients.

In addition to surgical excision, a variety of medical therapies are available for the treatment of BCC. Cryotherapy, topical pharmacological strategies, and photodynamic therapies are possible treatments for BCC. Metastasis of BCC is rare, but scrotal BCCs are much more likely to metastasize than nonscrotal BCCs, with a rate of up to 20% at 24 months postexcision; the most common sites of spread include the inguinal lymph node, lung, bone, and skin. Care must be taken to distinguish BCC of the scrotum from basaloid squamous cell carcinoma, which has aggressive histological features such as mitoses and comedonecrosis [26]. In advanced or metastatic diseases, surgical treatment does not provide radical excision, so its implementation is limited in these cases. As indicated, targeting the hedgehog pathway significantly affects BCC progression and patient outcomes [27]. Since many elements may interact in the Hh pathway, these drugs can be divided into groups: SHH inhibitors, SMO antagonists, and GLI inhibitors. The two most well established are sonidegib and vismodegib, the only registered oral agents for metastatic or advanced BCC [28].

In conclusion, because of the metastatic potential of scrotal BCC, long-term surveillance, including a complete metastatic examination, is recommended for such patients, and whether genital HPV infection is a noteworthy feature for these patients remains under investigation.

Data Availability

The clinical data and demographics of all cases used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest regarding the publication of this paper.

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