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PRIMARY CANCER OF THE SCROTUM IN PORT HARCOURT, NIGERIA; NATURAL HISTORY, LITERATURE REVIEW AND PROSPECTS FOR PREVENTION

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ABSTRACT

Introduction: Advanced primary scrotal cancer has poor prognosis. The objective of this study is to detect and employ any favourable aspects of the natural history of the disease to prevent it and improve early presentation for treatment by affected patients. **Materials and Methods:** Using a common proforma, each of consecutive urology patients treated at the hospital from 01/4/2004 to 30/6/2020, was evaluated clinically with relevant investigations. History, features and chronological changes in pre-existing scrotal lesions were documented. Data were collected contemporaneously. Using search terms, the PubMed/Medline computerized data base and texts were searched for publications made on primary cancer of the scrotum during the study period. These were reviewed and relevant data obtained. **Results:** Of 5250 consultations, four patients had scrotal squamous cell carcinoma, and another scrotal eccrine porocarcinoma. Their ages ranged from 59 to 70 years. Duration of pre-existing scrotal lesions(in months) were 120, 24, 10, 12, and,16 respectively. Time each patient first noticed his scrotal lesion(s) to the time of histological diagnosis of malignancy (in months) were 121,25,11,13, and 17 respectively. Most premalignant or pre-existent scrotal lesions were reported to be amenable to curative preventive excisional treatment. Typical natural history of common variants of the disease characterized by slow progression from benign lesion(s) to malignancy was noted. **Conclusion:** We recommend informed regular preventive scrotal self-examination (RPSSE) from adolescence, excision biopsy and histology of detected scrotal lesions, and active surveillance of affected patients by clinicians.

KEYWORDS: Primary scrotal cancer; natural history; prevention; early detection.

1.0 INTRODUCTION

Advanced primary scrotal cancer has poor prognosis.[1] In our experience reported previously patients with the disease commonly presented late for treatment.[2] Such delayed presentation was associated with high tumour burden, high morbidity and mortality. Poverty and poor compliance with treatment schedules were compounded by previous wasteful expenditure of their scarce funds on prolonged previous failed unorthodox alternative treatments. Different reports in the literature of delayed presentation by patients with the disease suggest that this trend may be fairly global.[3,4,5,6,7,8,9] The aim of this study is to present a series of patients with primary scrotal cancer managed by us in our local institution, collate the experiences of others reported in the literature, to form the basis for a programme that encourages physical participation of all consenting male subjects in early detection, treatment and prevention of the disease.

2.0 MATERIALS AND METHODS

2.2 Methodology: Data collection was done contemporaneously with evaluation and treatment of consecutive male urology patients seen at the University of Port Harcourt Teaching Hospital(UPTH), Port Harcourt, Nigeria, for treatment. Those with histologically confirmed primary malignant lesions of the scrotum were further studied and included in this

report. The study period was from 01/4/2004 to 30/6/2019. Only lesions of the scrotal wall (scrotal skin, dartos, external spermatic fascia, cremasteric fascia/ muscle, internal spermatic fascia and the parietal layer of tunica vaginalis)[10] were considered in this study. Lesions arising from the scrotal contents were excluded.

Each patient had detailed clinical assessment and relevant laboratory tests. Personal data including age, occupation, presenting complaints, history of scrotal lesion(s) and when first noticed, mode of onset, duration of observed scrotal lesions (s) before presentation for treatment, morphological changes in the lesions, previous interventions, number of sexual partners and history of sexually transmitted infections were recorded. Examination of the external genitalia, the inguinal regions, with digital rectal examination (DRE) of the prostate gland, sacrum, pelvic sidewalls and palpable extent of the rectum was done for possible findings of extra-scrotal regional nodal/pelvic primary malignancies.

Investigations done on each patient included full blood count,(FBC), assay of serum electrolytes, urea and creatinine, serum prostate-specific antigen (serum PSA), urine microscopy culture and sensitivity, and urine cytology, serology for HIV1and 2. Abdominopelvic Ultrasonography and trans-rectal ultrasonography of the prostate were done. Two of the patients had abdominal and pelvic computerized axial tomographic scans. Incisional biopsy of each scrotal lesion was done. Histology was done by UPTH histopathologists. Clinical photographs of the malignant ulcers and associated inguinal lymphadenopathy were obtained. Cases of primary scrotal cancer diagnosed in the hospital during the study period are presented here in details considered relevant to this report.

2. 2.1 Literature Review

Using search terms 'Primary Cancer of the Scrotum', 'Premalignant Scrotal lesions', risk factors of of primary scrotal cancer cancer, duration and type of premalignant scrotal lesions, types of scrotal cancers, the PubMed/ Medline and PubMed Central databases were searched for publications made during the study period. Related articles and full texts of the publications were studied and cited as references. Other relevant texts in the English Language were also consulted. Data were gleaned and presented.

3.0 RESULTS AND DISCUSSION

3.1 Presentation of case series

Patient A; This patient was 70 years old. His scrotal lesion started as an itchy papule at the mid-anterior part of his left hemi-scrotum 10 years before he presented for treatment. The lesion ulcerated two years before presentation as a result of uncomfortable itching (about eight years after the onset of the papule). He neglected the initial scrotal lesion and so its initial diagnosis could not be made. However, incisional biopsy of the ulcer at presentation at the hospital showed that he had non-keratinizing poorly differentiated squamous cell carcinoma of the scrotum.

Patient B. This was a 67-year old fisherman**.** He had a pruritic papule at his left hemi-scrotum which he neglected for about 2 years before he presented to the hospital for treatment. The papule broke down into an ulcer about one year of its onset as he frequently scratched it. The resultant ulcer was treated at different patent medicine shops for approximately one year before he presented at UPTH. He presented because the ulcer was non-healing and progressively increased in size with constitutional features of weight loss and loss of appetite. Histology of incisional biopsy of the ulcer showed that it was squamous cell carcinoma of the scrotum.

Patient C (2007). Patient C was a 65-year old Ex-soldier who resorted to farming after retirement. A small pruritic papule developed at his left hemi-scrotum more than 10 months before he presented to the hospital for treatment. The lesion ulcerated on scratching. He presented for treatment following failed attempts at treatment of the resulting ulcer at a local patent medicine shop , and because of the large size of the ulcer, general constitutional symptoms and associated swelling at the groin. His ulcer had clinically malignant features which, with its histology report, showed that he had squamous cell carcinoma of the scrotum.

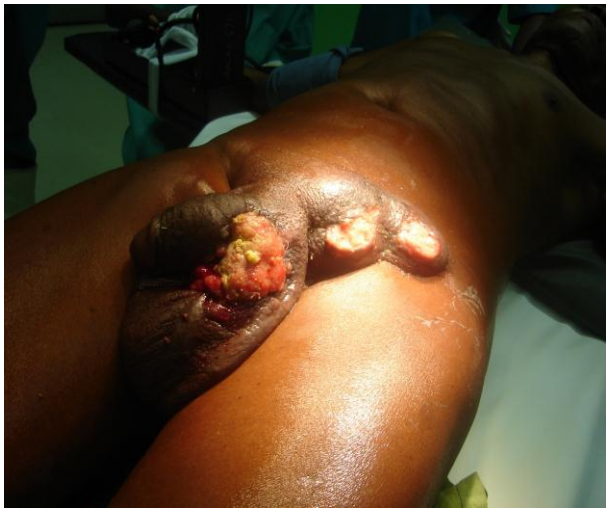

Figure 1: Patient C. Immediate intraoperative clinical photograph. Primary squamous cell carcinoma of the scrotum involving mostly the left hemi-scrotum. The edges of the lesion are raised and everted. An area of necrosis and bleeding is noticed at the inferior aspect of the lesion. The median septum of the scrotum and proximal one-third of the ventrum of the penis are involved. There is bilateral inguinal lymphadenopathy with ulceration of the left inguinal nodes. This patient presented late for treatment.

Figure 2: Rapidly developed fascio-cutaneous gangrene involving parts of both thighs, the whole phallus, and ventrum of the scrotum. The patient had itchy lesions about the scrotum and proximal parts of the phallus. On scratching bullous eruptions with rapidly spreading gangrene developed. He was HIV positive.

Patient D (2011): This patient was a bricklayer, 62-year old, HIV-positive and presented with a 6-month old ulcer at his left hemi-scrotum. The scrotal ulcer developed at the site of a small papule which he described as the 'size of a small pea' and progressively increased to the size of a tennis ball'. The papule was painful and broke down into a non-healing ulcer 6 months after it was first noticed. The ulcer persisted with inappropriate treatment for about 6 months before he was seen at the hospital. Histology reports with other tests showed that it was an eccrine porocarcinoma of the scrotum (Stage D).

Patient E.(2012): Patient E was a 59-year old trader. His scrotal lesion started as a black painless papule at the left hemi-scrotum. The lesion was painless for about one year and became painful 6 months before he presented at the hospital, and ulcerated 4 months after onset of pain. Further evaluations, including biopsy and histology showed that he had advanced squamous cell carcinoma of the scrotum.

3.2. Durations of the premalignant or initial scrotal lesion(s) (in months) were 120,24, 10,12 and 16 for patients A, B, C, D and E respectively. The intervals between the time of first notice of scrotal lesion by each patient and the time of histological diagnosis of scrotal cancer were (in months) A, 121; B, 25; C 11; D,13; and E, 17. The mean and median of these durations were 36.4 and 17 months respectively. The premalignant lesions could not be diagnosed or accurately characterized because they were not presented by the patients.

Ages of the patients with confirmed scrotal cancer ranged from 59 to70 years. One hundred and seventeen (117) publications were considered relevant to this study and reviewed. Twenty (17.1%) had sample sizes which ranged from 30 to 471 patients; ninety seven (82.9%) were either case reports, or had sample sizes less than 30 patients each.

Table 1: Durations of premalignant scrotal lesions before onset of malignant scrotal ulcers developed/ treatment as seen in the literature.

Reference	Number of patients	Type of (first) premalignant lesion	Duration of first lesion scrotal	Type of scrotal Cancer
Cases Reported in Our study	5	Unknown	mean-36.4 months median17mths	SCC - 4 EPC - 1
Krause W et al[11]	1	Intraepithelial EMPDS Early surgical excision	10 yrs before Diagnosis	Surgical Excision of EMPDS
Qing Y et al[12]	20		1-9 years average 4.7years before diagnosis	EMPDS
Prada D et al[13]	1	"Pruritic erythematous skin rash"	1 year	EMPDS
Ueda M et al.[14]	1	HPV Type 82 of the scrotum	-	Bowen's carcinoma
Redondo M E et al[15]	1	an excrescence in the right hemi-scrotum for several years.	-	Basal cell carcinoma of the scrotum
Aldewereld W et al[16]	1	Rash on the scrotum	Several years	EMPDS
Metin A et al[17]	1	Giant condyloma accuminata of the scrotum Surgical excision	Wide surgical excision	
Majid Ahmed Talikoti et al.[18]	1	Scrotal filanasis > 40yr + pain conservative with Chenotherapentic drugs	Leiomyosarcoma, Complete excisional surgery	
Zhihua Kang et al[19]	246	EMPDS Mean delay in diagnosis = 3. 6yrs; a case persisted for 30yr before diagnosis + pruritus, pain, rash, exudation	usually wide excision	

SCC, squamous cell carcinoma; EPC, eccrine-porocarcinoma; EMPDS, extramammary Paget's disease of the scrotum; mths, months; yrs, years.

3.2 DISCUSSION

We carried out this fundamental study because of the advanced nature of primary scrotal malignancies in patients we treated over the years. Such patients usually presented late with high tumour burden that posed treatment challenges with poor prognosis. The natural history of primary squamous cell carcinoma and eccrine porocarcinoma of the scrotum as observed in the patients with the disease in this study appears consistent with various observations in the literature.[7,10,18,19] In each case presented, the history was characterized by initial apparently inflammatory scrotal lesion, period of benign pathology of the scrotal lesion(s) (latent period) ulceration and subsequent development of malignancy, early malignancy, loco-regional and then distant metastases with severe morbidity. Important features of some of the primary scrotal malignant tumours include their relatively slow-growth and the role of chronic irritation in their aetiopathogenesis and complications.

We reviewed the findings and opinions of various authors on the delayed presentation, delayed diagnosis and treatment of various primary scrotal malignancies (apart from the series observed in our study) and observed that the phenomenon does not seem to be peculiar to SCC or eccrine porocarcinoma of the scrotum encountered in this study. Extra mammary Paget's disease of the scrotum (EMPDS), not seen in this study, but described elsewhere as 'an intraepithelial apocrine adenocarcinoma'[20,21,22] and found more in some parts of the world, is usually characterized by an initial period of slow intraepithelial non-invasive growth.[23] In one study a delay in diagnosis of EMPDS of 12 – 132 months (1 – 11 years) was observed, lending credence to the slow growth of the tumour.[24] EMPDS was also described as slow- growing in different other studies.[26,16,20,27]

Other primary scrotal cancers, basal cell carcinoma of the scrotum.[27] and even round cell liposarcoma, which usually has very high metastatic features at non-scrotal sites[28,29], were reported in one study to have had a relatively indolent course at the scrotum.[28] In the experience of others, the documented periods of slow growth varied from 10 months to 10 years.[11,16,20,29]

The absolute causes of slow growth and long latency of some malignant scrotal lesions will require another study. We surmise that the rather tenuous blood supply of the epidermis may partly explain the intra-epidermal slow growth of EMPDS. However, the slow growth of EMPDS may be due to under-expression, or lack of expression of HER-2 /neu, which was observed in a study in Texas, the USA.[30] Not all scrotal premalignant lesions, and or malignancies may have long latent periods, or are slow-growing respectively. Sarcomas, lymphomas melanomas and neuroendocrine malignancy of the scrotum usually have more rapid malignant courses.[18,31,32,33] Such rapidly growing scrotal tumours are rather rare in the literature. Their early stages may be detected by a good preventive scheme, and early treatment effected to achieve favourable prognosis.

Clinical features suggestive of chronic scrotal irritation (CSI) in the natural history of scrotal benign lesions and their malignant transformation were documented in some studies.[34,35,36,37,38] Pruritus, scratching of site of scrotal lesion and resorting to repeated unorthodox alternative treatments by affected patients often result in secondary infections, perineal and scrotal gangrene and sometimes severe sepsis. This was the problem with one of our patients who had a ventral scrotal tumour, immunopaenia, and tested positive for HIV 1and 2 (Figure 2). The molecular mechanisms that cause these symptoms, including the release of bradykinin, prostaglandins, histamine and intermediate molecules at the site of injury were well described by Kim E Barrett and Her colleagues.[39] Pain and pruritus may cause other complications that may affect the course of morbidity and mortality associated with the primary malignant scrotal lesion(s). These include agony and anxiety in severe pain,[42] scratching of the inflamed pruritic scrotal cutaneous lesion(s), which unwittingly causes further inflammation and chronicity of the lesion.[43] Both symptoms may signify pathological advancement of scrotal lesions and/ or malignant transformation.[44]

The five patients in our series never reported to us for treatment with the pre-existing scrotal lesions but presented with advanced malignancy. We therefore relied on each patient's retrospective description of chronological morphological changes of the pre-existent scrotal lesions. However, pre-existing scrotal lesions and / or risk factors identified in different studies published in the literature are treatable, or can be prevented, and when diagnosed early, curable before advanced malignant transformation (Table 1). Many of these include the following:- "human papilloma virus tumours (condylomata) (HPV) hydradenitis suppurativa, chronic scrotal infection with abscesses, inflamed epidermal cysts, lichen plannus"[33,45,46]; psoralen plus ultraviolet A (PUVA) used in treatment of psoriasis[47,48]; and Bowenoid papillosis and erythroplasia of Queyrat[49,50,51,52] as well as previous cutaneous malignancies at other cutaneous sites.[21] In some cases, like in this study, no specific diagnoses of the premalignant lesions were made. The lesions were merely described as pruritic, painful or painless scrotal lesions.[15,16] Most are amenable to excisional treatment.

3.3 Limitations of the study

The heterogeneous nature of the reviewed studies may be considered a source of error in the description of the natural history of the tumour. This is because many of the publications which similarly described the history of the disease were case reports involving one or few patients, or had small sample sizes. This is not unexpected of reports on rare tumours. However, many different publications which had greater sample sizes[17,18,19], reported the same pattern of occurrence of

premalignant, or pre-existing apparently benign scrotal inflammatory lesion(s), persistence of such lesion(s) over a latent period of benign pathology, and then malignant transformation. The patients might not have given accurate description and histories of their pre-existing scrotal lesions. This could partly be due to delayed presentation for treatment, forgetfulness, ignorance of prognostic significance of the lesions, poverty, negligence, shyness or a combination of these. However, the histories were vetted. A margin of error in the histories given by patients may be inevitable and tolerated without affecting the outcome or objectives of this study. The periods of delay in reporting and in making diagnosis which ranged (in months) from 10 to120 and11to 121 respectively were rather preposterous but similar to observations in different studies in the literature.[12,16,21,24,53]

3.4 Knowledge Gap

There is a knowledge gap with respect to two theoretical concepts that would be most valuable in predicting onset of clinical scrotal malignancy when a pre-malignant scrotal lesion has developed. These are the concepts of "**total preclinical phase" (TPCP),** and that of "**length bias**". The TPCP is defined as*" the time interval between the biological disease initiation and the time at which symptoms of the disease leads to clinical diagnosis"*.[54] There is no evidence in the consulted literature, and not to our knowledge of all recorded literature, that the exact times of biological initiation of the cascades of molecular and cellular events that culminated in primary scrotal malignancy in each patient with known pre-malignant or previously benign scrotal lesions have been routinely determined. The second concept**, "length bias"**, was enunciated by Feinleib and Zelen, and relates to the rate (per unit time) or velocity of evolution of the cellular and molecular processes that occur from biological initiation of the disease (including premalignant, pre-invasive and invasive periods) to final diagnosis.[55] For instance, if a patient develops a scrotal condyloma accuminatum, which is a pre-malignant lesion, after how long from the time the condyloma formed may cells of the scrotal tissues at that site initiate molecular and cellular events that would result in clinical malignancy? What is the time interval between these initial molecular event(s) and clinical malignancy? If the premalignant lesion were an inflamed epidermal cyst or hydradenitis suppurativa, what would these time intervals be in the same individual? The answers to these questions would be important in prevention of primary scrotal cancer but will require further studies.

3.5 Prospects for Prevention

(i) The external anatomical location of the scrotum with its primary premalignant lesion(s) will be readily accessible to the patient for **frequent scrotal self-examination and active surveillance** by the clinician.

(ii)The natural histories of primary SCC of the scrotum, and EPC of the scrotum respectively encountered in the 5 patients in this study, and the slow-growing nature of many common scrotal tumours offer additional prospects for prevention of the disease.

(iii) The minimum duration of 10 months (median 16 months) of pre-existing scrotal lesion(s) before malignant transformation was enough opportunity for preventive treatment of each lesion

(iv) Different reports of delayed presentation for treatment of scrotal cancer in this study and other reports in the literature from different continents[4,26,27] suggest that perhaps many factors.[56,57,58,59] that cause late presentation for treatment are fairly global. These identified delays in reporting for treatment by patients, and post-diagnosis delays in treatment constitute problems that can be considered and solutions factored into a well-planned prevention programme.

(v) The common premalignant scrotal lesions encountered in the literature are usually amenable to various forms of preventive, conservative or excisional surgical treatments if detected and reported early (Table 1)

(vi) Although adolescents were not encountered in the case series in this study, our literature survey revealed that adolescents and young adults form 27% of all sexually active persons, and that with their propensity for risky sexual behaviour, 50% of sexually transmitted infections affect them.[56,57] Secondly, many scrotal inflammatory lesions may result from sexually transmitted infections. Adolescents and young adults should be included in a programme of prevention and early detection of primary scrotal cancer.

3.6 Scrotal Self-Examination(SSE): Agony or obnoxious features associated with scrotal pathology compelled the patients in this study to have SSE. Their findings were elicited on questioning. However, they seemed to lack appropriate knowledge of scrotal cancer, its prognostic significance, and the capacity to fund appropriate therapy of the scrotal lesions they bore. What they did was **'COMPELLED SSE'(CSSE**).We will also classify SSE as **'REGULAR PREVENTIVE SCROTAL SELF-EXAMINATION(RPSSE)**'. The presence of persisting, non-healing scrotal lesions with or without symptoms can easily be detected by RPSSE, and appropriate reports made for evaluation and treatment, followed by active surveillance by the appropriate clinician.

The concept of scrotal self-examination is not new; it was advocated for early detection of testicular cancer by Mukuhi NG AnG' A.[60] The concept may be popular but RPSSE does not seem, at present, to be of widespread practice worldwide. In studies on testicular self-examination (TSE) aimed at early detection of testicular cancer, it was observed that the practice of TSE was low in study populations, and these included populations of some advanced societies.[61,62,63] This report should therefore serve as additional evidence to further buttress the need for formulation and acceptability of a well-articulated programme of **regular preventive scrotal self-examination**, early detection and preventive

curative treatment of persistent benign inflammatory and premalignant scrotal lesions.

3.7 Recommendations

We recommend the programme of **regular preventive scrotal self-examination (RPSSE)** for early detection of persistent benign and premalignant scrotal lesions. Duration of persistence of scrotal lesions before treatment requires careful considerations. However, monthly SSE, as advocated for TSE[65] can detect lesions that have persisted for approximately 3 to 4 weeks. Health care system which encourages early evaluation and excision of scrotal lesions, and active surveillance by multidisciplinary teams that include urologists and histopathologists will be desirable.

The structure, health education, technique, process including frequency of RPSSE, input of medical personnel, prevention, diagnosis and treatment of premalignant and malignant lesions, involvement of different strata of primary, secondary and tertiary healthcare services, and cultural acceptability will require another study. From the foregoing, it is logical to start the programme with subjects at adolescent ages and above. Similar studies advocated monthly TSE[64], health education on techniques of TSE, testicular malignancies and prognostic advantages of their early detection and curative treatment.[65] It is therefore expected that health education will be an important part of the programme.

3.8 CONCLUSION

Most common types of primary scrotal cancer arise from pre-existing inflammatory scrotal lesions. The relatively long periods of benign scrotal pathology of these lesions offer opportunities for screening programmes for early diagnosis, and curative treatment of such scrotal lesions, prevention and/ or early detection of scrotal cancer. Literature review shows that most of these lesions are curable (Table1).

We advocate a Screening progamme withss
(i). Monthly **regular preventive scrotal self – examination (RPSSE**) from adolescence.
(ii) Surgical excision biopsy and histology of detected scrotal lesions at designated hospitals.
(iii) A programme of active surveillance of affected patients by clinicians. Details of the RPSSE programme that will have global acceptability, or acceptability to each population will require another study.

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