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Lesions of the Foreskin – Histopathological Study of Circumcision Specimens

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Abstract
Foreskin or prepuce is the anatomical covering of male external genitalia. It covers the distal part of external surface of penis. Diseases of foreskin may manifest as an array of pathological conditions which includes nonspecific inflammation, premalignant conditions like Lichen sclerosus et atrophicus (LSA) or Balanitis xerotica obliterans (BXO) and malignant tumours like squamous cell carcinoma. Previous studies have shown strong association of squamous cell carcinoma arising in the settings of long standing lichen sclerosus of the penis. Hence, overall, benign lesions constituted 97.16% and malignant cases were reported in 2.8% of cases.
BXO is many times missed clinically and hence the definite diagnosis is made only by histopathological examination.
We studied 106 specimens of foreskin following medical indication for circumcision in a tertiary care hospital. The study period was 1.5 years and included 71 paediatric patients and 35 adult patients. Majority of the patients presented with phimosis. The chronic nonspecific inflammation was observed as the most common lesion (n=83, 77.58%) whereas granulomatous inflammation was identified in3cases (2.8%).We also observed 13 cases of Balanitis xerotica obliterans (12.15%), out of which 5 cases (38.46%) were diagnosed on clinical grounds while rest were histopathological diagnoses. The incidence of BXO in pediatric age group was 4.22%. Well differentiated Squamous cell carcinoma was reported in 3 of the cases (2.8%). Since majority of the foreskin pathologies present with clinical symptoms of phimosis, microscopic examination following circumcision is a must, to correctly detect the histopathological lesion.
Keywords: *Foreskin, Balanitis xerotica obliterans, circumcision, phimosis, SCC.*

Introduction

The prepuce or foreskin is an integral part of male external genitalia that forms the anatomical covering of glans penis. The foreskin of the penis is remarkably thin, dark and loosely connected to tunica albuginea. It has features of true skin but is devoid of subcutaneous adipose tissue. Histologically, the foreskin comprises of five

layers: epidermis, dermis, dartos muscle, lamina propria and squamous mucosa. The mucosal epithelium is non keratinizing squamous, similar to that of the glans. Skin adnexa are absent; however, scarce small sebaceous glands not associated with hair follicles may be rarely identified[(1)].

The foreskin may be a site of variety of pathological processes ranging from inflammatory lesions and dermatoses to frankly malignant lesions like carcinoma. One of the most commonly encountered genital inflammatory lesion is Lichen sclerosus et atrophicus (LSA). Balanitis xerotica obliterans (BXO)is a term used as a synonym for lichen sclerosus of the glans penis and prepuce[(1)]. Itis a chronic atrophic mucocutaneous inflammatory condition of unknown etiology preferentially affecting anogenital areas. Although extra genital lichen sclerosus is not premalignant, the relationship of anogenital lichen sclerosus and squamous cell carcinoma is well documented. In a prospective study the incidence of squamous cell carcinoma among long standing lichen sclerosus of penis was 5.8-9.3%.[(2)(3)]

Circumcision is one of the most commonly performed operative procedure. It is usually done for religious and ethnic reasons but sometimes done for medical indications. Phimosis is the most common medical indication for circumcision. Many institutes do not perform histopathological examination after circumcision. However there is a place for routine histopathological examination after circumcision for medical indications[(4)]. BXO is largely under diagnosed and may be often missed clinically. The diagnosis is made only on histological examinations in such cases[(5)].

The literature review shows only few studies dealing with histopathology of prepuce after circumcision. Hence in this study, we aim to study the spectrum of histopathological lesions occurring in the foreskin after circumcision for medical indications.

Materials and Methods

The present study was retrospective observational study. In this study, we observed 106 circumcision specimens received from January 2016 to July 2017 in the Department of Pathology of Government Medical College, Miraj. Data was collected from pathology database. All specimens were received from Department of Surgery. The corresponding patients medical records were studied and reviewed for demographic information, focussing primarily on indication for circumcision and presence of clinical evidence of BXO if any.

All the specimens were fixed in 10% formalin. After fixation, bits were given from representative areas of preputial skin. All grossly visible lesions were sampled. If no lesions were visible grossly, two to three sections were submitted randomly. Small biopsies were submitted entirely. The tissue bits were processed. After processing and embedding in paraffin blocks, sections were cut at 5 micron thickness. Sections were stained by routine hematoxylin and eosin stain and microscopic examination was carried out.

Results

In this retrospective study we evaluated 106 specimens of foreskin received after circumcision for medical indications. Patients age ranged from1 year to 80 years. Majority of the patients belonged to age group 0-20 years (n=75, 70.75%) followed by 6th decade (n=8, 7.54%). Most of the patients belonged to paediatric age group (n=71, 66.99%) and the rest were adults (n=35, 33.01%). (Table 1)

Table 1 Distribution of cases on the basis of age

Age distribution in years	No of cases	percentage
0-10	66	62.26%
11-20	9	8.49%
21-30	5	4.72%
31-40	1	0.95%
41-50	7	6.60%
51-60	8	7.54%
61-70	6	5.66%
71-80	3	2.83%
81-90	1	0.95%
Total	106	100%

The most frequent clinical symptom was phimosis (n= 90, 84.9%). Few patients presented with other clinical symptoms like paraphimosis, growth over prepuce, urinary retention etc. In 9 of the cases, clinical diagnosis was BXO. (Table 2)

Table 2 : Distribution of cases according to clinical presentation

Clinical presentation	No. of cases	percentage
Phimosis	90	84.90%
Paraphimosis	2	1.89%
Growth over prepuce	2	1.89%
Urinary retention	3	2.83%
BXO	9	8.49%
Total	106	100%

The various histopathological lesions observed in our study were BXO, inflammations and malignancies (Table 3). The benign lesions constituted 97.16% and malignant cases were reported in 2.8% of cases. More than one diagnostic entity was assigned to one case wherein BXO was seen associated with granulomatous inflammation.

The commonest pathology identified in our study was non specific inflammation in 87 out of 106 cases (83.01%). Out of total 87 cases of inflammation, 4 patients showed acute inflammatory changes in the form of mucosal ulceration and infiltration by polymorphs and few mononuclear cells. The rest of the 83 cases displayed chronic inflammation with infiltration by mononuclear cells and showed varying amount of fibrosis.

Granulomatous inflammation was observed in 3 out of 106 cases (2.8%). There were two cases of foreign body granulomas observed in paediatric patients. Microscopically, there was collection of histiocytes and occasional foreign body giant cells around greyish refractile foreign material (Fig. 1). The third case of granulomatous inflammation was seen in association with BXO.

13 cases of BXO were identified in 106 patients (12.15%). Grossly, whitish thickened areas were noted on foreskin. (Fig 2) On microscopic examination, characteristic findings of epithelial atrophy, dense hyalinization in subepithelial region with band like infiltrate of lymphocytes beneath it were observed in the cases of BXO (Fig 3). Few of the cases of BXO also showed hyperkeratosis, vacuolar alteration of basal layer and edema of papillary dermis. One of the cases of BXO was seen associated with granulomatous inflammation. Microscopy of this caserevealed BXO along with few granulomas composed of epithelioid cells and occasional Langhans type of giant cell surrounded by lymphocytes in the dermis.

Malignancy was reported in 3 out of 106cases (2.8%), all of which were well differentiated squamous cell carcinoma. The two patients presented with preputial growth varying from 0.5 cm to 1 cm in largest dimensions. Microscopic examination showed proliferative squamous epithelium invading the deeper tissue to form a tumour composed of clusters and sheets of well differentiated neoplastic squamous cells with presence of individual cell keratinization and keratin pearls(Fig 4 and 5). The third patient presented with phimosis and bilateral inguinal lymphadenopathy. Gross examination revealed irregular whitish firm area measuring 4x3mm on mucosal aspect of foreskin. Microscopic examination in this case showed a focus of squamous cell carcinoma.

Table 3: Distribution of lesions on foreskin based on histopathology

Histopathological lesion	No of cases	percentage
Chronic inflammation	83	77.58%
Acute inflammation	4	3.73%
Granulomatous inflammation	3	2.80%
Balanitisxeroticaobliterans (BXO)	13	12.15%
Malignancy	3	2.80%
No specific lesion	1	0.94%

The age-wise distribution of the foreskin lesions is given in Table 4.

The chronic inflammation was seen most commonly in the first decade of life, while in adults it was observed more frequently in sixth decade. Out of the total 13 cases of BXO, majority

of the cases were observed in adults (n=10) while 3 cases were diagnosed in paediatric age group (0-12 years). All the malignancies were seen in the age group of 61 to 80 years.

Table 4: The age-wise distribution of the foreskin lesions

Age distribution	Chronic inflammation	Acute inflammation	Granulomatous inflammation	BXO	Malignancy	No specific lesion
0-10	60	1	2	3	0	0
11-20	8	0	0	1	0	0
21-30	3	0	0	2	0	0
31-40	1	0	0	0	0	0
41-50	3	2	0	2	0	0
51-60	5	0	0	4	0	0
61-70	1	0	1	1	2	1
71-80	1	1	0	0	1	0
81-90	1	0	0	0	0	0
Total	83	4	3	13	3	1

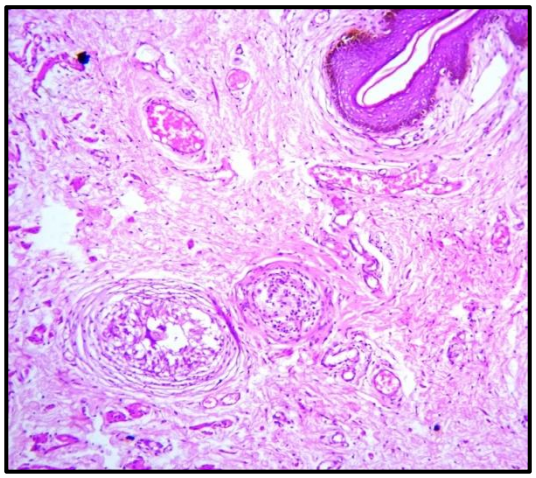

Fig. 1. Photomicrograph showing foreign body granulomas in the dermis, larger one shows greyish white refractile material in the centre. H&E stain X100

Fig 2. Gross photograph of BXO of foreskin showing white thickened patches on the mucosa.

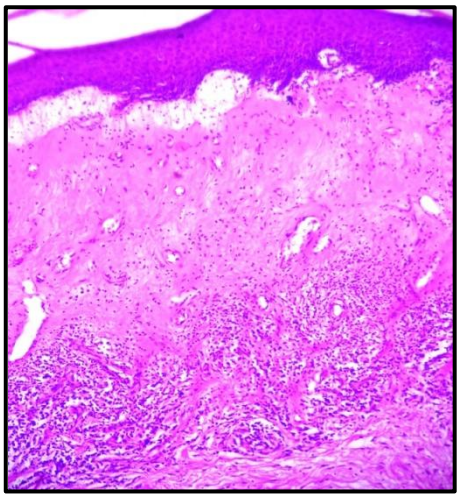

Fig. 3. Photomicrograph of BXO showing atrophic epidermis, dermal collagenization and band like infiltrate beneath it. H&E stain X100

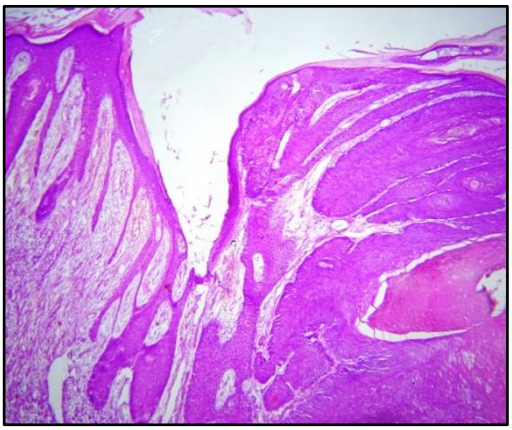

Fig 4 Photomicrograph showing well differentiated squamous cell carcinoma arising from mucosa. H&E stain X100

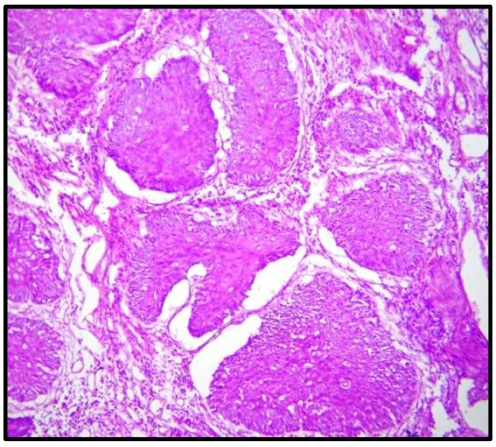

Fig 5. Photomicrograph showing clusters and sheets of neoplastic squamous cells invading the deeper tissue.
H&E stain X100

Discussion

There have been very few studies dealing with histopathology of prepuce in the literature[4][6]. Many of the institutes do not perform routine histopathological examination following circumcision. But Naji H, et al proved that there is a place for routine histopathology after circumcision for medical indications[4]. Many pathological entities like inflammations, premalignant lesions and malignancies have been reported in foreskin, important among which is BXO.

The most common lesion we encountered in our study was chronic nonspecific inflammation(n= 83, 77.58%). Histopathology showed variable degrees of lympho-plasmacytic infiltrate, oedema and congested blood vessels. The subepithelial fibrosis was noted in significant number of cases. The common causes of chronic nonspecific inflammation of foreskin are poor hygiene, irritants, balanoposthitis, contact dermatitis, diabetes mellitus, immunosuppression and so on [7][8].

Granulomatous inflammation is a rare variety of inflammation encountered in foreskin specimens. It is characterised by either non-infectious or infectious granulomas. Non-infectious granulomas due to foreign body reaction, Crohn's disease, sarcoidosis, BCG instillation for bladder cancer are reported very rarely in literature [9][10][11][12]. Infectious granulomas are seen in bacterial infections like tuberculosis, fungal infections like candidiasis and parasitic infestations like filariasis. In our study, we came across 3 cases of granulomatous inflammation. Two of the cases were seen in paediatric patients. Microscopy revealed foreign body granulomas around foreign material in the dermis. The reason for foreign body reaction in foreskin may be due to application of herbal medicine or oil based ointments for foreskin inflammatory conditions like balanoposthitis. The other case of granulomatous inflammation was seen in a 61year old man who presented with phimosis and burning micturition. Microscopic examination showed evidence of BXO while the deeper dermis showed typical granulomas composed of epithelioid cells, histiocytes and peripheral mantle of lymphocytes along with occasional Langhans type giant cell. After going in the depth of clinical details, patient gave history of pulmonary tuberculosis in the past which was treated few years back.

BXO was first described by Stuhmer in 1928[1]. Lichen sclerosus is a chronic mucocutaneous condition affecting the epidermis and dermal connective tissue that most commonly involves the genital and perianal skin of both males and females. Itis most common dermatological lesion seen in prepuce. Etiology of BXO is unknown but autoimmune mechanism has been suggested (13). It usually presents as phimosis. Clinically BXO manifests as a well defined and marginated white patch on the glans penis or prepuce that envelopes or involves the urethral meatus, the navicularis and the penile urethra but not the bulbar urethra resulting in a urethral strictures. It also may manifest as a lichenoid scale with a roughened surface. In long standing cases, the lesion is firm because of underlying fibrosis, and hence may present as phimosis[1]. The progression of sclerotic lesions in BXO may also lead to symptoms of paraphimosis or urinary obstruction.

Histologically, lesions of BXO show striking atrophy of epidermis frequently admixed with hyperplastic areas. There is thick band of hyalinization in subepithelial region, beneath which there is band like infiltrate of lymphocytes. Other characteristic histological features seen in BXO are vacuolar alteration of basal layer, edema of papillary dermis, dermal-epidermal clefting etc. According to Innocenzi D et al, four patterns of BXO have been described. Pattern 1 has prominent lichenoid inflammatory infiltrate in the dermis. Pattern 2 is characterized by band like infiltrate separated from the dermis by a band of dermal sclerosis and pattern 3 showing prominent sclerosis with minimal or absent inflammatory infiltrate. Pattern 4 has overlapping features between the first and third pattern, occasionally showing areas of epidermal thickening with loss of normal keratinocyte cytoarchitectural differentiation, mitoses and apoptotic cells[14].

In our study we found histological evidence of BXO in 13 out of 106 cases, i.e. 12.26%. Our calculated incidence was consistent with reported incidence of 10.6% in the study conducted by Liatsikos and colleagues[15]. The incidence of genital lichen sclerosus in young boys has been estimated at about 15% but the precise frequency is not known [4]. Out of 13 cases of BXO, 3 cases were seen in paediatric patients and 10 cases were seen in adult to elderly patients. The incidence of BXO in paediatric age group was 4.22% (3 in 71 patients).

In our study, there were 13 cases of BXO which were diagnosed on histopathology. In 5 of these cases, clinical diagnosis was BXO, while in other 8 cases clinical diagnosis was phimosis only. Hence 8 cases out of 13 (61.53%) were missed clinically but were identified only because of histopathological examination.BXO cannot be excluded on the basis of a negative clinical examination and hence histopathological analysis of foreskin is necessary to arrive at the correct diagnosis.

BXO has well documented correlation with development of squamous cell carcinoma[2][3]. BXO has been shown to have a strong association with penile squamous cell carcinoma variants of pseudohyperplastic, verrucous, and papillary type. Lichen sclerosus were preferentially associated with non-HPV variants of SCC [16].

The most common malignant tumour of prepuce is squamous cell carcinoma. The carcinoma involving only prepuce is very rare. In majority of the times, prepucial SCC presents as extension of carcinoma penis. The incidence of malignant/ dysplastic lesions in foreskin is 5% according to a previous study by West et al[6]. In our study we documented 3 cases (2.8%) of malignancies, all of which histologically represented squamous cell carcinoma. Malignancies were exclusively seen in elderly patients. One of the case presented with phimosis associated with bilateral inguinal lymphadenopathy. After circumcision was done, foreskin sample was received in our histopathology section. On gross examination, a small irregular greyish white thickened area over prepuce was noticed. The initial sections did not show any evidence of malignancy. After thorough sampling and deeper sections from the block, a tiny focus of well differentiated squamous cell carcinoma was detected. This patient also had metastatic disease in inguinal lymphnodes which was later proved on histopathology. Hence careful gross examination and proper sampling of circumcision specimens should be done to rule out malignancy.

Summary

In summary, this study provides a review of foreskin pathology in our institution. Results have shown that inflammatory lesions constitute the bulk of foreskin pathology. On the other hand neoplastic etiologyaccounts for a very minor percentage. Balanitis xerotica obliterans, afore-runner of malignancyis one of the significant histopathological entity seen in prepuce which may be missed clinically. Discrepancies between clinical impressions and pathologic findings are frequent, and thus biopsy may serve as an important diagnostic modality even in the absence of clinical suspicion for a disease.

Meticulous gross examination and careful histopathological examination of circumcision specimens, is necessary to rule out malignancye specially in elderly patients.

Also as the entire spectrum of prepucial pathologies may have similar clinical symptoms, histopathological evaluation of foreskin is thus necessary to confirm the pathological entity.

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