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Review

Balanitis xerotica obliterans: a review of diagnosis and management

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Abstract

Balanitis xerotica obliterans (BXO), or penile lichen sclerosus, is a progressive sclerosing inflammatory dermatosis of the glans penis and foreskin. It is associated with significant morbidity and may result in impaired urinary and sexual function. It was initially described by Stuhmer in 1928, named after its pathological features, and is considered the male equivalent of vulvar lichen sclerosis (LS).[3,40] The etiology of BXO is uncertain; however, autoimmune disease, local trauma, and genetic and infective causes have been proposed. BXO occurs most commonly on the prepuce and glans penis. It is considered to have premalignant potential to transform into squamous neoplasia. This postulation rests on retrospective studies and parallels drawn with vulvar LS and squamous cell carcinoma (SCC) development. Histologically, BXO and vulvar LS are considered the same disease.[41] There is a paucity of evidence-based guidelines to assist with appropriate follow-up for patients with BXO.

Epidemiology and Pathophysiology

The true prevalence of BXO is unknown, and reported figures likely underestimate the prevalence of disease, given failure to present for medical review and misdiagnosis. A large UK study demonstrated that while general practitioners are worried about a nonretractile foreskin, and do make surgical referrals, BXO is poorly recognized, and first-line treatment is almost never initiated in the primary care setting.[1] Kizer *et al.*[2] indicated that BXO has an incidence of 0.07% from a single clinic using the United States Military Ambulatory Data records. This same study found BXO to be twice as common in Hispanic and African-American patients as Caucasian patients. There is very little data to substantiate an accurate estimate of BXO prevalence.

BXO occurs across all age groups, from infants aged 6 months up to the elderly, but is most common in middle-aged uncircumcised men.[3,4] Like most inflammatory dermatoses of the penis, BXO is more prevalent in uncircumcised males secondary to accumulation of secretions and epithelial debris between the penis and foreskin.[5] This then causes subclinical trauma, chronic irritation, and balanitis.[6,7] Chronic inflammation in BXO leads to subsequent fibrosis, replacement of parenchymal tissue with nonfunctional tissue. Upregulation of proinflammatory cytokines and chemokines induces expression of growth factors, which stimulate fibroblasts, differentiation of myofibroblasts, and eventually production of extracellular matrix.[8]

It is estimated that 10–40% of surgically treated cases of phimosis in boys occur in the context of BXO.[9] A German study looking at circumcision for secondary phimosis (nonphysiological) found that BXO had been implicated in 15% of cases of juvenile circumcision. In this study, 225 boys with BXO aged 2–23 were identified, with a mean age of 7. It was concluded that assuming 1% of boys require surgery for phimosis, prevalence in young males should be approximately 0.1–0.4%.[10]

Post-micturition dribbling or microincontinence has been proposed as a theoretical etiologic factor in the pathogenesis of BXO. In a study by Bunker *et al.*, it was demonstrated that 91% of men with diagnosed BXO reported micro-incontinence, compared with 14% in the control group.[11] Furthermore, in uncircumcised men, urine is more likely to pool between the prepuce and glans penis, whereupon occlusion precipitates the Koebner phenomenon and subsequent inflammation.[12] It is also argued that the distribution of BXO mirrors the areas subject to urine under occlusion, and unlike LS in women, BXO tends to spare the anogenital region, which is shielded from urine by the scrotum. This chronic irritation of susceptible epithelium is considered to be a predisposing factor to the development of BXO.[13]

An association between human papillomavirus (HPV) and BXO has been reported in children, with two small studies of 23[14] and 11[15] patients, identifying HPV by PCR in 52 and 64% of cases, respectively. HPV infection is also documented in young girls and may be suggestive of abuse as it is thought that nonsexual transmission can occur in children; however, the meaning of these figures is unclear.[16] This may suggest BXO as a predisposing factor for HPV infection or that HPV has

some role in the pathogenesis of BXO. However, HPV is more common in uncircumcised males[17] and may be a confounding factor. On the other hand, given the cohort are children, they are less likely to have been exposed to HPV infection.[18] This increased incidence is not clearly emulated in the adult BXO population, and there is ongoing debate about the BXO/HPV link. In a series by Perceau *et al.*,[19] no patients with BXO associated penile squamous neoplasia were found to be HPV positive, yet Nasca *et al.*[20] noted a PCR positivity of 80% for HPV 16 in a similar cohort. Furthermore, a recent systematic search of 27 papers reporting the prevalence of HPV in LS identified that HPV was present in 22% of LS cases. It also highlighted HPV 16 as the most common genotype.[21]

There is also growing evidence for a possible autoimmune cause. In vulvar LS lesions, Farrell *et al.*[22] demonstrated increased levels of interferon gamma, tumor necrosis factor, and interleukin-1. Chan *et al.* found IgG autoantibodies to extracellular matrix proteins in 80% of LS patients and also that there is an association between BXO and the MHC class II antigen HLA-DQ7. This region is understood to confer increased risk of autoimmune disease such as type 1 diabetes mellitus, rheumatoid disease, and systemic lupus erythematosus.[23] BXO has also been associated with obesity, smoking, and cardiovascular disease.[24]

On the basis of familial cases and association with HLA antigens, genetic factors have been also proposed in the pathogenesis of BXO. Such cases have been demonstrated in identical and nonidentical twins, mothers, and daughters, and 12% of women with LS report a family history.[25] This volume of evidence is not available in the male population, however increased frequencies of HLA-DR11, DR12, and DQ7 have been reported in men with BXO.[26] It is worth noting that in the previously mentioned German study on BXO in young males, three sets of identical twins were included, and a set of non-twin brothers were identified and treated.[7]

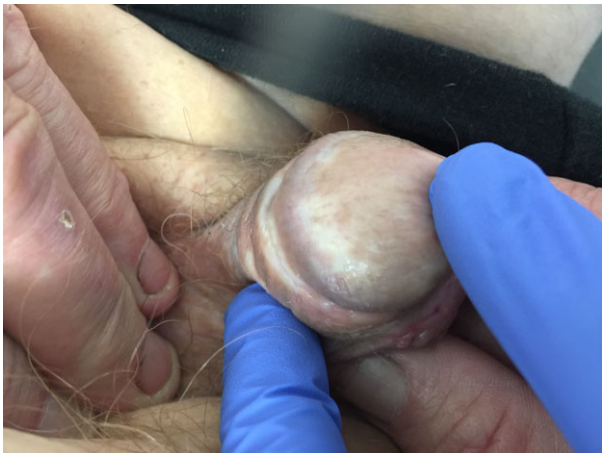

Figure 1 Classic BXO

Clinical Presentation

BXO typically presents with white plaques and induration of the glans, prepuce, and coronal sulcus. Early manifestations may be subtle with nonspecific hypopigmented or erythematous macules, or purple-white plaques with defined margins. A sclerotic white ring at the distal aspect of the prepuce is typical (Fig. 1). Other areas less commonly involved include the frenulum, urethral meatus, and fossa navicularis. Telangiectasias and purpura of the glans are sometimes present. Inflammation and thickening of the prepuce may result in adhesion to the glans, resulting in phimosis, or paraphimosis, in which retraction leads to constriction of the distal penile shaft.[4] In this process, there is fibrous replacement of the coronal sulcus and frenulum. Chronic cases may lead to atrophy of the glans.

BXO may be asymptomatic, however, some men experience paresthesia, pruritis, dysuria, and in rare cases symptoms associated with urinary retention in the context of phimosis.[15] It may also cause significant psychological distress in addition to physical symptoms. It runs a relapsing and remitting course, with periods of quiescence, but is nonetheless progressive.

The diagnosis of BXO is usually made clinically however should be confirmed histologically. Biopsy may also assist in excluding differential diagnoses such as lichen planus and subclinical penile squamous neoplasia.

Differential Diagnosis of BXO

- Balanitis (infective)
- Sqamous neoplasia
- Plasma cell balanitis (Zoon's balanitis)
- Lichen planus
- Psoriasis
- Balanitis circinata
- Contact dermatitis
- Fixed drug eruption

Histology

Early BXO is characterized by moderate lymphocytic infiltrate in the superficial dermis and basal epidermis, associated with epidermal basal vacuolar change.[15] As lesions develop, there is loss of elastic fibers in the papillary dermis, the epidermis becomes atrophic with surface hyperkeratosis, and dermal band-like inflammatory infiltrate is displaced downward by subepidermal edema. The edema is later replaced by fibrosis.[15]

Complications

The most common complications of BXO are secondary to progressive sclerosis. Phimosis, paraphimosis, painful erection, urinary retention, urethral stenosis, and altered flow are

acknowledged as understood complications. Retrograde damage to the bladder and kidney has also been documented.[27,40]

BXO is considered a premalignant disease. Based on a number of studies, malignant transformation is estimated at between 4 and 8%, similar to vulvar lichen sclerosis at 5%.[28] An Italian study reported that in a cohort of 86 men with BXO, 5.8% went on to develop premalignant change or invasive SCC.[29] A recent retrospective review found that 13.6% of patients with BXO had evidence of penile intraepithelial neoplasia.[30] This high figure is possibly attributable to nearly 50% of this cohort being referred by urologists. It nevertheless suggests that malignant transformation is not uncommon. Larger retrospective studies include one in Paraguay which examined surgical specimens for invasive SCC and found that 33% of cases had associated BXO[31] and a similar study in London in which 28% of 155 patients with penile SCC had BXO.[32] A smaller retrospective study from Oxford found that 11 of 20 patients with penile SCC had BXO on histological examination.[33]

A long lag time has also been observed between symptoms of BXO and diagnosis of penile squamous neoplasia, with Nasca *et al.* reporting between 10 and 23 years.[17] Paucity of information regarding the true incidence of BXO dictates that establishing a link with penile squamous neoplasia is difficult.

Treatment

Daily use of potent topical corticosteroids (TCS) is the recommended first-line therapy for BXO in adult males and boys, for example, one fingertip unit of 0.05% clobetasol propionate ointment, as per the British Association of Dermatology (BAD) guidelines.[34–36] Patients should promptly be referred to a dermatologist and urologist in the event of urinary symptoms. There are no randomized controlled trials for treatment of BXO.

BAD guidelines suggest that should signs persist beyond 3 months, the diagnosis should be reconsidered and a biopsy performed. In boys, the same guidelines suggest that those with phimosis be referred to a pediatric urologist for circumcision following 1–3 months of failed TCS. Problems with TCS application must also be addressed through weight loss, as poor efficacy may be secondary to a buried penis. They also suggest 6 monthly follow-up and reintroduction only in the case of relapse. However, based on the findings of Lee *et al.*, we suggest that once clinically resolved, maintenance therapy should continue at a minimum of once weekly application.[34]

TCS are the mainstay of treatment, however, use of acitretin and adalimumab has been documented. In 2010, a Greek double bind placebo-controlled trial with a cohort of 49 demonstrated complete resolution of BXO in 36% of patients taking acitretin 35 mg daily for 20 weeks.[37] Lowenstein and Zeichner used intralesional adalimumab, 40 mg biweekly and then 8 weekly, to achieve stable mild disease in a case of recalcitrant BXO. It was injected subcutaneously at 1 cm intervals around the penile shaft.[38]

Circumcision is indicated in the instance of phimosis and paraphimosis. Urethroplasty or meatoplasty may also be necessary in the event of meatal stenosis. Surgical management is frequently, but not always, curative (Fig. 2). TCS should thus continue postoperatively, and there should be a low threshold to re-biopsy should concerns regarding squamous neoplasia development arise.

Discussion

Vulvar LS has a malignant transformation rate of 5%, which is considered significant enough to warrant routine follow-up and long-term suppressive therapy with TCS.[39] Studies thus far suggest a pathological continuum between BXO and penile squamous neoplasia.

As has been noted by Lee *et al.* in a large prospective cohort study on vulvar LS, "it is a basic premise in dermatological practice that chronic inflammatory skin diseases frequently require ongoing suppression."[34,40,41] This same rationale should be applied to management of BXO. In this same study, titration of TCS to disease severity meant that atrophy was not seen with chronic application over 2 years. This required regular follow-up is necessary to ensure maintenance of normal skin texture and color. Any signs of atrophy warranted decreased potency of TCS, and if hyperkeratosis was seen, potency was increased. Symptomatic treatment fails to treat subclinical disease, asymptomatic disease, and scarring; thus ongoing treatment under supervision is necessary to prevent progression. Most importantly, in this cohort of 507 women, 357 were compliant, and over 2 years none developed vulvar SCC.

Three major impediments hinder the progression of understanding BXO and its management: poor recognition by primary care providers, failure on the patient's part to self-examine and present, and a related lack of data regarding prevalence.

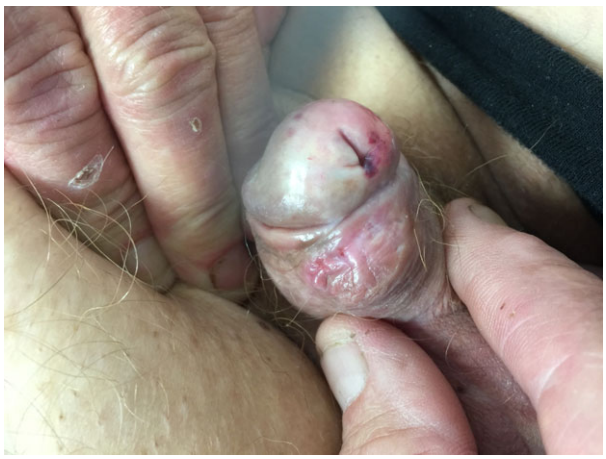

Figure 2 Site of surgery post SCC excision

Unlike women, who have regular pap smears and genital examination at some point during pregnancy, younger men do not have routine reasons for genital medical examination. A number of large studies have examined the attitudes of young males to testicular cancer, with most citing embarrassment, lack of knowledge, and cultural barriers as the major factors precluding self-examination and seeking medical attention.[42,43]Many studies have also shown that those who are aware of testicular cancer do not necessarily enact the self-care measures.[44–47] A large qualitative study in Australia drew data from focus groups and found that reluctance to self-examine and seek help was frequently related to "male" values of stoicism, avoidance, and robustness.[48]

Larger studies are currently required to discern the prevalence of BXO and accurately gauge the increased risk of developing penile squamous neoplasia. Furthermore, increased frequency of male genital examinations by primary care providers is likely to destigmatize and normalize checking for genital pathology. A full female genital examination includes examination of the skin, speculum examination, and bimanual palpation for ovarian masses. Should a similar examination be normalized in men, greater opportunity would arise for detection of skin disease, testicular cancer, and prostate cancer.

BXO is a physically and psychologically debilitating disease, with potentially devastating sequelae in the event of complications or extensive surgery. In the absence of data in men, it follows that management of BXO should also revolve around chronic, individualized TCS therapy, titrated to disease severity, in addition to possible surgical management where necessary.

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