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# Balanitis Xerotica Obliterans - from Etiology to Prognosis

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## Abstract

Balanitis xerotica obliterans is a disease of undetermined origin, despite strong evidence of autoimmune etiology and association with autoimmune diseases such as hyperthyroidism, vitiligo, hypothyroidism and DM I.BXO mainly affects individuals of Caucasian origin, and its incidence is not very common in patients younger than 2 years of age.The strong association of the pathology with the penis allied to a constant underdiagnosis can contribute to the increased prevalence of complications such as phimosis, meatal stenosis and, less frequently, renal failure, which translates into more expenses with treatment and palliation of the consequences of BXO. Early detection is a key element in the prevention of these complications, and the therapeutic strategy of choice - circumcision - is operationally simple, entails few costs to the National Health System and is extremely effective as a therapeutic and preventive measure.

**Keywords:** Balanitis xerotic obliterans; Circumcision; Phimosis; Lichen sclerosus; Penile carcinoma; Autoimmune

## Introduction

Balanitis xerotica obliterans is an important inflammatory disease of the glans, foreskin and urethral meatus that makes it impossible to retract and is a risk factor for penile carcinoma.

The first case of BXO was described by Stuhmer in 1928, since there have been advances in understanding the pathogenesis of the disease, and advances in electron microscopy techniques, which allowed the establishment of the autoimmune nature of this disease.

Its emergent detection and subsequent therapeutic contributes to a lower health expenditure with penile carcinoma.

## Epidemiology

It's difficult to estimate an exact prevalence, since patients can show themselves in different specialists - pediatricians, dermatologists, urologists, which makes it difficult to cross data due to the lack of articulation between the different services.

In the article developed by Kizer in 2003, they report an incidence of 0.07% in a cohort study, occurring at all ages, beginning as early as 6 months of age, not being common in children under 2 years [1,2]

It's more common in Caucasians and is reported as rare in other ethnicities.

A study developed by Bochove-Overgaauw in 2009, diagnosed BXO in 37 of 135 biopsies (27%), with a mean presentation of 6.5 years, with 4% of patients being submitted to meatal stenosis [3].

## Etiology

There are still some risk factors that have a true impact on the development of the disease, and the exact etiology is unknown, however, some theories have been proposed:

**Autoimmune Theory, Molecular Mechanisms and Genetic Factors:** Specific organ antibodies were found in patients with BXO and there is an increased incidence of other AI diseases in these patients (diabetes, varicose veins, alopecia). Retrospective identification based on diagnostic codes in which patients completed a questionnaire were examined and performed analyzes such as blood cell count, glucose, thyroid function tests, auto antibodies and serology for Borrelia and if the histology had not been performed, performed a biopsy of the skin. 34 % of these patients had a history of atopy (asthma / atopic eczema) and 51.4 % had a family history of positive atopy. 11 had both characteristics (past and positive family history). In general, 18.75 % presented autoimmune disease in 1st degree relatives (hyperthyroidism, vitiligo, hypothyroidism and diabetes mellitus I) [4].

These patients are not more prone to autoimmune thyroid disease or pernicious anemia, despite a higher incidence of autoimmune phenomena when compared to the normal population [5,6].

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An association was established between lichen sclerosus and autoimmune disease in men compared to the general population [6].

Immune nature turns out to be a crucial point in understanding the pathogenesis of this disease.

According to available literature, only MYOPODIN and CABLES appear to be relevant for the development of BXO and SCC [7]. However, the expression patterns of CABLES1 and MYOPODIN require further studies to assess their importance in pathogenesis.

ECM1 Antibodies (on chromosome 1q21) were identified in adult BXO patients, with a reduced expression of this gene in the pediatric population. Further studies are needed to understand the implication of this gene in the pathogenesis of BXO [8,9,10].

No changes were found in procollagen I, III and IV as well as genes associated with collagen metabolism such as PLOD2 and LOX [11,12].

On the other hand, there was an increase in the expression of TGF-B2 - it was significantly over-regulated in juvenile LS, and there was also supra-regulation of IL-4 and CCL5 [13].

There is a strong association in LS patients with HLA-DQ7, HLA-D08, HLA-DQ9 and HLA-DRABII2 - suggesting a genetic background. The high production of pro-inflammatory cytokines such as IFN-Gamma, CXCR3, CXCL9, CXCL10, CXCL11, CCR5, CCL4 and CCL5 is specific for an IFN-gamma-mediated Th1 immune response [14,15].

In a study developed by Gross, et al, it was found that T lymphocytes involved in SL had T-cell restricted intracellular antigen (TIA-H) and cytotoxic granzyme B (GrB) - related to cytotoxic activity in their granules [16].

Micro-RNA-155, involved in the regulation of the immune response, was also over-regulated [14].

**Infection:** A high frequency of HPV has been found in CRP in pediatric patients with penile LS, and these patients are more likely to develop and carry HPV subtypes that progress to dysplasia [17].

It is highly unlikely that Borrelia burgdorferi plays an etiological role in BXO and hepatitis C has been investigated because of the possible association with LS. Autoimmunity associated with hepatitis C may be responsible for the development of LS in these patients [18,19].

- Local Factors: Factors such as meatal stenosis that causes high pressure when bladder emptying causes irritation of Littre glands, leading to inflammation, fibrosis and LS development.

## Clinical Presentation

The BXO can present with a white ring in the glans and respective discoloration, secondary phimosis, dysuria and sensation of swelling with the urination. It may be asymptomatic [13,20].

Symptoms such as non-retractibility of the foreskin, swelling and dysuria are the most frequent. The pathognomonic sign of BXO includes a peri-meatal whitish area associated with an erythema in this area and initially the patient notices some areas of discoloration of the glans or in the external area of the foreskin, accompanied or not by pruritus. At this stage, it is often confused with candidiasis and poorly treated with anti-fungal [11,21].

Peri-anal involvement is extremely rare [22].

Rarely courses with glans atrophy [23].

## Therapeutic Approach

It is useful to the doctor who approaches this pathology to perform blood tests with hematological counts, glucose, dosages of antibodies and thyroid function in order to establish correlations with systemic diseases that present higher incidence with the presentation of this pathology.

The collection of clinical history, physical examination and diagnostic studies such as urofluxometry, urethrography and urethroscopy as well as biopsy are also indicated in cases of suspected BXO.

If the biopsy is not compatible with BXO, an infectious etiology should be excluded and the collaboration of the Dermatology service should be considered.

In case the biopsy is compatible with BXO, consider an autoimmune disease and consider the collaboration with the Immunology service. In case the patient presents with urethral stenosis, meatal stenosis and / or intact foreskin, opt for the surgical approach. If, on the other hand, the patient does not present with urethral or meatal stenosis, and the foreskin is not intact, the preferred approach is a topical medical treatment with Clobetasol Propionate 0.05 % or Betamethasone Diproprionate 2 times per day, 2 to 3 months, avoiding applying local irritants to the injured site and emphasizing the importance of hand washing for genital hygiene.

A study by Depascuale et al. reflecting the experience in his unit that was in charge of treating more than 500 patients with BXO during a period of 14 years suggested a treatment protocol that consists of the following guidelines:

- If the pathology is limited to the foreskin, circumcision is curative and provides histological material for confirmation of disease;

- If there is associated glandular discoloration, but without cicatrization, ulceration or fusion of the foreskin, simple circumcision also presents as a therapeutic option of 1st line, being curative;

- If the coronal groove is obliterated by adhesions and the skin of the glans is in full condition, it is recommended to resection the groove with careful dissection of it. Subsequently the re-epithelialization of this zone will take care of the curative process.

- If the glans is deeply disfigured, the complete restructuring of the glans with skin grafts is recommended. This procedure improves the aesthetic appearance and has the advantage of avoiding the progression to squamous carcinoma.

- BXO localized to the meatus responds best to topical steroids and minor surgery, however the stenosis is likely to recur if there is confirmed involvement of the distal urethra.

- Treatment of urethral BXO consists of excision of the urethral portions involved and subsequent replacement with mucous mucosa or buccal mucosa with bladder mucosa in the case of a more extensive involvement [21].

The use of systemic treatments is sometimes attempted, but the long-term effects need to be considered in a cost-benefit ratio. Retinoid have proven to be drugs effective in a placebo-controlled study, however the side effects lead to its discontinuation [2,25].

## Differential Diagnoses

The differential diagnosis of BXO includes vitiligo, erythroplasia of Queyrat, lichen planus, localized scleroderma, and leukoplakia. A biopsy can be considered when there is doubt of the diagnosis [26].

Association with Malignancies in Balanitis Xerotica Obliterans

Squamous cell carcinoma is the most serious malignant complication of BXO, and the carcinogenic route is likely to be independent of HPV, but has yet to be established [7].

Also noteworthy was a study conducted by Powell, which reinforces the association of BXO and penile carcinoma, in which analyzing samples of patients with penile ECC, in about half of the patients, Xerotic Obliterating Balanitis was an associated finding [2].

## Prognosis

As previously mentioned the possible evolution for squamous cell carcinoma ends up being a condition that entails a greater follow-up by the health services, and the Urologist, Dermatology or General and Family Medicine specialist [24].

The prognosis of BXO is closely related to its early detection and intervention. If the BXO is detected at an early stage, the prognosis is usually very good. It is important to note that spontaneous remission may occur [5].

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