Lichen sclerosus and granuloma annulare of the foreskin: a significant association

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Abstract
Lichen sclerosus (LS) is considered to be a disease resulting of local immune dysregulation. A delayed-type hypersensitivity reaction and cell-mediated immune response are hypothesized to be the pathogenesis of granuloma annulare (GA). The case is presented of an uncircumcised 45-year-old man who developed lesions of LS and GA in his foreskin. Both processes were treated with circumcision. GA is rarely located in the foreskin. As far as we are aware, only one previous case presented this location. We describe herein for the first time LS associated with GA in the foreskin. Both processes have a common autoimmune pattern suggesting a link between them. Although we cannot exclude that comorbidity may be a coincidence, we think this combination of lesions is not just coincidental but significantly associated through immunopathological mechanisms.

Keywords: autoimmune disease, foreskin, granuloma annulare, lichen sclerosus, penis.

Introduction
Lichen sclerosus (LS) is a chronically relapsing disease with a potential for atrophy, destructive scarring and functional impairment preferentially located in the anogenital skin [1]. The process is lymphocyte-mediated of presumed autoimmune etiology. LS can occur with concomitant autoimmune disease, positive family history for autoimmune disease [2–4] and presence of tissue-specific antibodies [5]. Genital mucocutaneous LS is associated with an increased risk for squamous cell carcinoma [1, 6].

Granuloma annulare (GA) is a self-limited dermatosis, of unknown etiology, characterized by necrobiotic dermal papules that have an annular configuration. Clinical variants of the disease include localized, generalized, perforating, subcutaneous, and erythematous (or patch) forms. Although the pathogenesis remains uncertain, the process possibly represents a delayed type hypersensitivity reaction. Vázquez-López et al. [7] suggested that at least localized GA belongs to the spectrum of autoimmune diseases. Moreover, De Paola et al. [8] reported the simultaneous occurrence of LS, diffused GA and autoimmune thyroiditis. These authors considered this combination not coincidental.

In this report, we document the coexistence of LS and localized GA in the foreskin of a 45-year-old man, and we discuss their co-morbidity. Penile GA is rare and an uncommon presentation of the disease. To the best of our knowledge, the association of LS and GA lesions in the foreskin has not been reported.

Case report
A 45-year-old man exclusively heterosexual sought medical advice for swelling of the glans and difficulty in retracting the foreskin. The patient denied any history of trauma, diabetes mellitus, rheumatoid arthritis, scleroderma, psoriasis, allergic processes, hepatitis, alopecia areata, vitiligo, or exposure to toxic chemicals or injectable materials. There was no history of sexually transmitted disease and he was not taking any regular medication. There was no family history. Risk factors for papilloma virus infection, human immunodeficiency virus (HIV) infection or syphilis were not present. Physical examination of the penis revealed a serpiginous area with grouped flesh-colored papules, on the cutaneous surface of the foreskin. The papules coalesced into annular plaques measuring 1.8×1.2 cm. Other zones showed white-gray, atrophic patches and plaques extensively involving the skin and mucosa of the foreskin. They globally measured 2.5×1.3 cm. Routine blood tests showed no abnormalities. The PSA (prostate-specific antigen) was normal. He was treated with local Oxytetracycline and Hydrocortisone Acetate. The patient did not improve with this treatment and 44 days after he underwent circumcision under general anesthesia. In the intervention, an extensive sclerosis of the foreskin was noted. Review at 48 days after surgery showed a surgical bed in the process of healing.

Three fragments of foreskin measuring 2.2×1.9 cm, 2.3×1.3 cm, and 2.2×0.8 cm were received. The histopathological study showed two separate types of lesions. One type showed epidermal compact ortho-hyperkeratosis and effacement of the rete ridge pattern. Occasionally, the rete ridge pattern was partially preserved with presence of lymphocytes within the basal cell layer in association with some apoptotic or hydropic keratinocytes. There was fibrosis, thickening and hyalinization of the collagen in the papillary dermis. Beneath this, there was a zone of moderate to scarce lymphocytic infiltration. Predominant CD3+ lymphocytes were observed with a mixed population
of CD4+ and CD8+ T-cells. Telangiectases throughout the upper half of the dermis were seen (Figure 1). Significant junctional cleavage (clefting) at the dermoepidermal junction was present (Figure 2). The whole lesion showed features of lichen sclerosus in advanced stage.

The other type of lesion showed foci of altered collagen bundles and deposit of basophilic mucin surrounded by palisaded macrophages, lymphocytes and occasional eosinophils in the upper- to mid-reticular dermis (Figure 3). These granulomas were well developed (Figure 4) but multinucleated giant cells were not observed. Nuclear fragments were present in the necrobiotic areas.

Multiple palisaded necrobiotic granulomas formed a geographic pattern within the dermis revealing a broad intense expression of CD68+ macrophages. There was a superficial and deep perivascular lymphocytic infiltrate. T-cell markers (CD3, CD4 and CD8) were mainly detected in the perivascular lymphocytic infiltrate with CD4+ predominating over CD8+ lymphocytes. The mucin stained with Alcian Blue (pH 2.5) (Figure 5) and colloidal iron. The overlying epidermis showed no alterations. The lesion was considered a dermal (necrobiotic) palisade granuloma with features of localized granuloma annulare.

Both types of lesion were completely separated without showing intermingled areas.
Lichen sclerosus (LS) is a chronic inflammatory disease that affects the skin. It is more prevalent in women, but it can occur in men of all ages. There is a bimodal age incidence with peaks in boys and adult men. The mean age at diagnosis is 42 years. The estimated prevalence may be as high as one in 300 men [9]. LS is a disease of the uncircumcised men. This process involves the foreskin in 70% of cases [1]. It is a progressive lymphocyte-mediated disease that affects epidermis and dermis skin components. Diverse etiopathogenic factors have been proposed including infection, environmental factors, exposure to urine, drugs, metabolic disease, association with melanocytic lesions, and autoimmunity [10]. Association with acid-fast bacilli, spirochetes and Borrelia burgdorferi has been negated [10–12]. Human papilloma virus (HPV) has been detected on the surface of the lesion and it has been considered as a “passenger” virus or an innocent bystander [10]. Hepatitis C virus is highly unlikely to play an etiopathogenic role in the process [13]. The role of Epstein–Barr virus is unknown [14]. LS demonstrate koebnerization and can arise or recur at areas that have undergone trauma, surgery, constant friction, sunburn or radiation treatment [10]. Some authors consider LS a non-specific pathological response to urinary exposure in the uncircumcised male [15]. However, it has not been found any factor capable of producing the disease in the urine. It has been reported that beta-blockers may influence the clinical expression of LS [16], but the role of drugs in the causation of disease is not known. A case-controlled study suggested that elevated body mass index, diabetes mellitus, coronary artery disease and smoking were associated with LS through systematic microvascular disease [17]. It has been postulated that LS might be an immune response triggered by a melanocytic lesion in cases in which the patients show such a concomitant pigmentary lesion. Thus, changes of LS extended beyond the melanocytic proliferation [18]. There is increasing evidence that autoimmunity plays a pathogenic role and there appears to be a genetic susceptibility to LS. An important clinical feature of LS is the association with autoimmune disorders including autoimmune thyroiditis, alopecia areata, vitiligo, pernicious anemia, rheumatoid arthritis, scleroderma, type I diabetes mellitus [2–4], immunobullous disease [19] and celiac disease [20]. Some cases are associated with a local lymphocytic vasculitis [21] indicating a local immune dysregulation. Circulating IgG autoantibodies targeting extracellular matrix 1 (ECM1) protein have been reported in men with LS [5]. However, anti-ECM1 antibodies are not the causative mechanism but represent an epiphhenomenon [5]. Human leukocyte antigen (HLA) DR11, DR12, and DQ7 occur more frequently in men with the disease [3]. Thus, it has been held that the origin of LS is immunologic with a mechanism of inheritance.

GA is a relatively common cutaneous disorder classically presenting on the dorsal aspect of hands and feet that may affect patients of all ages. Clinical presentation includes localized, generalized, subcutaneous, perforating, and patch forms. Localized GA is often asymptomatic, and usually diagnosed in patients before 30 years of age. Incidence is highest in women. Localized form constitutes 75% of cases. More than 50% of patients with this form have spontaneous resolution within two years [22]. GA is a collagenolytic blue granuloma [23] characterized histopathologically by four patterns: palisading (necrobiotic) granuloma, interstitial incomplete form, sarcoidal type, and pseudolymphomatous form [24].

As far as we are aware, only 20 cases of GA of the penis have been described to date [25–39] (Table 1).

### Table 1 – Penile granuloma annulare: review of the literature

<table>
<thead>
<tr>
<th>Case / Reference</th>
<th>Age [years]</th>
<th>Location</th>
<th>Site</th>
<th>Associations</th>
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<tr>
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<td>25</td>
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<td>Subcutaneous</td>
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<tr>
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<td>Subcutaneous</td>
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</tr>
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<td>Subcutaneous</td>
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<td>4 / [26]</td>
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<td>Dermis</td>
<td>Asthma</td>
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<tr>
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<td>Subcutaneous</td>
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<td>Dermis</td>
<td>Lichen sclerosus</td>
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</table>
Most of these lesions were located in the shaft and they were subcutaneous. The present case is the second case reported in the foreskin and the only case associated with LS. The GA was of collagenolytic (necrobiotic) granuloma type located in the dermis.

GA has also been reported to follow viral infections (including HIV, Epstein–Barr virus, and herpes zoster), trauma, malignancy (mostly lymphoma or prostate carcinoma), insect bites, tuberculosis skin tests [22], dyslipidemia [40] and drugs including Amlodipine, gold, Allopurinol, Diclofenac, Quinidine, intranasal Calcitonin [41] and Thalidomide [42]. There is no significant association with B. burgdorferi [12]. The pathogenesis of GA has been linked to the dermal dendritic macrophage network, delayed hypersensitivity reaction and cell-mediated immune response with mainly T-helper cells [43]. Thus, immunohistochemistry shows predominant CD4+ cells in the lesions. These cells secrete interferon-γ, tumor necrosis factor-α, and macrophage-inhibiting factors, causing macrophages to persist in the area. The activated macrophages contribute to the process releasing lysosomal enzymes and cytokines that cause characteristic focal collagen degeneration (so-called necrobiosis) and mucin deposit. Some reports have indicated an association of GA with autoimmune or connective tissue diseases like type 1 diabetes mellitus, autoimmune thyroid disease, giant cell arteritis, and Sjögren’s syndrome [44–47]. Vázquez-López et al. [7] suggested that localized GA belongs to the spectrum of autoimmune diseases. Other authors consider vasculitis as a potential mechanism [48]. Furthermore, De Paola et al. reported the simultaneous occurrence of LS, diffused GA and autoimmune thyroiditis [8]. These authors considered this combination of lesions closely related. One of the characteristics of autoimmune diseases is that more than one autoimmune disease of a different spectrum tends to develop in affected individuals. The various autoimmune diseases might arise from breakdown of a common mechanism of immunological self-tolerance [49]. There is accumulating evidence that CD4+ helper/inducer type T-cells, which produce cell-mediated tissue destruction or help B-cells to form autoantibodies, are the key mediators of diverse organ specific and systemic autoimmune diseases [49]. In GA, there is a predominance of T-helper inducer cells in the infiltrate and the histopathology resembles the conditions of known delayed hypersensitivity pathogenesis (hypersensitivity type IV mechanism), including tuberculosis and sarcoidosis. The infiltrate of LS is rich in T-helper and suppressor lymphocytes. Thus, LS and GA should be recognized as two cutaneous manifestations associated with autoimmune diseases. Furthermore, both processes can be associated with local vasculitis [21, 48].

It is interesting to note that 23.8% of the cases of GA (Table 1) were associated with asthma or tuberculosis highlighting late phase reaction or delayed hypersensitivity, which is thought to contribute to the etiology of GA.

LS associated with GA has never been reported to simultaneously occur in the foreskin. Both processes have a common immune dysregulation pattern suggesting a link between them. One of these processes could contribute to trigger an autoimmune response in the genital skin. However, we cannot exclude that co-morbidity is exclusively a coincidence. Thus, further investigations are needed to better understand the etiopathogenesis.

Conclusions

GA is rarely located in the foreskin. We describe for the first time LS associated with GA in the foreskin. Our case suggests that LS and GA are closely related, and that both processes should be recognized as two cutaneous manifestations associated with immune dysregulation. Further studies need to be performed to elucidate the mechanisms of association of both entities.

Conflict of interests

The authors declare that they have no conflict of interests.

Consent

Written informed consent was obtained from the patient for publication of this case report and all accompanying images.

References


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