Zebras in foreskin dermatopathology: a review

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ZEBRAS IN FORESKIN DERMATOPATHOLOGY-A REVIEW

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Figures count = 4
Précis:
Uncommon foreskin dermatopathology conditions were reviewed.
ABSTRACT:

Objectives: To review uncommon foreskin dermatopathology conditions clinically and pathologically.

Methods: A database search of PubMed and Google Scholar were extracted between March 1\textsuperscript{st} 2009 and March 1\textsuperscript{st} 2019 using the search terms “foreskin”, “prepuce”, “penis”, “pathology”, “dermatology” and “rare”. The search was limited to “humans” and “dermatopathology”. Full article texts were reviewed. Reference lists were screened for additional articles. Patient details (diagnosis, dermatopathology, treatment, and follow-up if available) were extracted. We excluded articles written in the non-English language, unusual variants of common conditions and cases of common dermatologic conditions.

Results: A list of 369 articles were identified and another screening identified 30 articles for rare foreskin pathologies. Those are divided into categories based on etiologies, a- benign, including congenital (e.g. aposthia), infectious (GVHD and Histoplasma), autoimmune (Crohn’s disease and pyoderma gangrenosum) and benign neoplasms (neurofibroma, apocrine hidrocystoma, verruciform xanthoma, porokeratosis, penile cutaneous horn, localized amyloidosis), and b- malignancies, including primary (myeloid sarcoma, basal cell carcinoma, Kaposi’s sarcoma, MALToma), and metastasis.

Conclusions: We reviewed and discussed unusual benign and malignant dermatopathology conditions that can affect the foreskin.
FORESKIN ANATOMY AND HISTOLOGY

The foreskin is a specialized, junctional mucocutaneous tissue that covers the external part of
the distal penis. Its physiological function is very complex. According to the World Health
Organization, the foreskin provides moisture, secures normal development during embryological
life, or may enhance sexual pleasure via abundant neural receptors. Moreover, the prepuce plays
an immunological role due to the presence of Langerhans cells.

The foreskin is developed at 8-9 weeks of gestation, derived from the skin of the penile shaft
and grows forward to cover the glans penis. As a junctional tissue, the foreskin receives its
innervation from the dorsal nerve of the penis and branches of the perineal nerve. The pelvic
plexus supplies autonomic innervation via S2-S4; parasympathetic and T11-L2 supply
sympathetic innervation. Figure 1 shows the normal histology of the foreskin, which consists of
the inner mucosal squamous epithelium, lamina propria, dartos muscle, dermis, outer stratified
squamous epithelium, and the preputial sac. Table 1 shows the rare dermatopathology conditions
that affect the foreskin.

RARE BENIGN LESIONS

Congenital

Congenital foreskin anomalies in children

Prepuce congenital anomalies that affect children are a source of concern to parents, who are
concerned about psychological side effects as well as anatomic considerations. Twelve months is
the recommended age for surgical intervention. These conditions include hypospadiac prepuce,
which is defined as a ventrally deficient prepuce with fully attached dorsum. It could be isolated
or accompanied with distal hypospadias, and in either circumstance surgery is the treatment of
choice. Some conditions alter the configuration of the penis, such as inconspicuous/concealed penis, which occurs due to prenatal endocrinopathy leading to normal penile shaft size but abnormal skin coverage. This condition is subdivided into the buried penis, megaprepuce, webbed penis, and trapped penis. These are all considered variants of the inconspicuous penis. All can cause discomfort, weak urine stream, and false positive urine cultures because the urine flushes the skin during micturition. In terms of management, surgery is recommended by age 3 as the conditions may improve with age. Circumcision is contraindicated for buried penis and megaprepuce as it may cause a trapped penis and the need for free skin graft afterwards.

The foreskin can be affected by focal lesions, including penile/scrotal cysts, which can be congenital epidermoid or acquired inclusion cysts, which occur post-surgery. Parameatal cysts are epidermoid cysts that originate from the median raphe at any level from the urethral meatus. Management of these cysts is excision and although recurrence is a possibility it has not been reported. In addition, penile vascular anomalies and neurogenic lesions are very rare with few case reports and individualized treatment by a specialist is the key to address these conditions.

**Aposthia**

Aposthia is a very rare congenital abnormality in which the prepuce is absent (i.e. natural circumcision). As a result of the developmental absence of a prepuce, a malformation of the glanular urethra will ensue. The term “naturally circumcised” has been reported in 4 conditions: 1) no phimosis present, 2) a relatively short prepuce without phimosis, 3) fully retractable prepuce during erection and 4) circumcised penile appearance without an erection. Most patients present with associated hypospadias and are often referred for surgical repair of the urethra.
Infectious

Phimosis secondary to graft versus host disease

Phimosis is nonretractability of the prepuce. It may occur physiologically in young children in 96% due to adhesions between the prepuce and glans penis. Physiological phimosis is treated with topical 0.1% betamethasone and may resolve after 4 weeks of treatment but may also resolve spontaneously by the age of 10 or 12. Therefore, uncomplicated cases are usually followed by a wait-and-see strategy.

Pathologic phimosis is attributed to common and rare causes leading to chronic inflammation that can prevent foreskin retraction due to the formation of adhesions. Common causes include eczema, psoriasis, lichen planus, and lichen sclerosus. Graft-versus-host-disease (GVHD) is a common complication of bone marrow transplantation that rarely affects the genitourinary system. A few reports have documented this rare phenomenon. Lichen planus and/or poikiloderma (hypopigmentation, hyperpigmentation, telangiectasias, and atrophy) are the most common cutaneous manifestations. In advanced cases, epidermal atrophy and dense focal dermal fibrosis are noted with minimal signs of inflammation.

Topical 0.1% betamethasone ointment cream applied to the prepuce twice daily for 6 weeks in combination with gentle attempts to retract the foreskin is an effective nonsurgical treatment reported to be successful in up to 75% to 85% of cases of phimosis. Surgical intervention includes circumcision, or preputial plasty (dorsal slit) is recommended if no response was seen with steroids.

Histoplasma phimosis
Cutaneous Histoplasma infection is very uncommon though systemic Histoplasmosis is endemic in the southeastern and midwestern United States. A few reports have described penile Histoplasmosis, most commonly among immunocompromised patients and secondary to hematogenous spread in the context of systemic involvement. It presents as painless nodulo-ulcerative lesions of the glans and shaft of the penis without regional lymphadenopathy. The diagnosis can be made based on histomorphology and anti-Histoplasma immunostaining. Treatment is with itraconazole 200 mg daily for a month.

Autoimmune

Penile extra-gastrointestinal Crohn’s disease (PCD)

Genital Crohn’s disease is an extremely rare condition. It was first described in 1965. Diagnosis is challenging but a history of Crohn’s disease can provide a clue. Four categories summarize the cutaneous manifestation of Crohn’s disease; a) granulomatous cutaneous disease, including perianal, peristomal and metastatic disease; b) aphthous like and linear ulcerations, mucosal cobblestoning and nodules with granulomas; c) nutritional changes, including acquired zinc deficiency, striae and changes associated with malabsorption; d) a diverse group of disorders such as pyoderma gangrenosum, erythema nodosum, necrotizing vasculitis, epidermolysis bullosa acquisita, finger clubbing, palmar erythema and pustular response to trauma. These manifestations sometimes are mistaken for contact dermatitis, candidiasis; and sexual abuse. The treatment is challenging with various degrees of success (10-50%). Based on a prospective study of 11 cases between 2003 to 2017, the management relies on topical corticosteroids as a first-line for mild PCD. Topical tacrolimus was effective with a full clearance of penile ulcers in one case. Seven patients received adalimumab 40 mg fortnightly to weekly, which was effective
with complete resolution in five patients. In two of those patients, it was used alongside topical
tacrolimus and metronidazole. Infliximab 5 mg/kg 8 weekly was effective in one patient.
Prophylaxis with phenoxyethylpenicillin/ erythromycin was effective at preventing further
episodes. Tumor necrosis factor-α inhibitors are recommended at an early stage.11

**Penile pyoderma gangrenosum**

Pyoderma gangrenosum (PG), is an extremely rare inflammatory ulcerative disease that
usually occurs with systemic manifestations and rarely affects the penis.12 The diagnosis is by
biopsy to exclude other causes of genital ulcers—infecious diseases (syphilis, chancroid, genital
herpes, cutaneous tuberculosis, donovanosis, amoebiasis, and deep fungal infections), drug
eruptions, traumatic ulcerations, Behcet’s disease, and neoplasms. Clinically PG presents with
small tender papules or pustules that evolve into painful ulcers with characteristic violaceous
undermined edges. Lesions may be solitary or multiple and heal with an atrophic cribriform scar.
Systemic corticosteroids (methylprednisolone 0.5-1 mg/kg/d) or cyclosporine (5 mg/kg/d) are the
first line of therapy for disseminated and localized disease. Infliximab (5 mg/kg) is used for
patients with PG associated Crohn’s disease. Other reported experimental effective treatments
are mycophenolate mofetil, tacrolimus, or plasmapheresis.12

**Benign neoplasms**

**Neurofibroma**

Primary neurofibroma of the glans is another very rare benign lesion, most often in
children.13 It arises from Schwann cell proliferation, which is positive for S100 marker,
2. Clinically, it has been described as an asymptomatic penile mass along with multiple café-au-lait spots and complete resection is curative and a key to avoid recurrence\textsuperscript{14}.

**Apocrine hidrocystoma**

Apocrine hidrocystoma is a benign adenomatous cystic proliferation of apocrine glands, which rarely occurs on the genitalia and is most prevalent in adults between 30 and 70 years of age\textsuperscript{15}. It is subdivided into proliferative or non-proliferative based on Ki-67 proliferation index. In the proliferative type, true complex papillae with a fibrous core are seen and usually associated with atypia, mitotic activity and increased Ki-67 staining, whereas, in the non-proliferative type, there may be some structures that resemble papillary projections but lack the fibrous core\textsuperscript{16}. Excision of apocrine hidrocystoma is generally curative with recurrence a remote possibility. Other treatments described are simple needle puncture to electrodesiccation, anticholinergic creams, and CO2 laser treatment\textsuperscript{15}.

**Verruciform xanthoma (VEGAS)**

Other conditions affecting mucous membranes (e.g., verruciform xanthoma) may rarely also affect the foreskin and glans penis. Verruciform genital-associated xanthoma (VEGAS) is an asymptomatic wart-like benign lesion of unknown pathogenesis\textsuperscript{17}. The classic histologic appearance consists of foamy histiocytes within elongated dermal papillae and epithelial acanthosis\textsuperscript{17}. A biopsy is required and complete excision by surgery, fractionated CO2 laser or treatment with imiquimod cream have all been described in case reports to be curative if completely excised otherwise recurrent cases have been reported\textsuperscript{17}.
Porokeratosis

Porokeratosis, Figure 3, is a rare penile condition that present as spreading plaques with thin ridge-like borders and central atrophy\textsuperscript{18}. It is often misdiagnosed as condyloma, syphilis, granuloma annulare, lichen simplex chronicus, or eczema\textsuperscript{18}. Therefore, it has been suggested that this condition is underreported due to treatment as a sexually transmitted disease\textsuperscript{18}.

Biopsy shows corneal lamella with underlying dyskeratotic cells and management by cryotherapy, carbon dioxide laser, surgery, topical 5-fluorouracil, imiquimod, or topical diclofenac\textsuperscript{19} has provided a resolution of lesions in some, but not all. Topical glucocorticoids or retinoids achieved only symptomatic relief\textsuperscript{18}. It is also important to follow up these patients as malignant transformation has been reported in nearly all types of porokeratosis but has not been reported in genital porokeratosis\textsuperscript{18}.

Penile cutaneous horn

A penile cutaneous horn is very rare and can be a benign, premalignant lesion or malignant. For premalignant lesions, surgical excision with careful histological examination is the mainstay of treatment\textsuperscript{20}. Histopathology demonstrates extreme hyperkeratosis, epithelial dysplasia, and papillomatosis of the epithelia, without evident signs of malignancy\textsuperscript{21}. Twenty percent are associated with underlying squamous cell carcinoma (SCC). The key is that the base of the lesion needs to be examined very carefully as this is where the SCC can be. Chronic preputial inflammation, phimotic foreskin, the trauma of circumcision, and viral infection have been implicated in penile cutaneous horn formation\textsuperscript{22}.

Localized amyloidosis
The cutaneous form of amyloidosis is an uncommon lesion with asymptomatic, benign and indolent behavior, that is easily differentiated from other genital lesions such as condyloma, verrucous carcinoma, and pearly penile papules\textsuperscript{23}. The characteristic microscopic features on H&E, \textit{Figure 4}, and the positivity for Congo red and amyloid P component usually confirm the diagnosis. It is important to exclude systemic amyloidosis by investigating myelomatous (AL type), infectious (AA type), familial (ATTR type) or another systemic disease (b2 microglobulin)\textsuperscript{23}. The management by local excision alone has been reported to be curative with no progression or systemic involvement\textsuperscript{23}.

\textbf{Rare malignant lesions}

\textbf{Primary malignancies}

\textbf{Myeloid sarcoma}

Foreskin myeloid sarcoma is a very rare presentation of myeloid sarcoma (MS). In acute or chronic leukemia, myeloid cells can proliferate outside the bone marrow, giving rise to cutaneous lesions including erythematous to violaceous papules, nodules, plaques, or persistent non-healing ulcer. The condition is subdivided into well or poorly differentiated types based on the presence of numerous maturing myeloid elements or blasts, respectively. The lack of megakaryocytes or erythroid precursors in the lesion distinguishes it from extramedullary hematopoiesis (EMH). In neonates, the lesion is associated with TORCH (Toxoplasma, Rubella, and Herpesvirus) infection\textsuperscript{24}. In adults, myelofibrosis often coexists with rare association with chronic myeloid leukemia. The demonstration of Janus kinase 2 gene mutation in the cutaneous lesion with primary myelofibrosis supports the consideration that cutaneous EMH in chronic myeloid disease is a metastasis of the abnormal neoplastic cells and subsequent differentiation.
along divergent myeloid lineages. In the setting of an unknown hematological malignancy, the diagnosis of MS is often challenging. Local therapy may improve symptoms but does not influence survival$^{25}$.

**Basal cell carcinoma of foreskin**

Genital basal cell carcinoma (BCC) is very rare with only 22 reported cases$^{26}$. BCC involves the penile shaft with scrotum and pubic area spread occasionally$^{26}$. Proposed risk factors include trauma, HPV infection, and aging. The treatment is surgical excision with complete recovery$^{26}$.

**Kaposi sarcoma**

Kaposi's sarcoma is a human immune-deficiency virus-related malignant neoplasm that is extremely rare in the foreskin, therefore poses a diagnostic and management challenge. It has been reported to present as paraphimosis and painless purple papule or macule on the foreskin without urethral discharge or lymphadenopathy$^{27}$. Biopsy showing groups of spindle cells, extravascular erythrocytes, and macrophages filled with hemosiderin and immunohistochemistry for human herpesvirus-8 provides a diagnosis$^{27}$. Besides treating the patient with highly active antiretroviral therapy, for small and single lesions surgical excision is recommended, while for multiple skin lesions or large-size radiation therapy has been recommended$^{28}$.

**Mucosal-associated lymphoid tissue lymphoma (MALToma)**

Extranodal marginal zone B cell (MALT) lymphoma of the foreskin is extremely unusual. In general, MALToma is the third most common non-Hodgkin lymphoma accounting for up to 8%
of cases\textsuperscript{29}. Clinically, it has been reported to present as a painless lobulated lesion without lymphadenopathy\textsuperscript{29}. The histopathologic characteristics are a neoplastic expansion of marginal zone B cells, which are immunoreactive to CD20 and CD79a but are negative for CD10, CD5, CD23, and CD1\textsuperscript{29}. The most effective treatment by surgical excision, local radiotherapy, or chemotherapy (rituximab) remains controversial\textsuperscript{29}.

**Metastasis**

The foreskin has rich vascularization and an extensive lymphatic network with the adjacent organs, yet penile metastasis is extremely rare, and the main source is primary pelvic tumors, including 70\% with primary tumor in the genitourinary tract, 21\% in the gastrointestinal tract; 5\% in the respiratory system, and the remaining 4\% as metastases from primary bone tumors and malignant melanoma\textsuperscript{30}. Patients usually present with malignant priapism, penile masses or nodules, ulceration, obstructive or irritative urinary symptoms, and hematuria. However, asymptomatic cases, though very rare, can occur and mandate penile clinical examination when a patient presents with a primary pelvic tumor. Metastasis to the foreskin should be differentiated from primary penile Paget’s disease, squamous cell carcinoma in situ with a pagetoid pattern, a superficial spread of malignant melanoma, penile koilocytosis, pagetoid dyskeratosis, clear-cell papulosis, and mucinous metaplasia. Therefore, positive immunostaining for CK7 and GATA3 and negativity for p16 can help distinguish a metastasis from primary penile lesions.

**REFERENCES:**


Legends:

Figure 1. Foreskin anatomy and histology.

Figure 2. Neurofibroma of the skin with keratin horn (arrow) showing a non-encapsulated proliferation of all elements of a peripheral nerve. Schwann cells (positive S100 marker) with wire like collagen fibrils (wavy serpentine nuclei, pointed ends) are the main component with fibroblasts and collagen.

Figure 3. Porokeratosis of the skin showing keratin-filled epidermal invagination with an angulated, parakeratotic tier (cornoid lamella).

Figure 4. Foreskin with localized amyloidosis showing sheets of eosinophilic, amorphous, fissured material in dermis and subcutaneous tissue (arrow).

Table 1. Summary of the rare foreskin dermatopathologies with their correspondent clinical features and the main treatment strategies.
<table>
<thead>
<tr>
<th>CONDITION</th>
<th>CLINICAL</th>
<th>TREATMENT</th>
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</thead>
<tbody>
<tr>
<td><strong>BENIGN LESIONS</strong></td>
<td></td>
<td></td>
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<tr>
<td>Congenital</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congenital foreskin anomalies</td>
<td>hypospadas, inconspicuous/concealed penis.</td>
<td>Surgery by a specialist and newborn circumcision is contraindicated.</td>
</tr>
<tr>
<td>Aposthia</td>
<td>prepuce is absent and a malformation of the glanular urethra.</td>
<td>Surgery.</td>
</tr>
<tr>
<td><strong>Infectious</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phimosis secondary to GVHD</td>
<td>nonretraction of prepuce secondary to bone marrow transplantation.</td>
<td>Topical 0.1% betamethasone BID x 6 wks. Circumcision or preputial plasty if unresponsive on steroid.</td>
</tr>
<tr>
<td>Histoplasma phimosis</td>
<td>immunocompromised patients with painless nodul-ulcerative lesions of the glans and shaft of the penis without regional lymphadenopathy.</td>
<td>Itraconazole 200 mg daily for a month.</td>
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<tr>
<td><strong>Autoimmune</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Penile Crohn’s Disease</td>
<td>ulceration, edema, abscesses, fissures and phimosis involving the scrotum, penile shaft, glans penis or urethral meatus.</td>
<td>Topical corticosteroids are 1st line. Topical tacrolimus, Adalimumab 40 mg with topical tacrolimus or metronidazole. Infliximab 5 mg/kg 8 weekly. Prophylaxis with phenoxymethylpenicillin/erythromycin. TNF-α inhibitors.</td>
</tr>
<tr>
<td>Penile pyoderma gangrenosum</td>
<td>Small tender papules or pustules -&gt; painful ulcers with violaceous undermined edges.</td>
<td>1st line = Methylprednisolone (0.5-1 mg/kg/d) or cyclosporine (5 mg/kg/d). CD = Infliximab (5 mg/kg)²².</td>
</tr>
<tr>
<td><strong>Benign neoplasms</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurofibroma</td>
<td>Asymptomatic penile mass and café-au-lait spots.</td>
<td>Complete excision is key to avoid recurrence.</td>
</tr>
<tr>
<td>Apocrine hidrocystoma</td>
<td>Asymptomatic growth on the penis.</td>
<td>Simple needle puncture to electrodesiccation, anticholinergic creams, carbon dioxide vaporization, and laser treatment.</td>
</tr>
<tr>
<td>Verruciform xanthoma (VEGAS)</td>
<td>Asymptomatic wart-like benign lesion of unknown pathogenesis.</td>
<td>Biopsy is required and complete excision by surgery/fractionated CO2 laser.</td>
</tr>
<tr>
<td>Malignant Lesions</td>
<td>Primary Malignancies</td>
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<td>-----------------------------------------</td>
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<tr>
<td>Porokeratosis</td>
<td>Spreading plaques with thin ridge-like borders and central atrophy(^{18}).</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cryotherapy, carbon dioxide laser, surgery, topical 5-fluorouracil, imiquimod, or topical diclofenac. Follow up (malignant transformation)(^{18}).</td>
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<tr>
<td>Penile cutaneous horn</td>
<td>Curved white lesion projects outward from the penis(^{21}).</td>
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<tr>
<td></td>
<td>Surgical excision with careful histological examination (premalignant)(^{21}).</td>
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<tr>
<td>Localized amyloidosis</td>
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<tr>
<td></td>
<td>local excision alone, with no reported progression or systemic involvement(^{23}).</td>
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| Myeloid sarcoma                         | Erythematous to violaceous papules, nodules, plaques, or persistent non-healing ulcer\(^{24}\). |
|                                        | Local therapy may improve symptoms but does not influence survival\(^{25}\).               |
| Basal cell carcinoma                    | Erythematous scarring, painful lesion on the foreskin with dyspareunia\(^{26}\).           |
|                                        | Surgical excision\(^{26}\).                                                               |
| Kaposi’s sarcoma                        | Painless purple papule or macule on the foreskin without urethral discharge or lymphadenopathy\(^{27}\). |
|                                        | Small/single lesions \(\rightarrow\) surgical excision, multiple/large \(\rightarrow\) radiation therapy\(^{28}\). |
| MALToma                                 | Painless lobulated lesion without lymphadenopathy\(^{29}\).                               |
|                                        | Effective therapy remains controversial (surgery, radiation or rituximab)\(^{29}\).       |
| Metastasis                              | Primary cancer (Lung, stomach, colon, liver, bladder, prostate)\(^{30}\).                |
|                                        | Treat the primary tumor\(^{30}\).                                                       |
Figure 2.

S-100 staining
Figure 3.

Keratin-filled epidermal invagination