

### Genital (non-venereal) conditions

By Christina Kraus, MD, Sama Kassira Carley, MD, and Lance Chapman, MD, MBA



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GENITAL (Non-Venereal Conditions)	CLINICAL	PATHOLOGY	MANAGEMENT	COMMENTS
<b>Benign Conditions</b>				
<b>Tyson granules (ectopic sebaceous glands)</b>	Yellow to skin-colored papules, most commonly on labia minora. Asymptomatic.	Additional sebaceous glands (not sebaceous hyperplasia).	Reassurance.	May be confused with cysts, milia, molluscum, or condyloma acuminata.
<b>Vulvar vestibular papillomatosis</b>	Soft pink elongated papules, sometimes filliform. Can have associated vulvar pruritus, pain, burning.	Finger-like protrusions of subdermal tissue.	Reassurance.	Analogous to pearly penile papules. Commonly misdiagnosed as genital warts. Will not change color when exposed to acetic acid.
<b>Hidradenoma papilliferum</b>	Pink to red or skin-colored small cystic nodule, some appear solid, usually <1cm. Rare benign tumor. Usually asymptomatic.	Well-differentiated papillary glandular pattern; inner layer of cuboidal myoepithelial cells.	Benign, but can be locally excised.	Most commonly found on vulva.
<b>Angiokeratomas of fordyce</b>	Red to black papules or plaques with mamillated surface.	Ectasia of blood vessels in the papillary dermis associated with acanthosis and hyperkeratosis of the epidermis (resembles bloody seborrheic keratosis).	Reassurance or laser treatment.	Can be associated with oral contraceptives or increased venous pressure of pregnancy. Consider Fabry's if pediatric patient.
<b>Lichen simplex chronicus (LSC)</b>	Lichenified or scaly erythematous plaques, often with overlying excoriations. Intensely pruritic.	Irregular acanthosis, papillary dermal fibrosis; may see superficial epidermal necrosis if excoriated.	Eliminate irritants (overwashing, incontinence), potent CS ointment bid initially & taper with response, calcineurin inhibitors as second line.	Often seen in patients with history of atopy. Can be primary diagnosis or secondary to psoriasis, candida, lichen sclerosis.
<b>Contact dermatitis (allergic or irritant)</b>	Erythematous glazed plaques, often subtle scale, +/- fissures.	Spongiosis, edema of papillary dermis.	Eliminate irritants, midpotency CS ointment; barrier protection with petrolatum; consider patch testing.	Methylisothiazolinone is a common allergen in personal care products.
<b>Psoriasis</b>	Similar features to cutaneous psoriasis but often with less scale due to friction/moisture of this area. Vulva is a frequent area of koebnerization.	Elongated rete ridges, hypogranulosis, confluent parakeratosis.	Topical treatment is often unsatisfactory. Options include potent CS, TCI, systemic medications.	Differential diagnosis includes tinea cruris, intertrigo, lichen sclerosis. Often limited to hair-bearing areas.
<b>Lichen sclerosus (LS), also known as balanitis xerotica obliterans when occurs on glans penis</b>	Starts as well-demarcated erythema and progresses to shiny, hypopigmented sclerotic papules and plaques with atrophic wrinkled parchment paper appearance. May extend to perineum and involve anus in "figure-of-eight" in women. Often ecchymoses. Leads to scarring which can result in fusion and clitoral phimosis.	Epidermal atrophy, hyperkeratosis, hyalinized upper dermis with band of lymphocytes; loss of elastic fibers which is not seen in morphea.	Ultrapotent CS ointment (clobetasol 0.05% or halobetasol 0.05%); mid-potency steroids (i.e. triamcinolone 0.1% ointment) or calcineurin inhibitors for maintenance. In males, circumcision.	Usually occurs in states of low estrogen (children, postmenopausal women). Evaluate for extragenital involvement. Increased risk of developing squamous cell carcinoma (SCC). Antibody to ECM-1.
<b>Lichen planus (LP), erosive</b>	Classic presentation is well-demarcated erosions, lacy white reticulation (wickham striae), often scarring and distortion of normal anatomy.	Lichenoid interface dermatitis, sawtooth rete ridges, no parakeratosis or eosinophils.	Ultrapotent CS ointment +/- systemic agents (i.e. MTX, mycophenolate mofetil, rituximab); potentially surgical treatment for lysis of adhesions.	Four types: papules/plaques, erosive, hypertrophic, lichen planopilaris. Erosive LP is much more common in women.
<b>Aphthous ulcers and complex aphthosis</b>	Varying sizes, may be single or multiple, erythematous or gray/necrotic base, often punched out. Minor ulcers (<1cm and heal without scarring) or major ulcers (>1 cm and sometimes heal with scarring).	Nondiagnostic; acute and chronic inflammatory infiltrate, spongiosis.	Rule-out HSV & syphilis. Topical lidocaine, clobetasol ointment, intralesional Kenalog, short course of oral prednisone, colchicine, or dapsone.	Most patients with genital aphthae have history of oral aphthae.

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<b>Behcet's disease</b>	Multisystem disease with recurrent genital aphthous ulcers. Genital ulcers identical to those of complex aphthosis though often larger, more painful and higher frequency of recurrence. Scrotum, penis, vulva are most commonly involved areas.	Dense mixed perivascular infiltrate (neutrophils, histiocytes, lymphocytes, eosinophils), leukocytoclasia, neutrophilic abscesses, extravasation of red blood cells.	Treatment of mucocutaneous manifestations is same as treatment for complex aphthosis. More severe disease requires systemic therapy with azathioprine, MTX, cyclophosphamide, cyclosporine, thalidomide, or TNF alpha inhibitors.	Recurrent oral and genital ulcers are the most common clinical manifestation. Must rule-out HSV in genital lesions, as cannot distinguish clinically.
<b>Crohn's disease</b>	May present as perianal skin tags and genital edema and progress to "knife-cut" fissures particularly in skin folds with linear ulceration.	Noncaseating granulomas with minimal lymphocytic infiltrate.	Treatment should be directed towards underlying intestinal disease. Intralesional triamcinolone, incision and drainage, oral prednisone and TNF alpha inhibitors for management of cutaneous symptoms.	Monitor closely as potential for nonhealing lesions to develop into SCC.
<b>Pemphigus vulgaris</b>	Non-specific superficial erosions or more rarely flaccid bullae.	Intraepidermal blister or acantholysis with DIF showing intercellular IgG pattern and high serological desmoglein 3 and/or 1 titers.	First line: oral corticosteroid. Treatment should be aimed at immunosuppression (with azathioprine, MTX, mycophenolate, or rituximab) in combination with tetracycline antibiotics and supplementation with oral niacinamide. In severe cases, IVIg or plasmaphoresis.	Genital involvement is second most common after oral.
<b>Bullous pemphigoid</b>	Polymorphous lesions such as classic tense bullae or non-classic urticarial, lichenoid, or eczematous lesions.	Subepidermal bullae with eosinophils and lymphocytes in the dermal papillae, linear C3 pattern on DIF, and serological high antibody titers to BP180 and BP230 antigens.	Oral corticosteroid with steroid-sparing agent (such as an immunosuppressant). As in PV, may adjunct with tetracycline and niacinamide.	Genital involvement is exceedingly rare in adults but can be the only location of disease manifestation in children (up to 50% of cases).
<b>Cicatricial pemphigoid</b>	Erosions and scarring, very rarely shows vesicles. Associated with significant pain and pruritus.	Subepidermal bullae with eosinophils and lymphocytes in the dermal papillae, similar DIF to BP, serological antibody titers to BP180.	Oral corticosteroids and immunosuppressive medications may be used, but treatment is often disappointing. Potent topical corticosteroids with pain control may have good results in localized disease. Dapsone and cyclophosphamide for severe or rapidly progressive disease.	Surgical therapy may be utilized to improve quality of life in some cases.
<b>Hailey-hailey</b>	Non-specific superficial erosions.	Severe acantholysis, mutations in ATP2C1 gene.	Topical antimicrobial washes, potent topical corticosteroids, and topical tacrolimus have been shown to be beneficial. Surgical therapy may improve quality of life. Some evidence for low-dose naltrexone.	Most commonly affects the vulva in conjunction with intertriginous disease but can present solely on the genitalia. Few cases of SCC within lesions in the anogenital region.
<b>Epidermolysis bullosa acquisita (EBA)</b>	Non-specific superficial erosions.	Subepidermal cleavage with mixed inflammatory infiltrate, linear IgG pattern at the basement membrane is most common on DIF; serological antibody titers to Collagen VII.	Oral corticosteroids and systemic immunosuppressants have been used, with no consistent data on success. Reports of use of dapsone with prednisolone have been somewhat successful in younger patients.	Commonly localized to the genital region. Some reports of associations with IBD, SLE, DM, and monoclonal gammopathies.

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<b>Pearly penile papules</b>	Yellow to skin-colored papules on prepuce and shaft of penis. Asymptomatic.	Sebaceous glands.	Reassurance as anatomic variant of normal.	Analogous to vulvar vestibular papillomatosis.
<b>Epidermoid cysts and milia</b>	Cysts - dome-shaped white, yellow or skin-colored papules, often with central plug, on vulva, scrotum or penile shaft. Usually asymptomatic but may become inflamed. Milia - 1-2 mm shiny papules.	Cyst with lining resembling surface epidermis but no adnexal structures; loose keratin within cyst.	Treatment generally not indicated. Symptomatic cysts can be excised and milia can be cauterized.	
<b>Idiopathic scrotal calcinosis</b>	Rare condition with multiple firm yellow to white subcutaneous nodules on scrotum. Usually asymptomatic.	Nodules of calcium deposited in dermis with surrounding fibrous capsule and granulomatous inflammation.	Surgical excision.	Pathogenesis is still controversial.
<b>Lichen nitidus</b>	Monomorphic skin-colored to white papules. Usually asymptomatic, but can be pruritic.	Focal lymphocytic infiltrate in dermis with ret ridges forming surrounding collarettes: "ball in claw."	Topical steroids for alleviation of pruritus. Can consider cryotherapy, topical retinoids, UV-B phototherapy.	
<b>Median raphe cysts</b>	Linear yellow to white cysts extending along ventral midline anywhere from urethral meatus to anus.	Cyst usually located in dermis, lined by pseudostratified columnar epithelium, and does not connect with overlying epidermis.	Surgical excision.	Congenital abnormality in development of male genitalia.
<b>Fournier's gangrene</b>	Starts as red indurated plaque that becomes increasingly edematous and painful, associated with necrosis, crepitus, ecchymoses, bullae, with rapid spreading along fascial planes.	Deep biopsy would reveal extensive acute inflammatory infiltrate and necrosis, intravascular thrombosis, evidence of bacteria, extending to the fat and even involving skeletal muscle.	Broad-spectrum antibiotics with gram-positive and gram-negative coverage, CT/MRI, and surgical exploration with possible debridement.	Urologic emergency. Usually polymicrobial infection, with nidus being the GI tract.
<b>Malignant and Pre-Malignant Conditions</b>				
<b>Vulvar intraepithelial neoplasia (VIN) or penile intraepithelial neoplasia (PIN):</b>	Two types of VIN/PIN: The usual type is secondary to HPV infection while the differentiated type is secondary to vulvar or penile dermatoses (i.e. LP or LS).			
<b>1. HPV-related VIN or PIN (usual type) - Note: <u>erythroplasia of queyrat</u> is PIN of prepuce/glans and <u>bowenoid papulosis</u> is PIN of shaft</b>	Various morphologies - often warty or flat-topped papules and plaques, may be confluent, various colors.	Warty and/or basaloid pattern of <i>in situ</i> dysplasia.	Close follow-up. Local excision or laser ablation.	Often spontaneously regresses in women <35 years old.
<b>2. Non-HPV related VIN or PIN (differentiated type)</b>	More commonly a solitary plaque or nodule, often seen overlying lesions of LS or LP.	Keratinizing pattern of <i>in situ</i> dysplasia.	Excision, usually with wider margins than that recommended for HPV-related VIN.	
<b>Squamous cell carcinoma (SCC)</b>	Early on it is difficult to distinguish clinically from VIN/PIN. If nodular or ulcerated, more likely SCC than VIN/PIN.	Multiple histological subtypes. Warty or basaloid and keratinizing; full thickness dysplasia.	Excision. If >1 mm invasion, sentinel lymph node biopsy.	Of note, BCC very rarely occurs on nonmucosal surfaces of genitalia.
<b>Verrucous carcinoma</b>	Warty exophytic nodule. Labia majora is most common site on female genitalia. Difficult to distinguish clinically from condyloma acuminatum or SCC.	Irregular papillomatosis, acanthosis, lack of cellular atypia, well-differentiated glassy keratinocytes with rounded border; nonspecific inflammatory infiltrate.	Surgical excision.	Considered a variant of well-differentiated SCC.

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<b>Malignant and Pre-Malignant Conditions</b>				
<b>Melanoma</b>	Same features as extragenital melanoma, but more likely to be amelanotic. Labia majora, clitoris, and glans penis are most common sites.	Histology most commonly that of mucosal lentiginous melanoma rather than superficial spreading or nodular; poorly nested, confluent melanocytes at the dermal-epidermal junction.	Wide local excision. If extensive local disease or recurrent, radiation or immunotherapy (ipilimumab) should be considered. Prognosis determined by tumor thickness.	Distinguish from seborrheic keratoses and genital melanosis. Compared to extragenital melanomas, genital melanomas are more likely to be amelanotic. Also, more likely to arise <i>de novo</i> .
<b>Extramammary paget's</b>	Well-demarcated erythematous pruritic plaque, may be erosive.	Pagetoid cells in epidermis; IHC: pankeratin +, CEA/CK7 +.	Thorough workup to evaluate for concomitant internal malignancy. Mohs or wide local excision is first line therapy.	Associated with visceral malignancy in 10-20% of cases.

**Abbreviations:**

PID - pelvic inflammatory disease. LAD - lymphadenopathy. CNS - central nervous system. VDRL - Venereal Disease research Laboratory Test. RPR - Rapid Plasma Reagin. TTPA - T.palladium particle agglutination test. FTA-ABS - Fluorescent treponemal antibody test. SPHA - solid phase hemabsorption test. PEH - pseudoepitheliomatous hyperplasia. DFA - direct fluorescent antibody assay. BID - twice a day. QD - once a day. KOH = Potassium hydroxide. PAS - Periodic acid-Schiff. GMS - Grocott-Gomori's methenamine silver stain. TCA - Trichloroacetic acid. ART - antiretroviral therapy. AIDS - acquired immunodeficiency syndrome. q4h - every four hours. CV - cardiovascular. CS - corticosteroids. NSAIDs - non-steroidal anti-inflammatory drugs.

**References:**

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2. Edwards L, Lynch PJ. *Genital Dermatology Atlas*. 2nd ed. Lippincott Williams & Wilkins; 2012.