Pagetoid Dyskeratosis of the Male Genitalia: Case Report and Review

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Abstract
Pagetoid dyskeratosis is a benign incidental pathologic finding that has been reported in many distinct skin lesions on various locations of the body. A man who had pagetoid dyskeratosis within lesions of the penile shaft is described and similar cases of pagetoid dyskeratosis in lesions of the male genitalia are reviewed.

The patient was a 26-year-old healthy man who developed several asymptomatic penile papules that were refractory to topical imiquimod 5% cream and cryotherapy. Snip biopsies were performed and microscopic examination revealed pagetoid dyskeratosis. PubMed was searched for the following terms: cell, clear, dyskeratosis, genitalia, pagetoid, penile, penis, prepuce, scrotum, and shaft. The papers containing these terms and their references were reviewed. Pagetoid dyskeratosis has been observed in lesions on the prepuce and scrotum; this case report now expands the distribution of this finding to the penile shaft. Clinicians and pathologists should be aware of this intriguing potential incidental finding within skin lesions of the male genitalia.

Categories: Dermatology, Pathology, Urology
Keywords: cell, clear, dyskeratosis, genitalia, pagetoid, penile, penis, prepuce, scrotum, shaft

Introduction
Pagetoid dyskeratosis is a benign incidental pathologic feature. It has been observed in several skin lesions [1]. Herein, a man with penile papules that demonstrated pagetoid dyskeratosis is described, and patients with pagetoid dyskeratosis of the male genitalia are summarized.

Case Presentation
A 26-year-old man with no history of genital dermatoses developed new penile lesions; he was evaluated on several occasions by his primary care physician. The clinical impressions of his lesions included both condyloma acuminata and molluscum contagiosum. On separate occasions, he was treated with either topical imiquimod 5% cream or cryotherapy with liquid nitrogen. Two months later, he noticed new lesions on his penile shaft and sought medical evaluation by a dermatologist.

Clinical examination showed three 1-2 mm asymptomatic, flesh-colored papules located on the proximal portion of the dorsal penile shaft: proximal, middle, and distal, respectively (Figure 1). The site was cleaned with an alcohol swab, the lesions were circled, and lidocaine HCl 1% with epinephrine 1:100,000 was injected locally. The lesions were elevated with Adson forceps and subsequently removed with Metzenbaum scissors. Hemostasis of the biopsy sites was achieved with the application of 20% aluminum chloride. The biopsy sites were treated with topical mupirocin 2% ointment three times daily until the wounds healed.

FIGURE 1: Clinical features of pagetoid dyskeratosis
Distant A) and closer B) views with markings and distant C) view without markings show the clinical features of pagetoid dyskeratosis that presented as proximal (arrow), middle (asterisk), and distal (circle) asymptomatic, flesh-colored papules on the proximal dorsal penile shaft of a 26-year-old man.

Microscopic examination was performed; hematoxylin and eosin-stained slides of the lesions were inspected with light microscopy. The most proximal lesion revealed focal dermal fibrosis. In addition, there were multiple large, round intraepidermal pale cells presenting singly and in clusters (Figure 2). The cells resembled those seen in extramammary Paget’s disease, containing condensed pyknotic nuclei with perinuclear halos of clear cytoplasm. Additionally, they demonstrated premature keratinization without acantholysis or parakeratosis.

FIGURE 2: Pathology of the proximal papule

Pathology features of pagetoid dyskeratosis are present in the asymptomatic, flesh-colored papule at the base of the dorsal penile shaft of a 26-year-old man. There are multiple large, round intraepidermal pale cells extending singly and in clusters upwards in the epidermis. The pagetoid cells (arrows) contain condensed pyknotic nuclei with perinuclear halos of washed out cytoplasm. Additionally, they demonstrated premature keratinization without acantholysis or parakeratosis. In addition, areas of focal dermal fibrosis were also noted. (Hematoxylin and eosin: A: x10; B: x10; C: x20; D: x20; E: x40; F: x40).

The middle lesion revealed a dilated follicular ostium as well as similar changes of pagetoid cells with premature keratinization (Figure 3). The distal lesion only demonstrated sparse superficial dermal fibrosis with mild perifollicular lymphocytic inflammation. The light staining pagetoid cells were not present. Immunoperoxidase staining with p16 was negative within the lesional keratinocytes of all three lesions, making a human papillomavirus infection unlikely.
FIGURE 3: Pathology of the middle papule

Pathology features of another asymptomatic, flesh-colored papule on the proximal dorsal penile shaft of a 26-year-old man also demonstrate pagetoid dyskeratosis. The opening of the hair follicle is dilated. Pagetoid cells (arrows) with premature keratinization are also prominent within the epidermis. (Hematoxylin and eosin: A: x4; B: x10; C: x20; D: x20).

There has been no recurrence or new lesions in the subsequent six months.

Discussion

Pagetoid dyskeratosis is an incidental pathologic change. It may occur with several different skin conditions. It is characterized by the presence of intraepidermal keratinocytes that resemble those of extramammary Paget’s disease [1].

This phenomenon was initially interpreted by Mehregan and Civette as artefactual and potentially being related to intraepidermal anesthesia, occlusion, and moisture, or poor sample fixation [2-3]. However, in 1988, Tschen et al. suggested that it more likely represented a process of induced premature keratinization, terming the entity "pagetoid dyskeratosis" since the cells appear similar to those observed in lesions of extramammary Paget’s disease [1]. Subsequently, this pathologic finding has been observed by many other investigators in several distinct anatomic sites and lesions; however, the pathogenesis of pagetoid dyskeratosis remains poorly understood.

The clinical presentation of pagetoid dyskeratosis is variable. It is typically an incidental finding in other primary skin lesions that have been biopsied (Table 1) [1, 4-5]. Hence, the morphology of the lesion-containing pagetoid dyskeratosis corresponds to that lesion’s primary diagnosis.
| Clinical lesion         | Diagnostic features                                                                 |
|-------------------------|--------------------------------------------------------------------------------------|
| Acrochordon             | Pedunculated flesh-colored lesion with a narrow stalk                                |
| Actinic cheilitis       | Dryness and scaling of the lower lip, often with edema, erythema, and ulceration     |
| Angiokeratoma           | Red to flesh-colored papules on the face; biopsy shows proliferation of fibroblasts with increased number of blood vessels |
| Basal cell carcinoma    | Pea-sized nodule with telangiectasia; biopsy shows proliferation of neoplastic basal cells that invade the dermis |
| Dermal fibrosis         | Histopathology shows proliferation of fibroblasts with increased fibrous connective tissue in the dermis |
| Dermatofibroma          | Firm, hyperpigmented nodule which disappears when the adjacent skin is squeezed.    |
| Dilated follicular ostium| Pathology shows widening of the follicular opening                                   |
| Epidermal inclusion cyst| Cystic, skin-colored, dome-shaped nodule with a central pore                       |
| Fibrous papule          | Firm, benign, flesh-colored, dome-shaped papule; biopsy shows proliferation of fibroblasts with a fibrotic stroma |
| Folliculitis            | Erythematous, follicular-based papules                                              |
| Hemangioma              | Red papules; pathology shows a benign proliferation of vessels in the dermis        |
| Irritationfibroma       | Small, smooth, pale, pink, benign fibrous tumor of the oral mucosa                   |
| Lentigo                 | Uniformly tan or brown macule with sharp margins; pathology shows hyperpigmentation of the basal layer of the epidermis |
| Lichen sclerosus        | Pruritic, erythematous, atrophic, whitish papules coalescing into plaques; biopsy shows thinning of the epidermis |
| Melanocytic nevus       | Flesh-colored or hyperpigmented, symmetric, uniform, sharply demarcated, round macules, patches, papules, or nodules |
| Milia                   | Small white cystic papules caused by keratin retention                                |
| Mucocele                | Bluish, translucent, fluid-filled papule or nodule of the oral mucosa resulting from chronic irritation |
| Oral-fibrous hyperplasia| Mucochal color, smooth-surfaced, soft nodular benign mass that may be hyperkeratotic or ulcerated |
| Oral ulcer              | Focal loss of mucosal layer                                                          |
| Scabies                 | A mineral oil preparation of a skin scraping demonstrates the presence of mites, eggs, or scybala |
| Seborrheic keratosis    | Scaling, tan or brown, greasy papule or plaque with a “stuck-on” appearance          |
| Soft fibromas           | Flesh-colored benign tumor composed of fibrous or connective tissue                  |
| Squamous cell carcinoma | Nodular, intact or ulcerated; lesion; biopsy shows malignant keratinocyte invading the dermis |
| Verrucous hyperplasia   | Pink papillary exophytic mucosal mass; biopsy shows verrucous projections of hyperplastic epithelium |

**TABLE 1: Clinical Lesions in Which Pagetoid Dyskeratosis Has Been Observed**

Pagetoid dyskeratosis is most commonly found in intertriginous areas [1]. However, it can be found nearly anywhere on the body, including the anus (hemorrhoids), buttocks, cervix, extremities, face, hands, nipple, trunk, and vulva [1-2, 5-11]. Pagetoid dyskeratosis of the male genitalia has only been previously described by two other groups of investigators [12-13].

The first study to observe pagetoid dyskeratosis involving the genitalia of men was conducted to examine the histopathology of 281 consecutive patients undergoing circumcision for phimosis. Pagetoid dyskeratosis of the prepuce was incidentally found in 105 individuals (37.4%). The pagetoid cells were most often seen in the superficial layers of the epidermis but were also occasionally present in the parabasal layer [12].

The second report of male genitalia with pagetoid dyskeratosis included a 54-year-old man with a 10-year history of pruritus involving the scrotum. Cutaneous examination of the scrotum revealed mild erythematous and skin-colored patches with focal areas of hyperpigmentation. Histopathologic analysis was consistent with pagetoid dyskeratosis [13].

Our patient had a history of penile shaft and suprapubic lesions that were clinically assessed to be associated with human papillomavirus or pox virus or both. They were treated topically with either imiquimod or liquid nitrogen cryotherapy and resolved. However, he subsequently developed new small papular lesions affecting the previously treated area of his proximal penile shaft that morphologically was not classic in appearance.
for condyloma acuminatum or molluscum. Indeed, the most prominent feature observed during evaluation of the biopsied lesions was the pagetoid dyskeratosis within the epidermis; the subtle accompanying changes in the dermis (perifollicular inflammation and/or mild dermal fibrosis) correlated with the clinical presentation of the papules.

Microscopically, pagetoid dyskeratosis consists of large round epithelial keratinocytes with pyknotic nuclei and perinuclear halos of washed out cytoplasm. The cells demonstrate premature keratinization into orthokeratotic squames without acantholysis or parakeratosis. They can present individually or in groups often extending upwards in the epidermis. Atypia and mitoses are usually absent [4].

Immunohistochemical staining for high molecular weight cytokeratin and pancytokeratin demonstrates a strong positive signal in the pagetoid cells in comparison to the surrounding keratinocytes [5, 9]. Carcinoembryonic antigen, epithelial membrane antigen, human papillomavirus, and low molecular weight cytokeratin immunohistochemical stains are negative [7]. Staining of pagetoid dyskeratosis cells with alcian blue, Fontana-Masson silver, Mayer’s mucicarmine, Mowry’s colloidal iron, and periodic-acid Schiff typically yields negative results [5, 7].

The pathologic differential diagnosis of pagetoid dyskeratosis includes other conditions with clear cells in the epidermis (Table 2) [3, 14-16]. In some circumstances, immunoperoxidase staining or other stains (in addition to hematoxylin and eosin) may help differentiate these conditions. In our patient, the possibility of condyloma acuminatum was excluded by negative expression of the cells after p16 staining.
### Pathologic Differential Diagnosis

| Pathologic differential diagnosis | Differentiating features |
|----------------------------------|--------------------------|
| Balloon cell melanoma            | Hyperchromatic nuclei surrounded by abundant vacuolated cytoplasm, nests of melanocytes at the DEJ, + S100 |
| Breast carcinoma                 | Hard, non-mobile, single breast mass with irregular borders; various histologic features depending on type of carcinoma (e.g., ductal, lobular, mixed) |
| Clear cell squamous carcinoma in situ | Erythematous, sharply demarcated, solitary papule on the lower extremities; basal layer intact, + PAS |
| Clear cell basal cell carcinoma  | Typical features of conventional basal cell carcinoma with clear cells |
| Clear cell Bowen’s disease (squamous cell carcinoma in situ) | Well-demarcated, erythematous, irregularly bordered plaque with short or scale; atypia, large nuclei, mitoses, no perinuclear halo, intact basal membrane |
| Clear cell eccrine carcinoma     | Rapidly growing, multinodular dermal neoplasm; ductal differentiation and intracytoplasmic lumen formation, mitoses, prominent nuclei; + low weight CK, + CEA, + PAS |
| Clear cell hidradenoma           | Granular cells surrounding tubular lumina, hyalinized stroma, + PAS |
| Clear cell myoepithelioma         | Dermal clear cells merging with duct-like structures, + S100, + calponin, + EMA |
| Clear cell papulosis             | White macules and papules distributed along the hair follicles; + mucicarmine, + CEA |
| Clear cell squamous carcinoma    | Hydropic degeneration of neoplastic cells, invasion of basal layer; + mucicarmine, - PAS |
| Clear cell syringoma             | Association with diabetes mellitus; nests of eccrine ducts, tadpole-like structures in a fibrous stroma, + PAS |
| Condyloma acuminatum             | Papillated; smooth or soft exogenital papules or plaques; + p16 |
| Extramammary Paget’s disease     | Pruritic eczematous, well-demarcated plaque, most often on the vulva; + CK7, + PAS |
| Langerhans cell histiocytosis     | Langerhans cells with "coffee-bean" nuclei, histiocytoses, Birbeck granules, + CD1a, + S100 |
| Pagetoid dyskeratosis            | Pyleotic nuclei with perinuclear halo, + high weight CKs |
| Pagetoid melanoma                | Neoplastic proliferation of amelanotic melanocytes often in nests, + S100, + HMB45, - PAS, - CK, - CEA |
| Paget’s disease of the breast    | Eczematous changes of the nipple and areola; + mucicarmine, + CEA, + CK7 |
| Renal cell carcinoma             | Flank mass, hematuria, paraneoplastic syndromes; lipid and glycogen-rich cytoplasm |
| Sebaceous adenoma                | Benign proliferation of sebaceous cells |
| Sebaceous carcinoma              | Eyelid lesions; atypia, mix of undifferentiated and sebaceous cells, scalloping of the nuclei |
| Sebaceous epithelioma            | Malignant proliferation of irregularly shaped cells, half of which demonstrate sebaceous differentiation |
| Superficial spreading malignant melanoma | Irregularly bordered, multi-colored, pigmented plaque; atypical, hyperchromatic, neoplastic melanocytes that lack cellular maturation; + S100, + HMB45 |
| Toker cell of the nipple         | Found in the nipple epidermis of some normal women; + mucicarmine, + CK7 |
| Tricholemmal carcinoma           | Atypia, mitoses, + PAS |
| Tricholemmoma                    | Lobular growth of clear cells around hair follicles, peripheral palisading, + PAS |

### TABLE 2: Pathologic Differential Diagnosis of Pagetoid Dyskeratosis

| CD: cluster of differentiation; CEA: carcinoembryonic antigen; CK: cytokeratin; DEJ: dermal-epidermal junction; EMA: epithelial membrane antigen; HMB: human melanoma black; PAS: periodic acid Schiff; -: negative; +: positive |

The pathogenesis of pagetoid dyskeratosis remains to be definitively established. Tschen et al. hypothesized that the cells represent a small population of the normal keratinocytes that are induced to proliferate by an external trigger, such as mechanical trauma or friction [1]. Piqué-Duran et al. found that lesions of the axilla more frequently demonstrated pagetoid dyskeratosis in comparison to those of other locations; they suggested that this observation supports the theory that moisture and friction contribute to the development of pagetoid dyskeratosis [14]. Pagetoid dyskeratosis is an incidental finding. Typically, there are no clinical sequelae. Therefore, management is directed toward the primary lesion.

### Conclusions
Pagetoid dyskeratosis is an intriguing benign pathologic feature. It has been observed in a variety of cutaneous lesions located on various areas of the body. Pagetoid dyskeratosis of the male genitalia is uncommon and has been previously described on either the scrotum or the prepuce; our patient’s lesions were on the proximal penile shaft. The differential diagnosis of pagetoid dyskeratosis includes other conditions characterized by clear cells in the epidermis. In particular, in men with genital lesions, the differential diagnosis includes venereal warts. This was excluded based on microscopic findings and negative p16 staining. Pagetoid dyskeratosis-directed therapy is usually not necessary and management of the patient is based upon treating the primary skin lesion.

Additional Information

Disclosures

Human subjects: Consent was obtained by all participants in this study. Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work. Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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