Extramammary Paget's Disease Associated With Genital Wart and Lichen Sclerosus

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Abstract- Extramammary Paget’s disease is an uncommon intraepithelial adenocarcinoma in genital and perianal regions. Genital wart is the most common sexually transmitted disease caused by human papilloma viruses and vulval lichen sclerosus is chronic pruritic dermatitis in genital area which could be able to change to invasive squamous cell carcinoma. We report a patient who had simultaneous lichen sclerosus, genital wart and extramammary Paget’s disease of the vulva. We could not find any significant association between them in literature.

Keywords: Extramammary paget's disease; Lichen sclerosus; Genital wart; Human papillomavirus

Introduction

Extramammary Paget’s disease (EMPD) is a rare intraepithelial adenocarcinoma of apocrine gland-bearing skin and the vulva is the most common site of involvement. Pruritus, burning, irritation and pain are common symptoms (1). These symptoms could be reported in vulval lichen sclerosus (LS) which is associated with anatomical disruptions such as atrophy, resorption or fusion of labias and sclerosis. Uncommonly, LS shows squamous hyperplasia and invasive squamous cell carcinoma which is not human papillomavirus (HPV) related (2), but there is no report about transformed LS to EMPD. Genital warts are HPV related and usually asymptomatic diseases, but there has not been any association between HPV or genital wart and EMPD in several studies (3-5). We present here a case that developed EMPD, LS and verrucous lesions on the vulva.

Case Report

A 65-year-old woman was referred to our clinic with a ten-year history of vulval itching and burning. A number of antifungal treatments and topical steroids had been used with no improvement. She was multiparous with 7 children, went through menopause when she was 50 and did not take hormone replacement therapy. In past medical history, she had fibrocystic changes in her breasts and one caesarian section for the 7th child and tubal ligation in her late 40s.

Physical examination revealed white verrucous tissue on the anterior segment of labia minor, as well as atrophy and fusion of the anterior and posterior segments of labia minor (Figure 1).

Figure 1. An atrophic vulva with fusion of labia and verrucous lesions on anterior part of the vulva. (The locations of biopsies were marked by A and B)

A primary diagnosis of LS vs. lichen planus, wart, and squamous cell carcinoma was made.

Two punch biopsies were taken from the white
Extramammary Paget’s disease

Verrucous lesion on the anterior segment (sample A) and non-verrucous partially atrophic lesion on the posterior segment of labia minor (sample B).

Histopathologic findings for sample A and B in the epidermis were hyperkeratosis, acanthosis in most areas, focal epidermal atrophy (in sample B), focal papillomatosis (in sample A), spongiosis, koilocytic changes with mild to moderate dysplasia and focal basal vacuolar changes. There were atypical cells mainly in the lower half of the epidermis which composed of clear cytoplasm, vesicular nuclei with prominent nucleoli and high nuclear/cytoplasm (N/C) ratio, which were suggestive of EMPD (Figure 2A). The underlying dermis showed fibrosis, edema, dilated blood vessels, patchy zones of subepithelial homogenous collagen fibers deposition and marked lymphocytic infiltration.

For definite diagnosis special PAS staining and immunohistochemistry (IHC) evaluations were performed. PAS staining was positive. IHC evaluations were positive for Carcino embryonic antigen (CEA) (Figure 2B), Cytokeratin 7 (CK 7), epithelial membrane antigen (EMA), Growth cystic disease fluid protein (GCDFP) but negative for S100, Cytokeratin 20 (CK20), c-erb B2, P53. All of these findings were in favor of primary EMPD.

DNA analysis in paraffin blocks of both tissue samples was performed and tested for the following HPV genotypes: 6, 11, 16, 18, 26, 31, 33, 35, 39, 40, 42, 43, 44, 45, 51, 52, 53, 54, 56, 58, 59, 66, 68, 70, 71, 73, 74, 81, 82; but only genotype 11 was detected in both specimens.

According to these findings, primary EMPD, genital wart and LS were proposed.

Screening tests for underlying malignancy including mammography, pelvic ultrasound, cystoscopy, and sigmoidoscopy were done with no evidence of malignancy.

Gynecologic oncology consult was done, and then vulvectomy was performed with complete excision of the whole lesion with free margins, as confirmed by histopathology of the excised tissue. The vulva healed well but previous fusion remained permanent. She was followed up every four months. She was doing well, and there was no clinical evidence of recurrence.

Discussion

This case was interesting to us because of simultaneous development of EMPD, LS and genital wart in an individual patient; in addition, HPV DNA was detected in verrucous and non-verrucous lesions.

The histogenesis of EMPD is still questionable; probably it is a form of intraepithelial adenocarcinoma, but in 6% to 20% of EMPD is associated with an underlying adenocarcinoma in the skin adnexa or Bartholin’s glands (2). Stem cells of the bulge region of hair follicle may be an origin for EMPD cells (6). EMPD clinically presents as red or brown pruritic plaques, which might become erosive and infiltrative (2), but crusting, scaling, papillomatous, lichenified and ulcerated lesions could be seen (1). It could masquerade as LS (7), condyloma lata (8) and condyloma acuminata (5). Associations of EMPD with epidermal hyperplasia have been identified, including squamous hyperplasia, fibroepithelioma-like hyperplasia and papillomatous hyperplasia (9). EMPD in the axilla, as well as condyloma acuminata in the external genitalia, has been
reported (10). There are some reports that it could be mimicking or accompanying condyloma acuminatum in anogenital region (11,12).

Our patient had atrophy and fusion of labia that was similar to LS in this regard. On the other hand, there were papillomatous lesions on the anterior part of the vulva which were HPV11 positive that represented genital wart. Squamous hyperplasia could occur on the background of LS as well, but it has not been HPV related (2). Hence, we proposed this lesion as genital wart superimposed on LS.

In the atrophic region on the posterior segment of the vulva, EMPD was approved histopathologically and HPV 11 DNA was found as well. In previous studies, simultaneous HPV6-positive condyloma acuminatum, HPV31 positive Bowen's disease and non HPV-associated EMPD in an individual clinically condyloma-like lesion was reported which Paget cells were negative for HPV DNA, but already the role of latent HPV in EMPD has been suspected, so we should consider EMPD in any verrucous lesion of anogenital region (5).

According to HPV positivity, mild to moderate dysplasia and LS in the vulva, Pagetoid squamous cell carcinoma (PSCC) in situ vs. EMPD should be proposed. PSCC in situ of the vulva is CK7 positive the same as EMPD, so this marker could no longer be considered specific for EMPD; but PSCC has no mucin, no CEA expression in contrary to EMPD and usually coexist with non-pagetoid SCC (6). So PSSC in situ was ruled out for our patient.

HPV positivity in sample B was unusual to us but would be explained by these paradoxical theories: 1) HPV may occasionally be found in some lesions of anogenital Mammary-like glands, so it plays no causal role in the etiology of EMPD (4). 2) High tendency for recurrence, multicentricity and rare invasiveness in EMPD all would show a viral etiology for these lesions and failure to detect it in previous studies is probably due to multiple technical errors (3). So the role of HPV as a trigger in EMPD is still equivocal.

References