CASE 23.1

An 85-year-old female from Bangkok

Chief complaint

Itchy rash at genitalia for 8 months

Present illness

The patient complainted of longstanding vulvar pruritus. For 8 month her daughter could noticed a genital rash which continuously progressed in size and tenderness.

Past history

Her underlying diseases are hypertension, dyslipidemia.

Physical examination

General appearance: elderly woman not pale, no jaundice
Cardiovascular, respiratory system and abdomen: normal
Breast and nipple: normal
Lymph node: not palpable

Skin examination:

A large solitary ill-defined erythematous macerated plague at left labia majora and minora. Multiple discrete erythematous to brownish papules at right labia majora (Fig. 23.1.1)

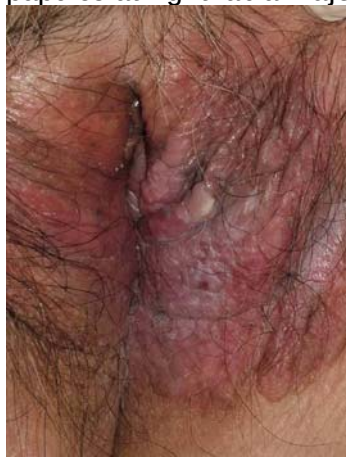

Fig. 23.1.1

Histopathology (S09-8323A) (Fig.23.1.2, 23.1.3)

- Proliferation of pagetoid cells at all layers of epidermis and some extend along the hair follicle
-Pagetoid cells with large pleomorphic nuclei and pale abundant cytoplasm
- Dense superficial inflammatory cells infiltration in the upper dermis

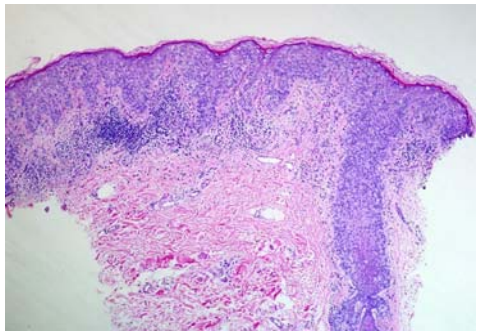

Fig. 23.1.2

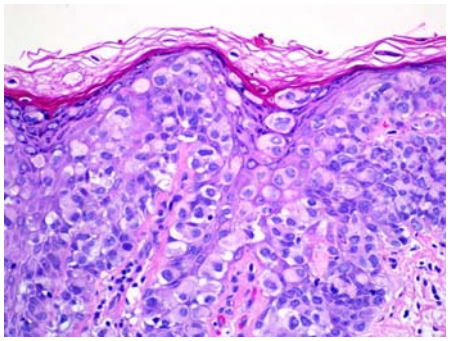

Fig. 23.1.3

Further investigations

CBC, urinalysis, BUN, Cr, LFT: normal
Consultation for gynecologic examination: normal
CEA, CA19-9, AFP: pending result
Consultation for gastrointestinologist and sonography of whole abdomen: pending result

CASE 23.2
A 75-year-old man from Bangkok
Chief complaint
Pruritic scrotal rash for 1 year
Present illness
Within one year, he noticed that there is slowly progressed, slightly tender and itchy rash at his right side of scrotal sac. KOH preparation was negative for fungus. The lesion did not improved by the topical corticosteroid.
Past history
His underlying diseases are DM type 2, hypertension, dyslipidemia and benign prostate hyperplasia.
Physical examination
General appearance: elderly man, not pale, no jaundice
Cardiovascular and respiratory system: normal
Breast and nipple: normal
Abdomen: Soft, not tender, liver and spleen are not palpable
Lymph node: not palpable
PR: enlargement of prostate gland, no rectal shelf
Skin examination:
A Solitary ill-defined erythematous ezematous plague at right scrotum and base of penis (Fig. 23.2.1)

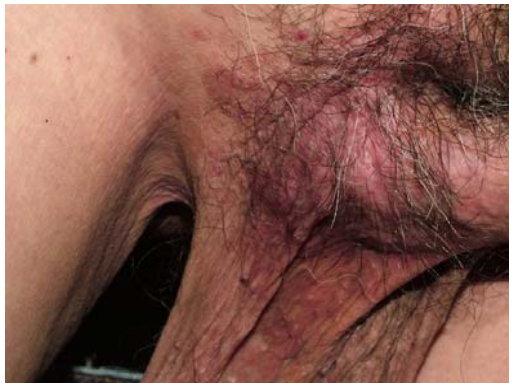
Fig. 23.2.1

Histopathology (S09-4741A) (Fig. 23.2.2, 23.2.3)
- Proliferation of paget's cell both in small nests and solitary unit at all layers of the epidermis
- Paget's cells with large nuclei, pale abundant cytoplasm and devoid of intercellular bridges
- Superficial inflammatory cells infiltrate in the upper dermis

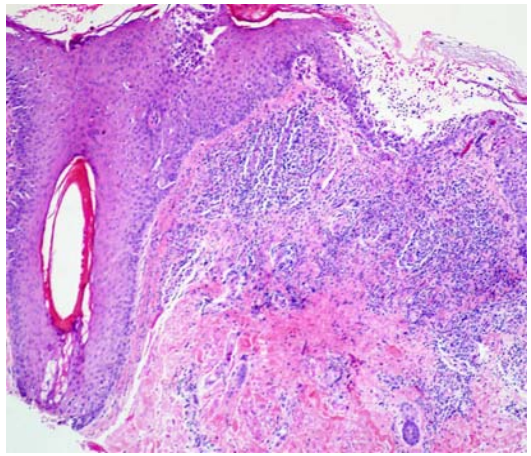

Fig. 23.2.2

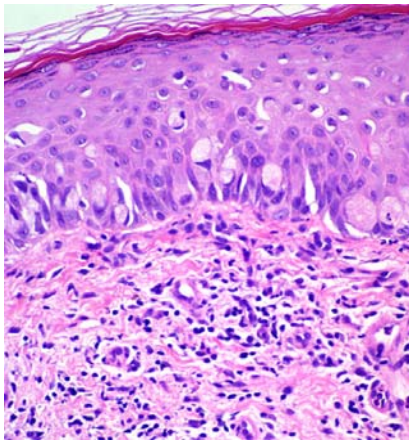

Fig. 23.2.3

Further investigations

CBC, urinalysis, Chest X-ray, stool examination: normal
BUN, Cr, LFT, CEA, CA19-9, PSA, AFP: normal level
Ultrasonography of whole abdomen: unremarkable study
Esophagogastroduodenoscopy: hemorrhagic gastritis
Colonoscopy: colonic polyps
Esophagus, gastric, colonic biopsies showed no evidence of malignancy.

CASE 23 .3

A 66-year-old man from Nonthaburi

Chief complaint

Asymptomatic rash at left inguinal area for 6 months

Present illness

The patient was presented with progressively, asymptomatic, red rash at his right inguinal area for 6 months. The rash showed no improvement after initial treatment with topical corticosteroid.

Past history

His underlying disease is benign prostate hyperplasia.

Physical examination

General appearance: not pale, no jaundice
Cardiovascular, respiratory system and abdomen: normal
Breast and nipple: normal
Lymph node: not palpable

Skin examination:

An ill-defined erythematous ezematous plaque at left inguinal area, left scrotum and shaft of penis (Fig. 23.3.1)

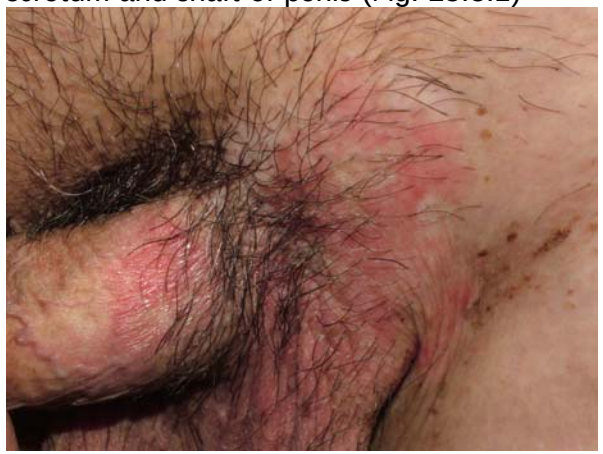

Fig. 23.3.1

Histopathology (S09-7686A) (Fig. 23.3.2, 23.3.3)

- Proliferation of paget's cell both in small nests and solitary unit at all layers of the epidermis
- Paget's cells with large nuclei, pale abundant cytoplasm and devoid of intercellular bridges
- Superficial inflammatory cells infiltrate in the upper dermis

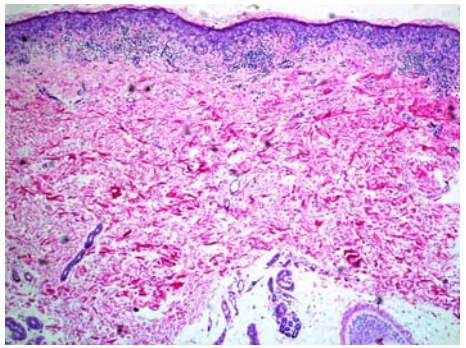

Fig. 23.3.2

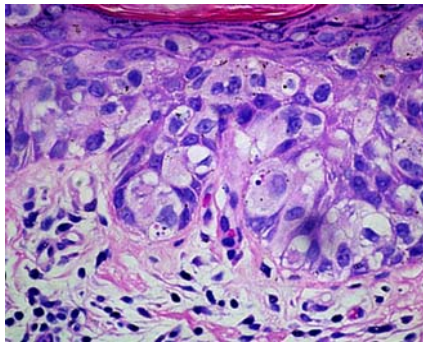

Fig. 23.3.3

Further investigations

CBC , urinalysis, Chest X-ray: normal
BUN, Cr, LFT, CEA, CA19-9: normal level
PSA: 10.86 ng/ml (normal range 0-4 ng/ml)
Ultrasonography of whole abdomen: unremarkable study
Lt and Rt lobes prostate biopsies: benign prostate hyperplasia
Consultation for gastrointestinologist: pending result

Diagnosis: Extramammary Paget disease
Presenter: Sinijchaya Sahawatwong
Consultant: Ploysyne Busaracome

Discussion:

Mammary Paget's disease (MPD)

Mammary Paget's disease is an adenocarcinoma localized within the epidermis of the nipple and/or the areola of the breast, It is much more frequent in women and usually develops during the sixth decade of life. [1]

The currently admitted pathogenesis is the epidermotropic spread of Paget cells(PC) from the underlying mammary carcinoma and migrate via the lactipherous ducts. A motility factor 'heregulin-a', secreted by epidermal keratinocytes, bind to the HER2/neu family receptors expressed by PC and attract PC within the nipple epidermis. [2] In the rare MPD cases that are not associated to an underlying breast cancer('MPD stage 0' or 'extramammary Paget's disease of the breast'), the disease could develop in the epidermis from Toker cells, which are present within the epidermis of the nipple/areola. [3]

MPD usually presents as a unilateral, scaly, fissured or oozing erythema of the nipple and/or the areola. It is occasionally, slightly infiltrated and has an erosive or crusted surface. Retraction or ulceration of the nipple is often noted. Patients frequently experienced symptoms such as itch, tingling, burning or pain.

MPD is almost always associated with underlying in situ or invasive intraductal adenocarcinoma of the breast. [4] The tumors are often multifocal. Breast nodules are found in 30–50% of cases cancer, otherwise the tumor is detected by imaging examinations. Without treatment, the skin lesions invariably spread
progressively before the development of an overt breast cancer

Survival rate of MPD is affected by lymph node status and the presence of underlying breast mass .

Extramammary Paget disease (EMPD)

Extramammary Paget's disease (EMPD) is a rare neoplastic condition of apocrine gland-bearing skin. It affects predominantly patients aged between 65 and 70 years.

There are at least two different forms of EMPD due to distinct pathogenetic mechanisms:

• The 'primary' or cutaneous EMPD form seems to originate
in the skin. This form is the majority of EMPD cases which is not associated to a distant adenocarcinoma and limited to the epithelium. The precursor cell could correspond to undifferentiated pluripotent cells of the epidermis and/or its adnexa.

• The 'secondary' form of EMPD is associated to an underlying (distant) adenocarcinoma and would be due to epidermal invasion of malignant adenocarcinoma cells. This form would represent an epidermotropic metastasis
of the underlying tumor. [1]

The clinical features of EMPD are similar to MPD. The valva is the most common affected area. Other commonly affected areas are perianal region, scrotum and penis. Axilla EMPD occasionally presented. [5-6] Ectopic EMPD develops in skin areas that are usually devoid of apocrine sweat glands has been reported. [1]

The association with underlying internal carcinoma is approximately 15 percent. Those are carcinomas of rectum, bladder, urethra, cervix and prostate

Prognosis depends on the presence of an underlying or distant cancer. Primary EMPD has a favorable prognosis that worsens if the lesions become invasive, namely, if the histological depths of invasion exceed 1 mm. The overall mortality is higher in forms associated with an underlying tumor.

Histopathology of MPD and EMPD

MPD and EMPD are similar in histology. There are clusters of Paget cells, which are, large cells with faintly basophilic and finely granular cytoplasm with large nuclei, containing prominent nucleolus, in the epidermis and sometimes extend to epithelial of the hair follicle or sweat gland duct. PC are devoid of intercellular bridges and can be pigmented. They must be differentiated from intraepidermal cell with pagetoid appearance, including melanoma, pagetoid Bowen's disease and mycosis fungoides. PC contain intracellular mucopolysaccharides, therefore, cells frequently show positive staining for diastase-periodic acid-Schiff, mucicarmine, Alcian blue at PH 2.5 and colloidal iron.

Immunohistochemistry is beneficial for identification of PC and for differentiation from other pagetoid cells. PC stain positive for carcinoembriogenic antigen(CEA) and mucin core protein 1(MUC1). CAM5.2 and CK7 are more sensitive markers but CK7 is not specific. Toker cells, Merkel cells and Pagetoid Bowen's disease can also be positive for CK7. Primary EMPD are usually positive for gross cystic disease fluid protein-15(GCDFP-15) and MUC5AC, whereas secondary EMPD are usually positive for CK20 and MUC2. Melanoma cells, unlike PC, are positive for S100, Melan-A and HMB-45. However, immunohistochemistry can not replace the role of investigation for underlying malignancy in EMPD case.

Treatment.

The standard treatment of MPD andEMPD is surgical excision. However, for MPD, breast conserving surgery combined with breast irradiation has proposed to be alternative treatment. [7] A recent study comparing various modalities of surgical excision (radical or conservative) found no significant differences in terms of overall or disease-free survival. [8] Adjuvant therapy with radiation, chemotherapy, or hormonal therapy is recommended base on lymph node status and specific features. In the absence of detectable breast cancer the therapeutic attitude is not uniform.

For EMPD, Mohs micrographic surgery provide 16% recurrence rate for primary EMPD and 50% for recurrent EMPD, lower than 33%-60%recurrence rate from standard surgery. [9] Radiotherapy can be proposed for inoperable lesions or as adjuvant treatment to surgical excision. The results are better in primary *in situ* EMPD. LASER surgery has been reported for treatment.[10,11] But recurrences occurred. [12] Topical 5-fluorouracil may reduce the margins of the lesions or render them better visible, rendering resection more efficacious. Imiquimod has been successfully used in a small number of EMPD cases. [13-15] Dynamic phototherapy yields satisfactory results.

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