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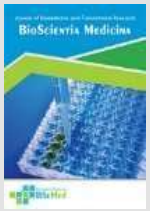

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Extramammary Paget's Disease of the Vulva: A Rare Case Report

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A B S T R A C T

Background: Extramammary Paget's Disease (EMPD) is a rare disease characterized by intraepithelial involvement of the skin by non-squamous carcinoma cells in areas containing apocrine glands such as the vulva, perineum, perianal area, scrotum, and penis. **Case presentation:** A 48 year old woman complained of a non-healing wound in the genital area for 1 year. The wound feels painful and does not bleed easily. No lumps were found anywhere else. The patient works as a private employee with minimal exposure to sunlight. No history of trauma. There is a history of surgical biopsy with the result of a malignant tumor with an impression Extramammary Paget Disease. **Conclusion:** We present a case of a rare malignant tumor with EMPD impression of the vulva, extending to the perineum and suprapubic.

1. Introduction

Extramammary Paget's Disease (EMPD) is a rare disease characterized by the involvement of non-squamous carcinoma cells in the intraepithelial layer of the skin.[1] This disease most often occurs in areas containing apocrine glands such as the vulva, perineum, perianal area, scrotum, and penis.[2] Extramammary Paget's disease is relatively rare with a reported incidence ranging from 0.1 to 2.4 patients per 1,000,000 people per year.[3] EMPD lesions typically manifest in individuals aged 45–75 years, with the peak age of occurrence varying depending on the anatomical location involved. In particular, the onset of EMPD in the vulva tends to appear in individuals aged 50-65 years, while the involvement of the scrotum and penis usually occurs at a more advanced age, namely in the 70-year age group. The presentation of EMPD commonly includes erythematous plaques in the genital area of patients aged 60 to 80 years, which are often misdiagnosed initially as an inflammatory condition, resulting in considerable treatment delays.[4] Extramammary Paget's Disease (EMPD) generally attacks individuals of Caucasian descent, although the incidence in other racial groups is less common. In studies in the Western world, EMPD shows a higher prevalence in women, with a male-to-female ratio ranging from 1:2 to 1:7.[5] However, in Asian populations, the ratio of EMPD between men and women is almost the same, which may be due to cultural differences such as

conservatism in older Asian women leading to less appropriate diagnosis in women experiencing EMPD.[2]

Studies show only 7% to 40% of EMPD have an underlying internal malignancy.[6] Most cases present as primary intraepidermal neoplasms of glandular origin, classified as primary EMPD. Another small percentage is referred to as secondary EMPD, which is characterized by the presence of intraepithelial spread of malignant adenocarcinoma cells from an underlying internal malignancy.[2] In this case report, we present a rare case of malignant tumor with EMPD impression.

2. Case Presentation

A 48-year-old woman complained of a non-healing wound in the genital area for 1 year. Initially, there is a discoloration of the skin in the pubic area. Over time, the lesion turns into a small wound the size of a coin. Over time, the wound grew to the size of a Rp. 100,000.00 Rupiah note in the last 6 months. The wound feels painful and does not bleed easily. No lumps were found anywhere else. The patient works as a private employee with minimal exposure to sunlight. No history of trauma. There is a history of surgical biopsy with the result of a malignant tumor with an impression of Extramammary Paget Disease. The patient appeared mildly ill with compos mentis consciousness. The patient's ECOG score was 0. The patient's vital signs were within normal limits, with blood pressure 110/70 mmHg, heart rate 86 times/minute, respiratory rate 20 times/minute, and temperature 36.7°C. The conjunctiva does not appear anemic and the sclera does not appear icteric. The shape and movement of the chest are symmetrical, vesicular breath sounds are heard equally in the right and left lobes of the lungs, and crackles and wheezing are not heard. The patient's heart sounds are regular, and S1 and S2 are pure. The patient's abdomen is flat and soft and there is no abdominal tenderness. The patient's bowel sounds were within normal limits. The patient's acral feels warm with a capillary refill time of under 2 seconds. There were no visible tremors in the patient's extremities. On the vaginal vulva, there was a wound measuring 10 cm x 8 cm x 1 cm which extended to the perineum and suprapubic. The wound appears hyperemic, there are scales, and the boundaries of the lesion are clear with irregular edges. Figure 1 shows the appearance of the lesion. There is tenderness in the lesion when palpation is performed.

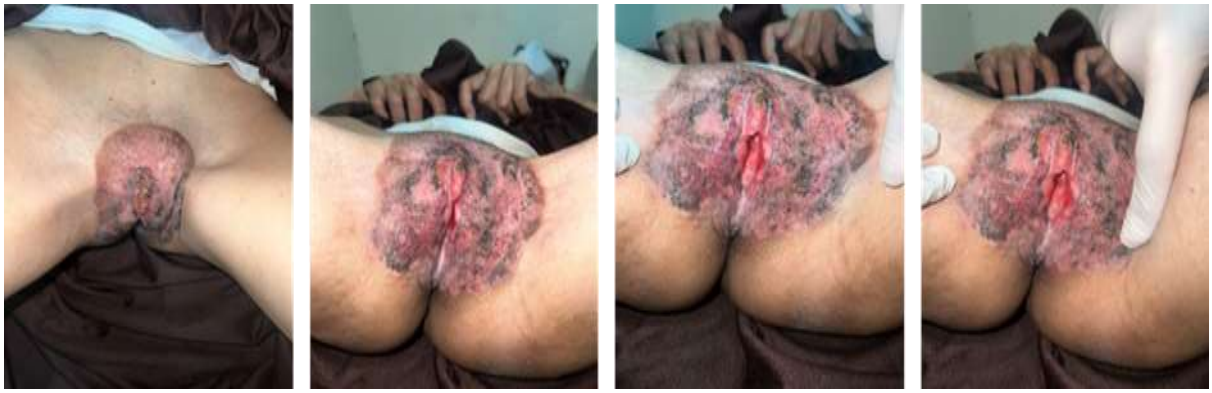

Figure 1. Appearance of the lesion in the patient.

From the anatomical pathology examination, macroscopic examination showed that the skin was brownish-white and supple. On microscopic examination, it appears that the preparation is coated with keratinized squamous epithelium. In the intraepithelial layer, groups of malignant cells are visible, with round oval nuclei, bizarre, pleomorphic, hyperchromatic, coarse chromatin, vacuolated cytoplasm, with gaps between Paget cells and keratinocytes, accompanied by foci of melanin pigment with the basal layer still intact. The subepithelial layer contains a distribution of lymphocytes and histiocytes.

The dermis layer consists of dermal adnexa and swollen fibro-collagen connective tissue stroma. The conclusion from the anatomical pathology examination was that the tumor was malignant with the impression of EMPD. During an ultrasound examination (USG), echotexture of the right and left mammae showed heterogeneous fibro glandular tissue (composition C). No calcification or tissue distortion was seen. The cuticular and subcuticular tissues are not thickened. There is no apparent retraction of the nipple. No ductal dilatation was seen. On right and left axillary ultrasound, there were no solitary/multiple hypoechoic/hyperechoic/isoechoic nodules at levels I, II, and III. No solitary/multiple hypoechoic/hyperechoic/isoechoic nodules were found in the supraclavicular and parasternal bilaterally. The impression from this examination is that bilateral mammary ultrasound does not show solid/cystic lesions, which indicates a negative result (BIRADS 1), and no enlarged lymph nodes are seen in the bilateral axillary, supraclavicular, and parasternal areas. The results of mammary ultrasound are shown in Figure 2.

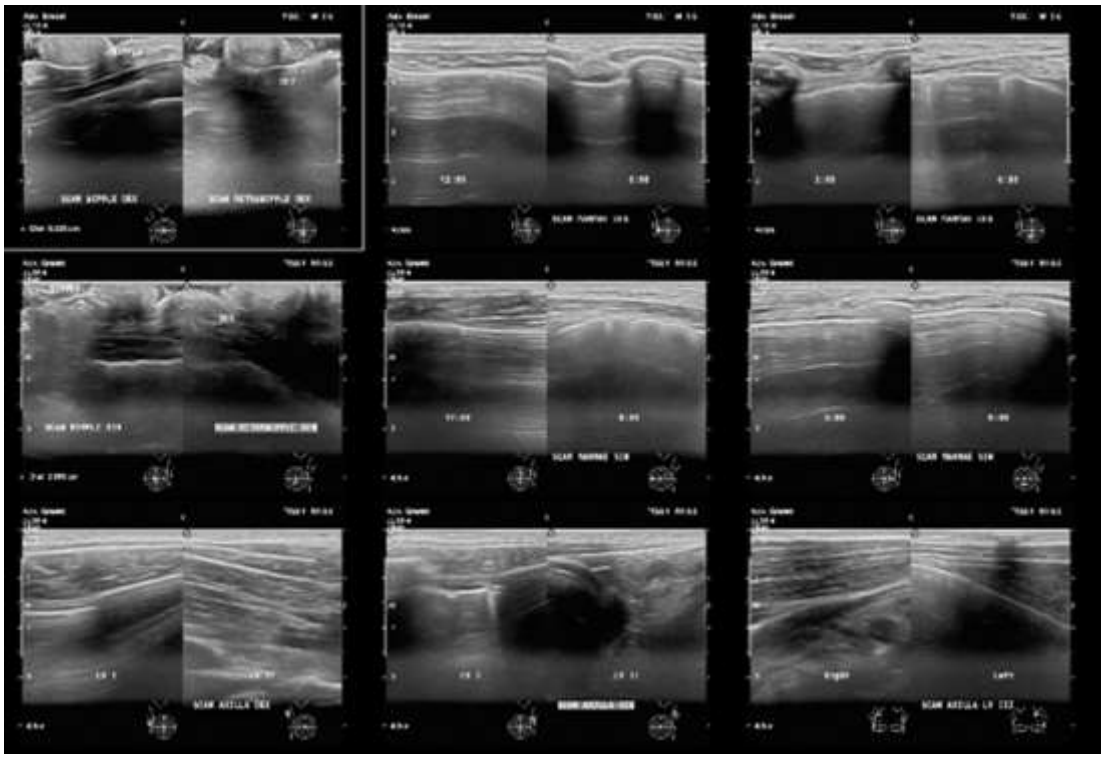

Figure 2. Results of mammary ultrasound.

On abdominal ultrasound examination, the liver does not appear enlarged, with sharp angles, a flat surface, homogeneous parenchymal texture, and no visible nodules/masses. The portal vein and hepatic vein are not dilated. There was no visible fluid collection around the liver. The size of the gallbladder does not appear enlarged with normal walls. The intra/extrahepatal bile ducts do not appear dilated, and there is no visible hyperechoic shadow with acoustic shadow. The spleen is not enlarged, the parenchymal texture is homogeneous, and there are no nodules/masses. The splenic vein is not enlarged. The size of the pancreas is not enlarged, with normal contours and homogeneous parenchymal texture, no visible masses/calcifications. The pancreatic duct is not dilated. Both kidneys were normal in size, with normal contour, normal parenchyma, and normal echo intensity. The border of the parenchymal texture with a normal central echo complex. There is no visible hyperechoic picture acoustic shadow. The

pelvicalyceal system appeared normal. The proximal ureter is not visualized. The urinary bladder is not filled sufficiently, the wall appearance is difficult to assess, and there is no visible hyperechoic shadow with acoustic shadows/masses. There was no visible fluid collection around it. No hypoechoic nodule shadows were seen in the paraaorta and parailiaca. The impression on the abdominal ultrasound examination was that there were no intrahepatic metastases, no enlargement of the paraaortic/parailiac lymph nodes, and visualization of the liver, spleen, gallbladder, pancreas, bilateral kidneys, and urinary bladder did not show any abnormalities. The results of an abdominal ultrasound are shown in Figure 3.

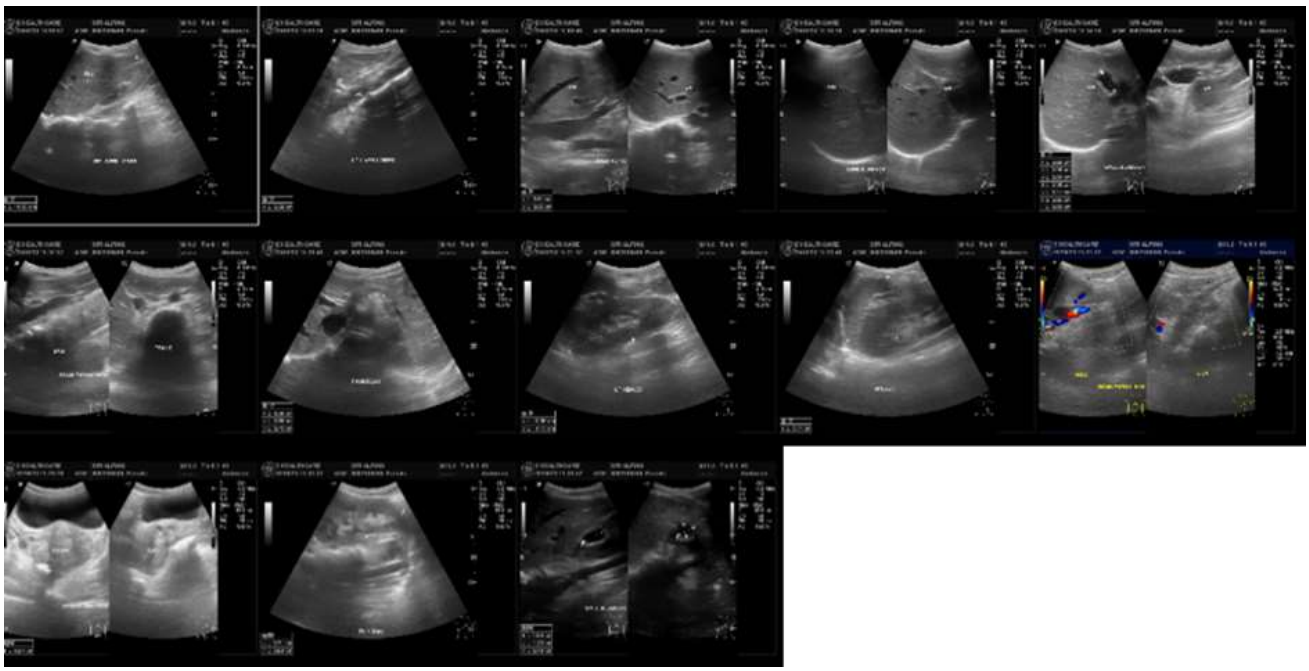

Figure 3. Abdominal ultrasound results.

The results of a pelvic MRI with contrast showed a pear-shaped uterus, with a slightly enlarged size of ± 5.25 x 5.30 x 8.05cm, in a retroflexed position. Multiple isointense lesions appeared on T1WI with clear borders, regular edges, and a size of ± 1.56 x 1.38 x 1.95cm in the posterior uterine corpus myometrium and a size of ± 1.46 x 1.42 x 1.43cm in the anterior uterine corpus subserosa. The lesion appeared hypointense on T2WI and was not visible in a restricted area on DWI-ADC. At T1post contrast scanning seems to give enhancement. The endometrial line does not appear thickened with a thickness of ± 5.7mm (normal < 10 mm). The junctional zone does not appear widened, namely ± 4.2mm in the posterior part and ± 5.5mm in the anterior part (Normally < 12 mm). The anterior and posterior portio is still intact. Hypointense lesion appears on T1WI with well-defined, regular edges, multiloculated, measuring ± 2.09 x 1.57 x 1.60cm which appears to originate from the endocervix. The lesion appeared to give a hyperintense signal on T2WI and was not visible in a restricted area on DWI-ADC. At T1post contrast, scanning is an invisible enhancement. The anterior, posterior, right lateral, and left parametrium appeared regular. There was no visible fluid collection in the cul-de-sac. On the right ovary, a lesion was visible unilocular with firm borders, and regular edges, ± 1.36cm in diameter. The lesion gives changes in signal intensity, hypointense on T1WI, and hyperintense on T2WI, but does not give a restricted area on DWI-ADC. In post contrast scanning there is no enhancement, indicating the presence of a functional follicular cyst. There is a

lesion on the left ovary unilocular with firm boundaries, and regular edges, ± 1.11cm in diameter. The lesion gives a change in signal intensity that is hypointense on T1WI, hyperintense on T2WI and does not provide a restricted area on DWI-ADC. contrast scanning invisible enhancement, which indicates the presence of a functional follicular cyst. The right and left fallopian tubes do not appear dilated. At level I, the endopelvis, uterus, and proximal 1/3 of the vagina (fornix zone) appear intact, and the uterosacral ligament also still appears intact. At level II of the endopelvic, the posterior medial 1/3 of the vagina (transitional zone) appears intact, the posterior urinary bladder also appears intact. At level III the endopelvis, urethra, and distal 1/3 of the vagina (sphincter zone) appear intact. The vulva appears thickened and gives enhancement on T1 post-contrast scanning, but no lesions were visible on the vulva. The urinary bladder appears to be sufficiently filled with walls that are not thickened. The paravesical space appears intact. The position, size, and shape of the rectum are within normal limits. The rectal wall appears regular, with the lumen size still within normal limits. Perirectal fat looks normal. On the pelvic wall, forming muscles pelvic wall: bilateral obturator internus, bilateral obturator externus, bilateral pectineus, bilateral piriformis, bilateral iliococcygeus, bilateral pubococcygeus, levator ani, and puborectalis and its fascia still appear intact.

On the peritoneum, culdesac and rectovagina space looks intact, with a regular surface, does not appear thickened, is not filled with fluid. Onpost contrast scanning invisible enhancement. In the pelvic and rectoperitoneal lymph nodes, there was no visible enlargement of bilateral obturator lymph nodes, bilateral internal iliac, bilateral external iliac, common iliac (N=8mm), bilateral presacral and perirectal (N=10mm), and bilateral inguinal (N=15 mm). The impression from an MRI examination of the pelvis with contrast is: thickening of the vulva with enhancement that is suggestive of being caused by an inflammatory process, mild enlargement of the uterus accompanied by multiple solid masses that appear to originate from the posterior uterine corpus myometrium and anterior uterine corpus subserosa suggestive of multiple intramural and subserosal type leiomyomas, visible the presence of a multiloculated cystic mass that appears to originate from the endocervix is suggestive cystic cervicitis with differential diagnosis tunnel cluster, and there was no visible enlargement of bilateral obturator lymph nodes, bilateral internal iliac, bilateral external iliac, common iliac, bilateral presacral and perirectal, and bilateral inguinal. Figure 4 shows the results of a contrast-enhanced pelvic MRI examination of this patient.

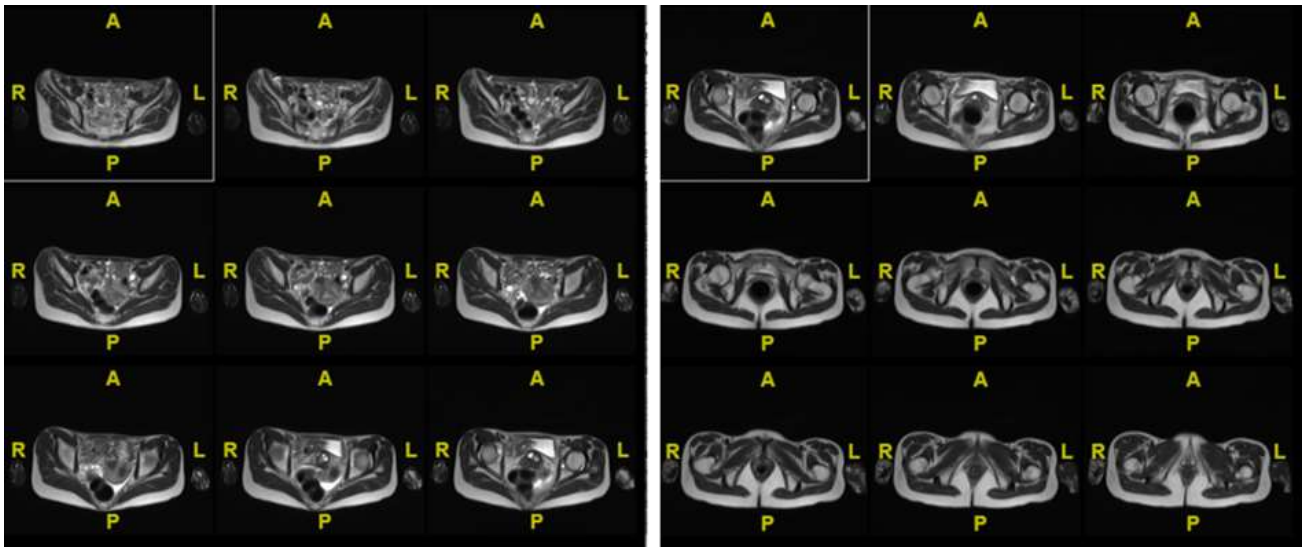

Figure 4. Results of MRI examination with contrast in the pelvis.

On chest X-ray examination (PA view), the photo appears asymmetrical with sufficient inspiration. Visualized bone and soft tissue were within normal limits. The trachea appears to be in the center. The mediastinum does not appear dilated. The heart does not appear enlarged. The sinuses and diaphragm were within normal limits. In the lung area, the hilum is within normal limits, there are normal broncho vascular patterns, there are infiltrates in the upper and lower fields of the right lung and in the upper and middle fields of the left lung, and there is fibrocalcification in the upper fields of the lungs bilaterally. The impression from the chest X-ray examination was suspected of post-primary pulmonary tuberculosis and there was no cardiomegaly. Figure 5 shows the results of a chest X-ray examination.

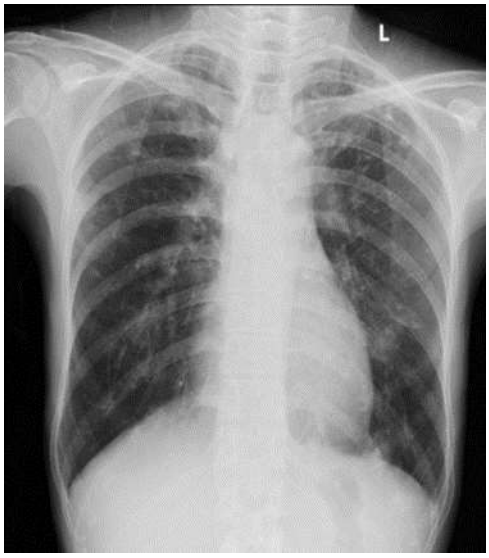

Figure 5. Results of thoracic X-ray examination.

On serum examination, the urea/creatinine ratio in this patient was 14.5/0.68. ECG examination was within normal limits. Spirometry examination showed FVC 1.71 (79%) without bronchodilators with a predictive value of 2.16, and FEV1 1.56 (95%) with a predictive value of 1.65. Pulmonary function tests showed a mild restrictive condition. The patient was diagnosed with EMPD. Based on the patient's gender, there are several examinations that can be considered, such as mammography, pap smear, pelvic ultrasound, cystoscopy, colonoscopy, and computed tomography of the abdomen and pelvis. Immunohistochemical examination (CPI) may be performed afterward to determine whether the results are consistent with primary EMPD (CK 7+/CK 20-/GCDFP-15+) or secondary EMPD (CK 7+/CK 20+/GCDFP-15-). If the results are consistent with primary EMPD, a histopathological examination of the tumor can be performed. If the examination results show a tumor in situ, there is no need for a sentinel lymph node biopsy (SLNB) examination. If the examination results show invasion of the papillary dermis reticular dermis or deeper layers, it is necessary to carry out an SLNB examination to see whether there is lymphovascular invasion, lymph nodes, and distant metastases. If the results are consistent with secondary EMPD, tissue-specific antigen examination, such as uroplakin, CDx-2, and prostate antigen can be performed to determine whether there is an underlying malignancy in the organ.[6]

Several studies show data regarding the prognosis of EMPD. In general, patients with EMPD have a good prognosis.[6] The 5-year survival rate varies depending on the stage of disease, with rates of 87% for all primary EMPD patients, 92% for localized EMPD, 77% for regional metastases, and 16% for distant

metastases. Factors such as older age at diagnosis, primary location in the perianal area, distant metastases, radiotherapy, and higher N stage, M stage, and AJCC stage were associated with decreased survival. Patients aged 65-74 years and 75 years or older had shorter survival compared with those aged less than 65 years. In addition, patients with a primary location in the truncal skin or scrotum showed better survival compared with patients with a primary location in the perianal area. In addition, EMPD with distant and regional metastases shows a worse prognosis compared with local EMPD, and patients receiving radiotherapy showed reduced survival.[7] Specifically, the prognosis for patients with Vulvar Paget's Disease (VPD) is generally good with 5-year overall survival ranging from 75% to 90%.[6] Despite high disease control rates (50–100%) at primary diagnosis, local recurrence rates of VPD are high, which can lead to repeated surgical interventions that can be disfiguring and impact the patient's quality of life.[8]

Management of EMPD includes a variety of strategies, including non-surgical interventions, surgical procedures, and systemic therapy. The main non-surgical modalities are topical imiquimod, photodynamic therapy/photodynamic therapy (PDT), radiation therapy, and laser ablation. Topical imiquimod works by stimulating the innate immune pathway by eliciting the production of inflammatory cytokines such as IL-6, IFN-alpha, and TNF-alpha so as to provide antitumor effects. This treatment offers a small degree of clinical improvement with the drawback of a lack of complete response. Photodynamic therapy/photodynamic therapy (PDT) involves the use of photosensitive drugs such as aminolaevulinic acid, which after exposure to certain wavelengths of light will produce toxic free radicals to eradicate tumor cells. Although non-invasive, PDT has several disadvantages, including pain, photosensitivity, and palliative properties. Radiation therapy, administered in doses ranging from 10 Gy to 64 Gy, serves as primary or adjuvant treatment, although it is accompanied by potential side effects that include mucosal and dermatological toxicity, leukopenia, and varying degrees of colitis, cystitis, and urethritis. Laser ablation techniques using Neodym: YAG, CO_2, and holmium lasers offer several advantages such as shorter surgical duration and less bleeding, but require a longer healing time.[9] In this case surgical intervention was planned, specifically wide local excision and reconstruction of the patient's lesion. Surgical interventions such as excision, biopsy punch, and Mohs micrographic surgery provide lower recurrence rates through wide local excision. However, this intervention has disadvantages, namely in lesions with irregular tumor boundaries with unclear boundaries and satellite lesions that cannot be seen. In metastatic cases, combination drug therapy such as FP, FECOM, and PET therapy is an optimal choice, although comprehensive data regarding the associated harms are still limited due to insufficient sample size.[9]

Regular and close monitoring of EMPD patients is recommended due to the potential risk of recurrence. Patients with non-invasive EMPD are recommended to undergo examination twice a year for a minimum of 3 years, followed by annual evaluations for a minimum of 10 years. For cases of invasive EMPD or those associated with tumors in underlying distant organs, follow-up should be performed more frequently, with a proactive approach to biopsy suspicious skin lesions. Monitoring protocols should include routine vulvar examination, vulvoscopy, repeat biopsies if suspected, and imaging such as CT/MRI to identify lesions in distant organs.[6,8]

3. Discussion

Extramammary Paget’s Disease (EMPD) was first documented in 1889 by Radcliffe Crocker. Crocker documented cases of Extramammary Paget's Disease (EMPD) involving the scrotum and penis, which have histological similarities to Mammary Paget’s Disease (MPD) which was first identified by Sir James Paget in 1874. Furthermore, in 1901, William Dubreuilh described a case of vulvar EMPD.[2] The vulva is the main anatomical location that can be affected by EMPD, occurring in approximately 65% of EMPD

cases. Other locations commonly affected by EMPD are the perianal area (20%) and the male genitals, which include the scrotum or penis (14%). Cases of EMPD occurring in atypical sites such as the axillae, buttocks, thighs, eyelids, external auditory canal, and other areas rich in apocrine glands are rarely documented.[2]

Extramammary Paget's Disease (EMPD) is classified into primary and secondary. Primary EMPD is described as a lesion that initially develops as an epidermal intraepithelial neoplasm (carcinoma in situ). Primary EMPD can occur with invasion and/or as a manifestation of primary adenocarcinoma occurring in appendage skin or subcutaneous vulvar glands. Secondary EMPD is defined as a primary EMPD-like lesion that develops from the epidermotropic spread of malignant cells or direct extension of an underlying internal neoplasm. Secondary EMPD may result from anal or rectal adenocarcinoma, urothelial neoplasm, adenocarcinoma, or other related tumors.[10]

Histologically, EMPD is characterized by the presence of epidermal Paget cells (PC), which are malignant glandular epithelial cells with abundant clear cytoplasm, usually containing mucin, along with a pleomorphic and hyperchromatic nucleus.[11] Hyperkeratosis and parakeratosis often appear. Invasion of adnexal structures may occur. Additionally, a dense inflammatory infiltrate consisting of lymphocytes, histiocytes, neutrophils, eosinophils, and mast cells is commonly identified in the upper dermis of EMPD.[12] This inflammatory infiltrate potentially underlies the pruritus and eczema appearance present during the initial clinical presentation.[2]

Previous studies have described several factors that have the potential to be associated with a poor prognosis in EMPD, namely: skin invasion, distant metastasis, concomitant malignancy, male gender, and tumors located in the perianal anatomical area.[13] The risk factor that may influence this patient's condition is the presence of concurrent malignancy, which is shown in the results of the anatomical pathology examination. In recent studies, it was shown that the expression of molecular proteins involved in cell proliferation and survival, such as HER2 and mTOR, in Paget cells (EMPD tumor cells) correlated with invasion, metastasis, and overall survival of tumor cells. HER2 activation triggers multiple signaling cascades, including the RAS-RAF-MEK-ERK pathway and the PI3K-AKT-mTOR pathway, which promote cell growth and promote cell survival. In addition to HER2, activation of downstream molecules in the RAS-RAF-MEK or PI3K-AKT-mTOR pathways may also contribute to the development of EMPD.[14]

4. Conclusion

We present a case of a rare malignant tumor with an EMPD impression of the vulva, extending to the perineum and suprapubic.

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