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Unmasking Extramammary Paget Disease: A Case Report on the Importance of Biopsy in Persistent Dermatitis

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ABSTRACT

Introduction: Extramammary Paget's disease (EMPD) is a very rare cutaneous neoplasm that occurs predominantly in locations with apocrine glands. In Asia, the incidence of EMPD is extremely low, ranging from 0.04 to 0.12 cases per 100,000 population. The clinical features of EMPD resemble chronic inflammation, making it difficult to distinguish from other skin disorders. Here, we present a rare case of EMPD in Indonesia.

Case report: A 67-year-old woman presented with a 5-year history of erythematous plaque over her vulva and pubic area. The cutaneous lesions were painful and progressed slowly. Lesions manifest as well-defined erythematous plaques with irregular margins, an overlying scale or crust, and hypopigmentation or hyperpigmentation. The patient had received topical treatment for one year, but the condition remained unchanged. Histopathologic findings showed infiltration of anaplastic cells with round, pleomorphic, and hyperchromatic nuclei. Immunohistochemical staining showed CK7+, CK20-, p63+, and GATA3+. The growth confines itself to the epidermis, without penetrating the basal membrane. **Discussion:** A comprehensive examination, including lymph node palpation, can diagnose EMPD, and a skin biopsy and histopathology confirm the diagnosis. Immunohistochemical staining is essential for ruling out other possible diagnoses. Surgery is the primary treatment for EMPD. Given the risk of recurrence and additional malignancies, a close follow-up is recommended for the first 5 years.

Conclusion: The diagnosis of EMPD is a challenge due to the nonspecific clinical appearance, leading to delayed therapy. A skin biopsy is recommended for chronic anogenital skin lesions that don't respond to topical therapy.

Keywords: *Extramammary Paget's disease; pubic, vulva, histopathology, diagnosis*

1. INTRODUCTION

Extramammary Paget's disease (EMPD) is a rare cancer that primarily occurs in areas with apocrine glands, most commonly in the anogenital region. EMPD is classified into two types: primary, where malignant cells originate from the intraepidermal part of the gland, and secondary, where an adenocarcinoma or other underlying threat spreads. [1] EMPD prevalence varies from 0.6 to 3.3 cases per 100,000 people in Europe and the United States. [2-3] The incidence rate in Asia is lower, ranging from 0.04 to 0.12 cases per 100,000 people. [4-5] White or Caucasian races account for 71.3% of EMPD cases, while other races are less common. [3] The apparent EMPD lesion is a well-defined, irregular erythematous plaque with a scale or crust that may have changed pigmentation. [1] EMPD's clinical presentation is similar to inflammatory conditions, challenging differentiation from other skin disorders. Non-specific clinical findings can lead to misdiagnosis and prolonged treatment delays.[6] Diagnosing EMPD requires a skin biopsy for histopathological examination. Immunohistochemistry is crucial for differentiating primary and secondary EMPD and ruling out other potential diagnoses.[7] This case report aims to provide a concise clinical picture, diagnosis, and implementation for EMPD. This report can serve as a reference for clinical practitioners encountering similar cases, helping to prevent misdiagnosis.

Case Report

A 67-year-old woman came to the Dermatology and Venereology Outpatient Clinic of Dr. Soetomo General Academic Hospital. She complained of red spots in her genital area and lower abdomen. Red spots appeared on the vulva area five years ago. They are about 3 cm in size, painful when the skin is dry, but not itchy or prone to bleeding. Over time, the red spots become larger. In 2018, doctors suspected an infection and referred the patient to Dr. Soetomo's outpatient clinic for fungal infections and allergies. However, the results were negative. The patient received treatment for a year with no improvement. Patients received topical therapy, but didn't remember the specific medication details. Treatment was stopped due to the COVID-19 pandemic. The patient has a history of hypertension and tuberculosis, no history of autoimmune conditions. The family did not make any similar complaints.

The patient has normal vital signs. Dermatological exams found a 10 cm erythematous plaque with scales and fissures on the vulva and pubic region. The palpation examination revealed no enlarged inguinal lymph glands. The patient is suspected to have extramammary Paget's disease. The differential diagnoses were lichen sclerosus et atrophicus and Bowen disease.

The skin biopsy shows anaplastic cells inside, with round and pleomorphic nuclei and hyperchromatic features. The epidermis confines the infiltrative growth, which does not breach the basal membrane. The dermal layer shows lymphocyte infiltration at the dermoepidermal junction. Immunohistochemical staining shows CK7+, CK20-, p63+, and GATA3+ (Pic 3). Histopathological and immunohistochemical results confirm EMPD. Based on the medical history, physical examination, and supporting tests, the patient has been diagnosed with extramammary Paget's disease. We refer the patient to an oncology surgeon for surgery.

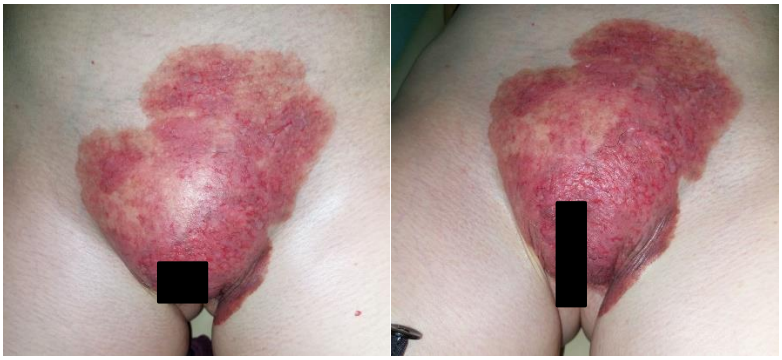


Figure 1. The clinical description of the patient during the visit to the Dermatology and Venereology Clinic revealed a well-defined erythematous plaque in the vulva and pubic region. It exhibited scales and fissures, with a diameter of approximately 10 cm.

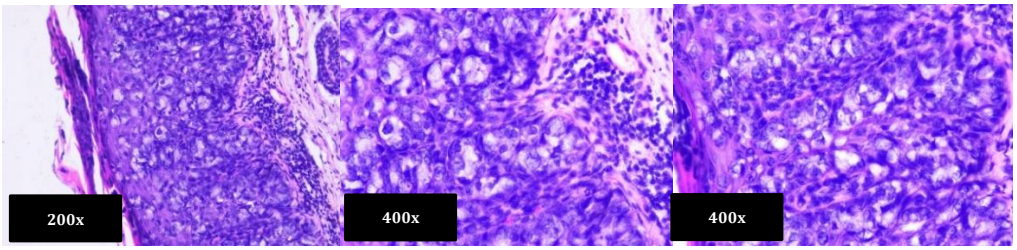
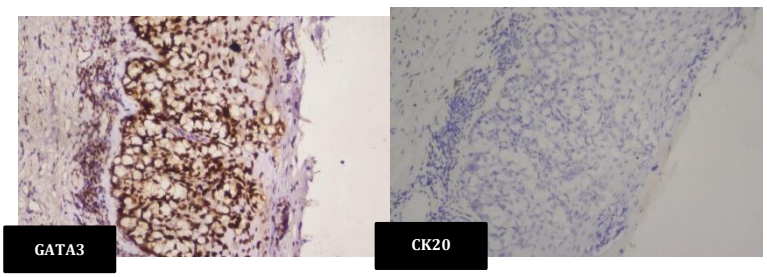


Figure 2. The skin biopsy reveals infiltration of anaplastic cells with round, pleomorphic nuclei, and hyperchromatic features. The infiltrative growth is limited to the epidermis and does not penetrate the basal membrane. In the dermal layer, there is a lymphocyte infiltrate at the dermoepidermal junction.



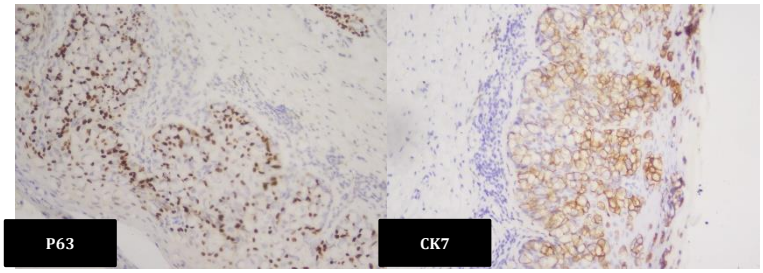


Figure 3. Immunohistochemical staining showed CK7+, CK20-, p63+, and GATA3+.

2. DISCUSSION

In this case, EMPD was found in a 67-year-old patient. This is consistent with previous literature, where EMPD occurs in elderly individuals aged between 60 and 80 years, with an average age of 65.87 years. A study in China in 2016 reported that EMPD cases occurred in 4 out of 10,000,000 people. This data suggests that the prevalence of EMPD in Asian countries is much lower compared to the prevalence in European and American populations. [4]. The pathogenesis of EMPD is still not fully understood. Some reports state that the pagetoid cells found in the vulvar epidermal layer are precursors of Paget cells. Based on genomic analysis of EMPD lesions, somatic mutations have been identified in a series of genes. Stasenko et al., in 2020, presented genomic sequencing results from 26 patients with vulvar EMPD, where the most dominant gene mutations were found in PIK3CA (35%), ERBB2 (27%), and TP53 (27%).[8] The genotype and gene expression in specific races may play a role in the differences in incidence rates in Asia compared to other countries. However, there is currently no further research that specifically addresses this aspect.

The confirmation of EMPD diagnosis can be achieved through a comprehensive examination of the organ systems and thorough skin inspection, including palpation of the lymph nodes, and is confirmed through skin biopsy. Once the diagnosis is confirmed, additional examinations are necessary to determine if there is any underlying malignancy. In this case, the observed lesion is an erythematous plaque that originates in the vulva area and extends to the pubic region, resembling a chronic inflammation that does not improve. The location of the lesion aligns with studies in Japan, indicating that the vulva is the predominant site in 88.9% of female EMPD cases. EMPD located in the vulva often presents with initial lesions starting from the labia majora and gradually spreading outward.[9] Based on histopathological examination, EMPD is characterized by Paget cells, which are anaplastic epithelial cells with clear cytoplasm, pleomorphic and hyperchromatic nuclei, located in the epidermal layer that can extend down to the basal layer.[6] The findings in this case have a similar pattern, where anaplastic cells are confined to the epidermis but do not penetrate the basal membrane. Immunohistochemical examination is necessary to rule out other possible diagnoses. GATA3 and CK7 are sensitive indicators for all types of EMPD, while CK20 is typically used to differentiate between primary and secondary EMPD, with positive results often indicating secondary EMPD.[1,10] In this case, positive results for GATA3 and CK7, and negative for CK20 were obtained, leading to a diagnosis of primary epidermal-type EMPD, where there is no invasion into the dermis. Literature indicates that EMPD more commonly occurs as a primary condition without any underlying malignancy.[1]

The differential diagnosis for this case includes lichen sclerosus et atrophicus and Bowen's disease. Both diagnoses present clinically as lesions resembling chronic inflammation and can occur in the genital area. Lichen sclerosus et atrophicus (LSA) is a chronic inflammatory disorder affecting connective tissue and is suspected to be an autoimmune reaction. LSA clinically manifests as whitish sclerotic plaques progressing to atrophy, possibly accompanied by erosions. In women, LSA most commonly occurs in the vulva. This form may resemble EMPD lesions with hypopigmentation. The differential diagnosis of LSA can be ruled out because histopathologically, it should show hydropic degeneration of basal cells, atrophy, and hyperkeratosis.[11] In contrast, the skin biopsy points towards neoplasia in this case. Bowen's disease is an in situ squamous cell carcinoma with a clinical presentation of well-defined erythematous plaques, irregular borders, and scales or crusts. It typically occurs in sun-exposed areas and the anogenital region. Histopathological findings in Bowen's disease, especially the pagetoid type, can resemble EMPD with limited atypical cell infiltration confined to the epidermis.[12] However, the diagnosis can be differentiated through immunohistochemical staining, where Bowen's disease shows positive results for p63 but negative for CK7. Therefore, this differential diagnosis can be ruled out.[13]

Surgery is the primary therapeutic option for EMPD cases. The main goal of management is comprehensive excision to achieve negative margins while preserving functional and cosmetic aspects. Wide local excision (WLE) has long been used as the standard for EMPD management. However, considering the clinically unclear margin boundaries, high rates of local recurrence, and the potential for metastasis, Mohs micrographic surgery (MMS) is more recommended.[6] In cases where surgery is not feasible, several non-surgical treatment alternatives such as radiotherapy, topical imiquimod (IMQ), photodynamic therapy (PDT), and laser ablation can be considered.[13] The recurrence rate following the WLE procedure reaches 37%, and 11.2% for the MMS procedure.[14] Ghazawi et al. demonstrated that EMPD is associated with an increased risk of other malignancies, occurring in 87 out of 544 EMPD patients, especially in cases of invasive and metastatic types.[9]

Considering the risk of recurrence and the development of other malignancies, regular follow-up is recommended during the first 5 years after the diagnosis.[14] Based on the analysis by van der Linden et al., vulvar EMPD has a good prognosis, especially in the intraepithelial type, with a 5-year survival rate reaching 98%. However, in the invasive type, this figure drops to 50%.[15] The presence of nodules in the primary lesion, enlargement of lymph nodes, depth of skin invasion, and metastasis through the lymphatic system are significant factors for the prognosis of EMPD.[16]

3. CONCLUSION

Extramammary Paget's disease is a rare case with a pathogenesis that is not fully understood. EMPD generally occurs in older individuals and has a predilection for skin containing numerous apocrine glands. Misdiagnosis is often encountered due to the nonspecific clinical appearance, leading to delayed therapy. A skin biopsy is recommended in cases of chronic inflammation in the anogenital area that does not respond to topical treatment. Currently, surgery is the primary therapeutic option for EMPD cases. Regular evaluation is necessary given the risk of recurrence and the potential development of other malignancies.

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