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Authors: Julia Zawistowska, Leszek Kozłowski, Katarzyna Pochodowicz, Karolina Rogowska, Angelina Lęgas, Joanna Smalira, Weronika Rogala, Bartosz Przybysz, Jakub Kawalec, Weronika Rutkowska-Kawalec

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CASE REPORT

Insights into an uncommon case: axillary extramammary Paget's disease and TP53 mutation

Short title: Julia Zawistowska et al., Axillary extramammary Paget's disease and TP53 mutation

Julia Zawistowska[1] (https://orcid.org/0009-0001-5202-2768), Leszek Kozłowski[2] (https://orcid.org/0000-0001-8557-3892), Katarzyna Pochodowicz[3] (https://orcid.org/0000-0003-0353-6989), Karolina Rogowska[3] (https://orcid.org/0009-0007-7857-0782), Angelina Lęgas[4] (https://orcid.org/0009-0001-9841-2833), Joanna Smalira[3] (https://orcid.org/0009-0003-7207-1393), Weronika Rogala[3], Bartosz Przybysz[5] (https://orcid.org/0009-0004-6422-5249), Jakub Kawalec[6] (https://orcid.org/0009-0003-6388-1239), Weronika Rutkowska-Kawalec[7] (https://orcid.org/0009-0002-4283-6458)

[1]Voivodeship Hospital in Bialystok, Białystok, Poland
[2]Bialystok Oncology Centre, Poland
[3]Praski Hospital in Warsaw, Poland
[4]University Clinical Centre of the Medical University of Warsaw, Poland
[5]Bielanski Hospital in Warsaw, Poland
[6]Specialist Hospital for Pulmonary Diseases Zakopane, Poland
[7]Tytus Chałubiński Regional Hospital in Zakopane, Poland

Corresponding author:
Julia Zawistowska
Voivodeship Hospital in Bialystok
M. Curie-Skłodowskiej 26 St., 15–950 Białystok
e-mail: juzawistowska@gmail.com
phone: +48 784301588

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ABSTRACT

Extramammary Paget's disease (EMPD) is a rare malignancy primarily affecting areas rich in apocrine glands, such as the genitalia, perianal region, and axilla. Here is presented a case report of a 43-year-old woman with an unusual manifestation of EMPD in the axillary region, complicated by a history of multiple primary malignancies and a TP53 mutation. The patient's oncological history includes two separate occurrences of breast cancer along with papillary thyroid carcinoma. Genetic testing confirmed a TP53 mutation, prompting prophylactic bilateral oophorectomy with salpingectomy. In 2021, the patient presented with an erythematous skin lesion in the right axilla, initially resembling a benign spot but later exhibiting concerning features indicative of EMPD. Histopathological examination of the excised lesion confirmed the diagnosis. Immunohistochemistry was positive for CAM5.2 and HER2 and negative for S-100, HMB45, CKHMW, SOX10 and P63 The patient remains free of recurrence at 32 months of follow-up. This case highlights the diagnostic challenges associated with axillary EMPD, emphasizing the importance of careful evaluation and consideration of rare malignancies, particularly in patients with a complex oncological background. The co-occurrence of EMPD with multiple malignancies raises questions about potential underlying genetic predispositions and shared etiological factors, warranting further investigation into the pathogenesis of EMPD and its association with other cancers. Understanding these mechanisms may facilitate improved management strategies for patients with similar clinical profiles.

Keywords: Paget's disease, empd, tp53, breast cancer, multiple malignancy

Introduction

Paget’s disease of the breast occurs when cancer cells invade the nipple‘s epidermis and occasionally the areola as well. In 90% of instances, breast cancer coexists with nipple changes. There is also a much rarer, extramammary form of Paget‘s disease. It commonly affects areas rich in apocrine glands, such as the perianal, vulvar or scrotal skin. [1]

Paget‘s disease of the breast is a rare condition, with extramammary Paget‘s disease (EMPD) comprising only 6.5% of all Paget‘s cancers [2]. Its rarity, coupled with the complexity of its diagnosis and management, makes it a particularly challenging issue in clinical practice. EMPD was initially identified in 1889 by Crocker, who noted lesions on the penis and scrotum that had a similar histologic appearance [3]. Most cases described in the literature involve Caucasian female patients (male-to-female ratios of 1:2–1:7), who are between the ages of 50 and 80 [2, 4]. Approximately 45 cases of axillary EMPD have been described so far, with patients from Japan making up the bulk of these instances [5]. This case report aims to present a rare case of extramammary Paget‘s disease in the axillary region of a 43-year-old woman with a confirmed presence of a TP53 mutation and a history of other malignancies. This case underscores the complexity of oncological management in patients with multiple malignancies and the possible associations of extramammary Paget‘s disease with other tumours.

Case report

A 43-year-old female with a history of primary malignancies of the breast at separate instances, with several years between diagnoses, underwent radical mastectomy with delayed reconstruction for both cases. Firstly, in 2007, a radical mastectomy was performed on the left breast, followed by six cycles of chemotherapy containing: 5-fluorouracil, epirubicin, cyclophosphamid, trastuzumab and pertuzumab (FEC HP). Pathological examination revealed invasive apocrine carcinoma and ductal carcinoma in situ (DCIS) of the left breast, with negative estrogen receptor (ER) and progesterone receptor (PR) status, and HER2 amplification (3+). The tumour was multifocal and classified as T1N0M0. In 2015, the patient presented with carcinoma ductale in situ of the right breast, which, as mentioned before, was also treated surgically. Additionally, she underwent total thyroidectomy for papillary thyroid carcinoma, followed by radioiodine therapy in 2015. Also, given the presence of a confirmed germline mutation of the TP53 gene, the patient opted for prophylactic bilateral oophorectomy with salpingectomy in 2017. Finally, in 2021, she presented to the breast clinic

with a skin lesion in the right axilla measuring 2 × 1.7 cm, which was erythematous with irregular surface, crusting, scaling, and areas of ulceration. Its onset occurred approximately two years prior, initially manifesting as a skin tag-like spot which was the size of a pinhead, free of pain or pruritus and not raising suspicion. However, the subsequent enlargement, change in structure, and onset of itching prompted the patient to seek dermatologic evaluation. Dermatoscopic findings raised suspicion of extramammary Paget‘s disease, leading to referral to an oncology centre for further evaluation. Upon presentation to the clinic, the patient reported that no specific treatment had been applied to the lesion before evaluation. However, she had tried over-the-counter topical creams with minimal improvement in symptoms. There were no palpable axillary nodes on either side. The breast examination revealed nothing unusual. The family history of the patient included breast cancer in her mother, ovarian cancer in her maternal aunt, and breast cancer in her grandmother. Additionally, her underage son was diagnosed with extrahepatic cholangiocarcinoma, which was surgically removed. Genetic testing confirmed the presence of a TP53 mutation, similar to his mother‘s case. The skin lesion was surgically removed in its entirety along with a margin, resulting in a specimen measuring 3.7 × 2.2 × 1.4 cm. Subsequently, the excised tissue underwent histopathological examination, which confirmed the presence of extramammary Paget‘s disease, characterized by the presence of Paget cells with large and prominent nucleoli and pale cytoplasm (Fig. 1, 2). Immunohistochemistry showed that Paget cells were positive for CAM5.2, HER2 and negative for S-100, HMB45, CKHMW, SOX10 and P63 (Fig. 3–7). The patient was closely monitored by the breast clinic and underwent regular imaging studies, as well as a biopsy of suspicious spots. These included a lichenoid inflammatory infiltrate-like skin patch on the right breast and scar tissue from the previous right breast surgery. The histopathological results revealed benign lesions in both cases. The patient is currently at 32 months of follow-up and has shown no signs of recurrence.

Discussion

Extramammary Paget‘s disease is an uncommon condition, accounting for just 6.5% of all recognized Paget‘s malignancies [2]. When considering axillary lesions, the rarity becomes even more pronounced, as they are observed in just 0.9% of patients with EMPD [6, 7]. This underscores the exceptional uncommonness of the described case, making it a poorly understood clinical situation with limited available information in the literature. The scarcity of literature on axillary Paget‘s disease presents significant diagnostic challenges, as it may often be mistaken for other benign or malignant skin conditions, such as eczema, superficial

fungal infections, contact or seborrheic dermatitis, malignant melanoma, Bowen's disease and Langerhans cell histiocytosis. Other features of the disease, including long asymptomatic phase and slow progression of the disease over time may also be linked to diagnostic delay and possibly worse prognosis [8, 9]. The lack of established guidelines or consensus on management strategies due to the rarity of the condition further complicates treatment decisions. The majority of EMPD cases involve female Caucasian patients who are between the ages of 50 and 80 [1]. The study patient‘s case, at 43 years old, falls outside the typical age range described for EMPD. The diagnosis described above naturally raises questions about potential association with other (past, present or future) malignancies. Firstly, it is worth mentioning that in extramammary Paget‘s disease (EMPD) there is generally accepted agreement on the classification into two main subgroups: primary and secondary. Primary EMPD originates in the epidermis or skin appendages and typically presents as a solitary lesion in areas rich in apocrine glands such as genitalia, perianal region, and axilla. Secondary EMPD occurs as a result of underlying malignancies, most commonly adenocarcinomas of the gastrointestinal or genitourinary tracts. The Paget cells in secondary EMPD are thought to represent intraepithelial spread from the primary tumour site [9]. When considering the association with underlying internal malignancy, it is important to note that 7% to 40% of cases describing extramammary Paget‘s disease are connected with it, perianal EMPD being the most common subtype [1, 9, 10]. The underlying cancers are typically found close to the cutaneous lesion, often within dermal adnexal glands or nearby organs [1]. It has been found that in 35 % of studied cases regarding axillary EMPD, there were underlying malignancies. Breast and apocrine gland adenocarcinomas may be linked to EMPD under the armpit [11]. Literature reports various associations with different types of malignant tumours, which could be synchronous or metachronous [12]. In this particular case, the extensive oncological history appears quite remarkable, especially considering the patient‘s relatively young age. The occurrence of two distinct and likely temporally independent breast tumours, as well as papillary thyroid carcinoma years before the manifestation of EMPD is rather unusual. Currently, the association between thyroid cancer and extramammary Paget‘s disease remains poorly understood. A literature review uncovered a documented case of a 49-year-old woman with a history of thyroid follicular carcinoma, who was diagnosed with vulvar EMPD. The authors emphasize that this case appears to be the first reported instance of EMPD in association with thyroid carcinoma [12]. Notably, there may be connections between these cancers that need to be looked into more in further research. Moreover, the presence of a TP53 mutation in the patient adds another layer of complexity to her oncological profile,

because of the genetic predisposition to multiple malignancies. On the other hand, the presence of the mentioned mutation necessitates continuous oncological monitoring. Given the potential for delayed diagnosis of underlying malignancies in extramammary Paget‘s disease, this ongoing observation seems to be beneficial. Disregarding the patient‘s medical history, the initial diagnostics would likely focus on breast cancer and metastasis to the axillary lymph nodes. However, in this case, the patient had undergone bilateral mastectomy and axillary lymph node dissection years before the onset of extramammary Paget‘s disease in the axilla. It is important to note that even radical mastectomy does not eliminate the possibility of breast cancer recurrence. Tumour dormancy theory suggests that patients with breast cancer may have latent micrometastases that are triggered by stressful events, like major reconstructive surgery and can cause metastasis and recurrence [13–15]. Furthermore, on radiological imaging, recurring tumours may be hidden by breast implants or scar tissue [16].

In this instance, after the surgical treatment of axillary EMPD, the patient was monitored at the breast clinic, which included imaging studies and biopsies of any suspicious lesions. A histopathological investigation eventually proved benign disease despite signs suggesting a possible recurrence.

This underscores the intriguing nature of the patient‘s clinical presentation and raises questions about potential underlying genetic predispositions or shared etiological factors that may contribute to the development of EMPD as well as other malignancies over time. Further investigation into the underlying mechanisms driving the co-occurrence of EMPD and other malignancies may provide valuable insights into the pathogenesis of EMPD and inform future management strategies for patients with similar clinical profiles. It is worth mentioning that there have been a few documented occurrences of familial EMPD in the literature. However, up until now, no specific genes have been linked to this [17].

Conclusion

This case depicts a rare instance of extramammary Paget‘s disease affecting the axillary region of a 43-year-old woman with a complex oncological history, including multiple primary malignancies and a TP53 mutation. EMPD, especially in the axilla, poses significant diagnostic challenges due to its rarity and resemblance to other skin conditions and requires careful attention due to its possible connection with other malignancies. The patient‘s oncological background, comprising two breast tumours, papillary thyroid carcinoma, and a TP53 mutation, highlights the complexity of her presentation and raises questions about potential

genetic predispositions for EMPD. More investigation into the processes causing EMPD and other cancers to co-occur may shed light on the pathophysiology of the illness and guide future management.

Article information

Ethics statement: *This case report is based on the medical history of a patient who provided her informed consent for the use of her case details. The patient was informed about the purpose of the case report and provided additional information relevant to the described case. As this study involved the retrospective analysis of anonymized patient data and did not include any experimental interventions, formal approval from an Ethics Committee was not required. Written informed consent was obtained from the patient for the publication of this case report and any accompanying images. Confidentiality of the patient's identity has been strictly maintained.*

Author contributions: *Conception and Design: Julia Zawistowska, Dr. n. med. Leszek Kozłowski; Data Collection: Angelina Lęgas, Bartek Przybysz, Jakub Kawalec; Analysis and Interpretation of Data: Katarzyna Pochodowicz, Karolina Rogowska, Joanna Smalira; Drafting of Manuscript: Weronika Rogala, Weronika Rutkowska-Kawalec; Critical Revision of Manuscript for Important Intellectual Content: Julia Zawistowska, dr n. med. Leszek Kozłowski.*

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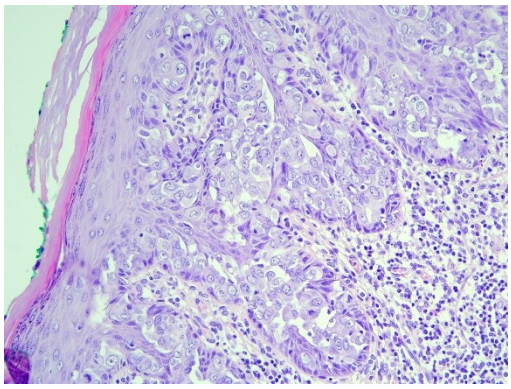

Figure 1. Histopathologic appearance of extramammary Paget disease. Haematoxylin and eosin (H&E)

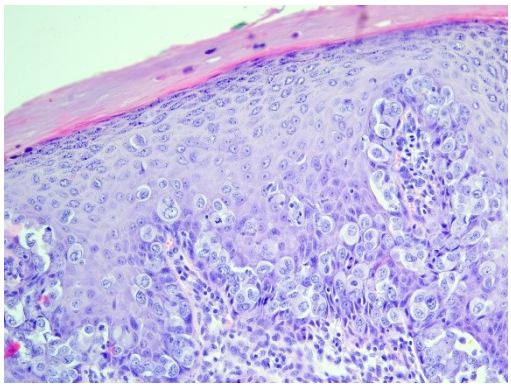

Figure 2. Histopathologic appearance of extramammary Paget disease. Haematoxylin and eosin (H&E)

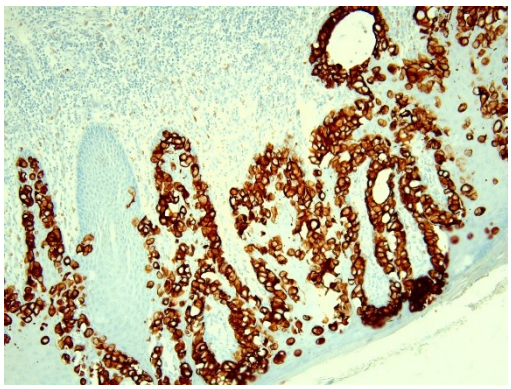

Figure 3. Positive CAM5.2 immunostaining

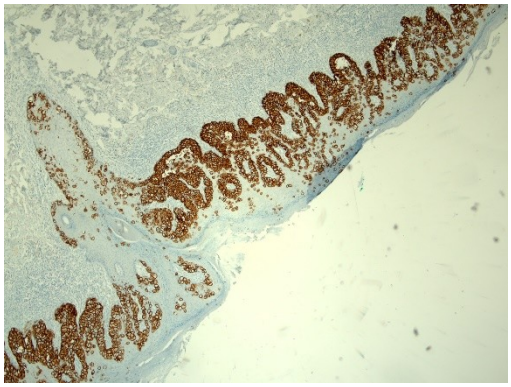

Figure 4. Positive HER2 immunostaining

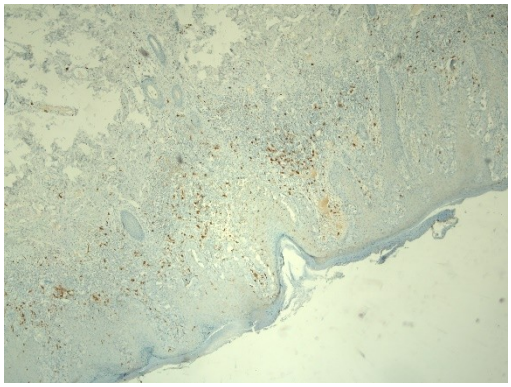

Figure 5. Negative S100 immunostaining

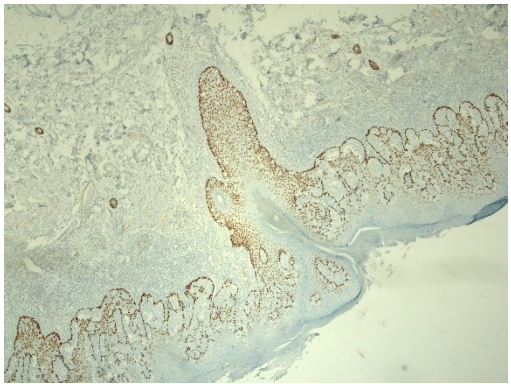

Figure 6. Negative P63 immunostaining

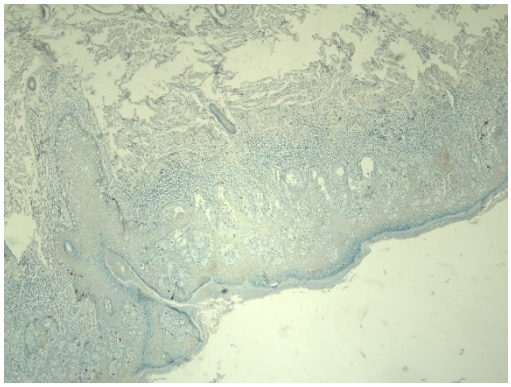

Figure 7. Negative HMB45 immunostaining