JSM Breast Cancer and Research

Case Report

Rolquin C, et al., 2023

Diagnosis of Mammary Paget's Disease by Cytology Sampling. Case Report and Brief Review of the Literature

Christina Rolquin[1], Madilyn Thomas[1], Meha Munir[1], Victoria DeTrolio[1], Jonathan Nguyen[1], Viviana Crespo[1], Hadel Go[2], Alan Bencosme[3], Jessica Jahoda[1,4], and Mohamed Aziz MD[4]*

[1]Department of Pathology, American University of the Caribbean School of Medicine, 1 University Drive at Jordan Dr, Cupecoy, Sint Maarten

[2]Department of Pathology, Rowan University Medica School, New Jersey, USA

[3]Florida Atlantic University, Wilkes Honors College, Florida, USA

[4]Research Writing & Publication (RWP) LLC, Division of Research, New York, USA

Abstract

Mammary Paget's disease (MPD) of the breast is a rare form of breast cancer. It accounts for a very small percentage of breast cancers in women, and much less in men It rarely occurs as an isolated entity and is usually associated with carcinoma in situ or invasive adenocarcinoma in most cases. In situ histology is seen in one third of the cases. Paget's disease is rarely diagnosed in people under the age of 45. Paget's disease affects people of all ethnic and racial groups. However, people of Asian descent are less likely to be affected. Surgical treatment of Paget's disease (radical or conservative) is controversial. There is no established standardized treatment, and treatment decisions are based on other associated conditions. There is currently no evidence that either surgical approach (conservative surgery or mastectomy) improves survival. Prognosis depends on the presence of a palpable mass and the invasiveness of the cancer. We present a case of a 37-year-old woman who presented with recurrent mixed ductal lobular carcinoma associated with Paget's disease. Paget's disease diagnosis was completely established based on cytology material sampling only. The patient was treated with bilateral mastectomy with no nipple sparing. The patient was followed for four years with no evidence of metastasis or recurrence.

Introduction

Mammary Paget's disease (MPD) of the breast is an uncommon malignant breast tumor representing 1-3% of all breast cancer diagnoses, with most cases being unilateral and a limited number of reports of bilateral disease. It affects a wide age range of 20 - 90 years, with a peak incidence between sixth and seventh decade (mean: 64 years) [1]. Paget's disease was first described by Sir James Paget in 1847 when he shared the malignant transformation of ten women with ulceration on an eczematous background of the nipple. The typical clinical presentation includes a unilateral vesicular, erythematous, or eczematous rash that may involve both the nipple and areola of the breast accompanied by an abundant, clear, or slightly yellowish exudate [2]. Patients often report experiencing initial signs of itching and burning sensations prior to the presentation of physical skin findings [2]. Skin changes that appear benign but do not respond to topical therapies require further workup to rule out malignancy. Paget's disease is associated with underlying cancers such as ductal carcinoma in situ (DCIS) and infiltrating ductal carcinoma (IDC) in more than 90% of cases [1]. A recent study reported that in cases of Paget's disease without underlying DCIS and IDC, skin changes are characterized by eczematous crusts, while the presence of bloody discharge was predominant in patients with recurrence or progression to malignancy [3]. Additionally, the presence of palpable mass was associated with advanced disease with a lower survival rate [3].

Methods of identifying MPD and guiding surgical management include ultrasound, mammography, and magnetic resonance imaging. However, biopsy and microscopic examination is required for a definitive diagnosis. Biopsy typically reveals large cells with clear cytoplasm and eccentric, hyperchromatic nuclei with prominent nucleoli throughout the epidermis [4]. The treatment, as well as the prognosis in the case of Paget's disease, is closely related to the existence of a palpable tumor formation and the presence of mammographic signs of breast malignancy [2]. Mastectomy with or without axillary lymph node dissection has been standard therapy for many years [5]. Recent reports have shown that breast-conserving strategies, nipple excision or central lumpectomy with a lymph node biopsy, combined with radiation therapy is a suitable alternative for patients with limited disease and is equivalent to mastectomy in regards to disease-free survival [5,6]. The 5-year survival rate of patients with Paget's disease of the breast is greater than 80% in the general population; however, the survival rate is statistically decreased among the older and African American populations. The significant indicators of prognosis

Submitted: 29 August 2023 | **Accepted:** 22 September 2023 | **Published:** 26 September 2023

***Corresponding author:** Mohamed Aziz*, Division of Research, Writing & Publication (RWP) LLC, 2475 Lefferts Place Bellmore NY 11710

Copyright: © 2022 Rolquin C, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Citation: Rolquin C, Thomas M, Munir M, DeTrolio V, Nguyen J, et al. (2023) Diagnosis of Mammary Paget's Disease by Cytology Sampling. Case Report and Brief Review of the Literature. JSM Breast Cancer Res 4: 6.

were age at diagnosis, tumor size, and lymph node status [1]. We present a case of recurrent breast carcinoma associated with Paget's disease diagnosed by cytology material, including cellblock preparation. We also discuss the epidemiology, clinical presentation, histology, therapeutic, and prognostic aspects of mammary Paget's disease.

Case Presentation

A 37-year-old woman presented with an erythematous ulcerating lesion involving the left nipple and areola. The patient reported that the changes began at the nipple and areola area, then spontaneously continued to progress with extension into the skin of the breast. She had a history of moderately differentiated estrogen positive HER-2 negative breast carcinoma with mixed ductal and lobular features three years prior to current presentation. The breast carcinoma was a stage II, 2.8 cm with negative sentinel lymph node (SLN) and negative for metastasis. The patient underwent lumpectomy with adequate margins followed by radiation and hormonal therapy.

Physical examination at presentation showed a slightly elevated erythematous eczematous lesion involving the left nipple and areola with extension into the adjacent skin. Nipple scrape preparation was performed by using a scalpel to scrape the nipple and adjacent skin; it was smeared on 3 glass slides and stained with Papanicolaou and Diff Quick stains. Additional smear scrapings were performed and washed in 75% alcohol and processed for cellblock preparation. Adequate diagnostic material was obtained. Cytology material showed dispersed groups and single atypical cells, in background of anucleate squamous cells and acellular debris. Isolated and loosely clustered malignant glandular cells with enlarged nuclei, prominent nucleoli and large pale cytoplasm were identified (Figure *1* A-B). Cytologic differential diagnoses included nipple adenoma, malignant melanoma, and squamous cell carcinoma. Although the cytomorphology was consistent with Paget's disease, immunohistochemistry (IHC) studies were utilized for definitive diagnosis using the cellblock preparation. The tumor cells were positive for CK7 and cytokeratin CAM 5.2, PAS stain and HER-2. The tumor cells were negative for CK20 and CK 5/6, HMB45, Melan-A, S100, ER and PR. The cytomorphology and IHC profile was diagnostic of mammary Paget's disease. As mammary Paget's disease is associated with in situ or invasive breast carcinoma in most cases, further investigations were initiated including imaging studies. Mammographic studies showed an area of ill-defined thickening in the upper inner quadrant of left breast, but was inconclusive for definitive evaluation. MRI studies confirmed the presence of an irregular 1.2 cm mass in the left breast. An MRI guided left breast mass biopsy was performed. Histomorphology was consistent with recurrent breast carcinoma with mixed ductal and lobular features in association with mammary Paget's disease. The biopsy showed the characteristic Paget's cells scattered through the epidermis (Figure *2* A-B), that was positive for CK7, cytokeratin CAM 5.2 and negative for Melan-A (Figure *3* A-B-C). The invasive tumor showed poorly differentiated malignant glandular cells with mixed ductal and lobular features (Figure *4* A-B). The recurrent tumor differed from the primary tumor showing poorly differentiated carcinoma with negative ER, PR, and positive HER-2.

Molecular testing showed BRCA1 and BRCA2 positive gene mutation and the patient decided to undergo bilateral non-nipple sparing mastectomy in addition to treatment of Paget's disease. A sentinel lymph node was negative. The tumor was completely excised with adequate margins with immediate bilateral breast reconstruction. The patient underwent post operative Herceptin

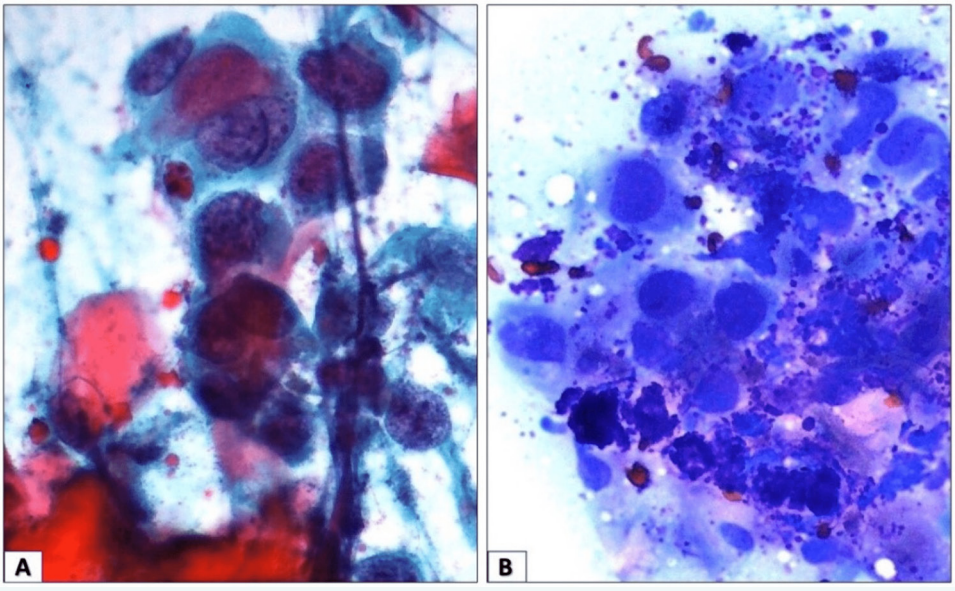

Figure 1 Cytologic examination of the left breast Paget's disease
1A: Dispersed groups and single malignant glandular cells, in background of anucleate squamous cells and acellular debris (Papanicolaou stain).
1B: Isolated and loosely clustered malignant glandular cells with enlarged nuclei and large cytoplasm (Diff Quick stain)

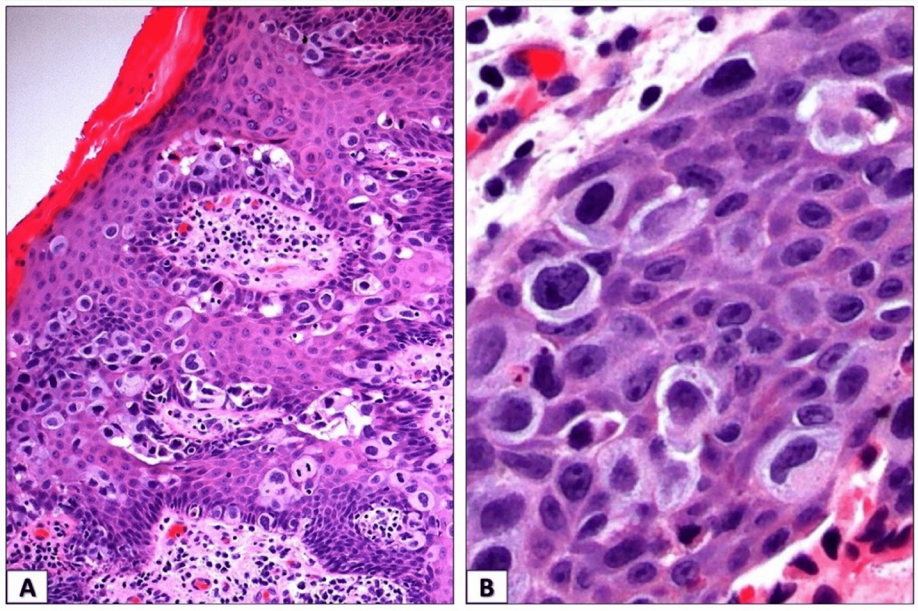

Figure 2 Left breast Paget's disease as seen in mastectomy specimen
2A: Intermediate power view showing the characteristic Paget cells scattered through the epidermis (H&E stain X40)
2B: Higher power view showing malignant Paget cells with large irregular nuclei and large cytoplasm (H&E stain X60)

treatment and was followed for four years with no evidence of recurrence or metastasis.

Discussion

Mammary Paget's disease (MPD) is a malignant disease that usually presents as a red, sore nipple with erosions and sometimes bleeding. Most often, ductal adenocarcinoma of the breast spreads to the skin of the nipple and areola. MPD is a rare breast cancer that can present like dermatological pathologies such as eczema, malignant melanoma, psoriasis, or contact dermatitis [5]. Often an insidious onset, this progressive disease can allow for physical exam findings of retraction of the nipple, ulceration, or bleeding, unilaterally and rarely bilateral. Some studies suggest the cause can be linked to a HER2 gene mutation that allows for the malignant cells to migrate [5].

MPD is an uncommon disease usually presenting in postmenopausal women. A detailed history should be taken, focusing mainly on the lesion's presentation, duration, associated symptoms such as bleeding, nipple discharge, pain, burning, itching, scaling, etc. Early symptoms and signs can be pruritus and excoriations from itching, and recurrence of small vesicles [7]. Lesions are usually present centrally but may be peripheral while the size usually ranges from 3 mm to 15 cm in diameter [8]. They may be associated with serosanguinous discharge. Additionally, a palpable associated mass is present in 50 percent of cases [7]. Both benign and malignant processes can produce visible symptoms in the skin of the nipple. Later progression of the disease is characterized by destruction and ulceration of the nipple alveolar complex [8].

Microscopically, Paget's disease is characterized by the presence of large, pale, atypical cells with abundant cytoplasm and hyperchromic nuclei showing prominent nucleoli. Paget's cells are seen scattered within the epidermal layer of the nipple and areola and extend to the surrounding skin with advancement of the disease. [9]. There is characteristically intraepidermal presence of malignant cells through the lactiferous channels within the epidermis mainly concentrated at the basal layer. Some studies suggest it is possible that lactiferous ductal cells spread giving rise to Paget cells, which migrate retrograde into the overlying epidermis [5]. Paget cells are voluminous, with abundant cytoplasm, large nuclei, distinct nucleoli, occasional mitotic features, and varying degrees of pigmentation that can easily be mistaken for malignant melanoma. Tumor cells express CK7 and CK8/18, but not CK5/6, p63, and HMB45. IHC studies can distinguish MPD from Paget-like intraepithelial melanoma, intraepithelial squamous cell carcinoma, and Paget-like reticular histiocytosis. [10]. The characteristic tumor cells of Paget's disease patients are the same in young patients, middle-aged and elderly patients, therefore, there is no age-related difference in terms of pathological diagnosis and differential diagnosis [11].

The recent integration of cytology and radiology has enabled a non-invasive or minimally invasive, safe, accurate, and inexpensive diagnosis of suspicious masses that was previously possible only by surgical biopsy techniques. Therefore, cytologists are increasingly called upon to diagnose disease using image-guided samples taken from different organs. Cytology facilitates timely diagnosis and treatment and is an integral part of multidisciplinary approaches to various tumor diagnoses. On-site cytological assessment allows for additional needle passes if necessary, increasing diagnostic yield. This process climaxes in multidisciplinary meetings, such as tumor boards, where clinical, radiological, cytological, and laboratory assessment results are

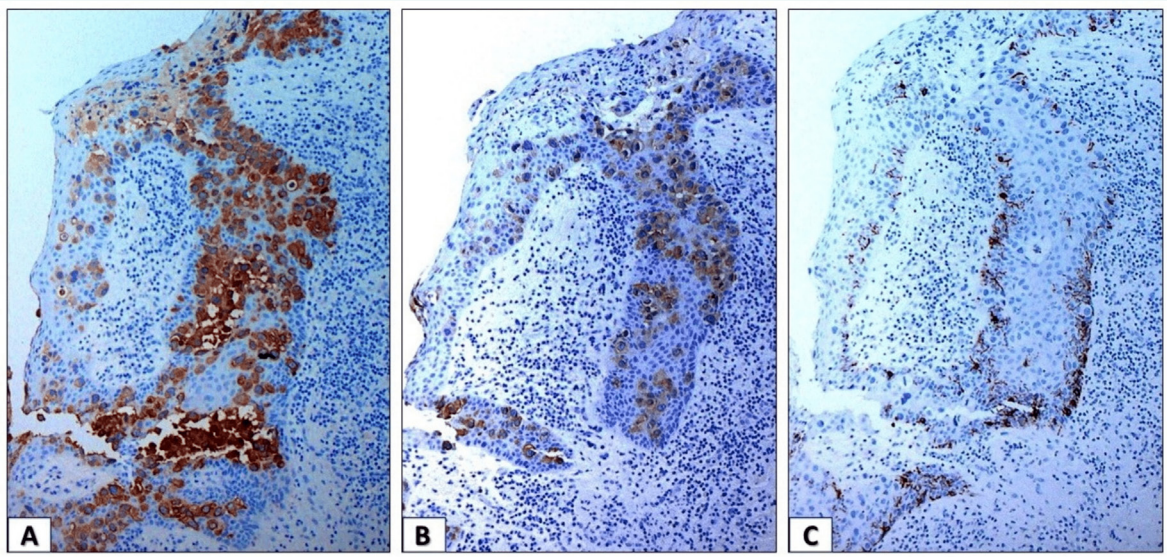

Figure 3 Immunohistochemistry studies of left breast Paget's disease
3A: Paget cells positive for CK-7
3B: Paget cells positive for cytokeratin CAM 5.2
3C: Paget cells negative for Melan-A (only basal melanocytes are stained)

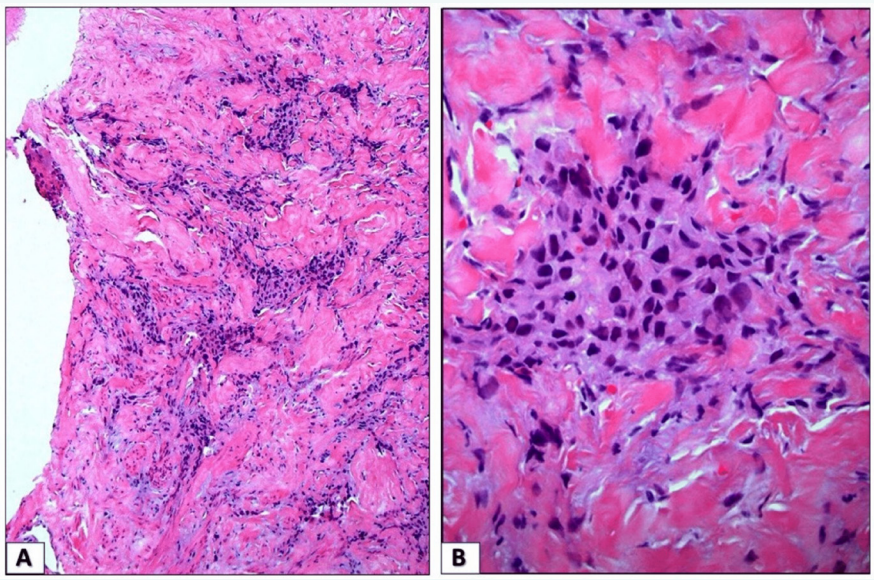

Figure 4 Left breast invasive carcinoma
4A: Infiltrating malignant sheets and clusters of malignant glandular cells (H&E stain X20)
4B: Malignant poorly differentiated glandular cells (H&E stain X40)

discussed and treatment is planned [12, 13]. The case presented here proved that scrapings alone of the lesioned skin to obtain representative diagnostic cytology material was successful to establish definitive diagnosis of MPD including confirmatory IHC studies.

It is uncommon to find a case of mammary Paget's disease that does not have an underlying malignancy, and is purely localized to the nipple. When patients present with the usual symptoms of Paget's disease, and there is no improvement after a 2-week course of topical corticosteroids, a diagnostic imaging work-up and biopsy should be performed to confirm the diagnosis of Paget's disease and to search for possible underlying breast carcinoma [14]. Oftentimes there is an undiagnosed invasive breast cancer or in situ ductal carcinoma. Adjuvant therapy is often recommended in the treatment of patients with Paget's disease to prevent cancer from recurring; treatments

include radiation, chemotherapy, hormone therapy (tamoxifen), or immunotherapy [15]. Prognostic factors are determined by first distinguishing Paget's disease from other differential diagnoses. The pathological markers S-100 and Melan-A are used to distinguish Paget's from malignant melanoma, as they share some clinically overlapping features.

There is currently uncertainty about the etiology of MPD, the relationship between its subtypes, and its lineage with the underlying invasive cancer. G. Zhang et al. reported that whole-exome sequencing showed that chromatin remodeling genes have the same mutations in both MPD and extramammary Paget's disease (EMPG). Their study showed that MPD and EMPD share some genomic features, such as early changes in genes that change how chromatin is organized. Furthermore, they reported that MPD and its underlying ductal carcinoma represent independent carcinogenic events. They said their results provide an approach to developing diagnostic tools and therapeutic interventions for MPD [16].

The literature is rich with reports of interesting and uncommon cases of MPD. V. G. Martin et al. reported an interesting case of MPD in an adolescent female with an accessory nipple [15]. J. S. Broecker et al. reported an unusual case of a 63-year-old Caucasian female who developed a right breast skin lesion discrete from the nipple that was subsequently diagnosed as Paget's Disease of the breast. They reported that the patient underwent a segmental mastectomy preserving the nipple and final pathology demonstrated residual Paget's disease of the skin and did not reveal any additional underlying breast carcinoma [17]. L. Miller et al. reported a case of erosive adenomatosis of the nipple in which an initial diagnosis of Paget's disease was considered. They reported that histologic findings of erosive adenomatosis of the nipple eliminated the diagnosis of invasive carcinoma or Paget's disease, which can have clinical features like those of erosive adenomatosis of the nipple [18]. A. Latif et al. reported an unusual case of bilateral invasive histiocytoid lobular breast carcinoma with massive bilateral Paget's disease. They reported the association of massive bilateral Paget's disease with the histiocytoid variant of lobular carcinoma [19]. Although rare, melanoma of the nipple may mimic Paget's disease. C.H. Lin et al. reported a case of an 86-year-old woman who presented with persistent, erythematous, ulcerative changes of her left nipple for several months. They expressed the importance of histologic examination with IHC studies to establish the correct diagnosis [20].

Conclusions

Mammary Paget's disease can mimic many benign and malignant lesions and requires histological examination and immunohistochemistry studies to establish the correct diagnosis. For persistent nipple erythema and eczema that does not respond to topical treatment, Paget's disease should be considered. Ultrasound, mammography, and magnetic resonance imaging can help detect potential cancers so they can be treated surgically. A simple non-invasive procedure in the form of skin scraping using a scalpel, can be adequate to conclude the definitive diagnosis of mammary Paget's disease with immunohistochemistry studies on cellblock cytology preparation. Our case supports cytology material efficacy in fully diagnosing a cancer case using confirmatory IHC studies without requiring tissue biopsy. Cytology facilitates timely diagnosis and management and is integral to a multimodal approach to various tumor diagnoses. Our case also shows that cytology smear preparation sampling alone, with cellblock preparation, can provide a definitive diagnosis of mammary Paget's disease.

Human subjects

Ethical review and approval were not required for the study on human participants in accordance with the local legislation and institutional requirements. The paper has been sufficiently anonymized to keep patient's confidentiality

Conflicts of interest

In compliance with the ICMJE uniform disclosure form, all authors declare the following:

Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work.

Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work.

Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

Patient's consent

Patients was lost to follow up, all attempts to reach the patient or family member are unsuccessful. Therefore, the paper has been sufficiently anonymized to keep patient's confidentiality.

Author contributions

Study concept and design: Jessica Jahoda and Christina Rolquin, Writing the manuscript: Christina Rolquin, Meha Munir, Madilyn Thomas, and Victoria DeTrolio, Data collection: Jonathan Nguyen, Viviana Crespo, Hadel Go and Alan Bencosme. Reviewing and editing the manuscript: Jessica Jahoda and Mohamed Aziz, Critical review, and final approval: Mohamed Azi

Acknowledgement

Special thanks to Brian Duong, Rehana Hassan, and Jenna Zudell, MD candidates at the American University of the Caribbean, for their assistance in reviewing the final manuscript.

References

1. Sisti A, Huayllani MT, Restrepo DJ, et al.: Paget disease of the breast: a national retrospective analysis of the US population. Breast Disease. 2021, 39:119-26. 10.23750/abm.v91i2.8399

2. Şandru F, Dumitraşcu MC, Petca R, Miulescu RG, Popa A: Paget disease of the breast- Therapeutic approach depending on the form of presentation. Journal of Surgical Sciences. 2020, 7: 175-180.

3. Kim YJ, Lee KH, Lee WJ, Won CH, Chang SE, Choi JH, Lee

MW: Clinicopathological characteristics of mammary Paget's disease: A single-center 25-year experience in Korea. The Breast. Journal. 2020, 26:806-8. 10.1111/tbj.13651

4. Gupta A, Pujani M, Goyal S: Paget s Breast Disease-A Diagnostic Dilemma-A Case Report with Review. Biomedical Journal of Scientific & Technical Research. 2021, 35:27765-8. 10.26717/BJSTR.2021.35.005717

5. Dubar S, Boukrid M, Bouquet de Joliniere J, et al.: Paget's Breast Disease: A Case Report and Review of the Literature. Front Surg. 2017, 4:51-2017. 10.3389/fsurg.2017.0005- 10.3389/fsurg.2017.00051

6. Barth D: Bilateral Paget's Disease of the Breast—Case Report of Long-Time Misdiagnosed Tumors with Underlying Ductal Carcinomas and Review of the. Literature. Case reports in dermatological medicine. 20143, 2014:10.1155/2014/152836

7. Yasir M, Khan M, Lotfollahzadeh S: Mammary Paget Disease. [Updated 2022 Dec 3]. In. StatPearls [Internet, Treasure Island (FL): StatPearls Publishing; 2023.

8. Sakorafas GH, Blanchard K, Sarr MG, Farley DR: Paget's disease of the breast. Cancer treatment reviews. 2001, 1:9-18. 10.1053/ctrv.2000.0203

9. Alvero R: Paget's disease of the breast. Ferri's Clinical Advisor. 2017, 2017:915. 10.3389/fsurg.2017.00051

10. Liu J, Zhao Z, Zhou J, Zhang J: An unusual presentation of Paget's disease of the nipple in a young woman: a case report. International journal of clinical and experimental medicine. 2015, 8:4694.

11. Lv CY, Cheng XK, Guo ZY, Liu L, Cai J, Lei T, Tang Y. Mammary Paget's Disease of Young Females: Case Reports and Comparison With Middle-Aged and Elderly Patients: Clinical Pathology. 2023, 16:2632010. 10.1177/2632010X231162700

12. Noeske M, Truong PM, Coelho M, Balbi A, Aziz M: Diagnosis of Respiratory Papillomatosis in Cytology Preparations: Case Report and Brief Review of the Literature. Vol. 42019,

13. Bellizzi AM, Stelow EB: Pancreatic cytopathology: a practical approach and review. Archives of pathology & laboratory medicine. 2009, 1:388-404.

14. Markarian S, Holmes DR: Mammary paget's disease: an update. Cancers. 2022, 13:10-3390. 10.3390/cancers14102422

15. Martin VG, Pellettiere EV, Gress D, Miller AW: Paget's disease in an adolescent arising in a supernumerary nipple. Journal of cutaneous pathology. 1994, 21:283-6. 10.1111/j.1600-0560.1994.tb00275.x

16. Zhang G, Zhou S, Zhong W, et al.: Whole-exome sequencing reveals frequent mutations in chromatin remodeling genes in mammary and extramammary Paget's diseases. Journal of Investigative Dermatology. 20191, 139:789-95. 10.1016/j.jid.2018.08.030

17. Broecker JS, Sewell CW, Shehata BM, Memis B, Adsay NV, Styblo TM: An atypical presentation of Paget's disease of the breast without nipple involvement: case report and review of the literature. Pathology-Research and Practice. 20171, 213:1454-6. 10.1016/j.prp.2017.06.002

18. Miller L, Tyler W, Maroon M, Miller 3rd OF: Erosive adenomatosis of the nipple: a benign imitator of malignant breast disease. Cutis. 19971, 59:91-2.

19. Latif A, Ruhangaza D, Stastka P, et al.: Bilateral Invasive Histiocytoid Lobular Breast Carcinoma with Massive Paget's Disease. Case Report of Rare Tumor with a Controversial Histogenesis and Review of the Literature. JSM Breast Cancer Res. 3:7.

20. Lin CH, Lee HS, Yu JC: Melanoma of the nipple mimicking Paget's disease. Dermatology Online Journal. 2007, 13:10.5070/D38wx447j8