

**VILNIUS UNIVERSITY  
MEDICAL FACULTY**

The Final thesis

**Paget's Disease of the Breast. Diagnosis, Treatment and Prognosis**

**Kamlah Alakmeh, VI-year, 1<sup>st</sup> group**

Department/Clinic: Clinic of Obstetrics and Gynaecology

Supervisor

Dr. Rasa Vansevičiūtė-Petkevičienė

The Head of Department/Clinic,

Prof. Dr. Diana Ramašauskaitė

2024

[Kamlah.Alakmeh@mf.stud.vu.lt](mailto:Kamlah.Alakmeh@mf.stud.vu.lt)

## Table of content

<b>SUMMARY :</b> .....	<b>3</b>
<b>KEYWORDS</b> .....	<b>3</b>
<b>INTRODUCTION</b> .....	<b>3</b>
<b>LITERATURE SELECTION STRATEGY</b> .....	<b>4</b>
<b>INTRODUCTION</b> .....	<b>4</b>
<b>DESCRIPTION</b> .....	<b>6</b>
<b>EPIDEMIOLOGY</b> .....	<b>7</b>
<b>RISK FACTORS</b> .....	<b>8</b>
<b>CLINICAL PRESENTATION</b> .....	<b>8</b>
<b>DIFFERENTIAL DIAGNOSIS</b> .....	<b>9</b>
<b>ECZEMATOUS DERMATITIS OF THE NIPPLE</b> .....	<b>9</b>
<b>EROSIVE ADENOMATOSIS OF THE NIPPLE</b> .....	<b>10</b>
<b>PSORIASIS</b> .....	<b>10</b>
<b>BOWENS DISEASE</b> .....	<b>10</b>
<b>MAMMARY DUCT ECTASIA</b> .....	<b>11</b>
<b>CUTANEOUS MELANOMA</b> .....	<b>11</b>
<b>IMAGING METHODS</b> .....	<b>12</b>
<b>MAMMOGRAPHY</b> .....	<b>12</b>
<b>ULTRASOUND</b> .....	<b>12</b>
<b>BREAST MRI</b> .....	<b>13</b>
<b>BIOPSY</b> .....	<b>13</b>
<b>STAGING</b> .....	<b>14</b>
<b>HISTOPATHOLOGY</b> .....	<b>14</b>
<b>IMMUNOHISTOCHEMISTRY</b> .....	<b>15</b>
<b>TREATMENT AND PROGNOSIS</b> .....	<b>16</b>

**FOLLOW-UP AFTER TREATMENT ..... 18**

**CONCLUSION..... 19**

**REFERENCES..... 21**

Summary :

Mammary Paget's disease is a rare form of breast cancer that is commonly misdiagnosed, resulting in a prolonged diagnostic process, leading to poorer prognosis and higher mortality rates. This narrative literature review comprehensively reviews the epidemiology, risk factors, clinical presentations, differential diagnosis, diagnostic procedures, treatment modalities, and prognosis associated with Mammary Paget's disease. Mammary Paget's disease of the breast is primarily observed in the presence of ductal carcinoma in situ or invasive ductal carcinomas. Nevertheless, Paget's disease of the breast may occur without underlying carcinoma. Due to the wide variability of clinical presentation and the similarity to many common skin diseases, diagnosing Mammary Paget's disease remains challenging for clinicians, and the condition can be overlooked or misdiagnosed easily. This thesis discusses the newest clinical studies and data regarding diagnostic peculiarities, treatment, and prognosis of Mammary Paget's disease of the breast. Furthermore, this review summarizes recent research on the subject, including biopsy changes, pathogenesis, treatment, and prognosis. Prompt diagnosis and intervention are crucial in improving treatment outcomes. This review aims to create awareness of this rare disease, especially indicating the importance of early diagnosis to improve the prognosis of Patients diagnosed with this disease.

Keywords

Paget's disease of the breast, Mammary Paget's disease, Nipple eczema, Pruritic rash, Breast cancer, Dermal invasion

Introduction

Mammary Paget's disease of the breast is an infrequent form of breast tumor, which is primarily observed in the presence of ductal carcinoma in situ or invasive ductal carcinomas. Eczematous changes, erosions, and ulcerations of the nipple and areolar epidermis are clinically characterized (1). The clinical presentation of Paget's disease is similar to many common skin rashes, so the condition can be overlooked or misdiagnosed easily (2). As Paget's disease of the breast occurs only rarely and there are commonly only small sample studies, there are still ongoing debates regarding the prognosis and treatment of the disease. This literature review summarises the epidemiology, risk factors, clinical presentations, differential diagnosis, diagnostic procedures, biopsy changes, pathogenesis, and the treatment and prognosis of Paget's disease of the breast.

### Literature selection strategy

A selective literature search on PubMed using the search words "Paget's disease of the breast," "Mammary Paget's disease," "nipple eczema," "pruritic rash," "breast cancer," and "dermal invasion" was performed. The time frame was set from 2014 until 2024. Also, general Internet research using the same terms was performed.

### Introduction

Mammary Paget's disease clinically presents as inflammation of the skin in the nipple area and is classified as adenocarcinoma of the epidermis of the nipple and areolar region. The typical clinical presentation of Paget's disease of the breast includes eczematous ulcerative or vesicular lesions with clear yellowish exudate (2).

Paget's disease of the breast is difficult to diagnose in clinical practice. Especially in the initial stages without a palpable mass, it is commonly mistaken for eczematous or other dermatological diseases. It is frequently treated as such for a prolonged time before being diagnosed correctly (3).

These typical changes were already described in 1307 by John of Arderene and later in 1856 by Velpeau, but Sir James Paget was the first to describe the connection between scaling crusts of the nipple and breast cancer in 1874. This was based on observations of 15 women between the ages of 40 and 60 who first presented with skin changes on the nipple-areolar complex and later developed breast cancer (4).

With 0.5-5% of all breast carcinomas, Mammary Paget's disease of the breast is an uncommon form of breast cancer, mainly affecting the nipple-areola complex. Approximately half of the cases of Paget's disease present with changes in the nipple-areolar complex in combination with a palpable mass. Most of the patients present with an underlying ductal carcinoma in situ or invasive disease. Lymph node involvement is found in up to 60% of these cases. In the case of a palpable mass, the associated Paget's disease is mainly accompanied by ductal invasive carcinoma in situ. Commonly, the mass is located centrally, but in up to 41% of the cases, it may be in the breast periphery, with multifocal or multicentric locations.

Paget's disease of the breast can be challenging to diagnose as it resembles certain dermatologic diseases, but especially those patients who present with local recurrence after treatment are overlooked as the clinical findings are often attributed to post-radiotherapy changes. It is crucial to remember that new changes in the nipple-areolar region after breast conservation therapy should receive a prompt diagnostic biopsy (5). Mammary Paget's disease presents mainly by slowly progressing scaly or oozing erythema of the nipple and areola. More advanced lesions can be described as demarcated, eczematous plaques with pink or red color. The surface may sometimes appear erosive, scaly, and/or crusty (6).

The diagnosis of Paget's disease is mainly based on the clinical findings. Nevertheless, in suspected Paget's disease, imaging methods should be performed to detect a commonly present underlying carcinoma. Also, radiological findings are essential for the assessment of appropriate treatment options. Mammography and MRI investigations should, therefore, be performed. Mammography may depict a mass or calcification of invasive cancer or ductal invasive carcinoma. However, it is not a reliable procedure for detecting mammary Paget's disease as it is limited in its depiction of underlying ductal invasive carcinoma in women with Paget's disease. Usually, if Paget's disease is suspected and the mammography shows normal results, an ultrasound examination is performed. If the ultrasound is negative, an MRI should also be performed. It is susceptible to detecting breast cancer, especially in patients with normal mammographic and sonographic findings, and MRI investigations can help in the preoperative evaluation of the patients. They might facilitate appropriate further treatment decisions (7).

A biopsy confirms the diagnosis. The histopathological hallmark for establishing a diagnosis is the so-called Paget cells, malignant glandular epithelial cells.

Mammary Paget's disease presents mainly by slowly progressing scaly or oozing erythema of the nipple and areola. More advanced lesions may be described as well as demarcated,

eczematous plaques with pink or red color. The surface may sometimes appear erosive, scaly, and/or crusty.

The treatment of mammary Paget's disease is still under debate; for a long time, the standard treatment was mastectomy, either with or without axillary lymph node dissection; however, conservative breast surgery combined with radiation therapy is a feasible alternative in case of limited disease (6). In the past years, oncoplastic breast surgery has also emerged, in which plastic surgery techniques are added to the therapeutic arsenal for the treatment of breast cancer, which results in increasing numbers of breast-conserving surgeries. Nevertheless, mastectomy is still the most performed surgery for the treatment of mammary Paget's disease (8).

Depending on the pathology and immunohistochemistry results, appropriate adjuvant treatment should also be used. Generally, radiation therapy is used after the surgery depending on the presence and type of underlying cancer, as neoadjuvant or adjuvant chemotherapy, as well as targeted therapy included in the treatment (9).

It is essential to consider Paget's disease of the breast as a differential diagnosis in longstanding, therapy-resistant skin changes of the breast as a delay in treatment results in more advanced disease stages and a worse prognosis. Also, more research would be necessary for a deeper understanding of the disease and evaluation of treatment options.

## Description

Paget disease of the breast is an uncommon form of breast cancer; it accounts only for approximately 1-4% of all breast cancers (2).

Unilateral intraepidermal infiltration of the nipple or areola with malignant glandular epithelial cells is typical for Paget's disease. Classically, the disease starts insidious, over several months or even years. The main presenting feature simulates chronic eczematous dermatitis, so the main presenting features include pruritus, pain, and burning sensation, which can be accompanied by exudate, hemorrhage, and, in later stages, ulcerations and invaginations of the nipple. Nevertheless, many cases present without symptoms with a palpable mass lesion, which is present in 14-44% of cases (10).

Mammary Paget's disease of the breast can be divided into three groups, according to underlying pathology: Paget's disease with invasive ductal carcinoma (IDC), Paget's disease with ductal carcinoma in situ (DCIS), and Paget's disease of the nipple without concurrent breast cancer. This division is essential in terms of patient prognosis.

According to the data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER), Paget's disease with invasive ductal carcinoma has the worst prognosis out of the three subtypes. Also, the data suggest that breast cancer, in combination with Paget's disease, has a worse prognosis compared to isolated forms of breast cancer (11).

Currently, there are two theories regarding the pathogenesis of Paget's disease of the breast: the epidemiologic theory and the transformation theory. The Epidermotropic theory postulates that Paget cells arise from an underlying mammary adenocarcinoma by migration of neoplastic ductal epithelial cells through the lactiferous system to the epidermis of the nipple. It is further hypothesized that the spread of Paget cells of the nipple epidermis from the lactiferous duct system may be regulated by a motility factor that disposes its effect via the Human Epidermal Growth Factor Receptor (HER2). Similar molecular markers were discovered in Paget cells found in parenchymal breast tumors, like overexpression or amplification of the gene HER2. Around 85% of cases of Paget's disease of the breast are stained with anti-HER2 monoclonal antibodies (2,12,13).

On the other hand, the transformation states that mammary Paget's disease arises from epidermal keratinocytes, which are independent of an underlying breast malignancy and represent an epidermal carcinoma in situ. This theory was introduced by George Thin in 1881. He claimed that the secretions of the breast ducts continuously damage the epithelium, transforming these keratinocytes into cancer cells. A small percentage of Paget's disease of the breast occurs without underlying parenchymal cancer. Whenever the underlying malignancy is present, it is often located peripheral to the nipple, suggesting two independent neoplastic processes. This theory was also widely accepted. Furthermore, there have been demonstrations of "pre-Paget" cells with the appearance intermediate between keratinocytes and Paget cells, suggesting epidermal cells can pick ductal cell characteristics as they undergo malignant transformation. Nevertheless, this theory lost popularity because it was demonstrated that if enough sections are taken for a biopsy and studied, it can usually be shown that the large lactiferous ducts immediately beneath the nipple are affected as well (2).

## Epidemiology

Breast cancer is the fifth most common cancer-related cause of death and is currently the most diagnosed cancer worldwide. Therefore, it is a considerable health burden with increasing incidences. Breast cancer accounted 2020 for 6.9% of all cancer-related deaths worldwide. According to the National Institute of Cancer, the lifelong probability of being

diagnosed with breast cancer is currently 12.9%. Breast cancer can affect both women and men, but it is by far more common in women. Most cases of breast cancer are diagnosed in women aged 65-74 years (14)

Mammary Paget's disease is an out-of-ordinary form of breast cancer. It occurs in 1-4% of women with breast cancer and 1-2% of men affected by breast cancer (15). Paget's disease of the breast can affect patients of both genders and mainly affects people ranging from 26-88 years. Postmenopausal women in their sixth decade are mostly affected (2,16). Paget's disease of the breast is also more commonly found in Caucasian women compared to other ethnicities (2,10,11)

### Risk factors

There are no specific risk factors known for Paget's disease of the breast. However, as it occurs in more than 90% of patients with underlying breast cancer, mainly ductal carcinoma in situ or invasive ductal carcinoma, the risk factors for breast cancer apply to Paget's disease of the breast as well (2,10).

These risk factors include female sex, age older than 50 years, a past medical history that is positive for breast diseases like lobular carcinoma in situ or atypical hyperplasia, a positive family history of each of two breast or ovarian cancers, or both. Further risk factors include dense breast tissue as identified by the mammogram, exposure to radiation, especially to the chest, inherited gene mutations like BRACA1 and BRACA2 increases the risk of breast or ovarian cancer, hormone replacement like estrogen therapy after menopause, white race as these women tend to be disposed to develop breast cancer as well as drinking ample amounts of alcohol in addition to consumption of too much dietary fat. (2,10,11).

### Clinical presentation

Paget's disease of the breast develops usually slowly over months or even years. Mammary Paget disease most commonly presents as a unilateral rash, generally starting from the nipple and extending with a centrifugal growth pattern to the areola and, in more advanced stages, to the surrounding skin. The lesions are typically located centrally within 2 cm of the areola,



Even though a unilateral presentation is more common, it may also present bilaterally. The skin rashes can vary from 3 cm to 15 cm in diameter.

The presentation of mammary Paget's disease can differ massively; it may present as eczematoid, erythematous, thickened, moist, or crusted lesion with irregular borders. Furthermore, it can present with or without fine scaling, induration, infiltration, secretion, or bleeding. In later stages, ulcerations and nipple invagination can be observed. In some cases, the presentation resembles psoriasis with dry patches and scales; in others, it resembles inflammatory and eczematous conditions. Hyperpigmented lesions like superficial spreading Melanoma can be observed as well. In the beginning, the lesions are often asymptomatic; later on, pruritus, burning sensation, and pain can occur; in advanced stages, serous and/or bloody papillary discharge may be observed, as well as the destruction of the papillary areolar complex.

Typically, these patients present with a history of a longstanding eczematous pruritic lesion in which topical treatment was not successful previously. In some patients, breast lumps and or lymphadenopathies are present (10,12,17).

It is essential to take a detailed anamnesis of the patients, especially regarding the duration of the symptoms and what treatment was used. Also, a detailed dermatological history may be valuable, especially regarding earlier skin diseases. It would also be helpful to cover the personal risk profile for breast cancer, including family history, use of hormone replacement therapy, and social history. (2).

Dermoscopy can examine the lesions further, but no dermoscopic criteria exist for the classic form of Paget's disease. Also, the pigmented form of Paget's disease resembles melanomas in dermoscopy, making it difficult to differentiate the two disease entities. A biopsy and further immunohistochemical examinations are necessary for differentiation (7).

### Differential diagnosis

As the clinical presentation of Mammary Paget's disease varies largely, several differential diagnoses should be considered.

### Eczematous dermatitis of the nipple

Eczematous dermatitis of the nipple is a localized form of dermatitis that involves the nipple and areola. It is characterized by erythema as well as scaling. Patients may also complain

about itching and pain. It is more common in teenage girls, but it can affect every age and gender group. Typically, eczematous dermatitis of the nipple occurs bilateral, but it also can present unilaterally. Clinical features may include erythematous papules and plaques with blisters, oozing, crusting, or erosions. Due to the very similar presentation, Mammary Paget's disease is commonly mistaken for eczematous dermatitis of the nipple. In case of minimal or no response to conventional treatment of Eczematous dermatitis of the nipple, Paget's disease of the breast should be considered as a possible differential diagnosis (17)

### Erosive adenomatosis of the nipple

Erosive adenomatosis of the nipple is a benign neoplasm of the nipple. It usually presents unilaterally with erosion, serous discharge, nodularity, swelling, itching, and erythema of the nipple. Also, ulceration of the nipple is a joint presentation. A lump in the breast or lymphadenopathies is usually not present. Typically, it affects middle-aged women in their fourth and fifth decades of life; only rarely it affects men or children. Histopathological erosive adenomatosis of the nipple is characterized by the proliferation of lactiferous ducts and gland-like structures in the stroma with clear borders (19).

### Psoriasis

Psoriasis is a chronic inflammatory skin disease with a 1-3% incidence. Usually, psoriasis affects the scalp, knees, elbows, sacral region, and joints. The nipple-areolar region is rarely mentioned in the literature, but several cases of this isolated involvement exist. Psoriasis is clinically characterized by well-defined borders of erythematous plaques or bright pearlescent white squamous lesions on papules. Even though it is only rarely mentioned in the literature, psoriasis of the nipple-areolar complex should not be forgotten to rule out in case of ineffective treatment of eczematous lesions and as a possible differential diagnosis for Paget's disease (20)

### Bowens disease

Bowen's disease is an in-situ squamous cell carcinoma of the epidermis. The clinical presentation depends on the age of the lesion, site of origin, and degree of keratinization. In

places where keratinization is absent, these lesions are erythematous and velvety. In keratinized epithelium, the erythema is masked by scaling in lesions. Lesions occur usually solitary. These lesions are typically asymptomatic; pruritus may occur in more extensive lesions. Usually, Bowen's disease progresses slowly and demonstrates a well-demarcated, erythematous, and scaly patch or plaque. In the nipple, Bowen's disease can spread by lactiferous ducts and may present as raised pruritic, scaly plaque or as an eczematous lesion with crusting bleeding or ulceration (21).

### Mammary duct ectasia

Mammary duct ectasia is a non-proliferative inflammatory disorder of the large breast duct; it affects the nipple-areolar complex. Focal dilatation of the lactiferous duct system results in periductal inflammation and fibrosis. Patients present with intermittent nipple discharge of varying colors, pain, and tenderness of the nipple and areola. Other symptoms may include an inverted nipple or palpable breast lump (22).

### Cutaneous Melanoma

Cutaneous Melanoma is a malignant tumor formed from pigmented cells called melanocytes. It is one of the most aggressive cancers seen in humans. Melanomas are usually found accidentally during routine skin examinations, as most are present without symptoms. Occasionally, persistent scratching, bleeding, or crusting of a pigmented lesion alerts patients to the presence of a related nodule (23). It is vital to mention that Mammary Paget's disease with melanocytic proliferation can mimic malignant Melanoma in situ. Pigmented mammary Paget's disease is a rare clinicopathological entity of Paget's disease of the breast. It may resemble a cutaneous melanoma in situ clinically as well as histologically. Special immunohistochemical staining is necessary to distinguish Paget's disease with melanocytic proliferation from Melanoma in situ. It is suggested that dual labeling of Melan-A and Phosphorylated Histone H3 (PHH3) could help distinguish both diseases and reach the correct diagnosis (24).

Several other differential diagnoses can be considered for mammary Paget's disease. Due to similarities in clinical presentation, further investigations are needed to exclude the

mentioned differential diagnosis and confirm the diagnosis of Paget's disease of the breast. Generally, a histological examination with immunohistochemical examinations helps differentiate between the diseases and make the correct diagnosis.

### Imaging methods

Diagnosing mammary Paget's disease is usually entrenched by clinical findings and confirmed by biopsy with immunohistochemical examinations. Nevertheless, imaging should be performed to detect underlying carcinoma and to assess appropriate treatment options (7).

### Mammography

Even though mammography is essential for the diagnosis and management of Paget's disease of the breast, it has some limitations. Several studies showed that mammography might show negative results in the presence of Paget's disease, even in the presence of an underlying carcinoma. The numbers differ widely. While Günhan-Bilgen et al. reported that 15% of the cases had a negative mammography, Ikeda et al. mentioned that the findings were negative in up to 50% of cases with typical clinical features of Paget's disease. Nevertheless, mammography is the initial radiological investigation for detecting underlying invasive carcinoma or ductal carcinoma in situ.

In case of negative mammographic results, an ultrasound is performed.

Common mammographic findings include skin thickening in the nipple-areolar region, asymmetric density, nipple retraction, or a discrete mass. Pleomorphic calcifications can also be observed, which may or may not be allied with skin thickening or architectural distortion. Mammography is also performed to follow up on patients after conservative breast surgery to rule out recurrence (25,4).

### Ultrasound

Ultrasound examination may be used to confirm mammography findings but also in case of negative mammography.

Typical findings of ultrasound examination in mammary Paget's disease of the breast include heterogenous hypoechoic areas in the breast parenchyma, the presence of a discrete mass, or

dilated ducts. However, ultrasound examination may show only non-specific changes, like skin thickening in the nipple-areolar region (25).

A small-scale study from Ogata et al. suggested using Doppler sonography to detect Paget's disease of the breast. They postulate that increased blood flow signaling is present in nipples affected by Paget's disease. In contrast, no apparent blood flow signals are detected in unaffected nipples and nipples affected by dermatitis. Therefore, they postulate that it would be helpful to establish Doppler Doppler sonography of the breast as a first-line investigation in case of suspected Paget's disease of the breast (26).

In cases with a high suspicion of Paget's disease or histologically confirmed Paget's disease with negative mammography and negative ultrasound, breast MRI is performed (25).

### Breast MRI

Breast MRI is a decidedly sensitive modality. It can be used in cases where both mammography and ultrasound findings are negative for Paget's disease of the breast. MRI findings may include thickening and enhancing the nipple-areolar complex, an underlying mass, enhancing ductal carcinoma in situ, or combining these findings. Variable enhancement patterns of the normal nipple-areolar complex range from absent to mild or intense. Nevertheless, by comparing the two sides, asymmetric enhancement can be noticed in the nipple-areolar region, with the affected region showing irregular, discoid, or irregular enhancement in the case of mammary Paget's disease (27)

Even if there is no clinical suspicion of Paget's disease, nipple involvement can be seen. If no mass is visible in the subareolar region, the whole breast must be examined, as further treatment is based on imaging findings.

MRI examination of the breast plays an essential role in the diagnosis of Paget's disease not only in case of negative ultrasound and mammography but also in preoperative imaging for confirmation of underlying ductal carcinoma in situ, even if there is no palpable mass present (26,27)

### Biopsy

A biopsy is necessary to confirm the diagnosis of Mammary Paget's disease. Different types of biopsies can yield the material needed. A diagnosis can be made from a wedge biopsy, shave biopsy, or punch biopsy.

The wedge biopsy, where a small wedge of the tissue is cut out, is commonly used in suspected Paget's disease cases. The epidermis is adequately represented, and a part of the lactiferous duct is likely included.

A shave biopsy is less likely to contain enough Paget cells, especially if the surface lesion is ulcerated, as only the surface is scraped.

For a Punch biopsy, a small cutting device is inserted into the center of the lesion, and a small tissue plug is removed. The Punch Biopsy will include the underlying stroma and likely include a part of a duct, but there is commonly only a little epidermis to examine (7). Also, scrape cytology is a possibility for histological diagnosis as it is a cheap and easy-to-perform examination in the office. However, an experienced cytologist would be needed to interpret the examination, and varying numbers of false negatives are mentioned in the literature (2).

Nori et al. suggest the use of a semiautomated core needle biopsy with a 14 gauge needle for the histological diagnosis of Paget's disease. In their retrospective study, all cases of Paget's disease of the breast could be identified by histological examination (28). Currently, the golden standard for diagnosing breast invasive carcinoma is ultrasound-guided core needle biopsy. With a core needle biopsy, it is possible to get more information regarding cancer, including whether it is invading or not, the tumor type as well as the grade of the tumor, and also information on whether estrogen and progesterone receptors are present. Furthermore, with samples from a core needle biopsy, the pathologist can also assess the HER2 status and the KI-67 proliferative index. All this information is crucial in guiding the treatment (29)

## Staging

Mammary Paget's disease can be classified according to the TNM classification for breast cancer. If an underlying carcinoma is present, it is staged according to the stage of the underlying tumor. The stage of the underlying tumor does not change due to the presence of mammary Paget's disease. If there is no underlying tumor in Paget's disease, the Tis staging for carcinoma in situ applies, and it is staged as Tis (Paget's disease) (2, 30).

## Histopathology

The main histological hallmark for diagnosing Paget disease of the breast is the presence of Paget cells. Paget cells are malignant, intraepithelial Adenocarcinomatous cells with pale mucin-positive cytoplasm and pleomorphic nuclei with prominent nucleoli. Commonly, the

underlying dermis shows reactive changes, including a lymphocytic inflammatory infiltrate and edema. Paget cells occur in various sizes, but they are widely prominent. They may present singly or in small groups within the epidermis of the nipple (2).

There are numerous histological variants of Paget cells. They may occur as a columnar adenocarcinoma-like cell type. Paget cells may also present as a spindle cell type, which is angular, elongated, and arranged in nested patterns. They also grow in compact masses.

Another presentation of Paget cells could be as an anaplastic cell type; they may present as pleomorphic tumor cells in a full-thickness, distorted epidermis. Also, apoptotic tumor cells, mitotic figures, and multinucleated tumor cells are standard; this pattern resembles Bowen's disease. Further investigations are necessary to differentiate between Paget's disease of the breast and Bowen's disease. Positive immunoperoxidase staining for the presence of specific markers, including CEA, epithelial membrane antigen, and c-erb B-2, may favor the diagnosis of Paget's disease.

Another possible presentation would be the acantholytic cell type. This may overlap with the anaplastic variant. Prominent acantholysis may lead to misdiagnosing mammary Paget's disease as an acantholytic disorder.

Also, pigmented cell types are possible. These are present in rare cases of pigmented mammary Paget's disease, which can be confused with Melanoma (31). Some histological features may help to differentiate Paget cells from Melanoma. Paget cells are above the basal keratinocytes with some ductal formation, while melanoma cells are located in all epidermis layers, including the basal layer with intraepidermal pagetoid spread. Paget cells are also not seen freely in the dermis, but melanoma cells may exist. Still, further immunohistochemical stainings are necessary to correctly differentiate pigmented Paget's disease of the breast from Melanoma (32).

### Immunohistochemistry

Immunohistochemical stains may help establish the diagnosis of Mammary Paget's disease. Most Paget cells express low molecular weight cytokeratin, cytokeratin – 7. Also, there are cytokeratin-7 negative forms of Paget's disease of the breast; they occur only rarely, but still, this is a diagnostic problem. As most of the cases of Mammary Paget's disease have an expression of CK7, GATA3, and HER2, these markers can be used for immunohistochemical confirmation of Mammary Paget's disease even in CK-7 negative cases (33)

In the past years, it has been noted that GATA-binding protein 3 is found in breast carcinomas and Paget's disease of the breast. In most cases, there is also an overexpression of human epidermal growth factor receptor 2 (HER2) and an underexpression of estrogen and progesterone receptors (33, 34). Due to these observations, several studies researched what molecular subtypes are primarily present in mammary Paget's disease in comparison to other forms of breast cancer. The molecular subtypes were generally grouped into luminal subtype A, which included a positive estrogen or progesterone receptor, HER-2 negative, and a Ki-67 index of  $< 15\%$ . The luminal subtype B consists of a positive estrogen or progesterone receptor, HER-2 receptor, which can be either positive or negative, and a Ki-67 index of  $> 15\%$ ; the HER-2 subtype has negative estrogen and progesterone receptors and is HER-2 positive, and the basal-like subtype is triple-negative for estrogen, progesterone, and HER2. These studies showed the predominant subtype of Mammary Paget's disease is the HER-2 subtype. In comparison, the luminal subtype is the most common subtype present in breast cancer. There are also reports of triple-negative cases of mammary Paget's disease, but they occur only rarely. HER-2 subtypes account for 60-80% of molecular subtypes in Paget's disease of the breast (35).

As most Paget cells are positive for the expression of HER2, it has been proposed that HER2 plays a significant role in the pathogenesis of mammary Paget's disease. These findings impact treatment and prognosis as HER2 is a transmembrane tyrosine kinase receptor that regulates cell growth. Its overexpression is related to high-grade aggressive tumors and a poor prognosis (36).

### Treatment and Prognosis

The treatment of Paget's disease of the breast is still under debate. For a long time, radical mastectomy with or without axillary lymph node dissection was the treatment of choice. Nevertheless, sentinel lymph node biopsy is standard for all patients who undergo surgery (7). Because of the multifocality of mammary Paget's disease, a simple central resection commonly results in incomplete removal of the lesions, which made radical mastectomy the treatment of choice(2).

Over the past decades, breast-conserving surgery followed by radiotherapy gained popularity and seems to be an acceptable alternative to mastectomy, especially in patients with early-stage in situ or invasive Paget disease. The treatment modality depends on the stage of the



disease and whether there is an underlying tumor present or not, resulting in some contraindications for breast conservative surgery, including extended microcalcification or multicentric cancer as well as poor cosmetic results, which are indications for a radical mastectomy (38).

Especially over the past two decades, there have been significant improvements in operating techniques for mastectomy, breast-conserving surgery, and axillary preservation. Breast-conserving surgery can now be performed on larger tumors, and the use of neoadjuvant chemotherapy increased the rates of breast-conserving surgeries. The field of oncoplastic breast surgery emerged in this context. This means that plastic surgery techniques are added to the treatment of breast cancer, which increases the number of breast-conserving surgeries compared to mastectomies even further. Also, if mastectomy is necessary, immediate reconstruction with implants is performed to reduce the duration of surgeries and decrease the complication rates. Due to oncoplastic breast surgeries, patients who receive breast-conserving operations can be treated with local skin flaps using the plug-flap technique or other techniques that prepare the areolar region for further tattooing to get better aesthetic results.

Chemotherapy is used in various regimens for the treatment of underlying disease depending on the present tumor and its immunohistochemical properties. Hormone therapy can also be used in this context. Due to the overexpression of HER2 in patients with Paget's disease, targeted therapies may be used in this context, but this has not been thoroughly evaluated in the literature, which leaves the primary treatment of Paget's disease of breast surgery and adjuvant radiation therapy (8, 39).

Currently, radiotherapy without previous surgery is only recommended in patients who refuse surgical treatment or are unfit for surgery, as there is limited research with inconsistent results regarding its effectiveness (40,41).

Alternative therapies, including photodynamic therapy, are under investigation. Photodynamic therapy was used as a less invasive therapy for the treatment of mammary Paget's disease. Therefore, a topical or intravenous photosensitizer drug is administered, and a specific wavelength of light is used to activate the drug. This drug binds with oxygen to destroy the affected cells. However, limited data are available, and more research is necessary to determine its safety and effectiveness (42).

The prognosis of Mammary Paget's disease depends mainly on the initial presentation of the disease as well as the presence of underlying invasive ductal carcinoma and the presence or absence of axillary lymph node metastasis (2). Furthermore, the prognosis depends on the

histological types of Paget's disease, so the traditional American Joint Committee on Cancer (AJCC) stage system cannot adequately predict the prognosis of the patients entrenched in this classification. Recent studies suggest the use of several biomarkers and prognostic factors to predict the prognosis more effectively in breast cancer. These factors include c-erbB-2, Ki-67, cyclin D1, Bcl-2, age, marital status, tumor size, and lymph node status. These factors are used for breast cancer, but there is due to the low incidence of mammary Paget's disease, no prognostic prediction model for Paget's disease based on these factors. Different studies show different results; Zhao et al. (43) found that mammary Paget's disease with invasive ductal carcinoma had the worst prognosis compared to other histological breast cancers, while the study of Hu et al. presented data showed that patients with Paget's disease of the breast with underlying invasive ductal carcinoma had the best prognosis (44). The International Agency for Research on Cancer announced in 2012 that the 5-year recurrence-free survival was 75–90% for those with DCIS and 63–75% for those with invasive carcinoma. In the presence of ductal carcinoma in situ, the 5-year overall survival rates are 94–98%, and in cases with invasive carcinoma, 73–93%, depending on the presentation stage and tumor biology. However, the relationship between tumor genomics and survival has yet to be characterized for mammary Paget's disease. The prognosis is worse if lymphadenopathy is present (2,4). The study of Chen et al. 1. Demonstrates that the presence of Paget's disease in both ductal carcinoma in situ well as invasive ductal carcinoma is related to poor tumor characteristics, including high histological grades, advanced AJCC stages, low HR-positive ratios, and high HER2-positive ratios, and that concurrent mammary Paget's disease is associated with a worse prognosis compared to ductal carcinoma in situ alone or invasive ductal carcinoma alone. They also postulate that the HR status, as well as the HER2 status, do not affect the prognosis of breast cancer with mammary Paget's disease (10). As this is very controversial, more large-scale studies are needed for further evaluation.

#### Follow-up after treatment

The follow-up after treatment for Paget's disease includes regular physical examinations for the first five years every three to six months and after five years annually. Routine imaging of the chest wall or reconstructed breast after mastectomy is not indicated. Diagnostic mammography after six months following completion of radiation therapy for patients with breast conservation therapy is primarily indicated—afterward, annual check-ups for the first five years, followed by yearly screening mammography. Postmenopausal patients who are

receiving tamoxifen should have close monitoring for symptoms of uterine cancer or endometrial hyperplasia. Bone health should be checked, especially in post-menopausal women, as well as premenopausal women who receive tamoxifen or GnRH or women who receive aromatase inhibitors. This includes baseline bone mineral density examination, testing of 25-oH vitamin D, and checking for inquiries about new osteoporotic fractures after low-impact trauma. Lymphedema management with a compression sleeve is prescribed and changes at least every six months if needed. Physical therapy for improving range of motion is initiated, and the patients are advised to encourage age-appropriate cancer and general health guidelines (45).

## Conclusion

In conclusion, Paget's disease of the breast is a rare form of breast cancer. It mainly affects the nipple-areolar complex. It is commonly associated with underlying ductal carcinoma in situ or invasive disease. Early detection and initial therapy are critical to improve the efficacy of the treatment for mammary Paget's disease. Another important aspect is patient education. Patients should pay close attention to changes in their breasts, including redness, itching, or flaking, and seek early medical advice if they notice these changes. Also, healthcare providers should further educate patients about the importance of regular breast self-examination and mammography check-ups to diagnose Paget's disease and other forms of breast cancer in the early stages. Commonly, the diagnosis is delayed as clinicians do not consider Paget's disease of the breast as a differential diagnosis, and prolonged treatment for dermatological diseases results in advanced cancer stages.

The treatment of Paget's disease of the breast depends on several factors, including the stage of the disease, the presence of underlying breast cancer, and the individual patient's health status. The surgical approach is the primary treatment modality for mammary Paget's disease. For a long time, mastectomy was the treatment of choice. Currently, the number of breast-conserving surgeries is increasing. In some cases, removing the lymph nodes may also be necessary to evaluate the possible spread of the cancer. Following surgery, radiotherapy is commonly used to target any remaining cancerous cells, reducing the chance of recurrence. Chemotherapy may be used in case of underlying breast cancer or if the disease has spread beyond the breast. Hormone therapy, such as tamoxifen, may also be prescribed depending on immunohistochemical results. Alternative treatment options that promise to be more

effective and less invasive treatments for Paget's disease of the breast were examined in small-scale studies. However, more extensive clinical trials are needed to assess the safety as well as efficacy of these novel approaches. In conclusion, early detection, prompt treatment, and ongoing research are crucial in effectively managing Paget's disease of the breast. Raising awareness of the disease, advocating for regular screening, and supporting research efforts can improve the outcomes and enhance the quality of life for patients affected by this rare form of breast cancer.

## References

1. Chirappapha P, Adireklarpwong L, Sornmayura P, Lertsithichai P, Rattadilok C. Large mammary Paget disease without underlying breast carcinoma. *Plast Reconstr Surg Glob Open* [Internet]. 2022;10(10):e4606. Available from: <http://dx.doi.org/10.1097/gox.0000000000004606>
2. Yasir M, Khan M, Lotfollahzadeh S. *Mammary Paget Disease*. StatPearls Publishing; 2023.
3. Ooi PS, Draman N, Yusoff SSM, Zain WZW, Ganasagaran D, Chua HH. Mammary Paget's disease of the nipple: Relatively common but still unknown to many. *Korean J Fam Med* [Internet]. 2019 [cited 2024 Mar 18];40(4):269–72. Available from: <http://dx.doi.org/10.4082/kjfm.17.0143>
4. Markarian S, Holmes DR. Mammary Paget's disease: An update. *Cancers (Basel)* [Internet]. 2022 [cited 2024 Mar 18];14(10):2422. Available from: <http://dx.doi.org/10.3390/cancers14102422>
5. Sandoval-Leon AC, Drews-Elger K, Gomez-Fernandez CR, Yepes MM, Lippman ME. Paget's disease of the nipple. *Breast Cancer Res Treat* [Internet]. 2013;141(1):1–12. Available from: <http://dx.doi.org/10.1007/s10549-013-2661-4>
6. Dubar S, Boukrid M, Bouquet de Joliniere J, Guillou L, Vo QD, Major A, et al. Paget's breast disease: A case report and review of the literature. *Front Surg* [Internet]. 2017 [cited 2024 Mar 18];4. Available from: <http://dx.doi.org/10.3389/fsurg.2017.00051>
7. Gaurav A, Gupta V, Koul R, Dabas S, Sareen R, Geeta K, et al. Practical consensus recommendatons for Paget's disease in breast cancer. *South Asian J Cancer* [Internet]. 2018;07(02):083–6. Available from: [http://dx.doi.org/10.4103/sajc.sajc\\_107\\_18](http://dx.doi.org/10.4103/sajc.sajc_107_18)
8. Pelorca RJF, de Oliveira-Junior I, da Costa Vieira RA. Oncoplastic surgery for Paget's disease of the breast. *Front Oncol* [Internet]. 2023;13. Available from: <http://dx.doi.org/10.3389/fonc.2023.1151932>
9. Fetisova EY, Zikiryakhodhaev AD, Volchenko NN. Diagnosis and treatment for Paget's breast cancer: state of the art. *Vopr Onkol*. 2015;61(6):908–12.
10. Chen S, Chen H, Yi Y, Jiang X, Lei H, Luo X, et al. Comparative study of breast cancer with or without concomitant Paget disease: An analysis of the SEER database. *Cancer Med* [Internet]. 2019;8(8):4043–54. Available from: <http://dx.doi.org/10.1002/cam4.2242>
11. Aguayo-Carreras P, Bonilla-García L, Pérez-López I, Cuenca-Barrales C, Tercedor-Sánchez J. Paget's Disease of the Breast: A dangerous imitator of eczema. *Sultan Qaboos Univ Med J* [Internet]. 2018;17(4):487. Available from: <http://dx.doi.org/10.18295/squmj.2017.17.04.021>
12. Lopes Filho LL, Lopes IMRS, Lopes LRS, Enokihara MMSS, Michalany AO, Matsunaga N. Mammary and extramammary Paget's disease. *An Bras Dermatol* [Internet]. 2015;90(2):225–31. Available from: <http://dx.doi.org/10.1590/abd1806-4841.20153189>

13. Pan B, Zhao D, Liu Y, Li N, Song C, Li N, et al. Establishment and characterization of breast cancer organoids from a patient with mammary Paget's disease. *Cancer Cell Int* [Internet]. 2020 [cited 2024 Apr 28];20(1). Available from: <http://dx.doi.org/10.1186/s12935-020-01459-6>
14. Arzanova E, Mayrovitz HN. The epidemiology of breast cancer. In: *Breast Cancer*. Exon Publications; 2022. p. 1–20.
15. Dalberg K, Hellborg H, Wärnberg F. Paget's disease of the nipple in a population based cohort. *Breast Cancer Res Treat* [Internet]. 2008 [cited 2024 Mar 19];111(2):313–9. Available from: <https://pubmed.ncbi.nlm.nih.gov/17952590/>
16. Nipple eczema [Internet]. *Dermnetnz.org*. [cited 2024 Mar 18]. Available from: <https://dermnetnz.org/topics/nipple-eczema>
17. Sun Y-S, Zhao Z, Yang Z-N, Xu F, Lu H-J, Zhu Z-Y, et al. Risk factors and preventions of breast cancer. *Int J Biol Sci* [Internet]. 2017 [cited 2024 Mar 18];13(11):1387–97. Available from: <http://dx.doi.org/10.7150/ijbs.21635>
18. Crignis GSN de, Abreu L de, Buçard AM, Barcaui CB. Polarized dermoscopy of mammary Paget disease. *An Bras Dermatol* [Internet]. 2013 [cited 2024 Mar 21];88(2):290–2. Available from: <http://dx.doi.org/10.1590/s0365-05962013000200023>
19. Ying S, Fang H, Qiao J. Erosive adenomatosis of the nipple: A clinical diagnostic challenge. *Clin Cosmet Investig Dermatol* [Internet]. 2020 [cited 2024 Mar 18];13:587–90. Available from: <http://dx.doi.org/10.2147/ccid.s260534>
20. Saritas AG, Dalci K, Topal U, Beydola S, Acikalın A, Rencuuzogullari A. Psoriasis, a rare disease of the nipple-areola A case report. *Ann Ital Chir* [Internet]. 2019 [cited 2024 Mar 18];8. Available from: <https://pubmed.ncbi.nlm.nih.gov/32390650/>
21. Palaniappan V, Karthikeyan K. Bowen's disease. *Indian Dermatol Online J* [Internet]. 2022 [cited 2024 Mar 18];13(2):177. Available from: [http://dx.doi.org/10.4103/idoj.idoj\\_257\\_21](http://dx.doi.org/10.4103/idoj.idoj_257_21)
22. Hamwi MW, Winters R. Mammary Duct Ectasia. 2024 [cited 2024 Mar 18]; Available from: <https://pubmed.ncbi.nlm.nih.gov/32491597/>
23. Naik PP. Cutaneous malignant melanoma: A review of early diagnosis and management. *World J Oncol* [Internet]. 2021 [cited 2024 Mar 18];12(1):7–19. Available from: <http://dx.doi.org/10.14740/wjon1349>
24. Sripathi S, Ayachit A, Kadavigere R, Kumar S, Eleti A, Sraj A. Spectrum of imaging findings in Paget's disease of the breast—A pictorial review. *Insights Imaging* [Internet]. 2015 [cited 2024 Mar 18];6(4):419–29. Available from: <http://dx.doi.org/10.1007/s13244-015-0415-z>
25. Da Costa D, Taddese A, Cure ML, Gerson D, Poppiti R Jr, Esserman LE. Common and unusual diseases of the nipple-areolar complex. *Radiographics* [Internet]. 2007 [cited 2024 Mar 18];27(suppl\_1):S65–77. Available from: <https://pubmed.ncbi.nlm.nih.gov/18180236/>

26. Ogata H, Mitsuzuka Y, Honma N, Yoshida M, Sumazaki M, Saito F, et al. Sonographic visualization of nipple blood flow can help differentiate Paget disease from benign eczematous nipple lesions. *PLoS One* [Internet]. 2018;13(5):e0197156. Available from: <http://dx.doi.org/10.1371/journal.pone.0197156>
27. Rao S, Wang A, Liu W, Yin H, Li J, Tsang LS-L, et al. Mammary Paget disease with melanocytic proliferation mimicking malignant melanoma in situ: A case report. *Front Med (Lausanne)* [Internet]. 2022;9. Available from: <http://dx.doi.org/10.3389/fmed.2022.839954>
28. Nori J, Bicchierai G, Amato F, De Benedetto D, Boeri C, Vanzi E, et al. A new technique for the histological diagnosis of Paget's disease of the breast using a semiautomated core needle biopsy with a 14-gauge needle. *Radiol Med* [Internet]. 2021;126(7):936–45. Available from: <http://dx.doi.org/10.1007/s11547-021-01358-4>
29. Hoda SA, Rosen PP, Brogi E, Koerner FC. *Rosen's breast pathology*. 5th ed. Philadelphia, PA, USA: Lippincott Williams and Wilkins; 2020.
30. Brierley JD, Gospodarowicz MK, Wittekind C, editors. *TNM classification of malignant tumours*. 8th ed. Nashville, TN, USA: John Wiley & Sons; 2016.
31. Lee JH, Kim TH, Kim S-C, Kim YC, Roh MR. Pigmented mammary Paget disease misdiagnosed as malignant melanoma. *Ann Dermatol* [Internet]. 2014 [cited 2024 Mar 21];26(6):747. Available from: <http://dx.doi.org/10.5021/ad.2014.26.6.747>
32. Journal Article. Mammary Paget disease workup [Internet]. *Medscape.com*. 2023 [cited 2024 Mar 19]. Available from: <https://emedicine.medscape.com/article/1101235-workup>
33. Cai Y, Cheng Z, Nangong J, Zheng X, Yuan Z. Using immunohistochemistry to classify the molecular subtypes of Paget's disease of the breast. *Cancer Med* [Internet]. 2023;12(13):14104–11. Available from: <http://dx.doi.org/10.1002/cam4.6066>
34. Arain SA, Arafah M, Said Raddaoui EM, Tulba A, Alkhawaja FH, Al Shedoukhy A. Immunohistochemistry of mammary Paget's disease. Cytokeratin 7, GATA3, and HER2 are sensitive markers: Cytokeratin 7, GATA3, and HER2 are sensitive markers. *Saudi Med J* [Internet]. 2020;41(3):232–7. Available from: <http://dx.doi.org/10.15537/smj.2020.3.24949>
35. Wachter DL, Wachter PW, Fasching PA, Beckmann MW, Hack CC, Riener M-O, et al. Characterization of molecular subtypes of Paget disease of the breast using immunohistochemistry and in situ hybridization. *Arch Pathol Lab Med* [Internet]. 2019;143(2):206–11. Available from: <http://dx.doi.org/10.5858/arpa.2017-0578-OA>
36. Drews-Elger K, Sandoval-Leon AC, Ergonul AB, Jegg AM, Gomez-Fernandez C, Miller PC, et al. Paget's disease of the nipple in a Her2-positive breast cancer xenograft model. *Breast Cancer Res Treat* [Internet]. 2020;179(3):577–84. Available from: <http://dx.doi.org/10.1007/s10549-019-05490-8>
37. Scardina L, Di Leone A, Magno S, Franco A, Biondi E, Sanchez AM, et al. Paget's disease of the breast: Our 20 years' experience. *Front Oncol* [Internet]. 2022;12. Available from: <http://dx.doi.org/10.3389/fonc.2022.995442>

38. Gilmore R, Prasath V, Habibi M. Paget disease of the breast in pregnancy and lactation. In: *Advances in Experimental Medicine and Biology*. Cham: Springer International Publishing; 2020. p. 133–6.
39. Piras A, Boldrini L, Venuti V, Sanfratello A, La Vecchia M, Gennari R, et al. Mammary Paget's disease and radiotherapy: a systematic literature review. *Eur Rev Med Pharmacol Sci* [Internet]. 2021;25(4):1821–7. Available from: [http://dx.doi.org/10.26355/eurrev\\_202102\\_25076](http://dx.doi.org/10.26355/eurrev_202102_25076)
40. Journal Article. Mammary Paget disease [Internet]. Medscape.com. 2023 [cited 2024 Mar 19]. Available from: <https://emedicine.medscape.com/article/1101235-overview>
41. Paget's Disease of the Breast - symptoms, causes, treatment [Internet]. National Organization for Rare Disorders. 2015 [cited 2024 Mar 19]. Available from: <https://rarediseases.org/rare-diseases/pagets-disease-of-the-breast/>
42. Zhao Y, Sun H-F, Chen M-T, Gao S-P, Li L-D, Jiang H-L, et al. Clinicopathological characteristics and survival outcomes in Paget disease: a SEER population-based study. *Cancer Med* [Internet]. 2018;7(6):2307–18. Available from: <http://dx.doi.org/10.1002/cam4.1475>
43. Mbanderson.org. [cited 2024 Mar 19]. Available from: <https://www.mdanderson.org/content/dam/mdanderson/documents/for-physicians/algorithms/cancer-treatment/ca-treatment-breast-invasive-web-algorithm.pdf>
44. Hu T, Chen Z, Hou M, Lin K. Overall and cancer-specific survival in patients with breast Paget disease: A population-based study. *Exp Biol Med (Maywood)* [Internet]. 2022;247(3):187–99. Available from: <http://dx.doi.org/10.1177/15353702211056264>
45. Mammary Paget disease workup [Internet]. Medscape.com. 2023 [cited 2024 Apr 28]. Available from: [https://emedicine.medscape.com/article/1101235-workup?form=fpf&scode=msp&st=fpf&socialSite=apple&icd=login\\_success\\_ap\\_match\\_fpf](https://emedicine.medscape.com/article/1101235-workup?form=fpf&scode=msp&st=fpf&socialSite=apple&icd=login_success_ap_match_fpf)