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Paget's Disease of the Breast, underlying breast cancer mimicking as Benign Dermatological Conditions: Clinical Challenges and Diagnostic Considerations

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Abstract: Mammary Paget's disease (MPD), also known as Paget's disease of the breast, is an uncommon dermatological cancer of the nipple-areolar complex that can cause anything from redness and itching to more serious symptoms like breast lumps, destruction of the nipple-areolar complex, or nipple discharge. It is typically linked to either invasive ductal carcinoma or an underlying ductal carcinoma in situ. MPD can cause delayed diagnosis and improper therapy because it frequently presents as various benign and malignant dermatological disorders, such as eczema, atopic dermatitis, psoriasis, and squamous and basal cell carcinomas. Since only one-third of patients have a palpable lump when they first arrive, MPD should be suspected in patients who are older and have unilateral, persistent lesions. In order to distinguish MPD from other skin illnesses, our review paper highlights the major findings of clinical features and diagnostic workup. It also includes case studies of MPD mimicking other skin conditions. According to a study of the literature, research advises against using mammograms and ultrasounds alone to diagnose MPD, especially when there isn't a palpable lump. This demonstrates that the MRI is a better and more precise imaging method. However, because MRI results can occasionally be negative when there is a biopsy-proven MPD present, any suspicious lesion needs to be biopsied in order to undergo histological and immunohistochemical analysis. This highlights the need for clinicians to explore any suspicious lesion of the nipple or breast using the complete triple evaluation technique to exclude an underlying cancer. It is vital to establish therapeutic criteria to treat any nipple lesion to limit the risk of misdiagnosing any underlying cancer, which can be potentially lethal if left alone.

Introduction:

Mammary Paget's disease (MPD), first identified by Sir James Paget in 1874, is an uncommon condition affecting the nipple, often linked to underlying breast cancer. Paget described it as a persistent, ulcerating skin lesion with a yellowish discharge, and over time, it became clear that it was associated with more severe conditions, such as breast carcinoma [1,2]. In his study, Paget observed 15 female patients with similar symptoms, all of whom later developed breast cancer. Initially mistaken for a benign skin condition, it was later understood to be malignant in nature. A parallel condition, extramammary Paget's disease, can also occur in the genital area of both men and women. While the two conditions share similar histological features, they have distinct causes and mechanisms [2,3]. MPD is a form of intraepithelial malignancy, typically characterized by the presence of large malignant cells, known as Paget cells, within the squamous epithelium of the nipple. These cells can spread to the areola and adjacent skin. Occasionally, Paget's disease may even appear in accessory nipples or other abnormal breast tissues [5]. The disease is most commonly diagnosed in postmenopausal women, particularly those in their 50s or 60s. It accounts for about 1% to 3% of all breast cancer diagnoses. In the majority of cases, MPD is associated with either ductal carcinoma in situ (DCIS) or invasive ductal carcinoma (IDC), typically in the central or multifocal regions of the breast. The presence of invasive cancer plays a major role in determining the prognosis. Additionally, bilateral cases—where tumors develop simultaneously in both breasts—occur in approximately 1% of all breast cancer cases, which makes it harder to assess the overall disease progression.

Research shows MPD (Mammary Paget's Disease) appears rarely in men since 1% of cases emerge and the affected patients usually reach age 68. Epidemiological research reveals that Paget's disease occurrence has decreased by 45% throughout the previous two decades. The discovery of DCIS (ductal carcinoma in situ) during regular mammography screenings has been the main reason for this downward trend [6,7]. According to the literature Paget's disease presents in three distinct forms based on its relationship to the underlying DCIS (ductal carcinoma in situ) and its distance from the nipple: (1) Paget's disease arising from DCIS located within 2 cm of the nipple in lactiferous ducts, (2) Paget's disease accompanied by invasive carcinoma spreading beyond 2 cm from the nipple-areolar complex, and (3) Paget's disease occurring without an underlying carcinoma (Figure 1) [8].

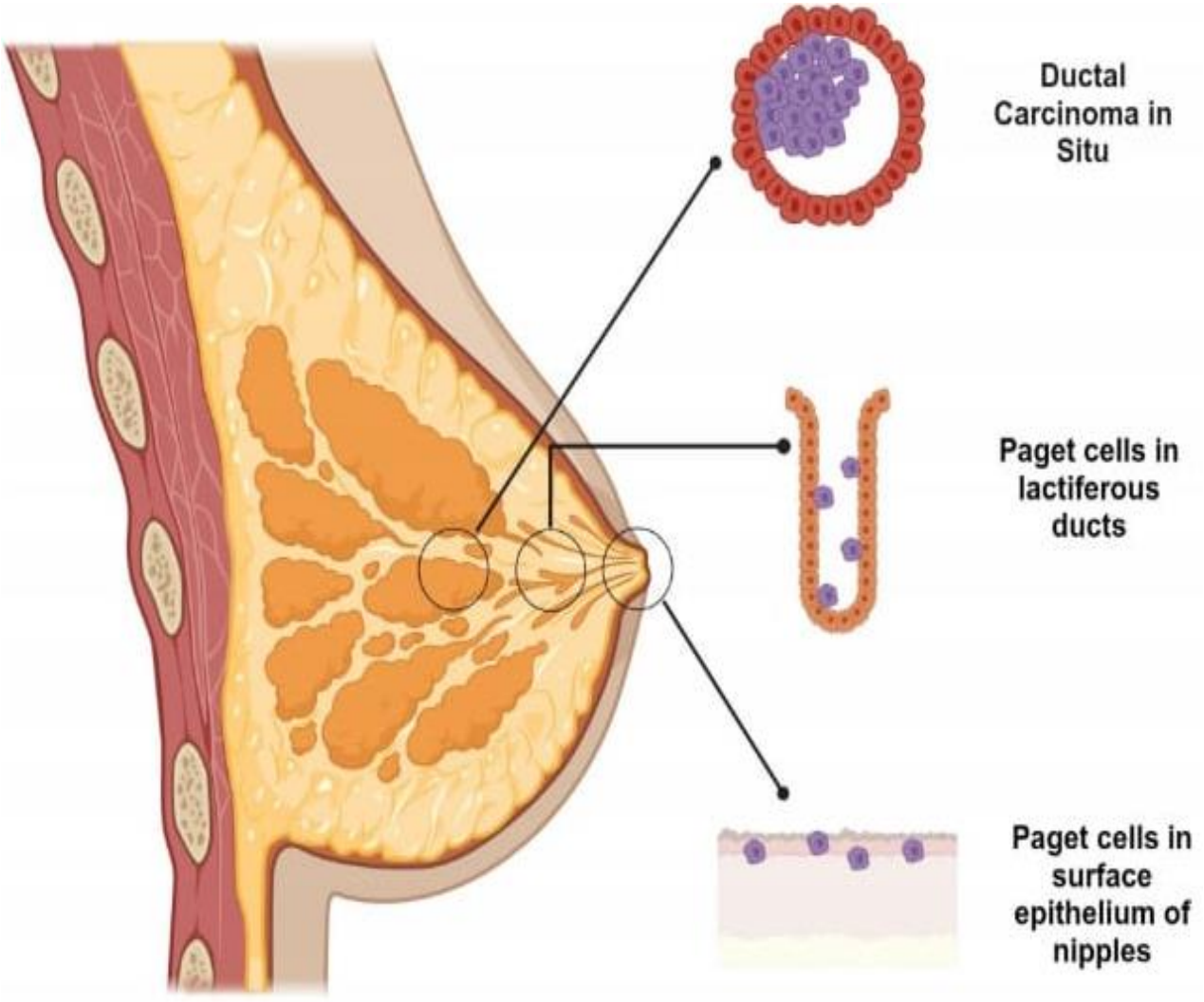

FIGURE 1: MPD with underlying carcinoma

Medical professionals must understand that Paget's disease shows multiple occurrences throughout the breast tissue and resembles standard breast cancer forms. The appearance of MPD matches regular skin rashes which leads to incorrect diagnoses or medical professionals overlooking this condition. The diagnosis of this condition depends mainly on physical examination and medical history review to assess symptom duration. The diagnosis of persistent unilateral nipple changes requires diagnostic methods that include

nipple cytological scraping and MRI or biopsy to perform histopathological analysis and immunohistochemical staining. The advances in radiological methods do not eliminate the need for tissue biopsy when breast lesions appear suspicious because this prevents missed cancer diagnoses [9,10]. According to Ashikari et al. MPD required six to 11 months for diagnosis whereas ductal carcinoma typically needs one to two months for proper identification [11]. The following article examines MPD diagnostic criteria while discussing conditions that resemble Paget's disease to help pathologists and clinicians achieve early diagnosis.

Pathogenesis

Scientists have yet to determine MPD's origins because different hypotheses exist about how this condition develops. Two main theories about MPD development have become widely accepted in the field. According to the epidermotropic theory Paget cells develop from mammary adenocarcinoma when neoplastic ductal epithelial cells move from ducts to reach the nipple epidermis. Research indicates that Paget cells and ductal epithelial cells display comparable immunohistochemical results yet Paget cells exhibit staining patterns that differ from the nipple epidermal keratinocytes. Histological investigations have shown that ductal carcinoma cells directly connect to Paget cells found in the nipple. The HER2/neu (human epidermal growth factor receptor) demonstrates frequent overexpression in Paget's disease because Pelorca et al. [14-17] report that 83.5% of MPD cases belong to the HER2 or luminal HER2 molecular subtypes. The motility factor known as heregulin-α produced by epidermal keratinocytes works through HER2 binding to direct malignant cells to the nipple surface. The high rate of breast cancer diagnoses in MPD cases supports this theory since it occurs in more than 90% of MPD patients. The intraepidermal transformation theory receives less acceptance than its alternative. The independent development of epidermal keratinocyte malignancies appears possible when they arise without connection to breast cancer and through degeneration or in situ transformation processes. The theory suggests that Paget cells develop from either pluripotent keratinocyte stem cells or apocrine gland duct cells which subsequently become malignant.

Several studies have documented cases of Paget lesions without dermal invasion, as well as the presence of desmosomal connections between Paget cells and adjacent cells, which may prevent their migration. In 1881, George Thinn introduced the transformation theory, which proposed the development of carcinogenesis in the absence of an underlying carcinoma. He suggested that continuous secretions from the breast ducts cause damage to the epithelium, leading to the transformation of keratinocytes into malignant cells. Some researchers have observed specific pre-Paget cells, which appear to be intermediate between keratinocytes and Paget cells. This observation supports Thinn's theory, indicating that epidermal cells could potentially acquire ductal cell characteristics as they undergo malignant transformation. Despite various studies, no definitive evidence has conclusively proven either theory, though the epidermotropic theory has gained broader acceptance (Figure 2) [2,3,15,18-20].

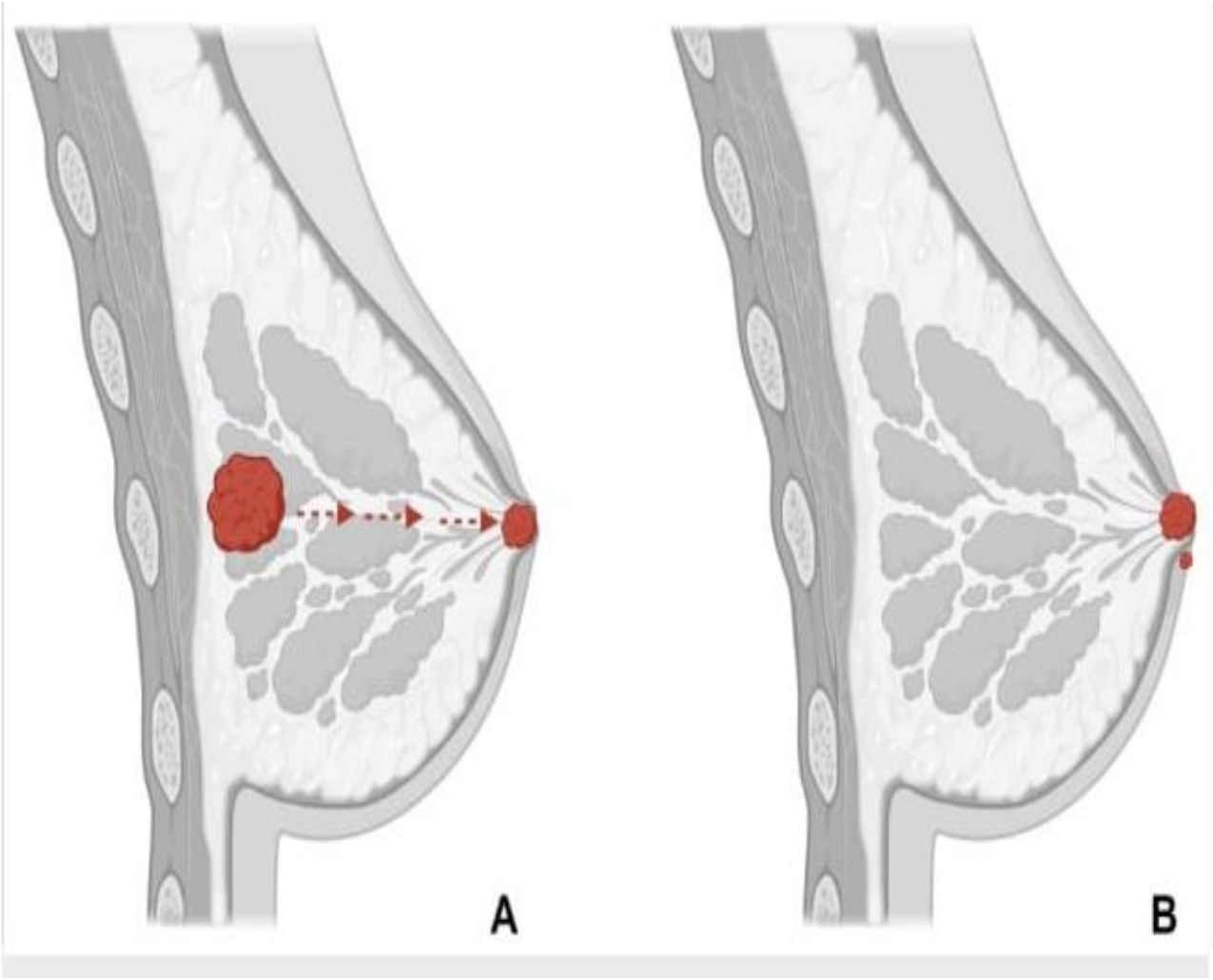

FIGURE 2: Pathogenesis of MPD

(A) Epidermotropic theory: Paget cells originate in the underlying adenocarcinoma, with neoplastic epithelial cells migrating through the ductal system to the nipple epidermis. (B) Intraepidermal transformation theory: Paget cells arise from degeneration or in situ transformation of epidermal keratinocytes in the nipple-areola complex.

Risk factors

The risk factors for Mammary Paget's disease overlap with those of regular breast cancer and include aging population and obesity alongside alcohol intake and BRCA1 and BRCA2 genetic mutations together with prior chest radiation exposure and hormone replacement therapy usage and prolonged oral contraceptive use and breast cancer heredity. The research conducted by Zheng et al. analyzed Chinese women with primary breast cancer through a multi-center retrospective study to examine demographic and risk factors in MPD patients relative to other breast cancer types. Research results showed that age together with menstrual status and education level and parity and breastfeeding practice and age at menopause and family history of breast cancer and metabolic rate showed no differences between groups [21]. The research by Jamali et al. showed that MPD reaches its peak occurrence between 5 to 10 years after the peak time for invasive breast carcinoma [22]. The majority of MPD patients remain childless whereas breast cancer patients with different types have given birth [23].

Diagnosis

The symptoms of MPD usually appear as skin changes inside the nipple-areola complex through itching and

eczema alongside redness. A defined lesion patch appears first before developing into an eczematoid or erythematous plaque. The manifestation of Paget's disease differs from non-cancerous eczema because it appears only on one side of the body [8,11]. The disease evolution results in skin damage that causes erosion of the tissue and ulceration of the skin surface alongside serous or bloody discharge together with nipple deformities including flattening or inversion. Advanced Paget disease stages present with crusted lesions, scaling skin and skin dimpling as well as fissures according to medical reports. The rash produces a diameter which extends to 15 cm according to research [1,24]. The majority of patients feel burning sensations and pain during the pre-visual skin change period of their condition while 15% to 20% of patients report these symptoms [25,26]. Rare occurrences show Paget's lesions spreading from the nipple into adjacent perimammary skin and the opposite breast according to medical reports [27,28]. Medical reports have documented the appearance of brownish skin lesions which look like superficial melanoma [29]. The significant indicators for dermoscopy of MPD lesions include unorganized pink patches and white lines. The appearance of pigmented skin lesions includes gray granules and dots whereas ulcers and white scales are found in non-pigmented skin lesions [30].

Because MPD can look like the skin condition eczema doctors sometimes wrongly diagnose it therefore patients receive topical creams without identifying the true cause of their condition [8,31]. A persistent nipple condition that includes pain or erythema along with persistent itching warrants MPD investigation [32]. A clinical examination of 52 Paget disease patients confirmed that most women presented with observed nipple masses along with redness, itching, ulceration, yet bleeding and discharge appeared less frequently [33]. Tumors at an advanced stage sometimes display spread to lymph nodes in the armpit area. The research on 20 MPD patients determined that axillary lymph node metastasis occurred in fifty percent of cases and several patients displayed this condition when no breast lump could be detected [23,34]. The research showed that 13% of patients who did not have detectable breast lumps had axillary lymph node metastasis [11]. The research by Fu et al. determined that almost every patient with undetectable breast masses had carcinoma combined with Paget's disease [35].

Imaging

If the skin changes do not improve after two weeks of corticosteroid treatment, further diagnostic steps, including imaging and biopsy, are recommended [2]. A thorough evaluation should involve high-quality imaging to rule out cancer, given the strong link between Mammary Paget's disease (MPD) and breast carcinoma [8]. Studies suggest that patients with palpable masses typically exhibit multifocal disease, whereas those without a mass may still have multifocal or multicentric lesions [36]. Mammography is the first choice for detecting potential malignancies in MPD cases, with breast ultrasound considered if mammogram results are unclear [2]. For patients who show no abnormalities on mammograms or ultrasounds and do not have palpable masses, breast MRI is recommended [37]. Although mammography plays a vital role in diagnosing and managing Paget's disease, it is not foolproof, with up to 50% of patients presenting normal mammograms [8]. Typical mammographic findings include thickening of the skin around the nipple-areolar complex, changes in breast tissue density, nipple retraction, identifiable lumps, or microcalcifications [2,37].

In a study conducted by Pelorca et al., 85.9% of patients underwent mammography, and abnormalities were detected in 87.7% of cases, with microcalcifications being the most frequent finding (58.9%), followed by nodules (37%) [38]. Challa and Deshmane examined 20 women with MPD, performing mammography on 11 of them. Two patients showed no abnormalities, while among the nine with identified issues, five had fine microcalcifications, two had underlying masses, and two exhibited increased skin thickness around the nipple. Two patients had multicentric calcifications involving more than two quadrants, and multicentricity was observed in 25% of cases [34]. Mammography often misses some malignancies, with detection rates varying from 15% to 65% in different studies [29,32,39]. Besides detecting underlying masses or DCIS, mammography is also crucial in monitoring patients who have undergone conservative breast surgery, helping to rule out recurrence [37].

Mammography has a high sensitivity of 97% for detecting cancer in patients with a palpable breast lump, but in the absence of a lump, it only identifies underlying malignancies in about half of the cases [2,4,40]. Therefore, a negative mammogram does not entirely exclude the possibility of cancer [1]. Ultrasound is used to confirm mammographic findings and is also helpful when mammograms are normal. Ultrasound can detect parenchymal heterogeneity, hypoechoic areas, dilated ducts, distinct masses, and skin thickening [37,40]. It can also evaluate axillary lymph nodes [2]. However, microcalcifications often do not appear on ultrasound. In some cases, areas of DCIS with pleomorphic calcifications seen on mammograms are better visualized through ultrasound, though ultrasound may not always clarify mammogram findings and can sometimes only show skin thickening [37].

When combined with mammography, ultrasound does not significantly increase the detection sensitivity of underlying lesions. However, it is valuable for characterizing abnormalities or guiding biopsies of any palpable masses detected by mammography [3]. In a study by Günhan-Bilgen and Oktay, ultrasound identified masses in 35 out of 52 MPD cases, most of which were irregular or lobulated (95%), without posterior shadowing [32]. MRI is particularly sensitive for detecting breast tumors, especially when both mammography and ultrasound fail to identify abnormalities. It can highlight papillary-areolar complex thickening, nipple enlargement, in situ ductal lesions, and invasive tumors, even when clinically suspected [40,41]. MRI can also demonstrate different patterns of enhancement, such as asymmetric, irregular, or discoid, and is especially useful for evaluating the extent of disease in patients who might require breast-conserving surgery (BCS). For those with suspected or confirmed MPD, MRI helps identify multifocal or multicentric lesions that may not be visible through clinical examination or other imaging tests [2].

In Pelorca's study with 85 MPD patients, ultrasound was performed in 79 individuals (92.9%), detecting solid lumps in over 70% of cases. MRI was conducted on a subset of patients, identifying tumors in nearly 70% of cases and nipple-areolar complex thickening in around 43%. The study found no significant differences in imaging results between clinical or hidden Paget's disease forms, whether assessed with mammography, ultrasound, or MRI [38]. Another study by Siponem et al. showed that MRI had the highest sensitivity for detecting invasive carcinoma (100%) and DCIS (44%), followed by mammography (74% and 39%) and ultrasound (74% and 19%) [2,42]. However, Morrogh et al. reported that MRI failed to detect cancer in three out of 34 women with biopsy-confirmed MPD [39].

MRI is highly sensitive but may have a lower specificity, leading to the identification of abnormalities that could result in unnecessary mastectomy rather than breast-conserving surgery. If MRI is used, it is crucial that it be performed at a facility capable of MRI-guided biopsies, and patients should be informed about the high false-positive rates associated with MRI, which may require additional biopsies [3]. For example, a 52-year-old woman with changes in nipple color had a negative mammogram and no palpable lump, but an MRI revealed underlying carcinoma, including diffuse segmental enhancements indicative of DCIS [43]. While Paget’s disease is mainly diagnosed based on clinical signs, imaging findings may not rule out hidden breast cancer, especially in the absence of detectable lumps or palpable abnormalities [37].

Histopathological and Immunohistochemical Features of MPD

Fast MPD diagnosis becomes possible through tissue scraping because the affected area shows specific cellular traits including high nuclear-to-cytoplasmic ratio and vacuolated cytoplasm of enlarged cells. The diagnostic process includes three biopsy methods which include superficial shave biopsy of the epidermis as well as wedge biopsy and punch biopsy. A wedge biopsy serves as the preferred choice because it collects sufficient epidermal tissue. When Paget cells are located in ulcerated areas medical personnel will find insufficient cells through shave biopsy while punch biopsy yields limited epidermal and stromal samples for diagnostic examination [44]. Standard medical practice recommends surgical removal of Paget disease as the primary treatment approach that should be considered even when biopsy results are unclear. Medical professionals perform full-thickness biopsies primarily

to evaluate nipple-areolar skin changes [45].

Paget cells exist as the diagnostic sign for MPD. The cells of intraepithelial adenocarcinoma present as various-sized structures which exist in the basal layer while missing the cellular connections that join cells together. Small clusters and large sheets of cells adopt a nest-like or glandular arrangement while replacing the normal epidermal cells. The cellular cytoplasm of Paget cells contains high amounts of neutral mucopolysaccharides along with mucin positivity. Under microscopy viewing Paget cells display pale vacuolated cytoplasm which contains clear material and show hyperchromatic pleomorphic nuclei together with one or two prominent nucleoli [46]. There is commonly a dense lymphocytic inflammatory infiltrate in the dermis layer near the surface. The benign Toker cells originating from sebaceous glands possess abundant cytoplasm that can potentially resemble Paget cells. Scientists have confirmed that these cells exist in 10% of regular nipple samples and occasionally arise in both supernumerary nipples and apocrine glands [47]. Immunohistochemical staining serves as a vital tool to identify different molecular subtypes of MPD for proper therapeutic decisions and survival predictions and disease staging. The evaluation technique supports doctors to differentiate MPD from other medical conditions that may affect the nipple. Research indicates that HER2 overexpression occurs commonly in patients with MPD. The analysis of breast tissue cells revealed ER expression in 40% of cases and PR expression in 30% of cases. Among breast cancer subtypes Luminal A and B occur more frequently in other cancer types but MPD exclusively presents with HER2 positive characteristics. Research has confirmed that cytokeratin exists in 95% of examined Paget cells. GATA-3 staining serves as an important diagnostic tool for MPD since Paget cells use heregulin-α to create a chemotactic movement that enables their nipple epidermis spread [48-54].

MPD mimicking dermatological conditions

MPD can sometimes be mistaken for a variety of benign or chronic skin conditions, such as chronic eczema, atopic dermatitis, contact dermatitis, psoriasis, erosive adenomatosis, squamous cell carcinoma, basal cell carcinoma, and malignant melanoma (Figure 3, Table 1).

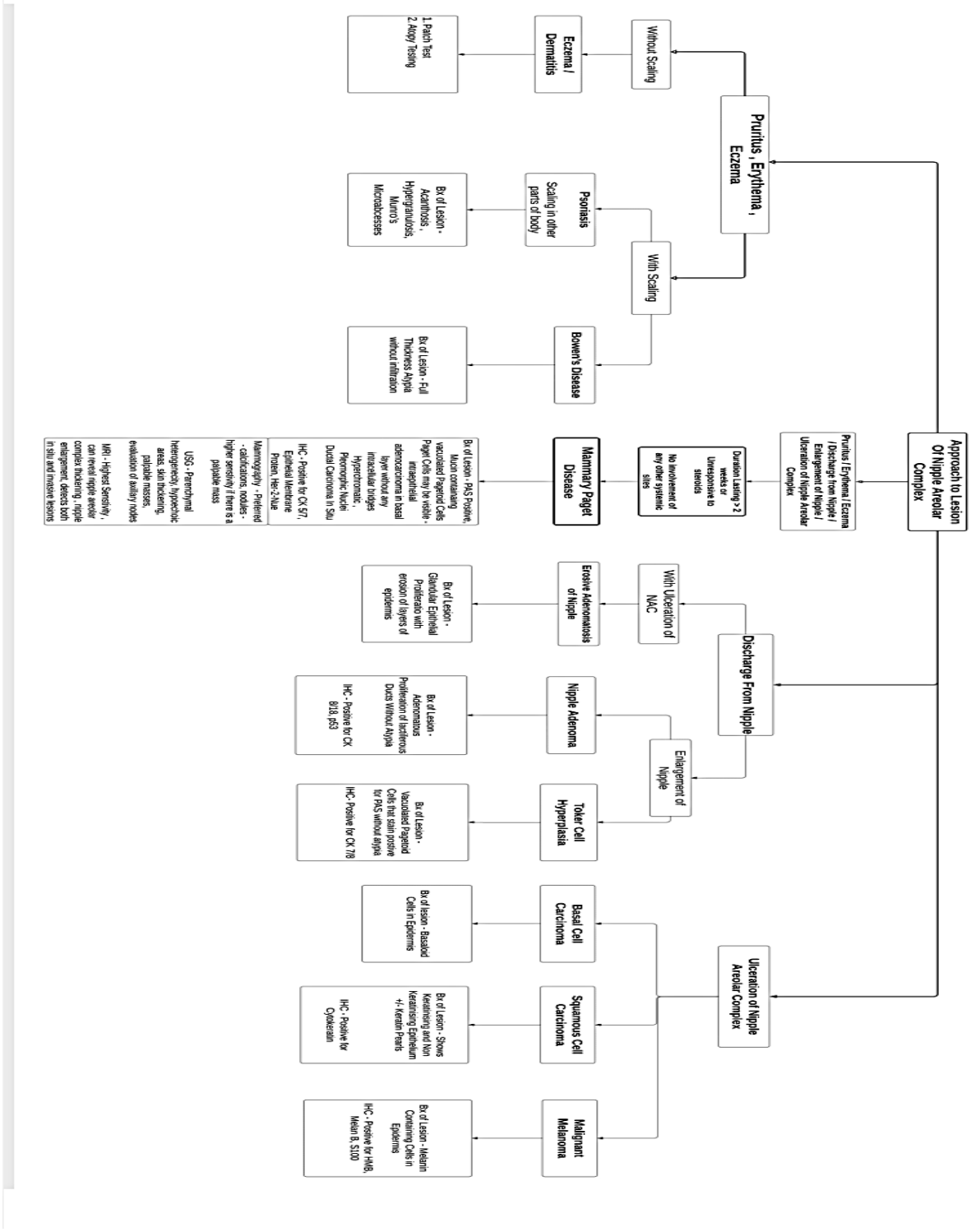

FIGURE 3: Diagnostic flowchart of the differential diagnosis of nipple areola complex diseases

Disease	Clinical Features	Diagnostics (HPE)	Diagnostics (IHC)
MPD (Mammary Paget's Disease) **(44-54)**	Scaling, eczema, erythema, ulceration, erosion, hyperpigmentation of nipple and discharge from the nipple.	Incisional biopsy shows PAS-positive mucin-containing vacuolated pagetoid cells.	Positive for CK 7/8, epithelial membrane antigen, CEA, HER2/neu, mammary Paget's disease marker.
Chronic Eczema **(55-61)**	Scaling, erythema, hyperpigmentation, lichenification.	Medical history and symptom description analysis, triggers, and physical examination.	Patch testing, skin biopsy, blood tests for IgE.
Atopic Dermatitis **(62-65)**	Erythema, papules-vesicles, erosions, pruritus.	Clinical examination, history of eczema, and elevated IgE levels.	-
Contact Dermatitis **(63-68)**	Erythema, papules-vesicles, erosions, pruritus.	Clinical examination and identification of the contact allergen.	-
Psoriasis **(69-73)**	Defined patches with scales, erythema, infiltration, and pruritus.	Clinical examination, biopsy for acanthosis, hyperkeratosis, Munro microabscesses, and Kogoj's pustules.	-
Bowen's Disease **(88, 89)**	Patchy lesions, slow growth, irregular borders, scaling, itching, burning.	Dermoscopy, biopsies, and histopathological examination of biopsies.	-
Erosive Adenomatosis **(87)**	Ulcers on the nipple or areola, discharge pain, and itching.	Clinical examination, biopsy for histopathological examination.	-
Nipple Adenoma **(77-84)**	Firm nodules, crusting, or erosion of the nipple, possible sub-areolar calcifications.	Determined by biopsy. Adenomatosis proliferates ducts with surrounding myoepithelial cells, without cellular atypia.	Positive for CK 8/18 and p53.

Toker Cell Hyperplasia (74-76)	Changes in nipple appearance: growth, color, burning, discharge.	Biopsy to differentiate from MPD, with PAS-positive mucin-stained cells.	Positive for CK 7/8 and epithelial cell markers.
Malignant Melanoma (97-100)	Black ulcerative/crusting erosion of the nipple-areolar complex.	Biopsy needed to differentiate from MPD; HPE for melanocytic patterns and absence of skin invasion.	Positive for HMB-45, Melan-A, S-100.
Invasive Squamous Cell Carcinoma (90, 91)	Scaly ulcerative lesions of nipple-areola complex.	Biopsy for histopathology.	Positive for cytokeratin markers.
Basal Cell Carcinoma (92-95)	Ulcerative lesions of nipple-areolar complex.	Clinical examination and biopsy.	Positive for Ber-EP4.

TABLE 1: Differential diagnosis of skin lesions of the nipple-areola complex

PAS: periodic acid-Schiff; CK: cytokeratin; CEA: carcinoembryonic antigen; HER2/neu: human epidermal growth factor receptor 2; HMB: hydroxymethylbutyrate; HPE: histopathological examination; IHC: immunohistochemistry; MPD: mammary Paget's disease; IgE: immunoglobulin E

Benign Conditions

Eczema: Mammary Paget's disease (MPD) gets mistaken for the skin condition eczema which affects numerous patients through skin irritation. Numerous MPD cases were mistakenly diagnosed as eczematoid dermatitis thus leading to delayed appropriate medical care. Doctors diagnose eczema by taking patient histories while examining the skin and testing skin areas with allergens. The medical diagnosis of chronic eczema needs a skin biopsy because it presents bilaterally while IgE antibody levels remain elevated in most cases. A 46-year-old female patient experienced her left breast develop a red ulcerated plaque that progressively grew worse until the actual MPD condition became evident according to Bansal et al. It took three years of receiving steroid treatments and antibiotics before MPD received its proper diagnosis through biopsy testing. A 24-year-old woman underwent incorrect diagnoses for thirteen years until MPD was finally acknowledged as her true condition according to Kanwar et al.

Atopic dermatitis: It stands as a skin problem which affects the nipple and approximately 23% of patients. The skin condition shows erythema as well as papules and vesicles with frequent itching being a symptom. When patients continue scratching their skin tissue can become thickened which is known medically as lichenification. For accurate diagnosis of Paget's disease doctors must perform biopsies on the nipple and areola area but punch biopsy results might be false. Medical testing of atopic dermatitis reveals acanthosis alongside spongiosis and lymphocytic exocytosis when examining the skin while the dermis contains lymphocyte and eosinophil cell infiltration. The chronic stage of this condition shows higher levels of mast cells together with Langerhans cells and eosinophils and develops hyperkeratosis. The immunohistochemistry analysis will show TH-2 cytokines (IL2 and IL13) specific to atopic dermatitis in both the epidermis and perivascular dermis tissue.

Dermatitis: Doctors should investigate allergic contact dermatitis as an ongoing nipple eczema treatment-resistant case. Doctors start diagnostic procedures by

performing patch tests to determine the allergens that might be causing reactions since nickel and items found in fabric cleaners and nipple creams have been established as possible allergens. New symptoms of contact dermatitis usually manifest as vesicles and erythema and persistent itchiness begins to appear 24-48 hours after allergen exposure. The friction from nursing and lactation pump usage along with occupations and habits increase the likelihood of developing irritative dermatitis. The histological features of irritative eczema include eosinophilic spongiosis together with acanthosis and lymphocytic exocytosis while perivascular infiltration of lymphocytes and neutrophils is commonly observed.

Psoriasis: Psoriasis functions as a persistent autoimmune disease which occasionally impacts the nipple and areola. The most typical psoriasis manifestation includes plaque-type lesions with redness and scaling and skin tissue swelling which frequently emerges after physical trauma (Koebner phenomenon). Psoriasis appears extremely rarely on the nipple and areola yet reports exist of patients with breast cancer background experiencing these symptoms. The histological examination of psoriasis shows regular acanthosis together with stratum granulosum thinning and parakeratosis and neutrophilic infiltration which includes Munro's microabscesses in the stratum corneum. A patient's presentation of MPD and psoriasis suggested potential simultaneous development of these conditions according to medical reports.

Toker cell hyperplasia exists as a benign condition that should be distinguished from MPD. Toker cells exist as isolated firm non-pigmented lesions which can appear either in one nipple or both nipples. The cells most often occur in female bodies and exist either normally or as hyperplastic forms. Atypical and hyperplastic Toker cells display some histological similarities with Paget cells through their positive reactions to estrogen receptor (ER) and progesterone receptor (PR). The markers CD138 and p53 show negative results in these cells while ER and PR remain positive thus distinguishing them from Paget's cells. The results of immunohistochemical examinations on atypical Toker cells show weak HER2/neu protein expression. The research conducted by Di Tommaso et al. revealed that among 390 mastectomy patients Toker cells appeared in 40 cases yet atypical findings were observed in 12.5% of these cases. The correct diagnosis of eczema-like symptoms requires extensive clinical evaluation that includes both tissue sampling and laboratory testing of tissue specimens. The diagnostic process becomes more complex when atypical cells including Toker cells appear because it requires precise determination of whether the condition is benign or malignant.

The histological features of psoriasis typically show consistent acanthosis, a reduction in the stratum granulosum, parakeratosis, neutrophil infiltration beneath the corneal layer (Kogoj's spongiform pustules), and the presence of neutrophils within the stratum corneum (Munro's microabscesses) [72]. Interestingly, a rare case involving both psoriasis and Mammary Paget's disease (MPD) was reported in an elderly woman [73].

Di Tommaso et al. investigated the frequency of Toker cell hyperplasia along with distinctive features to differentiate abnormal cells from Paget's disease-related malignant cells. The appearance of Toker cell hyperplasia includes a small solitary firm lesion that lacks pigment and does not cause discomfort. The condition affects one or both nipples primarily among female patients. The analysis of over 390 breast mastectomy patients revealed Toker cells in the nipples of 40 patients. The examined cells consisted of normal Toker cells in 60% of cases and hyperplastic Toker cells in 27.5% of cases while 12.5% of cases contained both hyperplastic and atypical Toker cells. The analysis through immunohistochemical methods revealed that Toker cells displayed positive reactions to estrogen receptors (ER) and progesterone receptors (PR) while remaining negative for both CD138 and p53. The immunoreactivity of HER2/neu was weak in specific atypical Toker cells but remained absent in Paget cells. Immunohistochemical tests demonstrated that both Toker and Paget cells expressed cytokeratin 7 (CK 7) and epithelial membrane antigen (EMA) while remaining negative for p63. The research team employed CD138 and p53 staining together to distinguish atypical Toker cells from Paget cells. The research emphasizes the necessity of correct identification between Toker cells and malignant Paget cells which occur in Paget's disease [74].

An 83-year-old woman visited gynecological services with a non-pruritic, erythematous and non-tender eczematous nipple lesion that had existed for 17 years according to Ramos et al. The possible diagnoses included both chronic eczematous nipple conditions and Paget's disease of the nipple. The punch biopsy showed isolated epithelioid cells existing in the epidermis while the PAS staining test produced negative results. The final diagnosis of Toker cell hyperplasia excluded Paget's disease of the nipple because immunohistochemical results showed CK 5/7 positivity but p53 negativity [75]. A 47-year-old woman showed an eczematous lesion on her right areola for ten years according to van der Putte et al. The biopsy analysis showed a single-cell type collection that stayed within the epidermis yet left all other tissue layers and their environment unaffected. The initial assessment identified the lesion as MPD but subsequent analysis confirmed it as mammary gland hyperplasia within the epithelium which met all criteria for Toker cell hyperplasia diagnosis [76]. Nipple adenoma exists as a rare condition that doctors must distinguish from MPD through specialized laboratory testing including histopathological and immunohistochemical analysis [77]. The proliferation of lactiferous ducts leads to the development of nipple adenoma which represents a rare form of benign condition. A firm nodule alongside crusting and erosion and ulceration and nipple discharge are among the clinical manifestations of this condition [78]. Nipple adenoma exists as a condition that may present with or without visible mass tissue beneath the nipple [79].

The significant proliferation of myoepithelial cells in nipple adenoma causes the nipple to enlarge and swell without spreading to other parts of the body. The condition leads to nipple destruction that produces symptoms which doctors might mistake for Paget's disease [80]. The clinical characteristics shared by nipple adenoma and MPD make their differentiation a difficult task for healthcare providers. The progression rate of Paget's disease surpasses nipple adenoma since it causes intense itching and skin damage yet nipple adenoma shows a distinct feature as a single nipple lesion with less noticeable exudate. The two conditions require histopathological evaluation because their clinical symptoms lack specificity for proper differentiation. The definitive diagnosis of nipple adenoma requires both biopsy examination and surgical removal of the tissue [82]. Nipple adenomas remain undetectable by mammography but calcifications might occasionally show up [83]. Biopsy results show that the lesion exists in the retroalveolar area with a gray appearance as a non-encapsulated mass that contains ductal and adenomatous proliferation surrounded by epithelial and myoepithelial cells. Immunohistochemically, nipple adenomas show positive staining for CK 8/18, CK 5/6, and p63 [84].

Paget's disease stands apart from other conditions due to its exclusive feature of Paget cells that include malignant epithelial adenocarcinoma cells of varying sizes. The oval-shaped vacuolated cells with mucin content show positive results for periodic acid-Schiff (PAS) stain. The immunohistochemistry results for this condition display positive staining patterns for CK 7/20 together with the possibility of detecting carcinoembryonic antigen (CEA) and cytokeratin [53,54]. A 63-year-old woman developed a giant nipple adenoma according to Ono et al. who initially exhibited nipple erosions and excoriations that doctors mistakenly thought were MPD. The final pathological examination revealed nipple adenoma containing myoepithelial cell proliferation and positive CK 5 and 14 staining results [85].

Erosive adenomatosis of the nipple exists as a very uncommon medical condition. The research by Gnangnon et al. presented a case study that detailed the benign breast neoplasm characteristics through its ductal nipple nodule manifestation. Nodules from this condition destroy nipple tissue which results in extreme pain and milky discharge and altered nipple appearance. A 45-year-old female patient showed a progressively enlarging mass located on her left nipple. The patient received treatment for erosive adenomatosis through nipple resection followed by breast reconstruction surgery. The benign nature of this condition leads to clinical symptoms that resemble those of malignant nipple conditions including MPD so proper treatment planning becomes necessary. The most successful treatment option is surgery which leads to positive prognostic outcomes for patients [87].

The clinical presentation of nipple adenoma and erosive

adenomatosis and MPD matches yet their diagnostic approaches and therapeutic options remain distinct from one another. The correct diagnosis of these conditions depends on early histopathological examination which leads to proper treatment approaches for improved patient results.

Malignant Conditions

Only a small proportion of Mammary Paget's Disease (MPD) cases—roughly 1%—are diagnosed in men, with the average age of these male patients being 68. Notably, some studies have observed a 45% reduction in the occurrence of Paget's disease over the past 20 years. This decline is largely attributed to the advancements in mammography screening, which have led to the early detection of ductal carcinoma in situ (DCIS) [6,7]. The scientific community has categorized Paget's disease into three distinct types, based on the underlying pathology:Bowen's disease shares similar characteristics with other skin conditions, such as psoriasis and eczema. In addition, Bowen's disease's clinical manifestations may often lead to a differential diagnosis of seborrheic keratosis, actinic keratosis, and a host of other benign skin conditions. Due to its similar phenotypic features and clinical presentation, Paget's disease is frequently referenced as a differential diagnosis of Bowen's disease. The physical manifestation of Bowen's disease often possesses a scaley, rough, or crusted surface. The borders surrounding these asymmetrical lesions are often characterized as ill-defined, a distinguishing feature of the condition. In addition, the color of the lesion may vary from light pink to rugged brown or even a scarlet crimson on highly melanated individuals, such as those of African descent. However, it is essential to note that Bowen's disease may manifest differently from person to person, and the previously listed characteristics are not exclusive to making a diagnosis [88]. Unexpectedly, a diagnosis of basal cell carcinoma was made and proceeded accordingly, reflecting the masquerading capacity of basal cell carcinoma [94]. Moennich et al. reported a case of a 47-year-old woman who had complained of spontaneous bloody discharge from her right nipple. On a shave biopsy, atypical basaloid cells were found and stained positive for antihuman epithelial antigen (Ber-EP4). Surgery proceeded with the histological diagnosis of basal cell carcinoma of the nipple-areolar complex. During the surgery, when the mass was subjected to a frozen section, the larger specimen showed features of atypical and pleomorphic ductal cells similar to Paget's disease, and the larger specimen when subjected to IHC stained positive for CK 7 and HER2/neu. The initial plan was abandoned, and surgery for lumpectomy with nipple removal and adjuvant radiation was proceeded with [95].

Malignant Melanoma and Pigmented Paget's Disease: A rare variant of Paget's disease, known as pigmented MPD, can mimic malignant melanoma both clinically and histologically. Paget's disease produces melanocyte-stimulating factors from pagetoid cells that cause melanin deposition throughout the tissue area thus creating a pattern that resembles melanoma in situ. The pigment that appears as melanoma originates from epithelial cells in the nearby area. Malignant melanoma starts as a dark mole on the nipple that evolves into tissue spread leading to nipple ulceration [96]. The histopathology examination of MPD reveals cells containing melanin that might be mistaken for melanoma cells. Special stains called mucicarmine reveal mucin-containing vacuoles within Paget's cells but these structures do not exist in malignant melanoma cells [51,54]. The distinction between these two entities requires immunohistochemical staining methods. The immunohistochemical tests show that S100 and HMB proteins are present in melanoma cells but absent in Paget's cells which express CK 7 [96]. Malignant melanoma demonstrates a negative reaction to both estrogen and progesterone receptor tests (ER and PR) which distinguishes it from MPD [51,53,54] The distinction between Paget's disease and melanoma proves difficult because both conditions share comparable tissue examination results and the way samples are obtained. The diagnosis of MPD typically requires core needle biopsies yet fine needle biopsies used for melanoma diagnosis may potentially spread tumor cells. Medical experts suggest performing an excision biopsy on all suspicious lesions [97].

The research by Dehner et al. documented ten cases of nipple primary melanoma while one case showed MPD as a concurrent finding. The diagnosis of primary malignant nipple melanoma requires exclusion of

pigmented MPD since this condition remains quite rare [98]. Pigmented Paget's disease led to a misdiagnosis of malignant melanoma according to Saito et al.'s report [99]. The medical report by Lee et al. detailed how pigmented MPD manifested as a dark-colored mass on the nipple. The histological examination first pointed toward malignant melanoma because it revealed neoplastic cells that contained pigmentation. The immunohistochemical test revealed CK 7 positivity which confirmed the diagnosis of MPD instead of melanoma because melanoma would have shown HMB and S100 positivity [100].

Management

Various patient-specific factors affecting MPD treatment decisions include clinical symptoms together with diagnostic results. Multidisciplinary teams provide most treatment plan development for patients who include oncoplastic surgeons along with radiologists and breast care nurses and other specialists like medical geneticists and clinical psychologists and palliative care specialists. Surgical treatment represents the primary approach for MPD while BCS or mastectomy selection depends on nipple-areola complex DCIS or IDC status and patient presentation and quality of life [101,102]. Healthcare professionals use National Comprehensive Cancer Network (NCCN) guidelines as their primary source for making treatment choices regarding MPD. The guidelines recommend individualized surgical decisions that consider breast cancer coexistence because it determines which surgical procedure would be most appropriate. A patient's treatment plan following NCCN guidelines depends on diagnostic tests such as breast and nipple-areola complex (NAC) biopsies to select the optimal treatment approach. The treatment options for DCIS include BCS without lymph node removal or total mastectomy with sentinel lymph node biopsy (SLNB) instead of axillary dissection and breast/nipple reconstruction can be performed. Patients diagnosed with isolated NAC Paget's disease without breast cancer have four treatment options that include central lumpectomy followed by NAC removal and whole-breast radiation therapy or total mastectomy with or without SLNB or central lumpectomy with NAC removal and no radiation therapy [101,102].

Mastectomy used to be the standard treatment for MPD until recent developments allowed BCS to become a suitable option for patients who do not have underlying carcinoma through wide local excision of the NAC combined with adjuvant therapy. The approach proves appealing because it generates better patient satisfaction results. The possibility of positive surgical margins continues to be a concern because it may lead patients to require additional surgeries or complete mastectomy procedures [103,104]. The research by Kollmorgen et al. revealed that 29% of MPD cases without carcinoma needed mastectomy due to their peripheral location which made wide local excision impossible [19]. For patients without palpable masses or abnormal mammograms, BCS with wire-guided local excision, followed by radiotherapy, can be an effective surgical option [25]. One study comparing the 10-year survival rates of patients who underwent BCS versus mastectomy found a comparable survival rate—67% for BCS and 79% for mastectomy. However, the sample size for the BCS group (n=12) was significantly smaller than that for the mastectomy group (n=102) [105]. The European Organization for Research and Treatment of Cancer Trial recommended that BCS with whole-breast radiotherapy, if clear surgical margins are achieved, is a reasonable treatment approach for MPD and localized DCIS, with a 5% recurrence rate at five years post-operation [103]. This treatment strategy demonstrates the importance of personalized care and the flexibility in surgical options depending on the extent of the disease and the patient's overall health and preferences.

The study by Chen et al. demonstrated that patients who underwent mastectomy or BCS experienced cancer-specific survival rates of 92% and 94% respectively over a 15-year period for patients with or without DCIS [106]. The research conducted by Dalberg et al. demonstrated that BCS produced better disease-free survival results of 94% compared to 85% for mastectomy after ten years [107]. The meta-analysis conducted by Li et al. with 685 patients demonstrated that local recurrence occurred in 5.6% of patients who underwent mastectomy while BCS resulted in 13.2% recurrence. The authors pointed out that diagnostic inconsistencies along with different treatment approaches prevented researchers from concluding which procedure offered superior outcomes between mastectomy and breast-conserving surgery. The patients who experienced relapse after breast-

conserving surgery developed invasive breast cancer resulting in unfavorable outcomes [108]. The procedure of sentinel lymph node biopsy (SLNB) should be performed during mastectomy when invasive cancer exists after histopathological examination to prevent complete lymph node dissection [109].

Patients receiving BCS combined with radiotherapy treatment for MPD and DCIS experienced a 90% overall survival rate during 15 years and a 97% breast cancer-specific survival rate [110]. A review of 38 research studies demonstrated that BCS treatment with radiotherapy produced better local recurrence results than BCS without radiotherapy [101]. The lack of radiotherapy during BCS resulted in local recurrence rates reaching 40% and 33% in separate studies. The authors determined that cone excision stands as an inappropriate treatment method for MPD [111-113]. Post-resection breast or nipple reconstruction following resection becomes vital for patients to reach their aesthetic goals in the secondary management phase. The restoration of breast symmetry after total or skin-sparing mastectomy procedures uses Grisotti mastopexy and Wise-pattern mammaplasty and oncoplastic surgeries as standard techniques. The Grisotti flap technique delivers outstanding aesthetic results when treating Paget's disease patients with central cancer locations. The reconstructive process requires psychological attention because patients might choose immediate or delayed nipple-areolar reconstruction through skin flaps or medical tattooing to match reconstructed nipples and areolas with opposite sides. A patient underwent left mastectomy followed by SLNB and immediate TRAM flap reconstruction from the ipsilateral abdomen through pedicled transverse rectus abdominal muscle (TRAM) technique. Medical professionals consider the deep inferior epigastric perforator (DIEP) flap as the best option but its use remains restricted because it requires microvascular surgery and specialized surgical expertise [2]. Neoadjuvant chemotherapy is gaining popularity for breast cancer treatment and has shown improvements in clinical outcomes [114]. According to NCCN guidelines, chemotherapy is recommended for MPD associated with invasive ductal carcinoma (IDC), but not for MPD linked with DCIS. Therefore, the presence of invasive carcinoma is an important consideration when deciding on chemotherapy [115]. MPD cases are predominantly classified as HER2-positive, and hormone-sensitive chemotherapy can help reduce disease recurrence and extend survival by targeting tumor cells. For cases of MPD without invasive components or with DCIS and estrogen receptor (ER)-positive cells, low-dose tamoxifen (5 mg daily for three years) is recommended as an adjuvant treatment [46].

Recent studies have shown promising results with Glypican-3 (GPC3), a cell surface proteoglycan often overexpressed in certain cancer types, serving as a potential biomarker to differentiate MPD and IDC from other breast cancer subtypes. GPC3 expression is specifically found in HER2-positive tumors, suggesting its potential as a therapeutic target for breast cancer subtypes expressing GPC3 [116].

Prognosis and complications

Mammary Paget's Disease (MPD) can lead to a variety of complications that significantly affect patient outcomes, with local recurrence being the most common. Even after successful treatment, there remains a risk of the disease returning. However, recent research suggests that the likelihood of recurrence following breast-conserving surgery (BCS) is similar to that observed in patients who undergo mastectomies [107]. Additionally, individuals with invasive carcinoma are more prone to experiencing local recurrence than those with non-invasive carcinoma [101]. This finding aligns with numerous studies indicating that MPD has a negative impact on breast cancer survival. A study by Ordz-Pagan et al. illustrated this by comparing the survival rates of patients with breast cancer alone versus those with MPD, showing a five-year survival rate of 93.8% for breast cancer patients alone compared to 81.2% for those with MPD [117]. Beyond local recurrence, MPD also presents the risk of distant metastases, which are often seen in the bones, lungs, liver, and brain. Lymph node involvement is particularly common in MPD cases [118]. When MPD occurs alongside invasive ductal carcinoma (IDC), the likelihood of axillary lymph node metastasis increases [33]. Both recurrence and metastasis often necessitate aggressive treatment strategies, including systemic chemotherapy, additional surgical procedures, and adjuvant therapies [42].

Several demographic factors have been found to correlate with poorer five-year survival rates, including race, age, and gender. Black patients tend to have a shorter survival time compared to other ethnic groups. Additionally, older patients generally have lower survival rates [119]. Though MPD is less common in men, their prognosis is generally worse, with a five-year survival rate for women ranging between 30-50%, while in men, it drops to 20-30% [120]. Pathological factors such as lymph node status, tumor grade, cancer stage, and the presence of metastases also play a significant role in survival outcomes. Lymph node involvement is a strong predictor of survival, with patients who have negative lymph nodes showing a five-year survival rate of 75-95%, compared to only 20-25% for those with positive lymph nodes [5]. The involvement of axillary lymph nodes further indicates a worse prognosis [33]. DCIS (ductal carcinoma in situ) patients have a better survival outlook compared to those with invasive carcinoma. The five-year survival rate for DCIS ranges between 94-98%, while for invasive carcinoma, it ranges from 73% to 93% [121]. These pathological factors highlight the importance of early detection and timely intervention to improve patient prognosis.

CONCLUSIONS

MPD is a rare, localized lesion found on the nipple-areolar complex, frequently associated with underlying breast cancer. The disease often begins with vague symptoms such as itching, eczema, or redness of the nipple, which can easily be mistaken for benign skin conditions, including dermatitis or eczema. As the disease progresses, the nipple-areolar complex may erode, resembling more aggressive malignant conditions like squamous cell carcinoma or basal cell carcinoma. The persistent redness and itching commonly raise concerns for both patients and doctors, signaling the need for further investigation.

MPD presents unique diagnostic and treatment challenges that healthcare providers must navigate. To improve early detection and treatment outcomes, it is crucial to establish standardized diagnostic criteria to minimize the risk of misdiagnosis. Each patient should receive personalized care, considering the specific manifestation of their disease and associated risks. Future research should aim to integrate advanced molecular diagnostics with traditional imaging and histopathological techniques, while also exploring novel therapeutic approaches to enhance patient care.

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