CASE REPORT
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Paget disease of the breast diagnosed during pregnancy: a case report

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ABSTRACT

Paget disease of the nipple is a rare manifestation of breast cancer, accounting for approximately 0.5%–5.0% of cases, and occurs predominantly in postmenopausal women. Its presentation in young women is uncommon and, during pregnancy and lactation, is considered exceptional, often being associated with delayed diagnosis due to physiological breast changes and clinical similarity to benign conditions. A 33-year-old pregnant woman presented with bloody nipple discharge and a progressive lesion on the left nipple, initially treated as dermatitis and mastitis. Prior imaging studies did not reveal significant abnormalities Persistent symptoms prompted biopsy of the areola-nipple complex, whose histopathological and immunohistochemical studies confirmed the diagnosis of Paget disease of the nipple with overexpression of human epidermal growth factor receptor 2 (HER2). The patient initially underwent breast-conserving surgical excision; however, due to involved margins and the finding of extensive ductal carcinoma *in situ* associated with a poorly differentiated invasive focus, a unilateral total mastectomy was performed, with the sentinel lymph node negative for metastasis. Adjuvant treatment was administered in the postpartum period with paclitaxel and trastuzumab, and the patient remained free of recurrence to date. This case highlights the diagnostic challenges of Paget disease of the nipple during the gestational and puerperal period and underscores the importance of early biopsy of persistent lesions of the areola-nipple complex, regardless of seemingly benign radiologic findings, to enable timely diagnosis and improved prognosis.

KEYWORDS: Paget disease, mammary; breast cancer; case report; pregnancy.

INTRODUCTION

Paget disease of the nipple (PDN) is a rare manifestation of breast cancer, accounting for 0.5%–5.0% of cases[1-3]. It involves the areola-nipple complex and, in most cases, is associated with underlying ductal carcinoma *in situ* or invasive carcinoma[4]. Although more frequent in postmenopausal women, its occurrence in young patients and, especially, during pregnancy and lactation is uncommon and represents an important clinical challenge[5].

During this period, physiological breast changes — such as increased glandular density, engorgement, and common inflammatory processes — make physical examination difficult and reduce the sensitivity of imaging methods, contributing to diagnostic delays[4,6]. Additionally, the initial presentation is often nonspecific, with erythema, scaling, crusting, and pruritus, frequently mistaken for contact dermatitis or puerperal mastitis[1,2].

Thus, unilateral and persistent nipple lesions during pregnancy or breastfeeding should be investigated early. Diagnosis is confirmed by biopsy with immunohistochemistry, and imaging studies help evaluate underlying disease[2,7]. Treatment depends on the associated carcinoma, and prognosis is more favorable with early detection[8,9]. This article describes a rare case of PDN identified during pregnancy, highlighting the particularities of this context.

CASE REPORT

A 33-year-old female patient was referred during pregnancy (second trimester) from the hospital's Human Milk Bank to the Breastfeeding Medicine Clinic for a left nipple lesion (Figure 1) and a history of bloody nipple discharge that began before pregnancy.

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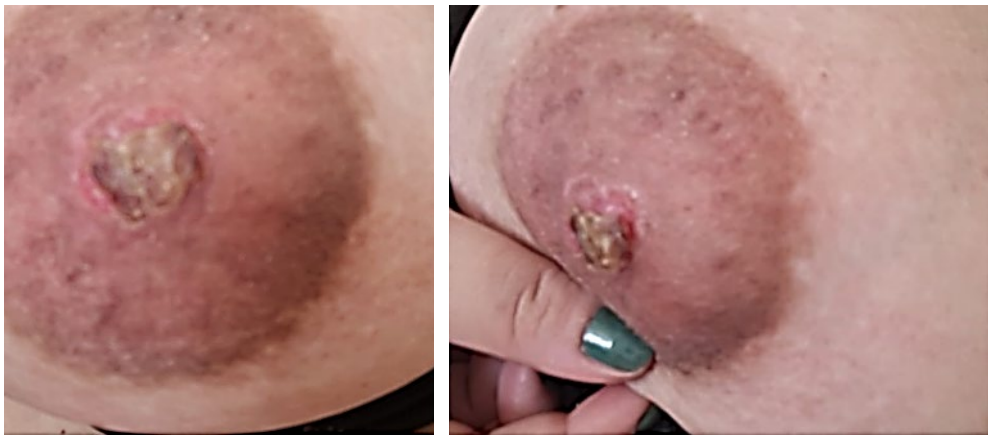


Figure 1. Left nipple lesion corresponding to Paget disease of the nipple at the time of evaluation and biopsy.

Imaging studies (breast ultrasound and mammography) from the previous year were reported as normal. During pregnancy there was worsening of the condition, with continuous breast pain, intermittent edema, and local inflammatory signs. She was evaluated in the clinic and a skin biopsy of the lesion showed a partially eroded and necrotic epidermis with occasional large cells. In the underlying dermis there was fibrosis, vascular ectasia, fibrin deposition, and a mixed inflammatory infiltrate rich in eosinophils, with occasional large cells. Immunohistochemistry was therefore recommended for diagnostic clarification, with Paget disease of the left nipple considered the main hypothesis. The immunohistochemistry performed confirmed the diagnosis of Paget disease of the nipple, with overexpression of human epidermal growth factor receptor 2 (HER2). At the same time, the breast ultrasound was classified as BI-RADS 2. Contrast-enhanced magnetic resonance imaging was considered; however, because of the need for prone positioning in the pregnant patient, it was decided to wait until after delivery. Elective induction at 37 weeks was discussed and declined by the patient. On the third postpartum day, bilateral MRI was performed (Figure 2), which showed a pattern compatible with lactation/early puerperium, asymmetry and slight dermal thickening of the left nipple, without underlying suspicious lesions (BI-RADS 6). The mammogram requested to investigate associated intramammary disease was classified as BI-RADS 0. After diagnostic confirmation, the patient initially underwent left central lumpectomy with a 5 mm gross margin. Pathology showed margin involvement by ductal carcinoma *in situ* (Figure 3), indicating the need for further surgery to widen the margins. Diffuse involvement by poorly differentiated invasive carcinoma (grade 3) was also found, with the largest focus measuring 6.1 mm. Excision of the left axillary sentinel lymph node was performed, which showed no metastases (0/3); angiolymphatic invasion was identified and there was no perineural invasion or microcalcifications, defining the

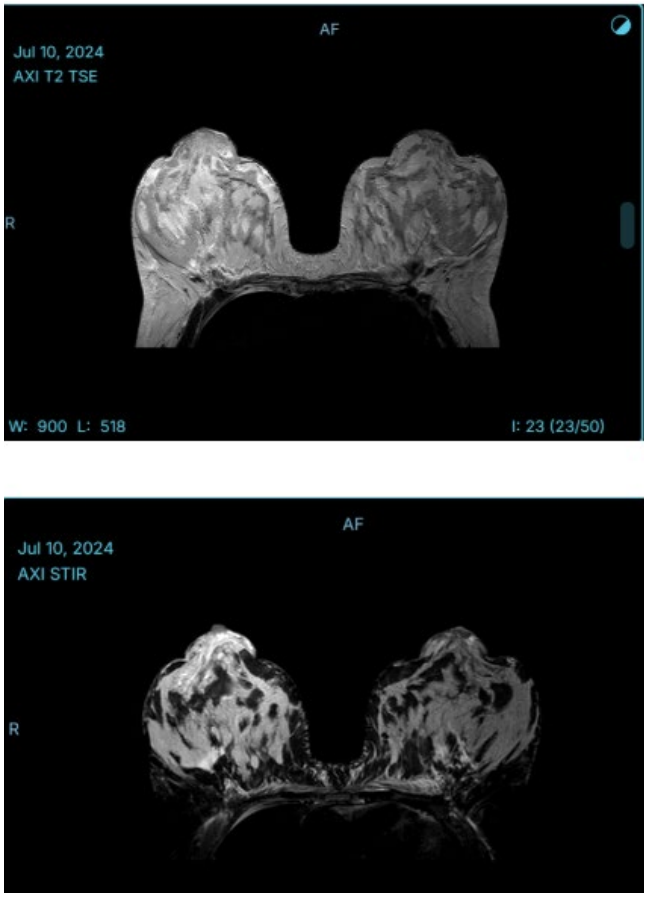


Figure 2. Magnetic resonance imaging in a patient with Paget disease of the nipple, performed in the postpartum period.

staging as pT1bN0(sn). In light of the oncologic context, the reintervention without clear margins, and the patient's preferences, a unilateral total mastectomy was chosen. Examination of the right breast showed no neoplasia, only ductal ectasia and simple cysts — benign findings related to the puerperal/lactational

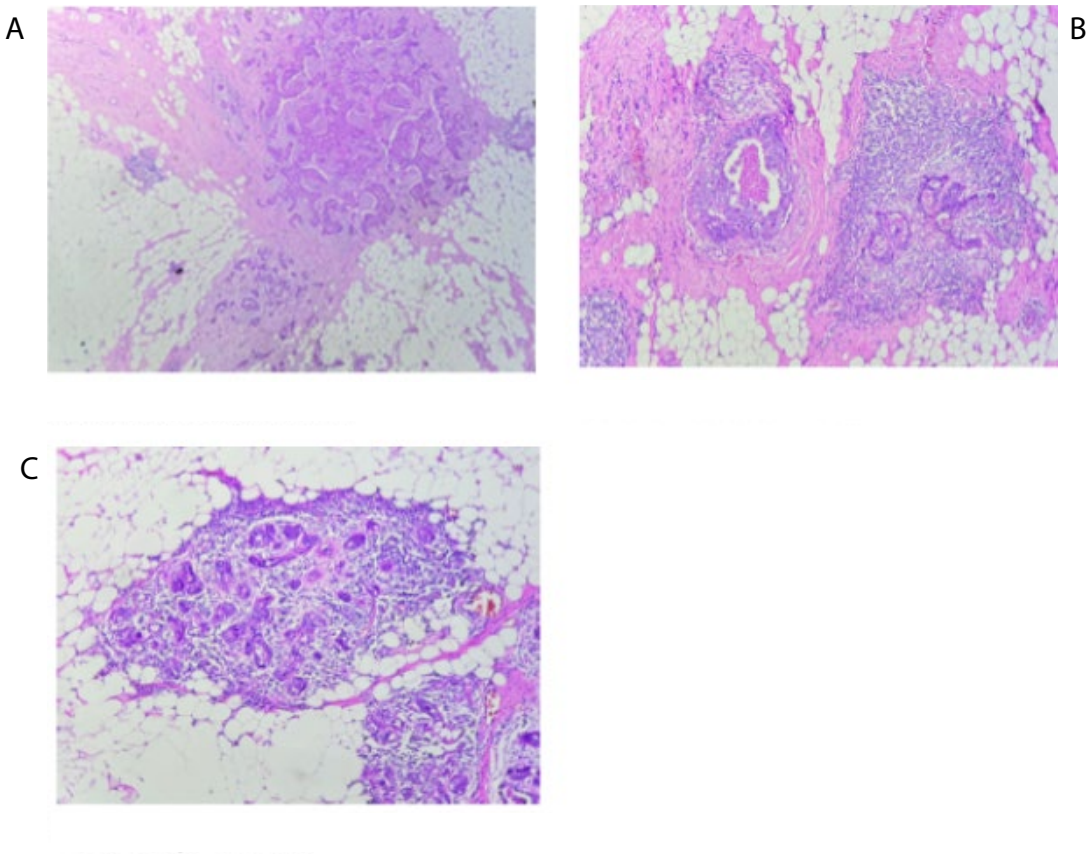


Figure 3. Microscopic examination of the surgical specimen demonstrating ductal carcinoma in situ and invasive carcinoma following left central: a) lumpectomy. invasive ductal carcinoma; b) Ductal carcinoma in situ; c) Lobular involvement.

state. Next-generation sequencing genetic testing of BRCA1 and BRCA2 did not identify pathogenic variants. Adjuvant treatment with trastuzumab in combination with paclitaxel was initiated after the left total mastectomy. The patient received 12 weekly cycles of paclitaxel and trastuzumab every 21 days for one year. Trastuzumab was completed six months ago, and there is currently no evidence of recurrence. In a subsequent procedure, delayed reconstruction with a silicone implant and contralateral mastopexy were performed.

DISCUSSION

PDN is a rare manifestation of breast cancer, accounting for approximately 0.5%–5.0% of cases, classically described in postmenopausal women[1-3]. Its occurrence in young women is uncommon, with an estimated <5% of cases affecting patients under 40 years. Presentation during pregnancy and lactation is considered exceptional and is mostly confined to case reports and small series[4-6]. The lack of robust population data reflects not only the low incidence but also likely underreporting, resulting from lower clinical suspicion and frequent confusion with benign breast conditions during the gestational–puerperal period[4,6]. PDN is highly associated with underlying breast carcinoma, which can remain clinically and radiologically occult in a significant proportion of patients[3,4]. Studies show that in up to about 50% of cases, the associated neoplasm is not identified by conventional imaging methods, especially in dense breasts and in particular hormonal contexts, such as those observed in young women, pregnant women, or lactating women[4,5]. In these scenarios, physiological breast changes can mask suspicious findings and contribute to false-negative results, underscoring the diagnostic limitations of imaging and the need for histopathological confirmation by biopsy of the areola-nipple complex regardless of seemingly benign radiologic findings[4,9]. The initial interpretation as dermatitis or mastitis and the sequence of inconclusive examinations are consistent with the disease's often nonspecific presentation and with the lower accuracy of imaging methods during the gestational-puerperal period[2,3]. During pregnancy and the immediate puerperium, increased glandular tissue and breast density, ductal prominence, hyperemia and edema, and greater vascularity reduce the sensitivity of both mammography and ultrasound for detecting disease underlying the areola–nipple complex[2,3]. Additionally, contrast-enhanced magnetic resonance imaging with gadolinium is usually avoided during pregnancy, and prone positioning may be unfeasible, limiting complementary evaluation[2,3,9]. These diagnostic challenges are widely described

in pregnancy- and lactation-associated breast cancer, in which diagnostic delays exceeding three months are common and are associated with more advanced disease stages[10]. In this setting, BI-RADS 0 or 2 reports during pregnancy and the early puerperium do not exclude underlying carcinoma. The literature emphasizes that the absence of a palpable mass or suspicious radiologic findings does not rule out malignancy in Paget disease of the nipple, especially in young or lactating women[4,6,10]. PDN Paget disease of the nipple is often associated with high-grade invasive carcinoma of no special type (NST) or with ductal carcinoma in situ, and only 0%–13% of patients have no associated breast lesions[11]. Contemporary studies reinforce the multifocal and multicentric nature of Paget disease, with rates that may exceed 90%, even in presentations apparently limited to the nipple[12]. Incisional biopsy of the nipple/areola with immunohistochemical confirmation is consistent with current recommendations, which indicate immediate histologic evaluation of persistent areola–nipple complex lesions regardless of seemingly benign imaging findings[2-4]. The literature emphasizes that nipple biopsy is the definitive diagnostic method, superior to cytology alone, especially in pregnant and lactating patients[4]. From a therapeutic standpoint, breast-conserving surgery is considered appropriate only when PDN is strictly confined to the areola–nipple complex, with no underlying extensive invasive carcinoma or ductal carcinoma in situ. Consistent with contemporary treatment algorithms, mastectomy is recommended when there is extensive in situ disease, multifocality or multicentricity, or when adequate surgical margins cannot be achieved[7,9]. Recent series show that oncoplastic surgery can be safe in selected cases of Paget disease of the nipple, without a negative impact on survival or local recurrence[13]. The choice of surgical strategy in Paget disease of the nipple should centrally consider the histologic extent of the underlying disease and the likelihood of achieving clear margins. Mastectomy may be an oncologically appropriate approach, particularly given the risk of multifocality, extensive ductal involvement, or depending on patient preferences[3,7-9]. Axillary evaluation by sentinel lymph node biopsy is recommended for proper staging, allowing axillary lymph node dissection to be avoided in the absence of nodal metastasis, in accordance with current guidelines and with the aim of minimizing morbidity without compromising oncologic control[11-14]. From a biological standpoint, approximately 80%–90% of Paget disease of the nipple cases show HER2 overexpression, a finding confirmed in modern series that demonstrate a predominance of HER2-positive and HER2-luminal subtypes[11,12,15]. From a systemic standpoint, the high frequency of HER2 overexpression in PDN underscores the relevance of anti-HER2 therapy in adjuvant management, particularly in cases associated with invasive carcinoma. The use of trastuzumab, often combined with taxanes, is well established for HER2-positive tumors and has a favorable impact on oncologic outcomes when administered in the postpartum period[11]. In contrast, anti-HER2 agents are formally contraindicated during pregnancy because of fetal risk, while anthracycline- and taxane-based chemotherapy regimens may be considered from the second trimester in selected situations after careful risk–benefit assessment[9]. In the context of PDN associated with pregnancy, the timing of initiation of systemic treatment should integrally consider tumor extent and the diagnostic limitations imposed during this period. The absence of radiologic evidence of underlying carcinoma during pregnancy, together with technical and ethical restrictions on performing contrast-enhanced MRI, may justify postponing systemic therapy until the postpartum period. The literature supports that, in the presence of clearly identified invasive or multicentric disease during pregnancy, surgical management in the second or third trimester is considered safe and does not compromise fetal prognosis, and the indication for systemic therapies should be individualized according to staging and tumor biological profile[4,9,10,16]. Regarding imaging methods, ultrasound remains the initial exam of choice during pregnancy; in the presence of suspicious or inconclusive findings, diagnostic mammography is recommended, as the fetal dose is negligible. Gadolinium-enhanced MRI remains contraindicated in pregnancy but may be used during lactation without the need to interrupt breastfeeding after contrast administration, preferably after prior breast expression[4,9,16].

Prognosis is more favorable when diagnosis occurs at early stages and varies according to the presence of a palpable mass, hormonal status, and invasion. Systematic reviews show that the noninvasive form has higher local recurrence but lower rates of metastasis and disease-related mortality compared with the invasive form[9,15]. Further studies confirm that invasive carcinoma associated with Paget disease of the nipple is associated with worse overall survival compared with disease confined to *in situ* carcinoma[12].

In summary, the physiological changes of pregnancy and the immediate puerperium impair the accuracy of breast imaging methods and may contribute to delayed diagnosis of PDN, particularly in young, pregnant, or lactating women[1-4,6,9,10,16]. In this context, early biopsy of persistent lesions of the areola–nipple complex is mandatory, regardless of seemingly benign radiologic findings[2-4,6,9,10]. The choice of surgical strategy should reflect the histologic extent of the underlying disease, reserving breast-conserving surgery for cases strictly limited to the areola-nipple complex and recommending mastectomy in the presence of extensive in situ disease or multifocality, in accordance with current guidelines and evidence[3,7,8,11-14]. Adjuvant treatment should be individualized according to staging and tumor biological profile, taking into account the high frequency of HER2 overexpression in Paget disease of the nipple. This feature supports the use of specific systemic therapies in the postpartum period, including paclitaxel-based regimens combined with trastuzumab when indicated, with the aim of reducing recurrence risk and optimizing oncologic outcomes[3,8,15].

CONCLUSION

Although rare, PDN represents an important diagnostic challenge, particularly in the context of pregnancy and lactation, periods in which physiological breast changes can mask early manifestations and mimic benign conditions. This case report reinforces that persistent lesions of the areola–nipple complex, especially when unilateral, should raise a high degree of clinical suspicion regardless of age or pregnancy status. The inherent limitations of imaging methods during this period can delay the identification of underlying carcinoma, making early biopsy of the areola-nipple complex, combined with immunohistochemical evaluation, a fundamental step in the diagnostic pathway. Timely recognition of the disease allows appropriate staging, definition of the surgical strategy, and planning of adjuvant treatment according to the tumor's biological profile, with a direct impact on oncologic outcomesThus, knowledge of the atypical clinical presentations of PDN and of the diagnostic and therapeutic particularities during pregnancy is essential to reduce diagnostic delays and optimize patient care.

AUTHORS' CONTRIBUTIONS

FGS: Project administration, Concept, Writing – review and editing, Investigation, Methodology, Supervision, Validation, Visualization. DB: Writing – review and editing, Investigation, Validation, Visualization. GDA: Formal analysis, Data curatorship, Writing – first draft, Investigation. NLFM: Formal analysis, Data curatorship, Writing – first draft, Investigation. GDT: Data curatorship, Writing – first draft, Investigation. NLW: Data curatorship, Writing – first draft, Investigation. HVSH: Data curatorship, Writing – first draft, Investigation. LENT: Data curatorship, Writing – first draft, Investigation.

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