

Large Mammary Paget Disease without Underlying Breast Carcinoma

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Summary: Mammary Paget disease is an uncommon type of breast cancer. Redness, scaling, and thickness involving the nipple and areola are common clinical symptoms. Invasive breast cancer was found in nearly 90% of these patients. Only a few cases of mammary Paget disease with no underlying cancer have been described, with a better prognosis. Treatment options include wide excision or mastectomy. However, if the lesion is very extensive, breast reconstruction may be required. We reported a rare case of extensive Paget disease in a 65-year-old woman who had a 7-year history of a 14×19 cm progressively enlarging erythematous scaling lesion that covered her entire left breast. No evidence of related malignancy or metastatic lesion was seen. A left mastectomy with sentinel lymph node biopsy and immediate pedicled transverse rectus abdominis myocutaneous flap reconstruction was chosen. There is uncertainty about axillary node metastasis since multiple enlarged and palpable left axillary lymph nodes were seen. She had axillary lymph node dissection instead. A histological examination confirmed the diagnosis of Paget disease of the nipple in the absence of underlying breast cancer and there was no evidence of axillary lymph node metastasis. This article emphasizes the need to pay close attention to diagnosis, progression, and treatment of the disease. (*Plast Reconstr Surg Glob Open* 2022;10:e4606; doi: [10.1097/GOX.0000000000004606](https://doi.org/10.1097/GOX.0000000000004606); Published online 17 October 2022.)

Mammary Paget disease is a rare condition found in approximately 1% to 5% of all primary breast cancer and was recognized over 140 years ago. In 1874, Sir James Paget first described the clinical features of the disease as chronic eczematous skin of the nipple and areola which very often develops subsequent breast carcinoma within 1 to 2 years.¹ However, the etiology and treatment of this disease remain controversial.

Approximately 50% of patients present with an associated mass. Over 90% of the women in this case have invasive breast carcinoma.^{2,3} Cases with no palpable mass are more likely to be noninvasive breast cancer in about 66% to 68% of cases.^{2,3} Only one other case of large mammary Paget disease without underlying breast cancer has been reported (Table 1). We report a rare case of extensive

Paget disease without underlying breast carcinoma that underwent mastectomy with immediate pedicled transverse rectus abdominis myocutaneous (TRAM) flap breast reconstruction for treatment, to relieve symptoms and improve quality of life.

CASE REPORT

A 65-year-old Thai woman without a family history of breast cancer was referred to our hospital in July 2021. The disease had been present for 7 years. At first, it was seen as tiny red scaling patches, with an average size of 2 cm at the left nipple and areola. Despite topical and oral medicine, the patient's condition did not improve. She chose to seek alternative treatment and refused to get medical care. The illness grew worse throughout the course of the second through sixth years. She then visited the second hospital in her seventh year. An incisional skin biopsy revealed Paget disease. She was then referred to our department. The patient had a 14×19 cm moist erythematous, crusty, thickened, and scaling lesion on her left breast with contact bleeding. There was no mass to be seen (Fig. 1). During the clinical examination, a left axillary lymph node was discovered.

Mammography of the affected breast was not possible due to extreme discomfort and bleeding. A left breast ultrasound revealed normal breast parenchyma with no tumor. An ultrasonography of the left axilla revealed numerous

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Fig. 1. Anterolateral view of large mammary Paget disease at the left breast.

nodes with fatty hilum loss. Fine needle aspiration of the left axillary lymph node under ultrasound guidance was done, and metastatic cancer has not been detected.

Computed tomography of the chest and upper abdomen showed no evidence of metastasis to the lungs or liver. Nuclear bone scan examination revealed no signs of bone metastasis.

The patient underwent left mastectomy and sentinel lymph node biopsy with immediate ipsilateral pedicled TRAM flap reconstruction. For this situation, we have several flap reconstruction alternatives, such as the DIEP (deep inferior epigastric perforator), free TRAM, and pedicle TRAM. The best method is the DIEP free flap; however, it has limitations because it needs microvascular surgery and more experience from the surgeon. Due to the lack of plastic surgeons in our situation, our oncoplastic breast surgeon opted for pedicle TRAM. To assure the vascular supply of the flap, we used indocyanine green (ICG), and the flap with zones I, II, III, and half of zone IV were included. Numerous left axillary lymph nodes were visible intraoperatively, and they were not stained by isosulfan blue. Regarding the uncertainty of axillary lymph node (LN) metastasis, a dissection of the axillary lymph nodes was performed (Fig. 2).

Gross examination revealed the left mastectomy specimen consisted of a breast measuring 23 × 22 × 3.5 cm. The covering skin showed a huge area of irregularly nodular surface, grayish brown discoloration, measuring 21 × 19 cm and free of all resection margins. In the serial section, there was no mass or lesion. No metastasis was found in 18 excised axillary lymph nodes.

Hematoxylin and eosin staining histology demonstrated the presence of scattered, numerous Paget cells with large, pale vacuolated cells with abundant cytoplasm, varying in size of basophilic and hyperchromatic nuclei, and the presence of mitotic figures. Without invading the dermis, the cells lie throughout the thickness of the epidermis (Fig. 3).

The findings of the immunohistochemical investigation were CEA positive, CK5/6 negative, CK7 positive, ER negative, PR positive in 10% of Paget cells, HER-2 positive

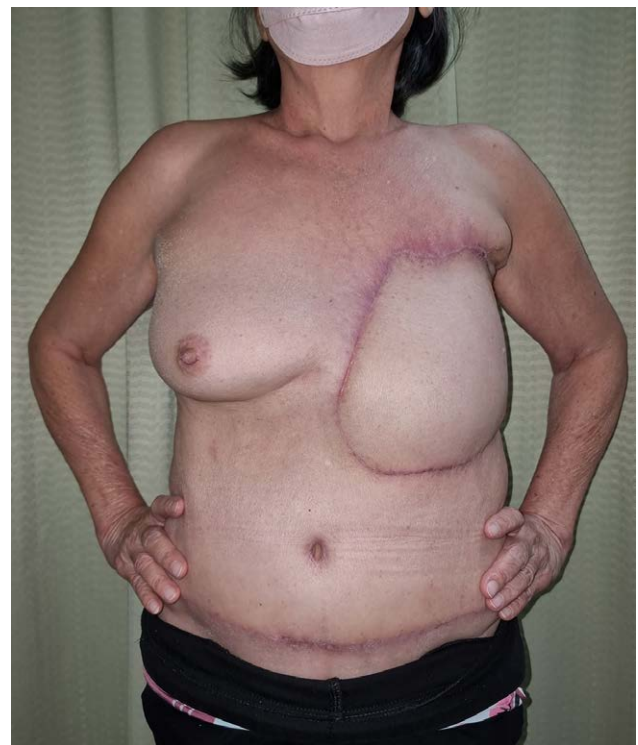


Fig. 2. Postoperative view after performing left mastectomy with axillary lymph node dissection with a pedicled TRAM flap.

3+ (staining in approximately 90–100% of Paget cells), and Ki-67 positive in 60% of nuclei. CD138 was negative, and P53 detected only membrane staining with no stain in other breast regions.

DISCUSSION

Mammary Paget disease is a rare condition and may be difficult to diagnose. The pathogenesis of disease is still inconclusive. Two widely accepted hypotheses that explain the origin and nature of the phenomenon are the epidermotropic theory^{1,4} and the in situ malignant transformation

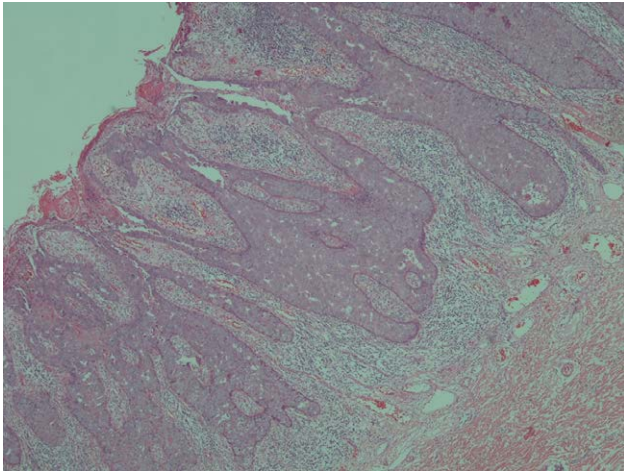


Fig. 3. Histopathological findings of resected tissues: pagetoid cells with many vacuolated cells occupying mainly the basal cell layer without invasion (H&E, × 100).

theory.^{1,5} The epidermotropic theory states that the cancer cells originate from the intraductal epidermis and migrate along the duct and spread through the lactiferous sinus to the nipple.⁴ Nevertheless, this rare case of mammary Paget disease appeared only within the nipple epidermis and was not associated with underlying malignancy. Another hypothesis explains that the case was an in situ malignant transformation. Paget cells arise in the nipple epidermis as malignant intraepithelial cells and form in situ independently of the underlying breast cancer. Hemidesmosome attachment between keratinocytes of the epidermis and Paget cells as an intracellular bridge of keratinocytes was found.⁶

Mammary Paget disease affects 1% to 5% of all breast cancers. An underlying invasive breast cancer or ductal carcinoma in situ is found in 80% to 90% of cases.^{1,2,4,5} Only rare patients appeared primarily within the nipple epidermis.^{2,3,5}

Mammary Paget disease may be confused with chronic eczema, dermatitis, psoriasis, Bowen disease, or malignant melanoma. Bowen disease histology reveals dyskeratotic cells with a squamous origin. Pagetoid cells with epidermal mucin can be seen in this condition, but unlike Paget disease, they do not form in the glandular structure. In mammary Paget disease, CEA, EMA, and CAM 5.2 may be positive, but not in Bowen disease. In Bowen disease, CK5/6 is positive, whereas in Paget disease, it is negative. Another common differential diagnosis, especially in pigmented Paget disease, is malignant melanoma that generally tests positive for S-100 and HMB-45. Paget cells and Toker cells can be distinguished by the presence of CD138 and p53, which are positive in Paget cells but negative in Toker cells. Nearly 90% of cases of mammary Paget disease have excessive HER-2 expression.⁵

Our case showed one of the small number of mammary Paget disease patients without an underlying carcinoma. From previous reports, only the case of Shibata et al was not linked to an underlying malignancy⁷ (Table 1). In our patient, this is another case of extensive pure mammary Paget disease. The histopathology from serial sections

Table 1. Case Series and Case Report of Large Mammary Paget Disease

Author	Year	No. Cases	Associated Breast Carcinoma	Size	Operative Technique
Shibata et al ⁷	2004	1	No	15 × 15 cm	Muscle-sparing mastectomy with sampling of an axillar lymph node
Helman and Kliman ¹	1956	27	Yes: invasive carcinoma	9 × 7 cm	Simple mastectomy followed by deep X-ray therapy
Bernhard ⁸	1966	3	Yes: invasive carcinoma with axillary lymph nodes metastasis	8 cm	Bilateral radical mastectomy
Nicoletti et al ⁹	2004	1	Yes: invasive carcinoma	Upper and the inferior lateral quadrants of the right breast, the axilla, extending 5 cm beyond the posterior axillary line, and up to the medial aspect of the proximal one-third of the arm	Mastectomy and ALND with pedicled myocutaneous latissimus dorsi flap (flap size 20 × 12 cm.)
Kanwar et al ¹⁰	2007	1	Yes: ductal carcinoma in situ	25 × 25 cm	Mastectomy with STSG

STSG, split-thickness skin graft; RT, radiation therapy; ALND, axillary lymph node dissection.

showed that there was no invasive or in situ in the underlying breast. Immunohistochemistry such as HER-2 positive, CK5/6 negative, CK7 positive, CD138 negative, p53 and CEA positive helped us to confirm the diagnosis of this disease. All of this information supported the belief that the disease was confined to the nipple and breast skin, which could be explained by the hypothesis of in situ malignant transformation, although it was previously postulated in rare cases. However, there are a small number of cases and variable nature of mammary Paget disease currently. More data can help us to explain the pathophysiology of this disease.

CONCLUSIONS

Mammary Paget disease without underlying breast cancer is a rare occurrence, particularly in large patients. The importance of accurate investigation and diagnosis cannot be overstated. The origin of this condition in situ malignant transformation is supported by a notion. Patients with extensive Paget disease may experience pain, bleeding, or ulceration. To improve survival and quality of life, complete surgical excision is required.

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REFERENCES

1. Helman P, Kliman M. Paget's disease of the nipple; a clinical review of 27 cases. *Br J Surg.* 1956;43:481–488.
2. Ashikari R, Park K, Huvos AG, et al. Paget's disease of the breast. *Cancer.* 1970;26:680–685.
3. Kollmorgen DR, Varanasi JS, Edge SB, et al. Paget's disease of the breast: a 33-year experience. *J Am Coll Surg.* 1998;187:171–177.
4. Muir R. The pathogenesis of Paget's disease of the nipple and associated lesions. *Br J Surg.* 2005;22:728–737.
5. Karakas C. Paget's disease of the breast. *J Carcinog.* 2011;10:31.
6. Sagebiel RW. Ultrastructural observations on epidermal cells in Paget's disease of the breast. *Am J Pathol.* 1969;57:49–64.
7. Shibata K, Nozu S, Tanaka T, et al. Gigantic mammary Paget's disease of a very elderly woman. *Surg Case Rep.* 2018;4:134.
8. Bernhard CM. Paget's diseases (cancer of the breast): clinical discussion and report of three cases. *Ann Surg.* 1966;163:931–936.
9. Nicoletti G, Scevola S, Ruggiero R, et al. Gigantic Paget disease of the breast. *Breast.* 2004;13:425–427.
10. Kanwar AJ, De D, Vaiphei K, et al. Extensive mammary Paget's disease. *Clin Exp Dermatol.* 2007;32:326–327.