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A peculiar case of Paget's disease of the breast

Mammary Paget's disease is a disorder of the nipple-areola complex of the breast that, while rare, is often associated with an underlying carcinoma. The typical aspect is usually an eczematoid change of the nipple or a red and ulcerative nipple's lesion or erythematous and crusted lesion, with or without mass-like lesion and infiltration and inversion of the nipple. It was described at first by Sir James Paget in 1874, [1] who classified the disease in mammary and extramammary type.
The mammary type (Paget' s Breast Cancer: PBC) has rare frequency. PBC occurs in 0.5-5% of all cases of breast cancer, it affects the mouth of the excretory ducts of the nipple, which is characterized by lesion of nipple's large ducts. PBC can be a superficial lesion or a nodule-tumor and it can be associated with underlying carcinoma in situ (DCIS) in more than 95% of cases, especially in postmenopausal women.
In a small percentage of cases, PBC can also be associated with an invasive breast cancer. Accuracy in the diagnostic phase, in order to distinguish PBC from others diseases is paramount and histological examination of lesion's biopsy has a crucial role. Prognosis and treatment depend on the type of underlying breast cancer and are based on the stage of cancer, but more importantly, on the prompt of an adequate multidisciplinary diagnostic pathway.

KEY WORDS: Histopathological Report, Oncological Outcomes Paget's Breast Cancer

Case Report

Last year, we observed a postmenopausal female patient (61 years old) with a very complex clinical history (drug allergy, cardiomyopathy, osteoporosis, upper body seborrheic keratosis and a history of a benign right side breast tumor removal 13 years before). The woman attracted our scientific interest for several reasons.
She underwent the main radiological studies used to enhance the visualization of the suspected signs of Paget breast cancer (Fig. 1).
She also underwent first level radiological exams (a mammography, a breast and axillary region ultrasound; Figs. 2, 3) and second level radiological exam (a mammopraphy with contrast medium CESM and a whole-body contrast-enhanced CT). The Ultrasound (US) report showed an evenly hypoechoic thickening of the superficial planes of the left breast and the presence of an enlarged axillary (5 cm in diameter) lymph node with a thickened cortical layer (Fig. 3).

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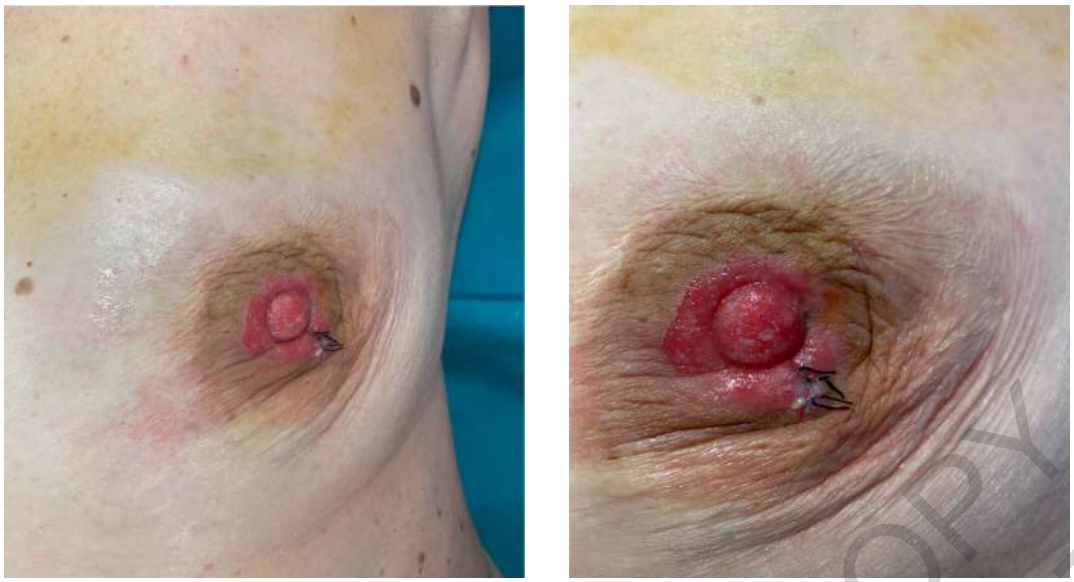

Fig. 1: Clinical aspect Paget Breast Disease.

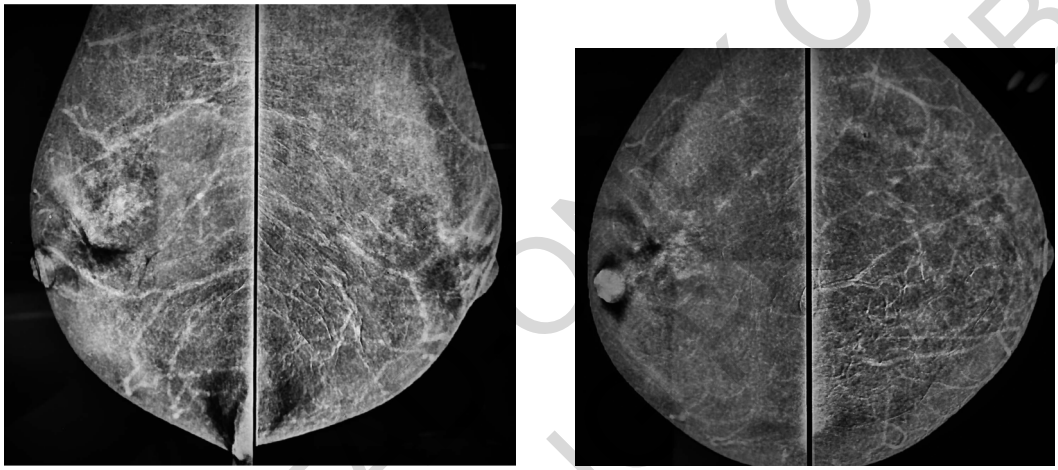

Fig. 2: Mammography.

A Contrast-Enhanced Spectral Mammograph (CESM) with the injection of 1,5 ml contrast medium per Kg (1,5 ml/Kg) followed, with no signs of a pathological outbreak.

In this clinical case, it would have been desiderable to perfom a MRI but the patient had a relative contraindication to such examination.

In consideration of suspicion of Paget's Breast Cancer, a contrast-enhanced Computed Tomography was performed, but no distant metastasis were present. The CT scan showed a thickened aspect of the (Nipple Areola Complex) NAC's skin on the left side and an axillary lymphadenopathies' clusters with an ovular morphology and a short longitudinal axis.

Before surgery, a biopsy of the patient's left NAC's lesion was carried out and the result confirmed the presence of Paget's disease of the breast. Histopathologically, the typical indicators of Paget's disease are usually a thickened epidermis, papillomatosis, hypertrophy of the interpapillary ridges, superficial hyperkeratosis, and the characteristic Paget cells, which have a clear and abundant cytoplasm, hyperchromic nucleus, positive for acid-Schiff staining (PAS) resistant to diastasis due to the presence of neutral polysaccharides(the glandular origin of Paget's cells). These Paget cells are localized at the surface layer of the areola and the nipple as single cell or small groups of cells.

The patient refused both a fine-needle-aspiration of the lymph-node and neoadjuvant protocol and underwent surgical treatment (left radical mastectomy and total left axillary lymphadenectomy), because of a suspected metastatic axillary disease, as A.N.I.S.C. protocols suggest. Fearing recurrence, the patient refused breast-conserving surgery. Total axillary dissection was chosen because of the suspect signs of invasion at pre-operative work-up and in order to customize treatment according to the patient's requirements.

The case report was interesting for several reasons:

– the patient presented a red eczematoid lesion of the left nipple-areola complex. Before being evaluated by a

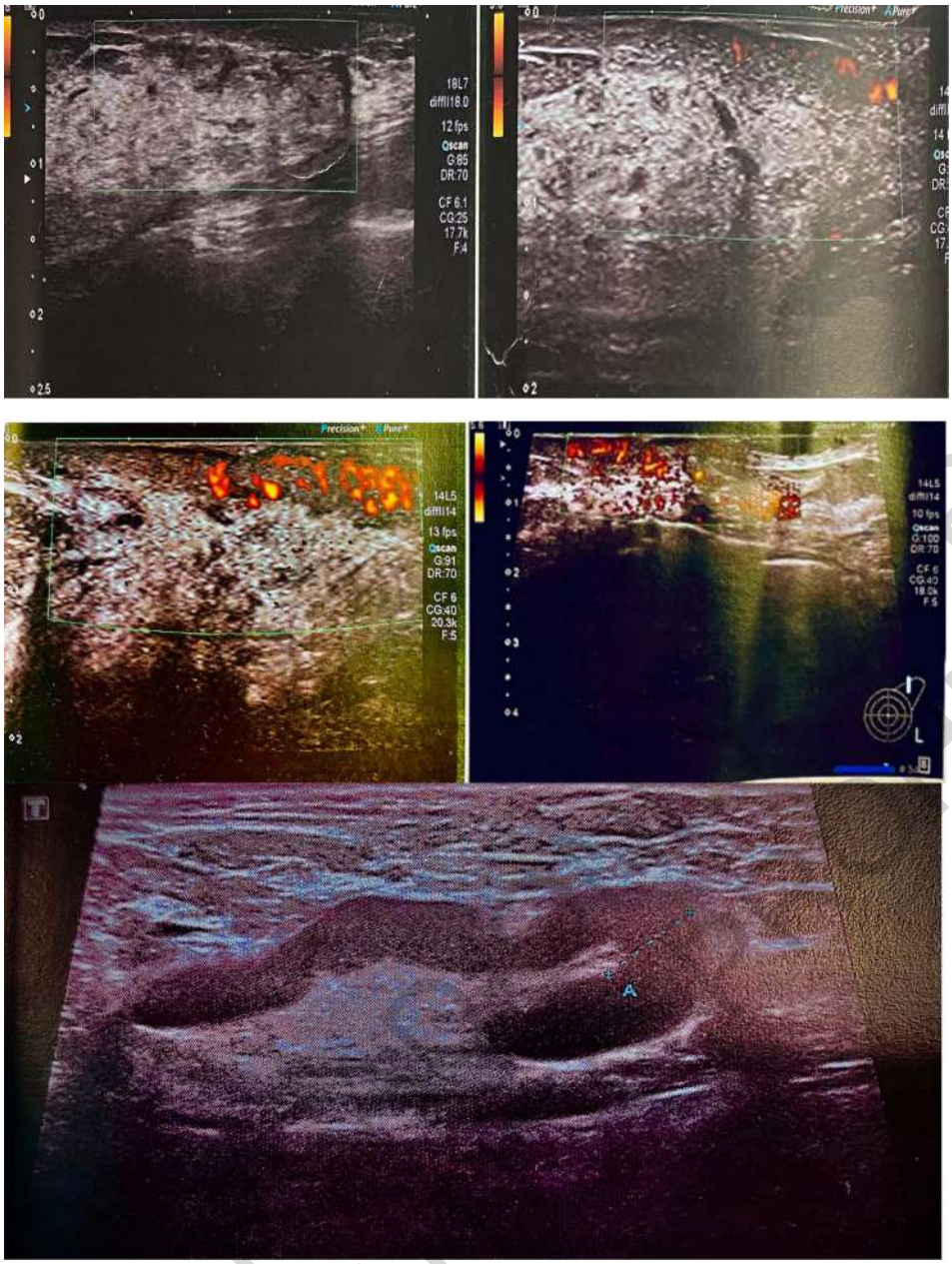

Fig. 3: Breast and axillary US in PBC.

breast specialist, the lesion had been incorrectly treated as a dermatologic affection for several months;
– the patient in 2008 underwent a large excision of right mammary parenchyma and sentinel node excision for a tumor with uncertain but not malignant behavior, as reported beforehand;
– she had a family history of breast neoplasms;
– her clinical history was characterized by several comorbidities with significant psychological negative effects and a resultant personality that we had to consider in order to formulate a personalized approach.
A microscopic examination of the breast confirmed the diagnosis.
The left mastectomy and ipsilateral axillary lymphadenectomy of this patient, fixed in formalin, was submitted to our Histopathology Laboratory and subjected to macroscopic exam (Figs. 4 A, B, C, D; 5).
It was around 16,5x11 cm in size with a 14x7 cm skin patch, including the areola-nipple complex with a red-pink eczematous scaly lesion. When cut, an underlying withish area, no more than 2 cm in diameter, of increased consistency was found. The surrounding parenchyma looked adipose. Eight lymph nodes, some whitish in colour, were found in the axillary adipose tissue. The formalin-fixed paraffin-embedded tissue material was cut in 3-4 µm thick sections and deparaffinised. The sections were stained with hematoxylin-eosin.
The characteristic histopathologic feature was the presence of adenocarcinoma cells (Paget's cells), singly or forming clusters spread throughout the basal portions of

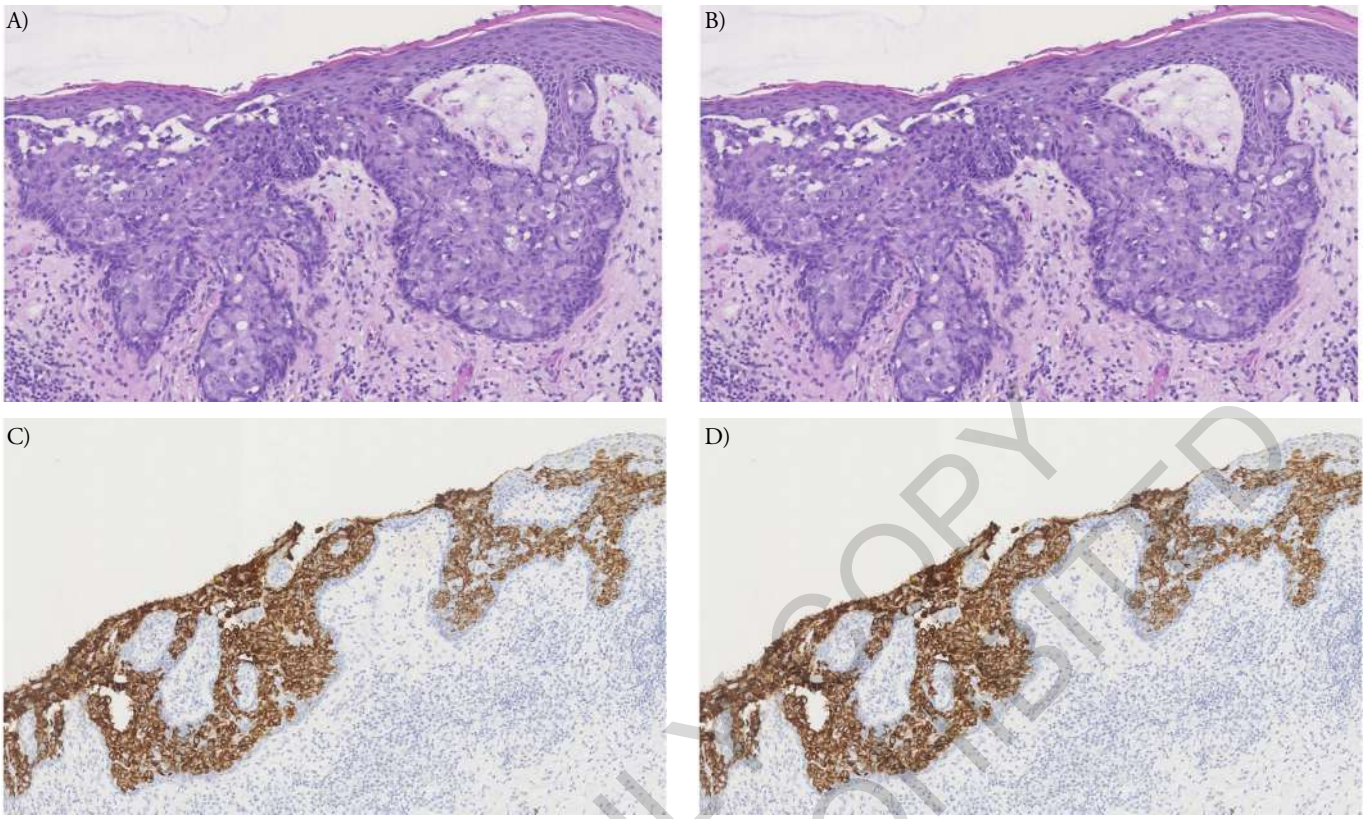

Fig. 4: A) Paget: carcinoma cells form a band in the deep epidermidis and they are scattered individually throughout the squamous epithelium (HE, 20x); B) Paget: intraductal carcinoma in terminal lactiferous ducts, with foci of stromal microinvasion (HE, 4x); C) Paget: cytokeratin reactivity. Paget's cells are CK7-positive (anti-CK7, 10x); D) Paget: HER2/neu. Strong membrane staining for HER2/neu protein highlights Paget's cells in the epidermidis (20x).

the nipple epidermis (Fig. 4A). The cells contained abundant pale cytoplasm and large irregular nuclei with prominent nucleoli. The underlying dermis showed a mild chronic inflammation.

Remarkably, an intraductal carcinoma was found in a terminal lactiferous duct in continuity with overlying Paget's disease with foci of stromal microinvasion (Fig. 4B).

On the other hand, there was no other invasive carcinoma elsewhere in the nipple and breast. Paget cells showed an expression of low molecular weight cytokeratins, such as CK7 (Fig. 4C) and HER2 (3+) protein overexpression (Fig. 4D) by immunohistochemistry. Surrounding keratinocytes were negative. ER and PR showed no staining of nuclei and the Ki-67 receptor was expressed at 30%.

The pathologic examination of axillary specimen showed massive metastasis in four out of eight lymphnodes (Fig. 5). They had the same immunoprofile (positive staining for CK7 and HER2) of Paget's disease and underlying microinvasive intraductal carcinoma in a terminal lactiferous duct in continuity with overlying Paget's disease of the left NAC.

The case report was particular interesting because the Paget was associated with and contiguous to an underlying galactophoric adenocarcinoma in the terminal lactiferous duct. However, this intraductal carcinoma had also a microinvasive aspect with a high Her-2 like profile score 3+(ER and PgR negative) and a middle-high proliferative feature as Ki-67 of 30% .

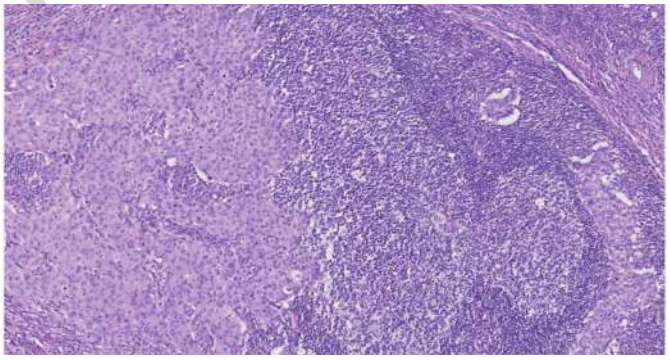

Fig. 5: Paget: Axillary lymph node and metastatic breast carcinoma Paget(HE, 10x).

The proliferation marker Ki-67 is usually an independent prognostic parameter, based on a strong correlation with the grading aspect (G1-2-3) [2]. Ki-67 has a similar behavior to Grading (G) associated with proliferation, as

similarly higher tumor stages or higher nodal status that indicates a more aggressive tumor.
In a Paget patient, conservative or demolitive surgery can be performed and a complete axillary dissection can be carried out in patients with clinically positive lymph node and/or a positive sentinel lymph node biopsy. If Paget's disease is linked to an invasive cancer, a mastectomy and total nodal dissection are the goal standard procedure, as was the case in our experience.
This combined biological aspect and molecular subtype might affect disease prognosis and decrease the changes of survival. These two parameters justified the choice of an adjuvant chemotherapy (EC+paclitaxel scheme and HER-2 antibody therapy). In our choice of treatment, the main factors involved in therapy decision-making were the higher grading, the metastasis nodal status and the 3+Her-2score.
In this case report, the follow-up period will last for approximately a further 6 months and no local recurrence has developed because a mastectomy was performed. This patient has been monitored carefully now for an entire year.

Discussion

The case report was illuminating because we found Paget's breast disease in conjunction with a micro-invasive high-grading ductal carcinoma and lymphatic metastasis.
The disease was associated with and contiguous to an underlying galactophoric adenocarcinoma, in the form of an intraductal carcinoma in the terminal lactiferous duct. However, this type also had a microinvasive aspect with a Her-2 like profile score 3+, ER and PgR status negative and a middle-high proliferative feature with Ki-67 at 30%. The intraductal carcinoma was in a terminal lactiferous duct in continuity with an overlying Paget's disease, with foci of stromal microinvasion and Paget cells showing expression of cytokeratins such as CK7 and HER2 (score 3+) protein overexpression.
This particular biological profile was enough to disseminate cell clones and metastasis to axillary lymph-nodes, skipping the infiltration of the rest of the mammary gland, showing a lymphatic predilection.
This histological finding, in our opinion, can reinforce the basic "*Epidermotropic Theory*" which explains the origin of Paget's disease, suggesting that Paget's cells arise from ductal cancer cells which have migrated from the underlying breast parenchyma.
In this peculiar case report, we cannot otherwise explain the cell migration directly from NAC complex's cell surface to lymph-nodes without an invasive mass or a neoplastic agglomeration in the retroareolar ducts or in the glandular parenchyma. The unique microinvasive intraductal carcinoma of the terminal lactiferous duct had a microinvasive aspect and this biological profile was decisive in influencing the aggressive behavior of this Paget's carcinoma and the " skip-gland infiltration mechanism".
Histologically, Paget cancer can be an "in situ" or invasive, and multifocal and/or multicentric underlying cancer, but the presence of superficial Paget's type with a unique ductal microinvasive focus and high lymph-nodes metastasis is rare, as we have pointed out. The biological profile could be decisive in explaining the biological mechanism of lymphatic invasion (a Paget cancer disease at an early stage without metastasis but with a high grading Ki 67: 30%).
The steroid receptor status is inversely correlated with Ki 67 and a higher rates of HR positivity are shown in the lowest proliferating tumors, but high Ki-67 levels are associated with Her-2 positivity. In this subtype of tumors, vascular and lymphatic invasion is often associated with a high biological-profile, as in this case with microinvasive aspect and aggressive behavior (lymphatic invasion and a high proliferation activity, low steroid receptor content and overexpression of Her-2 factor).
A Chinese study, published in 2018, explored the clinicopathologic characteristics and prognostic factors of Paget's disease in 137 patients with Paget's disease diagnosed in the Chinese Academy of Medical Sciences Cancer Hospital between January 2007 and May 2016. The authors concluded that Breast Paget's disease is a slowly progressive malignancy with good prognosis, but the HER-2 positivity, a high tumor stage, an axillary lymph-node metastasis and the presence of distant metastasis are significantly associated with poor prognosis [3-5].

Conclusions

The development of a full multidisciplinary interaction between all specialists is necessary to efficiently manage and to define on the best oncological and surgical treatments for patients with Paget's mammary disease. In this unusual clinical case, the various approaches were personalized and a sequential development between different specialists followed to establish the best oncological and surgical arrangements for this patient, respectful of her preferences.
Breast cancer with concomitant aggressive Paget is associated with a lower survival outcomes, especially if a suitable treatment plan is not found and if the case involves an invasive underlying cancer or multifocal disease [6].
The case report was particularly interesting because Paget's disease was associated with and contiguous to an underlying galactophoric adenocarcinoma in the form of an intraductal carcinoma in the terminal lactiferous duct, but this intraductal carcinoma had also a microinvasive aggressive aspect. This particular biological profile sufficed to disseminate cell clones and metastasis to axillary lymph-nodes, skipping the infiltration of the rest of the mammary gland, with a lymphatic predilection.
This histological finding and the case report, in our opin-

ion, can reinforce the basic "Epidermotropic Theory"of Breast Paget Disease [7] and the authors defined this biological behavior as "*skip-gland infiltration mechanism*".

Riassunto

Gli autori presentano un peculiare caso clinico di carcinoma mammario tipo Paget, in cui si sono evidenziate delle tendenze istologiche del bio-profilo particolarmente aggressive, oltre alla rinvenuta classica manifestazione superficiale di malattia interessante la cute del complesso areola-capezzolo, e nonostante venisse riscontrato un unico focolaio micro-invasivo.
Pur caratterizzandosi per la presenza infatti di un microfocolaio in un unico dotto lattifero terminale, infiltrante la cute del complesso areola-capezzolo, in questa paziente si è evidenziato uno spiccato linfotrofismo con metastatizzazione massiva dei linfonodi ascellari omolaterali, senza poter repertare un'invasività parenchimoghiandolare intermedia o poter riscontrare altro focolaio o cluster di micro-focolai nella medesima ghiandola interessata.
Il comportamento biocellulare del Paget diagnosticato, definito dagli autori *"skip-gland infiltration mechanism",* ha influenzato pertanto le scelte terapeutiche successive, oltre alle preferenze espresse dalla paziente, che si sono fatte convogliare in una omnicomprensiva decisione multidisciplinare di trattamento personalizzato.
La particolarità del case report è proprio definita dal comportamento biologico del ritrovato istopatologico, in cui si ritrova un carcinoma intraduttale microinvasivo in un solo dotto lattifero terminale in continuità diretta con il sovrastante Paget del complesso areola-capezzolo ma con un atteggiamento biocellulare di microinvasione stromale e metastatizzazione massiva linfonodale, come pure la presenza della immunoistochimica di alto grading (Ki 67 al 30% e Her-2 score 3+) conferma.
L'aspetto istologico rinvenuto e la tipizzazione immunoistochimica relativa infatti sembrano ulteriormente rafforzare concettualmente la teoria etiopatogenetica ormai ampiamente accreditata della "Epidermotropic Theory", ma il caso presentato permette specifiche osservazioni che possono orientare verso più ampi risvolti clinico-terapeutici già a partire dalla definizione della malattia così determinata ma anche dall'attesa verifica degli outcomes successivi in base alle strategie terapeutiche prescelte, considerazioni da vagliare su casistiche allargate ad altri casi sovrapponibili.

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