MR aspects of Paget's disease of the breast: role in the staging of disease

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Purpose

To describe MRI features of breast's Paget disease in patients who present typical clinical-pathological features suggestive for the pathology, and also to value the usefulness of MRI in loco-regional staging of the disease.
Paget's disease of the breast is a rare intra-epidermal adenocarcinoma that involves the skin of nipple and areola; it is often associated with in situ or invasive carcinoma arising from underlying the main ducts or other branches of the breast. It affects between 0.5 and 5% of all patients with breast cancer and occurs most frequently between the sixth and seventh decade of life, with a mean age between 56 and 62 years at diagnosis.

Paget's disease of the breast is histologically characterized by the invasion of pagetic cells of squamous epithelium nipple epidermis. These cells are large, atypical, with round or oval with abundant cytoplasm and clear, large hyperchromatic nucleus, and clearly recognized nucleolus that express simple cytokeratins of the glandular epithelium, such as cytokeratin 7. In 90% of cases of Paget's disease of the breast oncoprotein c-erbB-2/HER2/neu is over-expressed.

Paget's disease of the breast is clinically characterized by cutaneous changes of the affected breast; it may manifest as erythematous lesion of the epidermis of the nipple and areola, chronic crusted lesion, sometimes lightly exuding, or as ulceration of the nipple with an eventual bloody. The nipple can also become eczematous, and this aspect can gradually extend to the areola up to involving the surrounding skin.

Paget's disease can present in 3 ways:
A. Not associated with cancer (5-8% of cases)
B. Associated with underlying ductal carcinoma in situ (DCIS)
C. Associated with underlying invasive ductal carcinoma (30-70%).

Clinically, a palpable mass is present in 50-60% of women with Paget's disease. In the clinical suspicion of Paget's disease, mammographic evaluation has the goal to identify a concomitant breast cancer, although having a sensitivity lower than 50% in the absence of a palpable mass. US evaluation should be considered part of the initial evaluation, especially in cases where mammography is negative.

Breast MRI can confirm the clinical suspicion thanks to its high sensitivity and can provide a fundamental support in the identification of any associated carcinoma.

Two main hypotheses attempt to explain the origin of this disease. The epidermotropic theory postulates that Paget's cells derives from a concomitant breast cancer: Paget's cells are malignant cells from an underlying carcinoma (ductal carcinoma in many cases) which migrate along the basal membrane up to reach the main ducts of the nipple's epidermis (pagetoid migration). The intraepidermal transformation theory considers nipple's Paget disease as a carcinoma in situ independent from any possible...
underlying breast cancer: it sustains the hypothesis of the degeneration of glandular totipotent precursor cells, or the malignant ‘in situ’ of already present glandular cells in sense of malignant in the epidermis of the nipple (Toker’s cells) (Fig.1).

**Materials:**

7 breast MRI was retrospectively evaluated. Patients were aged between 44 and 72 years (mean age 58.1 years) and showed clinical manifestations suggestive for Paget’s disease such as introversion of the nipple, skin thickening, erythema, discharge, blood, and itchiness.

In all Patients a complete breast examination was performed, including complete clinical breast examination, bilateral mammography, breast ultrasound and, subsequently, breast MRI.

In all patients the definitive histopathological diagnosis of "Paget's disease of the breast" was made on the surgical specimen obtained from surgery.

The clinical, pathologic and imaging findings are was evaluated and, in particular, MRI findings were correlated with the breast clinical-radiological examination. We excluded patients without characteristic clinical manifestations of nipple's Paget disease even, although the definitive histopathological diagnosis of "pagetoid involvement of the nipple or invasion”.

**Radiological methods:**

MRI study was performed with 1.5-T magnet. Patients were in the prone position and, a dedicate breast coil was used. The patients were examined in the fertile phase in the first half of the menstrual period. The MR exam includes a short tau inversion recovery sequence (STIR) in the transverse plane, a STIR sequence in the coronal plane and a turbo spin-echo sequence (TSE) in the sagittal plane. The dynamic study is performed with gradient echo sequences (GRE) 3-D acquired in the coronal plane before administration of contrast medium and repeated six times after the intravenous injection of 0.2 mmol gadobenate dimeglumine per kilogram of body weight at a rate of 2.5 ml per second followed by 20 ml of saline.

Morphological findings are mainly analyzed in the non-contrast sequences. According to the ACR BI-RADS criteria, they are: changes in the nipple-areola complex (hyperintensity in the STIR sequences), any lesions in the breast parenchyma (shape and margins), skin involvement, axillary lymphadenopathy (axillary lymphnodes larger than 1.5 cm, rounded morphology, short axis-long axis ratio # 0.5).

Findings evaluated during the dynamic study are:

- presence of increased enhancement areas in the nipple-areola complex, in the retro-areolar parenchyma or far in the breast, intensity / time curve and possible enhancement of the skin.
In all patients, MRI is performed bilaterally in order to study the other breast to exclude eventual synchronous lesions.

Placing a region of interest (ROI, 5-9 pixels wide) on the enhancement areas shown in the acquisitions after gadolinium, intensity/time curves are constructed and classified as following: curve type I: gradual and progressive increase; curve of type II: wash-in and then plateau; curve type III: wash-in and wash-out. Areas of enhancement were classified as focus, mass-like and non-mass-like.
Fig. 1: The epidermotropic theory (on the left) and intraepidermal transformation theory (on the right).

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Results

At clinical breast examination, in all cases typical nipple changes of Paget disease are present and in particular: erythema, crusted lesions, ulceration and bloody discharge.

At MRI in the T2 weighted sequences, all cases showed intense, asymmetric hyperintensity of signal in the nipple-areola complex in the breast affected by skin lesions suggestive of Paget disease. After contrast medium administration, 3 / 7 cases shows a rapid wash-in followed by a plateau phase (curve II) and 4 / 7 cases shows wash-in followed by wash-out (curve III).

In 2 / 7 cases, the breast examination (mammography and ultrasound) was negative, while MRI showed alterations of the nipple without evidence of other areas of enhancement of pathological breast parenchyma, or without suspicious enlarged lymph nodes along the main lymphatic stations (Fig.1).

In 3 / 7 cases, at MRI, areas of increased enhancement were observed in the parenchyma with mass like pattern, oval morphology, and irregular profiles with intensity/time curves type II-III: in 1 / 3 case corresponding to a large cluster of micro-calcifications, in 2 / 3 with negative mammography and ultrasound.

In 2 / 7 cases, MRI showed diffuse non-mass multicenter enhancement of the parenchyma associated to the characteristic pattern of impregnation of the nipple. In both cases, the kinetic study of the kinetics of contrast-medium enhancement showed a rapid rising phase followed by a plateau phase (Curve I / T type II). In one of these cases, in addition to the multicenter involvement of the parenchyma, there was evidence of a diffuse skin thickening and the presence of some lymphnodes with suspicious features in the axilla; in this patient, the clinical, mammographic and ultrasound exam, showed diffuse glandular dishomogeneity without evidence of space-occupying lesions.

In all patients, bilateral breast MRI allowed us to study simultaneously the contralateral breast to that affected by the skin changes : in 1 / 7 cases breast MRI identified the presence of rounded and oval spots of impregnation in the contralateral breast, with intensity/Time curve type II.

Five of seven patients (71.4%) with clinical features of Paget disease showed a concomitant cancer, in 2 / 7 cases (28.6%) mammography showed alterations: in 1 / 7 micro-calcifications (Fig. 2) and in one of these cases diffuse glandular inhomogeneity but without evidence of mass.
Fig. 2: Female, 49 years with a negative familiar history for breast cancer. A nipple ulcerated lesion with blood secretion is visible at clinical examination. Mammography, does not show any alterations in the parenchyma. MRI, shows intense and asymmetric signal hyperintensity of the nipple-areola complex with a I/T curve of type III. The patient underwent a central quadrantectomy and the histological diagnosis was of Paget disease of the nipple with only localized pagetoid invasion of the skin.

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**Fig. 3:** Female, 62 years, her physical examination showed retraction the left nipple, modest non-spontaneous oozing of blood and parenchymal thickening in the left upper-outer quadrant. Mammography showed a large cluster of microcalcifications in the left upper-outer quadrant. MRI showed, a large area of increased enhancement, with irregular profiles and mass-like type pattern in the outer quadrant of the breast extending to the nipple with a pattern of rapid and persistent impregnation (curve I/T type II). The patient underwent mastectomy with a histological diagnosis of Paget's disease of the nipple associated with invasive ductal carcinoma.

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<tr>
<th>Pt</th>
<th>Clinical Manifestation</th>
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<th>US</th>
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<td></td>
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<td>Cluster of microcalcifications in upper-outter quadrant</td>
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<td>Paget’s disease with invasive ductal carcinoma</td>
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<td>Inverted nipple</td>
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<td>III</td>
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<tr>
<td>6</td>
<td>Inverted nipple; diffuse glandular inhomogeneity; skin thickening</td>
<td>Diffuse glandular inhomogeneity</td>
<td>Diffuse glandular inhomogeneity</td>
<td>Intense, asymmetric hyperintensity of the nipple; non-mass multi-center enhancement, skin thickening</td>
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<td>II</td>
<td>Paget’s disease with invasive ductal carcinoma</td>
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**Table 1:** Clinical manifestations related to imaging and histopathological diagnosis

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Conclusion

Paget's disease of the breast is a potentially aggressive clinical and biological entity with uncertain pathogenesis. In light of these considerations, breast MRI proves to have a key role in the diagnosis of Paget's disease and its loco-regional staging. Breast MRI is important for confirming the clinical suspicion of Paget disease demonstrating or excluding the presence of associated breast cancer particularly in patients with negative mammography and ultrasound, and finally evaluating the possible lymph node involvement in the main stations of lymphatic drainage.

Breast MRI can, therefore, influence and change the choice of therapy. Patients with Paget disease of breast cancer associated with an identified underlying cancer are candidated to a neoadjuvant chemotherapy followed by surgical treatment aimed at complete removal of the associated tumor.
References


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