Breast cancer: precancerous lesions
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Precancerous lesions of the breast

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Introduction

The main breast lesions unanimously recognised as precancerous are the atypical ductal and lobular hyperplasias, the atypical columnar cell hyperplasias, the lobular carcinomas in situ, papillary lesions and proliferative radial scars [1, 2].

A typical hyperplasias are increasingly found in screening programmes when suspicious areas of the breast are core-biopsed. From the imaging point of view, the morphological appearance of precancerous lesions is usually neither typical nor pathognomonic and they can only be assessed histologically using percutaneous interventions [3].

Lobular carcinoma in situ is often found on the occasion of cosmetic surgical procedures and in women with familial risk of breast cancer.

Papillary lesions become typically symptomatic as a dark brown nipple discharge. Usually mammography is negative in these instances and only ultrasound can sometimes show a relevant duct dilatation. Proliferative radial scars can perfectly mimic a breast cancer at mammography and only a pathological examination can provide the clinician with a conclusive diagnosis.

Characterisation of premalignant breast lesions

There is currently great interest in the detection and characterisation of putative precursor breast cancer lesions because of the possibility of chemoprevention. Knowledge of the biologic features of premalignant lesions, although limited, is rapidly evolving. Premalignant breast lesions have been examined for the presence of genetic alterations and for the expression of biomarkers [4].

Genetic alterations

Genetic alterations begin quite early in selected subsets of histologically benign lesions and studies show that precursor lesions significantly overexpress estrogen receptor (ER) and that progressive alterations accompany the transition from normal cells to hyperplastic lesions and to carcinoma in situ. Biomarkers to monitor the progression to invasive breast cancer are oestrogen receptors, p53, HER2-neu and Ki67 [5].

Assessing ER status may eventually be important in the clinical management of patients with premalignant breast disease. Its most promising role may be in identifying patients with high risk premalignant disease who are likely to benefit from antihormonal drugs used as chemopreventive agents [6], as was shown by the NSABP P-1 study, or, in subjects taking hormone replacement therapy (HRT), by the Tamoxifen Italian trial [7, 8].

The p53 tumour suppressor gene has also been studied in human premalignant breast disease. Mutations of the p53 gene may contribute to the development and progression of premalignant breast disease by several mechanisms such as increased proliferation, interference with DNA repair and clonal expansion through inhibition of programmed cell death. For these reasons, assessment of p53 status may become a useful prognostic tool in the clinical management of patients with premalignant breast disease.

Nearly all studies of HER2-neu in premalignant breast disease seem to indicate that increased proliferation and cell motility are associated with amplification and overexpression of this oncogene. Evaluation of the HER2-neu status may become a useful prognostic factor in patients with premalignant breast lesions, although its clinical role still remains to be defined.

Pathogenesis

Premalignant breast lesions are thought to arise primarily from stem cells in normal terminal duct lobular units [9]. Abnormal proliferation contributes to this overall growth imbalance through alterations of several growth-regulating mechanisms. Proliferation has been studied most extensively in ductal carcinoma in situ (DCIS): an unfortunate consensus has existed for many years to dichotomise these histologically diverse lesions into high-grade (also referred to as ‘comedo’) and low-grade (‘non-comedo’) subtypes, and the results of most biological studies of DCIS, including those evaluating proliferation, have been presented in this oversimplified manner [6].

Angiogenesis and vascular endothelial growth factor (VEGF) expression were recently evaluated by immunohistochemistry in all types of human pre-invasive breast lesions dissociated with invasive carcinoma [10]. The vascularisation of normal lobules was constant, regardless of their association with lesions. VEGF expression in normal glandular structures was lower than in lesions, with the highest levels found in ductal lesions when compared with lobular lesions. No correlation was found between VEGF expression and the degree and/or type of vascularisation.
**Diagnosis of premalignant lesions**

As previously stated, very little can be done with imaging techniques to diagnose most of the precancerous lesions of the breast. Atypical hyperplasias and *in situ* carcinomas can always be expected in the presence of a suspicious non-palpable lesion of the breast, particularly in women with a strong family history of the disease and/or with history of HRT. The diagnosis can only be made by histological examination and for this reason it is mandatory to biopsy all suspicious non-palpable lesions. Fine needle aspiration, which has been a very important diagnostic tool for the last 30 years, is inadequate in these patients and highly unreliable. Precancerous lesions, in fact, often present themselves as multifocal and the chances that the needle picks them up properly are not 100%; what is needed is a core-biopsy, i.e. a procedure which will extract a sufficient amount of tissue for the pathologist to make an accurate diagnosis. The introduction of core biopsies has considerably reduced the number of surgical procedures requiring hospitalisation and has increased the capability of senologists to develop appropriate ‘preventive surgery’ interventions, since the removal of a precancerous lesion is by far the most radical and effective way of preventing a given type of cancer.

The diagnosis of single or multiple papillomatosis can certainly be made with clinical examination. Usually the patient complains of a brown discharge from the nipple or of brownish stains found in the bra. Using gentle pressure on the different sections of the areola around the nipple it is generally quite easy to induce the discharge and to identify the duct affected by the papilloma. Ultrasound can help, in very experienced hands, to see a major dilatation of the relevant duct. If the diagnosis seems very probable with these two simple clinical procedures it might be unnecessary to perform a ductal galactography which is a complex and time-consuming procedure.

Finally, radial scars are always misinterpreted as possible invasive carcinomas at mammographic examination and they should be approached as such. Only the final pathological examination (the frozen section analysis can often be unreliable) will give the definitive diagnosis (and the good news to the patient).

**Treatment**

As far as treatment is concerned, precancerous lesions of the breast require a lot of attention and need experienced clinicians to tread the fine line between the too-little/too-much approaches by combining a correct diagnosis with adequate treatment and good cosmetic outcomes.

Radial scars could be defined as unexpected good news, so in terms of treatment they should always be approached as an invasive carcinoma, even if the radiologist expresses doubt. Since they usually present as quite small lesions, a proper preoperative localisation procedure should be performed to be sure not to miss the lesion during surgery. The radiolabeled localisation procedures (ROLL) are certainly more reliable than the traditional wires, but the wires are better than taking the risk of leaving the lesion in place due to the impossibility of finding it during the operation. The patient should also be prepared for a sentinel node biopsy in case a frozen section diagnosis is required, and in case it confirms the presence of an invasive carcinoma.

Ductal papillomatosis requires a simple surgical procedure, usually performed in day surgery and under local anaesthesia. The recommended incision is around the areola for a sufficient length to lift the nipple–areola complex and identify the duct containing the papilloma. If more than one papilloma is found and more than one duct is affected it is usually accepted that the operation should remove all the main ducts underneath the nipple, going at least 2–3 cm into the mammary gland. If only one duct is affected and the patient is considering pregnancy, the procedure should be limited to the affected duct.

Atypical hyperplasias need proper excision though this should be kept to a minimum so as not to cause unnecessary cosmetic damage for a clinical condition which is not dangerous. The surgical procedure, however, needs to be complete enough to allow a proper and certain pathological diagnosis which can be the basis for subsequent prevention strategies to be discussed with the patient according to her level of personal risk, her perception of this risk and her ultimate choice.

Lobular carcinoma *in situ* (LCIS) is actually a non-malignant condition, despite its name, and many would agree with the alternative proposed definition of ‘lobular disease’ to avoid the use of the word carcinoma, which inevitably will cause concern and anxiety to the patient and her family. LCIS is probably one of the most overestimated and overtreated clinical conditions of modern medicine. It is unfortunate to see how many unnecessary re-operations and even mastectomies after conservative surgery are performed on the pure basis of the presence of foci of LCIS.

DCIS, on the contrary, is a very serious and complex condition, which is found more and more in women as a consequence of the widespread use of mammography and its ability to visualise this lesion of the breast as ‘micocalcifications’. DCIS is a precancerous lesion mostly in the sense that it can recur in the same breast, and at every recurrence it runs the risk of becoming invasive. Micocalcifications should never be underestimated and when suspicious (e.g. not present in previous mammograms, concentrated in a small area) they should be assessed by means of a core biopsy or with diagnostic procedures such as Mammotome.

Recommended treatment of DCIS is usually conservative surgery followed by antihormonal prophylactic treatment and/or radiotherapy according to the pathological grading and the risk of invasiveness. The role of radiotherapy has never been fully assessed, despite the results of at least two important clinical trials. The main limitation of radiotherapy is that it prevents proper breast reconstruction in case a mastectomy becomes necessary as a consequence of repeated recurrence of the disease. Once again, a number of factors, including patient choice, need to be considered in planning and identifying the most appropriate treatment for each individual case of DCIS.

Attempts have been made to incorporate the size of the lesion, its histologic features, and the extent of the surgical excision into a prognostic index that would direct treatment selection. One such index is the Van Nuys Prognostic Index (VNPI), which
assigns scores of 1, 2 or 3 for histologic type, width of the surgical margin, and size of the lesion [11].

Lesions with low VNPI scores are said to be suitable for excision alone; those with intermediate scores (5–7) require the addition of radiation therapy, and those with high scores require mastectomy. Although such a simplification of the decision-making process is attractive, this index has a number of limitations. The index was developed using retrospective data on 254 patients and was validated using retrospective data on 79 patients from another institution. The use of the classification system is dependent on the reproducibility of the individual components. Because the histologic classification scheme and method of tumour measurement are not universal, or even in routine use, this is a significant issue [12].

Finally, although the VNPI is based on factors that most clinicians would consider important in predicting the behaviour of DCIS, whether these are the most important factors in determining outcome is not clear. In a subsequent report [13], the authors of the VNPI noted that, when DCIS was widely excised to negative margins, nuclear grade was not a predictor of recurrence in patients treated with excision alone or excision and radiation therapy. As noted previously, age and family history of breast carcinoma have been suggested to influence the risk of local recurrence in retrospective studies. For these reasons, several clinicians do not believe that VNPI is an appropriate substitute for an individualised assessment of the risks and benefits of the available treatment options for DCIS.

**references**