Journal of BUON **10:** 271-275, 2005

CLINICAL CASE

Invasive micropapillary carcinoma of breast: case report with literature review

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Key words: breast cancer, micropapillary breast carcinoma

Case presentation

An 81-year-old woman presented with a one week history of a discrete breast lump in the upper outer quadrant of the left breast. Clinical and radiological appearances suggested that the mass was malignant. Core biopsy was undertaken and histopathological examination showed a grade 2 invasive carcinoma, which was oestrogen receptor (ER) positive (100% of cells showed predominantly strong immunoreactivity; Allred score = 8 (range 0-8). She underwent left wide local excision and sentinel lymph node biopsy.

Histopathology of the therapeutic excision showed a 19 mm, grade 2 (T2, P3, M2), invasive micropapillary carcinoma (IMPCa) (Figure 1) with associated high grade ductal carcinoma *in situ* (DCIS). Foci of lobular neoplasia/lobular carcinoma *in situ* (LCIS) were also present. Despite extensive sampling of the tumour no lymphovascular invasion was identified and there was no evidence of metastasis in the 4 axillary lymph nodes received.

The carcinoma showed no membrane immunoreactivity for HER2 (score = 0, range 0-3) but showed positivity on the apical/stromal aspect (and focally on the luminal surface, when present) of the carcinoma cells for EMA (MUC1) with a reduction in E-cadherin staining noted at the apical/stromal aspect of the carcinoma cells clusters compared to the staining seen between the tumour cells (Figure 2). Following surgery, she underwent postoperative adjuvant radiotherapy and was advised to take tamoxifen (20 mg/day) for 5 years.

This case is an unusual variant of IMPCa of the breast which is normally reported to be an aggressive rare type of invasive breast cancer and is often associated with lymphovascular invasion, lymph node metastasis and thus a poor prognosis. The tumour in this patient was amenable to treatment, with potentially good prognosis as predicted by the Nottingham Prognostic Index [1] (NPI score 3.38).

Breast cancer is the leading cause of cancer-related death amongst women [2]. Various histological types of

Received 21-12-2004; Accepted 28-01-2005

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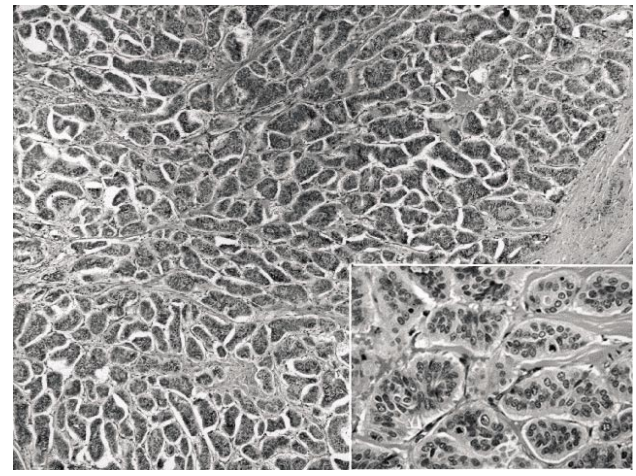

Figure 1. Main image: invasive micropapillary carcinoma (low -power, H&E). Islands of tumour cells are seen within clear spaces. Insert (high-power, H&E): tumour showing islands of high cytonuclear grade carcinoma cells.

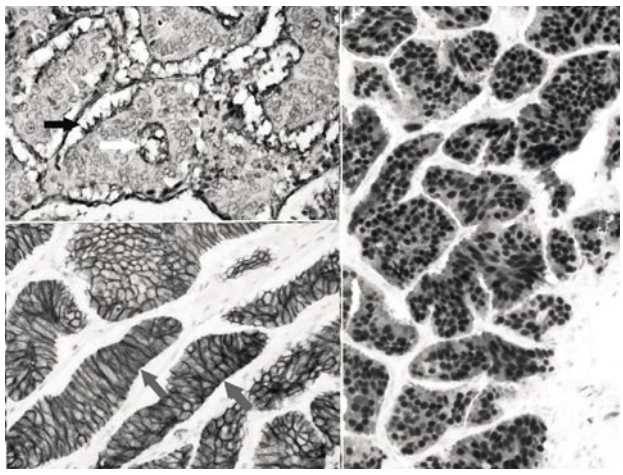

Figure 2. Top left: Epithelial membrane antigen immunohistochemistry. Black arrow shows positivity at the periphery of the carcinoma cell islands; white arrow shows positivity within the sparse central lumina present.
Bottom left: E-cadherin immunostaining. Grey arrows show no reactivity at the peripheral aspect of tumour cells (at the junction with surrounding spaces) but membrane reactivity is seen between tumour cells.
Right: Strong and moderate positive staining is seen in all tumour cell nuclei for oestrogen receptor.

invasive breast cancer have been identified, including the relatively recently described variant IMPCa of the breast. This has been reported to be an aggressive form of breast cancer with unusual histopathological features. The first example of IMPCa was retrospectively noted in an illustration in a series reported by Fisher et al. [3]. Its unique clinicopathological features were not described in detail until 1991 when Pettinato et al. [4] described in a study of 37 patients a "pseudopapillary (serous-like) carcinoma". Later, Peterson et al. [5] and Siriaunkgul and Tavasolli [6] described 13 and 9 cases, respectively, coining the term invasive micropapillary carcinoma with an "inside out" papillary growth pattern, with reverse polarisation of the papillary epithelial cells, as demonstrated by the position of the microvilli on the tumour cells [7] and by immunohistochemical studies [8]. Since then, other case series have been published, all confirming the unusual biological and histopathological features.

Epidemiology

The true incidence of IMPCa is unclear; Walsh et al. [9] described the largest series study to date, of 80 patients, and estimated that up to 7% of breast cancers may contain areas with morphology of this histological type. The pure form is rarer, comprising between 1.2% and 2.3% [9,10] of invasive breast carcinomas. IMPCa is said to occur at a younger age than other breast cancer [11,12]. Patients usually present with a palpable mass [13], but few cases are picked up by mammographic screening programs. However, IMPCa shows marked lymphotropism and most studies report that nearly 90% of women present with axillary lymph node involvement [13]. IMPCa has also been reported in men [13].

Investigations

Radiology

As with other breast cancers, assessment of these patients should include routine mammography, ultrasound and either fine needle aspiration or core biopsy. Gunhan-Bilgen et al. [14] reported the mammographic and sonographic findings in a series of 16 patients with histologically, diagnosed IMPCa; mammographically the tumour appears as a high-density mass with spiculate margins. There may be associated microcalcification, either isolated within the mass or outwith it, of either pleomorphic or punctuate appearance, or both, often in a clustered or segmental distribution. On ultrasonography, the tumour appears hypoechoic with a homogenous echotexture [14]. MRI studies are not well documented, but in a single case report Wong et al. [15] reported that the lesion was hypointense on T1 weighted images with an irregular margin and patchy intralesional enhancement, features which are highly suspicious of malignancy.

Histopathology

Fine needle aspiration cytology (FNAC)

Several studies have attempted to identify the cardinal cytological features of IMPCa. Pettinato et al. [16] described the cytological findings of IMPCa from samples obtained by fine needle aspiration. These were round, angulated, cohesive clusters of neoplastic cells with a pseudopapillary configuration. Single cells had a high nuclear grade with intact cytoplasm. Ng et al. [17] found similar patterns in their cytological examination of fine needle aspirates, describing the cells as three-dimensional tumour cell balls, abortive and sometimes branching papillae, angulated tumour cell clusters, morules and occasional acini. It was noted that the morules clustered together and were separated from each other by small, slit-like spaces. However, the definitive cytological feature of IMPCa

is the "inside out" appearance of the carcinoma cells [15] and it is often difficult to differentiate IMPCa from papillary and other forms of breast carcinoma on FNAC alone.

The gross macroscopic appearance of the excised IMPCa is not specific [13]. It appears as a firm solid mass with ill-defined margins and a solid, gritty, grey-white cut surface [10]. However, IMPCa has a distinctive low-power microscopic appearance, characterised by pseudopapillary structures surrounded by empty clear spaces [13] which are said not to be present in frozen sections [18], raising the possibility that these spaces are in fact artefactual. IMPCa is often found associated with an invasive ductal carcinoma / no special type (NST) lesion as a mixed tumour and the transition in histology can be clearly seen on low-power microscopy. Despite the variation in appearance they are also often of the same histological grade [19].

The structures are described as pseudopapillae because, unlike true papillae, the finger-like projections lack a fibrovascular core. The pseudopapillae have an "inside out" appearance, first described by Petersen [5], with reversal of the normal epithelial cell polarization. Thus the apical pole is orientated towards the stroma. Luna-More et al. [7] demonstrated the presence of microvilli on the carcinoma cell surface facing the stroma. Typically, one pseudopapillary structure is seen within each clear space [13] which is separated from other spaces by delicate strands of fibro-collagenous stroma. The majority of tumours are reported to be of histological grade 3 (68-87%) [9,13]. The neoplastic cells are often pleomorphic and hyperchromatic with large nuclei in a fine granular cytoplasm, which may be more eosinophilic than comparable ductal carcinomas [13,19]. Intracytoplasmic vacuoles may be seen.

One of the most prominent features of IMPCa is the marked lymphotropism of these tumours. Siriangkul's and Tavassoli's [6] first description of this carcinoma type estimated that the percentage of cases presenting with lymph node metastasis was 44%, but several later studies have reported figures as high as 90% with nodal metastases at the time of diagnosis [11-13,20]. This is not related to late presentation, rather the tumour metastasizes early as confirmed by series examining primary tumour size and the extent of lymph node metastasis [9]. Walsh et al. [9] found that 75% of tumours < 0.5 cm already exhibited spread to the axillary lymph nodes, all in micrometastatic form. This is higher than for other small invasive breast cancers, as shown in a series of 12,950 patients reported by Maibenco et al. [21], who estimated that 9.6% of tumours < 0.5 cm had lymph node disease. It is this propensity to metastasize at an early stage that gives IMPCa a poor prognosis relative to other breast carcinomas. Nevertheless, stage for stage, the prognosis of patients with IMPCa is as for any other breast cancer [19].

Molecular markers

Whilst steroid receptor status often reflects the differentiation of a breast carcinoma with a loss of steroid receptor expression associated with a more poorly differentiated lesion [13] (and thus a lower likelihood of response to hormone therapies such as tamoxifen, and a poorer prognosis), paradoxically, some groups have reported that the majority of IMPCa tumours are strongly ER-positive (68-91%) [9,10,20]. Conversely, others have suggested that most IMPCa cases are ER-negative [13,18]. Similarly, the proportion of IMPCa expressing progesterone receptor in the literature ranges from 20 -70% [9, 13]. No studies have described the behaviour of ER-positive IMPCa compared with ER-negative IMPCa but the consensus is that IMPCa prognosis can still be accurately predicted using the NPI [2,22].

Overexpression of HER2 is seen in approximately 20-30% of invasive breast carcinoma and is associated with a poorer prognosis. There is emerging evidence that HER2 may confer a degree of tamoxifen resistance in tumours which are ER-positive [23]. HER2 staining appears to be more frequently overexpressed in IMPCa, as demonstrated by Pettinato et al. [13], who reported that up to 95% of IMPCa cases showed significant staining for HER2. Other case series have noted that 50-60% of IMPCas overexpress HER2 [9,18], but even these series have found that higher proportions of IMPCa express HER2 when compared to equivalent carcinomas of NST. This overexpression of HER2 may potentially contribute to the aggressive nature of this tumour and may have implications for the use of tamoxifen when treating these patients.

As part of the investigation of the reverse polarity of the cells, Nassar et al. [8] examined the cellular localisation of the surface glycoprotein MUC1. MUC1 is expressed on the cell membranes in a variety of different tissue types but is exclusively present on the apical (luminal) surface. Thus, in normal breast, MUC1 is found on the apical/luminal surface of the epithelial cells lining the ducts and in other invasive carcinomas it can be seen immunohistochemically lining tubular and glandular structures, but in IMPCa MUC1 is strongly expressed on the stromal-facing (basal) surface of the neoplastic cell clusters. This supports immunohistochemically the

reverse polarisation of the epithelial cells in IMPCa. MUC1 is a transmembrane protein with a large rigid extracellular domain that is negatively charged; these features are thought to confer the ability of MUC1 to maintain lumen integrity in normal glandular tissue, counteracting the interaction between adhesion molecules and maintaining a lumen. Furthermore, studies have shown that increasing the expression of MUC1 results in decreased adhesion between adjacent cells and between cells and the extracellular matrix. It has been hypothesized therefore that the pattern of expression of MUC1 in IMPCa may be partly responsible for the detachment of the neoplastic cells from the stroma.

E-cadherin is also downregulated in the portion of the carcinoma cell membrane facing the fibrocollagenous stroma [13]. These are transmembrane proteins involved in calcium-dependent intercellular adhesion, specifically in epithelial cell-to-cell interactions. There is some evidence that the downregulation of E-cadherin expression is an important factor in the malignant progression of epithelial tumours [24] and the molecule is indeed considered by some to be a "metastatic suppressor gene". The absence of E-cadherin adhesion between the adjacent cell membranes of the malignant cells may contribute to the "inside out" pseudopapillary structures of IMPCa.

In an attempt to understand the genetic changes associated with the lymphotropism that occur in IMPCa, Thor et al. [25] undertook comparative genomic hybridisation (CGH) analysis to identify common chromosome alterations in the hope of finding a region associated with nodal metastasis. Losses involving 8p, whether it was loss of the entire arm or of the distal portion, and gains of 8q were the most common chromosomal abnormality observed in IMPCa. Changes in chromosome 17 and 1q were also commonly detected. Candidate genes on chromosome 8 that may be involved, include ERG3, TRAIL receptors, SCAM1, DR4 and DR5. When comparing the genetic changes between different invasive carcinoma types, it was found that the mean number of genetic changes found in IMPCa was lower than those seen in NST invasive carcinomas and in NST lesions with HER2 amplification, although IMPCa had more chromosomal changes compared to NST tumours which retained tubular histology [25].

Differential diagnosis

It is important to distinguish a primary breast IMPCa from metastatic tumours in the breast derived from primary carcinomas elsewhere, such as the bladder or ovary [13]. Ovarian serous papillary carcinoma and the micropapillary variant of transitional cell carcinomas of the bladder may metastasize to the breast and have a very similar histological appearance to breast IMPCa [14] and should be considered in the differential diagnosis. Although the mammographic appearances of metastasis may be helpful, accurate histological examination is essential. In addition, immunohistochemistry may be undertaken; cytokeratin 7 and ER positivity are frequently seen in primary breast carcinoma [26] and may not be present in metastases from other sources. Mucinous mammary carcinoma can also on occasions resemble IMPCa histologically but the carcinoma cell islands lie within pools of mucin in the former, rather than the typical clear spaces of IMPCa. MUC2 positivity is present in mucinous carcinoma and not in IMPCa [8]. Benign lesions may also occasionally mimic IMPCa, for example, the clear spaces seen in IMPCa can resemble pseudoangiomatous stromal hyperplasia (PASH) which should be excluded [18].

Prognosis

The deaths of patients with IMPCa are correlated with the frequency of positive lymph nodes and nodal tumour burden [19]. Skin invasion is also strongly predictive of an adverse outcome; Nasser et al. reported that 50% of those who died of disease had skin invasion compared to 3% of survivors [19]. A poorer outcome for IMPCa patients compared to a control group with NST invasive carcinoma has been described, but when controlled by lymph node status no statistically significant difference in survival was seen [13, 19]. Thus, stage for stage, IMPCa has a similar prognosis to other invasive breast carcinomas. The majority of IMPCa patients, however, present with more advanced disease and so the majority of cases have a poorer outcome. Factors associated with a poor outcome include a high histological grade, four or more positive lymph nodes, steroid receptor negativity and a high mitotic index [12]. These are essentially similar factors as recognized for other invasive breast cancers and are those used in the NPI (grade, lymph node stage and invasive tumour size) and the NPI has proven useful in predicting outcome in IMPCa [22].

Treatment and management

Surgical and adjuvant therapy recommended in IMPCa is similar to that of any other breast cancer stage for stage.

Conclusion

IMPCa is an unusual histological type of invasive breast carcinoma formed from pseudopapillae with reverse polarisation of epithelial cells producing tufts of neoplastic cells which nestle in artefactual clear spaces. IMPCa is an aggressive form of breast cancer that often presents at a more advanced stage compared to other breast carcinomas due to the propensity for invasion of vascular spaces and thus lymph node metastasis; it is therefore often associated with a poor prognosis. Despite this, stage for stage, this carcinoma has a similar prognosis to other breast cancers and should be treated like any other invasive breast cancer with similar staging/NPI.

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