ORIGINAL ARTICLE

Invasive micropapillary breast carcinoma: a retrospective study of classification by pathological parameters

Etienne MAHE, Marian FARAG* and Odette BOUTROSS-TADROSS

Department of Pathology & Laboratory Medicine, University of Calgary, *Department of Pathology & Molecular Medicine, McMaster University and Gander Medical Clinic, Newfoundland, Canada

Abstract

Micropapillary breast carcinoma has been recognized as a morphologically and biologically distinct form of breast carcinoma. Although data suggest that patient outcomes in cases of micropapillary breast carcinoma do not differ significantly from other breast carcinomas, the impact that a micropapillary component might have on the pathological work-up of a case of breast carcinoma remains an important point of discussion (especially as pertaining to the risk of lymphovascular disease). In this study, we perform an extensive retrospective study of the pathological parameters of seven years of breast surgical pathology cases to explore the relationship that micropapillary morphology might have with other important pathological parameters of a breast cancer case work-up (e.g. tumour size, lymphovascular invasion, lymph node status). We also analyze our data set to see if a micropapillary component would influence hierarchical classification by pathological parameters. Micropapillary features correlated with a higher frequency of ER positivity and lymphovascular invasion; there was no statistical difference between those cases with and without a micropapillary component from the perspective of other clinicopathological parameters, however. The presence of micropapillary features did influence classification, however, and produced a distinct cluster amidst comparison of other pathological variables.

Keywords: micropapillary, invasive breast carcinoma, pathological classification

INTRODUCTION

Invasive micropapillary breast carcinoma (IMC) is a rare entity in the spectrum of invasive breast carcinoma. This form of breast cancer, whether in its pure form or admixed with other types, is defined by its unique histology consisting of tight clusters of tumour cells, often arranged around central non-vascular lumena, contained within cyst-like spaces.1,2

Since the relatively recent identification of IMC in the mid 1990s, researchers have been quick to note the importance of this entity given its apparent greater risk of lymphovascular space invasion and lymph node metastasis.3,4 Early work also appeared to suggest a greater risk of higher stage disease and greater risk of death due to disease relative to other apparently more indolent histotypes of breast carcinoma.4

More recent and larger studies have borne out many of the early observations. IMCs appear more likely to invade lymphovascular spaces, tend to show more frequent lymph node metastasis and a greater number of positive lymph nodes.5-9 Studies have also highlighted the predictive value of IMC diagnosed on needle core biopsy in defining cases at increased risk of lymph metastases when compared to subsequent excision specimens.10 Other studies have suggested that axillary lymph node examination in cases of IMC are essential, especially in light of the absence of specific axillary ultrasonographic features in cases of IMC.11 Interestingly, however, modern studies question IMC histology alone as sufficient to portend a poor prognosis; rather it seems that IMC does not appear to behave significantly differently from node-status matched control invasive ductal carcinomas of the breast.12,13

Nevertheless, in addition to its unique histomorphology, a number of researchers have identified somewhat characteristic molecular
genetic features in IMC. Studies have demonstrated a remarkably high frequency of mutation or cytogenetic aberrations involving chromosome 8 in IMC cases relative to controls. A recent expression profile study of various special types of breast cancer has also suggested a unique molecular genetic disease profile for IMC.

Several studies have further undertaken to explain the remarkable tendency of IMC to invade lymphovascular spaces, even while other clinicopathological parameters would tend to suggest a relatively favourable clinical course. Several authors have suggested that the microvascular density of IMC may explain its aggressiveness: they observed a significantly higher microvascular density in cases of IMC relative to controls, also with a significant increase in higher grades and in cases with lymph node metastases. Subsequent studies have further suggested that tumour expression of tumour necrosis factor (TNF)-alpha, TNF-receptor II, loss of CD44 expression or vascular endothelial growth factor or E-cadherin overexpression may explain this increased microvascular density, possibly offering a means of targeted therapy.

In this study, we present the experience of a tertiary care centre in a recent retrospective review of invasive breast cancers. We explore how a micropapillary component relates to other clinical parameters of import in the pathological work up of an invasive carcinoma of the breast. We also perform hierarchical clustering by pathological parameters, a technique that has not yet been employed to assess the potential impact that a micropapillary component might have on the pathological classification of an invasive breast cancer. Agglomerative hierarchical clustering is an iterative statistical tool whereby data-points (or cases) are iteratively compared (in this case using Pearson’s correlation coefficient of the various pathological parameters for each case) and joined into classes on the basis of overall similarity. Similar tools are used frequently in the analysis of genomic data. From the context of analysis of clinicopathological factors, this tool has many advantages over more classical regression techniques in that it is unsupervised and does not require an a priori assignment of dependent and independent variables.

MATERIALS AND METHODS

We obtained institutional research ethics board approval to review the pathology materials and associated pathology report data of all breast cases accessioned in our institution from the calendar years of 2002 to 2009. Our institutional research ethics board assures that local research is performed in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000. The prescribed time period of review represented the most complete series of cases available to us at the time that the study was performed. Since our primary interest pertained to pathological parameters, we did not perform a review of the patient charts associated with each surgical case nor did we evaluate outcome data. Only unique cases of invasive breast cancer were included in the study (i.e. needle core biopsies, primary and secondary excisions, where applicable, obtained from the same patient were combined as one unique case inasmuch as laterality was common to all specimens). All applicable case file slides were reviewed by at least two authors (with the third as arbiter in equivocal cases) in concert with the specimen records; cases were also reviewed to ensure that the slides were representative of the tumour(s) relative to the gross specimen descriptions. Relevant pathological parameters (as recommended in the College of American Pathologists Breast Cancer Protocol were recorded for each case including: patient age at diagnosis, laterality of tumour, size, Nottingham Tumour Grade, presence of lymphovascular invasion, skin or nipple involvement, presence of lymph node metastasis (of at least micrometastasis) and number of nodes involved, TNM stage (as outlined in the AJCC 7th Edition Cancer Staging Manual) as well as ER, PR and Her2 status. Upon review of the histological slides, foci of invasive carcinoma demonstrating micropapillary features were identified and their relative percentage contribution to the total tumour volume (to the nearest 5%) was recorded; micropapillary features included tumour cells in cystically dilated spaces of any amount, with or without central luminal structures. Cases in which micropapillary features were noted with associated mucin were excluded (as these were assumed to represent mucinous lesions).

Statistical Analysis

Statistical tests including the student’s t-test, two proportion Z-test and Chi-squared test were used to compare those cases with a micropapillary component (MPP) and those cases without an identifiable micropapillary component (MPN). From within the MPP group, the receiver-
operator-curve statistic was used to assess the potential impact of a variable percentage of the micropapillary component on the likelihood of lymphovascular space involvement. Finally, agglomerative hierarchical classification using the standardized pathological parameters listed above was performed to evaluate the potential effect that a micropapillary component might have on classification by pathological parameters. Statistical calculations were performed using the XLStat Statistical package (Version 2013, Addinsoft). P-values of less than 0.05 were considered statistically significant.

RESULTS

A total of 326 unique carcinomas were available for review. From among these, 47 MPP cases were noted with the remaining 279 designated MPN (Table 1). Fourteen MPP cases (4% of total) were found to have micropapillary components occupying the entire tumour volume, with remainder having variable amounts. The mean age of those patients with a micropapillary component was 59.2 and not significantly different from the mean age of 61.4 in the MPN group (p = 0.35). There was also no difference in laterality of involvement (p = 0.25) in the cases relative to the MPN cases. Mean tumour size was 2.5 cm in both the MPP and MPN groups. The distribution of grade showed no difference between the two groups (p = 0.88). The presence of lymphovascular invasion was more frequent in the MPP cases (p = 0.034). There was also less frequent ER positivity in the MPP cases (p = 0.038); no significant difference between the MPP and MPN groups was observed for PR immunostaining. There were too few Her2 test results available for review for these data to be reliably included in the analyses. Further analysis of the MPP cases using ROC analysis demonstrated that a micropapillary component at or above 90% imparted the greatest likelihood ratio of lymphovascular space invasion, although this was not statistically significant (LR = 1.6, 95% CI = 0.62 – 4.0).

Hierarchical clustering

Agglomerative hierarchical clustering of the entire sample, incorporating all available pathological parameters (except for Her2 status as too few data points were available), derived three classes (Figure 1A). Class 1 included all but three cases with a micropapillary component and excluded those cases without a micropapillary

<table>
<thead>
<tr>
<th>Parameter</th>
<th>MPP cases (n = 47)</th>
<th>MPN Cases (n = 279)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age</td>
<td>59.2</td>
<td>61.4</td>
<td>0.35*</td>
</tr>
<tr>
<td>Laterality</td>
<td>62% left, 38% right</td>
<td>53% left, 47% right</td>
<td>0.25*</td>
</tr>
<tr>
<td>Mean Tumour Size</td>
<td>2.5 cm</td>
<td>2.5 cm</td>
<td>0.91*</td>
</tr>
<tr>
<td>Grade</td>
<td></td>
<td></td>
<td>0.88*</td>
</tr>
<tr>
<td>I</td>
<td>6%</td>
<td>29%</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>64%</td>
<td>47%</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>30%</td>
<td>24%</td>
<td></td>
</tr>
<tr>
<td>LVI</td>
<td>53%</td>
<td>30%</td>
<td>0.0034*</td>
</tr>
<tr>
<td>Skin or Nipple Involvement</td>
<td>10%</td>
<td>16%</td>
<td>0.39*</td>
</tr>
<tr>
<td>LN mets</td>
<td>38%</td>
<td>36%</td>
<td>0.95*</td>
</tr>
<tr>
<td>AJCC 7th Edition Stage</td>
<td></td>
<td></td>
<td>0.88*</td>
</tr>
<tr>
<td>I</td>
<td>28%</td>
<td>52%</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>55%</td>
<td>34%</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>17%</td>
<td>14%</td>
<td></td>
</tr>
<tr>
<td>ER positivity</td>
<td>93%</td>
<td>78%</td>
<td>0.038*</td>
</tr>
<tr>
<td>PR positivity</td>
<td>74%</td>
<td>61%</td>
<td>0.70*</td>
</tr>
</tbody>
</table>

*Applying student’s t-test
*Applying two-proportion z-test
*Applying the chi-squared test
FIG. 1A: Dendrogram of agglomerative hierarchical classification by pathological parameters. Class 1 is colored pink, class 2 is colored green and class 3 is colored red.

FIG. 1B: Profile plot of centroid parameters obtained after agglomerative hierarchical classification. This plot is a graphical representation of the different values of the parameters in the data points that form the mean values of the cases of the respective classes.
component with a specificity of essentially 100% (estimated specificity 99.8%, estimate 95% CI = 98.3-100); this result could not be replicated when the analysis was performed with exclusion of the micropapillary component. Classes 2 and 3 differed chiefly by means of grade, stage, presence/absence of lymphovascular invasion, lymph node involvement and ER/PR status: class 2 tended to show lower grade, stage and less frequent lymphovascular invasion/lymph node involvement while concurrently more frequently expressing ER and PR; class 3 demonstrated features opposite to those of class 2 (Figure 1B). Interestingly, while class 1 demonstrated similar features to class 3 in terms of grade, stage and lymphovascular space involvement, it tended to show a more close relationship with class 2 in terms of higher expression of ER and PR.

DISCUSSION

In this study we present a recent retrospective study of invasive ductal carcinomas of the breast with specific attention paid to those cases demonstrating a micropapillary component. Relative to other similarly sized studies, our data seem to corroborate the prevailing belief that invasive breast carcinoma with micropapillary components does show a greater tendency to invade lymphovascular spaces than invasive breast carcinoma lacking a micropapillary component. Additionally, our data suggest that the greatest likelihood of lymphovascular space invasion was associated with a micropapillary percentage of greater than or equal to 90%, although this result was not found to be statistically significant. This latter finding is of interest from a classification perspective, however, since it is this threshold of 90% that is often required in order that other types of invasive breast carcinoma be diagnosed as “special type” carcinoma according to the WHO scheme.2

In contrast to the only previous study of comparable size and methodology,25 we did not find any evidence to suggest a statistically significant difference between tumour size, presence of lymph node metastases or tumour stage of the cases with a micropapillary component relative to those without. Although there appeared to be a difference in ER expression in the cases with a micropapillary component relative to those without, this difference was only marginally significant (p = 0.038); the meaning of this observed difference is uncertain to us, especially since this result contradicts a study of comparable sample size.25 Some potential explanations for these discrepancies may relate to differences in methodology between our respective studies: in the previous study,25 the authors compared differences in tumour size between breast carcinoma cases with and without a micropapillary component categorically, whereas ours were compared by mean tumour size; the authors in the previous study25 employed a different staging rubric (using an older version of the AJCC scheme and incorporating data on distant metastases, the latter of which was unavailable to us); and finally, the previous authors25 used tissue microarrays for their immunostaining (and thereby based their interpretations on limited tumour samples) whereas our interpretations incorporated whole section immunostains.

Although there did not appear to be major differences between our cases with and without a micropapillary component when pathological parameters were considered individually, our use of agglomerative hierarchical clustering did appear to draw a rather striking line between these two groups. This result was seen despite the fact that other variables believed to be far more important for classification (such as grade, tumour size, lymph node status, stage and ER/PR status) were also included and did not seem to drive the clustering as strongly. This latter fact may stem from the “unsupervised” approach that hierarchical classification employs whereby variables are considered together and without preset dependent and independent roles. In summary, it would seem that for the purposes of classification, a micropapillary component present within an invasive breast carcinoma should be reported (especially if it occupies 90% or more of the total tumour volume), even though other pathological parameters might not be reliably predicted by it.

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