Invasive Micropapillary Carcinoma of the Breast

An Update

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• Context.—Invasive micropapillary carcinoma (IMPC) is a distinct variant of mammary carcinoma in which tumor cells are arranged in morule-like clusters devoid of fibrovascular cores and situated within empty stromal spaces. Identification of IMPC can be achieved by the assessment of morphologic features in conjunction with the characteristic “inside-out” staining pattern of epithelial membrane antigen and sialyl Lewis X highlighted by immunohistochemical analysis. Although recognizing micropapillary architecture is often not challenging, the criteria for distinguishing between mixed and pure IMPC remain imprecise. Some mucin-producing carcinomas can also have micropapillary histology, but there is no consensus on whether these tumors are variants of IMPC or mucinous carcinomas. The molecular genetic studies demonstrate that IMPCs have distinct molecular genetic profiles, supporting the theory that they constitute distinct pathologic entities. However, genomic analyses have not identified any specific genomic aberration that may explain the distinctive morphology and clinical behavior of IMPC.

Objective.—To provide an overview on the current concepts in the diagnosis and pathogenesis of IMPC of the breast, incorporating recent molecular genetic advances and prognosis-based reclassification.

Data Sources.—PubMed search and the cited references were reviewed.

Conclusions.—The recent evolution of prognosis-based reclassification and molecular genetic advances has enhanced our knowledge of the pathogenesis of IMPC of the breast. Additional studies might reveal consistent molecular alterations that underlie the formation of the inside-out growth pattern, and they might elucidate the molecular mechanisms responsible for the unfavorable clinical behavior of IMPC.


Invasive micropapillary carcinoma (IMPC) is a morphologically distinctive form of mammary carcinoma composed of small, hollow or morula-like clusters of cancer cells, surrounded by clear stromal spaces. The neoplastic cells characteristically display a reverse polarity, also known as an “inside-out” growth pattern, whereby the apical pole of the cells faces the stroma, not the luminal surface. The IMPC is a relatively rare tumor, first described in the breast by Fisher et al.1 in 1980, where this configuration was referred as having an “exfoliative appearance.” After 13 years, the term invasive micropapillary carcinoma of the breast was proposed by Siriaunkgul and Tavassoli.2 This morphologic pattern was subsequently identified in tumors of other organs, such as urinary bladder in 1994,3 colon in 2005,4 and lung in 2006,5 and the IMPC terminology was also adopted for those tumors. An IMPC of the breast is linked to higher frequencies of lymphovascular invasion (LVI) and lymph nodal metastasis (LNM), which has gained increasing attention in the past 20 years. The reported incidence of IMPC increased in 2008, after remaining steady from 2001 to 2007, but this was most likely due to increased recognition of this histologic subtype by pathologists.6,7 Although recognizing the micropapillary architecture is typically not challenging, the criteria for distinguishing between mixed and pure IMPC remain imprecise. Some mucin-producing carcinomas can also have this growth pattern; these tumors have been called invasive micropapillary mucinous carcinoma, micropapillary variant of mucinous carcinoma, or mucinous micropapillary carcinoma by cytoclastic examination.8 Because the histopathogenetic relationship between the micropapillary subtypes of mucinous carcinoma and IMPC is unclear, there is no consensus on whether these tumors are variants of IMPC or of mucinous carcinomas. This article updates the current concepts in the diagnosis of IMPC of the breast, incorporating recent prognosis-based classification and molecular genetic advances.
**Miscellaneous Pathology**

An IMPC shows a highly distinctive architecture, characterized by tufts of cells arranged in pseudopapillary structures devoid of fibrovascular cores and surrounded by empty, clear spaces lined by delicate strands of fibrocollagenous stroma (Figure 1). The clusters often have a serrated outer border. They display an inside-out arrangement, with the luminal aspect of the cell present on the outer surface of the cluster. Accurate diagnoses of IMPC would allow timely, albeit intensive, disease management.

Pure IMPC is rare, accounting for approximately 0.9% to 2% of breast carcinomas. The amount of micropapillary architecture in a tumor required for a diagnosis of IMPC is not well established yet. Some authors have used the term *micropapillary* for lesions with micropapillary growth that constitutes at least 50% of the tumor. Others restrict the term to the tumors that consist entirely of micropapillary growth. In practical terms, at least 75% of the micropapillary component should be identified in an IDC to be classified as pure IMPC. In a series of studies by Fu et al. and Guo et al., the IMPC component was identified in 4.8% to 6.2% of invasive breast cancers. In their studies, IMPC constituted less than 25% of the tumor volume in 9 of 51 cases (18%), 25% to 49% in 11 cases (22%), 50% to 75% in 12 cases (24%), and more than 75% in 19 cases (37%). The group with more than 75% IMPC component consisted of only 1.8% of the total IDC cases (n = 1056). The authors firstly proposed that it is neither the tumor size nor the amount of the IMPC component in the tumor but the presence of the IMPC component that correlates with the aggressive behavior of the tumor. Although it appears that breast carcinomas with increasing amounts of IMPC tend toward more aggressive behaviors, Chen et al. observed that tumors that had less than a 25% IMPC component were still associated with significantly higher incidence of LVI and LNM than was IDC-NOS. Walsh et al. found that IMPCs with tumor sizes smaller than 0.5 cm (pT1a stage) showed the same trends for lymphatic spread and nodal dissemination as larger tumors with the component. Ide et al. revealed 8.4% of invasive breast cancer contained the IMPC component in their cohort of 486 patients, and noted that the presence of the IMPC component alone was a significant predictive factor for LNM, even if it was detected in only a small proportion of the tumor. The study results from Acs et al. suggested that breast carcinomas with partial reservation of the cell polarity may have the same implications as micropapillary differentiation, and these tumors may represent parts of a spectrum of IMPCs. Complete or partial reversal of cell polarity may have a significant role in lymphatic tumor spread. Some studies have shown that a retraction artifact is correlated with lymphatic invasion and nodal metastasis and predicts a poorer outcome in early stage breast carcinoma. The retraction artifact may be an early stage in the development of micropapillary architecture. These studies suggest that IDC with any well-defined micropapillary carcinoma component is diagnostic of IMPC. Based on the above findings, we recommend that any IMPC component present in a tumor be carefully evaluated, and the percentage should be clearly stated in the pathology report.
Guo et al\textsuperscript{10} found that 55% (28 of 51) of the IMPCs had dense lymphocytic infiltrates, and 96% (27 of 28) of them developed LNM, significantly more than the 61% (14 of 23) in the group without lymphocytic infiltrates. Extranodal tumor invasion is also an important feature of IMPC. Zekioglu et al\textsuperscript{28} suggested that extranodal tumor invasion was responsible for the frequent local tumor recurrence in chest walls and supraclavicular nodes.

Before the era of sentinel lymph node biopsies, the most common surgical modality for patients with IMPC was total mastectomy with complete axillary lymph node dissection. Currently, breast conservation plus sentinel node biopsies have gained in popularity for stage I and II tumors with compatible outcomes.\textsuperscript{29-31} The results of a sentinel lymph node biopsy seem to guide further surgical intervention.

Chen et al\textsuperscript{9,21} studied 100 cases of IMPC with a 10-year follow-up and demonstrated that these tumors were associated with a poor prognosis, regardless of the proportion of their IMPC component. Molecular-genetic studies have revealed that pure and mixed IMPCs are remarkably similar at the genetic level,\textsuperscript{32} and they all harbor a constellation of genetic aberrations that are distinct from cases of histologic grade–matched and estrogen receptor–matched IDC-NOS.\textsuperscript{32,33} The recent evolution in molecular techniques and prognosis-based classification has enhanced our understanding of breast IMPCs. These new lines of evidence support our statement that the presence of an IMPC component should be listed in pathologic reports to facilitate the selection of appropriate clinical management.

Invasive micropapillary carcinoma with mucinous differentiation and invasive mucinous carcinoma with micropapillary carcinoma growth pattern (IMMPC) have been described in the literature.\textsuperscript{34,35} The prognostic significance of these relatively new variants/subtypes of invasive breast cancer has not been well studied. An IMMPC is an otherwise pure mucinous carcinoma (PMC), but it contains a component of micropapillary architecture, a growth pattern similar to that of an IMPC, with tumor cells showing an inside-out micropapillary arrangement. The micropapillary arrangements may be revealed by glycoprotein expression on the cell surface facing the surrounding extracellular mucin. For diagnosis, the micropapillary architecture should constitute more than 50% of the tumor epithelial components. Liu et al\textsuperscript{36} reviewed 531 cases of archived PMC and found 134 cases (25.23%) with IMPC components that justified a diagnosis of IMMPC (Figure 2, A through C).

\begin{figure}
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\includegraphics[width=\textwidth]{figure2}
\caption{Histologic features characteristic of invasive micropapillary mucinous carcinoma of the breast. A, Neoplastic cells are arranged in a pattern resembling invasive micropapillary carcinoma within mucin-filled stromal compartments. B, Lymph node metastasis. C, Micropapillary ductal carcinoma in situ with mucin production (hematoxylin-eosin, original magnifications $\times 100$ [A], $\times 50$ [B], and $\times 400$ [C]).}
\end{figure}
Compared with PMC without an IMPC component, IMMPC was found more frequently in younger patients and in tumors with increased LNM and LVI and human epidermal growth factor receptor 2 (HER2/neu) positivity (protein overexpression or gene amplification). In a stage-matched, Kaplan-Meier survival analysis, patients with stage II–III IMMPC suffered a decreased overall survival and a decreased recurrence-free survival. However, their prognosis was still better than that of patients with classic IMPC. Multivariate analysis proved that the presence of IMPC component in PMC was an independent predictor for LNM and unfavorable recurrence-free survival of patients. This was the first study to explore the prognostic significance of IMMPC in a large cohort, and the results argued for a more aggressive management of these patients. The IMMPC seems to constitute an entity with a biologic behavior that lies between IMPC and PMC without the IMPC component, and therefore, appropriate recognition of IMMPC is clinically important. Further study is required to validate the findings.

**IMMUNOPHENOTYPE**

For routine immunoprofiles, IMPC is frequently positive for estrogen receptor (approximately 70%–94%) and progesterone receptor (approximately 50%–84%) expression. One study of 624 patients with IMPC revealed a poor prognosis in the patients who had a tumor lacking in estrogen receptor expression. The status of the HER2/neu protein expression or gene amplification in IMPC is not consistent in literature. Some studies showed HER2/neu expression or gene amplification in IMPC and in LVI. Moreover, immunohistochemistry for sialyl Lewis X is useful for distinguishing IMPCs from artifactual stromal retractions in an IDC.

E-cadherin is a calcium-dependent, cell-adhesion molecule, expressed predominately in epithelial tissues. Numerous studies have demonstrated that reduction and/or loss of E-cadherin expression in carcinomas correlates positively with tumor invasion and metastasis. Fan et al reported that E-cadherin was present on the intercellular contact surface of tumor cells but not on the outer membranous surfaces of IMPC cells. The finding suggests that the tumor clusters are not bound to the surrounding stroma, which could be responsible for the peritumoral empty spaces in IMPCs, which may also facilitate LVI and metastasis. Others also found strong expression of E-cadherin among cancer cells in IMPC. Individual tumor cells are rarely identified within tissue and lymphovascular spaces. Strong adherence of cancer cells inside the clusters suggest that IMPC tumor progression from local growth to invasion to metastasis is by means of cell clusters (cell groups), rather than by individual cells.

The study by Guo et al suggested that high expression of vascular endothelial growth factor (VEGF)-C and VEGF receptor-3 could facilitate IMPC lymph node metastasis by increasing vascular density. Yu et al reported that...
lymphatic vessels were highly permeable in IMPCs, which tend to have high lymphatic vessel density and increased VEGF-C expression. Another study also found that expression of tumor necrosis factor-α and its receptor TNFR-II were upregulated in IMPC more than in IDC-NOS, and the upregulation was associated with tumor angiogenesis and lymph node metastasis. They also observed in IMPC upregulated immunoreactivity for CD146, a molecule associated with angiogenesis, which was significantly associated with high histologic grade, lack of estrogen receptor and progesterone receptor expression, p53 overexpression, and LNM.

**ELECTRON MICROSCOPY**

Using electron microscopy, Luna-Moreira and others found that IMPC tumor cells have microvilli on their cell membranes, lining the outer surfaces of the cell clusters. This peculiar arrangement of cells within the clusters with their apical surfaces polarized to the outside supports the microscopic observation of the inside-out growth pattern. In addition, abundant filaments were identified in the cytoplasm, suggesting that IMPC tumor cells have stronger ability to move and invade than does IDC-NOS. They also noted that, in the reticular interstitium with abundant lymphatic vessels, tumor cells contact the endothelial cells through their surface microvilli. This suggests that these vessels not only supply nutrition to tumor cells but also provide a likely path for tumor permeation and metastasis.

**MECHANISM OF METASTASIS**

The most significant biological characteristics of IMPC are the high frequency of regional LNM and high mortality. This trend is shared by the tumors with the IMPC growth pattern in other organs, including bladder, lung, stomach, colon, jejunum, pancreas, salivary gland, ureter, biliary tract, and thyroid, a fact that can be referred to as the IMPC phenomenon. Understanding the mechanism of its metastasis is critical for intervening in the clinical course; if the key steps in the metastasizing can be identified, the tools can be designed to target those steps. Many relevant studies have expanded our knowledge of IMPC metastases, including the immunohistochemical studies and electron microscopic investigations discussed above.

Tumor-infiltrating lymphocytes (TILs) are generally believed to represent a defensive mechanism of the human body against tumors. The TILs are the hallmark of medullary carcinoma (MC) of breast, which, despite cytologic anaplasia, has a better prognosis than IDC-NOS. However, Guo et al. observed that TILs in IMPC, especially when lymphoid follicles have formed, were correlated with a remarkable increase in LNM. To explore the underlying mechanism, they compared the expression levels of Fas in tumor cells and FasL in TILs in IMPC and MC and found both Fas and FasL expression levels were significantly less in IMPC than in MC. Furthermore, in IMPC cases with strong Fas expression, TILs were not predominantly CD8+ cells, in contrast to the finding in MC. Tumor-infiltrating lymphocyte expression of perforin and granzyme B was weaker in IMPC than in MC, indicating the TILs are at least functionally different in IMPCs and MCs. The group also found that cytokines and membrane proteins, such as stromal cell-derived factor-1 and its receptor CXCR4, and caveolin-1, have a role in the metastases of IMPC.

Breast cancer cells with a CD44+/CD24−/low phenotype have been proposed to have tumor-initiating properties, and this tumorigenic phenotype is considered a stem cell–like feature. Li et al. demonstrated that the ratio of CD44+ to CD24−/low tumor cells was higher in IMPCs than it was in IDC-NOS, and the increased CD44+ to CD24−/low ratio was associated with more-frequent metastasis of IMPC and a worse prognosis. Umeda et al. reported that down-regulation of CD44v6, a CD44 variant isoform, was specifically associated with LNM of IMPCs. Interestingly, Badyal et al. reported 7 cases of IMPC that regained CD44 expression at the LN site and hypothesized that its reexpression at the metastatic site had a role in the homing of tumor cells.

With deep sequencing, one study analyzed the transcriptionomes of IMPCs. Forty-five microRNAs (miRNAs) were identified that were differentially expressed in IMPC and IDC-NOS. A miRNA-specific reverse transcription-quantitative polymerase chain reaction–based analysis was then performed, and expression levels of let-7b, miR-30c, miR-148a, miR-181a, miR-181a*, and miR-181b were significantly different between the two groups. The different expression of these miRNA in IMPCs may be one of the reasons for the high frequencies of LVIs and LNMs.

Characterization of the genomic features showed that the gains of 1q, 8q, 17q, and 20q, and the losses of 1p, 8p, 13q, 16q, and 20q were more prevalent in IMPC than they were in IDC-NOS. Many genes related to maintaining polarity, cilia formation, and cell morphology are located in these regions. Hao et al. compared the expression of prostate stem cell antigen (PSCA) gene located at 8q24 in 66 cases of IMPCs and 67 cases of ICD-NOSs and found that its expression was significantly greater at both the protein and messenger RNA levels in IMPC than it was in IDC-NOS. They concluded that PSCA might have an important role in the LNM of IMPC. Promoter hypermethylation of the LZTS1 gene (located at 8q12) is frequently identified in IMPC, which leads to down-regulation of LZTS1 expression. Wang et al. studied the gene expression of LZTS1 protein in 100 cases of IMPC by immunohistochemistry and found down-regulation of LZTS1 protein in 62 of the 100 cases (62%), which was significantly associated with LNM. These data demonstrate that the loss or reduction of LZTS1 protein expression is associated with the LNM of IMPC. Further study is required to explore the underlying mechanisms.

**CONCLUSIONS**

This article updates the current understanding of breast IMPC with a focus on prognosis-related information and molecular genetic advances. Additional studies might reveal consistent molecular alterations that underlie the formation of the inside-out growth pattern, and they might elucidate the molecular mechanisms responsible for the unfavorable clinical behavior of IMPC.

**References**


