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Invasive carcinomas of the male breast: a morphologic study of the distribution of histologic subtypes and metastatic patterns in 778 cases

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Abstract The current investigation was conducted to evaluate the proportional distribution of the various histologic subtypes (including newly recognized variants) of male breast carcinomas, to determine whether any his-

tologic subtypes occur with a frequency that is markedly discordant with the expected frequencies from published data on parallel female breast tumors. We also aimed to document the distribution of malignancies metastatic to the breast. Seven hundred fifty-nine archived cases of primary invasive carcinoma involving the male breast were retrieved and subcategorized into histologic subtypes according to contemporary criteria. Six hundred forty-three (84.7%) tumors were pure infiltrating ductal carcinoma (IDC) not otherwise specified. The most common of the remainder included papillary carcinoma with invasion in the form of IDC ($n=34$), mixed IDC and mucinous carcinoma ($n=26$), and pure mucinous carcinoma ($n=21$). In 19 cases, metastases from other sites involved the breast, most commonly (58%) cutaneous melanoma. Invasive carcinoma of the male breast appears to display a morphologic spectrum and distribution of histologic subtypes that is comparable to those of the female breast, with some expected variation. Compared with published experience on their female counterparts, there is a two-fold increase in the frequency of invasive papillary carcinoma in the male breast. Finally, the most common tumor metastatic to the male breast in this series was cutaneous melanoma.

The opinions and assertions contained herein are the private views of the authors and are not to be considered official or as necessarily reflecting the opinion of the United States Government or any of its subsidiaries.

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Introduction

Breast cancer in males is relatively uncommon, with approximately 1,450 newly diagnosed cases annually in the United States, and an associated mortality rate that accounts for less than 0.2% of all cancer-related deaths in men [1, 4, 9, 15, 17, 20, 28]. However, recent epidemiologic studies suggest that the incidence of male breast

cancer has been steadily increasing [7, 14]. Utilizing data from the National Cancer Institute's Surveillance, Epidemiology and End Results database for the 26-year period between 1973 and 1998, Giordano et al. [7] found that the incidence of male breast cancer increased from 0.86 to 1.08 per 100,000 population. This increasing incidence, in addition to the better elucidation of the role of BRCA2 mutations in male breast cancer, has renewed interest in specifically identifying the underlying pathogenesis of male breast cancer and clarifying the specific differences, if any, between male and female breast cancer.

On a broad demographical level, male and female breast cancers are fundamentally similar with the main differences lying in older age of occurrence and lower incidence of the former. However, significant differences have been noted between male and female breast cancers with respect to the expression of a variety of biologic factors, including hormone receptors such as estrogen receptor, progesterone receptor, c-erbB-2, estrogen-inducible proteins such as pS2, Cathepsin D, hsp27, proteins related to basement membrane and extracellular matrix degradation such as the urokinase system of plasminogen activation and their inhibitors, and protooncogenes such as bcl-2 [2, 6, 7, 18, 21, 22, 24, 27]. At the morphologic level, male ductal intraepithelial neoplasia (ductal carcinoma in situ), in contrast to similar lesions in females, displays a distinct histologic profile in which the majority of tumors are of the papillary type, with cribriform, micropapillary, and solid types being much less common [13]. In particular, the comedo-type of DIN (comedo DCIS) is notably rare in the male breast [13]. For invasive carcinomas, the female and male tumors are morphologically indistinguishable [26] and many published studies on male breast cancer frequently represent the major histologic subtypes of nonlobular breast carcinoma, such as ductal, medullary, mucinous, and papillary [3, 7, 8, 12, 19, 22, 25]. However, these studies generally do not have the distribution and relative frequencies of the various histologic subtypes as their main focus, and as such, pathologically important distinctions such as signet ring vs colloid carcinoma (both subsumed under mucin producing carcinoma), or metaplastic carcinoma vs infiltrating duct carcinoma not otherwise specified are not emphasized. Over- or underrepresentation of a particular histologic subtype in male breast cancers may provide valuable insight into the etiopathogenetic differences between male and female breast cancers and may provide an important nidus for further studies.

In this study, we investigated the frequencies and distribution of the various histologic subtypes in a large data set of invasive carcinomas seen at a large tertiary center over a 40-year period. Our goals are to document these frequencies and distribution and to see whether any histologic subtypes are notably distinct in frequency of oc-

currence in the male breast, as compared with historical published data on similar lesions in the female breast. The frequencies and sites of origin of metastatic tumors to the male breast during the study period were also investigated.

Materials and methods

After approval from our institutional research review committee, cases of invasive carcinoma involving the male breast diagnosed between 1957 and 1997 were retrieved from the archived institutional files of the Armed Forces Institute of Pathology (AFIP, Washington DC, USA). The available records and slides on each patient were reviewed. All cases with ambiguous gender (even if one among the multiple entries for gender was coded as female rather than male) were excluded ($n=38$). Diagnostic designations were assigned according to contemporary WHO criteria [23]. All special types of carcinoma inclusive of mucinous, tubular, secretory, adenoid cystic, lobular, metaplastic, etc. ($n=116$) were reviewed extensively; many of these cases had been evaluated repeatedly as part of various previously published studies from the department and slides of good quality were available on these cases for review. Among the 643 cases of infiltrating duct carcinoma not otherwise specified, only cases with good quality and adequate representative slides ($n=365$) were graded, using the modified Scarf–Bloom Richardson scoring system. On 78 cases, the slides were so old that we could only confirm the presence of a ductal type carcinoma. The other 200 cases did not have all of the patients' slides pertaining to the lesion available and the final interpretation was based on the descriptions of morphology in the AFIP files. Because cases sent to AFIP are mostly for confirmation of diagnosis, information about therapy beyond what was in the surgical pathology report or the accompanying cover letter are generally not available. Some patients had repeated material sent to AFIP as the lesion recurred, which is how follow-up information was collected in a small subset of cases.

Information about age, operative procedure, nodal excision, and distant metastases were retrieved from the patients' AFIP files. Diagnostic designations were assigned largely based on morphologic and not immunohistochemical features since in many cases there were no blocks or unstained slides available for additional studies. Thirty of these cases were the subject of a previous report [13], which focused on in situ carcinomas and were reported in 1998. Another 113 cases, 8 of which were ductal in situ and another 9 papillary carcinomas, were subject of another report in 1969 [19]. Cases of nonhematopoietic or lymphoreticular malignancies metastatic to the male breast during this period were also catalogued.

Results

Seven hundred and seventy-eight cases of breast carcinoma were reported as involving the male breast during the study period. Seven hundred fifty-nine of these cases were considered primary to the breast and 19 as metastatic to it. The patients ranged in age from 9 to 94 years (mean 61 years). The age distribution available for 520 cases was as follow: 8 were ≤ 30 years, 22 were ≤ 40 years, 205 were 41 to 60 years, 251 were 61 to 80 years, and 34 were over 80 years of age. Among the 490 for whom the racial information was available, 401 were Caucasian, not of Hispanic origin, 82 were Black, not of Hispanic origin, 6 were Asians or Pacific Islander, 1 was Hispanic, and the race was unknown for 269. The carcinomas ranged from ≤ 1 mm (microinvasive) to 12 cm. Many of the cases with multifocal early invasion of 1 to 7 mm were associated with large solitary or multifocal papillary intraductal carcinomas. The various histologic subtypes and their proportional distribution are outlined in Table 1, whereas representative images are illustrated in Fig. 1. Pure *infiltrating duct carcinoma not otherwise specified* was the most common histologic subtype, representing 84.7% of all cases. Six hundred forty-three cases were in the latter group, including 34 cases associated with Paget's disease, 17 cases with prominent apocrine features in $<50\%$ of tumor volume (i.e., insufficient to qualify as apocrine carcinomas), 4 cases with prominent medullary features (tumor circumscription, cellular syncytia, sparse lymphocytic infiltrate), 2 cases of infiltrating duct carcinoma with signet ring cells ($<5\%$ of tumor volume), 3 cases of infiltrating duct carcinoma with focal clear cells ($<5\%$ of tumor volume), and 3 cases of carcinoma with osteoclast-like giant cells. Papillary intraductal carcinoma with invasion in the form of infiltrating duct carcinoma represented 4.5% (34/759 each) of all cases. Other well-represented histologic subtypes or combinations included mixed mucinous and infiltrating duct carcinoma ($n=26$, 3.4%), pure mucinous carcinoma (21, 2.8%), and adenoid cystic carcinoma ($n=8$, 1.05%). Other variants each constituted less than 1% of all cases (Table 1). Notably, there were three cases of lobular carcinoma. As noted previously, these diagnoses were not based on immunohistochemical confirmation by immunostain for E-cadherin, but all three showed archetypal morphologic features of lobular carcinoma with loosely cohesive single cell files and rare intracytoplasmic lumens. Two of these cases had evidence of lobular development in the surrounding breast but the slides available for review did not show lobular intraepithelial neoplasia (LIN). There were also three cases of mixed lobular and ductal carcinomas, in which these areas were spatially separate. The youngest patient, a 9-year-old boy was the only one with pure secretory carcinoma. Five of 759 cases were microinvasive (invasive

focus less than 1 mm in maximum size in a predominantly intraepithelial lesion); three of these five cases were multifocal, whereas the other two were unifocal. Of the 365 cases of infiltrating duct carcinoma not otherwise specified that were graded, 104 were grade 1, 137 were grade 2, and 124 were grade 3. Among the 93 with lymph nodes available for assessment, 61 (66%) cases had axillary metastases. Forty of the women with axillary node metastases also had distant metastases. The most common distant metastatic sites were lung, adrenal glands, and bone. In addition, there were 19 examples of metastases to the breast that were documented. Of these, 58% (11/19) were cutaneous melanomas, and 21% (4/19), 10% (2/19), and 10% (2/19) represented carcinomas from the prostate, lung, and larynx, respectively.

Table 1 Distribution of the various histologic subtypes in 778 invasive carcinomas involving the male breast

Histologic subtype	Number of cases	Percentage
Infiltrating duct carcinoma not otherwise specified, including ^a	643	84.7
Carcinoma associated with Paget's disease	34	
Carcinoma with prominent apocrine features	17	
Carcinoma with medullary features	4	
Carcinoma with osteoclast-like giant cells	3	
Carcinoma with focal signet rings	2	
Carcinoma with focal clear cells	2	
Pleomorphic carcinoma	2	
Carcinoma with no notable distinctive features	579	
Papillary intraductal carcinoma with invasion in the form of infiltrating duct carcinoma	34	4.48
Mixed infiltrating duct and mucinous carcinoma	26	3.4
Pure mucinous carcinoma	21	2.8
Adenoid cystic carcinoma	8	1.05
Tubular carcinoma	6	0.8
Small cell carcinoma	6	0.8
Invasive lobular carcinoma	3	0.39
Solid neuroendocrine carcinoma	3	0.39
Mixed lobular and ductal carcinoma	3	0.39
Adenocarcinoma with spindle cell metaplasia	2	0.26
Pure signet ring carcinoma (no in situ component)	1	0.13
Invasive cribriform carcinoma	1	0.13
Secretory carcinoma	1	0.13
Squamous cell carcinoma	1	0.13
Total	759	100
Metastatic lesions	19	
Final total	778	

^aSubsets included for information only (not WHO categories)

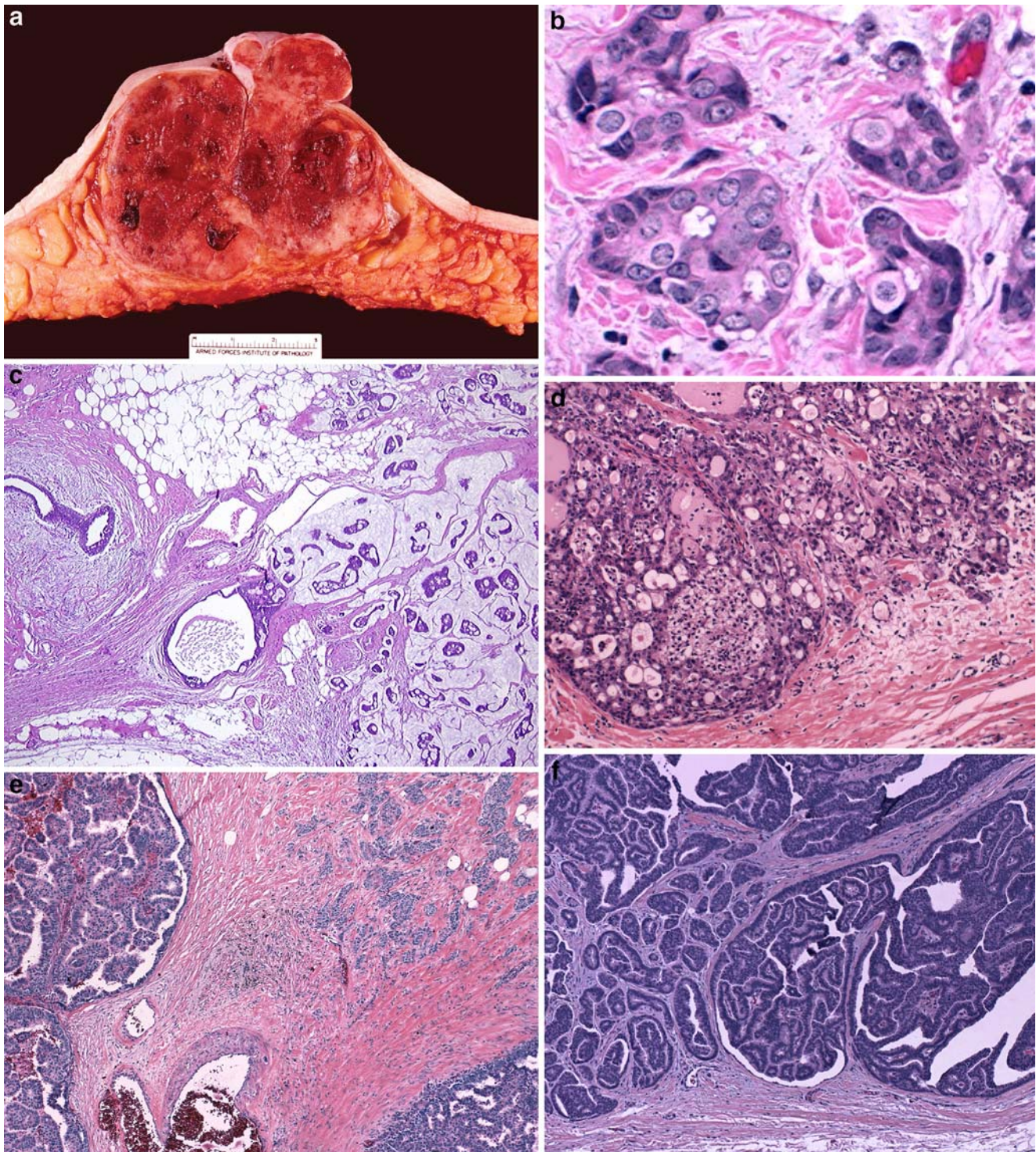


Fig. 1 Representative pathologic images of the various histologic subtypes. **a** and **b** Gross and microscopic images of infiltrating duct carcinoma, the most frequently encountered histologic subtype (**b** original magnification $\times 160$). **c** A colloid (*mucinous*) carcinoma (*right field*) occurring in a gynecomastoid breast (*left field*) (original

magnification $\times 100$). **d** The single case of a secretory carcinoma was in a 9-year-old boy, the youngest patient in this series (original magnification $\times 140$). **e** and **f** Examples of papillary intraductal carcinoma with invasion in the form of infiltrating duct carcinoma [original magnifications: $\times 100$ (**e**), $\times 120$ (**f**)

Discussion

The frequency, distribution, and morphologic spectrum of the various histologic subtypes of male breast cancer as compared with its female counterpart may provide a valuable insight into the etiology and/or pathogenesis of both. This was perhaps best illustrated in the study of ductal carcinoma in situ by Hittmair et al. [13]. The authors showed that in the male breast, papillary DCIS occurred with a much higher frequency (46% of pure lesions) than expected, while solid, micropapillary, and cribriform patterns occurred with a much lower frequency (22% of pure DCIS combined). Notably, only 5 of 114 cases were of comedo-type DCIS and only 7 of 114 cases were considered high grade. The authors concluded that predominance of papillary patterns among intraepithelial male breast lesions is a reflection of the relative abundance of ducts and the poorly developed terminal-ductal lobular units in male breast. Given the rarity of true comedo DCIS in male breast, the authors speculated that the fully developed lobular environment and the female type hormonal milieu may be a requirement for development of comedo DCIS [13].

In this study, we investigated in detail the frequencies and distribution of the various histologic subtypes in a large data set of invasive carcinomas seen at a large tertiary center over a 40-year period. Our findings suggest that invasive carcinoma of the male breast displays a morphologic spectrum and distribution of histologic subtypes that is comparable to invasive carcinoma of the female breast and that no specific histologic subtypes are notably over- or underrepresented with the exception of papillary and lobular variants.

Papillary intraductal carcinomas basically assumed an infiltrating duct carcinoma pattern once they invaded the stroma (Fig. 1e,f). A papillary component was present in 34 (4.5%) of 759 cases, representing the second most common histologic subtype. These papillary carcinomas appeared to have invaded either through massive expansion and total disruption of ductal confines with typical invasive patterns at their periphery or only focally disrupted the duct wall and invaded the surrounding stroma as an infiltrating duct carcinoma. The latter represents approximately 2% [5] of female breast invasive carcinomas and appears overrepresented in males. In a large population-based study, Giordano et al. [7] reported that 2.6% of invasive malignancies in males were papillary carcinomas, as compared with 0.6% in females ($p < 0.0001$). However, the differences between males and females with respect to the frequencies of the other histologic subtypes were also statistically significant. The significance of the papillary histologic subtype or papillary architecture in male ductal carcinoma requires further investigation but is most probably related to the architecture of the male mammary duct system with dominance of larger ducts.

The possibility of metastases to the breast should be considered when evaluating breast masses particularly if there is a history of cancer elsewhere. Nineteen cases of carcinoma metastatic to the male breast were seen over this study period, representing 2.4% (19/778) of all nonhematopoietic or lymphoreticular malignancies. This is again a twofold increase comparable to the 1.2% reported in female breast malignancies over a 10-year period [11]. Of the 19 metastatic tumors, 58% (11/19) were cutaneous melanomas, and 21% (4/19), 10% (2/19), and 10% (2/19) represented carcinomas from the prostate, lung, and larynx, respectively. It is interesting to note that prostatic carcinoma, which has been the subject of most reports of carcinomas metastatic to the male breast [10], was not the most common metastatic tumor in this series. The number of metastatic tumors in this series is relatively small, which is a limitation in interpreting the distribution of originating sites. Nonetheless, in the investigation of metastatic tumors to the male breast of an unknown primary site, our findings provide additional data on some of the most likely sites.

This study also confirms the occurrence of lobular carcinoma in the male breast. Three cases of invasive lobular carcinoma, diagnosed purely on a morphologic basis, were present among 759 cases (0.4%). Three additional cases of mixed lobular and ductal carcinoma were also diagnosed over this period (0.4%). Joshi et al. [16] found one (4%) lobular carcinoma out of 27 cases, while Goss et al. [8] found 4 (1.9%) cases out of a total of 229. In the series of Giordano et al. [7], lobular carcinomas constituted 1.5% for their male breast cancers. It is noteworthy that all of these cases were interpreted as lobular based on morphology without E-cadherin immunostain confirmation.

In summary, invasive carcinoma of the male breast appears to display a morphologic spectrum and distribution of histologic subtypes, which is comparable to invasive carcinoma of the female breast with some variation. As expected, lobular carcinoma is exceedingly rare but was encountered in this series. There appears to be a twofold increase in the frequency of invasive papillary carcinoma and metastatic cancers to the male breast as compared to published data in the female breast. Finally, the most common tumor metastatic to the male breast in this series was cutaneous melanoma.

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