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Original contribution

Invasive Paget disease of the breast: 20 years of experience at a single institution ☆

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Summary Mammary Paget disease with dermal invasion (invMPD) is rare, and its prognosis remains largely unknown. We reviewed MPD cases diagnosed at our institution and analyzed the clinicopathological characteristics of invMPD and non-invMPD to compare their incidences and outcomes. We retrospectively reviewed 205 cases of women diagnosed as having MPD between 1994 and 2013. Sixteen of 205 MPD cases (7.8%) had dermal invasion. Twelve of 16 invMPD cases had separate, underlying invasive breast carcinoma, and 3 invMPD cases had ductal carcinoma in situ. To exclude the influence of underlying disease on prognosis, we compared prognosis of invMPD with matched non-invMPD. The mean depth and extent of Paget cell invasion in invMPD cases were 0.637 and 1.268 mm, respectively. The horizontal extent of MPD was significantly larger in invMPD versus non-invMPD (mean, 14.31 mm versus 7.35 mm; $P = .002$). Distant metastasis and disease-related death were observed in 12.6% (24/189) and 12.1% (23/189) of non-invMPD patients, respectively, compared with 6.3% (1/16) and 6.3% (1/16) of invMPD patients; this difference was not significant ($P = .7$ and $P = .7$). Clinical outcomes of the invMPD patients were also not significantly different from the matched non-invMPD patients. In this study, MPD extent significantly correlated with MPD invasion. However, other clinicopathological parameters were not associated with dermal MPD invasion. Dermal MPD invasion was rare and did not predict regional lymph node metastasis or poor prognosis. The prognosis is usually similar for invMPD and non-invMPD, and MPD must be distinguished from locally advanced breast cancer presenting as satellite skin nodules.
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1. Introduction

Mammary Paget disease (MPD) is a very rare disease that occurs exclusively in the nipple-areola complex [1]. MPD accounts for 1% to 3% of all primary breast cancers [2,3], and most MPD has underlying invasive carcinoma or ductal carcinoma in situ (DCIS) of the breast parenchyma [4–6]. MPD of the nipple is considered to be DCIS involving nipple skin and extending from the lactiferous duct without invasion through the basement membrane. Therefore, MPD without underlying carcinoma of the breast parenchyma is classified as pTis [4]. Invasion of MPD tumor cells into the dermis is extremely rare; only 15 patients have been previously reported with this condition [7–10]. In the past cases in the literature,

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patients with MPD invasion into the dermis had a good prognosis [9,10]. This is in contrast to patients with direct skin invasion by breast cancer, who have a poor prognosis and are classified as having T4b disease by the American Joint Committee on Cancer and the Union for International Cancer Control [4]. However, little is known about the prognosis and clinical significance of invasive MPD (invMPD).

To evaluate the clinicopathological features, therapeutic strategies, and prognostic significance of invMPD and compare the prognosis of invMPD and non-invMPD patients, we retrospectively reviewed MPD cases diagnosed at our institution and analyzed the clinicopathological characteristics and clinical outcomes of invMPD and non-invMPD.

2. Materials and methods

2.1. Case selection

The surgical pathology archives at Samsung Medical Center were searched, and 359 MPD cases diagnosed between January 1, 1994, and May 31, 2013, were retrieved. A detailed morphologic review was performed by 2 breast pathologists (E. C., H. W. L.) to confirm the diagnosis of MPD. We excluded cases with diseases other than MPD, such as pagetoid involvement of lactiferous ducts by DCIS and Toker cell hyperplasia. In some cases, which were difficult to distinguish Paget disease from Toker cell hyperplasia by hematoxylin and eosin stain alone, we performed immunohistochemical stains for cytokeratin 7, Cam 5.2, or human epidermal growth factor receptor 2 (HER2) to confirm the diagnosis. We diagnosed a case as invMPD only if the dermal invasive foci of Paget cells were definitely separate from the underlying invasive carcinoma and were intimately related to the diffuse noninvasive intraepithelial spread of Paget cells. We excluded cases with continuous direct skin invasion of an underlying invasive carcinoma or definite satellite skin nodules with direct and continuous epidermal invasion and no extensive intraepithelial Paget cell spread. After a morphologic review using strict pathological criteria, 205 cases were identified for inclusion in this study. Clinical parameters including age, sex, surgery date, presenting symptoms, nipple discharge, underlying parenchymal disease data, treatment modality, and clinical outcomes were obtained by a thorough review of clinical records. At the time of analysis, the median follow-up period was 43 months (range, 7-226 months) and 24 patients (11.6%) had died from cancer. The study protocols including case selection, review of the slides, and collection of clinical parameters were approved by the Samsung Medical Center Institutional Review Board.

2.2. Histopathologic evaluation

Examination of histologic sections from MPD cases revealed several features: intraepidermal extent of MPD, presence of direct dermal invasion, and underlying parenchymal cancer data (presence and type of underlying cancer, size of underlying cancer, nuclear and histologic grading of underlying cancer, and regional lymph node metastasis). We investigated additional histopathologic features for invMPD cases: the total extent and depth of tumor invasion into the dermis and the invasion pattern. Depth of invasion was measured as the distance from the dermoepidermal junction to the deepest focus of tumor cell invasion. We performed immunohistochemical staining for overexpression or amplification of the estrogen receptor (ER), progesterone receptor (PR), p53, and HER2, and to evaluate subtype classifications (luminal A, luminal B, HER2 positive, and triple negative) [11,12]. We categorized immunohistochemical staining pattern for HER2 as negative (0, 1+), equivocal (2+), and positive (3+) [13]. In cases of all HER2-equivocal stains, we performed HER2 silver-enhanced in situ hybridization to confirm exact HER2 overexpression [14]. The underlying tumors were graded using the Bloom-Richardson grading system [15] and the Van-Nuys classification system [16].

2.3. Statistical analyses

A retrospective case-control study was designed to compare survival outcomes between invMPD patients and non-invMPD control patients that were matched with regard to age, therapy, and disease stage. Twice as many non-invMPD patients as invMPD patients were selected to compare prognosis between groups. TNM stage, age, procedure, and adjuvant therapy method were adjusted to facilitate proper comparison between the groups. Statistical analyses were performed with SPSS software, version 12.0.0.1 (SPSS Inc, Chicago, IL). χ^2 Tests or Fisher exact tests were used to compare frequencies between groups. Overall and disease-free survival were compared between invMPD patients and a matched set of patients with non-invMPD. Disease-free survival analysis was performed using the period from the date of surgery to the date of any first event or the date of last contact with patients or relatives (if alive). Overall survival was calculated from the date of surgery to the date of death or last visit. Survival was analyzed using the Kaplan-Meier method and compared with a log-rank test. The covariates were included in a multivariate analysis using a Cox proportional hazards regression model; hazard ratios and their 95% confidence intervals were assessed for each factor. All tests were 2 sided, and P values less than .05 were considered statistically significant.

3. Results

3.1. Incidence and clinical characteristics of invMPD

Dermal invasion of Paget cells was identified in 16 (7.8%) of 205 MPD cases. Clinical information for all 16 invMPD patients

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