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Original contribution

Clinicopathologic features of ductal carcinoma in situ in young women with an emphasis on molecular subtype

Christopher J. VandenBussche MD, PhD[a,*], Hillary Elwood MD[a], Ashley Cimino-Mathews MD[a], Zeid Bittar MD[b], Peter B. Illei MD[a], Hind Nassar Warzecha MD[b]

[a]*Department of Pathology, The Johns Hopkins Medical Institutions, Baltimore, MD 21287, USA*
[b]*Department of Pathology, University Hospital of Tuebingen, 72076 Tuebingen, Germany*

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Summary Young women with ductal carcinoma in situ treated by breast-conserving therapy have a higher recurrence rate than do older women, and a younger age at diagnosis is associated with worse overall survival after recurrence. This study explores the clinical, pathologic, and immunohistochemical characteristics of ductal carcinoma in situ lesions diagnosed in women 40 years and younger with a focus on molecular subtypes to elucidate features that may contribute to the purported worse outcome for this patient population. Forty-one patients diagnosed with ductal carcinoma in situ at age 40 years and younger were identified over a 10-year period; 31 cases were used to construct tissue microarrays. The microarrays were labeled with antibodies to estrogen receptor, progesterone receptor, HER2, Ki-67, CK5/6, epidermal growth factor receptor, and p53 and subsequently classified as luminal A, luminal B, HER2, basal-like, or unclassifiable triple negative. All patients had high-grade (73.2%) or intermediate-grade (26.8%) ductal carcinoma in situ. The molecular subtype breakdown was 61.3% luminal A, 22.6% luminal B, 13% HER2, and 3.1% unclassifiable triple negative. The mean Ki-67 by subtype was 4.2%, 14%, 9.5%, and 50%, respectively. Mastectomy was performed in 33 patients (80%). Eight patients (20%) underwent excisional biopsy without subsequent mastectomy. In addition to a predominance of high-grade lesions, young patients had a high proportion of luminal B subtype, which may contribute to an increased rate of local recurrence in this population. A larger series is necessary to confirm the impact that the molecular subtypes of ductal carcinoma in situ in younger patients might have on outcome.

1. Introduction

Ductal carcinoma in situ (DCIS) is uncommonly diagnosed in women younger than 40 years. Approximately 1780 cases of DCIS were newly diagnosed in this age group in the United States in 2011, constituting 3% of the total number of DCIS cases [1]. However, young women with DCIS treated by breast-conserving therapy have a higher rate of recurrence of DCIS or invasive cancer when compared with older women [2-9], and a younger age at diagnosis is associated with a worse overall survival in patients with DCIS after a recurrence [10]. It is not clear whether the factors contributing to this difference are related to treatment modalities or to the biology of the lesion. Some of the

* Corresponding author. Department of Pathology, The Johns Hopkins Medical Institutions, Baltimore, MD 21287, USA.
E-mail address: cjvand@jhmi.edu (C. J. VandenBussche).

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pathologic features of the DCIS such as large lesion size, cancerization of the lobules, and the presence of high-grade cytology with comedonecrosis are among the most frequently reported parameters more often observed in younger than in older patients with DCIS [2,5,8,9,11,12]. In other studies addressing this issue, none of the pathologic features were different among the 2 patient populations [13-15]. Furthermore, it is unknown whether recurrence and survival rates improve when younger patients with DCIS are treated with mastectomy as compared to breast-conserving therapy.

In the current study, our objective is to explore the pathologic and immunohistochemical characteristics of DCIS lesions diagnosed in women 40 years and younger at our institution, focusing on the molecular subtypes of these lesions, with the purpose of adding our findings to the literature on this topic and in an attempt to elucidate the features that may contribute to the purported worse outcome for young women with DCIS.

2. Materials and methods

This study was approved by the Institutional Review Board of the Johns Hopkins Medical Institutions. The pathology archives of The Johns Hopkins Hospital were searched for cases of newly diagnosed DCIS in women 40 years old and younger between the years 2000 and 2010. Patients with invasive carcinoma, including microinvasion as defined by any focus of invasion less than 1 mm, in specimens preceding or within 6 months of the diagnosis of DCIS were excluded from the study. Cases of in situ carcinoma with mixed ductal and lobular features and pure lobular carcinoma in situ were excluded from the study.

Demographic and clinical data including ethnicity, family history of breast or gynecologic malignancy, clinical presentation, and radiology findings as well as follow-up data for recurrence were retrieved from the hospital's clinical and radiology records. A "strong family history" was defined as having 1 first-degree relative diagnosed with breast cancer at younger than 50 years, or 2 or more relatives with breast cancer with at least one of them being a first-degree relative. All other situations with a family history of breast cancer were classified as having a "weak" family history. For each patient, we noted the final surgical procedure related to the diagnosis of DCIS (excisional biopsy or mastectomy) and whether the patient received additional radiation or hormone therapy. All pathology reports and available histology slides related to the diagnosis of the DCIS were reviewed by 2 board-certified pathologists (H. E. and H. N. W.). From the hematoxylin and eosin (H&E) sections, the DCIS grade (low or G1, intermediate or G2, high or G3), histologic pattern (cribriform, solid, micropapillary, flat, mixed), and the presence of central necrosis and microcalcifications were recorded. We also noted other lesions present in the adjacent breast tissue: atypical lesions such as atypical ductal or lobular hyperplasia (ALH) and flat epithelial atypia (FEA); proliferative lesions without atypia such as papillomas, sclerosing adenosis, usual ductal hyperplasia, columnar cell hyperplasia, and radial scars; and nonproliferative lesions such as cysts, fibrosis, and fibroadenoma. The size of the DCIS was recorded as reported in the pathology reports when available. If the overall gross size was not available from the report, the size was recorded as the largest of either the number of consecutive sections with DCIS × 0.4 cm (average section thickness) or the size of the largest focus present on 1 slide. The available sections from lymph nodes taken during a sentinel node biopsy or an axillary node dissection were also reviewed for the presence of lymph node metastases.

Mastectomy and lumpectomy specimens performed for DCIS diagnosed on core needle biopsy at our institution are processed as follows: the specimen margins are inked following standard protocol. Serial sections of an excisional biopsy/lumpectomy or of mastectomy quadrants are made. Any grossly identified lesion measuring less than 1 cm is submitted in its entirety. For lesions measuring greater than 1 cm, 25 to 30 sections of the tumor are submitted. If no macroinvasive or microinvasive carcinoma is identified in this first sampling, an additional 25 to 30 sections are submitted until the gross lesion is entirely evaluated. Representative sections of the remaining excision or quadrants are taken (eg, 2 sections per mastectomy quadrant in addition to grossly identifiable abnormalities). In addition, all gross findings are correlated with the radiographic impression, and additional sections are taken to encompass regions of radiographic concern that are not explained by the primary tumor. If additional regions of high-grade DCIS are found separate from the main tumor, additional sections of this quadrant are taken. Upon microscopic examination, any region of concern for microinvasion is further evaluated by immunohistochemistry for at least 2 myoepithelial markers (eg, p63 and smooth muscle myosin heavy chain). All cases of DCIS with microinvasion on H&E or on immunostains were excluded from the present study.

Two tissue microarrays (TMAs) were constructed using a previously described method [16] from cases with sufficient tissues. In total, 31 cases had sufficient tumor for inclusion on the TMAs. Each TMA consisted of 99 cores measuring 1.4 mm in diameter, consisting of 2 to 3 cores of DCIS and 1 core of benign breast lobules per case. The TMAs were labeled by immunohistochemistry (IHC) for estrogen receptor (ER; DCS; Rabbit monoclonal, SP1, 1:200), progesterone receptor (PR; DCS; rabbit monoclonal, SP2, 1:200), HER2 (DAKO Rabbit polyclonal, A0485, 1:600), Ki-67 (DAKO, mouse monoclonal, MIB1, M7240, 1:200), CK5/6 (DAKOCytomation, mouse monoclonal, D5/16 B4, 1:100), epidermal growth factor receptor (EGFR; DAKO-Cytomation, mouse monoclonal, E30, 1:20), and p53 (Novocastra, mouse monoclonal, DO-7, 1:200).

Based on the IHC results, the DCIS cases were classified using established criteria [17-19] into the following categories: luminal A (ER+ and/or PR+, HER2−), luminal B (ER+