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ORIGINAL ARTICLE

The utility of repeated cytologic evaluation of cerebrospinal fluid in individuals with metastatic breast cancer

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Introduction Metastasis of breast cancer to the central nervous system, either in the brain parenchyma or leptomeninges (LMC), is a late feature of the disease .

Detection of malignant cells in the cerebrospinal fluid (CSF) is the diagnostic standard for LMC. Repeated CSF examinations are often performed following an initial diagnosis positive for malignancy. This study evaluates the significance of repeated CSF evaluation in women with metastatic breast cancer to the central nervous system.

Materials and Methods Cases of adenocarcinoma of breast diagnosed by CSF cytology from 1990 through 2012 documenting: age, radiologic findings, treatment modality, and the number of repeated CSF cytology specimens and their respective interpretations.

Results Fifty-one patients were identified; 28 patients (54.9%) had a single initial positive CSF performed and 23 (45.1%) had multiple CSF cytology samples (range = 2-25, mean = 5.5). Despite interval "negative" and "atypical cells" results on CSF cytology specimens, all 23 patients with multiple samples had at least one follow-up positive CSF cytology sample.

Conclusion The prognosis of the patients with an initial CSF diagnosis of adenocarcinoma was poor, regardless of the respective interpretations on the repeated CSF specimens, even in the presence of interval negative CSF.

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Introduction

Metastasis of breast cancer to the central nervous system (CNS), either in the brain parenchyma or leptomeninges, is generally a late feature of the disease.[1] Breast cancer is the most common solid tumor to exhibit leptomeningeal (LM) spread.[1] Once the tumor cells reach the leptomeninges via multiple routes, they are postulated to spread via the cerebrospinal fluid (CSF).[1] Cytologic evaluation of the CSF is considered an integral part of evaluation of breast cancer patients that present with signs and symptoms that suggest leptomeningeal carcinomatosis (LMC) rather than an intraparenchymal mass.[2] Detection of malignant cells in the CSF is the diagnostic standard for LMC.[3] The recognition and reporting of these malignant cells is often challenging to the pathologist, especially given the implications for therapy and prognosis. The task is given even more significance when the pathologist examines multiple CSF samples that are provided to monitor response to intrathecal chemotherapy (ITC). Many such samples are scantly cellular and may contain atypical cells with degenerative and/or therapy-related changes that maybe difficult to discern as malignant from mimickers.[4] Repeated CSF cytology may be performed to increase sensitivity, or at each intrathecal administration of chemotherapy.[4,5] There are no standard guidelines for repeated CSF cytologic evaluation, however, nor are there studies that address the significance of the various cytologic interpretations of repeated CSF specimens following an initial positive fluid, including those that are reported as negative. This study evaluates the utility and significance of repeated CSF cytologic evaluation in women with metastatic breast cancer to the CNS.

Materials and methods

A retrospective review of all CSF samples at the Cleveland Clinic in Cleveland, Ohio, between 1990 and 2012 was performed from the Anatomic Pathology database. All CSF cytology cases with a diagnosis of "atypical cells, suspicious for malignancy" and "positive for adenocarcinoma" were selected. Confirmation of the primary site of malignancy was determined from review of the electronic medical record and/or correlation with the histopathologic diagnosis from a surgical biopsy or resection. Only patients with a histopathologic and/or a clinical diagnosis of primary breast cancer were included. Patients with a secondary malignancy were excluded. All CSF cytology diagnoses of "atypical cells, suspicious for malignancy" were grouped into the positive category.

The following data were collected from the electronic medical record, cytology, and surgical pathology reports: age of the patient at the initial diagnosis of invasive breast carcinoma, date of positive CSF cytology, duration of time between primary diagnosis and positive CSF cytology, number of repeated CSF cytology samples and corresponding diagnoses, radiologic findings (radiographic mass lesion [RML] versus no radiographic mass lesion [NRML]), treatment modality (neurosurgery, ITC, or whole brain radiotherapy [WBRT]), and length of survival after initial positive cytology. If the patient had a RML, the number of lesions was recorded. No radiographic mass lesion (NRML) clinically implied leptomeningeal carcinomatosis (LMC/carcinomatous meningitis) only.

Results

During the 22-year study period, 11,437 CSF cytology specimens were evaluated. One hundred forty-four samples from 71 patients had a CSF diagnosis of "atypical cells, suspicious for malignancy" or "positive for adenocarcinoma". Of the 71, 3 patients with adenocarcinoma on CSF cytology had an unknown primary and were excluded. Fifty-five of the 68 remaining patients (80.9%) had CNS metastasis from breast cancer, and 13 (19.1%) had other malignancies (8 lung, 2 stomach, 2 ovary, 1 pancreas). Of the 55 patients with a positive CSF for metastatic breast carcinoma, the medical record data was insufficient for 4 patients, yielding a total of 51 patients included in this study. The patients ranged in age from 29 to 73 years (mean age: 49 years).

The histopathologic subtype and grade of primary tumor were available for 39 and 26 cases, respectively. (Tables 1 and 2) Complete data on hormone receptor and HER2 status were available for 21 of the 51 patients (41.2%) (Table 3). From the clinical information available on the patients with triple negative breast cancer, 5 were ductal (4 high-grade, 1 intermediate), 2 were lobular (1 high-grade), 1 was mixed ductal/lobular, and 1 had an unknown histologic subtype.

Two of the 51 patients (0.4%) did not have a definitive diagnosis of malignancy (rare atypical cells), and one additional (0.2%) patient had a diagnosis of "negative for malignancy" on their initial CSF sample. Each of these 3 samples had a repeat follow-up "positive for malignant cells" CSF cytology. One of the 2 patients with atypical cells had a subsequent positive CSF 2 months later, during which 2 interval CSFs were negative. The second patient with an initial diagnosis of "atypical cells" had a repeat positive CSF two days later. The patient with an initial negative CSF had a follow-up positive CSF 3 weeks later. With the addition of these three patients, 51 patients with positive CSF for metastatic breast cancer were included in this study. Of these 51 patients, 28 patients (54.9%) had a single initial positive CSF performed and 23 (45.1%) had multiple CSF cytology samples (range = 2-25, mean = 5.5). Despite interval "negative" and "atypical cells" results on CSF cytology specimens, all 23 patients with multiple samples had at least one follow-up positive CSF cytology sample.

RMLs were identified in 9 of the 51 patients (17.6%), ranging in number from 1 to 4. No patients with only RML