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Original article

Isolated pachymeningeal metastasis from breast cancer: Clinical features and prognostic factors

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ABSTRACT

Purpose: To evaluate the clinical features and prognoses of patients with isolated pachymeningeal metastasis (IPM) from breast cancer.
Methods: We reviewed the medical records of all patients with metastatic breast cancer (MBC) treated from January 2009 to August 2016. Eligibility criteria included diagnosis of pachymeningeal metastasis based on brain magnetic resonance imaging and histologic diagnosis of primary breast cancer. We excluded patients with concomitant parenchymal or leptomeningeal metastases.
Results: Thirty-eight patients who matched our inclusion criteria were included in this study. The incidence of IPM in breast cancer was 1.5% of all patients with MBC. The molecular subtype distribution was: triple negative, 29.0%; ER+/HER2−, 44.7%; ER+/HER2+, 18.4%; and ER−/HER2+, 7.9%. All isolated pachymeningeal involvement resulted from the direct extension of skull metastases. The median time to IPM from systemic metastasis was 28.6 (95% CI: 23.6–33.6) months. The median time to IPM from skull metastasis was 5.2 (95% CI: 0–10.9) months. The median overall survival (OS) from IPM was 4.0 (95% CI: 2.5–5.5) months. In patients who received chemotherapy the OS was longer than for those who received radiotherapy or supportive care only [median OS 8.9 (95% CI: 0.0–18.4), 2.8 (95% CI: 0.5–5.0), and 0.8 (95% CI: 0.6–1.1) months, respectively ($p = 0.006$)]. Multivariate analysis revealed that good performance status and chemotherapy were associated with better survival outcomes.
Conclusion: Stratified evaluation is required for patients with skull metastasis from breast cancer, as pachymeningeal involvement can develop and be associated with unsuspected outcomes.

1. Introduction

Breast cancer is the second most common cause of brain metastasis [1], and 10–16% of all patients diagnosed with metastatic breast cancer (MBC) will develop brain metastases during the course of their disease [1–4]. The incidence of brain metastasis from breast cancer has been increasing, probably due to the advent of more precise neuroimaging technologies and the development of improved therapeutic options, leading to improvements in the long-term survival of breast cancer patients. The prognosis of brain metastases in breast cancer is poor, with a reported median survival of 6–7 months (range, 2–16 months) and 1-year and 2-year survival rates of approximately 20% and 2%, respectively [5,6]. Brain metastases generally tend to occur during the late stage of breast cancer. The median time from diagnosis of breast cancer to brain metastases is 2–3 years. Several risk factors for brain metastases have been reported. For instance, brain metastases are frequent in women with a triple-negative subtype and human epidermal growth factor receptor type 2 (HER2)-positive subtype cancer, with approximately 30% and 50% of all MBC patients with these subtypes developing brain metastases, respectively [7–10].

Brain metastases can occur in the brain parenchyma, leptomeningeal layer (arachnoid lining, subarachnoid space, and pial surface) and pachymeningeal layer (dura) [11]. The majority of brain metastases present in the parenchyma and are frequently symptomatic. Pachymeningeal metastasis, which is synonymous with dural metastasis, includes meatasis to the epidural space, which is usually a direct extension from skull metastases, and to the subdural space, either by direct extension from epidural metastasis

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or by hematogenous spread. In clinical practice, enhanced dural masses extending along the bone structures on brain magnetic resonance imaging (MRI) scans have been detected in patients occasionally. These patients may or may not present neurological symptoms and typically display distinct characteristics of breast cancer, in contrast to patients with brain parenchymal metastasis. Pachymeningeal metastases have not been studied in breast cancer, although several case reports, small patient series, and reviews have been published [12,13]. Many of these studies have included patients with concomitant brain parenchymal or leptomeningeal metastases, which has hindered the ability of the study to determine the direct effect of pachymeningeal metastasis on prognosis and treatment. Moreover, the optimal treatment and prognosis of IPM in patients with breast cancer have not been established. Nayak et al. performed a retrospective study of intracranial dural metastases; however, various types of cancer were included [14]. Here, we evaluate the clinical features and prognoses of breast cancer patients with pachymeningeal metastasis but without leptomeningeal or parenchymal metastasis. A better understanding of the clinical characteristics of this group of patients with breast cancer may help advance the development of treatments and improve survival outcomes.

2. Materials and methods

2.1. Patients

We retrospectively reviewed the medical records and imaging studies of all patients with MBC treated at Samsung Medical Center from January 2009 to August 2016. From this group, we identified patients who underwent evaluation by brain MRI. The inclusion criteria were: 1) diagnosis of pachymeningeal metastasis based on brain MRI; 2) histologic diagnosis of primary breast cancer; 3) negative cerebrospinal fluid (CSF) cytology if lumbar puncture was performed; and 4) negative for parenchymal or leptomeningeal metastasis based on brain MRI. We excluded patients with concomitant parenchymal or leptomeningeal metastases, as determined by either brain MRI or CSF cytology.

We collected various clinical data, including: baseline patient demographics and tumor characteristics (status of HER2 and hormone receptors), treatment for pachymeningeal metastasis, and radiological findings. Estrogen receptor (ER) and progesterone receptor expression were determined by immunohistochemistry (IHC); positivity was defined as IHC staining in at least 1% of all tumor cells. HER2 status was evaluated using a specific antibody (Dako, Glostrup, Denmark) and/or fluorescence in situ hybridization (FISH). Grades 0 and 1 for HER2, as assessed by IHC, were defined as a negative result, and grade 3 was defined as a positive result. Amplification of HER2 was confirmed by FISH test if HER2 was rated as grade 2 by IHC [15]. All procedures involving patients were reviewed and approved by the Institutional Review Board of the Samsung Medical Center (No. 2017-01-060).

2.2. Survival and statistics

Descriptive statistics are reported as proportions and medians. Kaplan–Meier estimates were used for the analysis of all time-to-event variables and the 95% confidence interval (CI) for the median time to event was computed. Overall survival (OS) was measured from the date of pachymeningeal metastasis to the date of death from any cause and the last follow-up visit. Univariate and multivariate analyses examined the impact of clinical and treatment parameters on the survival outcome using Cox proportional hazards analyses. Variables used to identify prognostic parameters for OS were age, performance status, molecular subtype, extent of metastases (visceral vs. nonvisceral), clinical symptoms, time from skull metastasis to pachymeningeal metastasis, and therapy (radiotherapy vs. chemotherapy vs. supportive care only). Nonsignificant variables were dropped individually, beginning with the least significant variable. Variables with a p value < 0.05 were considered significant for the analysis, and 95% CIs were calculated. All statistical analyses were performed using PASW Statistics version 23.0 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Patient characteristics

A total of 38 patients treated between Jan 2009 and Aug 2016 were included in this study. Fig. 1 shows the flow chart for patient inclusion. The incidence of IPM was 1.5% of all patients with MBC. The patient baseline characteristics are summarized in Table 1. The overall median age at diagnosis of IPM was 53 years (range, 27–70 years). Fifteen (40%) patients showed poor performance status (evaluated as $\leq$70 according to the Karnofsky performance status (KPS) scale), while 23 (60%) patients had a KPS >70. The molecular subtype distribution was as follows: triple negative, 29.0%; ER+/HER2−, 44.7%; ER+/HER2+, 18.4%; and ER−/HER2+, 7.9%. The most commonly involved metastatic sites were bone (100%), lymph nodes (24%), lung (24%), and liver (13%). A total of 15 patients (40%) had visceral metastasis at the time of pachymeningeal metastasis.

Headache and cranial neuropathy (n = 20) were the most common presenting symptoms and signs, followed by visual changes (n = 2), alterations in mental status (n = 2), and ataxia (n = 2). In 12 neurologically asymptomatic patients (31.6%), brain metastases were found on routine brain MRI scans. Skull metastasis was detected in all patients before pachymeningeal metastasis and pachymeningeal involvement always resulted from the direct extension of skull metastases.

The median time to IPM from the initial breast cancer diagnosis was 58.7 (95% CI: 45.4–72.1) months; three patients presented with pachymeningeal metastasis at the time of initial breast cancer diagnosis. The median time to IPM from systemic metastasis was 28.6 (95% CI: 23.6–33.6) months; and by subtypes, it was 10.4 months for triple negative; 30.9 months for ER+/HER2−; 28.4 months for ER+/HER2+; and 21.5 months for ER−/HER2+. The median time to IPM from skull metastasis was 5.2 (95% CI: 0–10.9) months.

3.2. Brain images of dural involvement

Five patients had a single pachymeningeal metastasis, 12 had multiple pachymeningeal involvement, and 21 had diffuse pachymeningeal involvement. Metastatic sites were: frontal (n = 7), parietal (n = 7), skull base (n = 8), occipital (n = 4), temporal (n = 3), diffuse cerebral hemisphere (n = 5), and infratentorial lesion (n = 4). Subdural hematoma (n = 2) and vasogenic edema (n = 6) were noted in eight patients. In three patients, involvement of venous sinuses led to obstruction of the sinus and compression of the cranial nerves. There was no significant difference in OS in relation to the characteristics of pachymeningeal involvement (single, focal, or diffuse type) or the location of pachymeningeal metastasis sites. The presence of hematoma and vasogenic edema did not affect the statistical significance of the median OS (3.43 vs. 4.7 months; $p = 0.155$), but most of these patients had died within 5 months.

3.3. Treatment and clinical outcomes

The treatment was not standardized and included