6 Cases of Breast Cancer-Associated Neoplastic Meningitis and Literature Review

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Research

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Abstract

Background: Neoplastic meningitis refers to malignant tumors invading the meninges and subarachnoid spaces, causing intracranial metastases similar to meningitis. Discovery of tumor cells in the cerebrospinal fluid is the gold standard for its diagnosis. In China, meningeal metastasis of breast cancer is a relatively rare type.

Methods: The clinical characteristics, imaging data, cerebrospinal fluid cytology and treatment options of 6 patients with meningeal metastasis of breast cancer treated in our hospital were analyzed.

Results: The median age of Neoplastic meningitis was 50 years old. The cerebrospinal fluid pressure of the 6 patients increased to varying degrees and tumor cells were found in the cerebrospinal fluid. Of the 6 patients, 2 received only supportive care, and the rest received chemotherapy and intrathecal injection. The shortest survival time was 1 week, and the longest survival time was over 33.2 weeks.

Conclusions: Patients whose initial Karnofsky Performance Scale scores were good and who received active and regular treatment after the diagnosis of NM had long overall survival time.

Background

Meningeal carcinomatosis (MC), also known as neoplastic meningitis (NM), is a type of central nervous system metastatic cancer which refers to the diffuse spread or focal infiltration of the primary malignant tumor of the whole body or central nervous system in the soft brain / meninges (including soft brain / meninges, arachnoid) and subarachnoid spaces through various pathways (blood, lymph, etc.), causing complex nervous system dysfunction without parenchymal brain metastases^[1–3]. Lung cancer is the most common cause of cancerous meningitis, followed by breast cancer, gastric cancer, and malignant lymphoma^[4, 5]. MC is usually in the middle and advanced stages of malignant tumors, and about 5% of breast cancer patients will have central nervous system metastases^[6, 7]. Patients with meningeal metastases from breast cancer often have a short survival time. The medium overall survival is about 8–20 weeks^[8–10]. The clinical manifestations of patients are not specific, headache is the most common symptom, and the diagnosis is difficult. At present, cerebrospinal fluid cytology is the gold standard for diagnosis, but about 40–50% of patients have negative initial tests^[11]. Repeated tests can improve diagnosis rate.

In this paper, we collected relevant clinical data of 6 patients with meningeal metastasis of breast cancer admitted to our hospital from March 2016 to December 2018, and analyzed their clinical characteristics, imaging examination and cerebrospinal fluid (CSF) cytology. Combined with case analysis and systematic review of related literatures, the understanding of meningeal metastasis in breast cancer was improved, which provided more evidence for future diagnosis and treatment.

Methods

Objects

A total of 6 patients who were diagnosed with meningeal metastasis of breast cancer in our hospital from March 2016 to December 2018 were collected. All 6 patients were female, aged 31 to 60 years, with an average age of onset of 50 years.

Methods

Analyze the clinical manifestations of all patients, including the age of onset, previous history, first symptoms, clinical symptoms and signs, treatment options, as well as laboratory examination, head MRI, skull CT plain scan and cerebrospinal fluid examination, and observe the patients' treatment and prognosis.

Results

A total of 6 patients were included in this paper. The characteristics of the patients were summarized in Tables 1 and 2. All 6 patients had a clear history of breast cancer. 5 of the 6 patients underwent pathological tissue immunohistochemical testing, of which case 4 was positive for human epidermal growth factor receptor 2 (HER2), cases 3 and 5 were positive for estrogen receptor (ER), and cases 2 and 6 had triple-negative breast cancer. Of the 6 patients, 4 patients had invasive ductal carcinoma, 1 had invasive lobular carcinoma, and 1 had no pathological examination. Tumor cells were found in the first lumbar puncture in 6 patients. The median age at diagnosis of NM was 50 years (from 31 to 60 years), with acute or subacute onset. 4 patients had intracranial high-pressure symptoms such as headache, nausea, and vomiting as the first symptoms, 1 patient had double vision i.e. oculomotor nerve palsy as the first symptom, and 1 had limb numbness as the first symptom. 2 patients had secondary seizures during the course of the disease, and 2 patients had hydrocephalus. 2 of the 6 patients had positive MRI enhancement scan, 3 patients had extracranial metastases which occurred earlier than intracranial metastases.

Cerebrospinal fluid pressure in all 6 patients increased to varying degrees (180–500 mm H₂O). Leukocytes were slightly elevated in 3 patients, protein in cerebrospinal fluid was elevated in 5 patients, chloride was low in 2 patients, and glucose levels were decreased in 3 patients. Tumor cells were found in the cerebrospinal fluid of 6 patients, which were scattered or severally distributed.

Cases 1

and 6 received only supportive care, and case 6 had triple-negative breast cancer. The time from diagnosis of breast cancer to meningeal metastasis in the 2 patients was 1 and 3 years, Karnofsky Performance Scale (KPS) scores were 70 and 30, and the survival time after diagnosis of NM was 7.14 and 1 weeks, respectively. Case 1 had bone metastases. Case 2 had triple-negative breast cancer with KPS scores of 70, and received systemic chemotherapy and local chemotherapy (intrathecal injection). The time from diagnosis of breast cancer to meningeal metastasis was 6 months, and the survival time

after diagnosis of NM was 8.24 weeks. Cases 3 and 5 had ER-positive breast cancer. Case 3 had KPS scores of 50 and received chemotherapy, radiotherapy, intrathecal injection and endocrine therapy. Case 5 had KPS scores of 80 and received chemotherapy and intrathecal injection. The time from diagnosis of breast cancer to meningeal metastasis was 5 years and 6 years, respectively. The survival time after diagnosis of NM was 9.56 weeks and > 14.5 weeks, respectively. Case 3 had lung, bone, and lymph node metastases before meningeal metastases, and case 5 had no extracranial metastases. Case 4 had HER2-positive breast cancer with KPS scores of 90, and received chemotherapy, radiotherapy, targeted therapy and intrathecal injection. The time from diagnosis of breast cancer to the occurrence of meningeal metastasis was 2 years, and the survival time after diagnosis of NM was > 33.2 weeks. Parenchymal brain metastases preceded meningeal metastases. Among the 6 patients, the shortest survival time was 1 week, and the longest survival time was over 33.2 weeks.

Of the 3 patients with unsatisfactory intracranial pressure control, 2 patients underwent ommaya sac implantation and 1 patient underwent cone craniotomy tube drainage, which effectively relieved the intracranial high-pressure symptoms.

Table 1
Patient details

Patient No.	Age (years)	Onset	Starting symptom	Time from diagnosis of breast cancer to meningeal metastasis	Metastasis	CT/MRI
1	57	Acute	Dizziness Headache Nausea Vomiting	1 year	Bones	-
2	46	Subacute	Headache Nausea Vomiting	6 months	-	+
3	60	Subacute	Diplopia Dizziness	5 years	Lungs, Bones Lymph nodes	-
4	52	Acute	Limb numbness Headache	2 years	Brain	+
5	54	Subacute	Headache	6 years	-	-
6	31	Subacute	Headache	3 years	-	-

Table 2
Clinical symptoms and treatment

Patient No.	KPS	Epilepsy	Hydrocephalus	The number of times found tumor cells in CSF	Treatments	survival time (weeks)
1	70	-	+	1	-	7.14
2	70	-	-	1	Chemotherapy Intrathecal injection	8.24
3	50	-	-	1	Chemotherapy Radiotherapy Intrathecal injection Endocrine therapy	9.56
4	90	-	-	1	Chemotherapy Radiotherapy Targeted Therapy Intrathecal injection	> 33.2
5	80	+	-	1	Chemotherapy Intrathecal injection	> 14.5
6	30	+	+	1	-	1

Discussion

In China, lung cancer and breast cancer are common solid tumors with meningeal metastases. Meningeal metastasis occurs in about 2% -5% of breast cancers, usually in the late stages of the tumor, and manifests as rapid and progressive neurological deterioration. The goal of treatment for NM is to improve nerve function, raise quality of life, and prolong the survival time of patients ^[12].

MC has various clinical manifestations and no obvious specificity. Therefore, MC patients with neurological symptoms as their first diagnosis are more likely to be misdiagnosed. In addition to the symptoms of the primary tumor, MC patients often show symptoms and signs of damage to specific areas of the central nervous system involved with tumor cells, characterized by polymorphism and multifocal lesions. Typical symptoms and signs appear in three areas of the nervous system: the cerebral hemisphere, cranial nerves, and the spinal cord^[13]. Brain dysfunction is mainly manifested as headache, nausea, vomiting, changes in consciousness level, extravertebral symptoms and seizures. The manifestation of cranial nerve involvement caused by MC is diplopia (mainly caused by injury to the VI pair cranial nerves, followed by the III and IV pair cranial nerves), facial nerve paralysis, impaired trigeminal nerve function and hearing loss. Among them, diplopia and facial nerve paralysis are the main and most common symptoms of cranial nerve involvement caused by MC. The most common manifestations of spinal cord involvement are fatigue, pee and stool dysfunction, limb paresthesia, neck or back radiculopathy and pain. Neck stiffness is present in less than 15% of MC patients^[7, 14, 15]. Others

can also show the inflammatory response of NM. Inflammation disrupts the fluidity of the cerebrospinal fluid, causing obstructive and communicating hydrocephalus. There can also be manifestations of cerebrovascular disease, such as cerebral infarction and cerebral ischemia. MC is highly suspected when there is a history of primary malignancies and symptoms of multiple neurological impairment. Some MC patients can also show a single symptom, such as elevated intracranial pressure and cauda equina syndrome. In this study, 1 case had diplopia as the main symptom, showing III, IV and VI pair cerebral nerve involvement. 1 case had spinal nerve involvement such as limb numbness as the first symptom, and 5 cases had intracranial high-pressure symptoms such as dizziness, headache, nausea, and vomiting as the first symptoms. 2 patients had seizures, and could also show the inflammatory response of NM. 2 patients had hydrocephalus. Studies have shown that ER-positive patients are more prone to bone metastasis than ER-negative patients, and the incidence of meningeal metastasis is lower than ER-negative patients. Case 3 had ER-positive breast cancer with bone metastasis.

According to literature reports^[14], in breast cancer-related meningeal metastasis patients, the median age of onset of breast cancer is 49.2 years, 78.2% of patients have invasive ductal carcinoma, and more than 50% of patients are in the third to fourth stages of the disease. 55.3% of patients are ER-positive, and HER2 is overexpressed in 47.4% of patients. The median survival time for patients diagnosed with breast cancer is 3.6 years (95% CI 2.54, 4.66). The median time from diagnosis of breast cancer to meningeal metastasis is 2.5 years (between 0.14 and 14.6 years). The median survival time of patients diagnosed with MC is 4.27 months (0.11–3.78), and 23% of patients have a survival time of more than 1 year after diagnosis of MC. Related studies have shown that invasive ductal carcinoma is prone to parenchymal brain metastasis, while invasive lobular carcinoma is prone to meningeal metastasis^[15]. Autopsy data from patients with metastatic breast cancer show that the incidence of MC in invasive lobular breast cancer is about 14%, while that in invasive ductal breast cancer is 1%^[16]. In the 6 patients in this study, the mean age of onset was 50 years. Of the 6 patients, 4 had invasive ductal carcinoma and 1 had invasive lobular carcinoma. The median time to meningeal metastasis in 6 patients was 2.6 years. The above were consistent with literature reports. In the pathological classification of breast cancer, triple-negative breast cancer is prone to MC metastasis and the chance is 21 ~ 40.5%^[14, 17]. In this study, 2 of 5 patients who underwent immunohistochemical testing had triple-negative breast cancer, which was consistent with previous studies.

Discovery of tumor cells in the cerebrospinal fluid is the "gold standard" for diagnosing MC, with specificity up to 100%. The sensitivity of the first lumbar puncture is 50%, and the sensitivity of two lumbar punctures can reach 90%^[18, 19]. Abnormalities of the cerebrospinal fluid in NM include: Increased cerebrospinal fluid pressure in approximately 46% of patients (> 200 mm H₂O), increased white blood cells in 57% of patients (> 4 / mm³), increased protein in 76% of patients (> 50 mg / dl), and decreased glucose in 54% of patients (< 60 mg / dl). However, these abnormalities are non-specific^[20, 21]. Cerebrospinal fluid pressure in all 6 patients increased to varying degrees (180–500 mm H₂O). Leukocytes were slightly elevated in 3 patients, protein in cerebrospinal fluid was elevated in 5 patients,

chloride was low in 2 patients, and glucose levels were decreased in 3 patients. Tumor cells were found in 6 cases at the first lumbar puncture, which were scattered or severally distributed.

Studies have found that the types of primary tumors, KPS and physical status (PS) of tumor patients, neurological conditions when diagnosing MC, large meningioma by imaging, MC-related encephalopathy, cerebrospinal fluid obstruction and the stage of systemic tumors are important prognostic factors^[22–24], and age is not a prognostic factor for patients. The prognostic factors confirmed by multivariate analysis include tumor characteristics, treatment options, and initial response to MC-related treatment. Recent studies have found no correlation of histological classification and cytological response with prognosis. KPS has been shown to influence the prognosis of MC patients in univariate analysis^[7, 25, 26]. In this study, patients with high KPS scores had a long survival time. Among them, case 4 had good initial KPS scores and received active and regular treatment after the diagnosis of NM. The patient had a long overall survival time. It has been reported that patients with HER2-positive breast cancer have an increased risk of brain metastases, but their survival time is prolonged compared with HER2-negative patients with brain metastases^[27]. Case 4 was HER2-positive, supporting this view. Cases 2 and 6 had triple-negative breast cancer. Case 2 received regular chemotherapy and intrathecal injection. After treatment, the symptoms eased and the survival time was 8.24 weeks. Case 6 had no formal treatment after the diagnosis of breast cancer. Subsequently, after the diagnosis of meningeal metastases, the disease progressed rapidly and the patient died quickly within 1 week. Both cases 3 and 5 were ER-positive. The initial KPS of case 3 was poor. Although receiving chemotherapy, endocrine therapy, etc., the survival time of case 3 was still shorter than that of case 5.

At present, there is no standard treatment for NM. Local chemotherapy (intrathecal injection) can directly deliver drugs to the cerebrospinal fluid and is a common method for treating MC^[28]. Studies have shown that although systemic chemotherapy drugs have limited ability to penetrate the blood-brain barrier, the concentration of drugs that can reach the cerebrospinal fluid is very low, systemic treatment is thereby not an effective method for the treatment of NM, it is still an independent factor affecting the prognosis of NM patients. Multiple retrospective analyses have shown that systemic chemotherapy can prolong the survival time of patients^[29–32], and can simultaneously treat active systemic tumors and meningeal lesions. Targeted therapy is a brand-new treatment method. It has become an important part of comprehensive treatment of NM together with traditional treatments such as surgery, radiotherapy, chemotherapy and local chemotherapy (intrathecal injection). There are two types of targeted therapy for breast cancer patients. One is endocrine therapy for ER-positive patients. For example, case 3 received exemestane for endocrine therapy. The other is endocrine therapy for HER2-positive patients. For example, case 4 received targeted therapy with Herceptin (trastuzumab). For patients with early ER-positive breast cancer, endocrine therapy is an important treatment method. It can inhibit the growth or activity of tumor cells by blocking the transmission of estrogen signals to the pathway or reducing estrogen levels to achieve the purpose of treating breast cancer. Tamoxifen and exemestane are used for endocrine therapy. For HER2-positive breast cancer, targeted drugs include trastuzumab, pertuzumab, and lenatinib. Trastuzumab dominates the metastatic treatment of breast cancer, which can effectively

reduce the risk of breast cancer recurrence and metastasis^[33–36], improve remission rate and prolong survival time. Endocrine therapy has therapeutic effects on both intracranial and extracranial lesions. Studies show that the concentration of tamoxifen and its metabolites in brain tissue and BM can reach 46 times that in serum, which can effectively control the symptoms of metastatic NM, slow the progress of the disease, and even completely relieve the condition. In this study, case 3 underwent endocrine therapy.

The treatment of different NM patients varies due to different general conditions and pathological types, but all patients diagnosed with NM should be actively treated with dehydration and intracranial pressure lowering treatment to ensure the time window of chemotherapy and radiotherapy. Commonly used dehydration drugs include mannitol, glycerol fructose, albumin and the like. Osmotic diuretics such as mannitol can also increase the permeability of the blood-brain barrier and improve the effect of systemic chemotherapy drugs. MC patients may have multiple complications at an advanced stage. Hydrocephalus is one of the common complications and an important cause of death. For MC patients with hydrocephalus, a new cerebrospinal fluid circulation pathway can be established through surgical treatment, which can reduce intracranial pressure, protect brain function, and effectively relieve clinical symptoms. This method does not affect other medical chemotherapy, can improve the quality of life, and significantly extend the survival time of patients. Among the 3 patients with suboptimal intracranial pressure control in this study, 2 patients underwent ommaya sac implantation, 1 patient underwent cone craniotomy tube drainage, and the intracranial high-pressure symptoms were effectively relieved.

Conclusions

NM is a common complication in breast cancer patients, and its incidence is increasing. Current research suggests that invasive ductal carcinoma is the most common pathological type in breast cancer patients with brain metastasis, but invasive lobular breast cancer is more prone to MC metastasis than invasive ductal breast cancer. Among different subtypes, triple-negative breast cancer has the highest risk of meningeal metastasis, followed by luminal A, HER2 positive and luminal B. Patients with HER2-positive breast cancer have an increased rate of brain metastasis, but have a longer survival time compared with HER2-negative breast cancer patients with brain metastasis. Regarding the factors affecting the prognosis of meningeal metastasis of breast cancer, different studies have reached different conclusions, but multiple studies have shown that PS, HR status, and treatment options have an impact on prognosis. Discovering tumor cells by cerebrospinal fluid cytology is the "gold standard" for the diagnosis of MC. Cerebrospinal fluid cytology combined with skull MRI can improve the accuracy of diagnosis. Intrathecal injection directly injects the drug into the cerebrospinal fluid, which can effectively increase the concentration of the drug reaching the central nervous system, reduce the toxic and side effects of systemic medication, and improve the prognosis, thereby an effective method for treating MC.

Abbreviations

NM

neoplastic meningitis; MC:Meningeal carcinomatosis; CNS:Central nervous system; CSF:Cerebrospinal fluid; CT:Computed tomography; MRI:Magnetic resonance imaging; KPS:Karnofsky Performance Scores; PS:physical status; HER2:human epidermal growth factor receptor 2; ER:estrogen receptor

Declarations

Ethics approval and consent to participate

This study has been approved by the Ethics Committee of the Second Hospital of Hebei Medical University. Written informed consent has been obtained from all patients or their legal surrogates.

Consent for publication

Not applicable.

Availability of data and materials

Study data are available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Study concept and design (JYF, PG, JYH and HB); acquisition and interpretation of the data (JYF, PG, YLZ, LTY, YZ and HB); drafting of the manuscript (JYF, PG and HB); critical revision of the manuscript for important intellectual content (JYF, JYH, YZ and HB); acquisition of funding (HB); administrative, technical, or material support (administrative, technical, or material support); study supervision (JYH and HB). All the authors read and approved the final manuscript.

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