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ORIGINAL ARTICLE

Leptomeningeal metastases arising from gynecological cancers

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Abstract

Background Most cases of leptomeningeal metastasis (LM) arise from solid tumors, such as breast cancer, lung cancer, or malignant melanoma. LM arising from gynecological cancers are extremely rare. Longer survival owing to recent advances in chemotherapy and other treatments has contributed to the increased frequency of gynecological cancers metastasizing to the central nervous system (CNS). Detailed information regarding LM is scarce; therefore, we conducted a study concerning LM arising from primary gynecological cancers.

Methods Among 24 patients with CNS metastases from gynecological cancer treated at our hospital between January 2011 and August 2018, those who were eventually diagnosed with LM were included in this retrospective study.

Results Among 24 patients with CNS metastases, five patients (20.8%) were diagnosed with LM. The primary cancer was endometrial in two, cervical in one, and peritoneal in two patients. Of these five patients, three developed LM as a complication 1–11 months after the treatment of brain metastases; one patient had multiple brain metastases diagnosed at the same time as LM, and one had LM alone, without accompanying brain metastases. The median survival after the diagnosis of LM was 23 (12–69) days, while the median survival of 24 patients after the initial diagnosis of CNS metastases was 106 (13–959) days.

Conclusion Although LM arising from gynecological cancers is considered rare, identification of LM may be important to predict prognosis and develop new therapeutic strategies.

Keywords Leptomeningeal metastasis · Gynecological cancer · Brain metastasis

Introduction

Leptomeningeal metastases (LM) are a catastrophic complication of advanced cancer that is caused by the spread of cancer cells to the central nervous system (CNS). The incidence of LM in patients with metastatic cancer is approximately 5–10%. The increased incidence is attributable to prolonged survival due to improved supportive care, chemotherapy regimens, and diagnostic imaging techniques [1, 2]. Patients with LM have a poor prognosis; the median survival from diagnosis of LM usually a few months [2, 3].

Breast cancer, lung cancer, and melanoma are the three most common causes of LM; LM arising from gynecological cancers are extremely rare [4–6]. However, like any other cancer, recent advances in anticancer therapy have helped prolong survival and have also increased the frequency of CNS metastases in patients with gynecological cancers [7, 8]. It is anticipated that LM from gynecological cancers may also become more common.

There are presently no established data on LM from gynecological cancers because of its rarity and lack of detailed studies. Therefore, physicians may be perplexed by the rapid disease progression of and the variety of symptoms. We herein present a retrospective clinical analysis of five cases of LM arising from gynecological cancers.

Materials and methods

Between January 2011 and August 2018, 2179 patients were treated at our hospital for gynecological cancers (except cases of carcinoma in situ and ovarian tumor with low malignant potential); of these, 24 patients (1.1%) had CNS metastases. Out of these 24 patients, 5 (20.8%) were diagnosed

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with LM (4 patients had both LM and brain metastases) and 19 (79.2%) had only brain parenchymal lesions.

We performed a retrospective chart review to obtain demographic data as well as details of initial gynecological cancer diagnosis, cancer type, histology, date of LM diagnosis, treatment for LM, and data about death or last follow-up. All CNS metastases were diagnosed using neuroimaging, and LM was diagnosed based on cytology of cerebrospinal fluid (CSF), neurological symptoms, and neuroimaging.

This study was approved by the Institutional Review Board of the Hyogo Cancer Center before the initiation of data collection. The study was conducted in accordance with the Helsinki Declaration.

Results

The characteristics of the five cases are summarized in Table 1. The primary cancer of LM was uterine corpus cancer in two patients, uterine cervical cancer in one, and primary peritoneal cancer in two patients. The histology types were varied; two cases (case 4 and 5) were diagnosed by cytology of ascites specimens and their details could not be identified before initial treatment. The mean age at the diagnosis of primary cancer was 55.2 ± 8.9 (range 39–64) years. All five cases were an advanced stage of cancers and required combined modality therapy as the initial treatment.

Leptomeningeal metastasis was diagnosed on the basis of positive CSF cytology testing in three patients and a combination of magnetic resonance imaging (MRI) findings and typical LM-related neurological symptoms in two patients (Table 2). Figure 1 shows the MRI findings of case 3 and case 5. The mean time from primary cancer diagnosis to LM diagnosis was 837.2 ± 428.9 (range 409–1382) days. Of these five patients with LM arising from gynecological cancers, three developed meningeal dissemination as a complication 1–11 months after the treatment for brain metastases; one patient had multiple brain metastases diagnosed at the same time as LM, and one had LM alone, without the accompanying brain metastases. Three patients received radiation therapy after the diagnosis of LM (one received whole-brain radiation to relieve symptoms of brain hypertension and two received lumbar radiation to alleviate pain in lower limbs). These symptoms were temporarily relieved after radiation therapy. The other two patients had mild consciousness disorder and developed lethargy at the diagnosis of LM. They received only the best supportive care because of rapid deterioration and progression to coma. Two patients

Table 1 Clinical characteristics of patients with leptomeningeal metastasis (LM)

Case	Age(years)[a]	Cancer type	Histology	TNM stage[b]	Initial treatment
1	64	Uterine corpus cancer	Serous carcinoma	T4N1M1	Op. + Chemo Tx
2	62	Uterine corpus cancer	Carcinosarcoma	T2N2M0	Op. + Chemo Tx
3	39	Uterine cervical cancer	Squamous cell carcinoma	T2bN1M0	Op. + CCRT
4	53	Primary peritoneal cancer	Adenocarcinoma	T3cN1M1	Chemo Tx + Op. + Chemo Tx
5	58	Primary peritoneal cancer	Adenocarcinoma	T3cN0M0	Chemo Tx + Op. + Chemo Tx

Chemo Tx chemotherapy, *Op.* operation, *CCRT* concurrent chemoradiotherapy

[a]Age at diagnosis of cancer

[b]International Union for Cancer Control, 8th edition

Table 2 Diagnosis and outcomes of patients with LM

Case	Initial symptoms	Diagnosis	Duration (days)[a]	Other organs[b]	Treatment for MC	Duration (days)[c]
1	Consciousness disorder + dysarthria	Cytology	1382	LN	BSC	15
2	Consciousness disorder	Cytology	458	Brain, lung, LN	BSC	12
3	Nausea + involuntary movements	MRI + CF	409	Brain, lung, LN, Vagina	WBR	23
4	Headache + dizziness	Cytology	1330	Brain	Lumbar radiation	57
5	WL + low back pain + vomiting	MRI + CF	607	Brain	Lumbar radiation	69

BSC best supportive care, *CF* clinical features, *LN* lymph nodes, *MRI* magnetic resonance imaging, *WBR* whole-brain radiation, *WL* weakness of lower extremities

[a]Duration from diagnosis of cancer to the diagnosis of LM

[b]Other organs involved with the disease at the time of LM diagnosis

[c]Survival duration after diagnosis of LM

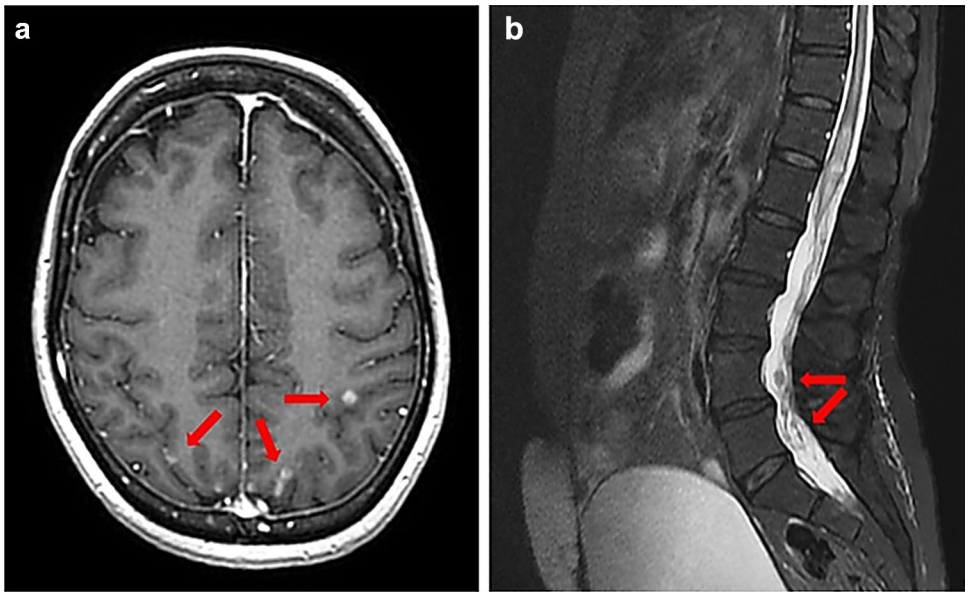

Fig. 1 MRI findings of case 3 and case 5. **a** Enhancement of metastatic nodules in the cerebral cortex, especially in the left occiput lobe in postgadolinium 3D axial T1-weighted sequence. **b** Multiple nodular lesions in the spinal canal, especially along the caudal and sacral edges in postgadolinium 3D FLAIR sagittal fat suppression T2-weighted sequence

with localized metastases in the brain at LM diagnosis showed relatively long survival duration of approximately 2 months (case 4 and 5).

The mean survival of five patients after LM diagnosis was 35.2 ± 23.3 days and the median survival was 23 (range 12–69) days. In contrast, the mean survival of 19 patients (non-LM) after initial CNS metastases diagnosis was 184.1 ± 220.8 days and the median survival was 114 (range 13–959) days (Fig. 2).

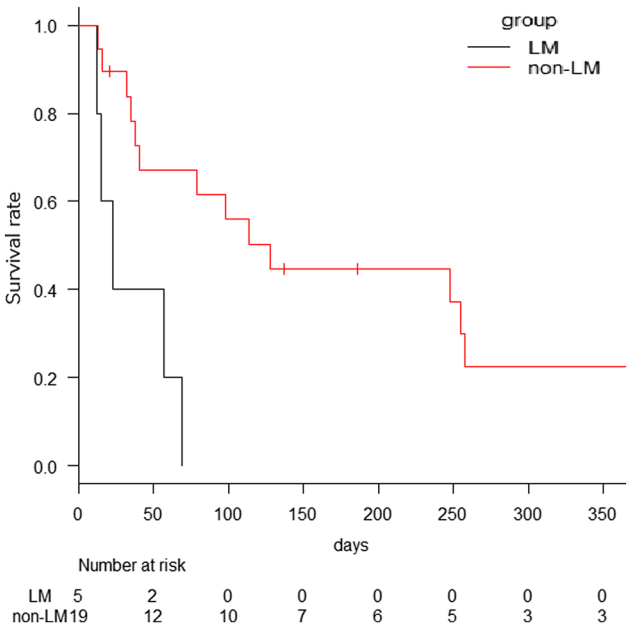

Fig. 2 Kaplan–Meier analysis of overall survival curves after diagnosis of leptomeningeal metastasis (LM: black line) and central nervous system metastasis without leptomeningeal metastasis (non-LM: red line)

Discussion

The incidence of CNS metastases depends on both the prevalence of primary cancer and its propensity to metastasize to the CNS. The incidence of CNS metastases from gynecological malignancies has been claimed to be rare [9, 10]; however, this may need to be reviewed. According to a report based on the brain tumor registry of Japan (2005–2008), lung and breast cancers are the most common sources of brain metastases. The frequency of gynecological cancers among all cases of brain metastases was 4.6% (ovary: 2.0%, uterus: 2.3%) [11] and this frequency approximated the incidence of gynecological cancers (ovary and uterus) in Japan during the period 2005–2008 (3.9–4.1%) [12]. This implies that the propensity of gynecological cancers to metastasize to the CNS may be average rather than low.

On the other hand, the incidence of LM arising from gynecological cancers seems to be even lower considering its prevalence compared to 5–10% LM incidence in general cancer patients [1, 2]. It is difficult to accurately determine the frequency of LM from gynecological cancers among all LM cases; however, Yust et al. reported that 0.03% (4/13,289) of patients with cervical cancer and 0.06% (8/13,126) of patients with ovarian cancer registered at the MD Anderson Cancer Center database between 1978 and 2011 developed LM [13]. In our study, 0.22% (5/2179) of the patients with gynecological cancer were diagnosed with LM. This high frequency may be attributable to improvements in diagnostic techniques, and the longer survival owing to advances in the treatment of gynecological cancer.

However, this may be much higher because the propensity to metastasize to the CNS is equivalent to overall cancers and the possible diagnosis of LM may not have been previously pursued in gynecological cancers due to the belief of rare frequency and the poor prognosis of patients receiving only palliative care in the terminal state.

Leptomeningeal metastasis was diagnosed according to the diagnostic criteria proposed by the present European Association of Neuro-Oncology–European Society for Medical Oncology (EANO–ESMO) guidelines [1]. These EANO–ESMO joint recommendations for the diagnosis and treatment of LM from solid cancers represented the first European guideline initiative on this topic. A definitive diagnosis of LM requires cytological identification of malignant cells within CSF; however, the sensitivity of CSF cytology testing is not high. In a recent large cohort study of LM patients, CSF cytology testing was positive in 66–90% patients [14]. Nevertheless, it may be difficult to perform invasive investigations, such as lumbar puncture, in terminally ill patients. The characteristic MRI findings such as sulcal enhancement or obliteration, linear ependymal enhancement, cranial nerve root enhancement, and leptomeningeal enhancement nodules, notably of the cauda equine, and CSF analysis results are complementary. In our study, malignant cells were detected in the CSF in three patients, confirming LM, and two patients were diagnosed with LM based on typical neuroimaging findings obtained by gadolinium-enhanced MRI and clinical signs (CSF cytology testing was negative in one patient and the other did not undergo lumbar puncture).

Comparing the outcomes of LM with those of CNS metastases is not entirely useful because some patients develop LM after brain metastases and their prognosis is extremely poor. In the present study, the median survival of patients with LM was 23 (12–69) days and this was shorter than that in published literature (a few months). Two patients with altered consciousness had especially short survival of around 2 weeks; this may be because of the rapidly increased intracranial pressure, although there were no signs of headache or vomiting.

The treatment for LM should be aimed at prolonging survival, with an acceptable quality of life, and preventing or delaying neurological deterioration [1]. There are no established standard treatments for patients with gynecological cancers with LM, and the survival benefit of the currently used treatments is not clear. In some randomized controlled clinical trials of currently available CNS chemotherapeutic agents, the median survival in carefully selected patients was only 3–4 months [15–20]. However, it is now possible to expect improvement in survival by active treatments like the addition of intrathecal pharmacotherapy to systemic treatment and systemic therapy using targeted agents and immunotherapy [21]. Individualized treatment strategies involving a combination of treatment modalities such as the new pharmacotherapies, involved field radiotherapy, and palliative care may help improve outcomes. Till date, few clinically useful surrogate markers have been identified in the context of gynecological cancers. In this study, we could not obtain any immunohistochemical data pertaining to primary cancers. However, identification of biomarkers based on molecular genetic characteristics may facilitate treatment decision-making and selection of appropriate pharmacotherapy; further studies in this respect should be conducted in the context of gynecological cancers like other cancers: lung, breast, and melanoma.

Performance status at diagnosis of LM is the most important prognostic factor and the EANO–ESMO guidelines recommend palliative care in patients with life expectancy < 1 month [1]. This indicates that early diagnosis of LM is a key imperative to institute active treatment and help prolong survival. None of the patients included in this study received systemic or intra-CSF chemotherapy. However, gynecologists should realize that LM arising from gynecological cancers is no longer rare and early diagnosis of LM should be a key focus area.

In conclusion, although LM from gynecological cancers is considered rare, the incidence may be much higher than what is currently perceived. Identification of LM may be important to predict prognosis and to develop new therapeutic strategies for patients with gynecologic cancers.

Compliance ethical standards

Conflict of interest The authors have declared no conflicts of interest.

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