Neoplastic Meningitis: A Retrospective Review of Clinical Presentations, Radiological and Cerebrospinal Fluid Findings

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Objective: *To review the clinical, radiological, and laboratory presentations of patients with neoplastic meningitis.*
Material and Method: *Patients with neoplastic meningitis were recruited by a retrospective search of cerebrospinal fluid (CSF) cytopathological report database of Siriraj Hospital between 1997 and 2006. Clinical information and CSF result of these patients were extracted from their medical records. Neuroimagings were reviewed by a neuroradiologist.*
Results: *The present study revealed 40 cases of neoplastic meningitis, which comprised of 17 cases with carcinomatous meningitis (CM) and 23 lymphoma/leukemia meningitis (LM) cases. In patients with CM, the majority (70%) had adenocarcinoma of lung or breast. Three of 17 cases with unknown primary tumor had carcinomatous meningitis as an initial presentation. In LM, most of the cases (70%) were diagnosed with acute lymphoblastic leukemia (ALL) and non-Hodgkin's lymphoma (NHL). The most common symptom among patients with CM and LM was headache follow by cranial nerve palsy. In CM cases, CSF cytology was positive in the first specimen in 15 cases (82.35%) and in 22 from 23 cases (95.7%) in LM cases. Overall CSF showed pleocytosis in 36 cases (90%), most of which were lymphocyte predominant. The most common findings from brain imagings were leptomeningeal enhancement and hydrocephalus.*
Conclusion: The common primary sites were lung and breast cancer in the CM group and ALL and NHL in the LM group. The common symptoms were headache and cranial nerve palsy. Routine CSF examination was abnormal in virtually all cases. Positive CSF cytology was a gold standard for a diagnosis of leptomeningeal metastasis. High index of suspicious and awareness were required to avoid miss diagnosis.

Keywords: *Carcinomatous meningitis, Leukemia meningitis, Leptomeningeal meningitis*

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Neoplastic meningitis is a common problem in neuro-oncology, diagnosed in approximately 5% of all patients with cancer. It has been reported in all kinds of tumor including solid tumors (carcinomatous meningitis: CM), and hematological malignancies (leukemic or lymphomatous meningitis: LM). The incidence of leptomeningeal metastasis varies according to the primary tumor site. Several clinical series have estimated that leptomeningeal metastasis occurs in 4 to 15% of patients with solid tumors, 7 to 15% of patients with lymphomas, and 5 to 15% of patients with leukemia[1-3].

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The pathogenesis is believed to be a spread of malignancy cells to the cerebrospinal fluid (CSF) compartment, which then the tumor cells disseminate to all regions of the central nervous system (CNS) via CSF, and thereby involve the entire neuraxis. As a consequence, the clinical presentation varies greatly depending on the part(s) of CNS involved (cranial nerves, spine, and cerebrum). Hence, a high index of suspicion needs to be entertained in order to make the diagnosis. The most useful laboratory test in the diagnosis of leptomeningeal metastasis is the CSF cytological examination[4], a standard method in clinical practice.

Here, the authors performed a retrospective analysis of patients diagnosed of leptomeningeal metastasis confirmed by an abnormal CSF cytological study at our center between 1997 and 2006. We aimed to find out the incidence of primary tumor sites and

their histopathology, clinical manifestations, CSF profiles and neuroradiological findings in order to enhance early detection of leptomeningeal metastasis in our practice.

Material and Method

Patients with neoplastic meningitis were recruited by a retrospective search of CSF cytopathological report database of Siriraj Hospital between 1997 and 2006. The inclusion criterion was adult patients (15 years old and above) with positive CSF cytological examination. The exclusion criterion was patient who was diagnosed with primary brain tumor. With these criteria, 40 patients were included. Clinical information of these patients was extracted from their medical records. Their neuroimaging at the time of diagnosis (including CT and MRI), if available, were reviewed by a neuroradiologist.

The following information was extracted; demographic data, age at diagnosis of the primary tumor, site and type of primary tumor. Clinical data regarding leptomeningeal metastasis were collected including signs and symptoms at presentation and CSF examination results, and numerical data result was described by using percentage, range, mean and median. The present study was approved by the Local Ethics Committee.

Results

Patient characteristics

Seventeen patients with CM and 23 patients with LM with positive cytology were identified. The mean age of CM group was 50-year-old, of which nine were male and eight were female, whereas the mean age of LM group was 33-year-old, of which 11 were male and 12 were female. Details of primary site of tumor were summarized in Table 1.

In patients with CM, the majority (70%) had adenocarcinoma of lung or breast. Three of 17 cases with unknown primary tumor had carcinomatous meningitis as an initial presentation. These three patients died without primary cancer identified.

In LM, most of the cases (70%) were diagnosed with acute lymphoblastic leukemia (ALL) and non-Hodgkin's lymphoma (NHL).

Clinical presentation

Six of the 17 patients with CM had CM as an initial presentation. Four of these were incorrectly diagnosed with Bell's palsy, idiopathic pachymeningitis, cerebral venous thrombosis and tension type headache before the diagnosis of CM was made. The other 11 cases were diagnosed during the progressive-dissemination course with median time from diagnosis of primary tumors to diagnosis of CM was three months (range 1 month to 7 years). All 11 patients in this group had the diagnosis made correctly.

LM cases were found only in patients who had been diagnosed with hematologic malignancies. Twenty-two from 23 cases were treated with chemotherapy, in which four cases had complete remission. Two cases were treated with bone marrow transplantation.

Common signs and symptoms were shown in Table 2. The most common symptom among patients with CM and LM was headache. Median time from the symptom onset to the diagnosis of CM was four weeks (range 1 to 24 weeks).

LM occurred within first year of primary disease in 16 cases (69.6%). Leptomeningeal involvement was diagnosed ranged from 1 to 120 months from diagnosis of underlying hematologic malignancies, in which top of the range value came from a 16-year-old diagnosed with Burkitt lymphoma who was in complete remission after a bone marrow

Table 1. Primary site and pathology of malignancy

CM (n = 17)		LM (n = 23)	
Tumor site and pathology	Number (%)	Pathology	Number (%)
Lung: adenocarcinoma	9 (52.9)	ALL	8 (34.8)
Breast: adenocarcinoma	3 (17.6)	ANLL	3 (13.0)
Skin: melanoma	1 (5.8)	CML	2 (8.7)
Orbit: rhabdomyosarcoma	1 (5.8)	NHL	8 (34.8)
Unknown	3 (17.6)	Burkitt's lymphoma	2 (8.7)

CM = carcinomatous meningitis; LM = lymphoma/leukemia meningitis; ALL = acute lymphoblastic leukemia; ANLL = acute non-lymphoblastic leukemia; CML = chronic myeloid leukemia; NHL = non-Hodgkin's lymphoma

Table 2. Clinical presentations

	CM number (%)	LM number (%)
Symptoms		
Headache	12 (70.5)	13 (56.5)
Alteration of mentation	7 (41.1)	2 (8.7)
Seizure	2 (11.8)	3 (13.0)
Cranial nerve palsy	7 (41.1)	13 (56.5)
Spinal symptom	7 (41.1)	7 (30.4)
Physical sign		
Papilledema	3 (17.6)	5 (21.4)
Stiffness of neck	7 (41.1)	4 (17.4)

Table 3. Latency from diagnosis of hematologic malignancy to diagnosis of LM

Time (month)	Number
<3	3
3-6	9
>6-12	4
>12-24	2
>24-36	3
>36-48	1
>48	1

transplant for 10 years. Table 4, summarized the distribution of disease latency from the diagnosis of malignancy to leptomeningeal metastasis. Eighteen patients with LM were diagnosed with leptomeningeal involvement within the first month after onset of symptom, with a median time of two weeks.

Cranial nerve involvement in both groups is summarized in Table 4. The most common cranial nerve involvement is CN VI palsy. LM causes cranial nerve dysfunction more frequently than CM.

CSF analysis

In CM cases, CSF cytology was positive in the first puncture specimen in 15 cases (82.35%). Two cases cytology was positive at the second puncture specimen (11.76%), and only one case was positive at the third puncture specimen. CSF showed pleocytosis in 15 cases (88.2%), most of which were lymphocyte predominant. Details of CSF results were presented in Table 5.

In LM cases, CSF cytology was positive in the first puncture specimen in 22 from 23 cases (95.7%). The only case that CSF cytology was positive in the fourth specimen was a patient with Burkitt's lymphoma who was in remission for about 10 years after bone marrow transplantation. CSF details in LM cases were also shown in Table 5.

Radiological findings

In CM patients, three Contrast enhanced computed tomography (CECT) of brain, and two Gadolinium enhanced magnetic resonance imaging (Gd-MRI) brain were available for review. In LM patients, 10 CECT brain and three Gd-MRI brain was found. Detail of findings is summarized in Table 6. The most common finding from brain images was leptomeningeal enhancement and hydrocephalus.

Table 4. Frequency of cranial nerve involvement

Cranial nerve	CM: number			LM: number			Total (%)
	Unilat	Bilat	Total	Unilat	Bilat	Total	
CN II	-	1	1	2	2	4	5 (10.2)
CN III	-	-	-	3	1	4	4 (8.2)
CN IV	-	-	-	2	-	2	2 (4.0)
CN V	1	-	1	3	-	3	4 (8.2)
CN VI	2	2	4	3	5	8	12 (24.5)
CN VII	3	-	3	4	1	5	8 (16.3)
CN VIII	1	2	3	-	1	1	4 (8.2)
CN IX	1	-	1	2	-	2	3 (6.1)
CN X	1	-	1	2	-	2	3 (6.1)
CN XI	-	-	-	-	-	-	0 (0)
CN XII	1	-	1	2	1	3	4 (8.2)

Unilat = unilateral involvement; Bilat = bilateral involvement

Table 5. Results of CSF

Parameter	CM		LM	
	Abnormal: n (%)	Median (range)	Abnormal: n (%)	Median (range)
High opening pressure	8 (47.0%)	18.5 (9.5-59)	12 (52.17%)	26 (9-60)
WBC >5 cell/mm^3	15 (88.2%)	16 (1-200)	21 (91.0%)	360 (2-6,200)
Protein (>40 mg/dl)	12 (70.58%)	136 (8-464)	14 (70.0%)	74.5 (24-3,844)
Glucose (ratio <0.6)	13 (76.4%)	36 (3-91)	15 (65.2%)	34.5 (1-106)

CSF = cerebrospinal fluid

Table 6. Neuroradiological involvement in patients with neoplastic meningitis

	Brain CT		Brain MRI	
	CM	LM	CM	LM
Number of cases	3	10	2	3
Skull	1*	0	0	0
Dura	1*	0	1	0
Leptomeninges	0	8	2	3
CN	1*	1	1	1
Other Parenchymal lesion†	3	1	2	1
Hydrocephalus	2	7	2	1

* Local invasion in the case of rhabdomyosarcoma of orbit
† Incidental non-relevant findings such as ischemic stroke and calcified cavernoma

Involvement of skull and dura were seen in only one case of Rhabdomyosarcoma that primarily involved the orbit.

Discussion

The incidence of neoplastic meningitis varies according to the tumor site. In recent studies, it occurs in 3% of patients with breast cancer (range 0.8 to 5%), 6% of those with small-cell lung cancer, 1% with non-small cell lung cancer, 0.015 to 0.25% with gastrointestinal tumors, 3% with unknown primary tumors, and 1.5% with melanoma[5-11]. Adenocarcinoma is the most frequent histology, and breast, lung, and melanoma are the most common primary sites to metastasize to the leptomeninges[12-14]. The disease is most commonly seen in patients with disseminated progressive systemic disease (60 to 70% of all patients) but it can present after a disease-free interval (20%)[13,15]. Neoplastic meningitis is the initial manifestation of systemic cancer in only 5 to 10% of patients[16]. There has rarely been a report of clinical presentation correlated with radiological findings and CSF examination of local (Thai) population.

In the present study, lung and breast adenocarcinoma were the most common primary sites accounting for 70.6% (12 of 17 cases) of CM with disseminated progressive systemic disease, followed by three cases (17.6%) with unknown primary tumors that had CM as an initial presentation. This result was similar to most series that lung and breast account for the most cases of the disorder in which adenocarcinoma is the most frequent histopathological diagnosis. Malignant melanoma, which was found in only one case in the present study, may reflect the low incidence of this condition in our country.

Most of LM cases (18 of 23 case, 78.2%) in the present study were diagnosed with hematologic malignancies either ALL or NHL. These findings were similar to other studies, which show that ALL and NHL tend to invade CNS more than other subtype[17,18]. LM is reported in 5 to 15% of patients with diffused high-grade non-Hodgkin's lymphoma. In acute lymphoblastic leukemia, 6% (range 1 to 10%) of adult patients show CSF dissemination at initial diagnosis, and another 31% (range 30 to 32%) develop CNS relapse during the course of the disease without primary CNS-directed therapy[19].

Tumor cells reach the subarachnoid space either through the blood (venous or arterial), by growing along nerves and vascular sheaths, or by direct extension from a tumor adjacent to CSF (parenchymal brain metastases, bony tumor lesions in the skull or spine)[20-22]. After reaching the subarachnoid space and leptomeninges, tumor cells are transported by the CSF to all regions of the CNS and thereby involve the entire neuraxis. The most common manifestations of cerebral hemispheric dysfunction are headache and mental status changes[12-15,23]. Other signs include confusion, dementia, seizures, and hemiparesis. Diplopia is the most common symptom of cranial nerves dysfunction with the abducens nerve being most frequently affected, followed by oculomotor nerve and trochlear nerve[12-15,23]. Trigeminal sensory

or motor loss, cochlear dysfunction, and optic neuropathy are also common findings[12-15,23]. Spinal cord signs and symptoms include weakness (lower extremities more often than upper), dermatomal or segmental sensory loss and pain in the neck, back, or following radicular patterns. Nuchal rigidity is only present in 15% of cases[12-15,23].

In the present study, headache was the most common symptom occurred in 62.5% of overall cases, but more common in CM than LM (70.5% vs. 56.5% respectively). Papilledema and stiffness of neck also accompanied in some cases, in which stiffness of neck was more common in CM than LM (41% vs. 17.4%). Cranial nerve involvement and spinal-cauda equina syndrome were also common findings apart from the headache. Table 5 showed that Abducent nerve was the most frequently affected cranial nerve, followed by cranial nerve VII, II, III, V, VIII, and XII, respectively. However, the incidence of abducens nerve palsy might be over-estimated due to some patients with abducent nerves palsy may have had it as a part of false localizing sign from increased intracranial pressure. Alteration of mental status was found more commonly in CM group. This might be resulted from a more delay in diagnoses or could be due to an aggressive course of diseases itself compared to LM group.

CSF routine testing is abnormal in nearly all cases. CSF pleocytosis is detected in 88.2% and 91% in CM and LM group respectively (overall 90%), the CSF protein concentrations is high in more than two-third of cases and the CSF glucose to blood glucose ration is decreased in more than two-third of cases. A raised opening CSF pressure (>200 mm H_2O) is reported in 47% and 52% of our patients with CM and LM, respectively. Nevertheless, CSF without pleocytosis could not totally exclude neoplastic meningitis, therefore, CSF cytology should be done in all cases with suspected neoplastic meningitis. A CSF volume of 10 ml increases the possibility of a positive and accurate CSF cytology[24]. In various case series, malignant cells were detected in the CSF of about 70-89% of patients with neoplastic meningitis, in whom the definition of neoplastic meningitis depend on a positive cytology[1,25-27]. Only two cases from 40 in the present study had 10 ml samples, most of the samples were less than 3 ml. These might cause many patients with leptomeningeal metastasis had false negative cytology and were not included. Among CM cases, CSF cytology was positive in first puncture specimen in 15 cases (82.35%), two cases cytology was positive at second puncture specimen (11.76%), and only one case was positive at third puncture specimen. In LM cases, CSF cytology was positive in first puncture specimen in 22 cases (95.7%). Repeated specimens of CSF cytology should be encouraged in clinically suspected patients (especially CM) with negative first CSF cytology but yield of later specimen might be lower.

The most common neuroimaging findings in both CECT and Gd-MRI of brain are communicating hydrocephalus and diffused leptomeningeal enhancement. Focal lesion such as cranial nerves enhancement is found in only a few cases by MRI, and CECT demonstrates an enhancement of cavernous sinus in one case. Most of the available imagings were abnormal in the present series. However, the authors could not conclude the abnormal radiographic findings in patients with CM and LM due to the small number of imaging available in the study.

Many studies show that MRI is more sensitive than CECT for the assessment of the brain[28,29]. Standard MRI assessment of patients with neoplastic meningitis should include both the brain and spine to examine the entire neuraxis. However, these neuroimaging findings are non-specific, and are compatible with neoplastic meningitis only in an appropriate clinical context. A lumbar puncture can also rarely lead to leptomeningeal enhancement as a consequence of a persistent lumbar CSF leak and the development of intracranial hypotension with associated venous vasodilation.

The present study was mainly limited by first, a retrospective nature. Many information about clinical manifestations in which the important object of study might be missed. Secondly, the inclusion criterion that needed positive CSF cytology report from Department of Pathology might not reflect the true incidence of metastatic neoplastic meningitis in clinical practice, which should be much more than these 40 cases in 10 years at our institution. For instance, many affected patients could had diagnosed from malignancy cells that found in routine CSF examination, had false negative cytology, or had contraindication for lumbar puncture.

The next study with these similar objectives should have a better design by accompanying neurologist, oncologist, and hemato-oncologist and should be performed in a prospective manner to get the best possible population and information. Enrolled population should be included all clinically suspected patients that proved leptomeningeal metastasis by either CSF cytology or later autopsy.

Conclusion

Most of the patients had been diagnosed with primary malignancy before neoplastic meningitis developed with the exception of few cases in CM groups. The common primary sites were adenocarcinoma of lung and breast cancer in the CM group, and acute lymphoblastic leukemia and non-Hodgkin's lymphoma in the LM group. The common symptom was headache and cranial nerve palsy. CSF was the most important investigation, in which routine CSF examination was abnormal in virtually all cases. Nevertheless, CSF without pleocytosis, revealed in 10% of the present study, could not be used to exclude this condition. Positive CSF cytology is a gold standard for a diagnosis of leptomeningeal metastasis. Overall, leptomeningeal metastasis is a common condition. High index of suspicious and awareness of this condition, contrast enhanced neuroimaging and repeated specimens of CSF cytology should help diagnosis this condition, which early detection and treatment are important to improve survival rate and quality of life.

What is already known on this topic?

Neoplastic meningitis is a common problem in neuro-oncology. However, the condition can be difficult to diagnose due to great variation of clinical presentation, especially in patient with no underlying malignancy elsewhere. CSF examination and neuro imaging studies help in making a diagnosis of this condition.

What this study adds?

This report described characteristic of clinical presentations, radiological findings, and CSF examination of the Thai patients, which has rarely been reported. Adenocarcinoma of lung and breast cancer is the most common in the CM group, and acute lymphoblastic leukemia and non-Hodgkin's lymphoma are the common in the LM group. Abnormal CSF was found in all cases but 10% are without pleocytosis. Positive CSF cytology is the gold standard for diagnosis of leptomeningeal metastasis.

Potential conflicts of interest

None.

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การศึกษาอาการ, ลักษณะภาพรังสีและผลการตรวจน้ำไขสันหลังของผู้ป่วยที่มีภาวะมะเร็งแพร่กระจายมาที่เยื่อหุ้มสมอง

ศรวิทย์ เจียรนัยศิลป์, ตุ้มทิพย์ แสงรุจิ, โชติพัฒน์ ด่านชัยวิจิตร, ณสุดา ด่านชัยวิจิตร

วัตถุประสงค์: เพื่อศึกษาอาการ, ลักษณะภาพรังสีและผลการตรวจทางห้องปฏิบัติการ ในผู้ป่วยที่มีมะเร็งแพร่กระจายมาที่เยื่อหุ้มสมอง

วัสดุและวิธีการ: ศึกษาย้อนหลังจากผู้ป่วยที่ได้รับการวินิจฉัยว่ามีภาวะมะเร็งแพร่กระจายมาที่เยื่อหุ้มสมอง จากผลการตรวจน้ำไขสันหลัง ในโรงพยาบาลศิริราช ระหว่างปี พ.ศ. 2540 ถึง พ.ศ. 2549 โดยนำลักษณะอาการ ผลการตรวจน้ำไขสันหลัง และลักษณะภาพทางรังสี มาวิเคราะห์โดย neuroradiologist

ผลการศึกษา: พบผู้ป่วย 40 ราย ซึ่ง 17 ราย มีภาวะมะเร็งแพร่กระจายมาจากที่อื่น และ 23 ราย เป็นโรคมะเร็งต่อมน้ำเหลืองและลิวคีเมีย พบว่าร้อยละ 70 ของการแพร่กระจายมาจากมะเร็งปอดและเต้านม มีผู้ป่วย 3 ราย ใน 17 ราย ที่ไม่ทราบมะเร็งต้นตอและมีภาวะมะเร็งแพร่กระจายไปที่เยื่อหุ้มสมองเป็นอาการเริ่มต้น ส่วนในกลุ่มโรคมะเร็งต่อมน้ำเหลืองและลิวคีเมีย พบว่าร้อยละ 70 เป็นชนิด acute lymphoblastic leukemia และ non-Hodgkin's lymphoma อาการที่พบได้บ่อยที่สุดได้แก่ปวดศีรษะ ในผู้ป่วยที่มะเร็งแพร่กระจายมาจากที่อื่น จะมีผลบวกในน้ำไขสันหลังในการตรวจครั้งแรก 15 ราย (ร้อยละ 82.35) และในกลุ่มมะเร็งต่อมน้ำเหลืองและลิวคีเมียจะมีผลบวกในน้ำไขสันหลังในการตรวจครั้งแรก 22 ราย จาก 23 ราย (ร้อยละ 95.7) จากผลการตรวจน้ำไขสันหลังพบว่า 36 ราย (ร้อยละ 90) มีภาวะ pleocytosis ซึ่งพบเซลล์ lymphocyte เด่น ลักษณะภาพทางรังสีที่พบบ่อยคือ enhancement ของเยื่อหุ้มสมอง และภาวะ hydrocephalus

สรุป: มะเร็งต้นตอของการแพร่กระจายมาที่เยื่อหุ้มสมอง พบว่ามาจากมะเร็งปอดและเต้านมมากที่สุด ส่วนในกลุ่มโรคมะเร็งต่อมน้ำเหลืองและลิวคีเมียพบว่ามาจากชนิด acute lymphoblastic leukemia และ non-Hodgkin's lymphoma มากที่สุด อาการที่พบได้บ่อยที่สุด ได้แก่ ปวดศีรษะ และ cranial nerve palsy การตรวจน้ำไขสันหลังพบความผิดปกติในผู้ป่วยเกือบทุกราย ดังนั้นการตรวจดูเซลล์ในน้ำไขสันหลังแล้วพบความผิดปกติสามารถใช้เป็นเกณฑ์ในการวินิจฉัยภาวะมะเร็งแพร่กระจายมาที่เยื่อหุ้มสมองได้ การให้ความสำคัญและตระหนักถึงภาวะนี้ในผู้ป่วยที่มีอาการทางระบบประสาทจะช่วยลดการพลาดในการให้วินิจฉัยลงได้