Carcinomatous meningitis from ovarian serous carcinoma: A case report

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Abstract. Multifocal dissemination of cancer cells from the primary tumor sites to the subarachnoid, pia mater and cerebrospinal fluid (CSF) of the brain and spinal cord causes carcinomatous meningitis (CM). CM is rarely observed in patients with gynecological cancer. The present study described a 59-year-old woman who was diagnosed with CM as a recurrence of stage IIIC ovarian cancer, after presenting with headache and decreased level of consciousness. During adjuvant therapy following surgical debulking, she developed nausea and vomiting. The post-contrast fluid-attenuated inversion-recovery magnetic resonance imaging showed leptomeningeal enhancement on all sulci, particularly around the falx cerebri and cerebellar hemisphere. CM was suspected and CSF cytology revealed adenocarcinoma cells, thus confirming the diagnosis. Overall, although CM is rare, clinicians should be aware of this complication when patients with malignancies experience neurological symptoms, including headache, nausea and vomiting. Knowledge of this clinical entity should assist clinicians in ascertaining accurate diagnoses.

Introduction

Epithelial ovarian carcinoma is a common cause of cancer death in women worldwide. Most cases are diagnosed at advanced stage due to absence of symptoms during the early stages and the lack of useful screening methods (1). Primary surgical tumor debulking and consecutive platinum-based chemotherapy is the standard treatment strategy for advanced stage ovarian carcinoma patients. Even though the initial standard treatment is effective, most patients experience recurrence (1). The most frequent site of metastasis is the peritoneum. Cerebral and meningeal metastases are considered rare (2).

Multifocal dissemination of cancer cells from the primary tumor sites to the subarachnoid, pia mater, and cerebrospinal fluid (CSF) of the brain and spinal cord causes carcinomatous meningitis (CM). This condition is also referred to as 'leptomeningeal carcinomatosis', 'leptomeningeal meningitis', 'leptomeningeal metastasis', or 'neoplastic meningitis' (3). The term 'carcinomatous meningitis' was first coined by Beerman in 1912 when describing a condition where in cancer cells metastasized to the meninges without visible invasion of the brain (4). A wide variety of symptoms are induced depending on the site of metastasis. This entity occurs in the advanced stages of any solid cancer and hematological cancer when cancer cells seed through the CSF and deposit in the meninges (3). Imaging modalities including computed tomography (CT) and magnetic resonance imaging (MRI) along with CSF analysis are useful to diagnose this entity; however, an early diagnosis is difficult. Radiotherapy and chemotherapy are employed as treatment options; however, the prognosis remains poor (1).

The present report describes the case of a 59-year-old female patient who developed CM as recurrence of ovarian cancer stage IIIC after presenting with headache and decreased level of consciousness.

Case report

A 59-year-old Japanese nulligravid underwent omentectomy and was diagnosed with ovarian high-grade serous carcinoma stage IIIC according to International Federation of Gynecologists and Obstetricians staging system. The gross findings of the resected omentum and the pathological specimens are shown in Fig. 1. The macroscopic image shows the omentum with disseminated tumors forming omental cake and the microscopic images reveals high-grade serous carcinoma with solid, papillary and glandular structure with nuclear atypia, large nucleoli, high nuclear to cytoplasmic ratio, and slit-like space. Hematoxylin and eosin staining was performed in an automated staining instrument (Tissue-Tek® Prisma™ Plus, Sakura-finetek) according to the manufacturer's instructions using Gill's hematoxylin V solution (Muto Pure Chemical Co., Ltd.) and pure eosin (Muto Pure Chemical

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Co., Ltd.) at the pathological department in our hospital. After six cycles of neoadjuvant chemotherapy combining carboplatin [area under the curve (AUC)=6 mg/ml/min], paclitaxel (175 mg/m^2), and bevacizumab (15 mg/kg) administered every 3 weeks, she underwent interval surgical debulking consisting of a total abdominal hysterectomy with bilateral salpingo-oophorectomy, pelvic lymphadenectomy, paraaortic lymphadenectomy and omentectomy without residual tumors. After the surgery, six cycles of adjuvant chemotherapy combining carboplatin (AUC=6 mg/ml/min), paclitaxel (175 mg/m^2), and bevacizumab (15 mg/kg) was administered every 3 weeks. Subsequently, maintenance therapy with bevacizumab (15 mg/kg) was initiated. After 10 cycles of bevacizumab as maintenance therapy, she began to develop nausea and vomiting. Despite receiving infusion at her family physician's clinic, her symptoms fluctuated but were generally persistent. A month after symptom onset, there was a noted decline in her consciousness which fluctuated but were generally persistent also. This prompted admission to our hospital for further examination.

Upon admission, her vital signs were as follows: Blood pressure 162/107 mmHg, body temperature 37.4˚C, and pulse rate 84 bpm. Her Glasgow Coma Scale was 15 (E4V5M6). Her laboratory data showed a normal white blood cell count (7,900/μl) and, an elevated C-reactive protein (CRP) level (3.35 mg/dl) (normal range: <0.3 mg/dl), a decreased Na/K/Cl (128/3.3/93 mEq/l) (normal range: 138 mEq/l< Na <145 mEq/l, 3.6 mEq/l< K <4.8 mEq/l, 101 mEq/l< Cl <108 mEq/l) and an elevated CA125 (114 U/ml) (normal range: <35.0 U/ml). The post-contrast fluid-attenuated inversion-recovery (FLAIR) MRI, which is a MRI technique that provides strong T2-weighted, CSF signal suppression and minimized gray matter-to-white matter contrast, showed leptomeningeal enhancement over all sulci especially around falx cerebri and cerebellar hemisphere (Philips Ingenia 3.0 was used to generate the images) (Fig. 2). These findings led to the consideration of meningitis, specifically CM, considering the existing ovarian carcinoma. Lumbar puncture was thus, performed and an opening pressure was 30 cmH_2O was noted. Biochemical analysis of CSF revealed increased number of cells (14/μl), protein concentration (78 mg/dl) (normal range: 10-52.6 mg/dl), and lactate dehydrogenase concentration (204 IU/l) (normal range: 0-50 mg/dl), and a decreased glucose concentration (4 mg/dl) (normal range: 50-80 mg/dl). Cytology of CSF revealed large tumor cells with increased nucleocytoplasmic ratio, prominent nucleoli, and centrally placed hyperchromatic nuclei which is consistent with adenocarcinoma cells leading to the diagnosis of CM (Fig. 3). Conventional Papanicolaou staining was performed in an automated staining instrument (HistoCore Spectra ST, Leica Biosystems) according to the manufacturer's instructions using OG-6 (Muto Pure Chemical Co., Ltd.) and EA-50 (Muto Pure Chemical Co., Ltd.) at the pathological department in our hospital. Giemsa staining was performed as fallows at the pathological department in our hospital; i) The slides were placed in May-Grünwald (Merck) for 3 min. ii) The slides were placed in phosphate buffer for 1 min. iii) the slides were placed in dilute giemsa solution (Merck) for 15 min. iv) the slides were rinsed in deionized water. v) the slides were air dried and evaluated. After the diagnosis, we proposed treatment with radiation therapy or intrathecal chemotherapy despite the lack of evidence of efficacy. However, the patient and her family opted for palliative care and she expired 30 days after the diagnosis.

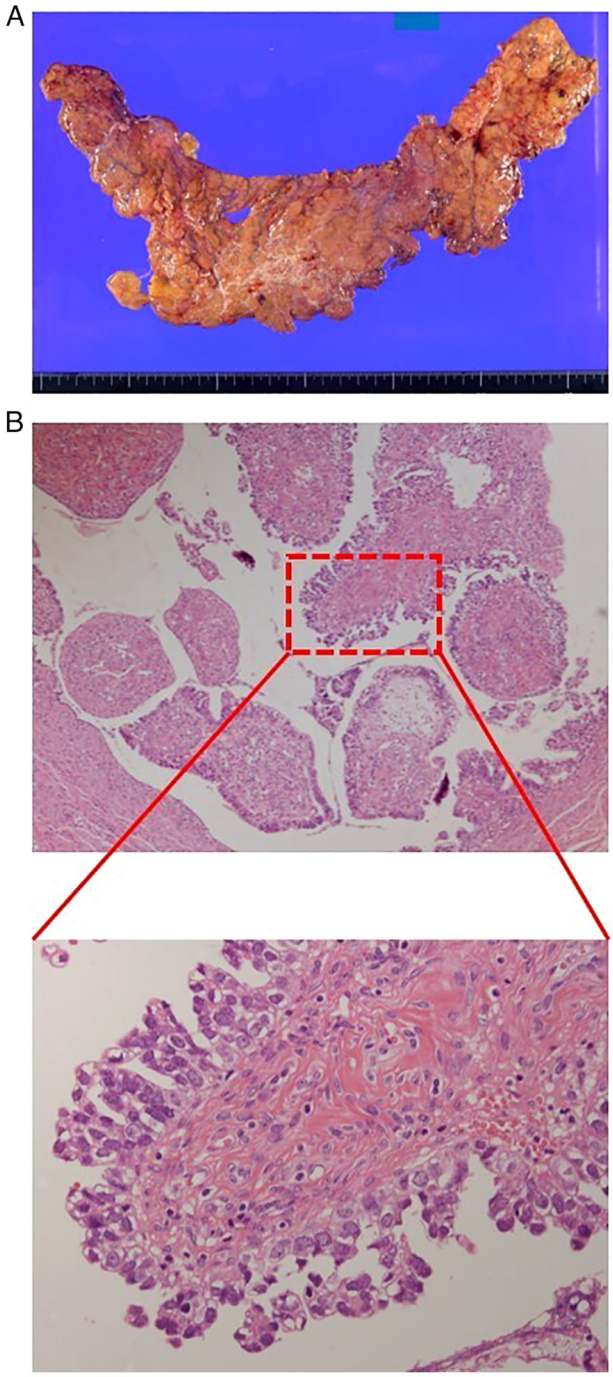

Figure 1. Images of resected omentum. (A) Macroscopic image. (B) Hematoxylin and eosin staining showed solid, papillary and glandular structure with nuclear atypia, large nucleoli, high nuclear to cytoplasmic ratio and slit-like space, which is consistent with high-grade serous carcinoma (magnification, x100 and 400).

Discussion

CM is caused by multifocal dissemination of cancer cells from the primary tumor sites to the subarachnoid, pia mater, and CSF in the brain and spinal cord. The incidence rate

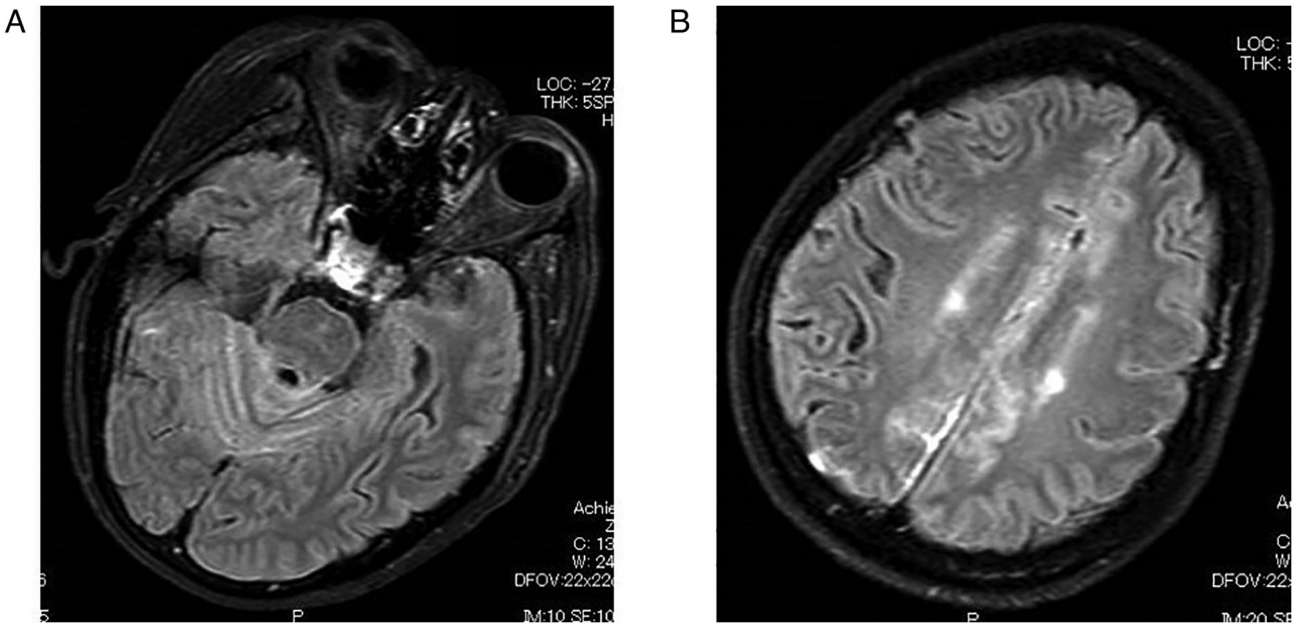

Figure 2. Axial images of spectral attenuated inversion recovery post-contrast fluid-attenuated inversion-recovery magnetic resonance imagery (repetition time, 11,000; echo time, 125; flip angle, 90˚). (A) Leptomeningeal enhancement over all sulci especially around the falx cerebri. (B) Leptomeningeal enhancement on sulci in the cerebellar hemisphere.

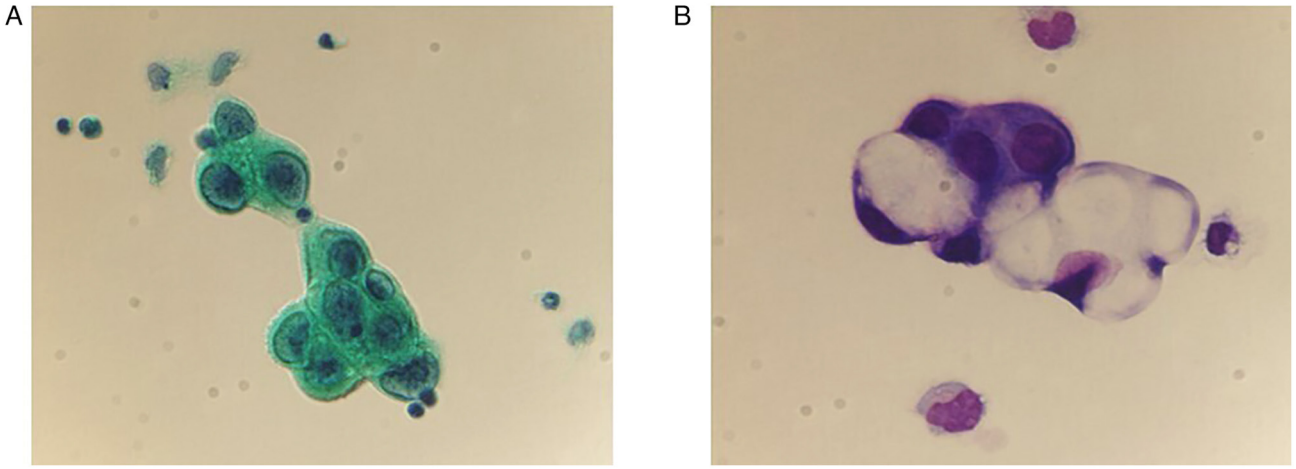

Figure 3. Cytology of cerebrospinal fluid. (A) Conventional Papanicolaou smear showing large tumor cells with increased nucleocytoplasmic ratio, prominent nucleoli and centrally placed hyperchromatic nuclei (magnification, 400x). (B) Giemsa staining smear showing large tumor cells with increased nucleocytoplasmic ratio and centrally placed hyperchromatic nuclei (magnification, 400x).

of CM in patients with solid tumors is reported to range from 3 to 5% (5). Melanoma, lung and breast cancers are the most common solid tumors known to cause CM. CM has been reported in 23, 9 to 25 and 5% of melanoma, lung cancer, and breast cancer patients, respectively. Nonetheless, CM may develop in all types of malignant tumors (5). Although CM may be caused by any malignant tumor, it is rarely observed in the patients with gynecological cancers. One study reported that only 0.06, 0.03, and 0% of ovarian, cervical, and endometrial cancer patients, developed CM, respectively (6). However, the development of CM in patients with ovarian cancer will likely increase due to the increase in overall survival resulting from the improvement of tumor control by more effective therapies.

The mechanisms of leptomeningeal invasion of tumor cells are thought to involve (1) hematogenous spread through the arterial or venous circulation, which is probably the most common route; (2) direct seeding from the existing brain or spinal parenchymal metastases in contact with the CSF; (3) direct extension from subdural or extradural tumor; or (4) direct extension from sites outside of, but adjacent to the central nervous system (7). For pelvic tumors, hematogenous spread from the pelvic venous plexus to the vertebral venous system, also known as the Batson's plexus, is considered one of the routes of spread to the leptomeninges (8).

The most common locations affected by leptomeningeal seeding are the posterior fossa, basal cisterns, and cauda equina, because of the slower CSF flow and the gravitational

effects (9). The most common symptoms described in CM patients with solid tumors were headache (39%), nausea and vomiting (25%), leg weakness (21%), cerebellar dysfunction (17%), altered mental status (16%), diplopia (14%), and facial weakness (13%) (10). Headache, the most common symptom, is caused by raised intracranial pressure (ICP) or meningeal irritation. In relation to the elevated ICP, nausea and vomiting accompany the headache, which is noted to be worse in the morning. As a result of meningeal irritation, headaches are correlated with nuchal rigidity that is worsened by leg flexion (Kernig sign) (3). However, nuchal rigidity is observed in only 15% of cases (9). Involvement of the spinal cord and its nerve roots in CM causes symptoms in the anatomically associated regions. Segmental numbness, pain, dysesthesia, and lower motor neuron pattern limb weakness are symptoms caused by spinal nerve cord involvement. Bladder and bowel dysfunction result from sacral nerve root involvement. Although the symptoms mentioned above are common, clinical signs and symptoms may still be absent in 25% of cases at the time of diagnosis (11). In the current case, the patient experienced headache, nausea, and vomiting due to raised ICP.

To diagnose this entity, obtaining a comprehensive history and physical exam including a neurologic exam is an essential first step. The appropriate neurologic exam and proficient knowledge of this entity leads physicians to suspect CM (3). Gadolinium-enhanced MRI is a useful modality to diagnose CM in which the sensitivity is 76% (12). Both focal and diffuse leptomeningeal enhancement of the brain in the T1-weighted image with contrast are typical findings (11). Although conventional gadolinium-enhanced T1-weighted images are largely employed to diagnose CM, there are cases where no enhancement is seen, such as in the current case. For these cases, FLAIR sequences with contrast have been reported to show better sensitivity in detecting CM (13). The common areas that show enhancement are the basilar cisterns, cerebral convexities, cerebellar folia, and ventricular ependymal regions (2). In the current case, FLAIR sequences were useful to arrive at the diagnosis.

Enhancement on MRI is observed in both CM and inflammatory meningitis; therefore, it is crucial to differentiate the two through CSF analysis (3). CSF analysis is crucial in diagnosing CM. CSF abnormalities have been reported in >90% of CM patients. These irregularities may present as the following: i) high CSF pressure >25 cmH_2O, detected in ~50% of cases (14); ii) elevated CSF protein levels, in ~80% of cases (15); iii) decreased CSF glucose level (hypoglycorrhachia), in ~25-40% of cases (14); iv) pleocytosis, in ~33-79% of cases (16); and v) a positive CSF tumor cytology, the most important and gold standard test to diagnose CM, detected in 45-55, 80, and 90% of cases at a first, second, and third lumbar puncture (7). Lumbar puncture just before gadolinium-enhanced MRI should be avoided because it may cause artificial contrast enhancement of the leptomeninges from persistent lumber CSF leakage and intracranial hypotension associated with venous vasodilation (5). In the current case, adenocarcinoma was detected on the first lumbar puncture and CSF characteristics showed an elevated opening pressure and protein level, and a decreased glucose level. These findings helped clinch the diagnosis.

The differential diagnoses that should be taken into consideration are as follows: i) Intraparenchymal primary brain lesions; ii) chronic or recurrent meningitis caused by a variety of bacterial, fungal, viral, or protozoal organisms; iii) meningitis caused by an autoimmune disease or drugs; and iv) paraneoplastic syndromes, including Lambert Eaton syndrome, Myasthenic crises, cerebellar degeneration, encephalomyelitis, neuropathies, and limbic encephalitis (3).

Because of its rarity, there is no standard treatment for this entity because there are currently no clinical trials to establish standard treatment for this disease. Most patients underwent intrathecal chemotherapy with or without radiation therapy. The efficacy of most systemic chemotherapy agents are limited due to the blood-brain barrier; therefore, intrathecal chemotherapy remains the mainstay of treatment for CM (3). The most common drugs for the intrathecal route are methotrexate, cytarabine, and less commonly, thiotepa (3). Radiation therapy for CM consists of diffuse radiation therapy to linear leptomeningeal contrast-enhanced lesions or focal radiation to nodular plaque-like meningeal deposits of malignant cells (3).

CM is usually caused by advanced stage disease; therefore, the prognosis of this entity is poor with a median survival time of 2 to 4 months even with treatment (17). Low CSF protein, normal CSF glucose level, preserved cognitive function, and controlled systemic disease are reported to be associated with better survival (6). In the current case, the patient demised 30 days after diagnosis without treatment.

Although CM is rare, clinicians should consider this unusual complication whenever patients with malignancies experience neurological symptoms including headache, nausea, and vomiting that cannot be easily explained or treated. With improved locoregional control and survival, CM will likely become more prevalent. Awareness of this condition should help clinicians maintain a high index of suspicion for CM and lead them to an accurate diagnosis. Therefore, owing to its rarity, case reports such as the one presented, are essential in facilitating the dialogue needed to spread awareness of this clinical entity.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

EU, TF and TS conceived and designed the study. EU, TF, KI, MY, MK, TI, YK and TY acquired, analyzed and interpreted the data. UE, TF and TS drafted and revised the manuscript. TF and TS confirm the authenticity of all the raw data. YK

reviewed the pathological specimens. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent was obtained from the patient for the publication of the case details and any associated images.

Competing interests

The authors declare that they have no competing interests.

References

1. Cannistra SA: Cancer of the ovary. N Engl J Med 351: 2519-2529, 2004.
2. Toyoshima M, Tsuji K, Shigeta S, Tokunaga H, Ito K, Watanabe Y, Yoshinaga K, Otsuki T, Niikura H and Yaegashi N: Leptomeningeal metastasis from gynecologic cancers diagnosed by brain MRI. Clin Imaging 41: 42-47, 2017.
3. Anwar A, Gudlavalleti A and Ramadas P: Carcinomatous meningitis. In: StatPearls. StatPearls Publishing Copyright © 2021, StatPearls Publishing LLC., Treasure Island (FL), 2021.
4. Delle Grottaglie B, Girotti F, Ghisolfi A, Tafi A and Pescia M: A case of carcinomatous meningitis with papilledema as the only symptom: Fvorable response to intrathecal chemotherapy. Ital J Neurol Sci 4: 95-97, 1983.
5. Gleissner B and Chamberlain MC: Neoplastic meningitis. Lancet Neurol 5: 443-452, 2006.
6. Yust-Katz S, Mathis S and Groves MD: Leptomeningeal metastases from genitourinary cancer: The University of Texas MD Anderson cancer center experience. Med Oncol 30: 429, 2013.
7. Le Rhun E, Taillibert S and Chamberlain MC: Carcinomatous meningitis: Leptomeningeal metastases in solid tumors. Surg Neurol Int 4 (Suppl 4): S265-S288, 2013.
8. Batson OV: The function of the vertebral veins and their role in the spread of metastases. 1940. Clin Orthop Relat Res: 4-9, 1995.
9. Chamberlain MC: Neoplastic meningitis. Oncologist 13: 967-977, 2008.
10. Clarke JL: Leptomeningeal metastasis from systemic cancer. Continuum (Minneap Minn) 18: 328-342, 2012.
11. Beauchesne P: Intrathecal chemotherapy for treatment of leptomeningeal dissemination of metastatic tumours. Lancet Oncol 11: 871-879, 2010.
12. Ko Y, Gwak HS, Park EY, Joo J, Lee YJ, Lee SH, Kwon JW, Shin SH and Yoo H: Association of MRI findings with clinical characteristics and prognosis in patients with leptomeningeal carcinomatosis from non-small cell lung cancer. J Neurooncol 143: 553-562, 2019.
13. Kremer S, Abu Eid M, Bierry G, Bogorin A, Koob M, Dietemann JL and Fruehlich S: Accuracy of delayed post-contrast FLAIR MR imaging for the diagnosis of leptomeningeal infectious or tumoral diseases. J Neuroradiol 33: 285-291, 2006.
14. Taillibert S, Laigle-Donadey F, Chodkiewicz C, Sanson M, Hoang-Xuan K and Delattre JY: Leptomeningeal metastases from solid malignancy: A review. J Neurooncol 75: 85-99, 2005.
15. Foo CT, Burrell LM and Johnson DF: An unusual presentation of carcinomatous meningitis. Oxf Med Case Reports 2016: omw068, 2016.
16. Nayar G, Ejikeme T, Chongsathidkiet P, Elsamadicy AA, Blackwell KL, Clarke JM, Lad SP and Fecci PE: Leptomeningeal disease: Current diagnostic and therapeutic strategies. Oncotarget 8: 73312-73328, 2017.
17. Thakkar JP, Kumthekar P, Dixit KS, Stupp R and Lukas RV: Leptomeningeal metastasis from solid tumors. J Neurol Sci 411: 116706, 2020.