Malignant melanoma meningeal metastasis with concurrent hemorrhagic cerebrospinal fluid: A case report

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Abstract. Malignant melanoma meningeal metastasis (MMMM) is a rare clinical condition with a poor prognosis. The observation of hemorrhagic cerebrospinal fluid (CSF) in this type of disease is relatively uncommon and may indicate disease progression. The present study reports the case of a 51-year-old male with malignant melanoma who presented with a headache. Imaging studies did not identify abnormalities; however, an analysis of the CSF revealed hemorrhagic changes. The results of cytological examination of the CSF showed melanoma cells, leading to the final diagnosis of MMMM. This case emphasizes the importance of monitoring neurological symptoms and conducting comprehensive CSF cytological examination in patients with melanoma, creating disease awareness in clinicians.

Introduction

Malignant melanoma is a highly aggressive and metastatic skin cancer. Although meningeal metastasis is rare (5-25%), it indicates a very poor prognosis (1). The symptoms of meningeal metastasis are diverse, including headaches, nausea, vomiting, seizures and neurological deficits (2), often meaning that the diagnosis is confused with that of other central nervous system diseases, thus increasing the diagnostic difficulty. Meningeal metastasis with concurrent hemorrhagic CSF is even rarer (0.9-4.7%) (3), further complicating the clinical diagnosis and treatment.

The present study reports a rare case of malignant melanoma meningeal metastasis (MMMM) with concurrent hemorrhagic CSF. By detailing the patient's clinical manifestations, imaging characteristics, diagnostic process and treatment plan, the study aims to provide a reference for the clinical management of similar cases.

Case report

In September 2022, a 51-year-old male patient presented with the chief complaint of a headache for >10 days, worsening for 1 day at People's Hospital of Leshan (Leshan, China). The patient had originally reported a persistent dull headache at the start of this period, with no specific localization, accompanied by nausea, vomiting (no projectile vomiting), unsteady gait, fever (37.5˚C) and night sweats. Symptoms did not resolve after rest and the patient was therefore admitted to Meishan City People's Hospital (Meishan, China) after 5 days, at the end of August 2022. Upon admission, the patient underwent a computed tomography (CT) scan of the head and digital subtraction angiography (data not shown), which showed no abnormalities. However, a lumbar puncture showed hemorrhagic CSF (Table I). Therefore, the patient was initially diagnosed with a subarachnoid hemorrhage and intracranial infection. After treatment for pain relief, reduction of the intracranial pressure and hemostasis, the patient was discharged from the hospital 4 days later, with improvement of the symptoms. However, only 1 day after discharge, the patient was admitted to the People's Hospital of Leshan with a worsening headache.

The patient's vital signs were stable, and there was a lack of apparent abnormalities in physical examinations of the heart, lungs and abdomen. Neurological analysis showed clear consciousness, coherent speech, normal cranial nerves, typical motor and sensory systems, and coordinated movement. The tests for neck stiffness were positive, Kernig's sign was negative and bilateral pathological signs were also negative.

There were no abnormalities observed in the following blood tests: Complete blood counts, biochemical indicators, coagulation function, pre-check for blood transfusion, autoimmune panel, tumor markers, T-spot and G test. There were no marked observations in the electroencephalogram or in the CT scans of the chest and abdomen. The results of magnetic resonance imaging (MRI) and enhancement of brain sections

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Table I. Cerebrospinal fluid analyses.

Date	Pressure, mmH_20	Appearance	Complete blood counts	Biochemical indicators	Genetic sequencing and cytological examination
August 2022	Initial, 360; final, 70	Red, turbid	RBC, $2.7x10^{10}$/l; WBC, $8.9x10^{7}$/l	Glucose, 0.86 mmol/l; protein, 1,958.5 mg/l; chloride, 130 mmol/l	None
September 2022	Initial, 300; final, 240	Pale yellow, slightly turbid	RBC, $4.0x10^{9}$/l; WBC, 3.5x107/l	Glucose, 0.40 mmol/l; protein 2,599.9, mg/l; chloride, 118 mmol/l	Second-generation sequencing of pathogen genes (negative)
September 2022	Initial, 60; final, 40	Red, clear	RBC, $5.7x10^{10}$/l; WBC, $2.1x10^{8}$/l	Glucose, 0.60 mmol/l; protein, 3,234.4 mg/l; chloride, 108.4 mmol/l	Cytology: Numerous melanoma cells (Fig. 3)

RBC, red blood cell; WBC, white blood cell.

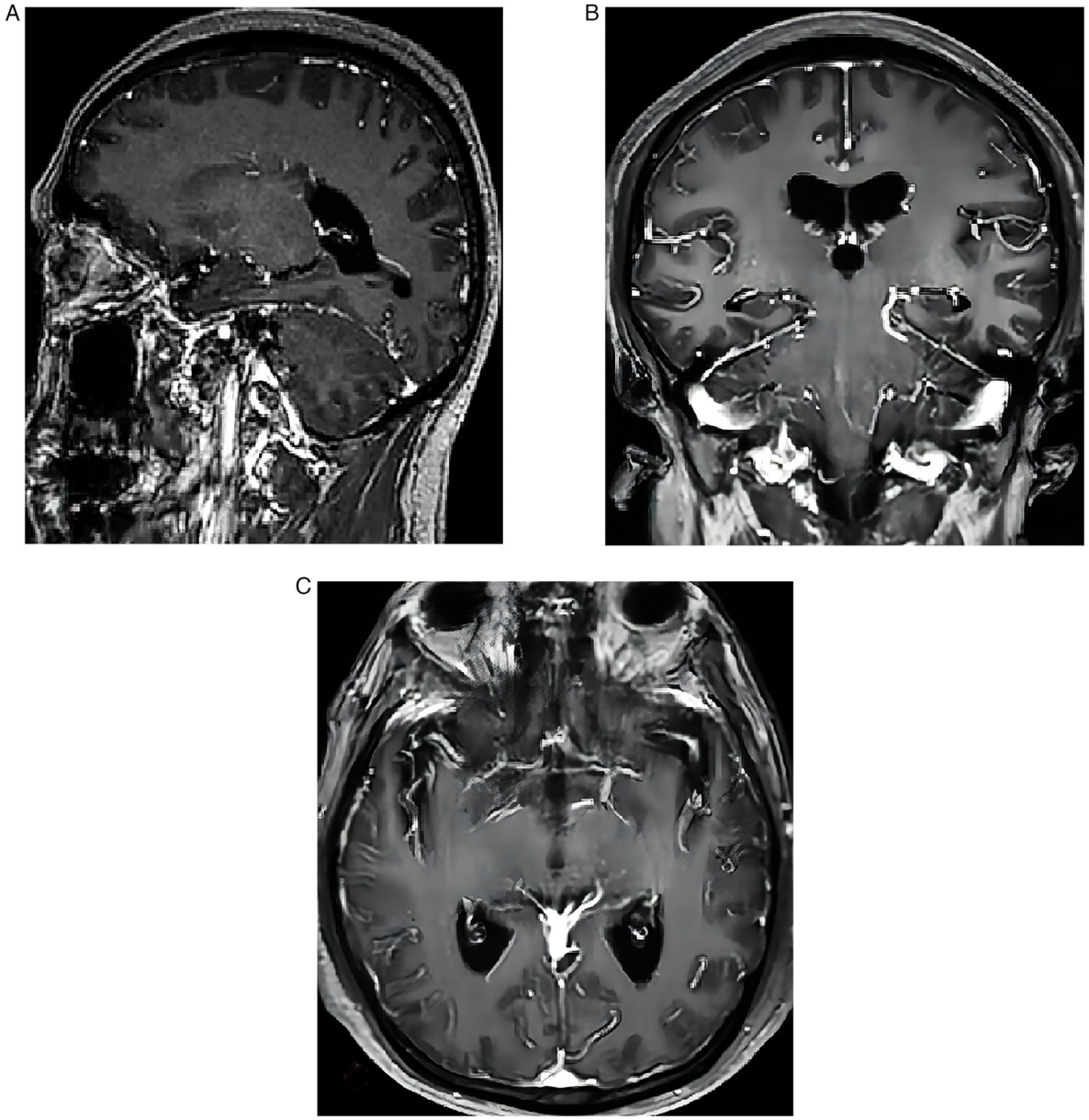

Figure 1. Head magnetic resonance imaging (A) plain scan and enhanced (B) coronal and (C) axial scan at admission showing cerebrovascular white matter hyperintensity, Fazekas grade 1.

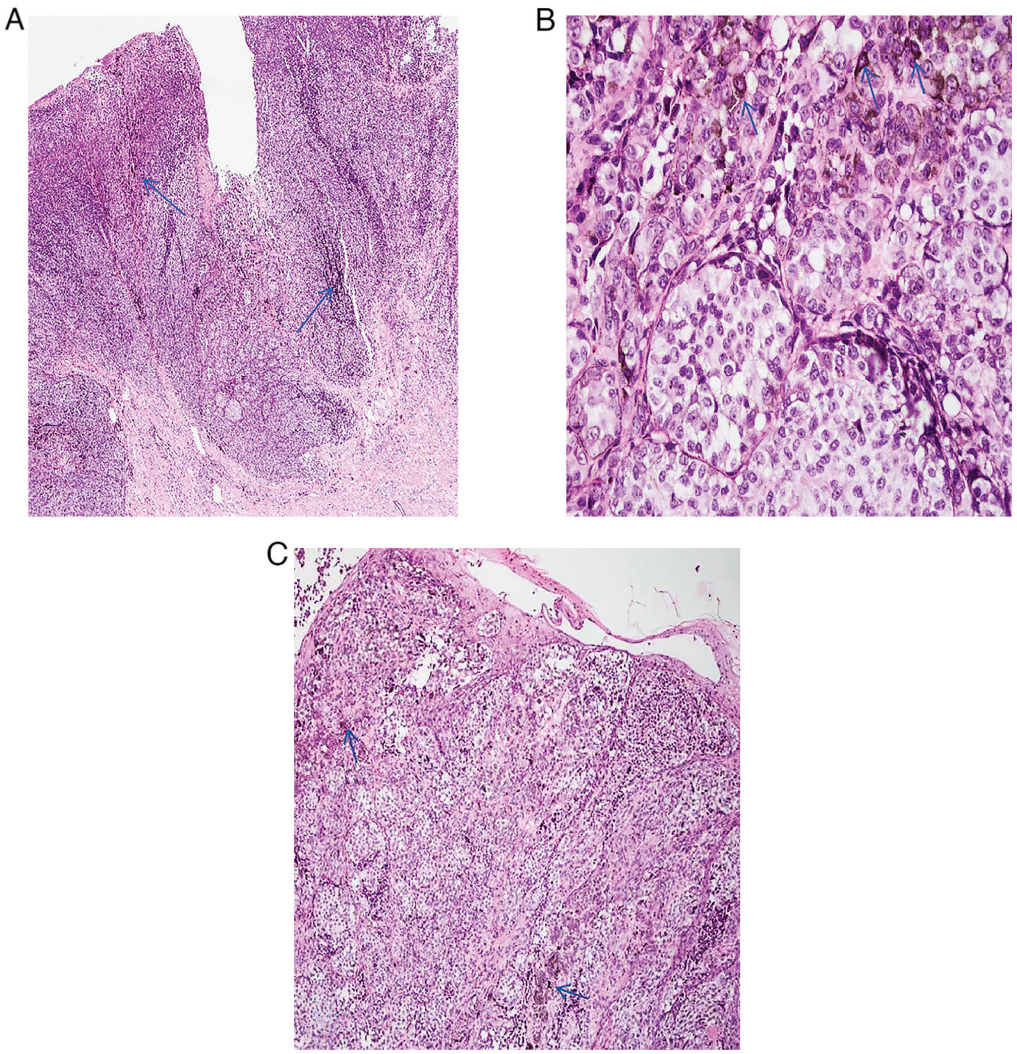

Figure 2. Biopsy results. Hematoxylin-eosin staining of tissue sections of skin lesions at (A) low (x40), (B) medium (100) and (C) high (400) magnification showed that the tumour cells were scattered in patches, grew in nests and invaded the entire epidermis and dermis. Irregular small patches of tumour cells infiltrated into the fibrous interstitium. The nucleoplasma ratio was high and the nucleoli were obvious; the cytoplasm was clear or eosinophilic, and pigment granules were seen in some of the cytoplasm.

revealed hyperintensity in the cerebrovascular white matter, Fazekas grade 1 (4) (Fig. 1).

The patient underwent lumbar puncture examination in Meishan People's Hospital, which showed cerebrospinal fluid leukocytes: 89X10^6/l (normal value: 0-8X106/l), erythrocytes: 27,000X10^6/l (normal value: 0X106/l), protein level: 1,958.5 mg/l (normal value: 150-450 mg/l), cerebrospinal fluid glucose: 0.65 mmol/l (normal range: 2.5-4.4 mmol/l) Targeted therapy (ceftriaxone, 2 g I.V. fluids, once a day; tranexamic acid 1g ivgtt qd and tramadol 50 mg qd analgesic therapy were administered, but the headache symptoms did not improve. After being transferred to Leshan People's Hospital, a repeat lumbar puncture performed on the first day after admission showed a decrease in the number of leukocytes and erythrocytes in the cerebrospinal fluid, suggesting that an infection may have occurred. After transferring back to People's Hospital of Leshan, a follow-up lumbar puncture examination 1 week after the initial examination showed a decrease in the number of white blood cells and red blood cells in the CSF ($4.0x10^9$/l; WBC, 3.5x107/l, respectively), suggesting a possible infection. Continuous treatment measures were administered, This included intravenous mannitol 125 ml ivgtt q8h to lower intracranial pressure, continued anti-infective treatment with ceftriaxone 2 g ivgtt qd, and anti-spasmodic and other treatments such as nimodipine 10 mg ivvp qd injection for one week. Second-generation gene sequencing was performed at Chengdu Hemer Yuning Medical Laboratory Center (Chengdu, Sichuan, China, and the results were negative, ruling out the possibility of infectious meningitis. However, the patient's headache symptoms still did not improve. The patient underwent a repeat lumbar puncture 1 week after admission to the hospital showing a significant increase in red blood cells, white blood cells, and proteins in the cerebrospinal fluid compared to the previous level (5.7x1010/l; WBC, 2.1x108/l and protein, 3,234.4 mg/l) with no obvious abnormalities on cranial CT and MRI. Further inquiry into the patient's medical history revealed that the patient had undergone surgery to remove a malignant melanoma at the proximal joint of the left thumb 3 months earlier. After surgery, tissue was fixed in 10% neutral

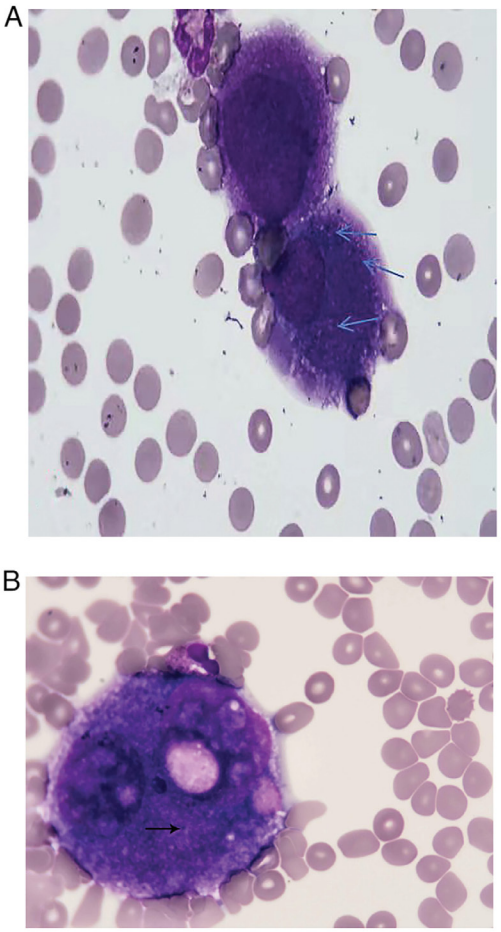

Figure 3. Cerebrospinal fluid cytology. (A) Uneven cell size, huge tumor cells are seen, some with large nuclei and little plasma, cytoplasm filled with fine diffuse black particles, coarse nuclear chromatin granules and clear nucleoli. (B) Figure also shows tumor cells with small nuclei and abundant plasma, irregular cytoplasm, long finger-like elevation of cytoplasm, and scattered black pigment granules can be seen, but with fine chromatin and clear nucleoli. Clusters of cells and cell aggregates are seen. Magnification, x100.

formaldehyde solution for 6-8 h at 20-25˚C. After fixation, the tissue was heated for 10 min and then stained with Eosin under a Leica DM2000 light microscope at a temperature of 20-25˚C for 5-10 min, and then examined at 40x, 100x, and 400x magnification, and finally diagnosed as malignant melanoma. (Fig. 2). CSF cytology was performed after 1 week using an Olympus CKX53SFC fluorescence microscope under 100x oil magnification, which revealed abnormal cells in the CSF. The staining procedure consisted of fixation with 9 drops of Ragis stain for 2 min at 20-25˚C, followed by the addition of 3 drops of PBS and staining for 13 min at a laboratory temperature of approximately 25˚C and humidity of approximately 45% (Fig. 3) that were labeled as malignant melanoma cells, as they contained pigment granules. The cells were different in morphology and size from those found in normal CSF. Due to the insufficient number of cells, further confirmation using other methods was not possible. A combination of the patient's past and current medical history led to a diagnosis of MMMM and carcinomatous meningitis. The patient was then automatically discharged from hospital the day after the diagnosis and refused any formal treatment. Subsequent to discharge, the patient gradually developed bilateral hearing loss, a poor appetite, multiple organ failure and other symptoms, and finally passed away >1 month after discharge.

Discussion

Combining multiple lumbar punctures, the retained sample was a homogenous and consistent CSF containing high protein and white blood cell levels. Despite a decrease in all markers early in the course of anti-infective therapy, the number of white blood cells continued to rise as the course continued. Tests for all types of pathogens were negative, and red blood cell fluctuations were inconsistent with the patient's clinical presentation. No metastatic lesions were detected, although the patient underwent a comprehensive cranial CT and MRI on both the previous admission and the current admission. CSF cytology was suggestive of the presence of melanoma cells, indicating that the patient's CSF hemorrhage was closely associated with meningeal metastases (5).

Leptomeningeal metastasis (LM) is an advanced form of distant metastasis from malignant tumors with a poor prognosis. The overall survival time is 6-8 weeks in untreated patients and can be extended to 3 to 9 months with intrathecal chemotherapy. The incidence rate is 1-8% of all cancer cases (6). Current studies suggest that LM is due to the activation of C3a receptors in the choroid plexus epithelium by tumor cell-derived complement C3, which disrupts the blood-brain barrier and increases endothelial permeability, thereby allowing plasma components, such as deregulatory proteins and other mitogens, to enter the CSF and promote tumor growth (7). Patients may present with brain parenchyma involvement, symptoms of meningeal irritation (dizziness and headache), cranial nerve involvement (vision/hearing loss) and spinal nerve root compression (numbness and weakness of the limbs) (8-10). Primary tumors include breast cancer, lung cancer, melanoma and finally, primary central nervous system cancer (11). Among the solid tumors, meningeal metastases occur in up to 10-15% of patients with advanced MM (12). Typical MRI findings show multiple or single rounded lesions of abnormal signal, and more commonly, homogeneous nodular or ring-like enhancement images on image enhancement (13). In addition, it is estimated that 66-90% of patients with LM have positive CSF cytology. Non-specific manifestations of CSF also include increased pressure, protein and leukocytes, and decreased glucose (14). The present patient was exhibited the aforementioned CSF features, and an increase in erythrocytes, which is currently uncommon in LM. The present case was of a middle-aged male with the sudden onset of a headache and a history of malignant melanoma, with treatments such as radiotherapy after surgical resection, although imaging did not show positive manifestations in the past Su and Wei (15) analyzed the characteristics of four cases of malignant melanoma and suggested that there can be no abnormal imaging. The present study is in line with the aforementioned report and to exclude the infection, bleeding and other etiologies before LM diagnosis, which is consistent with the diagnosis of LM. Although histopathological biopsy of the brain can detect the presence of cancerous tissue in the meninges, in recent years, the gold standard for the diagnosis

of LM has been the presence of tumor cells in the CSF (16). Further refinement of cerebrospinal fluid cytology is required, leading to standardized anti-tumor therapy.

In meningeal metastases, tumor cells are seen in the CSF, which tends to be clear and transparent in appearance. Cases of bloody CSF have rarely been reported (17,18). In the present case, the CSF had a significantly elevated erythrocyte count and a bloody appearance (puncture wounds had been excluded), and so a subarachnoid hemorrhage was considered, but the CT of the head in this patient did not show hemorrhagic changes in the sulcus and cranium, and the vascular examination ruled out aneurysms and arteriovenous malformations. The pathogenesis causing the subarachnoid hemorrhage is currently unclear. In the clinic, a small number of patients with herpes simplex virus encephalitis, the CSF also showed homogeneous erythrocytes, the mechanism of which may be related to the immune damage caused by the presence of immune complexes formed by antibodies to herpes simplex virus IgM in the cerebral vascular wall, which in turn causes necrosis of the vascular wall and erythrocyte exudation (19). In the current case, the patient's meningeal irritation sign was positive, which was considered to be intracranial infectious disease, and therefore anti-infective treatment was provided. Although the white blood cell count decreased slightly in the early stage, the symptoms were not relieved, and in the later stage, while still receiving anti-infective treatment, the white blood cell count was significantly elevated, but the genetic test for pathogens was negative, so the infectious disease was excluded. Solid tumours lead to meningeal metastases in about 1-8% of cases. It is not uncommon for melanoma, as a type of solid tumour, to develop meningeal metastases, up to 30%, and its metastases manifest as elevated cerebrospinal fluid proteins and white blood cells (16). There is currently no report of blood-containing CSF in melanoma. Even if there is blood-containing CSF in other solid tumor metastases, its imaging examination is positive, and there is no negative imaging combined with blood-containing CSF. Hematogenous CSF has not been reported so far. The abnormal cells in the bloody CSF of the current patient had the presence of pigment granules, and the cell morphology and size did not belong to the cell morphology found in normal CSF. However, the number of cells was not sufficient to be further confirmed by other methods, and thus, in combination with the patient's past and current medical history, we considered that a diagnosis of CSF metastasis should be made. However, the etiology of bloody CSF in patients with carcinomatous meningitis remains unclear, and we hypothesize that it may be as follows: i) Proliferation of cancer cells in CSF and invasion of the CSF circulatory system may lead to the obstruction of CSF pathways or damage to blood vessels, which may lead to hemorrhage; ii) invasion of cancer cells into the meninges may lead to rupture of the microvessels of the CSF or hemorrhage, which can lead to the production of bloody CSF (20); or iii) in carcinomatous meningitis, invasion of cancer cells can lead to disruption of the blood-brain barrier, making it easier for blood components (including erythrocytes) to enter the CSF, and the exact mechanism needs to be studied. Therefore, when unexplained bloody CSF is present, after excluding common bleeding disorders, it is necessary to learn more about previous tumor history and improve CSF exfoliative cytology to reduce misdiagnosis and underdiagnosis.

Current LM treatments offer traditional cancer treatment modalities, including surgery, radiotherapy, targeted therapy and intrathecal drug injections (20). Patients with LM receiving immunosuppressive agents show 1-year survival rates of 7 (MM), 16-24% (breast cancer) and 19% (lung cancer) (21,22). However, most of the current treatments are palliative, so the shortcoming of the present study lies in the fact that, due to the patient refusal of all treatments, the therapeutic aspects of MMMM with concomitant LM and the presence of bloody CSF are not yet clear, and further validation is needed in the future.

In summary, when patients present with unexplained symptoms of a headache and vomiting, there is no abnormality detected by cranial MRI or CT examination, and treatment effect is not satisfactory, doctors should be highly vigilant of the possibility of LM and cancerous meningitis. Additionally, when CSF shows bloody changes, in addition to considering diseases such as aneurysmal subarachnoid hemorrhage, cerebral hemorrhage, viral encephalitis and cerebral amyloid angiopathy-related inflammation, doctors also need to be alert to the risk of cancerous meningitis. Therefore, in cases of similar clinical manifestations but no obvious abnormal results with a past history of tumor, CSF should be performed and search for primary lesions to improve prognosis of LM.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contribution

HH conceived the study and critically reviewed the article. QM and BS conceptualized the study idea and drafted the manuscript. KC and XS performed data collection. WW and WC made recommendations for treatment and analyzed data. All authors read and approved the final manuscript. HH and QM confirmed the authenticity of all original data.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

The patient's family provided written informed consent for publication of the study.

Competing interests

The authors declare that they have no competing interests.

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