Received: 16 July 2023 | Revised: 10 August 2023 | Accepted: 20 August 2023

DOI: 10.1002/pcn5.137

PCN Reports
Psychiatry and Clinical Neurosciences
Open Access

CASE REPORT

Crucial differential diagnosis of rapidly progressive dementia: A case of leptomeningeal metastasis

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Funding information
None

Abstract

Background: Dementia that advances subacutely without accompanying neurological symptoms can often be misdiagnosed as a psychiatric condition. Leptomeningeal metastasis (LM), caused by the spread of malignant cells to the leptomeninges and the subarachnoid space, is a relatively unfamiliar condition to psychiatrists in this context. The diagnosis of LM remains challenging due to the scarcity of diagnostic tools possessing high sensitivity and specificity.

Case Presentation: We present the clinical presentation of a male in his seventies with LM secondary to gastric ring cell carcinoma. The patient exhibited an acute confusional state, visual hallucinations, irritability, and cognitive impairments over a 3-week period. Initially, the patient was misdiagnosed with several conditions, including alcohol withdrawal syndrome, psychosis, and delirium associated with dementia, as there were no noteworthy findings on neurological examination or the head magnetic resonance imaging (MRI). Given the rapidly progressive cognitive decline, we maintained vigilance for potential neurological conditions, and a repeat investigation using head MRI and cerebrospinal fluid analysis led to the diagnosis of LM.

Conclusion: This critical case report underscores the rarity of psychiatric-onset LM originating from gastric cancer and highlights the importance of comprehensive neurological evaluations.

KEYWORDS

acute confusional state, cerebrospinal fluid, leptomeningeal metastasis, magnetic resonance imaging, rapidly progressive dementia

BACKGROUND

Typically, dementia associated with neurodegenerative diseases manifests as a gradual cognitive decline over several years. However, there are cases of rapidly progressive dementia (RPD), in which cognitive impairment develops subacutely over months, weeks, or even days. It is crucial for clinicians to promptly recognize RPD as certain conditions presenting with RPD may have potential curative treatment options.[1] Within the subset of RPD cases associated with malignancies, chemotherapy or immune system dysfunction are often considered the primary cause, while metastases without paraneoplastic and autoimmune associations are rare occurrences.[2,3]

Leptomeningeal metastasis (LM), resulting from the spread of malignant cells to the leptomeninges and subarachnoid space and

dissemination of malignant cells within the cerebrospinal fluid (CSF), is an infrequent and late-onset complication of cancer. LM occurs in approximately 5%–8% of patients with solid tumors, particularly lung cancer, breast cancer, and melanoma.[4] In comparison to other solid tumors or hematological malignancies, LM induced by gastric cancer is relatively uncommon.[4–6] Furthermore, due to the variety of associated symptoms, diagnosing LM can be particularly challenging. It is important for general practitioners and psychiatrists to be aware that patients with LM may present with psychiatric symptoms. While treatment options for LM are limited, precise diagnosis is crucial for patients and their caregivers. In this case report, we describe a rare case of LM caused by stomach cancer, presenting with acute behavioral changes and cognitive decline. We discuss the clinical characteristics that can contribute to an accurate diagnosis, as well as the appropriate procedures and management strategies for LM presenting with psychiatric symptoms. When providing care for patients with delirium, particularly those with a known malignancy, psychiatrists should consider the possibility of LM as a potential causative factor for acute changes in mental status.

TABLE 1 CSF findings.

CSF analysis	
Cell counts	30.9/μL
Mononuclear cells	97%
Polymorphonuclear cells	3%
Protein	610 mg/dL
Glucose	50 mg/dL
Oligoclonal band	Positive
HSV-DNA	Negative
NSE	43 ng/mL
IgG index	4.71
Myelin basic protein	Negative
Anti-NMDA-R antibody	Negative

Abbreviations: CSF, cerebrospinal fluid; HSV, herpes simplex virus; NSE, neuron-specific enolase; IgG, immunoglobulin G; NMDA-R, *N*-methyl-D-aspartate receptor.

CASE PRESENTATION

The patient, in his 70s, had advanced stomach cancer. He had received chemotherapy at our hospital for a year, and systemic chemotherapy had been stopped because of poor response. On Day −19, his behavior and personality suddenly changed. He became irritable, had verbal outbursts, and showed anger towards family members and even strangers. On Day −14, he visited our hospital unexpectedly, and around the same time, he was seen walking naked by his neighbor. A week later, he managed to come to our hospital as scheduled, where he was attended to by his primary treating surgeon. Upon returning home after the visit, he experienced a sudden onset of confusion and further outbursts. From Day −7 to Day −2, he struggled to recall his own name and location. He remained consistently unclothed and was unable to dress himself, even with guidance from family members. On Day −1, he exhibited attempts to grasp objects in the air, prompting his family to consult the neurology department. Based on negative findings from the head magnetic resonance imaging (MRI) without gadolinium enhancement, neurologists suspected the presence of psychiatric conditions, such as alcohol withdrawal, delirium, or acute psychosis. On Day 1, he was referred to the neuropsychiatry department; however, his walking ability had deteriorated, leading to his transfer and admission to the neuropsychiatry ward in our hospital.

On admission, he showed a confusional state with a Glasgow Coma Scale score of E3V3M5. While he displayed some responsiveness to slight external stimuli, his responses were incoherent and accompanied by severe agitation. He also showed mild sweating. In the examination room, he consistently exhibited a tendency to reach out for objects in the air. Comprehensive neurological examinations were unremarkable. The patient's family members reported that he usually consumed approximately two cans of beer (700 mL in total) on a daily basis in the evenings. However, specific details regarding his recent drinking behavior remain unknown because he was living alone before admission to the hospital. Blood tests, including biochemistry, hematology, vitamin levels, antibody assessments, tumor markers, and infection screening, revealed no abnormal findings, indicating that the underlying causative factors of cognitive impairment remained unclear. Subsequent head MRI revealed no abnormal findings. Nonetheless, despite the absence of MRI abnormalities, the patient continued to exhibit psychiatric symptoms, including agitation, irritability, and visual hallucinations, raising suspicions of psychiatric disorders. Given the subacute onset and course of the presented case, further investigations were deemed necessary to rule out neurological conditions associated with RPD. CSF analysis was conducted, revealing noteworthy findings, such as elevated cell counts, remarkably increased protein levels as 610 mg/dL, xanthochromia, and positive oligoclonal bands. The findings are provided in Table 1. These findings led us to suspect an inflammatory response within the central nervous system, potentially indicative of encephalitis or meningitis.

On Day 1, empirical therapy for central nervous infectious diseases was initiated, while a methylprednisolone steroid pulse was administered for potential autoimmune-mediated encephalitis. Due to the patient's confusional state, cognitive function tests could not be conducted. The Functional Independence Measure (FIM; 1 being the worst and 7 being the best), indicated scores of 1 for eating and ambulation, and 2 for cognition. On Day 3, antibiotics and antiviral infusion were stopped as CSF cultures and PCR for herpes simplex virus were negative. However, CSF cytology revealed the presence of solitary atypical cells displaying irregular nuclei, densely stained chromatin, nuclear maldistribution, luminal vesicles, and mucus-like material within the cytoplasm. These findings strongly suggested the presence of poorly differentiated adenocarcinoma and ring cell

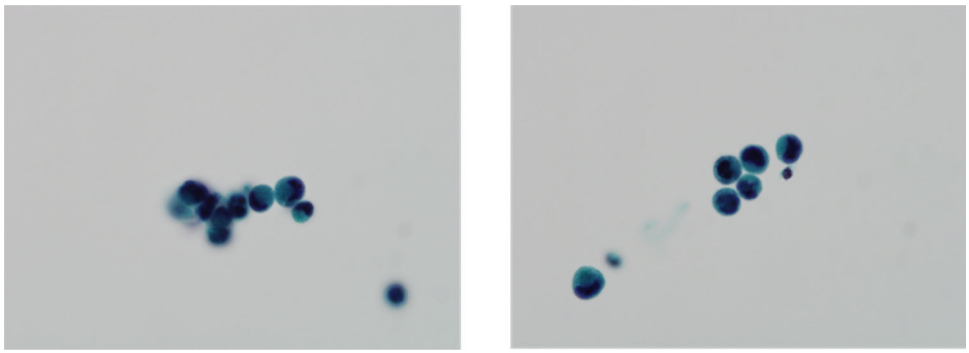

FIGURE 1 Cerebrospinal fluid (CSF) cytology reports. There are solitary atypical cells displaying irregular nuclei, densely stained chromatin, nuclear maldistribution, luminal vesicles, and mucus-like material within the cytoplasm, suggesting the presence of poorly differentiated adenocarcinoma and ring cell carcinoma.

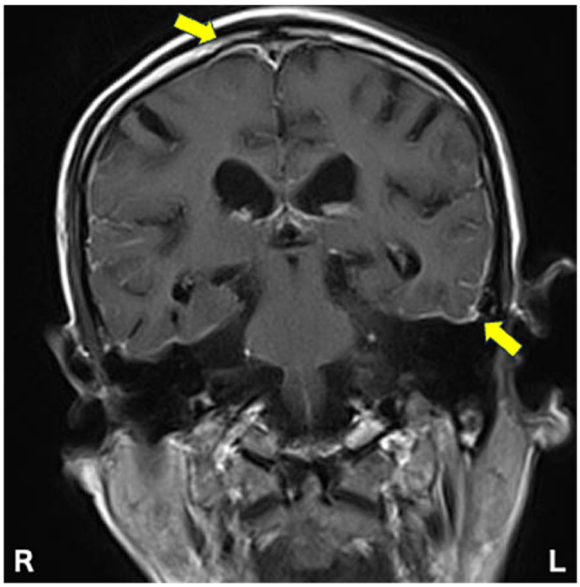

FIGURE 2 A coronal T1-weighted gadolinium-enhanced magnetic resonance imaging (MRI) revealed pia-arachnoid pattern thickened and enhanced dural (yellow arrows).

carcinoma, consistent with metastasis from gastric cancer (Figure 1). The patient's behavior improved with treatment, leading to continuation of steroid therapy (500 mg methylprednisolone per day for 2 more consecutive days, a total of 5 days). The diagnosis of possible LM was communicated to the patient, family members, and the primary surgeon, and it was collectively decided that the treatment approach would focus on palliative care given the patient's low-performance state. Betamethasone infusion was initiated and continued due to a better response.

On Day 5, a Mini Mental State Examination (MMSE) could be conducted, resulting in a score of 9/30, and FIM scores improved to 5 for eating, 4 for ambulation, and 6 for cognition. On Day 9, a follow-up MRI revealed pia-arachnoid pattern dural enhancement with gadolinium (Figure 2). Consequently, a definitive diagnosis of LM was established. On Day 10, there was a slight deterioration in activities of daily living and cognitive function, and the condition remained at a lower level despite betamethasone therapy to Day 25. MMSE was not feasible again, and FIM scores declined to 1–2 for all aspects of daily living. The presence of visual hallucinations remained unchanged, although the specific details of the symptoms were unknown as the patient was unable to provide an explanation. As time progressed, the patient's overall condition gradually deteriorated, and he ceased exhibiting the behavior of attempting to grasp something in the air. Ultimately, the patient died on Day 73. The overall course is illustrated in Figure 3.

DISCUSSION

We present a case of LM originating from signet ring cell carcinoma of the stomach, which primarily manifested as RPD. Initially, the case was primarily considered to be a psychiatric condition based on the absence of abnormal neurological and imaging findings. Clinicians should exercise caution as LM can present with a wide range of neuropsychiatric symptoms without obvious neurological signs. Additionally, this case report highlights the significance of repeated MRI investigations combined with CSF analysis for an accurate diagnosis of LM in clinical settings.

In the case of gastric cancer, the prevalence of LM is extremely low, affecting less than 1% (0.14%–0.24%) of patients during the course.[5,6] This low occurrence of LM in patients with gastric cancer contributes to the challenge of misdiagnosis. Moreover, symptom-based assessments are complex due to the diverse range of symptoms exhibited by LM patients, including headache, nausea/vomiting, confusion, cranial nerve palsy, seizures, ataxia, and spinal symptoms.[4–6] In the presented case, the patient demonstrated primarily neuropsychiatric symptoms and rapid cognitive decline without focal neurological signs. Since subjective symptoms were not available due to cognitive deficits, the presence of cranial nerve signs, particularly visual symptoms, becomes crucial for diagnosis.[7,8] We presumed that the patient experienced visual hallucinations based on his tendency to reach out for something in the air. However, it is

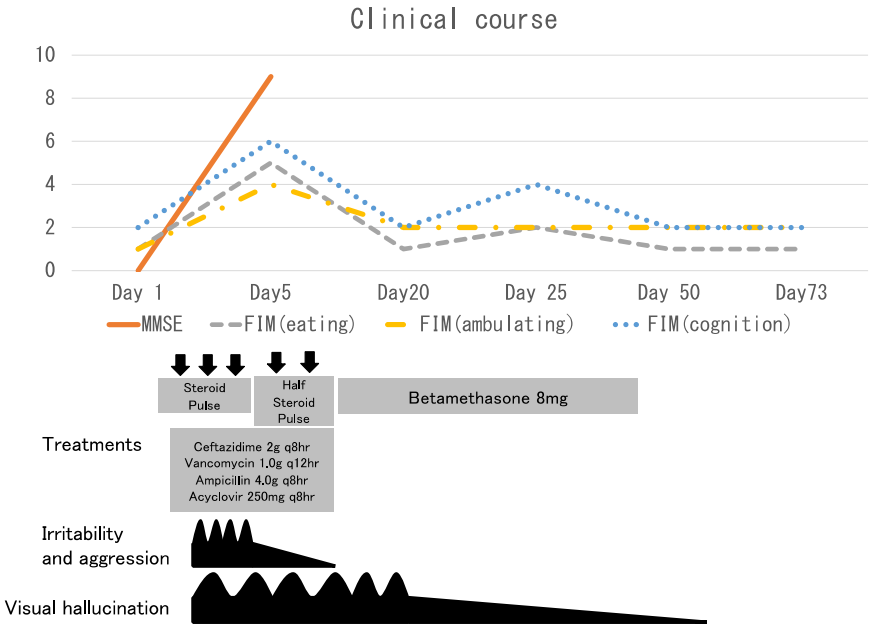

FIGURE 3 Overall clinical course is illustrated. FIM, Functional Independence Measure; MMSE, Mini Mental State Examination.

possible that this behavior was induced by visual loss resulting from metastasis to the optic nerve and abducens denervation, as reported in previous case studies.[9,10] Due to cognitive decline, the patient was unable to express what he had seen or felt throughout the course of the disease. In such situations, clinicians should avoid prematurely labeling these vague symptoms as clear-cut visual hallucinations associated with psychiatric disorders like alcohol withdrawal syndrome, delirium, and psychosis.

Although MRI is considered one of the gold standards for diagnosing LM, it is important to be aware of its limitations and potential pitfalls. The sensitivity of gadolinium-enhanced MRI is relatively moderate, ranging from 58.6% to 72.1%, which explains why the diagnosis of LM could not be ruled out based on negative MRI findings.[11,12] Furthermore, as demonstrated in our case, 51% of patients with LM who did not present with spinal symptoms or signs showed negative MRI findings.[11] Additionally, approximately 8% of patients with positive CSF cytology results exhibited negative MRI findings.[11] CSF cytology, despite its lower sensitivity ranging from 39.3% to 57.4%, remains a valuable diagnostic tool due to its high specificity.[13] However, there is also a critical pitfall: only the presence of pleocytosis, elevated protein levels, and hypoglycorrhachia without cytology examination in CSF analysis can suggest a neuroinfection and lead to misdiagnosis as infectious meningitis.[13] Therefore, it is important to acknowledge the limitations of imaging techniques and the need for a comprehensive evaluation when managing patients with malignancies who present with acute and atypical psychiatric symptoms.[4] Extensive investigations are often not pursued when patients with malignancy present with a confusional state as the majority of such cases are initially presumed to be delirium, which is a common occurrence in the context of malignancy.

Psychiatric symptoms, such as agitation, confusion, and depression, can be accompanied by the presence of LM.[12,13] Previous case reports have also documented the presence of visual hallucinations in association with LM.[10,14] In contrast to our presented case, these reports involved complex visual hallucinations and were accompanied by other spinal symptoms. The manifestation of abnormal behavior possibly induced by a potentially hallucinatory vision in our case warrants consideration of alcohol withdrawal syndrome or psychosis; however, these diagnoses should be made cautiously as hallucinations are typically characterized by complex and negative visual experiences.[15,16] In our presented case, a diagnosis of delirium due to stomach cancer could be considered; nevertheless, it is crucial to accurately identify the presence of metastases, as treatment options and prognosis differ.

CONCLUSION

The present case highlights a unique manifestation of RPD due to LM. The absence of notable neurological and imaging findings initially led to considerations of psychiatric conditions. Accurate diagnosis of LM is crucial, as it facilitated informed discussions between caregivers and patients regarding prognosis.

AUTHOR CONTRIBUTION STATEMENT

Yu Mimura acquired case data and drafted the manuscript. Hiroki Oi and Taketo Takata acquired case data. Michitaka Funayama and Masaru Mimura supervised the study and substantively revised the manuscript. All authors read and approved the final manuscript.

ACKNOWLEDGMENTS

The authors acknowledge family members of the patient.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

N/A.

ETHICS APPROVAL STATEMENT

This case report was conducted in accordance with ethical guidelines for case reports of the Japanese Society of Psychiatry and Neurology.

PATIENT CONSENT STATEMENT

We did not obtain the patient's consent because the presented case is a deceased person. We declare that the data do not reveal the identity of an individual and are thus not considered personal information for the individual and family; and this is not reported as academic research based on ethical guideline of the Japanese Society of Psychiatry and Neurology.

CLINICAL TRIAL REGISTRATION

N/A.

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How to cite this article: Mimura Y, Oi H, Takata T, Mimura M, Funayama M. Crucial differential diagnosis of rapidly progressive dementia: A case of leptomeningeal metastasis. Psychiatry Clin Neurosci Rep. 2023;2:e137. https://doi.org/10.1002/pcn5.137