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Case Report

Suspected Pembrolizumab-Associated Encephalitis Presenting as Altered Mental Status in an Elderly Patient with Cancer: A Case Report

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ABSTRACT

Immune checkpoint inhibitors such as pembrolizumab are increasingly used in cancer therapy and are associated with rare but serious immune-related neurological adverse effects, including autoimmune encephalitis. An 83-year-old woman with stage IV non-Hodgkin lymphoma presented with acute altered mental status—confusion, decreased verbal responsiveness, and inability to follow commands—after a single palliative infusion of pembrolizumab, her first and only dose. She had received no prior chemotherapy, radiation, or other systemic oncologic therapy. On examination, she was somnolent but arousable, disoriented and largely nonverbal, with bilateral upper-extremity weakness, reduced right-sided movement and sensation, and mild spasticity. Laboratory studies, neuroimaging and cerebrospinal fluid (CSF) analysis were performed to evaluate metabolic, infectious, vascular and structural causes. Several plausible contributors were identified: Klebsiella urinary tract infection, hyponatremia, hypotensive episodes, COVID-19 infection, and a subsequent left thalamic infarction — but none fully accounted for the prolonged, fluctuating course. Given recent pembrolizumab exposure, inflammatory CSF findings, and negative CSF infectious studies, pembrolizumab-associated encephalitis was suspected. Empiric treatment for suspected infectious causes produced no significant improvement. Intravenous methylprednisolone 75 mg every 12 hours (1.76 mg/kg/day) was started on hospital day 33; within 24–72 hours the patient became increasingly alert and verbal, able to follow commands, with motor function improving toward baseline. No other major diagnostic or therapeutic change occurred during that period. Corticosteroids were transitioned to oral prednisone 40 mg twice daily with a taper at discharge. Suspected pembrolizumab-associated encephalitis should remain in the differential for altered mental status in patients receiving immune checkpoint inhibitors when infectious, metabolic, hemodynamic, and vascular contributors do not fully explain the clinical course, although response to corticosteroids alone does not establish causality.

1. Introduction

Non-Hodgkin lymphoma is a common blood cancer that affects the lymphatic system and can arise from B cells, T cells, or natural killer cells. It can range from a slow-growing type, often showing "waxing and waning" lymph node enlargement over years, to an aggressive form with symptoms such as unexplained weight loss, night sweats, and fevers that can become life-threatening without prompt treatment. NHL encompasses various subtypes, each with distinct causes and features. Management depends on factors like stage, grade, lymphoma type, symptoms, age, and overall health. Standard treatments, including chemotherapy, monoclonal antibodies, and stem cell transplantation, have significantly improved survival for many patients[1].

PD-1 immune checkpoint blocking medications, such as pembrolizumab, have fundamentally changed how cancer is treated. It is a humanized monoclonal IgG4 antibody that targets the PD-1 receptor on lymphocytes, blocking its interaction with PD-L1. This prevents T-cell inhibition, thereby restoring immune system activity against tumor cells and improving cancer treatment outcomes[2]. However, this PD-1 immune checkpoint blockade drug has been linked to immune-related side effects, including encephalopathy, which can cause abrupt changes in mental status[3].

Altered mental status is defined as an abrupt shift in a person's level of consciousness, behavior, or cognitive function. There are many different causes of AMS, including toxic exposures, structural brain abnormalities, and metabolic and infectious etiologies. Among these, immune checkpoint inhibitor-associated encephalopathy has emerged as an uncommon but important consideration in patients receiving immunotherapy.

This case report presents a patient with non-Hodgkin lymphoma treated with pembrolizumab and presenting with AMS. It highlights the importance of considering immune-related adverse events in patients on immune checkpoint inhibitors and the need for a systemic approach when evaluating altered mental status in medically complex patients.

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2. Case Presentation

2.1. Patient Information

An 83-year-old female presented to the emergency department with an acute onset of altered mental status. At baseline, the patient is oriented to person and place and ambulates with a walker. Her past medical history is significant for hypertension, hyperlipidemia, and type 2 diabetes mellitus. Her home medications include hydralazine 50 mg three times daily, amlodipine 10 mg once daily, lisinopril 40 mg once daily, and rosuvastatin 40 mg once daily. She has no known drug allergies. Her oncologic history is notable for stage IV non-Hodgkin lymphoma, for which she received one cycle of pembrolizumab with palliative intent. Treatment was discontinued due to severe gastrointestinal side effects and zoster reactivation. She received pembrolizumab at a dose of 200 mg intravenously every 3 weeks. The last and only dose was administered approximately three weeks prior to the onset of altered mental status. No rechallenge with pembrolizumab was performed. Socially, the patient lives with her daughter and has caregiver support at home.

2.2. Clinical Findings

Upon admission, the patient was somnolent but arousable and oriented only to self when called by name. She was largely non-verbal and rarely followed simple commands. There was no facial asymmetry, and cranial nerves were otherwise grossly intact. Motor examination demonstrated bilateral upper-extremity weakness (2/5 bilaterally) and full strength in the lower extremities on formal testing, although spontaneous voluntary movement was minimal on the right. The discrepancy between full lower-extremity strength on formal testing and reduced spontaneous right-sided movement reflects the difference between strength elicited with directed examination and spontaneous voluntary movement. Muscle tone was mildly increased with spasticity, and reflexes were diminished in the upper and lower extremities, with muted Babinski responses bilaterally. Sensory examination showed withdrawal to pinprick in both lower extremities and the left upper extremity, with minimal response in the right upper extremity. Coordination and gait could not be assessed because of somnolence. Vital signs showed a blood pressure of 150/89 mmHg, heart rate of 93 bpm, temperature of 99.8 °F, respiratory rate of 21/min, and oxygen saturation of 96% on room air. She was subsequently admitted to the QHC emergency department with acute altered mental status. Additionally, she had been admitted twice earlier that year for altered mental status related to urinary tract infections.

2.3. Diagnostic Assessment

The initial workup included imaging, infectious disease screening, and a complete laboratory panel, which revealed mild anemia, hyponatremia, and a positive GenMark PCR test for SARS-CoV-2. A CT scan of the head was later done and showed no acute intracranial abnormalities. Diagnostic testing at this stage was aimed at identifying common metabolic, infectious, and structural causes of acute encephalopathy. Based on these findings, the differential diagnosis included toxic metabolic encephalopathy, delirium related to urinary tract infection, COVID-19, hyponatremia, and disseminated varicella-zoster virus infection. Given the patient's immunocompromised state, viral meningitis and encephalitis were also considered.

A comprehensive diagnostic evaluation was performed. This included laboratory studies, blood and urine cultures, and screening for infectious diseases. Magnetic resonance imaging (MRI) of the brain was performed without intravenous contrast using axial T1-, T2-, and FLAIR-weighted sequences, as well as axial and coronal diffusion-weighted imaging sequences. Because intravenous contrast was not administered, post-contrast enhancement could not be assessed. Image quality was further limited by motion artifact and head tilt. MRI demonstrated diffuse age-appropriate cortical atrophy with associated parenchymal volume loss, patchy periventricular and frontoparietal subcortical T2/FLAIR white matter hyperintensities consistent with chronic small vessel ischemic changes, and encephalomalacia involving the left external capsule extending into the left corona radiata, centrum semiovale, and left frontal deep white matter, compatible with chronic infarction. Despite motion degradation, diffusion-weighted imaging did not demonstrate findings suggestive of an acute, subacute, or territorial infarction. No mesial temporal lobe abnormalities, multifocal inflammatory changes, or other MRI findings suggestive of encephalitis were identified, although the incomplete examination and image degradation limited interpretation. Electroencephalography (EEG) was performed on hospital day 2 and demonstrated diffuse background slowing consistent with encephalopathy without focal epileptiform discharges or electrocardiographic seizure activity. These findings supported a diffuse cerebral dysfunction rather than a focal seizure process and were interpreted in conjunction with the patient's fluctuating mental status and later diagnostic findings. Lumbar puncture was obtained for cerebrospinal fluid (CSF) analysis, including cell counts, protein, glucose, infectious PCR panel, cytology, and autoimmune markers. Infectious evaluation included CSF HSV-1/2 PCR, VZV PCR, and a meningitis/encephalitis multiplex PCR panel, all of which were negative. Paired serum glucose of 275 mg/dL was obtained for interpretation of CSF glucose values. Given the patient's history of stage IV non-Hodgkin lymphoma, CSF cytology and flow cytometry were obtained to evaluate for CNS involvement. CSF cytology showed no malignant cells, and flow cytometry did not demonstrate an abnormal lymphoid population. Serum autoimmune testing included inflammatory markers (ESR and CRP), thyroid studies (TSH and free T4), anti-thyroglobulin antibodies, ANCA (c-ANCA and p-ANCA), anti-GQ1b antibodies, and a celiac antibody panel. Anti-thyroglobulin antibodies were obtained to evaluate for autoimmune thyroid disease and the possibility of Hashimoto encephalopathy. ANCA testing was performed to assess for systemic vasculitides with potential CNS involvement. Anti-GQ1b antibodies were obtained to evaluate for Miller Fisher syndrome and related disorders in the anti-GQ1b spectrum. The celiac antibody panel was performed to assess for gluten-related neurologic syndromes, including rare cases of gluten-associated encephalopathy. All results were within normal limits or negative. A serum paraneoplastic neurologic antibody evaluation was also performed and was negative, including amphiphysin, AGNA-1, ANNA-1, ANNA-2, ANNA-3, CRMP5-IgG by reflex Western blot, PCA-1 (PCA1-S), PCA-2 (PCA2-S), and PCA-Tr (PCA-Tr-S). The CSF autoimmune testing included NMDA receptor antibody testing and oligoclonal band testing, both of which were negative. Broader CSF autoimmune or paraneoplastic antibody testing was not documented as performed or available in the record; serum paraneoplastic antibody testing was negative.

Following extensive evaluation, no single definitive etiology was identified. Infectious, metabolic, hemodynamic, vascular, and immune-mediated causes remained considerations throughout the hospitalization, with urinary tract infection, hyponatremia, hypotension, and the later left thalamic infarction representing plausible contributors. Cerebrospinal fluid obtained on hospital day 11 showed a positive West Nile virus antibody assay and a negative West Nile virus IgM. The specific assay methodology and antibody class corresponding to the positive WNV-CSF result were

not specified in the available medical record. The exact significance of this isolated finding was uncertain and may reflect prior exposure rather than acute neuroinvasive infection. Additionally, WNV PCR was not documented as having been performed. In the absence of supportive clinical features, positive IgM serology, or confirmatory PCR testing, West Nile virus infection was not considered the primary cause of the patient's encephalopathy. An acute stroke was identified later in the hospital course; however, this did not fully explain the change in mental status as well as the diffuse encephalopathy. Serial neurologic examinations were performed throughout the hospitalization, although fluctuations in arousal and responsiveness sometimes limited individual assessments. Findings are therefore reported using the examination elements that could be reliably assessed at each time point. There were also overlapping features of infectious, vascular, and immune-mediated etiologies. Additionally, the timing of diagnostic studies relative to symptom onset may have affected the sensitivity of certain tests.

Infectious etiologies were evaluated through serial urine cultures, infectious screening, laboratory studies, and clinical monitoring. The patient was treated empirically with broad-spectrum antibiotics and antivirals early in the hospital course, followed by ceftriaxone and, after identification of a Klebsiella urinary tract infection, later by nitrofurantoin, with subsequent escalation to ertapenem based on resistance patterns. Serial assessments showed a downward trend in creatinine, lactate, temperature, and white blood cell count, followed by eventual normalization of these parameters. Despite antimicrobial treatment and stabilization of hemodynamic status following hypotensive episodes, the patient's altered mental status persisted and fluctuated without sustained neurologic improvement. Although urinary tract infection, physiologic stress, and hypotension likely contributed to the clinical picture, the lack of meaningful improvement after treatment made these etiologies less likely to be the primary drivers of the prolonged encephalopathy. Given the patient's complex presentation and multiple potential contributors to altered mental status, the major differential diagnoses considered during hospitalization, along with supporting and opposing evidence, relevant laboratory and hemodynamic trends, and treatment responses, are summarized in **Table 1**.

Table 1: Differential diagnoses considered for altered mental status

Etiology	Supporting evidence	Opposing evidence/treatment response
UTI / sepsis	Urine WBC 2.1 → 179 → 22.8/HPF; leukocyte esterase moderate → moderate → small; Klebsiella present	Pyuria improved, but AMS persisted despite broad-spectrum antibiotics.
COVID-19	Positive SARS-CoV-2 PCR	O_2 sat 96% RA; neurologic symptoms persisted despite remdesivir
Hyponatremia	Mild hyponatremia during hospitalization	Na 138 → 126 → 136 mEq/L; AMS persisted despite correction.
Hypotension	Episodes with SBP in the 70s; possible cerebral hypoperfusion	BP 82/48 → 110-120/60-70 mmHg after support; neurologic deficits persisted.
Urinary retention	~500 mL urine drained by catheterization	AMS persisted after bladder decompression
Medications	Multiple medications with potential CNS effects	No clear medication-related temporal relationship; AMS persisted after adjustments.
Thalamic infarction	New left thalamic infarct after hypotensive episode	AMS preceded infarct; infarct did not explain entire fluctuating course
Suspected ICI-associated encephalitis	Recent pembrolizumab exposure; mild CSF lymphocytic pleocytosis/protein elevation; negative infectious studies; improvement after steroids	No definitive diagnostic test; multiple competing etiologies

Abbreviations: AMS, altered mental status; BP, blood pressure; CNS, central nervous system; COVID-19, coronavirus disease 2019; CSF, cerebrospinal fluid; HPF, high-power field; ICI, immune checkpoint inhibitor; PCR, polymerase chain reaction; RA, room air; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SBP, systolic blood pressure; UTI, urinary tract infection; WBC, white blood cell.

2.4. Therapeutic Interventions

The full sequence of clinical events, investigations, treatments and neurologic responses across this admission is summarized in **Table 2**. Due to her history of shingles, the patient was empirically started on broad-spectrum antibiotics (Zosyn and vancomycin), ceftriaxone for potential bacterial meningitis, and acyclovir and remdesivir for suspected viral meningitis. Despite these treatments, her mental state did not improve during the first 24 to 48 hours. However, by day 4, her neurological status had partially improved. She was alert but persistently somnolent and oriented only to self. She remained nonverbal and did not follow commands. Her motor examination remained unchanged from prior assessment. Subsequent CSF testing showed a positive West Nile virus antibody assay and a negative West Nile virus IgM. This finding was considered of uncertain clinical significance and was not felt to represent acute neuroinvasive West Nile infection. Further CSF findings are summarized in **Table 3**; CSF analysis showed clear, colorless fluid with a glucose level of 85 mg/dL, elevated relative to the laboratory reference range, with a paired serum glucose of 275 mg/dL, yielding a CSF-to-serum glucose ratio of approximately 0.31; the CSF sample was obtained on hospital day 11. The relatively low CSF-to-serum glucose ratio was interpreted in the context of marked serum hyperglycemia rather than as isolated hyperglycorrhachia. In addition, CSF analysis showed elevated protein at 50 mg/dL, slightly increased cell count with 80% lymphocytic predominance, and minor RBC contamination. Infectious PCR was negative, but West Nile Virus CSF antibody was positive with negative IgM, indicating no evidence of acute infection. Urinalysis findings are summarized in **Table 4** and demonstrated progression from isolated heavy proteinuria on Day 1 to pronounced pyuria, glucosuria, leukocyte esterase positivity, and bacteriuria on Day 7, followed by partial improvement by Day 15 with reduced proteinuria and resolving inflammatory findings.

During her hospital course, a distended bladder was identified, leading to straight catheterization with approximately 500 mL of urine drained. On day 11, urine culture grew *Klebsiella* species, confirming a urinary tract infection. Ceftriaxone, which had been initiated empirically on hospital day 1 for suspected bacterial meningitis, was continued as directed therapy for the urinary infection. The patient was discharged on day 12 with nitrofurantoin

Table 2: Unified timeline of clinically relevant events, diagnostic findings, treatment and neurologic response

Hospital Day	Clinical / Neurologic Findings	Diagnostics / Cultures	Treatment/Response
0	Somnolent but arousable, oriented to self; attention impaired, largely nonverbal, rarely followed simple commands, UE 2/5 bilaterally; full LE strength; minimal voluntary movement on right, withdrawal to pinprick in bilateral LE and left UE; minimal response in right UE, mild spasticity; diminished reflexes; no facial asymmetry	Head CT: no acute intracranial abnormality; SARS-CoV-2 PCR positive	
1	Persistent AMS	MRI: incomplete, chronic changes, no acute infarct/definite encephalitis; blood and urine cultures obtained	IV Vancomycin/Zosyn, ceftriaxone
2	No significant improvement in the first 24–48 h	EEG: diffuse background slowing consistent with encephalopathy; no focal epileptiform discharges	IV acyclovir, remdesivir
4	Alert but somnolent, oriented to self, nonverbal, unable to follow commands, motor deficits unchanged, sensory deficits unchanged, persistent right-sided deficits		IV acyclovir, remdesivir
7	Persistent AMS	UA: pyuria, glucosuria, LE+, bacteriuria	
11	Persistent AMS	LP: 6 WBC/μL, 80% lymphocytes, protein 50; PCR negative; WNV Ab+ / IgM-, Klebsiella UTI	Ceftriaxone continued
12	Persistent/incomplete recovery	Klebsiella UTI	Discharged on PO nitrofurantoin
15	Readmission; recurrent AMS; SBP 70s after enema/laxatives	Repeat urine cultures	Hemodynamic support
16	Fluctuating AMS	Culture resistant to nitrofurantoin/Zosyn; sensitive to ertapenem	IV Ertapenem started
23	Unresponsive, unable to assess orientation, nonverbal, unable to follow commands, unable to reliably assess motor and sensory functions	Head CT: no hemorrhage; MRI: left thalamic infarct; EEG: diffuse slowing consistent with encephalopathy; no focal epileptiform activity	Supportive stroke management
26	Persistent encephalopathy, swelling of the lips and tongue		Discontinue lisinopril, continued supportive management.
33	Persistent encephalopathy; ICI encephalitis considered		Methylprednisolone 75 mg IV q12h started (1.76 mg/kg/day)
+24 h	Mental status: Alert to voice; oriented to self. Speech: Beginning to verbalize. Commands: Beginning to follow commands. Motor: Upper-extremity weakness persisted; lower-extremity strength not documented. Sensory: Persistent sensory deficits. Right-sided movement: Improving spontaneous right-sided movement.		Steroids continued
+48 h	Mental status: More alert and verbal. Speech: More verbal. Commands: Following commands consistently. Motor: Improved upper-extremity movement; lower-extremity strength not documented. Sensory: Improved. Right-sided movement: Improving spontaneous right-sided movement.		Steroids continued

continued on the next page

Table 2 (continued)

Hospital Day	Clinical / Neurologic Findings	Diagnostics / Cultures	Treatment/Response
+72 h	Mental status: Conversational; oriented to self. Speech: Conversational. Commands: Following commands. Motor: Near baseline; exact strength not documented. Sensory: Near baseline; exact findings not documented. Right-sided movement: No persistent reduction in spontaneous right-sided movement documented.		Steroids continued
43	Near baseline		Discharged to rehabilitation, taper prednisone to oral 40 mg twice daily, Bactrim prophylaxis

Abbreviations: Ab, antibody; AMS, altered mental status; CT, computed tomography; EEG, electroencephalography; ICI, immune checkpoint inhibitor; IgM, immunoglobulin M; IV, intravenous; LE, lower extremity; LE+ (urinalysis), leukocyte esterase positive; LP, lumbar puncture; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; PO, per os (by mouth); q12h, every 12 hours; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SBP, systolic blood pressure; UA, urinalysis; UE, upper extremity; UTI, urinary tract infection; WBC, white blood cell; WNV, West Nile virus; Zosyn, piperacillin-tazobactam.

Table 3: Cerebrospinal fluid analysis (CSF) obtained through lumbar puncture. Results that are not within the normal limit are bolded.

Test	*Normal Range*	Result
Appearance, CSF	*Clear*	Clear
Colour	*Colourless*	Colourless
CSF PCR Panel	*Not Detected*	Not Detected
Glucose, CSF	*45–80 mg/dL*	**85 mg/dL**
Lymphocytes	*60–70%*	**80%**
Monocytes	*15–45%*	20%
Protein, CSF	*15–45 mg/dL*	**50 mg/dL**
RBC Count	*0 cells/μL*	**10 cells/μL**
RBC Manual, CSF	*0 cells/μL*	**10 cells/μL**
Total Nucleated Cell Count including WBC	*0–5 cells/μL*	**6 cells/μL**
Total Nucleated Cell Count including WBC (Manual)	*0–5 cells/μL*	**6 cells/μL**
West Nile Virus CSF IgM	*Negative*	Negative
West Nile Virus CSF	*Negative*	Positive
Oligoclonal Band	*Absent*	Absent
NMDA Receptor Ab, CSF	*< 1:1*	< 1:1

Abbreviations: Ab, antibody; CSF, cerebrospinal fluid; IgM, immunoglobulin M; NMDA, N-methyl-D-aspartate; PCR, polymerase chain reaction; RBC, red blood cell; WBC, white blood cell.

for the UTI, along with rosuvastatin, lisinopril, and hydralazine for her chronic conditions.

Three days later (day 15 since first admission), the patient was readmitted to the hospital due to altered mental status. Her daughter reported that prior to admission, the patient had difficulty swallowing, poor appetite, and a history of constipation for the past few days, which was addressed in the emergency department with an enema and laxatives. Following these interventions, the patient's systolic blood pressure dropped to the 70s, prompting further evaluation. Urine cultures were obtained and revealed sensitivity to ertapenem with resistance to both nitrofurantoin and Zosyn, leading to an adjustment in her antibiotic regimen.

The patient's condition worsened on day 23, with her blood pressure again dropping to the 70s and becoming unresponsive. She was nonverbal and unable to follow commands. Orientation and attention could not be assessed. Motor and sensory examinations could not be performed reliably due to her unresponsiveness. No new focal deficit could be reliably established at that time. A stroke code was initiated, and a CT scan of the head revealed old infarcts in the left basal ganglia and external capsule but no signs of acute hemorrhage, hydrocephalus, or new territorial infarcts. A subsequent MRI of the brain demonstrated a small subcentimeter acute-to-subacute lacunar infarction in the left thalamus, with additional smaller foci of restricted diffusion adjacent to the posterior bodies of the bilateral lateral ventricles. These additional foci were not interpreted as definite acute or subacute infarctions. No mass effect or hemorrhage was identified.

The examination included axial and sagittal T1-weighted, axial FLAIR, proton-density, and T2-weighted sequences, as well as axial and coronal diffusion-weighted and coronal gradient-echo imaging. Sagittal FLAIR imaging was also obtained. The examination was performed without intravenous contrast; therefore, post-contrast enhancement could not be assessed. Although motion artifact degraded portions of the examination, the remainder was considered diagnostically adequate. The MRI also demonstrated diffuse age-appropriate cortical atrophy; patchy periventricular and periatrial T2/FLAIR hyperintensities consistent with chronic ischemic/hypertensive changes; and a chronic left basal ganglia/external capsule infarct extending toward the left corona radiata, with compensatory enlargement of the adjacent left lateral ventricle. A repeat EEG performed on hospital day 23 again demonstrated diffuse slowing consistent with encephalopathy without focal epileptiform activity. Thus, two EEG studies were performed during the hospitalization: an initial study on hospital day 2 and a repeat study on hospital day 23. Although the acute-to-subacute thalamic infarction likely contributed to the patient's decreased arousal and impaired responsiveness during the later hospital course, it did not fully explain the overall clinical presentation. The patient's altered mental status preceded identification of the infarction and was characterized by fluctuating encephalopathy rather than a persistent focal neurologic syndrome. The diffuse EEG abnormalities further supported a superimposed nonvascular encephalopathic process. Therefore, while the thalamic infarction was considered an important contributing factor, it was not considered to be the primary driver of the patient's prolonged altered mental status.

Table 4: Urinalysis values obtained throughout the course of care. Results that are not within the normal limit are bolded. Day 1 is the day of the presenting complaint.

Test	*Normal Range*	Day 1	Day 7	Day 15
Specific Gravity Urine	*1.005–1.030*	1.012	1.014	1.018
Protein Urine	*Negative*	**300**	**300**	**100**
Glucose Qualitative Urine	*Negative*	Negative	**500**	Negative
Ketones Urine	*Negative*	Negative	Negative	Negative
Bilirubin Urine	*Negative*	Negative	Negative	Negative
Blood Urine	*Negative*	Negative	Negative	Negative
Urobilinogen Urine	*0.1–1.0 mg/dL*	1.0 mg/dL	1.0 mg/dL	1.0 mg/dL
Nitrite Urine	*Negative*	Negative	Negative	Negative
Leukocyte Esterase Urine	*Negative*	**Moderate**	**Moderate**	**Small**
Squamous Epithelial Cells Urine	*0–5/HPF*	0-5/HPF	0-5/HPF	0-5/HPF
White Blood Cells Urine	*0–5/HPF*	2.1/HPF	**179.0/HPF**	**22.8/HPF**
Red Blood Cells Urine	*0–5/HPF*	3.4/HPF	1.5/HPF	**7.6/HPF**
Bacteria Urine	*None Seen*	None Seen	**Over Range**	None Seen
pH Urine	*4.5–8.0*	6.5	7.0	5.5
Appearance Urine	*Clear*	Clear	**Cloudy**	Clear
Color Urine	*Yellow*	Yellow	Yellow	Yellow
Cast Urine	*0-2/LPF*	0-2/LPF	0-2/LPF	**11-20/LPF**

Abbreviations: HPF, high-power field; LPF, low-power field.

A few days later, she developed swelling of the lips and tongue along with increased difficulty speaking, concerning for angioedema possibly related to her ACE inhibitor; lisinopril was discontinued. Given her cancer history, the oncology team was consulted and considered immune checkpoint inhibitor-related encephalitis as a possible diagnosis. On day 33, she was started on intravenous methylprednisolone 75 mg every 12 hours (1.76 mg/kg/day), consistent with oncology guidance for immune checkpoint inhibitor-related encephalitis, followed by a planned transition to oral prednisone. Had there been no response, escalation to IVIG or plasma exchange was planned per institutional protocol. The patient's subsequent stabilization and improvement following corticosteroid therapy supported an immune-mediated process. Neurological examination after treatment showed that she was alert, oriented to self, able to follow commands, and verbal, with motor function near her baseline. Causality could not be definitively established due to the overlap between infectious and vascular factors. By day 43, the patient's neurological status had stabilized. She was alert, oriented to self, able to follow commands, and verbal. Her motor examination had returned to documented pre-admission baseline, and she was subsequently cleared for discharge to rehabilitation.

Additionally, supportive care measures included blood pressure monitoring and management during hypotensive episodes, bowel regimen for constipation, and bladder decompression with Foley catheterization. The patient was placed on aspiration precautions to address swallowing difficulties. The patient was ultimately discharged to a rehabilitation facility for continued functional recovery.

2.5. Intervention Timeline

The intervention timeline for this admission is presented in **Table 2**.

2.6. Follow-Up and Outcomes

Recommendations for discharge included taking Bactrim daily to prevent pneumocystis pneumonia, starting oral prednisone at 40 mg twice daily with a planned taper over 4–6 weeks, and scheduling follow-up appointments with her oncologist and primary care physician to monitor steroid taper. At the time of discharge on hospital day 43, the patient was alert, oriented to self, following commands, and verbal, with motor function documented as near her pre-admission baseline. She was discharged to a rehabilitation facility with oral prednisone 40 mg twice daily and a planned 4–6-week taper. Pembrolizumab was not resumed. The patient tolerated corticosteroids without significant adverse effects and had no secondary infections during hospitalization. The patient was discharged with a corticosteroid taper plan using oral prednisone following completion of intravenous corticosteroid therapy. Pembrolizumab was not resumed and remained permanently discontinued. No subsequent outpatient records were available; therefore, the duration and outcome of post-discharge rehabilitation and long-term neurologic, cognitive, and functional recovery could not be confirmed.

2.7. Patient Perspective

Due to the patient's altered mental status, a direct patient perspective could not be obtained. Instead, a caregiver perspective was provided by the patient's daughter, who served as the primary historian and was familiar with the patient's baseline functional and cognitive status. The daughter described the patient's abrupt cognitive decline as distressing compared to baseline independence and noted marked improvement following initiation of corticosteroid therapy. Consent was obtained from the patient's legally authorized representative for publication of this caregiver perspective.

3. Discussion

This case highlights the importance of considering a broad range of potential causes of AMS when evaluating elderly and immunocompromised patients. The patient's encephalopathy was likely multifactorial. Recurrent urinary tract infection, hypotensive episodes, metabolic derangements, and a subsequent ischemic stroke were all plausible contributors to her altered mental status. Despite these competing etiologies, suspected pembrolizumab-associated autoimmune encephalitis remained an important diagnostic consideration because the identified infectious, vascular, metabolic, and hemodynamic abnormalities did not fully account for the clinical course, given the temporal relationship to pembrolizumab exposure and the patient's marked clinical improvement following corticosteroid therapy. Nevertheless, a definitive causal relationship cannot be established in this case given the overlapping infectious, vascular, metabolic, and hemodynamic contributors. The clinical improvement observed after corticosteroid initiation increased suspicion for an immune-mediated process but does not independently establish causality.

Pembrolizumab, an anti-PD-1 immune checkpoint inhibitor, has been associated with rare immune-mediated central nervous system adverse events, including autoimmune encephalitis. This occurs due to loss of immune tolerance, triggering T-cell-driven neuroinflammation, microglial activation, and sometimes the emergence or induction of paraneoplastic syndromes[4]. These mechanisms can lead to varied encephalitic symptoms—such as confusion, reduced consciousness, and neuropsychiatric changes often accompanied by inflammatory cerebrospinal fluid and abnormal MRI findings[4].

Immune checkpoint inhibitor-associated encephalitis is a rare but potentially serious neurologic immune-related adverse event, reported in approximately 0.16% of patients treated with immune checkpoint inhibitors[5]. Clinical presentations are heterogeneous and may include altered mental status, memory loss, psychiatric symptoms, speech impairment, and seizures. Because these manifestations can overlap with infectious, metabolic, vascular, malignant, and paraneoplastic conditions, diagnosis requires careful clinical evaluation, supported by cerebrospinal fluid analysis, brain MRI, EEG, and, when appropriate, autoimmune testing.

Diagnosis is primarily clinical and requires careful evaluation of infectious, metabolic, vascular, malignant, and paraneoplastic causes, supported when available by CSF, MRI, EEG, and autoimmune testing[6]. Because no single diagnostic test definitively establishes ICI-associated encephalitis, the temporal relationship to ICI exposure and response to immunosuppressive therapy may provide additional supportive evidence.

According to the American Society of Clinical Oncology, when immune-related encephalitis is suspected, immune checkpoint inhibitor therapy should be withheld and high-dose corticosteroids initiated after appropriate evaluation for infectious and other alternative causes[7]. Intravenous immunoglobulin or plasmapheresis may be considered in patients who do not adequately respond to corticosteroids. In the present case, corticosteroid therapy was associated with substantial neurologic improvement; however, because the patient had several competing causes of encephalopathy, this response should be interpreted as supportive of, rather than diagnostic of, an immune-mediated etiology. Early treatment improves outcomes, whereas delays heighten the risk of complications and death. No proven methods exist for primary prevention; risk reduction depends on baseline neurologic evaluation, patient education, and close monitoring for new neurologic symptoms[8].

Another reported case adds to the growing literature describing an association between pembrolizumab and altered mental status. A 63-year-old woman with grade III breast carcinoma developed persistent high-grade fever followed by progressive neurocognitive deterioration, including confusion, disorientation, irritability, and intermittent dystonic posturing after pembrolizumab administration[9]. An extensive infectious evaluation was unrevealing, while cerebrospinal fluid (CSF) showed marked lymphocytic pleocytosis and elevated protein levels, with negative bacterial and viral studies. Brain MRI showed no definitive acute abnormalities. Given the temporal relationship to pembrolizumab and exclusion of alternative etiologies, immune checkpoint inhibitor-associated encephalitis was suspected. High-dose intravenous methylprednisolone resulted in rapid defervescence and complete neurological recovery, providing a clear therapeutic response that supported the diagnosis.

These overlapping etiologies highlight the diagnostic challenge of recognizing suspected pembrolizumab-associated encephalitis in medically complex patients and underscore the importance of considering immune-mediated encephalitis when alternative causes cannot fully explain neurological deterioration.

4. Conclusion

This case highlights the diagnostic complexity of prolonged altered mental status in an elderly, immunocompromised patient with multiple potential contributing etiologies. Although infectious, vascular, metabolic, and hemodynamic factors likely contributed to the patient's encephalopathy, suspected pembrolizumab-associated autoimmune encephalitis remained an important diagnostic consideration because of the temporal relationship to immune checkpoint inhibitor exposure, the inflammatory CSF findings, and the clinical improvement following corticosteroid therapy. While causality cannot be definitively established, this case underscores the importance of maintaining a high index of suspicion for immune-related neurologic adverse events when alternative contributors do not fully explain the clinical course.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Institutional Review Board (IRB)

This case report was prepared in accordance with the principles of the Declaration of Helsinki. Ethical review and approval were waived for this case report, as institutional policy does not require Institutional Review Board approval for a single de-identified case report.

Informed Consent

Informed consent for publication of this case report and any accompanying clinical information was obtained from the patient's legally authorized representative.

Large Language Model

The authors used ChatGPT (OpenAI) to assist with language refinement and grammar checking during the preparation of this

manuscript. All scientific content, interpretation, and conclusions were reviewed and verified by the authors, who take full responsibility for the accuracy and integrity of the manuscript.

Authors Contribution

LE, HA, and RA all contributed to the preparation and critical review of the manuscript, and each agrees to be accountable for all aspects of the work. All authors reviewed and approved the final manuscript.

Data Availability

All data relevant to this case report are included in the manuscript. Additional information is not publicly available to protect patient confidentiality.

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