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Case Report **Medical Oncology**

SMART Syndrome Mimicking Tumor Progression in a Patient with Metastatic ALK-Positive Non-Small-Cell Lung Cancer: A Case Report

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Abstract

Background: Stroke-like migraine attacks after radiation therapy (SMART) syndrome is a rare, delayed complication of cranial irradiation characterized by subacute, potentially reversible neurological deficits and distinctive imaging features. Its diagnosis is particularly challenging in patients with metastatic brain disease, where clinical and radiological findings overlap with tumor progression, radiation necrosis, and seizure-related phenomena. ***Case Presentation:*** We report the case of a 43-year-old male with stage IV ALK-positive non-small-cell lung adenocarcinoma with extensive brain metastases who developed acute global aphasia and altered mental status following multiple courses of cranial irradiation, including stereotactic radiosurgery, and whole-brain radiation therapy in addition to subtotal resection of a frontal brain lesion. The patient had prolonged systemic disease control with sequential ALK inhibitors but experienced repeated intracranial progression requiring multimodal local therapies. During an acute neurological deterioration in November 2025, neuroimaging demonstrated extensive post-radiation and metastatic changes, and the differential diagnosis included tumor progression, radiation necrosis, and focal status epilepticus. Given the clinical context and imaging limitations, SMART syndrome was suspected. High-dose intravenous corticosteroids led to partial neurological improvement, supporting the diagnosis of radiation-induced cortical dysfunction. ***Conclusion:*** This case highlights the diagnostic complexity of SMART syndrome in patients with advanced metastatic brain disease and cumulative radiation exposure.

Keywords: COVID, ethnobotany, local population, medicinal plants, Pandermic.

INTRODUCTION

Anaplastic lymphoma kinase (ALK)-positive non-small-cell lung cancer (NSCLC) represents a distinct molecular subset of lung adenocarcinoma characterized by chromosomal rearrangements involving the ALK gene, which drive oncogenic signaling and tumor proliferation. This subtype accounts for approximately 3–7% of NSCLC cases and predominantly affects younger, non-smoking patients, often presenting with advanced-stage disease and CNS metastases [1]. The advancement of targeted therapies, particularly tyrosine kinase inhibitors has revolutionized the management of ALK-positive NSCLC by significantly improving systemic and intracranial disease control, progression-free survival, and quality of life compared to conventional chemotherapy [2]. Despite these advances, CNS involvement remains a major clinical challenge due to the blood–brain barrier limiting drug penetration and the frequent development of brain metastases, which contribute substantially to morbidity and mortality in this population. Radiotherapy, including stereotactic radiosurgery (SRS) and whole-brain radiotherapy (WBRT), remains a cornerstone for managing intracranial metastases in ALK-positive NSCLC, especially in cases of oligometastatic brain disease. However, repeated cranial irradiation can lead to complex late neurotoxic effects, including radiation necrosis and rare but increasingly recognized entities such as stroke-like migraine attacks after radiation therapy (SMART) syndrome. SMART syndrome is a delayed, reversible neurological complication characterized by transient focal cortical deficits, migraine-like headaches, seizures, and distinctive

cortical MRI abnormalities confined to previously irradiated brain regions [3].

The pathophysiology of SMART syndrome is not fully clear but is thought to involve radiation-induced endothelial injury, blood–brain barrier disruption, impaired cerebrovascular autoregulation, and cortical spreading depression, resulting in transient cortical dysfunction and vasogenic edema. These mechanisms overlap with those implicated in radiation necrosis, complicating differential diagnosis. Clinically, SMART syndrome presents with acute or subacute neurological symptoms such as aphasia, hemiparesis, seizures, and migraine-like headaches, often mimicking stroke or tumor progression. Neuroimaging typically reveals unilateral cortical T2/FLAIR hyperintensity and gyri form enhancement in irradiated areas, which may resolve partially or completely with corticosteroid therapy and supportive care. However, the syndrome's rarity, variable latency (ranging from months to decades post-radiotherapy), and overlapping features with other CNS pathologies pose diagnostic challenges [4].

CASE PRESENTATION

A 43-year-old Saudi male, a schoolteacher and lifelong nonsmoker, was initially diagnosed in early 2021 with stage IV lung adenocarcinoma when he presented with a three-month history of persistent cough. Diagnostic workup revealed metastatic adenocarcinoma of pulmonary origin on liver biopsy, with immunohistochemistry positive for cytokeratin 7 (CK7) and thyroid transcription factor-1 (TTF-1). Staging investigations demonstrated bone metastases at presentation, consistent with advanced disease. Molecular testing subsequently identified an anaplastic lymphoma kinase (ALK) rearrangement.

The patient initially received four cycles of carboplatin and pemetrexed, completed in May 2021. ALK positivity was reported after the initiation of chemotherapy, prompting a transition to targeted therapy. Maintenance treatment with alectinib was started on June 1, 2021, resulting in an excellent clinical and radiological response. However, treatment was complicated by renal dysfunction, with serum creatinine rising to approximately 300 µmol/L, necessitating dose reduction to 300 mg orally twice daily.

Attempts at dose escalation to 450 mg twice daily in February 2022 were limited by recurrent renal impairment and associated bradycardia. Despite normalization of renal function following dose adjustments, repeated rechallenges at higher doses resulted in recurrent creatinine elevation. Consequently, the alectinib dose was reduced to 300 mg twice daily in July 2022. Serial (PET-CT) scans performed in June 2022 and March 2023 demonstrated complete metabolic remission, with no evidence of fluorodeoxyglucose (FDG)-avid disease.

Development of Central Nervous System Involvement

In late July 2023, the patient was admitted with acute onset dizziness and loss of consciousness. Neuroimaging with (CT) and (MRI) of the brain revealed progressive intracranial metastatic disease. Concurrent CT imaging of the chest, abdomen, and pelvis showed stable pulmonary findings, resolution of liver metastases, and improvement in osseous lesions, indicating isolated central nervous system (CNS) progression. He was commenced on dexamethasone and subsequently received stereotactic radiotherapy to the brain metastases. Following radiotherapy, the patient developed secondary epilepsy and was started on valproic acid at a dose of 500 mg twice daily. A PET-CT scan in October 2023 again demonstrated no FDG-avid systemic disease. However, MRI of the brain in October 2023 showed radiological progression of intracranial disease. As a result, systemic therapy was switched to lorlatinib at a dose of 100 mg once daily in November 2023.

Subsequent CNS-Directed Therapies

Despite lorlatinib therapy, the patient developed progressive brain disease. In February 2024, he received CyberKnife stereotactic radiosurgery (SRS) delivering 18 Gy in a single fraction to progressing intracranial lesions. In August 2024, due to further progression, he underwent a left frontal craniotomy with subtotal resection of a symptomatic lesion. Histopathological examination confirmed metastatic non-small-cell lung carcinoma consistent with the known primary.

Postoperative imaging, including MRI of the brain and PET choline studies, demonstrated persistent metabolic and radiological activity in multiple intracranial lesions. Given the multifocal nature of disease, whole-brain radiation therapy (WBRT) was administered in October 2024, delivering a total dose of 30 Gy in 12 fractions. During this period, the patient tolerated lorlatinib well, reporting only intermittent mild to moderate headaches without associated nausea, vomiting, focal neurological deficits, or systemic symptoms. His (ECOG) performance status remained robust.

Further Disease Progression and Systemic Therapy

By October 2025, the patient reported worsening chronic cough, increased fatigue, and subjective weight loss. He also complained of dental pain with localized left jaw swelling. CT imaging demonstrated further systemic disease progression. Physical examination was largely unremarkable except for poor dental hygiene and inflamed gums without overt cellulitis. Given progression on both alectinib and lorlatinib, and the presence of radiation necrosis, combination chemotherapy with carboplatin, pemetrexed, and bevacizumab was proposed, with bevacizumab also intended to address radiation-induced

necrosis. Treatment was planned following dental evaluation.

Acute Neurological Decline and Suspicion of SMART Syndrome

On November 20, 2025, the patient was admitted with acute onset aphasia. Neurological examination revealed altered mental status with confusion, lack of orientation, and profound expressive and receptive language impairment. He was non-verbal and unable to follow commands. Cranial nerve examination was limited but showed equal and reactive pupils and symmetric facial movements. Motor examination demonstrated spontaneous movement of all limbs with mild weakness of the right hand. Sensory responses were preserved, and reflexes were symmetric.

The clinical picture was concerning for focal seizures with possible focal status epilepticus, global aphasia potentially related to post-ictal phenomena (Todd's aphasia), or progression of radiation-induced inflammatory changes. Levetiracetam was added to his existing valproic acid regimen, and electroencephalography was planned to evaluate for ongoing seizure activity. A non-contrast MRI of the brain was initially performed but was deemed limited. Given the patient's extensive history of cranial irradiation and the subacute neurological deterioration, a contrast-enhanced MRI was requested to evaluate for stroke-like migraine attacks after radiation therapy (SMART) syndrome. High-dose intravenous methylprednisolone was initiated (1 g daily), with partial improvement in aphasia noted after several days of therapy. Further management and follow-up were planned through neurology and oncology services.

DISCUSSION

SMART syndrome is an increasingly recognized, delayed complication of cranial irradiation characterized by transient stroke-like deficits, seizures, migraine-type headaches, and characteristic, but often reversible, cortical MRI abnormalities confined to previously irradiated brain regions. In the present case, SMART syndrome developed in a patient with metastatic ALK-positive non-small-cell lung cancer (NSCLC) after multiple courses of focal stereotactic radiosurgery, craniotomy, and whole-brain radiotherapy (WBRT), on a background of longstanding brain metastases and radiation necrosis [3]. This clinical context is particularly challenging because new neurological deficits and MRI changes can plausibly reflect tumor progression, radiation necrosis, treatment-related inflammatory injury, seizure activity, A systematic review proposed diagnostic criteria including: remote history of cranial radiotherapy, prolonged but reversible focal cortical symptoms (e.g., aphasia, hemiparesis, visual loss, seizures, confusion), unilateral cortical gadolinium enhancement with corresponding T2/FLAIR hyperintensity in irradiated regions, eventual partial or complete clinical recovery, and absence of tumor recurrence or alternative explanation. Clinically, SMART is dominated by symptoms referable to cortical dysfunction. Headache, migraines, nausea, photophobia, and vomiting, while focal deficits such as seizures, aphasia, hemiparesis, hemisensory loss, visual field abnormalities, and behavioral or cognitive changes occur in the majority of patients. In the current case, the abrupt onset of global aphasia, confusion, and mild focal weakness in a heavily pretreated brain raised differential diagnoses including focal status epilepticus with post-ictal (Todd's) aphasia [4].

The pathophysiology of SMART remains incompletely understood but is thought to reflect delayed radiation-induced endothelial damage, blood–brain barrier disruption, impaired cerebrovascular autoregulation, and cortical spreading depression leading to transient cortical dysfunction. These mechanisms overlap with those proposed for radiation necrosis and may explain the frequent coexistence or radiologic contiguity of SMART lesions with necrotic tissue. Management of SMART is not standardized, Supportive care, seizure control, and aggressive management of acute migraine-like symptoms are fundamental. Corticosteroids are frequently used to reduce vasogenic edema and inflammation, with many reports documenting clinical and radiologic improvement after pulse methylprednisolone or high-dose dexamethasone. Prognosis in SMART is generally described as favorable but heterogeneous. Many patients experience substantial or complete recovery within days to weeks [5].

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