

# Calcified Miliary Brain Metastases in Afatinib-Treated EGFR-Mutant Lung Adenocarcinoma

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*Received: 16th Dec, 2025; Revised: 8th Feb 2026; Accepted: 20th Feb, 2026; Available Online: 11th Mar, 2026*

## ABSTRACT

**Background:** Calcified miliary brain metastasis represents an exceedingly rare manifestation of intracranial spread, characterized by diffuse micronodular involvement of perivascular spaces.

**Case presentation:** We reported a 49-year-old male with EGFR-mutant lung adenocarcinoma who developed progressive cognitive and motor deterioration after one year of Afatinib therapy. Initial MRI showed multiple hyperintense lesions throughout the cerebral and cerebellar parenchyma. Follow-up computed tomography five months later revealed numerous diffusely distributed calcified nodules involving the cerebral hemispheres, cerebellum, and midbrain, consistent with progressive calcified miliary metastases.

**Conclusion:** This case illustrates an uncommon radiologic evolution of miliary metastasis during EGFR-tyrosine kinase inhibitor therapy. Calcification likely reflects a complex interplay of treatment-related necrosis, hypoxic microenvironments, metabolic derangements, and clonal tumor resistance. Awareness of this pattern is critical when evaluating new neurological deficits in patients receiving targeted therapy

**Keywords:** : Lung adenocarcinoma; EGFR mutation; Brain metastasis; Calcified metastasis; Miliary pattern; Afatinib

**How to cite this article:** Rizkiah IS, Al Adawiyah R, Ardiansyah D. Calcified Miliary Brain Metastases in Afatinib-Treated EGFR-Mutant Lung Adenocarcinoma. *Int J Drug Deliv Technol.* 2026;16(7s): 609-612; DOI: 10.25258/ijddt.16.7s.64

**Source of support:** Nil.

**Conflict of interest:** None

## INTRODUCTION

Miliary brain metastases are an uncommon form of intracranial dissemination, characterized by innumerable micronodules infiltrating the perivascular (Virchow–Robin) spaces. First described as “carcinomatous encephalitis,” this pattern is most frequently associated with lung adenocarcinoma, followed by breast carcinoma and cancers of unknown primary origin [1,2]. The incidence remains low—approximately 2.4% in lung cancer and 3.8% in breast cancer—but likely underrecognized due to subtle early imaging findings.

EGFR-mutant NSCLC exhibits a disproportionate tendency toward miliary dissemination, possibly driven by altered cell adhesion, increased vascular tropism, and enhanced perivascular migration mediated by EGFR pathway dysregulation [7,8,12]. Tyrosine kinase inhibitors (TKIs), including Afatinib, have markedly improved survival in EGFR-mutant NSCLC and demonstrate substantial CNS

activity. Nevertheless, intracranial progression with atypical radiologic evolution—including calcification—has been increasingly reported, although the mechanisms remain unclear.

Proposed processes underlying calcification of metastatic nodules include:

- Dystrophic calcification following TKI-induced tumor necrosis
- Metabolic alkalization facilitating calcium phosphate deposition
- Chronic hypoxia in infiltrated perivascular regions
- Oxidative stress and DNA damage induced by prolonged EGFR inhibition [4,6,9,12,17]

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Recognition of this rare imaging pattern is a diagnostic challenge, as miliary metastases may mimic neurocysticercosis, granulomatous disease, microhemorrhages, or metabolic calcifications [6,18].

We report a case of rapidly progressive calcified miliary metastases during Afatinib therapy in EGFR-mutant lung adenocarcinoma, highlighting an unusual treatment-associated radiologic evolution.

**Case Presentation**

A 49-year-old male was diagnosed with EGFR-mutant lung adenocarcinoma in December 2023 after presenting with chronic cough and exertional dyspnea. Staging confirmed stage IVb disease (T2N3M1b). Contrast-enhanced thoracic CT identified an irregular mass in the right medial lobe (Fig.1A). Afatinib therapy (40 mg daily) was initiated in February 2024 and continued without interruption.

In November 2024, the patient developed progressive confusion, spatial disorientation, and difficulty recognizing familiar individuals. No focal deficits were observed at this time. Brain MRI revealed multiple hyperintense lesions scattered throughout the bilateral cerebral hemispheres and cerebellum with minimal enhancement (Fig. 1B).

By April 2025, the patient reported worsening gait instability and rigidity. Neurological examination demonstrated disorientation, global hypertonia more prominent on the left, generalized hyperreflexia, and a right upper motor neuron facial palsy. No headache, seizures, vomiting, or elevated intracranial pressure symptoms were present. Laboratory studies were unremarkable.

Contrast-enhanced brain CT revealed extensive punctate-to-nodular hyperdense lesions averaging 124 HU distributed throughout the cerebrum, cerebellum, and midbrain, consistent with calcified miliary metastases (Fig. 1C, 1D). The findings represented clear radiologic progression from the prior MRI. The constellation of clinical deterioration and diffuse calcified lesions supported progressive calcified miliary brain metastases under ongoing Afatinib therapy.

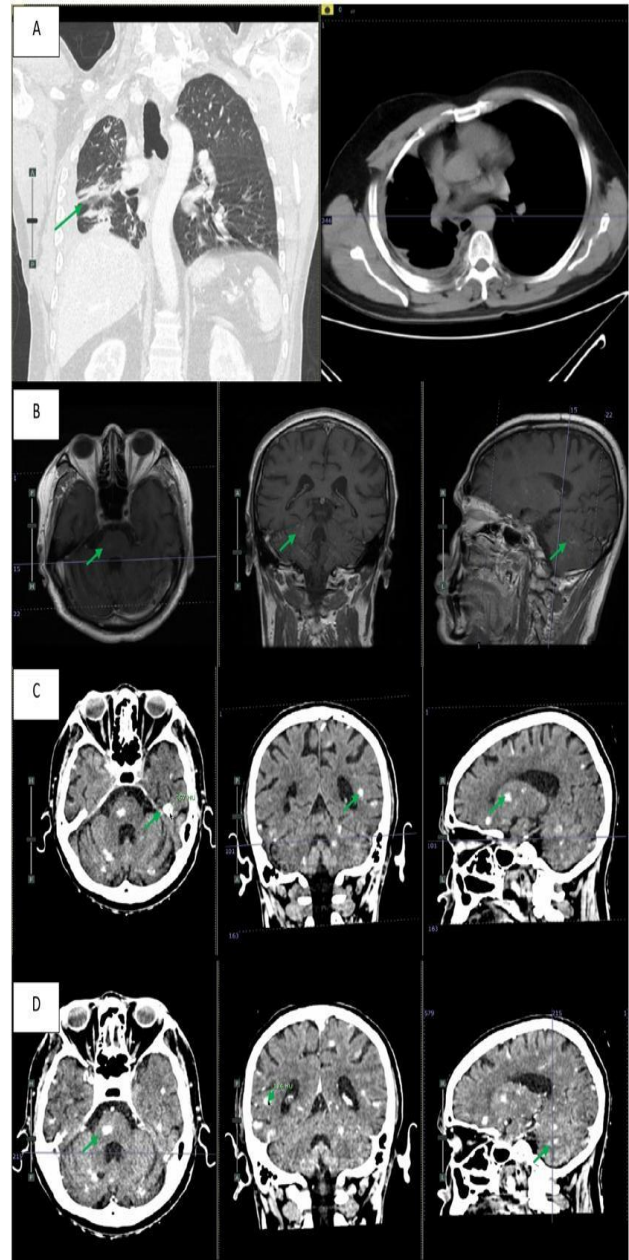


Figure 1. Lung and Brain Imaging (A) Contrast-enhanced thoracic CT scan showing an irregular lesion in the right middle lobe. (B) Contrast-enhanced brain MRI, T1-weighted sequence, revealing numerous hyperintense lesions in the brain parenchyma and bilateral cerebellum. (C) Follow-up non-contrast head CT scan demonstrating multiple calcified lesions of varying sizes in the cerebral hemispheres, bilateral cerebellum, and midbrain, suggestive of a metastatic process. (D) Follow-up contrast-enhanced head CT scan showing no contrast enhancement with the same calcified lesions.

**DISCUSSION**

Calcified miliary brain metastasis is an exceptionally rare radiologic entity characterized by diffuse micronodular infiltration of the perivascular spaces by malignant cells

[1,2]. Lung adenocarcinoma is the most common primary tumor associated with this pattern, and EGFR-mutant subtypes display an even greater propensity toward miliary spread [7,8,12].

### Pathobiology and Mechanisms of Calcification

Several mechanisms likely contribute to calcification within metastatic lesions:

1. **Dystrophic calcification** following TKI-induced necrosis  
TKIs may promote apoptosis and necrosis within tumor nodules, providing a substrate for calcium deposition [4].
2. **Chronic hypoxia in infiltrated perivascular spaces**  
Perivascular tumor growth restricts oxygen diffusion, promoting dystrophic calcification [13].
3. **Metabolic alkalization and altered calcium-phosphate homeostasis**  
Tumors exposed to TKIs may exhibit reduced glycolytic activity, shifting pH in favor of mineral deposition [6].
4. **Clonal selection and resistance mechanisms**  
Tumor clones resistant to Afatinib may undergo distinct microenvironmental adaptations facilitating calcification [17].

### Radiologic Considerations

Miliary metastases may be difficult to detect initially on MRI, appearing as subtle T2 hyperintensities with minimal or absent enhancement. CT is superior for depicting calcification and remains essential for distinguishing calcified metastases from neurocysticercosis, granulomatous infections, metabolic or toxic calcifications, chronic microhemorrhages [18].

The rapid transition from non-calcified MRI lesions to densely calcified CT nodules within five months, as seen in this case, is rarely documented. This evolution underscores the dynamic interplay between TKI therapy and tumor microenvironment remodeling.

### Intracranial Progression Despite EGFR-TKI Therapy

Although EGFR-TKIs penetrate the CNS, their CSF concentrations vary significantly [15]. Intracranial progression during Afatinib therapy may reflect:

- Subtherapeutic CNS drug levels
- Clonal heterogeneity

- Differential resistance pathways (e.g., T790M-negative clones, bypass signaling) [17]
- Advanced perivascular infiltration not responsive to TKI effects

Notably, neurologic deterioration typically worsens after TKI discontinuation due to “disease flare” [10]. However, progression during therapy—as in this case—indicates an uncommon but relevant clinical trajectory.

### CONCLUSION

Calcified miliary brain metastasis is a rare and diagnostically challenging manifestation of EGFR-mutant lung adenocarcinoma. Progressive calcification during Afatinib therapy likely reflects complex tumor–microenvironment interactions, including necrosis, hypoxia, metabolic shifts, and clonal evolution. Clinicians should consider miliary metastatic progression in EGFR-TKI-treated patients presenting with new neurological deficits, even in the absence of conventional MRI enhancement. Early CT imaging is crucial for identifying treatment-associated calcification.

### Funding Declaration

The authors declare that this study received no specific funding from any public, commercial, or not-for-profit funding agencies.

### Ethics and Consent to Participate

Ethical approval was not required for this case report in accordance with institutional policies. Written informed consent was obtained from the patient for publication of this case report and accompanying images.

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