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Lazarus effect of capmatinib in MET exon 14 skipping mutation-positive lung adenocarcinoma with extensive central nervous system metastasis

Tae Woo Kim[1], Kyung Mi Lee[2], Seung Hyeun Lee[3*]

[1]Division of Pulmonary, Allergy and Critical Care Medicine, Department of Internal Medicine,
Kyung Hee University College of Medicine, Kyung Hee University Hospital, Seoul, South Korea
[2]Department of Radiology, Kyung Hee University College of Medicine, Kyung Hee University Hospital, Seoul, South Korea

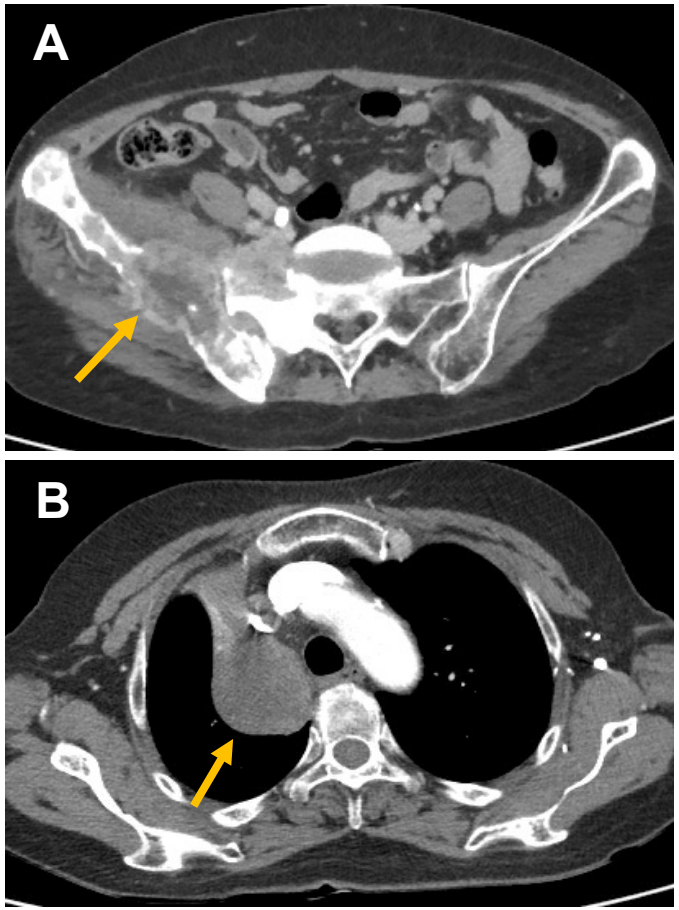
Background & Aim

- Mesenchymal–epithelial transition (MET) receptor tyrosine kinase activates several downstream signaling pathways involved in cell proliferation, differentiation, and migration.
- Central nervous system (CNS) metastases, especially leptomeningeal metastases (LM), are critical complications of lung cancer, especially in patients with driver oncogenes.
- However, the optimal treatment strategy for MET-positive non-small cell lung cancer (NSCLC) with CNS metastases is largely unknown.
- Here, we report a case of MET exon 14 skipping-positive metastatic lung adenocarcinoma with extensive brain and leptomeningeal metastasis, which dramatically responded to capmatinib.

Case presentation (1)

- A 65-year-old female complained right leg pain and edema sustained for two weeks.
- Lower extremities computed tomography (CT) angiography revealed diffuse deep vein thrombosis (DVT) and osteolytic and sclerotic lesions with extraosseous mass (Figure 1A), rivaroxaban was administered.
- A 6.2 x 4.3 cm mass in the right upper lobe (RUL) was revealed through chest CT(Figure 1B) and histopathologically diagnosed with adenocarcinoma.
- After additional image tests, stage IVB was diagnosed (Figure 1C).
- *Epidermal growth factor receptor* (*EGFR*) mutations, *anaplastic lymphoma kinase* (*ALK*) translocation, and ROS proto-oncogene 1 fusions were excluded and the tumor proportion score for programmed death ligand 1 (PD-L1) was 0%.
- Although pemetrexed and cisplatin were initiated as first-line treatments, follow-up chest CT scan showed enlargement of the primary lung mass (Figure 2A).
- After second-line paclitaxel, follow-up chest CT scans showed temporary partial response (Figure 2B) and then progressive disease (Figure 2C).

Case presentation (2)



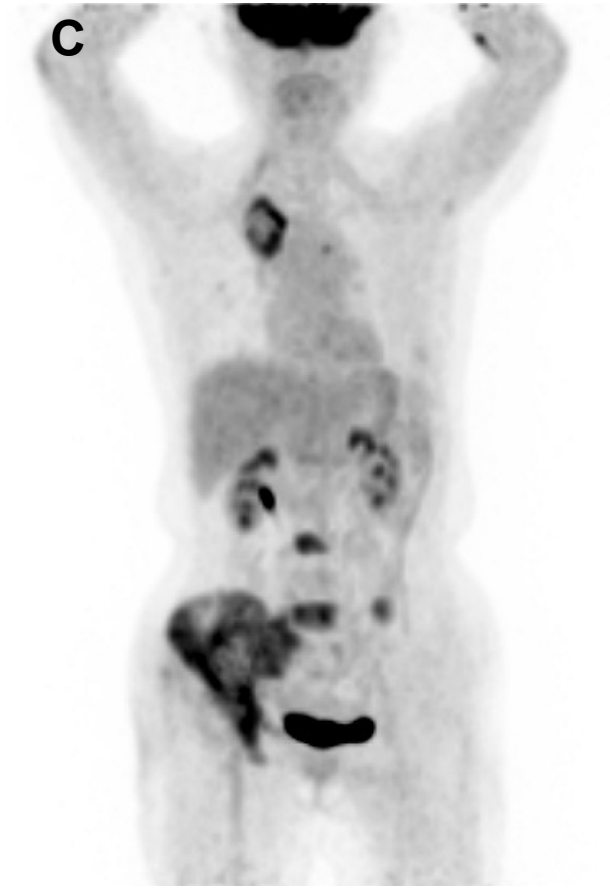


Figure 1. Radiologic images at diagnosis.

(A) Computed tomography (CT) angiography of the lower extremities showed osteolytic and sclerotic lesion with extraosseous mass at the right iliac bone (arrow).

(B) Chest CT scan showed a 6.2 x 4.3 cm sized mass in the right upper lobe(RUL) abutting the right brachiocephalic vein (arrow).

(C) Positron emission tomography revealed the hypermetabolic mass at RUL and multiple bone metastases.

Case presentation (3)

- Although next-generation sequencing (NGS) revealed a MET exon 14 skipping mutation, no MET inhibitor was approved in Republic of Korea at that time.
- The patient was enrolled to the Managed Access Program for capmatinib by Novartis after obtaining signed informed consent and atezolizumab monotherapy was administered.
- After two cycles of atezolizumab, she showed melena, stuporous mentality, and hypovolemic shock, which resulted from rivaroxaban-induced gastrointestinal bleeding.
- Chest CT and brain magnetic resonance imaging (MRI) test revealed an increased right lung mass (Figure 2D) and findings compatible with brain metastasis and leptomeningeal metastases (LM) (Figure 3A and B), respectively.
- Seven days after first capmatinib administered, the patient could open eyes without stimulation and became cooperative with verbal order.
- Ten days after capmatinib treatment initiation, she could eat by herself, and Eastern Cooperative Oncology Group (ECOG) performance status (PS) recovered from 4 to 2.
- A follow-up chest CT scan showed a markedly decreased right lung mass and improved atelectasis (Figure 4A).
- Surprisingly, extensive CNS metastases also nearly completely disappeared on brain MRI (Figure 4B and C).

Case presentation (4)

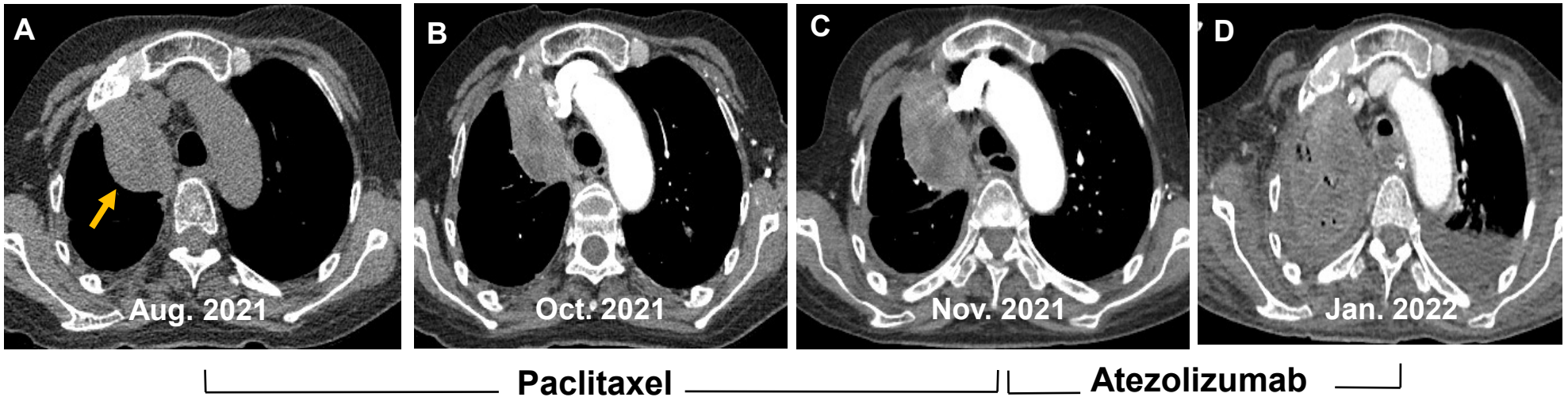


Figure 2. Chest CT images during clinical course. (A) After pemetrexed and cisplatin as first-line treatments, follow-up chest CT scan showed increasing size of the primary lung mass (arrow). (B) Tow cycles of paclitaxel decreased tumor size. (C) However, progression was observed after third cycle of the treatment. (D) After two cycles of atezolizumab, total atelectasis of the right lung due to an increased right lung mass external obstructing the right main bronchus with left pleural effusion.

Case presentation (5)

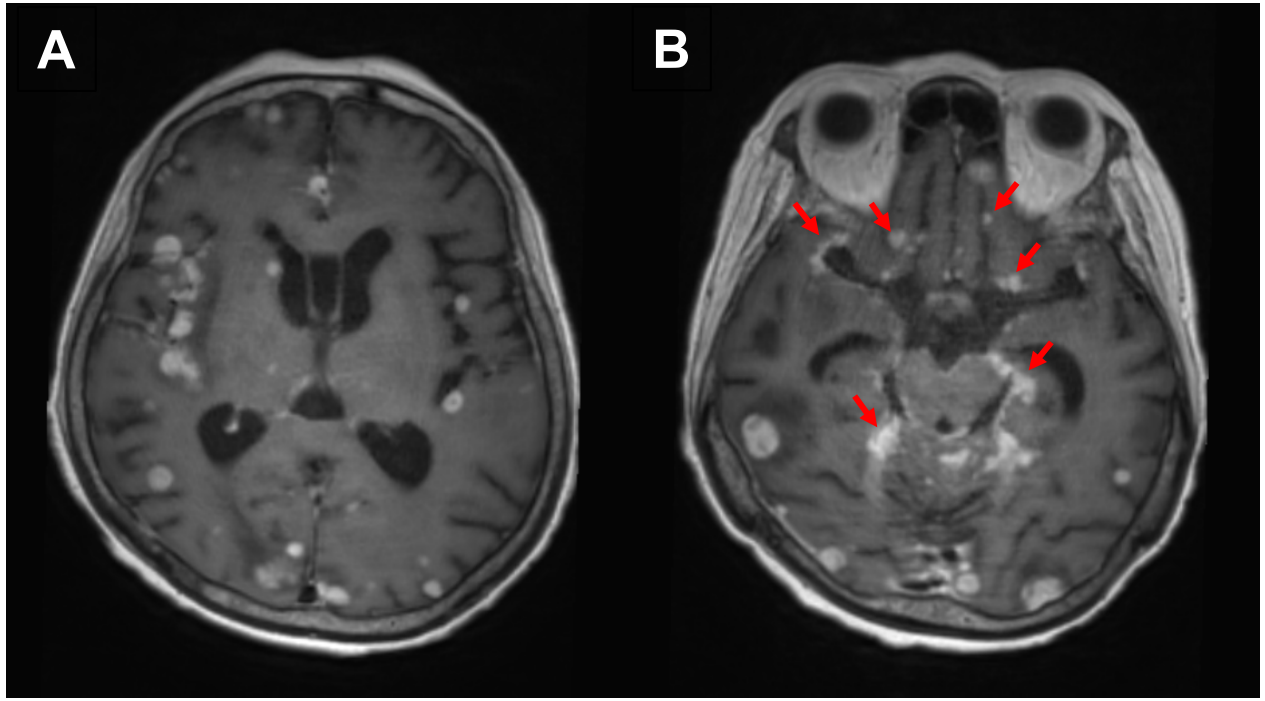


Figure 3. Brain magnetic resonance imaging (MRI). (A) Axial contrast-enhanced 3D black blood imaging before capmatinib treatment revealed numerous, rim and nodular enhancing brain metastases in bilateral cerebral cortex and subcortex, cerebellum, basal ganglia, thalamus, and spinal cord. (B) Enhancement along both the optic chiasm-optic tract, right trigeminal nerve, and both the seventh/eighth nerve complex (arrow), which were compatible with brain metastasis and leptomeningeal metastases (LM).

Case presentation (6)

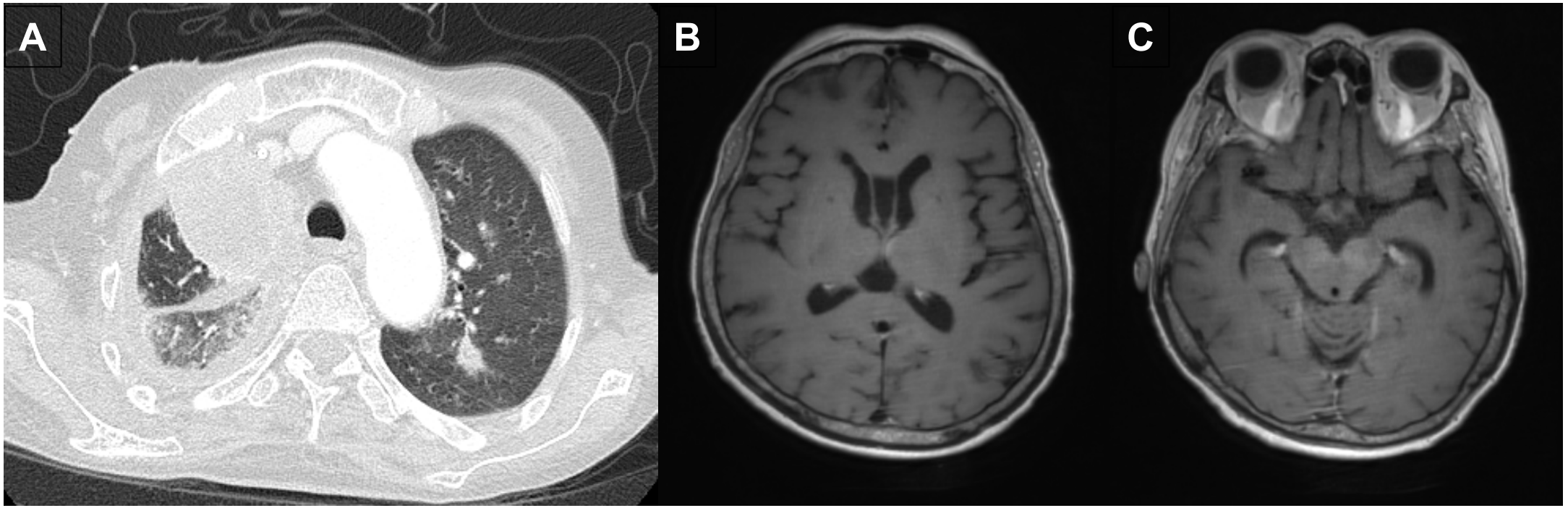


Figure 4. Image findings after capmatinib treatment. (A) Markedly decreased mass of right upper lobe and improved right total atelectasis were noted after two months of the treatment. (B and C) Extensive CNS metastases also nearly completely disappeared on brain MRI.

Discussion

- CNS metastasis is associated with poor prognosis of NSCLC despite aggressive local and systemic treatment and LM is a rare devastating type of CNS metastasis.
- In GEOMETRY mono-1 phase 2 trial, capmatinib showed effectiveness in intracranial metastasis, and current national comprehensive cancer network (NCCN) guideline recommends capmatinib for MET exon 14 skipping-positive NSCLC with brain metastasis patients.
- To the best of our knowledge, this is the first case of rapid radiological and clinical response to capmatinib in a patient diagnosed MET exon 14 mutation-positive lung adenocarcinoma and extensive CNS metastases with poor ECOG PS.

Conclusion

- Our report highlights the significant CNS activity of capmatinib, even in cases of leptomeningeal metastasis.

- In addition, this report emphasizes the importance of the active utilization of molecular profiling to detect rare but druggable genetic alterations for the better management of patients with lung cancer.