中文題目：表皮生長因子受體基因突變的肺腺癌病人使用 Erlotinib 後產生心包膜炎

英文題目：Temporary Pericarditis after Erlotinib Treatment in a Patient with Pulmonary Adenocarcinoma Harboring Mutation of Epidermal Growth Factor Receptor

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Topic: Temporary Pericarditis after Erlotinib Treatment in a Patient with Pulmonary Adenocarcinoma Harboring Mutation of Epidermal Growth Factor Receptor

Abstract: Acute, temporary pericarditis is an uncommon, life-threatening complications in patients receiving tyrosine kinase inhibitor of epidermal growth factor receptor. Such adverse effect has been reported in patients having chronic myeloid leukemia, but not in non-small cell lung cancers. We reported a patient with EGFR-mutant NSCLC who developed acute pericarditis, which quickly developed under erlotinib therapy. We considered the pericardial effusion to be related to erlotinib, based on clinical response to management as well as histologic studies.

Introduction: Tyrosine kinase inhibitor (TKI) of epidermal growth factor receptor (EGFR) such as erlotinib is the standard of treatment in patients with non-small cell lung cancer (NSCLC) harboring EGFR mutations. While treating with EGFR TKI, most of the responders have clinical and image improvement within 4-6 weeks and usually are accompanied by common adverse effects such as cutaneous and gastrointestinal manifestations [1]. Acute pericarditis due to other kinds of TKI has been reported in patients with chronic myeloid leukemia but not in lung cancers [2]. Here, we reported a patient with EGFR-mutant NSCLC who developed acute cardiac tamponade shortly after erlotinib treatment.

Case report: A 42-year-old woman was diagnosed as having stage IV (T2aN3M1b) adenocarcinoma of lung, right upper lobe. Genetic study of primary tumor revealed exon 19 deletion of EGFR gene. Her initial contrast-enhanced chest computed tomography (CT) revealed a primary tumor sized of 4 cm over right upper lobe, multi-levels of mediastinal lymphadenopathy, and minimal pericardial effusion (figure 1), as well as small emboli of pulmonary artery branches. The patient received rivaroxaban for pulmonary embolism with partial relief of dyspnea and started erlotinib treatment, 150mg daily after mutation report. After a 4-day treatment, she

was hospitalized because of exacerbation of dyspnea and orthopnea. Rapid progression of pericardial effusion with tamponade sign was found. Erlotinib was withheld, and she received pericardial window surgery for symptomatic relief. The pathology of the pericardium did not show malignant cells nor granulomas but intact lining of mesothelial cells (figure 2) with some acute inflammatory cells within the stroma (figure 3). Heart contractility was not impaired after window surgery. Erlotinib was reinstituted 4 days after discontinuation. Systemic steroid (1 mg/kg of prednisolone) was also prescribed for one week. The follow-up CT scans at 2 months of therapy revealed partial response to treatment, and there was no relapse of pericardial effusion.

Discussion: Serositis is a rare adverse event after tyrosine kinase inhibitors and was only reported in chronic myeloid leukemia. To the best of our knowledge, the case we demonstrated is the first one with acute pericarditis related to erlotinib for NSCLC. Several mechanisms have been proposed for pericarditis after TKI such as platelet-derived growth factor beta (PDGFRβ) inhibition, autoimmunity, or cardiac dysfunction [3]. However, our case did not match these explanations.

An immunohistochemistry stain of the pericardial specimen showed strong expression of EGFR protein (Dako EGFR pharmDx kit) (figure 2D) which supported the targeting evidence of erlotinib. This situation is very similar to the toxicity of skin while patients are treated with EGFR TKIs. Inflammatory process was also found from in the pericardial stroma, based on histologic findings (Hematoxylin and eosin stains) (figure 3). For acneiform skin toxicity from EGFR TKIs, the infiltrating inflammatory cells are dominated by monocytes, granulocytes, and T lymphocytes, similar to our histologic findings [4]. All of the above showed compatibility with erlotinib-induced acute pericarditis.

Another possibility of pericardial effusion is due to obstruction of lymphatics in the mediastinum. As figure 1 showed, there were multi-levels of mediastinal lymphadenopathy which might impede lymphatic drainage and further contribute to cardiac tamponade. It could also explain the presence of pericardial effusion before the use of erlotinib.

After reinstitution of erlotinib, our case did not suffer from recurrent pericardial effusions thereafter.

References

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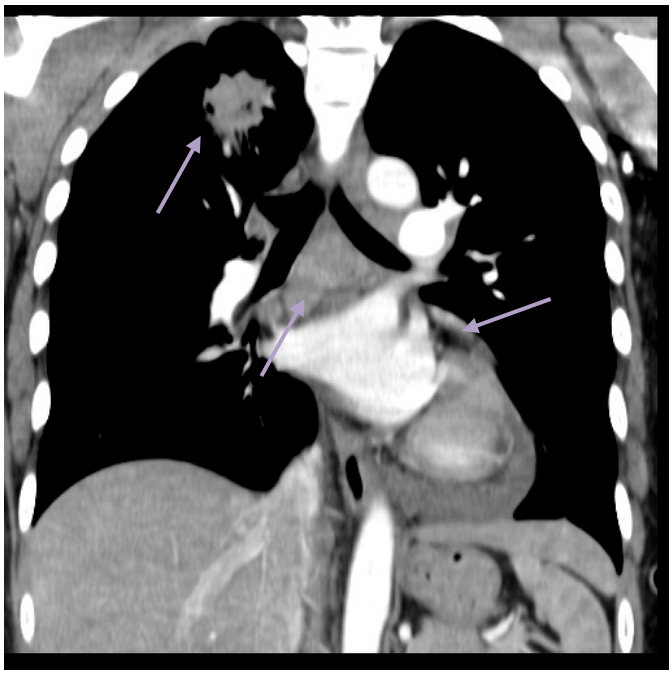

Figure 1. Chest computed tomography scans at initial presentation.

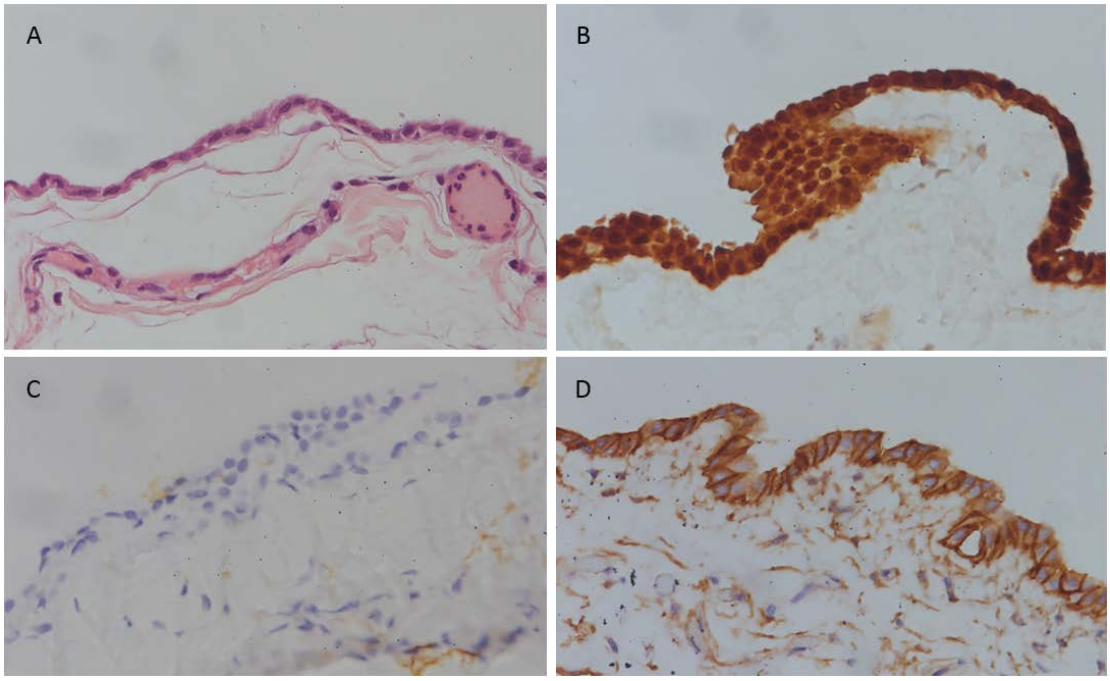

Figure 2. Histology and immunohistochemistry (IHC) staining of the pericardium. **A.** Hematoxylin and eosin (H&E) stain showed normal histology of mesothelial cells. **B.** The mesothelial cells are highlighted by calretinin antibody. **C.** There was negative thyroid transcription factor-1 (TTF-1) expression from IHC staining. **D.** IHC stain for EGFR showed positive expression by mesothelial cells.

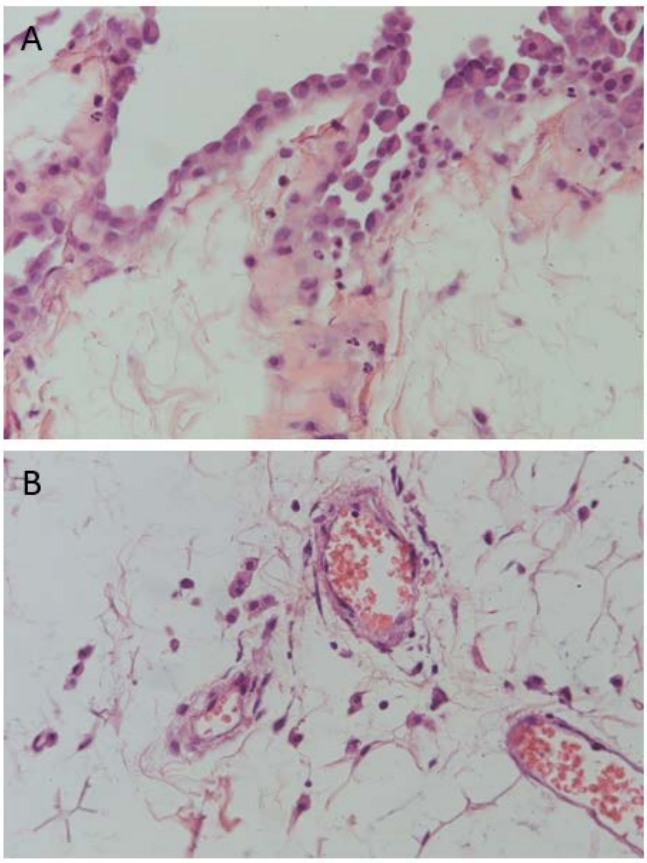

Figure 3. Evidence of inflammation from histologic analysis of pericardium (H&E stain). **A.** Focally infiltrating polymorphonuclear leukocytes. **B.** Stromal vascular congestion and perivascular infiltrates with small lymphocytes and histiocytes.