

Good Response to Gefitinib for Lung Adenocarcinoma with Hyperamylasemia: A Case Report

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Hyperamylasemia in patients with bronchogenic carcinoma has been reported rarely. Gefitinib, an oral tyrosine kinase inhibitor of epidermal growth factor receptor (EGFR) signaling, has shown activity for treating patients with refractory advanced non-small cell lung cancer (NSCLC). This report describes a case of lung adenocarcinoma coexisting with hyperamylasemia in a 67-year-old man. Abdominal computed tomography and ultrasonography demonstrated a normal pancreas. A mutational analysis of the EGFR gene indicated an in-frame deletion at exon 19. He underwent treatment with gefitinib. Chest radiography follow-up showed a partial response and the amylase level also decreased to normal. We suggest that treatment with gefitinib is an effective therapeutic option for this rare patient subset. (*Chang Gung Med J* 2008;31:606-11)

Key words: epidermal growth factor receptor (EGFR), EGFR mutation, non-small cell lung cancer, amylase, gefitinib

Hyperamylasemia in patients with bronchogenic carcinoma was first reported by Weiss et al. in 1951.⁽¹⁾ Thereafter, several similar reports, primarily of adenocarcinoma or focal adenocarcinomatous differentiation were published.⁽²⁾ Biochemical analysis typically revealed a predominant salivary type isoenzyme. Amylase messenger ribonucleic acid (mRNA) expression was identified in tumor tissue, strongly supporting the hypothesis that amylase is produced by malignant cells.⁽³⁾ Ultrastructurally, zymogen-like secretory granules located in the apical region of the tumor cells have been demonstrated in amylase-containing adenocarcinoma.⁽⁴⁾ Due to a lack of prospective studies, the prognosis for, and the management of, amylase-producing lung carcinoma remains unclear.

Gefitinib, an oral tyrosine kinase inhibitor of epidermal growth factor receptor (EGFR) signaling,

is the first approved molecularly targeted agent for treating patients with refractory advanced non-small cell lung cancer (NSCLC). This report presents a patient with lung adenocarcinoma with a high amylase level that responded dramatically to gefitinib.

CASE REPORT

A 67-year-old man presented with a dry cough, lower back pain and progressive shortness of breath for 2 months. He had smoked at least 1 pack of cigarettes per day for over 20 years, but had ceased smoking 3 years previously. The physical examination was unremarkable. Chest radiography (Fig. 1) and computed tomography (CT) (Fig. 2) revealed a mass, 3.4 cm in diameter, in the middle lobe of the right lung with paratracheal lymph node involvement. Bone scintigraphy with 20 mCi technetium-

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Fig. 1 Supine chest film shows a mass in the middle lobe of the right lung. A band-like shadow seems to connect the mass to the pleura (pleural tail sign). A left pleural mass lesion is also noted, as well as destruction of the left 6th rib. The wide mediastinum is caused by right paratracheal lymphadenopathy.

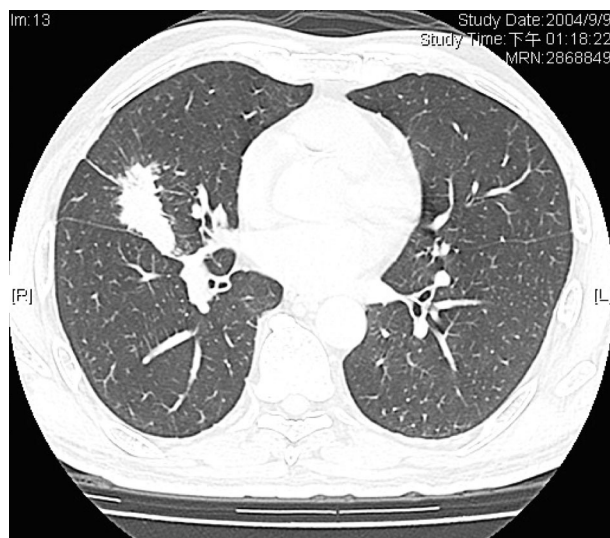


Fig. 2 Computed tomography (CT) with lung windows reveals a lobulated soft tissue mass in the lateral segment of the right middle lobe. A linear shadow extends from the mass to the pleura (pleural tail sign).

99 m methylene diphosphonate (MDP) revealed multiple metastases in the ribs, thoracic spine and pelvis. The biopsy obtained with chest CT guidance showed an adenocarcinoma. Although the Eastern Cooperative Oncology Group performance status was 2, the patient refused treatment with intravenous chemotherapy. He was followed-up regularly and analgesics drugs were prescribed for symptom relief.

Three weeks later, the patient complained of acute, right upper quadrant abdominal pain without nausea and vomiting. Laboratory analysis showed elevated serum amylase activity to 2609 U/L (enzymatic rate method, Beckman Coulter LX20, normal, ≤ 137 U/L) and a normal lipase level 29 U/L (Panteghini method, Beckman Coulter LX20, normal, ≤ 60 U/L). Abdominal CT (Fig. 3) and ultrasonography demonstrated a normal pancreas, a liver cyst, and a small gallbladder stone in the cystic duct. He also experienced episodic dizziness; however, magnetic resonance imaging (MRI) disclosed no significant abnormal findings in the brain. In addition, no abnormality in the salivary gland or disseminated intravascular coagulopathy (DIC) signs were found on physical examination. At that time, the patient was placed on a regimen of gefitinib 250 mg/day. His amylase level decreased to 151 U/L after 2 weeks of gefitinib therapy. Chest radiography later showed a partial response to gefitinib therapy.

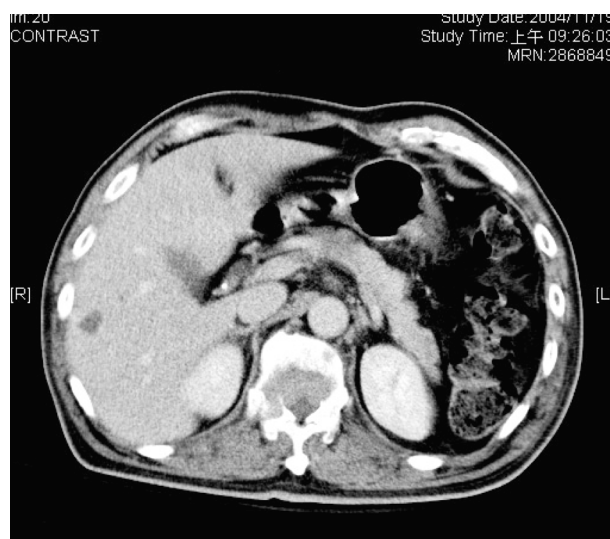


Fig. 3 Abdominal CT with contrast medium demonstrates a normal pancreas, a liver cyst, and a small gallbladder stone in the cystic duct. There is no ascites.

Mutational analysis of the EGFR gene, comprising exons 18, 19, 20, 21 in the tyrosine kinase domain, was done later using methods previously described.⁽⁵⁾ Sequencing analysis indicated that the EGFR gene harbored an in-frame deletion at exon 19 removing amino acids 747 - 751. The amylase level returned to normal 6 weeks after initiation of gefitinib therapy. The patient remained clinically well without pulmonary-related symptoms for 8 months after starting treatment with gefitinib. Subsequent roentgenograms (Fig. 4) showed a decrease in tumor size. The amylase level was still within normal limits. Meanwhile, repeated bone scintigraphy revealed diffuse bony metastases in progression. Radiotherapy was done due to bony metastases. Eight months after initiation of gefitinib therapy, the patient had a fever which lasted for about 1 week and a productive cough. Pneumonia was highly suspected. Unfortunately, he developed sudden respiratory failure and died the

day after admission.

DISCUSSION

Hyperamylasemia in patients with lung carcinoma is relatively rare, occurring in approximately 3% of all types of lung cancer.⁽⁶⁾ Previous pathologic, biochemical and immunohistochemical studies support the mechanism by which lung cancer cells can produce amylase, predominantly salivary-type isoenzyme.⁽²⁻⁴⁾ In our case report, hyperamylasemia was found incidentally during episodic epigastric pain. Abdominal CT revealed a normal pancreas but a small gall bladder stone, suggesting that the abdominal pain was due to the gall bladder stone. No abnormality in the salivary glands could be found on physical examination or MRI of the head and neck. Interestingly, the serum amylase level fell dramatically after the start of gefitinib therapy, and the lung tumor shrank as well. It is reasonable that hyperamylasemia is caused by lung adenocarcinoma, although electrophoresis for amylase isoenzyme patterns in serum and immunohistochemical staining are not available in our hospital.

Amylase, a digestive enzyme that hydrolyzes the glycoside bonds in starch and glycogen, is produced primarily in the pancreas and salivary glands. Amylase mRNA transcription has been detected in normal tissue, including bronchial epithelium, fallopian tubes, and parenchymal lung tissue, and in malignancy, including lung cancer tissue and cancer cell lines.⁽⁷⁾ Several studies have examined the relationship between epidermal growth factor (EGF) and amylase activity. In an animal study, amylase secretion from pancreatic acinar cells was regulated through EGFR down- signaling when a high concentration of EGF was added.⁽⁸⁾ EGF has an effect on cell proliferation in the salivary glands as well as the pancreas.⁽⁹⁾ Increased amylase secretion from pancreatic acinar cells via EGF stimulation is phosphatidylinositol-3-kinase (PI3K) -dependent. Wortmannin, a potent inhibitor of PI3K, was shown to inhibit cholecystokinin octapeptid (CCK-8) stimulated amylase secretion.⁽¹⁰⁾ Sensitization of NSCLC cells by wortmannin also involved the interaction between cell cycle regulation, DNA damage and apoptosis.⁽¹¹⁾ However, the role of wortmannin in amylase-producing lung cancer cells has yet to be clarified.



Fig. 4 Chest radiography after 8 months of gefitinib therapy demonstrates regressive changes in the right middle lobe mass. The left pleural mass lesion has also improved except for fracture of the left 6th rib. However, confluent acinar shadows are seen in the right lower lung field, which is suggestive of pneumonia.

Activation of tyrosine kinase (TK) through extracellular binding of various ligands to EGFR initiates a number of intracellular signaling events including Ras, mitogen-activated protein kinase (MAPK), PI3K and signal transducer and activator of transcription (STAT) which are implicated in cancer cell proliferation, growth, metastasis and apoptosis. Gefitinib, a small molecule tyrosine kinase inhibitor (TKI) competes with adenosine triphosphate for binding to the intracellular TK domain, thereby suppressing downstream signaling by preventing EGFR autophosphorylation. Two large phase II clinical trials evaluating antitumor activity in previously treated patients with NSCLC have demonstrated that gefitinib is active and well tolerated, achieving a response rate of roughly 10-15%.^(12,13) Clearly, it is important to identify surrogate factors that facilitate selection of NSCLC patients who are most likely to attain clinical benefit from EGFR-TKI therapy. Large clinical trials have identified several patient characteristics associated with increased responsiveness to EGFR-TKI including a history of never smoking, adenocarcinoma, Asian ethnicity and female gender.⁽¹⁴⁾ EGFR mutation has also been reported to be associated with a dramatic response to gefitinib in patients with advanced NSCLC.⁽¹⁵⁾

To the best of our knowledge, this is the first report in which gefitinib was administered to a patient with NSCLC with hyperamylasemia. The molecular mechanism of ectopic amylase production from lung cancer has yet to be elucidated. EGFR down -signaling might play an important role, as in the pancreas and salivary gland. In the present case, gefitinib therapy resulted in a decreased amylase level and lung tumor size. The patient condition worsened as proven by bone scan, although amylase levels were kept low. The clinical course suggests that gefitinib therapy was effective against the amylase-positive cell phenotype in addition to the non-smoking status, Asian ethnicity and female gender. Determination of the serum amylase level may be useful in routine practice in the examination of patients with lung adenocarcinoma. We believe that gefitinib is an effective therapeutic option for treating NSCLC patients with hyperamylasemia. However, there is still much to be learned regarding the role of EGFR-TKI in treating NSCLC patients with hyperamylasemia. Further prospective and basic

studies are required to clarify these issues.

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Gefitinib 對於肺腺癌合併高澱粉酶血症有良好反應——病例報告

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肺癌病人合併有高澱粉酶血症的例子並不多見，過去很少被報導。Gefitinib 是一種口服的酪氨酸酶抑制劑，能抑制上皮生長因子接受器的訊號傳遞，對於某些難以治療的晚期非小細胞肺癌有不錯的效果。本病例是報告一位合併有高澱粉酶血症的肺癌病人，成功的以 gefitinib 治療。因此我們建議 gefitinib 的治療對於這類少見的病人是一有效的治療選擇。(長庚醫誌 2008;31:606-11)

關鍵詞：上皮生長因子接受器，上皮生長因子接受器突變，非小細胞肺癌，澱粉酶，gefitinib

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受文日期：民國96年1月18日；接受刊載：民國96年9月27日

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