A case suggesting the efficacy of camostat mesilate in preventing recurrent pneumonia after total gastrectomy

TAKINAMI, Yoshikazu
Faculty of Education, Saitama University
Department of Emergency Medicine, Tannan Regional Medical Center

UCHIYAMA, Takashi
Department of Emergency Medicine, Tannan Regional Medical Center

KUMANO, Takanori
ITO, Yoshiyuki
ITO, Shigeji
Department of Internal Medicine, Tannan Regional Medical Center

Abstract
A 56-year-old man with a history of total gastrectomy for gastric cancer at age 44 visited the internal medicine department of our hospital because of a slight fever (> 37°C), chills and cough since the previous night. His white blood cell count was 44,200 cells/μl and C-reactive protein level was 8.4 mg/dl. Plain chest radiography showed opacity in the right upper lung field. Based on these findings, he was diagnosed with pneumonia and hospitalized. He responded to intravenous ceftriaxone sodium hydrate (2 g/day) for 8 consecutive days, and was discharged on hospital day 9. Coughing started again 2 weeks after discharge and he visited our department again 10 days after noticing the cough. Plain chest radiography showed opacity in the right lower lung field and he was diagnosed and hospitalized for the second time with pneumonia 48 days after discharge. He was discharged on hospital day 9 but visited our department again with a complaint of nighttime heartburn 9 days after the second discharge. Bile reflux after total gastrectomy was suspected as the cause of the recurrent pneumonia and oral administration of camostat mesilate (300 mg/day) was started. Although this treatment alleviated the condition, his adherence to the regimen gradually declined 9 months after the second discharge. He visited our department for a third time complaining of fever and coughing 15 months after the second discharge. Pneumonia in the left middle lung field was treated by a 7-day oral course of levofloxacin hydrate (500 mg/day). The importance of oral camostat mesilate was stressed to the patient and instructions on lifestyle changes were given to prevent reflux esophagitis. The patient has not had heartburn or cough since, and recurrence of pneumonia appears to have been prevented. This case suggests that silent aspiration due to esophageal reflux and aspiration pneumonia should be suspected in cases of recurrent fever without cough or sputum after total gastrectomy.

Keywords: total gastrectomy, esophageal reflux, recurrent pneumonia, camostat mesilate
1. Case Report

Patient: A 56-year-old man

History of present illness: The patient visited the internal medicine department of our hospital with the chief complaint of a slight fever (> 37°C), chills and coughing since the previous night. His white blood cell (WBC) count was 44,200 cells/μl and C-reactive protein (CRP) level was 8.4 mg/dl. Other blood test results were normal. Plain chest radiography showed opacity in the right upper lung field (Figure 1). On the basis of these findings, he was diagnosed with pneumonia and hospitalized.

![Figure 1. Plain radiograph of the chest at initial examination indicates opacity (arrow).](image)

History of past illnesses: Total gastrectomy was performed for gastric cancer at age 44.

History of smoking and alcohol consumption: He had smoked 40 cigarettes a day for 4 years when he was a university student. No alcohol consumption.

Occupational history: He had been involved in geological surveys for tunnel construction for 30 years.

Progress during hospitalization: Ceftriaxone sodium hydrate (CTRX, 2 g/day) was administered intravenously for 8 consecutive days, and this alleviated the inflammation response. The patient was subsequently discharged on hospital day 9. A sputum culture was negative.

Progress after discharge: Two weeks after discharge his coughing started again and 10 days after the onset of cough he visited our department again. His WBC count was 10,100 cells/μl and CRP level was 0.1 mg/dl, but plain chest radiography showed an infiltrative shadow in the right lower lung field. One-week treatment with cefcapene pivoxil hydrochloride hydrate (300 mg/day) was effective, but only for a brief period. Recurrent coughing worsened 20 days after the second hospital visit and he visited our department again 24 days after the second visit. WBC count was 27,600 cells/μl and CRP level was 2.2 mg/dl, and the infiltrative shadow in the right lower lung field was more prominent on plain chest radiography. He was hospitalized after the chest CT examination (Figures 2 and 3).

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Figure 2. Plain radiograph of the chest taken during the second hospitalization indicates opacity (arrow).

Figure 3. Computed tomography image of the chest taken during the second hospitalization shows an infiltrated shadow (arrow).

Progress during second hospitalization: CTRX (2 g/day) and ceftazidime hydrate (2 g/day) were administered intravenously for 4 consecutive days, and oral azithromycin hydrate (500 mg/day) was administered for 3 consecutive days. The patient was discharged on hospital day 9. A sputum culture was positive for *Klebsiella pneumoniae*.

Progress after second discharge: Because pneumonia reoccurred in a short period of time and an abnormally high WBC count is indicative of an early stage of infection, immunological examination was performed in the hematology department. However, no abnormalities were noted. However, 9 days after the second discharge the patient visited our department again with the complaint of nighttime heartburn. As the suspected cause of the recurrent pneumonia was bile reflux after total gastrectomy, oral camostat mesilate (300 mg/day) was started and it alleviated the condition.

From 9 months after the second discharge, however, the patient’s adherence to the regimen gradually declined. Fifteen months after the second discharge he visited our department for a third time complaining of fever and cough. His WBC count was 21,300 cells/μl and CRP level was 15.4
mg/dl. Plain chest radiography showed an infiltrative shadow in the left middle lung field (Figure 4).

Outpatient therapy with a 7-day course of oral levofloxacin hydrate (500 mg/day) alleviated the condition. A sputum culture was positive for *Escherichia coli*. The importance of oral camostat mesilate was stressed to the patient, and instructions on lifestyle changes were given to prevent reflux esophagitis, such as eating in moderation, avoiding going to bed straight after a meal, and leaving his belt reasonably loose. Heartburn and cough have not reoccurred thereafter and there has been no recurrence of pneumonia.

2. Discussion

There are two types of recurrent pneumonia depending on the cause. One is immune impairment, Patients with diabetes or such as functional impairment in the reticuloendothelial system in patients those who underwent splenectomy resulting in infection. The other is aspiration pneumonia due to functional causes such as aspiration of refluxed secretions (e.g., gastric secretions, bile, duodenal juice and pancreatic juice) and reflux esophagitis. This second type commonly occurs in individuals with impaired peristalsis after total gastrectomy or digestive tract surgery, or in those with impaired peristalsis of the digestive tract after spine surgery for back pain and disk herniation. In our patient, the possibility of damage to the pulmonary tract mucosa could not be excluded because of his 4-year smoking history and his work in tunnels. As impairment of the immune system was not detected, aspiration pneumonia due to reflux esophagitis that occurred after total gastrectomy 12 years earlier was suspected.

Kobayashi et al. analyzed pulmonary aspiration in 186 total gastrectomy patients. Among them, 16 (8.6%) had recurrent episodes (> 1 per year) of respiratory tract inflammation (r-RTI) and 45 (24.2%) had sporadic episodes (< 1 per year) of RTI (s-RTI). The r-RTI group frequently showed symptoms of esophageal reflux. They also showed marked inflammatory responses with various and atypical clinical courses. The swallowing provocation test in patients with r-RTI
showed swallowing disturbance (prolonged latency). Kobayashi et al concluded that aspiration of esophageal reflux contents was the most important risk factor for recurrent pulmonary complications in patients with total gastrectomy. The characteristic features common to patients with r-RTI (n=16) included esophageal reflux, pyrexia following nighttime esophageal reflux (which recurs but is easily ameliorated), evidence of a strong inflammatory response on laboratory findings that is indicative of acute exacerbation, and chest radiographic findings of overt but occasionally equivocal or multiple infiltrates (to be confirmed by chest CT). These findings are in agreement with those in the present case. Pellegrini et al reported that acidic gastric content may injure the esophageal mucosa in reflux esophagitis, but postgastrectomy esophageal reflux should be less symptomatic because gastric juice is absent. In the present case, the chief complaint was slight fever, and cough and other symptoms had not been severe despite the objective findings of blood tests and radiography.

Examining 5 cases of recurrent pneumonia after gastrectomy by upper gastrointestinal tract scintigraphy, Yokomura et al found that severe gastroesophageal reflux occurred in the supine position in 3 cases and on changing positions in the remaining 2 cases. Impaired esophageal function was also suspected in 4 cases. Provision of instructions on lifestyle changes to prevent reflux was able to reduce the frequency of pneumonia recurrence, suggesting that repeated aspiration was the likely cause of recurrent pneumonia. Consistent with this, the positive effect of instructions on lifestyle changes was also apparent in the present case.

We administered camostat mesilate in this case. This proteinase inhibitor is recommended for postgastrectomy reflux esophagitis to prevent reflux of bile, duodenal juice and pancreatic juice but not gastric acid. Its mechanism of action is inhibition of trypsin in refluxed digestive juices, which alleviates postgastrectomy reflux esophagitis. Together with instructions on lifestyle changes, camostat mesilate therapy was effective in the present case.

In summary, we have reported a case of aspiration pneumonia caused by reflux esophagitis after total gastrectomy. Our findings indicate that silent aspiration due to esophageal reflux and aspiration pneumonia without cough or sputum production should be suspected in cases of recurrent fever.

References

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