Case Report

Uracil-Tegafur-Induced Pleural Effusion Following Lung Cancer Surgery

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The patient was a 75-year-old female with a history of no smoking. Under a diagnosis of lung cancer, she underwent a right lower lobectomy in March 2008. She was started on oral Uracil-Tegafur (UFT) (400 mg/day) from April and in May developed fatigue, respiratory discomfort, and tachycardiac atrial fibrillation. Chest X-ray film showed an increase in right pleural effusion. Thoracentesis revealed a yellowish, serous exudate containing predominantly lymphocytes, with no evidence of malignancy. Despite continued diuretic administration for 5 months from July, it was difficult to control the pleural effusion, and her activities of daily living remained low. In December of the same year, the oral administration of UFT was terminated, which 2 weeks later resulted in a marked decrease in pleural effusion on chest X-ray film. Respiratory discomfort and fatigue also subsided, and her general condition improved markedly. Herein we report a case of oral UFT-induced pleural effusion following lung cancer surgery. (Ann Thorac Cardiovasc Surg 2010; 16: 281–285)

Key words: UFT, lung cancer, adjuvant chemotherapy, pleural effusion

Introduction

Oral Uracil-Tegafur (UFT) administration as adjuvant chemotherapy after lung cancer surgery is becoming increasingly common in Japan.[1–4] In this case, the patient received this treatment following lung cancer surgery. The initiation of chemotherapy resulted in the development of pleural effusion on the operated side, with symptoms of respiratory discomfort, but the discontinuation of oral UFT was immediately followed by a reduction in pleural effusion with improvement in the general condition. Our search of the literature failed to identify any previous reports of pleural effusion as an adverse effect of UFT. We report a case of UFT-induced postoperative pleural effusion.

Case Report

A 75-year-old woman was found to have a nodular shadow at the right basal segment on chest CT in June 2007 (Fig. 1A). Bronchoscopic brush cytology was performed, leading to a diagnosis of adenocarcinoma. She had no history of smoking, but she did have a history of taking an oral nonsteroidal anti-inflammatory drug and a combination of herbal medicines (Tsumura, Nos. 18, 43, and 52) for rheumatoid arthritis since the age of 65. Under a diagnosis of lung cancer (cT2N0M0, adenocarcinoma, stage IB), she underwent a right lower lobectomy and lymph node dissection in March 2008 (Fig. 1B). The postoperative pathological diagnosis was adenocarcinoma, pT2N1M0, stage IIB (Fig. 1C). No pleural invasion was observed (p0). She followed a favorable course, and she was discharged from the hospital on the 10th postoperative day when chest X-ray film showed good lung expansion (Fig. 2A).

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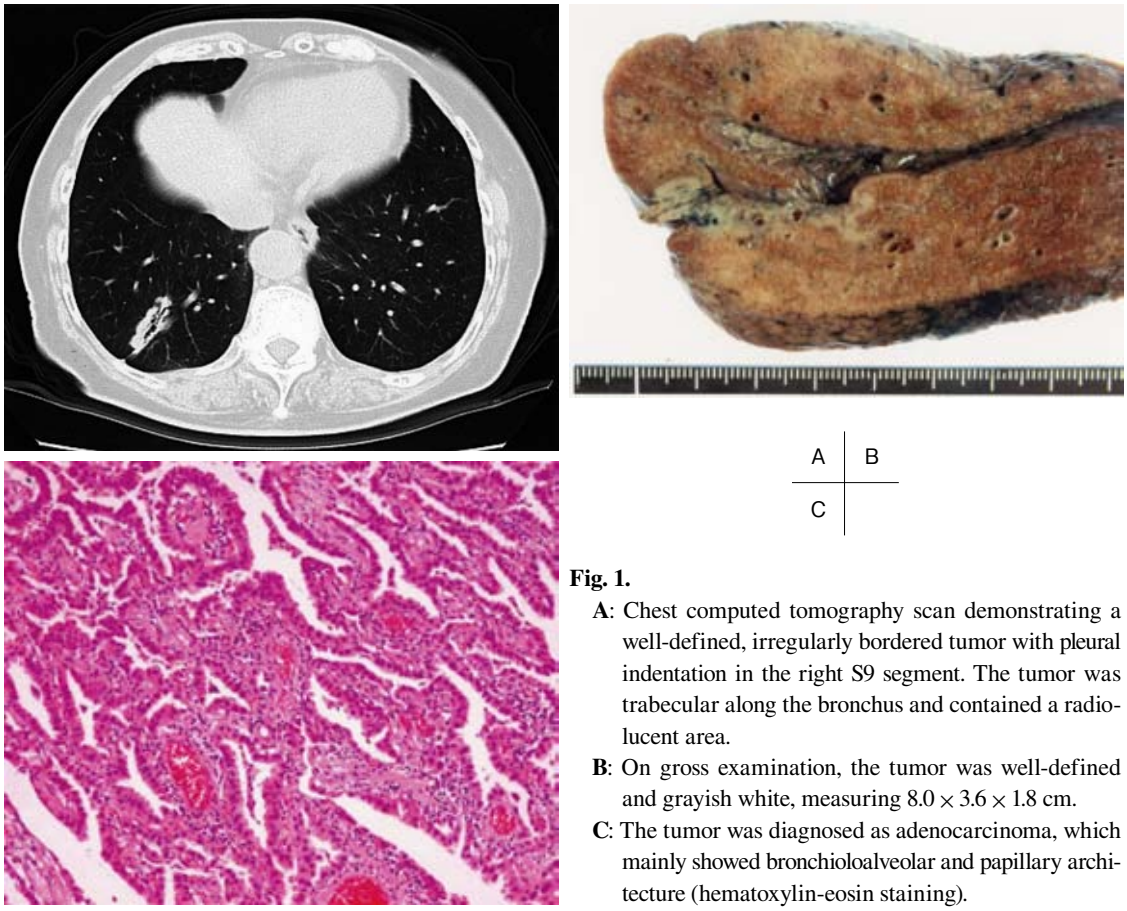

Fig. 1.
A: Chest computed tomography scan demonstrating a well-defined, irregularly bordered tumor with pleural indentation in the right S9 segment. The tumor was trabecular along the bronchus and contained a radiolucent area.
B: On gross examination, the tumor was well-defined and grayish white, measuring $8.0 \times 3.6 \times 1.8$ cm.
C: The tumor was diagnosed as adenocarcinoma, which mainly showed bronchioloalveolar and papillary architecture (hematoxylin-eosin staining).

Considering her advanced age, we found it difficult to administer systemic platinum-based doublet chemotherapy as postoperative adjuvant chemotherapy, so we started her on oral UFT (400 mg/day). In May, about 4 weeks after UFT administration began, she developed fatigue, respiratory discomfort, and tachycardiac atrial fibrillation without fever. Chest X-ray film showed an increase in right pleural effusion (Fig. 2B). Antithrombotic therapy with oral warfarin was started. Follow-up visits revealed no decrease in pleural effusion, but instead, a worsening of the above symptoms and a reduction in the activities of daily living. Therefore we performed thoracentesis in June and removed approximately 1300 ml of yellowish, serous pleural fluid, which predominantly contained lymphocytes (Table 1). Cytological examination showed no evidence of malignancy. Biochemical analysis of the pleural fluid revealed a total protein of 4.2 g/dl and a pleural-fluid-to-serum protein ratio of >0.5, indicating an exudative pleural effusion based on Light's criteria (Table 2). The pleural fluid contained almost no hemorrhagic components. Because the pleural fluid glucose level was less than 60 mg/dl, pleural effusion resulting from rheumatoid arthritis was most unlikely. The ADA level was within normal limits (<50 U/ml). Hematology tests were unremarkable, and no peripheral eosinophilia was observed. Echocardiography showed an estimated ejection fraction of 66% and no left atrial thrombosis, thus indicating no significant abnormality of the cardiac function. Lung expansion improved somewhat immediately after thoracentesis, but the pleural fluid increased over 2 weeks, and lung collapse occurred again. Oral administration of furosemide (40 mg/day) from July resulted in a slight reduction in pleural effusion, and to some extent this improved the respiratory discomfort, but not the fatigue. Chest CT revealed no recurrence of lung cancer in the lung fields or lymph nodes and no pulmonary edema in the lung fields, but a large volume of pleural fluid had compressed and collapsed the middle lobe. Despite continued diuretic administration for 5 months from July, pleural effusion was difficult to control, and anorexia, weight loss, fatigue, and low activities of daily living persisted.

Following a talk with the patient in December, oral

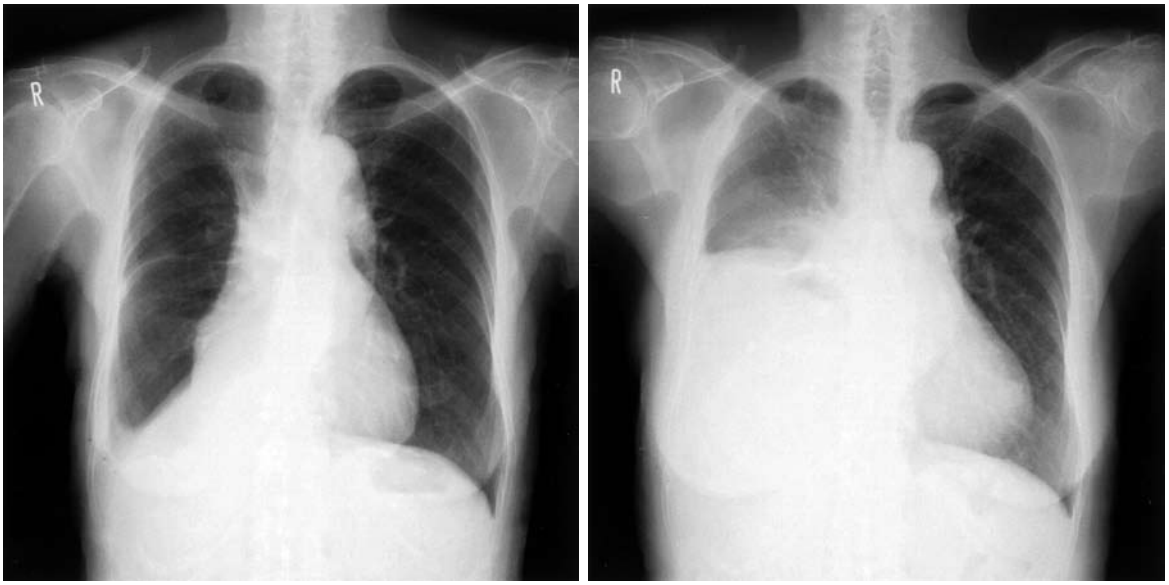

Fig. 2.
A: Chest X-ray film on the 10th postoperative day showed good lung expansion.
B: Chest X-ray film 1 month after the start of oral Uracil-Tegafur administration.

Table 1. Pleural effusion cell percentage differential

Cell counts	$30 \times 10^2/\mu l$
	Percentage differential
Neutrophils	0.0%
Lymphocytes	91.5%
Monocytes	7.5%
Eosinophils	0.5%
Basophils	0.5%

Table 2. Pleural effusion biochemical tests

ALP	49 U/l
LDH	98 U/l
Amylase	46 U/l
Glucose	112 mg/dl
TP	4.2 g/dl
Na	145 mEq/l
K	2.7 mEq/l
Cl	108 mEq/l
Ca	7.5 mg/dl
Specific gravity	1.029
Hemoglobin	0.1 mg/dl
Red blood cell counts	$1 \times 10^4/\mu l$
ADA	11.8 U/ml

UFT was discontinued after its intake for a total of 8 months, which 2 weeks later resulted in a marked decrease in pleural effusion on chest X-ray film (Fig. 3). Respiratory discomfort, fatigue, and anorexia also subsided, and the activities of daily living improved markedly. During a subsequent 3-month follow-up, pleural effusion did not increase, general condition improved further, and the patient now lives just as she did before surgery. We plan to follow her clinical course after lung cancer surgery on an outpatient basis while UFT is being discontinued.

Discussion

Kato et al. reported that the oral administration of UFT for 2 years after surgery improved the 5-year survival rate of patients with stage I lung adenocarcinoma.[1)] Since their report in 2004, such patients in Japan have been commonly administered oral UFT for 2 years after surgery.[2–4)] Although this patient had stage IIB adenocarcinoma, we believed that she could not tolerate intravenous drip chemotherapy; thus we selected chemotherapy with oral UFT.

In this patient, pleural effusion improved in a short period after oral UFT had been discontinued, strongly suggesting its involvement in pleural effusion. Reported adverse effects of UFT include hypoalbuminemia and edema, but not massive pleural effusion, such as seen in this case, making it difficult to pinpoint the cause. In this patient, pleural effusion was observed only in the thoracic spaces on the surgically treated side, and neither contralateral pleural effusion nor systemic effects such as systemic edema was noted. Regarding pleural effusion on only the surgically treated side, the following reasons can be considered, though they are merely hypothetical at present.

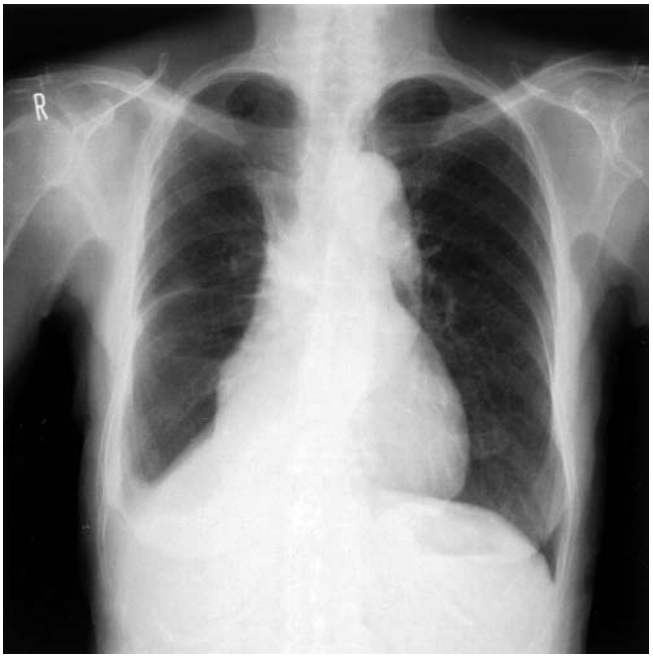

Fig. 3. Chest X-ray film after oral Uracil-Tegafur was discontinued.

One possible explanation is that some leaky capillaries existed on the resected surface, and that leukocyte adhesion molecules were up-regulated by the surgical procedure. An alternative explanation is a preferential distribution of UFT in the remaining thoracic spaces on the surgically treated side. It is possible that these spaces functioned as a third space in which UFT concentrated, and the accumulated UFT locally induced chemical pleuritis.

The patient continued to take herbal medicines in combination with UFT. Therefore some kind of interaction between the herbal medicines and UFT may have resulted in pleural effusion, though no studies have reported pleural effusion as an adverse effect of the herbal medicines taken by patients. Nor can we completely exclude the possibility of an interaction between UFT and rheumatoid arthritis or warfarin. Anticancer drugs, such as methotrexate, imatinib, mitomycin, interleukin-2, and all-trans-retinoic acid, have been reported to cause pleural effusion as an adverse reaction.[5–11] The suggested causes of pleural effusion as an adverse effect of anticancer drugs include cardiac dysfunction, renal insufficiency, supplemental intravenous fluids, hypersensitivity reaction, and increased capillary permeability.[5–11] The definite cause remains a subject for debate. And although the etiology of associated capillary leakage is speculative, increased capillary permeability has been suggested to be due to the up-regulation of integrin on the endothelium, activation of neutrophils and natural killer cells, or a release of such cytokines as tumor necrosis factor-α and IL-1.[5–11]

As with UFT, methotrexate is an antimetabolite, and one report exists of pleural effusion occurring after methotrexate therapy for trophoblastic tumors.[5] Walden et al. treated 317 trophoblastic tumor patients with 50 mg of methotrexate administered intramuscularly, and they reported that four of them developed pleural effusion without peripheral blood eosinophilia, as in this case.

In this patient, diuretic administration resulted in a slight decrease in pleural effusion, but did not offer significant long-term improvement. Pleural effusion is a very rare adverse effect, but if it is difficult to control during oral UFT administration after surgery, the drug should be temporarily discontinued to observe symptomatic changes in view of the possibility of UFT being the cause.

Besides the reason evident in the present patient, adverse effects, such as nausea/vomiting, diarrhea, liver dysfunction, and leukopinia, sometimes necessitate UFT discontinuation,[12–14] and compliance of oral UFT after lung cancer surgery is reported to be 50%–74% at 12 months.[1, 12] When considering oral UFT administration, we find it necessary for the doctor and patient to share information about the advantages and disadvantages as they apply to the patient and the patient's health status. And the doctor should closely follow up the patient on an outpatient basis.

In conclusion, we herein report a rare case of oral UFT-induced pleural effusion following lung cancer surgery.

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