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CASE REPORT

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Tegafur-uracil-induced pericardial effusion during adjuvant chemotherapy for resected lung adenocarcinoma: A case report

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Abstract

In Japan, oral administration of tegafur-uracil is recommended as postoperative adjuvant chemotherapy for patients diagnosed with primary lung adenocarcinomas of >2 cm size and staged as IA, IB, and IIA. Reports on chemotherapy-induced pericardial effusion are rare. Herein, we report a rare case of tegafur-uracil-induced pericardial effusion during postoperative adjuvant chemotherapy for primary lung cancer. A 60-year-old man underwent left lower lobectomy and mediastinal lymph node dissection for left lower lung adenocarcinoma. Lung cancer was staged as IB, and tegafur-uracil was administered as postoperative adjuvant chemotherapy from 1 month after the surgery. A computed tomography (CT) scan revealed a pericardial effusion 5 months after the surgery. A malignant pericardial effusion was suspected, and tegafur-uracil was discontinued. Pericardiocentesis could not be performed owing to a small amount of pericardial effusion. An ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography/CT scan revealed no abnormal FDG uptake. During a short follow-up period after discontinuation of tegafur-uracil, a CT scan revealed a decrease in pericardial effusion, suggesting that the pericardial effusion was induced by tegafur-uracil. Follow-up of pericardial effusion is required while administering tegafur-uracil. In cases of pericardial effusion without symptoms and no suspicious metastatic lesions in other organs, we should be concerned about tegafur-uracil-induced pericardial effusion.

KEYWORDS

adjuvant chemotherapy, adverse event, lung cancer, pericardial effusion, tegafur-uracil

INTRODUCTION

Tegafur-uracil is an oral anticancer drug containing tegafur, a prodrug of 5-fluorouracil, and uracil. In Japan, oral administration of tegafur-uracil is recommended as postoperative adjuvant chemotherapy for patients diagnosed with primary lung adenocarcinomas of >2 cm size and staged as IA, IB, and IIA (TNM classification of lung cancer, 8th edition).[1–3] The recommended dose and duration of tegafur-uracil is 250 mg/body surface area (m^2) for 2 years. Adverse events (AEs) related to the use of tegafur-uracil mainly include anorexia, nausea, diarrhea, myelosuppression, and liver dysfunctions[2]; however, severe AEs are rare. Herein, we report a rare case of tegafur-uracil-induced pericardial effusion during postoperative adjuvant chemotherapy for primary lung cancer.

CASE REPORT

A 60-year-old man with hypertension, dyslipidemia, interstitial pneumonia, and a 25.5 pack-year smoking history was identified with a pulmonary nodule on computed tomography (CT). Spirometry and the tumor marker carcinoembryonic antigen (CEA) were within normal limits. Transthoracic echocardiography revealed normal heart function. A CT scan revealed a 2.3 cm lung tumor in the left lower lobe (Figure 1a). The tumor was diagnosed as adenocarcinoma by CT-guided percutaneous

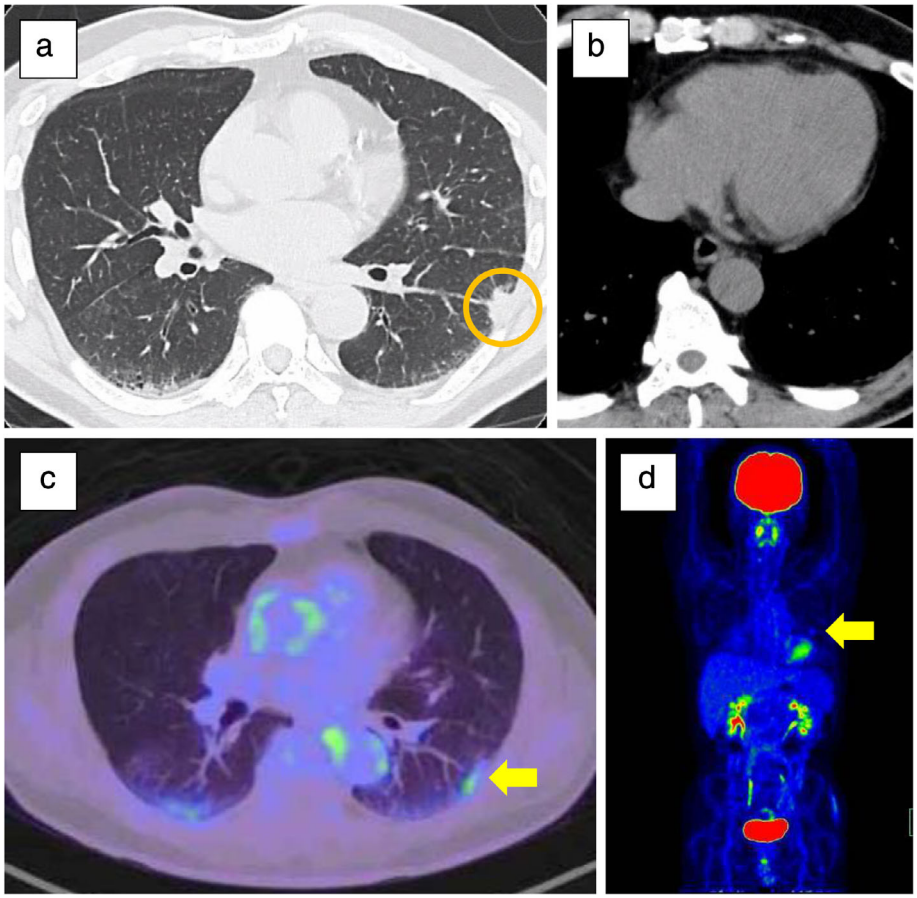

FIGURE 1 Preoperative imaging findings. (a) Computed tomography (CT) scan shows a lung nodule in the left lower lobe (orange circle) and interstitial pneumonia; (b) no pericardial effusion is observed; (c, d) ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography/CT scan shows FDG uptake (SUVmax: 2.2) in the lung nodule (yellow arrows) and no abnormal FDG uptake, suggesting distant metastasis

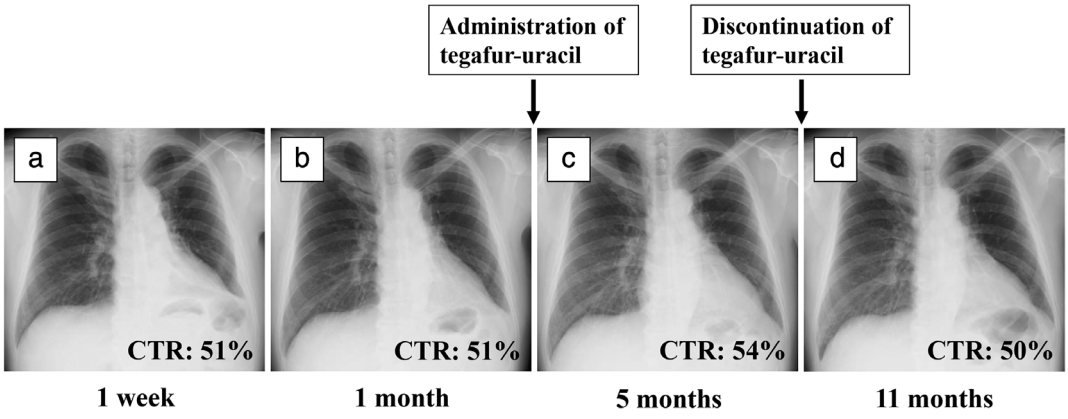

FIGURE 2 Chest radiography images after surgery. (a–d) Chest radiography images show an increase in the cardiothoracic ratio (CTR) compared to before administration of tegafur-uracil and a decrease in the CTR after discontinuation of tegafur-uracil

biopsy. No pericardial effusion was observed (Figure 1b). An ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET)/CT scan revealed FDG uptake maximum standard uptake value (SUV_{max}: 2.2) in the lung tumor, and no abnormal FDG uptake suggesting distant metastasis was observed (Figure 1c,d). The left lower lung cancer was diagnosed as clinical stage IA3 (T1cN0M0). The left lower lobectomy and mediastinal lymph node (LN) dissection (ND2a-1) were performed by video-assisted thoracoscopic surgery. No intraoperative injury to the pericardium was observed. The operative time was 183 min, and the estimated blood loss was 40 ml. No air leakage was observed postoperatively, and the chest drain tube was removed on postoperative day 1. No acute exacerbation of interstitial pneumonia was observed postoperatively. The postoperative course of the patient was uneventful, and the patient was discharged on postoperative day 9. The patient took celecoxib and rebamipide for 1 month after the surgery. Following pathological diagnosis, the lung adenocarcinoma showed pleural invasion beyond the elastic layer (pl1), which was staged as IB (T2aN0M0).

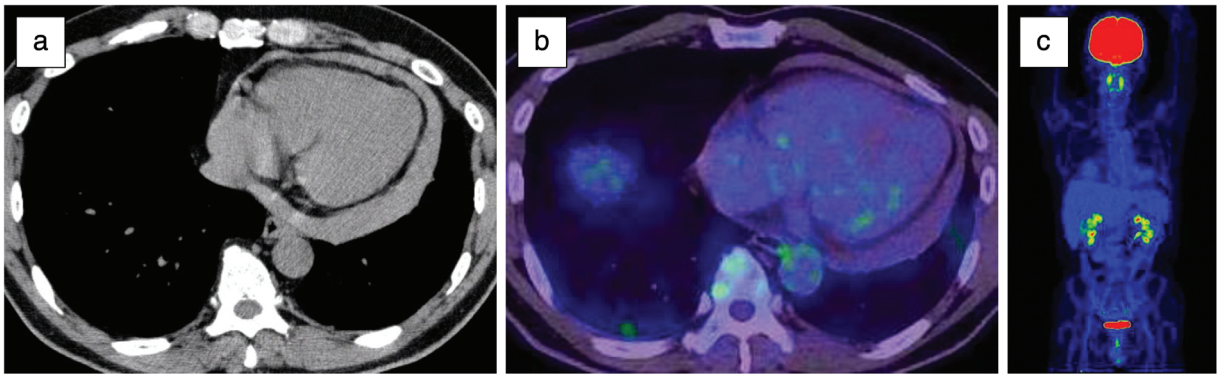

FIGURE 3 Imaging findings 5 months after surgery. (a) Computed tomography (CT) scan shows a small amount of pericardial effusion; (b, c) ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography/CT scan shows no abnormal FDG uptake, suggesting recurrence of the lung cancer in the whole body, including the pericardium

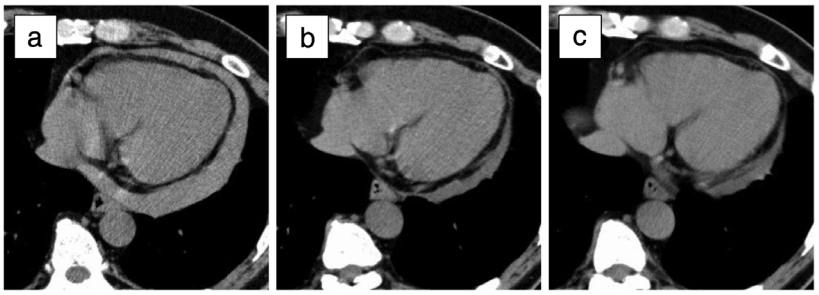

FIGURE 4 Computed tomography images of pericardial effusion. (a–c) The amount of pericardial effusion gradually decreased after discontinuation of tegafur-uracil

Tegafur-uracil (500 mg/day) was administered as postoperative adjuvant chemotherapy from 1 month after surgery. At 5 months after surgery, chest radiography images showed an increase in the cardiothoracic ratio (CTR) (Figure 2a–c), and a CT scan revealed a small amount of pericardial effusion (Figure 3a). No cardiac tamponade or signs of heart failure were observed. There was no history of flu-like symptoms or trauma. In laboratory tests, white blood cell count, C-reactive protein, hepatic and renal functions, thyroid hormone, brain natriuretic peptide, and CEA were within normal limits. Based on the above, recurrence of lung cancer was suspected. Pericardiocentesis could not be performed due to the small amount of pericardial effusion. We considered that tegafur-uracil was ineffective and it was necessary to change the chemotherapy regimen. Therefore, tegafur-uracil was discontinued. An FDG-PET/CT scan showed no abnormal FDG uptake, implying low possibility of lung cancer recurrence (Figure 3b,c). With careful follow-up after discontinuation of tegafur-uracil, a chest radiography image showed a decrease in CTR (Figure 2d) and a CT scan revealed a decline in the amount of pericardial effusion (Figure 4a–c). At 14-month follow-up after the surgery, a CT scan showed no further increase in the pericardial effusion and no recurrence of lung cancer.

DISCUSSION

The main causes of pericardial effusion include congestive heart failure, renal failure, hepatic cirrhosis, infection, hypothyroidism, malignant tumors, and trauma.[4–9] In this case, a malignant pericardial effusion was initially suspected based on the clinical course. Lung cancer is the most common cause of malignant pericardial effusion (53–60%).[9,10] The diagnosis of malignant pericardial effusion requires pathological examination following pericardiocentesis or analyses of pericardial biopsies.[11] However, echo-guided pericardiocentesis is reported to have a fatal complication in 3% of cases.[12] In this case, pericardiocentesis could not be performed due to a small amount of pericardial effusion as the procedure could be life-threatening. It is reported that patients with lung cancer having malignant pericardial effusion showed distant metastasis (76%), malignant pleural effusion (88%), and N2 or N3 LN metastasis (98%).[13] In this

case, an FDG-PET/CT scan showed no abnormal FDG uptake, implying low possibility of lung cancer recurrence. During a short follow-up period after discontinuation of tegafur-uracil, imaging findings revealed a decrease in pericardial effusion, suggesting tegafur-uracil-induced pericardial effusion. Pericarditis induced by 5-fluorouracil has been reported as a rare AE.[14,15] Notably, cardiotoxicity induced by 5-fluorouracil is usually reversible,[14] further supporting the possibility of tegafur-uracil-induced pericardial effusion in the current case.

In conclusion, oral administration of tegafur-uracil might cause pericardial effusion. In cases of pericardial effusion without symptoms and no suspicious metastatic lesions in other organs, tegafur-uracil therapy should be discontinued and short-term follow-up should be recommended.

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DISCLOSURE

None of the authors have any potential conflicts of interest relevant to this report.

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REFERENCES

1. Wada H, Hitomi S, Teramatsu T. Adjuvant chemotherapy after complete resection in non-small-cell lung cancer. West Japan study Group for Lung Cancer Surgery. J Clin Oncol. 1996;14:1048–54.
2. Kato H, Ichinose Y, Ohta M, Hata E, Tsubota N, Tada H, et al. A randomized trial of adjuvant chemotherapy with uracil-tegafur for adenocarcinoma of the lung. N Engl J Med. 2004;350:1713–21.
3. Hamada C, Tanaka F, Ohta M, Fujimura S, Kodama K, Imaizumi M, et al. Meta-analysis of postoperative adjuvant chemotherapy with tegafur-uracil in non-small-cell lung cancer. J Clin Oncol. 2005;23:4999–5006.
4. Winters WL Jr, Carter BL, Stauffer HM, Soloff LA. Pericardial effusion in congestive heart failure. Dis Chest. 1961;40:82–6.
5. Rostand SG, Rutsky EA. Pericarditis in end-stage renal disease. Cardiol Clin. 1990;8:701–7.
6. Shah A, Variyam E. Pericardial effusion and left ventricular dysfunction associated with ascites secondary to hepatic cirrhosis. Arch Intern Med. 1988;148:585–8.
7. Imazio M, Gaita F, LeWinter M. Evaluation and treatment of pericarditis: a systematic review. JAMA. 2015;314:1498–506.
8. Fernandes F, Vieira GS, Arteaga E, Ianni BM, Pêgo- Fernandes P, Mady C. Cholesterol pericarditis. A specific but rare cause of pericardial disease. Arq Bras Cardiol. 2001;76:391–4.
9. Strobbe A, Adriaenssens T, Bennett J, et al. Etiology and long-term outcome of patients undergoing pericardiocentesis. J Am Heart Assoc. 2017;6:e007598.
10. Muir KW, Rodger JC. Cardiac tamponade as the initial presentation of malignancy: is it as rare as previously supposed? Postgrad Med J. 1994;70:703–7.
11. Imazio M, Gaita F. Diagnosis and treatment of pericarditis. Heart. 2015;101:1159–68.
12. Hosomi Y, Ohkuma Y, Shibuya M. Treatment of malignant pericardial effusion [article in Japanese]. Gan To Kagaku Ryoho. 2008;35:906–9.
13. Okamoto H, Shinkai T, Yamakido M, Saijo N. Cardiac tamponade caused by primary lung cancer and the management of pericardial effusion. Cancer. 1993;71:93–8.
14. Killu A, Madhavan M, Prasad K, Prasad A. 5-fluorouracil induced pericarditis. BMJ Case Rep. 2011;2011:bcr0220113883.
15. Maréchal S, Racaru V, Houbiers G, Graas MP. Pericarditis following 5-fluorouracil administration [article in French]. Rev Med Liege. 2015;70:360–6.

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