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Tegafur deteriorates established cardiovascular atherosclerosis in colon cancer: A case report and review of the literature

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Abstract

BACKGROUND

Cardiac toxic effect of tegafur (S-1) is extremely rare, and there has been no report on this issue so far.

CASE SUMMARY

We herein report a typical case of single S-1 administration after radical operation for colon cancer. The patient had no background or medical history of acute coronary syndrome (ACS), and only aortic and coronary atherosclerosis was revealed by computed tomography (CT) before surgery. He complained of sternum pain during the fifth cycle of S-1 treatment. Electrocardiogram (ECG) and serum cardiac marker cardiac troponin T (cTnT) strongly suggested ACS, which was possibly caused by S-1 cardiotoxicity.

CONCLUSION

Monitoring protocols based on ECG, CT, and cTnT should be performed in real time to evaluate cardiac function during S-1 administration.

Key words: S-1; Acute coronary syndrome; Computed tomography; Electrocardiogram; Cardiac troponin T; Case report

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Core tip: Cardiac toxic effect of tegafur (S-1) is extremely rare, and there has been no report on this issue so far. We herein report a typical case and review the literature. The case might contribute to improving our understanding of the pharmacology and mechanism of S-1 in treating colon cancer. This report also emphasizes the group of cancer patients who have already been diagnosed with cardiovascular atherosclerosis and serves as a reminder to gastroenterologists that delicate monitoring protocols should be

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carried out in real time to evaluate the cardiac function of S-1-ongoing patients.

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INTRODUCTION

Colon cancer is a common malignancy originating from the digestive tracts. Its worldwide incidence is increasing year by year, and it ranks the third among gastric and intestinal tumors nowadays^[1]. Surgical operation is the cure, and chemotherapy is considered as a general adjuvant therapy to reduce recurrence and improve survival rate postoperatively. Tegafur/gimeracil/oteracil (S-1) is a new generation oral fluorouracil drug against gastric and colorectal cancer. Clinical data indicate that myelosuppression, gastrointestinal reaction, peripheral neurotoxicity, and liver damage are the main dose limiting toxicities. Reports on its cardiac injury are rare. In this case, non-ST segment elevation acute coronary syndrome (NSTEMI-ACS) was confirmed by electrocardiography (ECG) as well as the serum cardiac marker cardiac troponin T (cTnT) in a colon cancer patient during the fifth cycle of single S-1 chemotherapy.

CASE PRESENTATION

Chief complaints

Recurrent abdominal pain for half a month.

History of present illness

An 87-year-old male patient was admitted to our hospital on May 1, 2017 for recurrent abdominal pain with anal exhaust and defecation cessation for half a month.

History of past illness

He had a history of right inguinal herniorrhaphy 20 years ago and he denied histories of trauma, smoking or drinking, hyperlipemia, or chronic diseases such as hypertension and diabetes.

Physical examination

Upon physical examination, a 2 cm solid mass was found in his right lower abdomen.

Laboratory testing

Fecal occult blood test was positive. Albumin was 31.1 g/L, indicating low albumin. Serum CEA was 93.00 ng/mL (normal range: < 5.00 ng/mL) and CA199 was 113.7 U/mL (normal range: < 39.0 U/mL).

Imaging examination

Echocardiographic examination revealed mild tricuspid and aortic regurgitation insufficiency (Figure 1). Chest and abdomen computed tomography (CT) showed a soft tissue shadow in the ileocecal junction and adjacent ileum that was surrounded by multiple swollen lymph nodes, which was highly indicative of a tumor lesion (Figure 2A). Aortic and coronary atherosclerosis was also detected (Figure 2B). Colonoscopy further confirmed an ileocecal cauliflower-like space-occupying lesion (Figure 3A), followed by a pathological diagnosis of adenocarcinoma (Figure 3B).

FINAL DIAGNOSIS

Ileocecal adenocarcinoma and ACS.

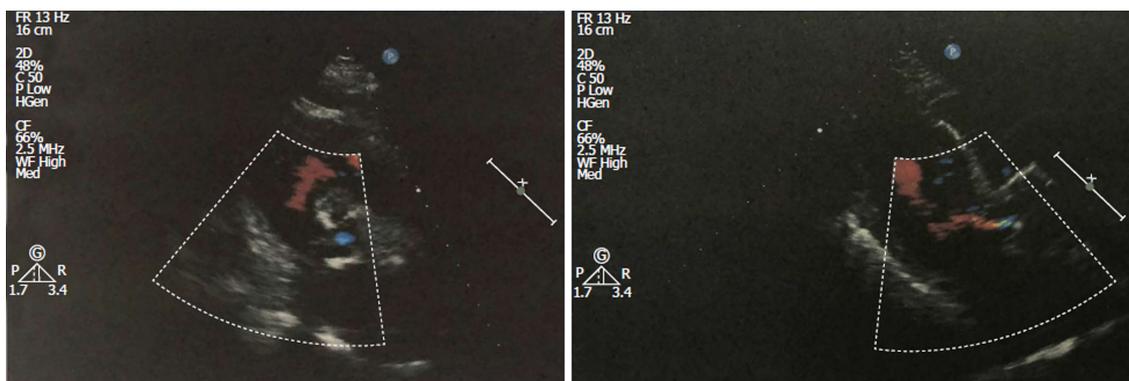


Figure 1 Echocardiographic examination on October 28, 2017.

TREATMENT

The patient underwent radical resection on May 4, 2017 and began S-1 capsule administration at one month after the operation.

OUTCOME AND FOLLOW-UP

The patient periodically went back to our hospital for review. He had no documented complaints of discomfort and showed no obvious adverse reaction until the fifth cycle of single S-1 chemotherapy on October 28, 2017. He developed retrosternal pain. ECG showed extensive ST-T segment depression along with inversed T wave (Figure 4). A serial of cardiac markers were continuously detected during the onset (Table 1), among which serum cTnT and pro-brain natriuretic peptide levels were extremely elevated. In retrospect of CT scan of the heart and after consultation with cardiologists, the patient was diagnosed with NSTEMI-ACS. Considering D-dimer was elevated after the outbreak of ACS (1.66 mg/L; normal range: < 0.55 mg/L), antiplatelet and anticoagulant protocols were applied to stabilize plaque. Improvement of myocardial metabolism and nutritional support were also applied.

DISCUSSION

Pharmacological effect of S-1

Adjuvant chemotherapy, such as 5-fluorouracil (5-FU), has been proven to reduce the high proportion of recurrence and metastasis of colon cancer, which are still the main cause of death after surgical resection. However, every coin has two sides. The common side effects of 5-FU are myelosuppression, diarrhea, mucositis, and hand-foot syndrome. In recent years, S-1 has become a new trend of anticancer first-line drug due to its better tolerance and fewer toxicity than 5-FU. It is a synergetic and modified agent of 5-FU consisting of the active ingredient tegafur (FT) and other two biological regulators, gimeracil (CDHP) and oteracil potassium (Oxo)^[2]. As a pro-5-FU, FT preserves bioavailability and can be converted into 5-FU through oral uptake, thus interfering DNA, RNA, and protein synthesis in tumor cells. The regulator CDHP inhibits the catabolism of 5-FU released from FT under the action of dihydropyrimidine dehydrogenase. Therefore, it contributes adequate concentration and therapeutic effect of 5-FU in peripheral blood and tumor tissue, which is similar to that of continuous intravenous infusion of 5-FU. Oxo, another regulator of S-1, concentrates in gastrointestinal tissue after oral administration. Oxo blocks 5-FU phosphorylation and reduces local toxicity^[3].

Cardiac toxic effect of 5-FU

The patient in our case had confirmed aortic and coronary atherosclerosis by CT examination before surgery. Considering no other obvious triggers within 4 months except single S-1 administration, ACS onset was considered to be related to cardiotoxicity of S-1. According to some reports, cardiotoxicity is of less frequency but more lethal during 5-FU treatment, with a classical manifestation of angina-like chest pain. The exact pathophysiological mechanism of cardiotoxicity of 5-FU has not yet been fully elucidated. One hypothesis is that 5-FU and its metabolites (*e.g.*,

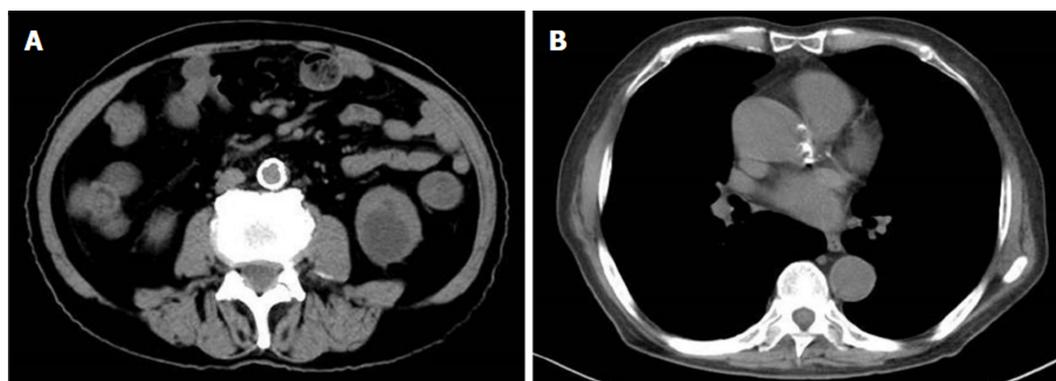


Figure 2 Pre-surgery computed tomography examination. A: A soft tissue shadow of the ileocecal junction and adjacent ileum surrounded by multiple swollen lymph nodes; B: Aortic and coronary atherosclerosis.

fluoroacetate) induce coronary vasospasm. This has been demonstrated in both animal models and human vascular samples during 5-FU infusion^[4,5]. Another theory is that 5-FU is catabolized to alpha-fluoro-beta alanine and subsequently to fluoroacetate, which is known to be highly cardiotoxic and neurotoxic^[6]. The original records on the side effects of tegafur date back to the last century. However, whether cardiotoxicity of 5-FU also applies to S-1 is barely documented.

CT, ECG, and cTnT in S-1 monitoring

Coronary CT angiography (CCTA) provides both detailed information on the cavity and wall of the coronary artery and the dynamic signal of blood flow in it, emphasizing its important diagnostic value for ACS. Its high-resolution images can exhibit the main branch stenosis of the coronary artery. In addition, CCTA is also applied for morphological evaluation of atherosclerotic plaque in the main coronary artery as well as its main branches^[7].

ECG is a first-line diagnostic technique for patients with chest pain. It is of great clinical significance in reducing disability and mortality of ACS by early diagnosis and in patients' better prognosis. ECG is more operable than the interventional examination and coronary angiography in ACS diagnosis. The characteristic of NSTEMI-ACS, ST-T alternation, such as depressed ST without ST elevation, is one of the most important indicators^[8].

cTnT is a structural protein of cardiac myocytes. When cardiac cells are injured, increased membrane permeability occurs, followed by cell apoptosis or necrosis. The cytoplasmic and structural cTnT will be released into the blood. Therefore, it is considered to be the "gold standard" for diagnosing myocardial injury, especially myocardial infarction, due to its rapid increase in blood to achieve the detection sensitivity^[9].

Individual susceptibility to cardiotoxicity is unpredictable when taking S-1. For those who have already been diagnosed with cardiovascular atherosclerosis and are highly likely to have a lethal strike, we recommend that delicate monitor protocols, based on ECG, CT and cTnT, should be carried out in real time to evaluate the cardiac function of S-1-ongoing patients. As such, high-risk patients may truly benefit from S-1 treatment since it may improve their prognosis for myocardial infarction prevention.

CONCLUSION

Individual susceptibility to cardiotoxicity is unpredictable in patients with gastric and colorectal cancer when they take S-1. Cardiotoxicity of S-1 should be considered in patients with cardiovascular atherosclerosis during anticancer therapy. Monitoring protocols based on ECG, CT, and cTnT should be carried out in real time to evaluate cardiac function during S-1 administration.

Table 1 Serum cardiac markers of the patient during acute coronary syndrome onset

Date	cTnI	cTnT (ng/L)	CK-MB (U/L)	Mb ($\mu\text{g/L}$)	PRO-BNP (pg/mL)	PCT (ng/mL)
28/10	-	146.2	43.0	230	/	/
29/10	-	1256.0	50.0	54	1077	0.059
01/11	-	1102.0	/	/	/	/
06/11	±	507.3	/	/	/	/

cTnI: Cardiac troponin I; cTnT: Cardiac troponin T; CK-MB: Creatine kinase-MB; Mb: Myoglobin; PRO-BNP: Pro-brain natriuretic peptide; PCT: Procalcitonin.

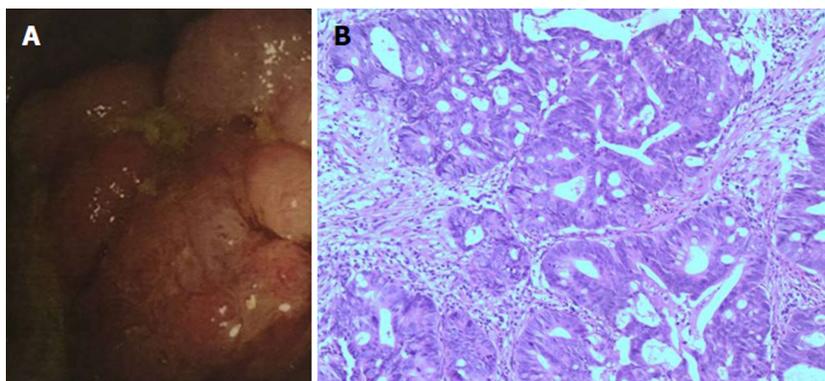


Figure 3 Diagnosis of a space-occupying ileocecal lesion. A: Colonoscopic examination; B: H&E staining showed adenocarcinoma (magnification, $\times 100$).

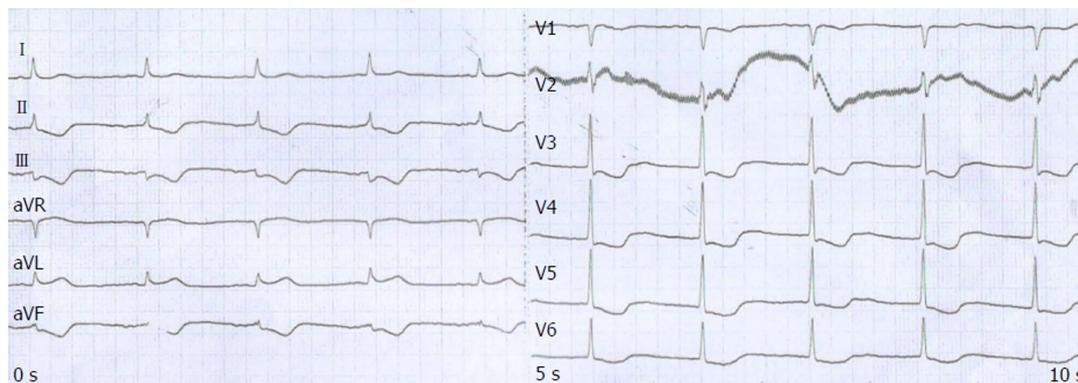


Figure 4 Electrocardiogram results on October 28, 2017.

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