



Contents lists available at ScienceDirect

## Journal of Cardiology Cases

journal homepage: [www.elsevier.com/locate/jccase](http://www.elsevier.com/locate/jccase)

## Case Report

## Atrial fibrillation observed in a patient with esophageal cancer treated with fluorouracil



Shohei Moriyama (MD)\*, Taku Yokoyama (MD), Kei Irie (MD), Mamoru Ito (MD), Kenji Tsuchihashi (MD), Mitsuhiro Fukata (MD), Hitoshi Kusaba (MD), Toru Maruyama (MD), Koichi Akashi (MD)

Department of Hematology, Oncology and Cardiovascular Medicine, Kyushu University Hospital, Fukuoka, Japan

## ARTICLE INFO

## Article history:

Received 11 June 2019

Received in revised form 18 July 2019

Accepted 30 July 2019

## Keywords:

Atrial fibrillation  
Esophageal cancer  
Fluorouracil  
Vasospasm

## ABSTRACT

Fluorouracil (5-FU), a commonly used anticancer agent, has potent cardiotoxicity that is mediated by vascular endothelial injury and vasospasm. Here, we report a patient demonstrating atrial fibrillation (AF), which was most likely induced by vasospasm mediated by 5-FU.

A 69-year-old man presented with dysphagia and was diagnosed with advanced esophageal cancer. Frequent paroxysms of atrial fibrillation (AF) were observed during combination chemotherapy including 5-FU. AF was refractory to disopyramide, but was sensitive to antianginal agents (nicorandil and nitroglycerin transdermal patch). Coronary angiography performed within the chemotherapeutic period demonstrated moderate stenosis in the right coronary artery (RCA). Severe spasm at the proximal portion of the atrial branch in RCA was induced by provocation test using acetylcholine. Our case indicated that 5-FU predisposed vasospasm in RCA and the subsequent atrial ischemia may lead to AF.

<Learning objective: Fluorouracil (5-FU), a commonly used anticancer agent, induces cardiac ischemic events and sometimes leads to the paroxysms of atrial fibrillation (AF). Coronary-dilating agents should be considered for the treatment of AF which occurs after the administration of 5-FU and is refractory to antiarrhythmic agents.>

© 2019 Published by Elsevier Ltd on behalf of Japanese College of Cardiology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

## Introduction

Fluoropyrimidine derivatives are the major anticancer agents used for patients with gastrointestinal cancer. However, they are reported to have potent cardiotoxicity such as vascular endothelial injury and subsequent vasospasm [1]. Fluorouracil (5-FU) and capecitabine, both of which are fluoropyrimidine derivatives, are the representative agents causing myocardial ischemia at a rate of 18% [2]. These agents have potent direct toxic effects on the coronary endothelium, and inhibitory effects on nitric oxide (NO) synthesis leading to coronary vasospasm. Here, we report a patient demonstrating atrial fibrillation (AF) observed after the adminis-

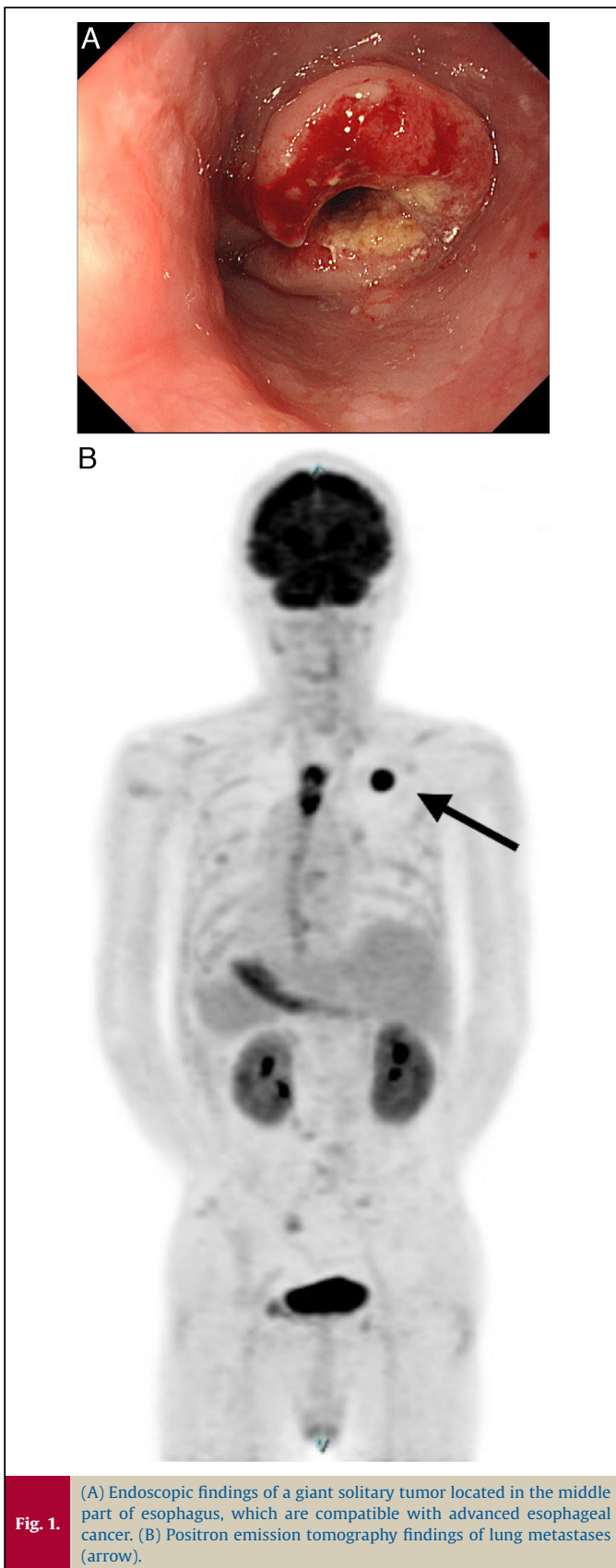
tration of 5-FU which likely induced vasospasm in the atrial branch of the right coronary artery (RCA).

## Case report

A 69-year-old man complained of dysphagia and was diagnosed with middle-thoracic squamous cell esophageal cancer of cT3N2M1(PUL) Stage IVB according to the TNM Classification of Malignant Tumors-8th edition. He was referred to Kyushu University Hospital for chemotherapy. Esophagogastroscopy showed a sub-obstructed esophagus and bleeding ulcer due to esophageal cancer. Positron emission tomography revealed lung metastases (Fig. 1). He was a current smoker and his past history included visceral inversion, hypertension, and chronic kidney disease. He experienced a single episode of paroxysm of AF, but no episodes of angina pectoris. Electrocardiogram (ECG) prior to the anticancer therapy showed sinus rhythm and no abnormalities in the

\* Corresponding author at: Department of Hematology/Oncology/Cardiovascular Medicine, Kyushu University Hospital, Maidashi 3-1-1, Higashi-ku, Fukuoka 812-8586, Japan.

E-mail address: [s-mori@med.kyushu-u.ac.jp](mailto:s-mori@med.kyushu-u.ac.jp) (S. Moriyama).



**Fig. 1.** (A) Endoscopic findings of a giant solitary tumor located in the middle part of esophagus, which are compatible with advanced esophageal cancer. (B) Positron emission tomography findings of lung metastases (arrow).

ST-T segment. Transthoracic echocardiography showed no wall motion abnormalities, no left ventricular wall thickening, and no left atrial dilatation. Left ventricular ejection fraction was 64.3%, and the dimensions of interventricular septum, left

ventricular posterior wall, and left atrium were 8 mm, 10 mm, and 26 mm, respectively. Considering that his performance status was satisfactory, biweekly DCF combination therapy (docetaxel 30 mg/m<sup>2</sup> day 1, 5-FU 800 mg/m<sup>2</sup> day 1–5, cisplatin 80 mg/m<sup>2</sup> day 1) was started. On day 6, asymptomatic AF was documented and terminated 1 h later. Anticoagulation was not performed due to a low CHADS2 score (1 point due to hypertension alone) and the high bleeding risk of the esophageal ulcer. Instead, a  $\beta$ -blocker (bisoprolol transdermal patch) was prescribed. Thereafter, sinus bradycardia was recorded prior to the 2nd course of chemotherapy and bisoprolol was discontinued. The chemotherapy regimen was changed to FP combination therapy (5-FU 800 mg/m<sup>2</sup> day 1–5, cisplatin 80 mg/m<sup>2</sup> day 1) due to an allergy to docetaxel. On day 4 of the 2nd course of chemotherapy, rapid AF was recorded with palpitations and mild oppressive pain in the chest. On day 5, syncope occurred due to rapid AF, showing a ventricular rate of 150 bpm (Fig. 2(A)). Intravenous disopyramide (50 mg) converted AF to a sinus rhythm after 3 s of sinus pause (Fig. 2(B)), but atrial tachycardia occurred soon after (Fig. 2(C)). Transdermal nitroglycerin patch was attempted as the patient had a chest discomfort and inferior leads (II, III, aVF) ECG showed slight ST-segment depression (Fig. 2(D)). Thirty minutes after placing the transdermal patch, AF was converted to a sinus rhythm. AF did not occur thereafter during the 2nd course of chemotherapy.

Dysphagia was exacerbated and lung metastasis showed progression based on the images of computed tomography (CT) performed after the completion of the 2nd course of chemotherapy. Hence, radiation (60 Gy/30Fr) accompanied by an FP regimen (5-FU 700 mg/m<sup>2</sup> day 1–5, cisplatin 50 mg/m<sup>2</sup> day 1) was performed as the 3rd course of anticancer therapy. AF recurred on day 4 during the 3rd course. AF sustained over the day 5, coronary angiography was performed, and 50% stenosis was observed at segment 2 of RCA as shown in Fig. 3(A). A provocation test using 50  $\mu$ g acetylcholine (ACh) induced diffuse spasms in RCA and severe (90%) spasms at the prior stenotic segment 2 accompanied with chest pain. Moreover, after the provocation test, the atrial branch of RCA showed 90% stenosis (Fig. 3(B)). Based on these coronary angiographic findings, nicorandil infusion and transdermal patches were attempted. Thirty minutes after administration of coronary dilating agents, sinus rhythm was restored without pause. In addition, the 4th FP-combination chemotherapy was successfully terminated without uncontrollable AF by readministration of transdermal nitroglycerin patch. After completion of whole chemotherapeutic regimen, AF did not recur leading to discontinuation of antianginal treatment.

## Discussion

We present a patient with advanced esophageal cancer treated with chemotherapy including 5-FU, which most likely induced vasospasm in RCA leading to the paroxysms of AF. Despite AF being associated with cancer treatment that was resistant to antiarrhythmic agents, we could complete the cancer therapy safely using coronary dilating agents.

Although the exact mechanisms remain unclear, AF is observed in a maximum of 1.4% of cancer patients during a chemotherapy regimen including 5-FU [2]. The present case demonstrated dextrocardia and had coronary risk factors such as hypertension, current smoking, and chronic kidney disease. Indeed, coronary angiography performed on this patient demonstrated moderate organic stenosis in the proximal portion of the atrial branch in RCA (Fig. 3(A)). In addition, a provocation test using 50  $\mu$ g ACh during the period of

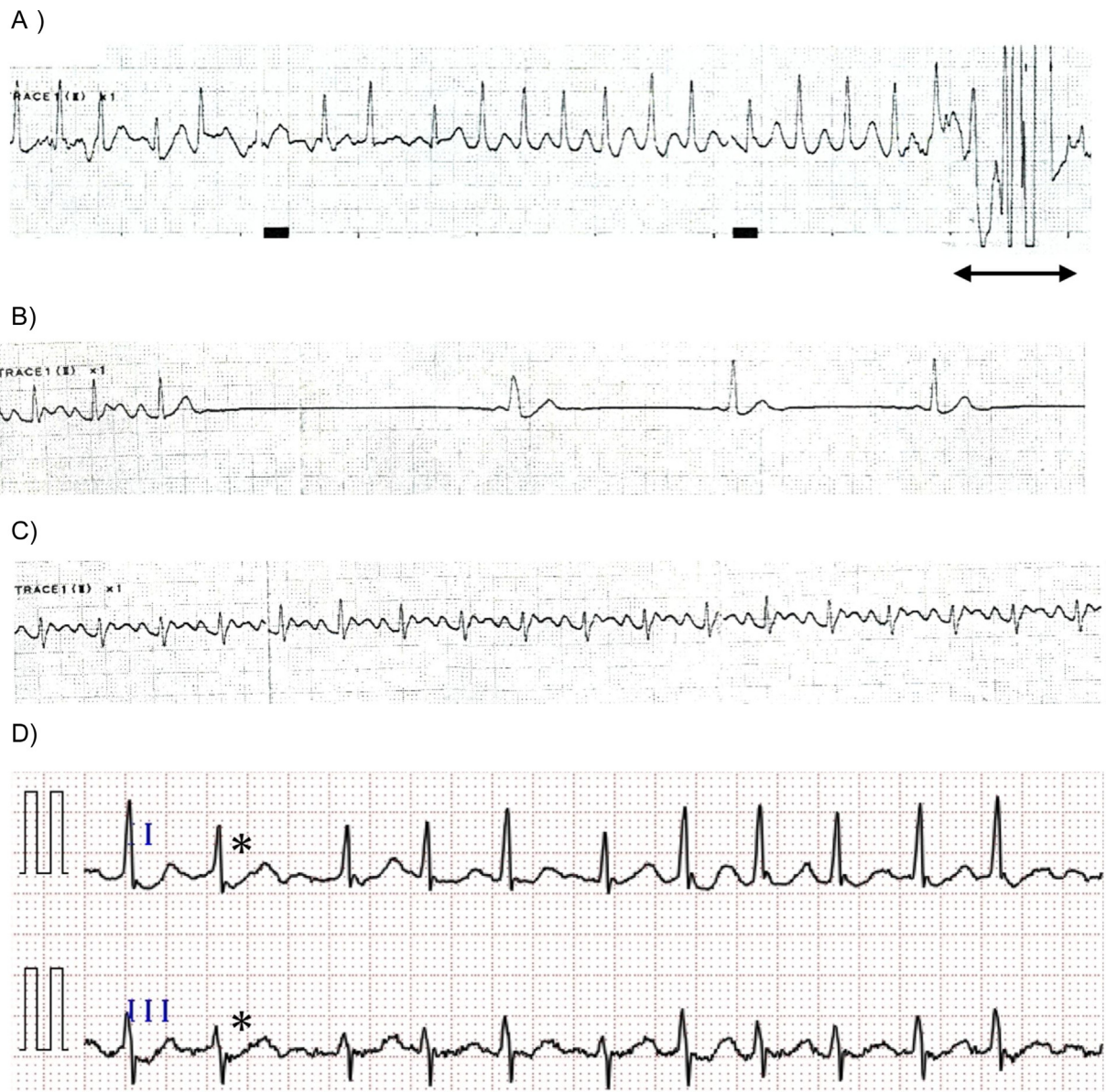


**Fig. 2.** Serial electrocardiogram (ECG) monitors demonstrated: (A) atrial fibrillation (AF) with a ventricular rate of 150 bpm and the last portion of motion artefact caused by syncope (bidirectional underline), (B) sinus pause with a duration of 3 s immediately after the termination of AF, (C) atrial tachycardia observed after the restoration of sinus rhythm, and (D) 12-lead ECG showing AF and mild ST depression in the inferior leads (II, III, aVF) (indicated by asterisks).

chemotherapy induced right coronary vasospasm, which included the atrial branch (Fig. 3(B)). Nicorandil infusion and transdermal patches restored sinus rhythm. These findings indicate that 5-FU caused vasospasm in the atherosclerotic RCA, and the subsequent atrial ischemia induced AF that was resistant to antiarrhythmic agents but sensitive to the coronary dilating agents.

The occurrence of AF in cancer patients is not rare and is due to comorbid inflammation, direct action of cancer, indirect action mediated by the autonomic nervous system, and the adverse effects of anticancer agents impairing coronary circulation [3]. Indeed, AF is a representative atrial arrhythmia, which is observed in patients with coronary artery disease (CAD). The prevalence of CAD in AF patients ranges from 17 to 46%, whereas the prevalence of AF in patients with CAD is low, up to 5% [4]. Our case strengthened literature reporting that acute cardiac ischemia sometimes underlies AF [5,6]. Alasady et al.

reported atrial branch involvement is an independent predictor of new-onset AF observed after myocardial infarction [5]. Atrial ischemia creates arrhythmogenic substrates in animal models of atrial arrhythmia. Using canine models, Nishida et al. observed ectopic atrial activity and unstable multiple reentry circuits leading to AF in the ischemic border zone of infarcted atria undergoing atrial branch occlusion [6]. In humans, the sinus node artery as well as the right atrial branch originate from the RCA. ECG monitoring in this case demonstrated sinus pause with a maximum duration of 3 s and subsequent atrial tachycardia after the termination of paroxysmal AF (Fig. 2(B)), which may reflect right coronary ischemia. Südhoff et al. demonstrated vasoconstriction of brachial artery after administration of 5-FU and ameliorating effect of nitroglycerin [7]. Arterial vasoconstriction induced by 5-FU administration may have aggravated ischemia leading to AF, which was successfully controlled by antianginal agents.



**Fig. 3.** (A) Right coronary angiogram of control shot showed 50% stenosis in segment 2 (arrow). (B) Provocation test of coronary vasospasm was performed using 50 µg acetylcholine. Moderate stenotic lesion of the segment 2 was aggravated due to severe (90%) stenosis (arrow), and atrial branch showed 90% stenosis at the proximal portion (arrow). These are flip horizontal because of the visceral inversion.

## Conclusion

The present case demonstrated coronary vasospasm induced by a provocation test using ACh, during the period of chemotherapy including 5-FU, and syncope due to rapid AF that was resistant to antiarrhythmic agents, but sensitive to antianginal agents. These findings indicate that 5-FU induced potent endothelial injury which caused vasospasm, and that atrial ischemia predisposes AF.

## Funding sources

We have no funding sources.

## Conflict of interest

We declare no conflict of interest.

## References

- [1] Kosmas C, Kallistratos MS, Kopterides P, Syrios J, Skopelitis H, Mylonakis N, et al. Cardiotoxicity of fluoropyrimidines in different schedules of administration: a prospective study. *J Cancer Res Clin Oncol* 2008;134:75–82.
- [2] Zamorano JL, Lancellotti P, Rodriguez Muñoz D, Aboyans V, Asteggiano R, Galderisi M, et al. 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines. *Eur Heart J* 2016;37:2768–801.
- [3] Farmakis D, Parisis J, Filippatos G. Insights into onco-cardiology: atrial fibrillation in cancer. *J Am Coll Cardiol* 2014;63:945–53.
- [4] Michniewicz E, Młodawska E, Lopatowska P, Tomaszuk-Kazberuk A, Malyszko J. Patients with atrial fibrillation and coronary artery disease – double trouble. *Adv Med Sci* 2018;63:30–5.
- [5] Alasady M, Abhayaratna W, Leong DP, Lim HS, Abed HS, Brooks AG, et al. Coronary artery disease affecting the atrial branches is an independent determinant of atrial fibrillation after myocardial infarction. *Heart Rhythm* 2011;8:955–60.
- [6] Nishida K, Qi XY, Wakili R, Comtois P, Chartier D, Harada M, et al. Mechanisms of atrial tachyarrhythmias associated with coronary artery occlusion in a chronic canine model. *Circulation* 2011;123:137–46.
- [7] Südhoff T, Enderle MD, Pahlke M, Petz C, Teschendorf C, Graeven U, et al. 5-Fluorouracil induces arterial vasoconstrictions. *Ann Oncol* 2004;15:661–4.