International Journal of Surgery Case Reports 92 (2022) 106836

Contents lists available at ScienceDirect

International Journal of Surgery Case Reports

journal homepage: www.elsevier.com/locate/ijscr

Case report

# Asymptomatic pulmonary thromboembolism diagnosed based on prolonged fever after gastric cancer surgery: A case report with literature review

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ARTICLE INFO

*Keywords:*
Deep vein thrombosis
Enoxaparin
Fever
Gastric cancer
Pulmonary embolism
Venous thromboembolis

ABSTRACT

*Introduction:* Venous thromboembolism (VTE) is a serious postoperative complication with potentially fatal outcome. However, asymptomatic VTE is difficult to diagnose and is often discovered by chance. We report a case of suspected VTE diagnosed based on prolonged fever after surgery and discuss the literature.

*Presentation of case:* A 48-year-old man was referred to us with a diagnosis of gastric cancer. Upper gastrointestinal endoscopy revealed a neoplastic lesion from the anterior wall of the mid-gastric mass to the upper part of the gastric body, and biopsy revealed adenocarcinoma. Contrast-enhanced computed tomography (CT) showed no obvious distant metastasis. The preoperative diagnosis was gastric cancer, cT4aN1M0 cStage III, and radical surgery was performed. During surgery, an intermittent pneumatic compression pump was used. Subcutaneous injection of enoxaparin was started postoperatively. A high fever continued on postoperative day 4, and high D-dimer level of 14.3 μg/mL was found. Contrast-enhanced CT scanning showed thrombus in the left upper lobe pulmonary artery A4/5. Lower extremity venous ultrasonography revealed a thrombus in the right soleal vein, and apixaban 20 mg/day was started that day. Thereafter, fever resolved quickly, and the D-dimer level gradually decreased. The patient was discharged from hospital on day 21 having made good progress.

*Discussion:* It sould be rememberd that there are VTE found in persistent fever after gastric cancer surgery. The main complaint was simply fever, and the fever disappeared with anticoagulant.

*Conclusion:* This cases suggests the importance of perioperative measures against VTE. Peri operative treatment with apixaban was safe and effective.

## 1. Introduction

As the consequences of venous thromboembolism (VTE) are sometimes unfortunate, it is important to prevent its development. Particularly, the presence of cancer can increase the risk of developing VTE by 4 to 7 times [1,2]. In 2006, a prospective epidemiological study conducted in Japan on the incidence of VTE after abdominal laparotomy reported that 24.7% (37/150) of patients with malignant tumors who underwent laparotomy of 45 min or longer developed postoperative VTE [3]. Therefore, along with elastic stockings and intermittent pneumatic compression, combined pharmacological prophylaxis with warfarin potassium, unfractionated heparin, low molecular weight heparin (LMWH), and factor Xa activity inhibitors may be useful. However, asymptomatic VTE is difficult to diagnose and is often diagnosed incidentally by imaging studies associated with other complications. At our institution, preoperative D-dimer measurement is performed in all patients undergoing abdominal surgery, and postoperative administration of enoxaparin is recommended. In this article, we report a patient in whom VTE was suspected and diagnosed based on high D-dimer level and prolonged fever after surgery, and discuss some of the literature.

## 2. Case report

The patient was a 48-year-old man with no chief complaint. He underwent upper gastrointestinal endoscopy that revealed a lesion suspected to be malignancy in the upper part of the stomach. The biopsy diagnosis was gastric cancer, sig > por2, and he was referred to our hospital for further investigation and treatment.

On initial examination, he was 169 cm tall, weighed 74 kg, and his body mass index was 25.9 kg/m$^2$. His abdomen was flat and soft with no

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https://doi.org/10.1016/j.ijscr.2022.106836
Received 3 December 2021; Received in revised form 3 February 2022; Accepted 10 February 2022
Available online 14 February 2022
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tenderness or spontaneous pain, and his lower limbs were neither red nor swollen and without tenderness or spontaneous pain. He had never undergone surgery.

Blood tests at the time of initial examination revealed CEA 0.8 ng/mL, CA-19 4.7 U/mL, CA125 10.8 U/mL, D-dimer <0.5 μg/mL, APTT 22.2 s, PT >120%, PT-INR 0.85, and no other findings of note.

Upper gastrointestinal endoscopy revealed a 40-mm Borrmann type 4 gastric carcinoma extending from the anterior wall of the mid-gastric curvature to the upper part of the gastric body, and biopsy revealed adenocarcinoma (sig > por2) (Fig. 1a). Upper gastrointestinal radiography revealed wall irregularity in the upper gastric bends. Contrast-enhanced computed tomography (CT) revealed wall thickening and sclerosis with contrast enhancement in the upper part of the gastric body, and enlarged lymph nodes with a short diameter of 11 mm. No other obvious distant metastasis was observed (Fig. 1b).

The preoperative diagnosis was gastric cancer, cT4aN1M0 cStage III (UICC TNM 8th edition), and total gastrectomy via open laparotomy due to advanced case, splenectomy, D2 lymph node dissection, and Roux-en-Y reconstruction were performed. The operation time was 296 min, and blood loss was 520 mL (Fig. 1c, d). An intermittent pneumatic compression pump was used during perioperative period, besides compression stockings were used until he was weaned from bed.

Postoperatively, the epidural catheter for pain control was removed on postoperative day (POD) 3, and subcutaneous injection of enoxaparin 2000 IU twice/day was started on POD 4. He had nighttime intermittent fever of over 38.5 °C since POD 2, but the fever was still present on POD 4, so blood testing was performed on POD 5. Laboratory findings revealed WBC 7.22 × $10^3$ μL, C-reactive protein 5.79 mg/dL, and the D-dimer was 14.3 μg/mL. Therefore, a contrast-enhanced CT scan was performed that showed a thrombus in the left upper lobe pulmonary artery A4/5 (Fig. 2b). It cannot be confirmed before surgery (Fig. 2a). In addition, it was confirmed that there was no pneumonia or urinary tract infection at the beginning of fever.

Blood gas analysis showed a $pO_2$ of 95 mmHg, $pCO_2$ of 37 mmHg, and $AaDO_2$ of 10.75. His anti-cardiolipin β2GP antibody, lupus anticoagulant, protein C/S activity, and antigen levels were all normal. Ultrasonography of the lower extremities revealed a thrombus in the central branch of the right soleal vein (Fig. 3). Cardiac ultrasonography revealed no obvious thrombus and no evidence of pulmonary hypertension.

Apixaban 20 mg/day was started on the same day, and the dosage was reduced to 10 mg/day after one week. After the start of oral administration of apixaban, fever was quickly relieved without any other drugs like antibiotics. D-dimer had decreased to 10.8 μg/mL 3 days later, 8.0 μg/mL 7 days later, and 4.1 μg/mL 14 days later. Contrast-enhanced CT scan was performed again on day 17 after the start of medication, and the thrombus in the left upper lobe pulmonary artery A4/5 had disappeared (Fig. 4). He was discharged from the hospital on

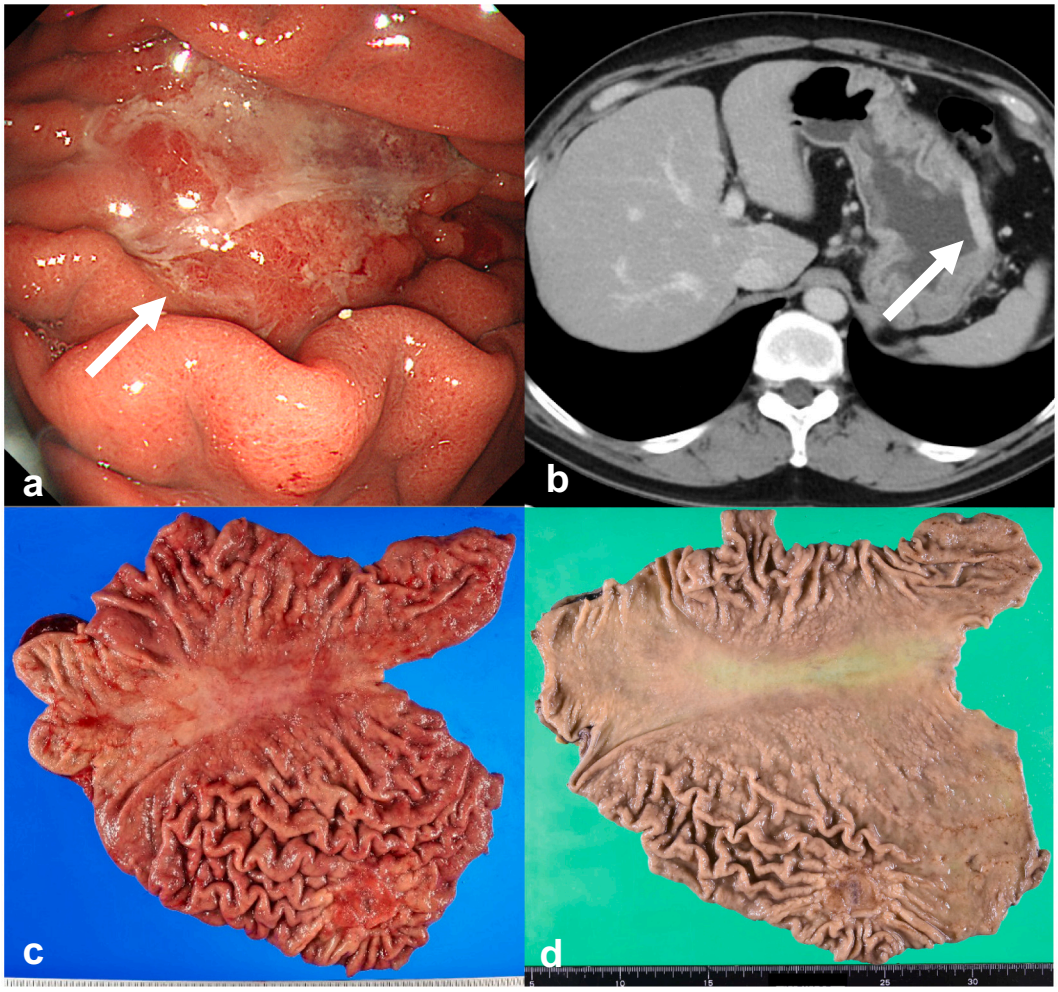


**Fig. 1.** Surgery, computed tomography (CT), and pathology images. a) The white arrow indicates a 40-mm Borrmann type 4 gastric carcinoma extending from the anterior wall of the mid-gastric curvature to the upper part of the gastric body. b) The white arrow indicates wall thickening and sclerosis with contrast enhancement in the upper part of the gastric body. c) The procedure consisted of open total gastrectomy, splenectomy, D2 lymph node dissection, and Roux-en-Y reconstruction. The operation time was 296 min, and blood loss was 520 mL. d) The pathological diagnosis of the gastric cancer was T4aN3bM0 Stage IIIc (UICC TNM 8th edition).

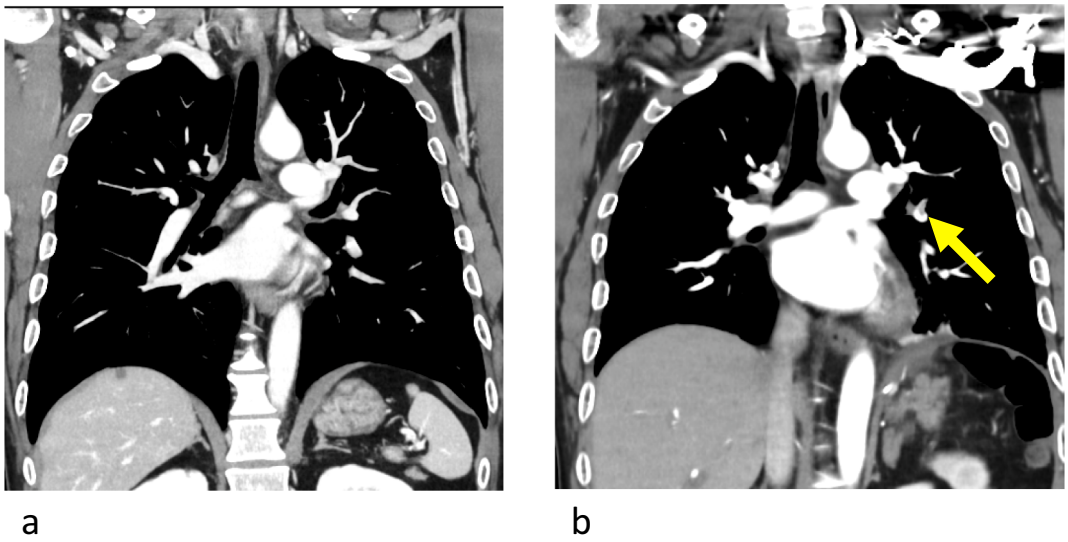


**Fig. 2.** Pre- and postoperative CT images. a) The preoperative coronal slice of contrast-enhanced CT showed no obvious thrombus in the pulmonary artery. b) Postoperative contrast-enhanced CT showed a thrombus in the pulmonary artery A4/5, as indicated by the yellow arrow. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

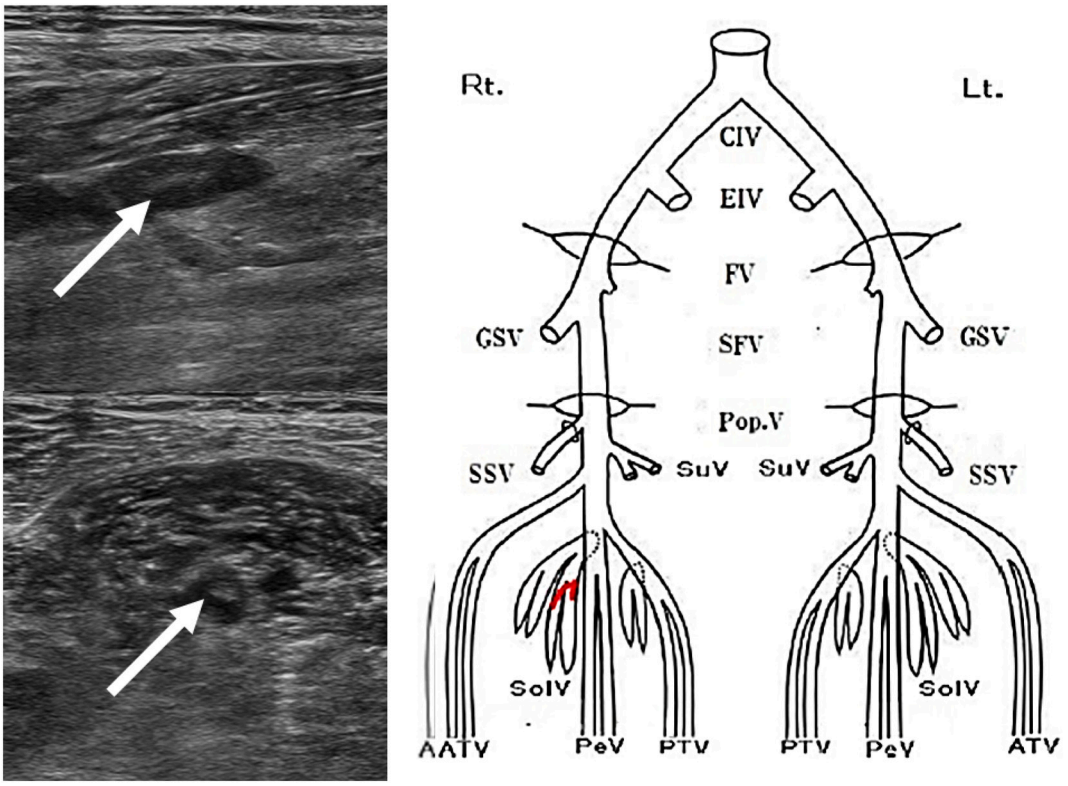


**Fig. 3.** Ultrasonography of the lower extremities revealed a thrombus in the central branch of the right soleal vein.

POD 21 having made good progress.

A lower extremity venous ultrasonography performed on day 8 after discharge showed reduction of the thrombus in the right soleal vein. Our treatment plan is to administer apixaban 10 mg/day during adjuvant treatment for 12 months and follow up with imaging every 3 months.

## 3. Discussion

VTEs, including pulmonary embolism (PE) and deep vein thrombosis, are an important cause of morbidity and mortality in cancer patients and are the second leading cause of death in these patients [4]. In patients with carcinoma, cancer itself is a risk factor for VTE, and there are often other risk factors for which various studies have been conducted.

In Italy, a prospective study of the incidence of VTE in 2373 patients undergoing cancer surgery found that age (>60 years), previous VTE, anesthesia time (>2 h), cancer stage, and length of bed rest (>4 days) were risk factors for VTE, and when these risk factors were present, the

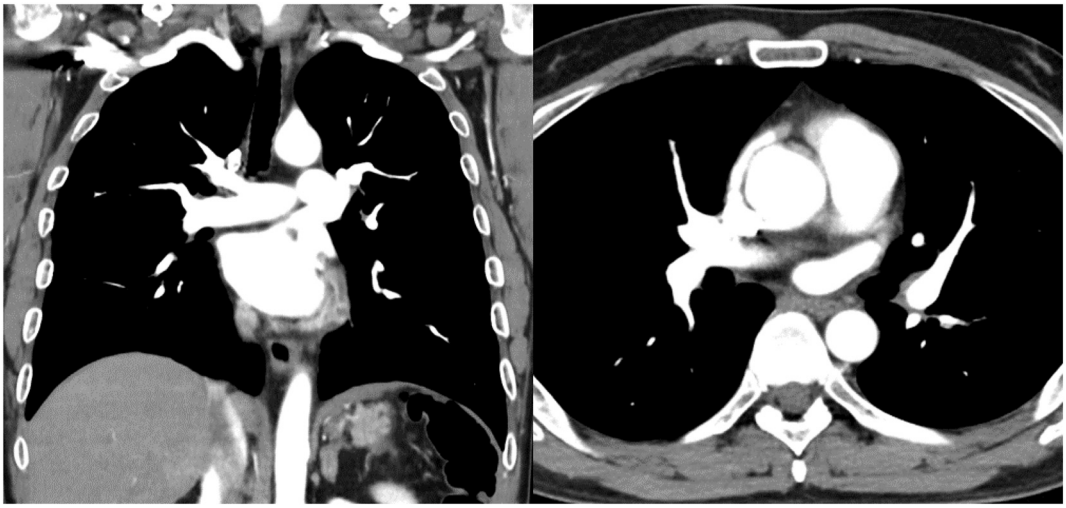

**Fig. 4.** Contrast-enhanced CT images obtained on day 17 after the start of apixaban show disappearance of the thrombus.

odds ratio of developing VTE was 2.6 to 6.0 [5]. This type of cancer-associated thrombosis is becoming increasingly recognized as important for both physicians and oncologists treating VTE. Therefore, prevention of VTE is an important issue for oncologists, as is early detection of even the slightest sign of VTE.

In general, symptoms of PE are not sensitive or specific, meaning that the presence or absence of a single symptom or clinical manifestation is not sufficient to rule out PE. Chest pain, with or without dyspnea, raises the suspicion of PE in 65% of patients. Dyspnea, usually acute but sometimes slowly progressive and not accompanied by an obvious alternative cause, suggests PE in 20% of patients [6]. Most studies on the diagnosis of PE involve patients who present with dyspnea, sudden chest pain, or worsening condition with no apparent cause [7,8], whereas only 5% of patients with suspected PE were actually diagnosed as having PE [9]. This raises the question of when and in whom the clinician should truly suspect PE. Searching for PE in every patient with dyspnea or chest pain is likely to lead to increased costs and testing without improved health outcomes. Therefore, when we considered potential good indicators, D-dimer came to mind.

D-dimer in plasma is a degradation product of cross-linked fibrin and is widely used in the diagnosis of VTE. D-dimer is elevated in the presence of acute thrombosis, so a normal D-dimer level is unlikely to indicate acute VTE. There are a number of D-dimer reagents with different characteristics, and as they are primarily used as exclusion tests, the sensitivity of the test used in a patient is important. Quantitative ELISAs or ELISA-derived tests are useful because they have the highest sensitivity (>95%) and specificity of about 40% [10,11]. There is a recommendation from 'ASCO Clinical Practice Guideline Update 2020'. From that recommendation, we should calculate D-dimer preoperatively for detecting thrombosis [12]. However, D-dimer has low specificity for VTE and is generally elevated after surgery. Tanaka et al. reported that D-dimer increases to about 20 μg/mL after gastric cancer surgery [13]. Therefore, D-dimer is not useful for confirming PE, and it should be measured only when PE is clinically suspected.

As the mechanism of venous thrombosis, intravenous thrombus is caused by venous stasis, blood hypercoagulability, and damage to the vascular endothelium. Innate immune cells, neutrophils and monocytes, bind to the activated vascular endothelium and together with platelets initiate thrombus formation and fibrin deposition. Neutrophils and macrophages that grow and infiltrate the clot due to the deposition of more fibrin and the accumulation of red blood cells and immune cells will regulate the production of plasmin and matrix metalloproteinases, setting the stage for the fibrinolytic therapy and collagen remodeling needed to resolve the clot. In the early stages of thrombolysis, fibrinolysis, which produces fibrin degradation products, occurs at a high rate, collagen fibrils begin to appear in the clot, and clot-associated immune cells induce the production of inflammatory cytokines and various proteases [14]. The result is thought to be a localized burning sensation and sometimes feverish symptoms in the patient. In fact, approximately 14% to 68% of patients with PE have fever [15,16], and the RIETE (Computerized Registry of Patients with Venous Thromboembolism) registry has shown that the mortality rate of patients with deep vein thrombosis with fever in the first 30 days is up to twice as high as that in patients without fever [17].

In the present case, we measured the D-dimer in view of the prolonged fever and the possibility of VTE. As a result, contrast-enhanced CT scanning was performed that led to a diagnosis of PE that was successfully treated with apixaban.

In general, for the treatment of VTE in cancer patients, national guidelines recommend that LMWH be administered for at least 3 to 6 months, followed by vitamin K antagonists [18–22]. In addition, the CLOT trial published in 2003 reported that dalteparin reduced the risk of recurrent VTE by a statistically significant 52% after 6 months of treatment compared to the vitamin K antagonists (conventional therapy), with a similar incidence of major bleeding and death [23]. Unfortunately, despite guideline recommendations, treatment with LMWH for cancer-related VTE has several limitations, including the inconvenience of subcutaneous injections for at least 6 months and the risk of heparin-induced thrombocytopenia. Furthermore, treatment with LMWH is associated with the same risk of major bleeding as conventional therapy.

Various analyses of LMWH and direct oral anticoagulants have been performed, and based on these analyses, guidance from the International Society for Thrombosis and Haemostasis standardization committee states that rivaroxaban and edoxaban can be considered, but an increase in upper gastrointestinal bleeding has been reported. In light of this, the Caravaggio trial, a multinational randomized non-inferiority trial to evaluate whether oral apixaban, one of the direct oral anticoagulants, is non-inferior to subcutaneous dalteparin in the treatment of newly diagnosed VTE in cancer patients, was conducted between 2017 and 2019 in 1115 patients. The results showed non-inferiority in recurrent VTE, with 32 (5.6%) patients in the apixaban group and 46 (7.9%) in the dalteparin group (HR 0.63, 95% CI 0.37–1.07, $p < 0.001$). In addition, bleeding was similar in the apixaban group (22 patients, 3.8%) and dalteparin group (23 patients, 4%) (HR 0.82, 95% CI 0.40–1.69, $p = 0.6$) [24]. In the present patient, apixaban was administered and appeared to be safe to use without obvious signs of postoperative bleeding. Based on these results, the 2nd update of CHEST guideline 2021 recommends oral

Xa inhibitors over LMWH at the beginning and during treatment for cancer patients with VTE [25]. Additionally, as mentioned earlier, rivaroxaban and edoxaban are associated with a higher risk of gastrointestinal bleeding than LMWH in patients with CAT and gastrointestinal malignancies, whereas apixaban is not associated with such a risk, suggesting that apixaban or LMWH may be a treatment option for patients with gastrointestinal malignancies. In case of high risk of bleeding, including preoperative malnutrition and obesity, LMWH may be safer because of the existence of antagonists.

Thus, we need to keep in mind that there are VTE found in patients who have persistent fever after gastric cancer surgery. In this case, the main complaint was simply fever, and the fever disappeared with anticoagulant.

## 4. Conclusion

We reported a case of VTE developing after gastric cancer surgery that caused a persistent fever. This case suggests the importance of perioperative measures against VTE. Perioperative treatment with apixaban was safe and effective.

We provide this article according to the SCARE 2020 Guidelines [26].

## Abbreviations

| | |
|---|---|
| CT | computed tomography |
| LMWH | low molecular weight heparin |
| PE | pulmonary embolism |
| POD | postoperative day |
| VTE | venous thromboembolism |

## Ethics approval and informed consent

Informed consent for participation in the study or use of his tissue was obtained from the patient.

## Consent for publication

Written informed consent was obtained from patient for publication of this case report and accompanying images.

## Data availability

All data generated or analyzed during this study are included in this published article.

## Sources of funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## CRediT authorship contribution statement

ME and YT contributed to study conception and design. SO contributed to the acquisition of data. YS contributed to the interpretation of data and drafted the manuscript. KY critically revised the manuscript.

## Research registration

N/A

## Guarantor

The guarantor is Yoshihiro Tanaka.

## Provenance and peer review

Not commissioned, externally peer-reviewed.

## Declaration of competing interest

Dr. Yoshida reports receipt of grants, personal fees and non-financial support from EA Pharma Co., Ltd., Sanofi, Yakult Honsha Co., Ltd., Chugai Pharmaceutical Co., Ltd., Taiho Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., Eli Lilly Japan K.K., Daiichi Sankyo Co., Ltd., Ono Pharmaceutical Co., Ltd., Merck Serono Co., Ltd., and Novartis Pharma K.K. and grants from Kyowa Hakko Kirin Co., Ltd. outside of the submitted work. Dr. Tanaka reports receipt of grants from Daiichi Sankyo Co., Ltd. outside of the submitted work. All of the other authors declare that they have no conflicts of interest.

## Acknowledgments

We would like to thank Rise Japan for English language editing.

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