

## Case Report

---

# Deep Vein Thrombosis as an Initial Symptom of Malignant Tumor: A Case Report of Angiosarcoma in the Iliac Vein

Takahiro Matsui Satoshi Nojima Eiichi Morii

Department of Pathology, Osaka University Graduate School of Medicine, Osaka, Japan

### Keywords

Deep vein thrombosis · Angiosarcoma · Iliac vein · Thromboembolism · Initial onset

### Abstract

Although deep vein thrombosis, as well as subsequent pulmonary embolism, is one of the major and fatal complications in cases of malignant neoplasm, it most often occurs after the diagnosis or treatment of the tumor. On the other hand, malignant tumors that develop with deep vein thrombosis as a specific initial symptom are extremely rare. Here, we report a case of angiosarcoma of the iliac vein, whose initial symptom was dyspnea due to pulmonary embolism. Although angiosarcoma arising directly from major blood vessels is rare, literature reviews, as well as our case, indicate that thromboembolism is an important initial symptom related to angiosarcoma from thick blood vessels and may contribute to immediate diagnosis and therapeutic intervention.

© 2021 The Author(s).  
Published by S. Karger AG, Basel

### Introduction

Each year, over 500,000 individuals in the USA and the European Union die from venous thromboembolism (VTE) [1]. Deep vein thrombosis (DVT) is regarded as one of the most dangerous diseases that cause lethal pulmonary embolism (PE). Nowadays, most clinicians are aware of the fear of this disease as well as risk factors such as immobilization, surgery, major trauma, obesity, and pregnancy. Cancer is another important factor of thrombosis, and

---

Correspondence to:  
Takahiro Matsui, matsuit@molpath.med.osaka-u.ac.jp

previous studies have indicated that VTE is the second leading cause of death in patients with cancer [2]. Patients with advanced-stage cancer appear to be at a greater risk of developing VTE [3], and many therapeutic interventions such as chemotherapy, supportive therapy, and surgery also carry their own increased risk [4]. However, there have been few reported cases of cancer that suffered VTE as an initial symptom of malignancy. In this article, we describe a case of angiosarcoma of the soft tissue in the iliac vein diagnosed by only autopsy, whose initial onset was DVT, as well as literature reviews.

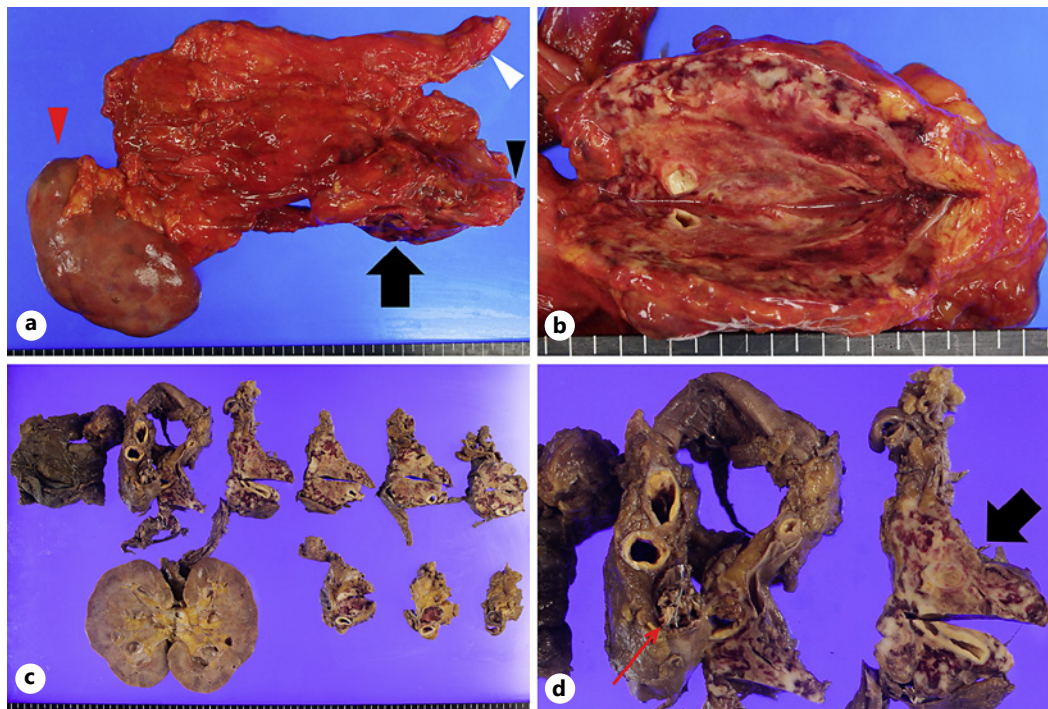
### Case Report

A 72-year-old Japanese man presented to the emergency department with dyspnea following swelling of the right lower limb. Physical examination was unremarkable, except for mild hypoxemia (SpO<sub>2</sub> 95%) and lower limb pitting edema. Laboratory findings showed elevated D-dimer levels (43.5 µg/mL). Enhanced CT images showed massive PE (Fig. 1a) as well as several nodules in the lungs. Moreover, an irregularly shaped tumor was also present from the retroperitoneum near the right ureter to the right pelvis, as well as DVT in the right iliac vein (Fig. 1b, c). He was transported to a nearby cardiovascular hospital and received anticoagulation therapy as well as inferior vena cava filter indwelling. From image inspection, retroperitoneal tumors, such as ureteral cancer, were suspected, although urine cytology did not show obvious atypical cells. A laparotomy biopsy of the tumor was scheduled. However, 2 months after onset, a re-examination of chest CT due to exacerbation of breathing difficulties showed a rapid deterioration of nodular lesions in the lungs. Although he was admitted to our hospital, respiratory failure combined with tumor metastasis, pneumonia, and alveolar hemorrhage made it difficult to perform a surgical biopsy. He died 8 days after admission due to progression of respiratory failure before the biopsy procedure.

A general autopsy revealed a mass lesion in the retroperitoneal right caudal side, in contact with the right anterior part of the lumbar spine. The tumor macroscopically involved the right common iliac artery and vein, as well as the right ureter (Fig. 2a). However, there was no hydronephrosis in the right kidney, and no irregular lesions were observed in the ureteral luminal surface, indicating the absence of ureteral cancer. The tumor had a diameter of approximately 7 cm, and the reddish area due to bleeding was observed macroscopically on the dividing surface (Fig. 2b). Macroscopic observation of the transverse plane revealed that the tumor was continuous with the region of the right iliac artery and vein (Fig. 2c, d). Histological analysis using Elastica van Gieson staining showed that collagen and elastic fibers around the right external iliac vein were degenerated and disrupted due to the proliferation of



**Fig. 1.** Computed tomography images at the first visit. **a** Enhanced chest CT scan showed massive pulmonary embolism (red arrowhead). **b, c** Abdominal CT scan showing right retroperitoneal tumor (red arrow in **b**). Right iliac vein dilated with a grayish thrombus inside (cyan arrowhead in **c**).



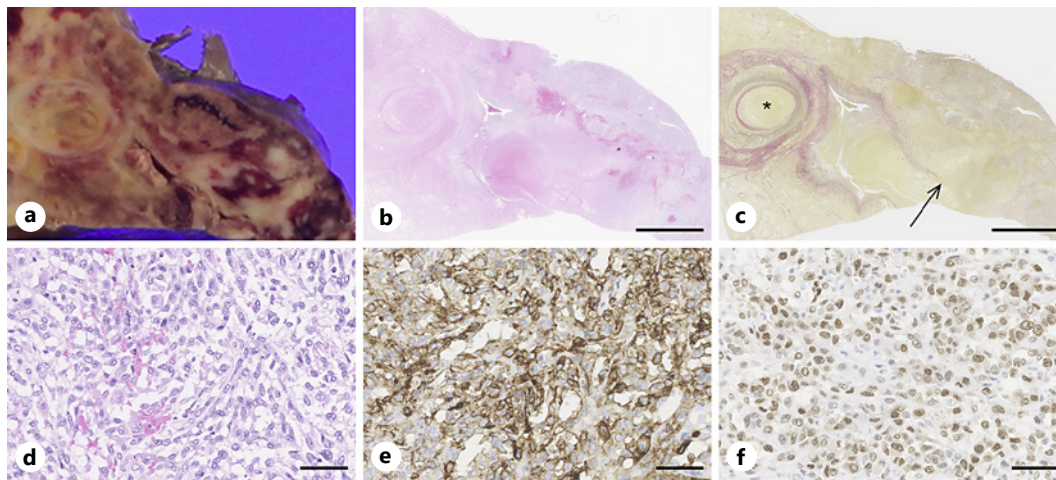
**Fig. 2.** Gross findings of the tissue resected by autopsy. **a** Tumor and surrounding tissue resected by autopsy. Tumor (black arrow) was around right iliac vessels (black arrowhead), while separated from left iliac vessels (white arrowhead) and left kidney (red arrowhead). **b** Cut surface of the tumor. Reddish area due to bleeding was observed macroscopically. **c** Transverse plane of the tumor after fixation. **d** Enlarged view of the transverse plane. The tumor (black arrow) was located on the caudal side of the IVC filter (red arrow).

spindle-shaped atypical cells (Fig. 3a–d). These atypical cells were observed in both the intraluminal and extraluminal areas, which caused vascular occlusion. Immunohistochemical staining showed that the atypical cells were positive for CD31 and Ets-related gene (ERG), which are endothelial cell markers (Fig. 3e, f). Based on these findings, we diagnosed angiosarcoma originating from the right external iliac vein as the cause of DVT and subsequent PE observed at the time of initial onset. Many tumor metastases with hemorrhage were observed in both lungs, as well as left pleural metastasis and bloody pleural effusion. These metastatic lesions and subsequent alveolar hemorrhages were considered to be the cause of fatal respiratory failure.

## Discussion

Angiosarcoma is a group of rare mesenchymal tumors transformed from vascular endothelial cells and comprises approximately 2% of soft tissue sarcomas and 5.4% of cutaneous soft tissue sarcomas [5]. Most angiosarcomas arise spontaneously without identifiable risks, but radiation exposure is an independent risk factor for secondary angiosarcoma, and radiation-associated sarcoma typically occurs 5–10 years after radiation exposure [6]. For clinical symptoms, deeper soft tissue and visceral lesions present as an expanding mass associated with pain or discomfort [5]. Angiosarcomas principally show hematogenous metastases, and the lungs are the most common site for metastases. Other common sites include the liver, bone, and lymph nodes.





**Fig. 3.** Histology of angiosarcoma in the right external iliac vein. **a** Magnified image of the tumor. Hematoxylin and eosin staining (**b**) and Elastica van Gieson staining (**c**) of (**a**). Although the vessel wall of the right internal iliac artery (asterisk) was intact, collagen fiber (red fiber in **c**) and elastic fiber (black fiber in **c**) around the right external iliac vein were degenerated or disrupted (arrow in **c**), and spindle-shaped atypical cells were observed on both intraluminal and extraluminal area. Scale bar, 5 mm. **d–f** Histological images of tumor cells. Tumor cells were spindle-shaped with irregular nuclei (**d**). The tumor cells were positive for CD31 (**e**) and ERG (**f**) by immunohistochemical analysis. Scale bar, 50  $\mu$ m.

Although angiosarcoma can arise in any soft-tissue structure or viscera, tumors arising directly from the heart or major blood vessels are rare [5], as well as in vessels in the iliac region [7–10]. Interestingly, many cases of angiosarcoma from the iliac vessels exhibit thromboembolism as an initial symptom. Gagner et al. [8] reported a case of epithelioid angiosarcoma arising from the external iliac vein, whose initial symptom was persistent leg swelling. In addition, Greenwald et al. [7] reported a case of angiosarcoma arising from the external iliac vein, whose initial symptom was chronic edema of the right lower extremity. Importantly, in both cases above, there were no intraluminal or extraluminal masses at the time of onset, even though the existence of vascular stenosis and tumors became apparent a few years after DVT when histological diagnosis became possible for the first time. These facts indicate that DVT is one of the most important symptoms as well as an important clue for early diagnosis of angiosarcoma in iliac vessels, although it is rare and difficult to diagnose.

The primary site of the cancer is frequently identified as a risk factor for thromboembolism, and patients with cancers of the pancreas, uterus, lung, stomach, kidney, and primary brain tumors are associated with the highest rates of VTE [4]. However, VTE is extremely rare as the first symptom of these cancers. Apart from the cancer-bearing condition itself, the biggest trigger related to VTE is a series of therapeutic interventions associated with cancer after diagnosis. The prothrombotic state of malignancy is often provoked by cancer treatments, including surgery, although the risk of thrombotic complications has been reduced over the years due to prophylactic interventions [3]. Various medications, including chemotherapy and angiogenesis inhibitors, are also important risk factors for VTE in cancer patients, and chemotherapy is associated with a 2- to 6-fold increased risk of VTE compared to the general population [4]. Moreover, central venous catheters, which are vital for cancer therapy, can result in the formation of catheter-related thrombosis [3]. Considering the above, VTE as an initial symptom of malignancy may help diagnosing some neoplasms. There are few reports of malignant tumors that cause DVT or PE as an initial symptom, except in cases of large

lesions of clear cell carcinoma of the ovary with metastases [11] or the case of a testicular tumor with inferior vena cava infiltration [12]. Angiosarcoma, unlike those tumors, has no other specific symptoms and is difficult to confirm with image inspection. Moreover, the vascular nature of angiosarcoma makes it prone to hemorrhage following needle biopsy [13]. Because of the risk of severe bleeding, percutaneous biopsy with a fine needle is not always recommended [14]. A previous report has indicated that surgical biopsy or laparoscopy will be more accurate and safer [15]. Considering the difficulty of histological diagnosis, DVT and related symptoms are important because they might contribute to the early diagnosis of angiosarcoma.

Treatment for angiosarcoma is challenging in many cases, and the prognosis is generally poor [5]. However, there is a case in the iliac region that shows long-term survival by early diagnosis and combined therapy of surgical resection followed by radiotherapy [10]. Moreover, several recent reports have indicated the usefulness of novel therapeutic options, including neoadjuvant chemotherapy and immunotherapy [16]. Recent studies have indicated the importance of detecting malignant neoplasms as early as possible in various cancer types [17]. We hope that this intractable disease can be overcome by accumulating findings that lead to accurate early diagnosis and cure.

### Statement of Ethics

Written consent for publication was obtained from the patient's next of kin. The study is exempt from ethics committee approval since this report is not about clinical research and is deidentified.

### Conflict of Interest Statement

The authors state that they have no conflicts of interest.

### Funding Sources

This work was supported in part by Grant-in-Aid for Early-Career Scientists from the Japan Society for the Promotion of Science (JP20K16192 to T.M.) and the grant from the Takeda Science Foundation (to T.M.).

### Author Contributions

T.M. participated in the concept of this case report, interpreted the histopathological slides and immunochemical studies, and wrote the manuscript. S.N. and E.M. were responsible for the concept of the case report and critically revised the manuscript for intellectual content. All authors have given approval for the final version to be published.

### Data Availability Statement

All data analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

## References

- 1 Mahmoodi BK, Cushman M, Anne Næss I, Allison MA, Bos WJ, Brækkan SK, et al. Association of traditional cardiovascular risk factors with venous thromboembolism: an individual participant data meta-analysis of Prospective Studies. *Circulation*. 2017 Jan 3;135(1):7–16.
- 2 Noble S, Pasi J. Epidemiology and pathophysiology of cancer-associated thrombosis. *Br J Cancer*. 2010 Apr 13;102 Suppl 1(Suppl 1):S2–9.
- 3 Abdol Razak NB, Jones G, Bhandari M, Berndt MC, Metharom P. Cancer-associated thrombosis: an overview of mechanisms, risk factors, and treatment. *Cancers*. 2018 Oct 11;10(10):380.
- 4 Khorana AA, Connolly GC. Assessing risk of venous thromboembolism in the patient with cancer. *J Clin Oncol*. 2009 Oct 10;27(29):4839–47.
- 5 Young RJ, Brown NJ, Reed MW, Hughes D, Woll PJ. Angiosarcoma. *Lancet Oncol*. 2010 Oct;11(10):983–91.
- 6 Gladdy RA, Qin LX, Moraco N, Edgar MA, Antonescu CR, Alektiar KM, et al. Do radiation-associated soft tissue sarcomas have the same prognosis as sporadic soft tissue sarcomas? *J Clin Oncol*. 2010 Apr 20;28(12):2064–9.
- 7 Greenwald U, Newman E, Taneja S, Rockman C. Malignant epithelioid angiosarcoma of the external iliac vein presenting as venous thrombosis. *Ann Vasc Surg*. 2004 Jul;18(4):493–6.
- 8 Gagner JP, Yim JH, Yang GC. Fine-needle aspiration cytology of epithelioid angiosarcoma: a diagnostic dilemma. *Diagn Cytopathol*. 2005 Dec;33(6):429–33.
- 9 Sattout AH, Deolekar MV, Tait WF, Williams GT. Femoral artery angiosarcoma presenting with distal embolization: report of a case. *Surg Today*. 2008;38(6):541–4.
- 10 Ibis K, Usta U, Cosar R, Ibis C. Angiosarcoma of common iliac vein. *BMJ Case Rep*. 2015 Jan 16;2015:bcr2014206103.
- 11 Neseek Adam V, Bulić A, Jokić A, Osmančević N, Matolić M, Brozović G. The use of inferior vena cava filters before surgery in women with ovarian cancer with the initial symptom of deep venous thrombosis: case report and review of literature. *Acta Clin Croat*. 2017 Sep;56(3):566–70.
- 12 Song Z, Lv S, Qin L, Cao H, Wu H, Deng D. Syncope as the initial presentation of pulmonary embolism in a young adult with testicular tumor: a case report and literature review. *Medicine*. 2018 Dec;97(52):e13798.
- 13 Chaudhary P, Bhadana U, Singh RA, Ahuja A. Primary hepatic angiosarcoma. *Eur J Surg Oncol*. 2015 Sep;41(9):1137–43.
- 14 Kang TW, Lee MW, Choi D, An C, Kim MJ, Joo I, et al. Safety of percutaneous biopsy for hepatic angiosarcoma: results of a multicenter Korean survey. *J Vasc Interv Radiol*. 2016 Jun;27(6):846–51.
- 15 Zheng YW, Zhang XW, Zhang JL, Hui ZZ, Du WJ, Li RM, et al. Primary hepatic angiosarcoma and potential treatment options. *J Gastroenterol Hepatol*. 2014 May;29(5):906–11.
- 16 Chen TW, Burns J, Jones RL, Huang PH. Optimal clinical management and the molecular biology of angiosarcomas. *Cancers*. 2020 Nov 10;12(11):3321.
- 17 Matsui T, Tamoto R, Iwasa A, Mimura M, Taniguchi S, Hasegawa T, et al. Nonlinear optics with near-infrared excitation enable real-time quantitative diagnosis of human cervical cancers. *Cancer Res*. 2020 Sep 1;80(17):3745–54.