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

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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.

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
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 (SpO2 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**).
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.
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

![Fig. 3. Histology of angiosarcoma in the right external iliac vein.](image)
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.
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