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Original Article

Venous thromboembolism detected by FDG-PET/CT in cancer patients: a common, yet life-threatening observation

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Abstract: Cancer patients are at markedly increased risk for venous thromboembolism (VTE). Early detection of VTE may decrease morbidity and mortality in this population. We conducted this study to evaluate the ability of FDG-PET/CT to detect thrombosis in cancer patients. This retrospective study included 131 cancer patients with a history of deep vein thrombosis (DVT) or pulmonary embolism (PE) referred for 2-deoxy-2-[^{18}F]-fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT). All subjects underwent PET/CT imaging 60 minutes after FDG injection. Images were visually assessed for increased FDG uptake within the venous lumen. For positive cases, clinical follow-up and Doppler ultrasonography and/or contrast-enhanced CT scans were reviewed. FDG-PET/CT revealed abnormal uptake in the venous system of 26 (19.8%) patients. Eighteen (69.2%) had a history of DVT, and 13 (50%) had a history of PE. The most common site of thrombosis was the inferior vena cava (IVC) (n=14, 53.8%), followed by lower extremities veins (n=9, 34.6%), jugular veins (n=2, 7.7%), and superior vena cava (n=1, 3.8%). The presence of thrombi was confirmed by reviewing clinical follow-up in 6 (23.1%) patients. Among this group, thrombosis was detected in lower extremity veins (n=4, 15.8%), jugular veins (n=1, 3.8%), and IVC (n=1, 3.8%). Our study demonstrates that thrombi prior to their clinical manifestation can be detected by FDG-PET/CT in cancer patients. Moving forward, physicians must carefully consider the venous system when reporting FDG-PET/CT for cancer patients.

Keywords: Venous thromboembolism, cancer, positron-emission tomography, computed tomography, FDG

Introduction

Venous thromboembolism (VTE), which can manifest as either deep vein thrombosis (DVT) or pulmonary embolism (PE), represents a major source of morbidity and mortality in cancer patients. Malignancy is associated with a several-fold increased risk of developing thromboembolic complications [1, 2]. Post-mortem analysis of cancer patients has demonstrated an incidence of VTE as high as 50%, and the overall survival rate among these patients plummets from 90% to 20% after the diagnosis of VTE [3]. Many DVT progress to PE within 3 months [4]. Therefore, the early detection of VTE may have the potential to decrease the occurrence of adverse events in cancer patients.

Structural imaging techniques such as venography, Doppler ultrasonography, and contrast-enhanced computed tomography (CECT) are commonly used to diagnose VTE. However, these modalities typically can only detect VTE

in the late stages of the disease [5]. In contrast, molecular imaging via 2-deoxy-2-[^{18}F]-fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) may identify signs of thromboembolic disease at an earlier stage and with greater sensitivity and specificity across the body. FDG has previously been widely used in the detection of intravascular inflammatory lesions [6, 7]. On the cellular level, thrombus formation begins with the accumulation of inflammatory infiltrates, leading to focally increased FDG uptake; therefore, FDG-PET/CT may be feasible in the detection of venous thrombi [8, 9]. Recent studies have aimed to answer this question, with varying success [10-12].

Molecular imaging is widely used for staging, prognosis, radiation therapy planning, and treatment response assessment in cancer patients [13-17]. We postulate that routine scans of cancer patients may also demonstrate molecular evidence of VTE prior to its clinical manifestations. Therefore, we conducted this retrospective study to evaluate the ability of FDG-PET/CT to detect incidental venous thrombosis in individuals with cancer.

Materials and methods

Subject selection

We cross-referenced the list of individuals who underwent clinical FDG-PET/CT at the Hospital of the University of Pennsylvania from December 2012 to December 2014 with the Abramson Cancer Center database of patients diagnosed with cancer. Patient characteristics are detailed in **Table 1**. Inclusion criteria were as follows: a history of cancer, a history of DVT or PE, completed FDG-PET/CT with an available clinical report, and lab results available within 2 months from the PET/CT imaging date. Exclusion criteria included unavailable imaging or clinical data. After applying inclusion and exclusion criteria, we enrolled 131 subjects in our study. Our protocol study was approved by the institutional review board. It was conducted in compliance with the Health Insurance Portability and Accountability Act (HIPAA).

Image acquisition

Each patient underwent FDG-PET/CT acquisition, either from the top of the head to the toes (total-body) or from the base of the skull to the mid-thigh. All imaging was performed using hybrid PET/CT scanners (Siemens Biograph 64 mCT, Siemens Healthineers AG, Chicago, IL, USA, and Philips Gemini TF, Philips medical system) 60 ± 10 minutes after intravenous injection of 5 MBq/kg of FDG. Three acquisition protocols were used for Gemini TF, Biograph mCT, and Ingenuity TF: one for BMI under 30, another for BMI between 30 and 35, and the third BMI over 35; the CT settings were 50, 100, and 150 mAs, respectively, and all at 120 kVp. For the PET acquisitions, the time per bed was 1.5, 2, and 3 minutes, respectively.

All scans were acquired in the cranial-to-caudal direction. For total-body scans, after scanning the entire torso, the time-per-bed was halved across the patient's legs. The reconstruction protocol for the Gemini TF PET/CT scanner was BLOB-OS-TF, 3 iterations with 33 subsets, and for the Siemens Biograph PET/CT scanner was OP-OSEM with corrections for point-spread-function and time-of-flight, 2 iterations with 21 subsets, and Gaussian postfilter with full-width-at-half-maximum 3.0 mm. Model-based scatter corrections and delayed coincidence random correction were used for both. The pixel size for the Gemini TF PET scanner was 4.0 mm × 4.0 mm, while for the Siemens Biograph was 4.07 mm × 4.07 mm. The slices were contiguous for the Gemini TF with a 4 mm slice thickness. On the Siemens Biograph, they overlapped by 1 mm, with a slice thickness of 4 mm.

Image and statistical analysis

Every patient's FDG-PET/CT scan was examined for evidence of venous thrombosis. Scans were independently assessed by two physicians trained in nuclear medicine. The investigators assessed all axial, sagittal, and coronal slices to qualitatively identify abnormal venous FDG uptake. FDG-PET interpretation was blinded to clinical data. Each patient was recorded as either "positive" or "negative" based on the focal or linear FDG uptake within the venous lumen. For positive cases, the location of the lesions was recorded, and then Doppler ultrasonography and/or CECT radiology reports were reviewed to confirm the presence of the thrombosis. Additionally, clinical data were evaluated for the presence of VTE risk factors. Descriptive statistics were calculated and com-

Table 1. Characteristics of patients (n=26) with thrombosis identified on FDG-PET/CT

Age (years)	
Mean	61.9
Range	24-82
Gender	
Female	11 (42.3%)
Male	15 (57.7%)
Race	
White	16 (61.6%)
Black	5 (19.2%)
Asian	2 (7.7%)
Hispanic	1 (3.8%)
Unknown	2 (7.7%)
Patients status	
Deceased	19 (73.1%)
Alive	7 (26.9%)
BMI (kg/m^2)	
Mean	25.4
Range	18.6-43.5
BMI between 18.5-24.5	15 (57.7%)
BMI between 25-29.9	5 (19.2%)
BMI between 30-39.9	4 (15.4%)
BMI more than 40	1 (3.8%)
Unknown	1 (3.8%)
History of thromboembolic events	
DVT	18 (69.2%)
PE	13 (50.0%)
Thrombosis site	
IVC	14 (53.8%)
SVC	1 (3.8%)
Lower extremity vein	9 (34.6%)
Jugular vein	2 (7.7%)
Confirmation with other imaging modality	
Yes	6 (23.1%)
No	20 (76.9%)
Underlying malignancy	
Lung cancer	7 (26.9%)
Lymphoma	6 (23.1%)
Gastrointestinal cancers	3 (11.6%)
Gynecological cancer	3 (11.6%)
Breast cancer	1 (3.8%)
Bladder cancer	1 (3.8%)
Melanoma	1 (3.8%)
Thymoma	1 (3.8%)
Head and neck	1 (3.8%)
Unknown	2 (7.7%)
Histological subtype of the cancer	
Adenocarcinoma	9 (34.6%)
SCC	3 (11.5%)
Diffuse large B-cell lymphoma	3 (11.5%)
Hodgkin's disease	2 (7.7%)
Non-small cell lung cancer	2 (7.7%)
Unknown primary	1 (3.8%)
Others	6 (23.1%)
Stage of the malignancy	
Stage 1	1 (3.8%)
Stage 2	1 (3.8%)
Stage 3	6 (23.1%)
Stage 4	14 (53.8%)
Unknown	4 (15.4%)
Treatment of underlying malignancy	
Chemotherapy	12 (46.2%)
Radiotherapy	7 (26.9%)
Surgery	9 (34.6%)
Presence of metastasis	
At the time of diagnosis	21 (80.8%)
At the time of PET/CT scan	23 (88.5%)
Underlying condition	
Pulmonary disease	5 (19.2%)
Renal disease	9 (34.6%)
History of infection prior PET/CT	11 (42.3%)
Presence of indwelling catheter	17 (65.4%)
Anemia	20 (76.9%)
Leukocytosis	1 (3.8%)
Leukopenia	2 (7.7%)
Thrombocytosis	4 (15.4%)
Thrombocytopenia	2 (7.7%)
Complete blood count (mean, mg/dl)	
WBC	8.2
Hgb	10.9
Platelet	313.6

BMI = body mass index, DVT = deep vein thrombosis, PE = pulmonary embolism, IVC = inferior vena cava, SVC = superior vena cava, SCC = squamous cell carcinoma, WBC = white blood cells, Hgb = hemoglobin.

piled using Microsoft Excel Version 16.29.1 (Microsoft, Redmond, WA).

Results

We retrospectively evaluated 131 cancer patients who underwent at least one FDG-PET/CT imaging for their malignancy who were diagnosed with either DVT or PE at any point. Our visual assessment revealed abnormal venous FDG uptake within 26 (19.8%) of the 131 patients. Characteristics and lab values of these 26 subjects are detailed in **Table 1**. The mean age was 61.9 years, and the mean BMI was 25.4 kg/m^2. Eighteen (69.2%) had a histo-

ry of VTE diagnosed by venous ultrasound, and 13 (50%) had a history of PE diagnosed by CT pulmonary angiography. The most common thrombosis site was the inferior vena cava (IVC), found in 14 (53.8%) patients. Other thrombosis sites included the lower extremity veins (n=9, 34.6%), jugular veins (n=2, 7.7%), and superior vena cava (SVC) (n=1, 3.8%). The presence of venous thrombosis using CECT and/or Doppler ultrasonography was confirmed in 6 (23.1%) patients, per attending radiologist reports. Among this group, thrombosis was detected in lower extremity veins (n=4, 15.8%, **Figures 1** and **2**), jugular veins (n=1, 3.8%), and IVC (n=1, 3.8%, **Figure 3**). The presence of thrombosis was not mentioned in the FDG-PET/CT report of any of these patients.

Discussion

In the present study, we demonstrated that venous thrombi may present as incidental findings on routine FDG-PET/CT imaging for cancer patients. In our cohort, the most common site for thrombosis was the IVC, followed by the lower extremities, jugular veins, and SVC. Thus, only a third of the lesions we identified on FDG-PET/CT could realistically have been detected by conventional imaging [18]. In addition, none of the venous thrombi we identified were reported in the available PET/CT reports; rather, most of them were interpreted as lymphadenopathy.

Several case reports have utilized FDG-PET/CT to identify incidental venous thrombosis in cancer patients [19-25]. However, only a handful of studies have reported on multiple subjects. Rondina *et al.* conducted a case series of 12 patients to evaluate the accuracy of FDG-PET/CT for the detection and evaluation of DVTs [26]. They reported that FDG uptake in affected vessels was visually higher than in unaffected vessels, and they noted a significantly increased maximum standardized uptake value (SUVmax) within affected veins. They also identified a significant negative correlation between DVT onset and FDG uptake. Similarly, Houshmand *et al*. presented results for metabolically active volume, total lesion glycolysis, and SUVmax relative ratios (sensitivity 84%, specificity 100%) [27]. Hara *et al*. utilized FDG-PET/CT to identify neutrophil-dependent thrombus inflammation in mice, and they determined that FDG accumulation decreases with time in the identification of experimental DVT [28]. Their findings suggest that PET imaging may have the potential to distinguish between newer and more mature incidences of VTE, which could help to determine if a patient will benefit from anticoagulation therapy [29]. Le Roux *et al.* also observed significantly higher FDG uptake within thrombosed-vessels in comparison to the contralateral non-affected vessels [30]. However, they did not identify a specific cut-off for SUVmax to differentiate between affected and non-affected vessels, limiting the use of this measurement in routine clinical practice. Finally, Miceli *et al.* observed an increased FDG uptake in vessels affected by septic thrombosis, but not within DVT-thrombosed vessels, in 11 acute and 16 scans of DVT patients [31]. The present study examined a larger patient cohort than any of these aforementioned studies, further suggesting a role for FDG-PET/CT in VTE.

Focal FDG uptake may be a molecular marker of VTE prior to the onset of clinical symptoms [32]. We confirmed the presence of venous thrombosis in 6 of 26 positive patients using additional imaging reports present in the patients' charts. Many unconfirmed patients did not undergo structural imaging to screen for VTE around the time of FDG-PET/CT imaging. Meanwhile, in subjects who did undergo structural imaging, these modalities might not have detected the lesions (e.g. IVC thrombosis, our most common finding). Thus, in cases with positive molecular findings but negative structural findings, we cannot differentiate between false-positive PET results and false-negative structural results.

Our study must be interpreted in the context of its limitations. Namely, the retrospective study design prevented us from confirming our findings by other imaging modalities for every case. Also, as this was a descriptive study, it did not include a control group, and the patients included had a history of cancer, DVT, or PE, which may have led to selection bias. Furthermore, some patients were on anticoagulant therapies, which may have resolved thrombi prior to confirmatory structural imaging. The prevalence of venous FDG signal in cancer patients without known VTE is largely understudied. As such, the relatively low uptake of individual thrombi, in addition to the lower quality of images utilized in the study, may have led to false-negative PET findings [30]. This may account

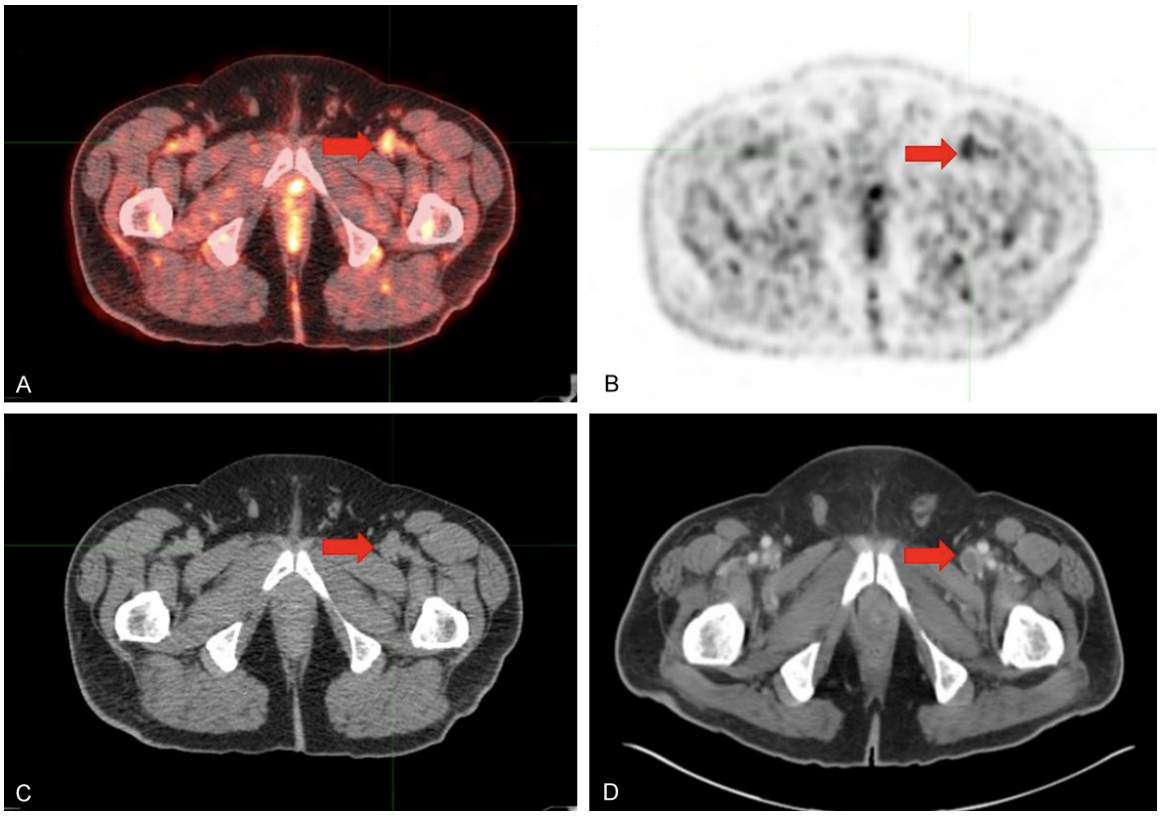

Figure 1. Venous thrombosis in the left common femoral vein of a 65-year old male with a history of metastatic melanoma. One day prior to FDG-PET/CT imaging, the patient had +1 edema of the left calf and foot. (A) Axial FDG-PET/CT, (B) axial FDG-PET, and (C) axial low-dose CT confirm high metabolic activity in the dilated lumen of the left common femoral vein, consistent with venous thrombosis. (D) Six-month follow-up, abdominopelvic contrast-enhanced CT scan showed a filling defect in the same location, suggestive of venous thrombosis.

for the small proportion of cases with documented venous thrombi. As such, patients with suspected venous thrombi as reflected through FDG signal may benefit from additional confirmatory imaging in conjunction with FDG-PET/CT, such as CT venography/arteriography or ultrasonography to guide anticoagulation therapy [18]. Moreover, the proximity of thrombi to other lesions exhibiting high metabolic activity, such as primary tumors or adjacent lymph nodes, may hamper the ability to visualize the former by the partial volume effect [33-35].

The introduction of total-body PET instruments will play a major role in assessing cancer patients with a predisposition to VTE [36, 37]. Oncologic PET/CT scans are routinely performed from the base of the skull to the mid-thigh [18]. However, the lower extremity is a common site for venous thrombosis, so many cases of VTE may be overlooked by the standard PET/CT protocol. In our cohort, we detected thrombosis of the lower leg veins within a melanoma patient who underwent full-body FDG-PET/CT imaging. Additionally, this approach may be combined with NaF-PET/CT for a stronger impression of the overall plaque burden in these patients [38-40]. As such, adopting total-body PET imaging may be of great importance to clinicians moving forward for the management of individuals with cancer.

Conclusion

Our study demonstrates that venous thrombosis can be detected using FDG-PET/CT imaging. Venous thrombosis is a common complication of cancer and chemotherapy. Early detection and management of VTE by PET imaging may alleviate a major source of morbidity and mortality in these patients. However, interpreting physicians rarely report suspicious venous lesions on FDG-PET/CT as VTE. In the future, physicians should carefully consider this

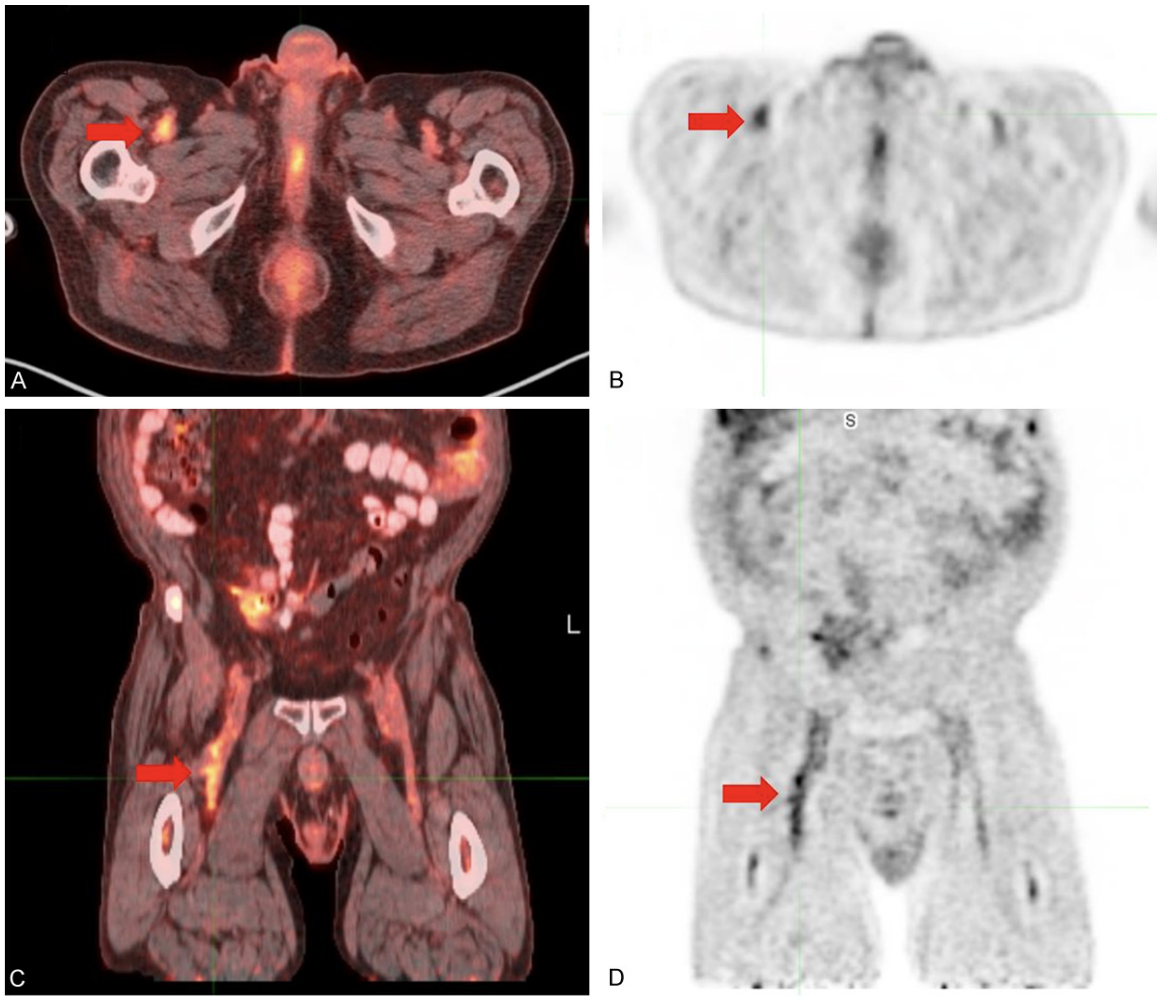

Figure 2. Venous thrombosis in the right common femoral vein, diagnosed prior to the ultrasound. (A) Axial FDG-PET/CT, (B) axial FDG-PET, (C) coronal FDG-PET/CT, and (D) coronal FDG-PET demonstrated high metabolic activity in the lumen of the right common femoral vein, consistent with venous thrombosis. Ultrasound performed two weeks later confirmed non-occlusive thrombus in the right common femoral vein.

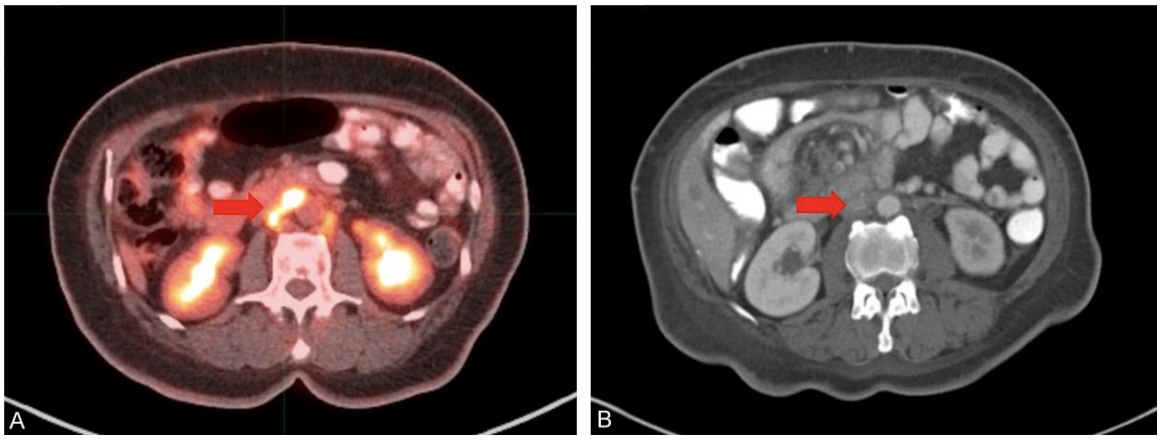

Figure 3. Venous thrombosis in the inferior vena cava (IVC) of a 70-year old female with a history of uterine carcinosarcoma. Patient underwent FDG-PET/CT for staging. (A) Axial FDG-PET/CT demonstrated increased intra-luminal radiotracer uptake in the IVC. (B) At 2-month follow-up, abdominopelvic contrast-enhanced CT scan showed filling in the IVC, suggestive of chronic thrombosis.

life-threatening pathology in their differential diagnosis and treatment approach.

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Disclosure of conflict of interest

None.

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