CASE REPORT – OPEN ACCESS

International Journal of Surgery Case Reports 28 (2016) 310–313

Contents lists available at ScienceDirect

International Journal of Surgery Case Reports

journal homepage: www.casereports.com

Deep venous thrombosis as the single sign of unexpected metastatic urinary tract cancer in a patient with a history of cutaneous melanoma: A case report

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ARTICLE INFO

Article history:
Received 2 August 2016
Received in revised form 8 October 2016
Accepted 9 October 2016
Available online 14 October 2016

Keywords:
Venous thromboembolism
Thromboembolic risk factors
Occult cancer
Melanoma
Urinary tract cancer
Case report

ABSTRACT

INTRODUCTION: Cancer is a recognized risk factor of venous thromboembolism (VTE) as it induces a prothrombotic state through various mechanisms of activation of coagulation. Recognizing occult cancer as a risk factor is equally important. In patients with no known thromboembolic risk factors, utilizing PET/CT as a screening tool may be considered in order to reveal occult malignancy associated with otherwise unexplainable VTE.

METHODS: This case report has been reported in line with the SCARE criteria.

PRESENTATION OF CASE: We describe a case of deep venous thrombosis of the lower leg as the single sign of metastatic urinary tract cancer. The patient had a history of cutaneous melanoma but no thromboembolic risk factors. Following treatment for deep venous thrombosis, the patient was referred directly to the plastic surgery department for further examination including PET/CT due to suspicion of metastatic melanoma.

DISCUSSION: Screening for occult cancer in patients with unprovoked VTE has so far not been shown to benefit survival. As new treatments emerge, significant improvement in prognosis might be expected with early diagnosis of occult cancer and initiation of treatment. Thus an open mind should be kept towards utilizing advanced diagnostic tools such as PET/CT to screen for occult cancer in patients presenting with unprovoked VTE.

CONCLUSION: This case highlights the importance of considering all possible causes and utilizing targeted diagnostic tools when assessing a patient with seemingly unprovoked deep venous thrombosis. A whole-body PET/CT scan ultimately proved significant in revealing occult metastatic cancer of a completely different origin than expected.

1. Introduction

The thromboembolic risk associated with cancer has been described for several specific malignancies including bladder cancer [1] and breast cancer [2,3] but only rarely for metastatic melanoma [4,5], and to our knowledge not for cutaneous melanoma.

Other known thromboembolic risk factors include immobilization, trauma, major surgery, pregnancy, obesity, certain drugs, advancing age, some hematological disorders, congenital coagulation factor abnormalities and more.

Both circulating tumor cells and solid tumors may exhibit procoagulant properties.

The presence of circulating tumor cells in peripheral blood has been shown in a prospective study by Mego M et al. [2] to exhibit a positive association with elevated plasma D-dimer levels in primary breast cancer, indicating a potential role for activation of the coagulation cascade by circulating tumor cells. A retrospective study by Mego M et al. [3] showed a direct association between circulating tumor cells and increased risk of deep venous thrombosis (DVT) in patients with metastatic breast cancer.

Studies so far have found associations between venous thromboembolism (VTE) and certain native properties of cancer cells as both direct activators of the coagulation cascade, and indirect activators by stimulating the prothrombotic potential of other cells.

There are several mechanisms involved and considered to be responsible for a hypercoagulable state in malignancy. It has been shown that constant expression of Tissue Factor (coagulation factor III) and Cancer Procoagulant (CP) protein by cancer cells, expression by cancer cells of fibrinolytic molecules, and cancer cell release of microparticles and cytokines can induce thrombosis [6,7]. Furthermore direct physical interaction between cancer cells and normal

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http://dx.doi.org/10.1016/j.ijscr.2016.10.020

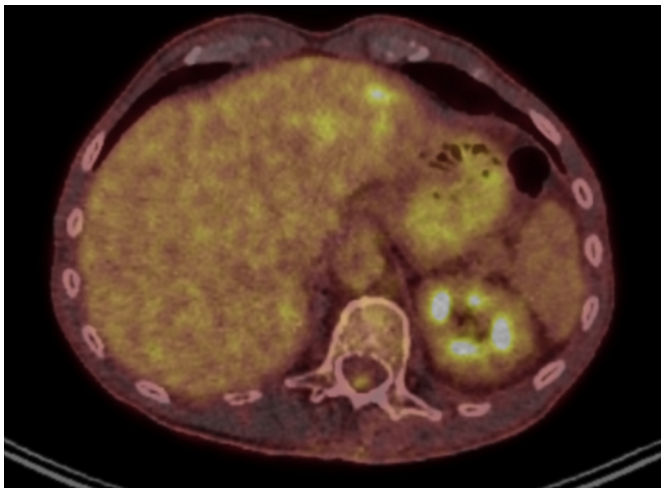

Fig. 1. PET-positive tumors in the liver.

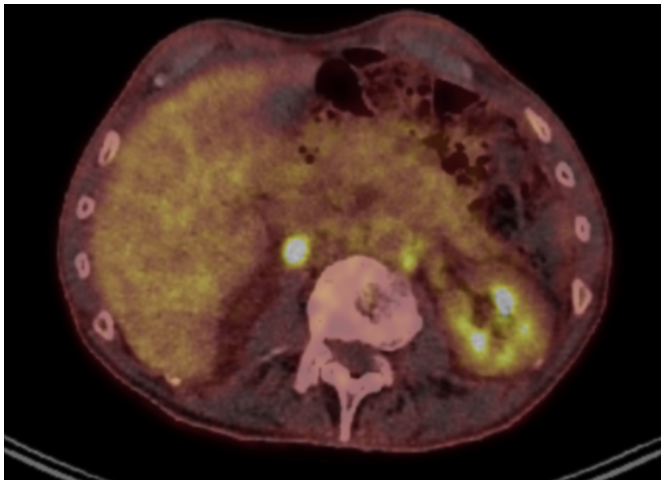

Fig. 2. PET-positive lymph node next to the inferior vena cava.

cells has been shown to result in localized clotting activation and platelet aggregation, and leukocyte-release of procoagulant cytokines [8].

We describe a case from a university hospital, which highlights the importance of utilizing targeted diagnostic tools when assessing the cause of VTE in a patient with no known risk factors of VTE.

The patient's history of cutaneous melanoma was the single piece of information prompting further examination, and a whole-body PET/CT scan ultimately proved vital in revealing an occult metastatic cancer, which furthermore was of a completely different origin than expected.

2. Methods

This case report has been reported in line with the SCARE criteria [9].

3. Presentation of case

A 78 year old retired, caucasian male was admitted to the medical emergency department by his general practitioner with measurable swelling and pain of the left lower leg developed over the course of a few days prior to admission. He was on oral Alendronate therapy following a high velocity femur fracture four years earlier, had a minor use of pipe tobacco, but was otherwise healthy and had no family history of thrombosis.

Blood tests and an ultrasound scan of the left lower leg were performed, and the patient was subsequently diagnosed with a DVT of the popliteal vein with an elevated Fibrin D-dimer plasma-level of 1.06 FEU mg/L (FEU: Fibrin Equivalent Units; normal value: <0.5 FEU mg/L).

Antithrombotic treatment with oral Rivaroxaban was commenced and the patient was discharged the day after for routine follow-up at the local anticoagulation clinic, and referred to the plastic surgery department for further examination due to suspicion of metastatic melanoma from cutaneous melanoma treated four years earlier.

Following examination at the plastic surgery outpatient clinic where no clinical signs of metastatic melanoma were found, the patient underwent a whole-body ^{18}F-FDG PET/CT scan, which revealed several areas suspicious of malignancy in both liver lobes (Fig. 1), in the mediastinal and retroperitoneal lymph nodes (Figs. 2 and 3) and in the long biceps tendon of the right shoulder.

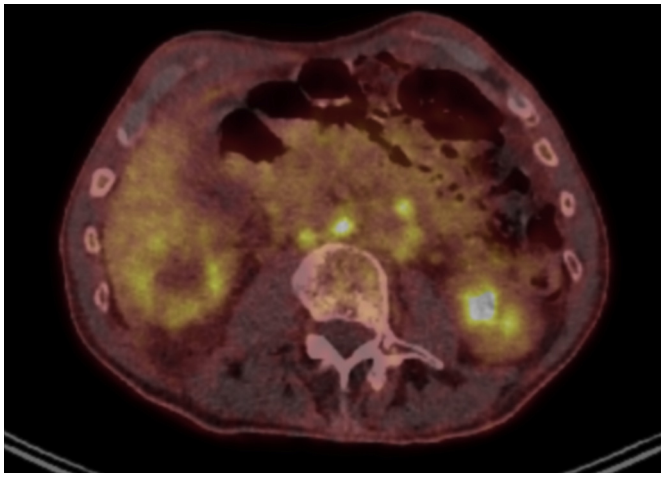

Fig. 3. PET-positive lymph nodes surrounding the abdominal aorta.

An ultrasound guided needle biopsy of the liver lesions unexpectedly revealed metastatic carcinoma cells of urothelial origin. Through further diagnostic testing and surgery by the urology department, the patient was eventually diagnosed with non-invasive papillary urothelial cancer of the bladder and urothelial carcinoma located at the right ureter ostium of the bladder.

Four years prior to the DVT the patient was diagnosed with cutaneous melanoma on the left leg. Histological examination showed a superficially spreading melanoma, Clark level 3, Breslow thickness 1.87 millimeters, containing more than one mitosis per square millimeter in the dermis, and showing signs of regression but no ulceration.

The melanoma was treated with wide local excision, and sentinel lymph node biopsy from the left inguinal region revealed no regional metastases. During the follow-up course the patient was not diagnosed with further melanoma and never experienced any general or specific symptoms of cancer or DVT.

Five months following excision of the melanoma and left-side inguinal sentinel node biopsy, the patient presented with a palpable mass in the left inguinal region, but had no discomfort or general symptoms of disease. The mass was removed and revealed a varicose vein with a thrombus and no signs of malignancy on histological analysis.

4. Discussion

Venous thromboembolism has been extensively shown to be associated with cancer as well as a significantly higher risk of a subsequent cancer diagnosis following unprovoked VTE [8,10–12].

Studies so far have found associations between VTE and certain properties of cancer cells as both direct activators of the coagulation cascade, and indirect activators by stimulating the prothrombotic potential of other cells.

Due to the patient's history of cutaneous melanoma, metastatic melanoma was initially considered a possible cause since no other risk factors for developing DVT were present.

Venous thromboembolism specifically associated with melanoma has not been commonly reported in the medical literature. Valente M et al. [5] described a case where severe VTE was associated with pulmonary metastases from a cutaneous melanoma treated four years earlier. A retrospective study by Sparsa A et al. [4] found a high incidence of VTE in metastatic stage IV melanoma with a prevalence comparable to pulmonary and gastrointestinal cancers.

As most cases of melanoma are primarily confined to the superficial layers of the skin, the majority of melanomas are as such not in direct contact with the blood stream as is the case with other malignancies. This might explain the low potential and lack of reported cases of VTE in cutaneous melanoma.

Two large retrospective population-based cohort studies have addressed the likelihood of diagnosing occult cancer following VTE and assessed the benefit of cancer screening. A Danish study [10] including 26,653 patients with unprovoked VTE, and a Taiwanese study [11] published in 2016 including 27,751 patients concluded that there was a strong association between unprovoked VTE and occult cancer. However, neither study could conclude that extensive screening for occult cancer would benefit survival.

The clinical value of using PET/CT as a standard screening tool to detect occult cancer in unprovoked DVT, remains a cause of debate in regard to improvement in overall survival and morbidity. A retrospective study [13] published in 2014 including 50 patients assessed the value of PET/CT screening for malignancy in patients with unprovoked VTE, but showed no diagnostic benefit of PET/CT compared to conventional CT scan and concluded that PET/CT had limited diagnostic value.

Our patient had no known risk factors for VTE by the time he presented with DVT, but did have a relatively recent history of melanoma, so there was no hesitation in referring him to a diagnostic whole-body ^{18}F-FDG PET/CT scan to examine for melanoma metastases.

As diagnostic technology evolves and new treatments emerge, a significant improvement in prognosis might be expected with early diagnosis of occult cancer and initiation of treatment.

Thus an open mind should be kept to future implementation of routine screening for occult malignancy in patients presenting with unprovoked VTE, using advanced diagnostic tools such as PET/CT.

5. Conclusion

Although the definitive cause of DVT remained undetermined, recognizing occult cancer as a risk factor continues to be important, especially in patients with no known thromboembolic risk factors, as demonstrated in this patient.

In the present case, knowledge of previous melanoma was the single piece of information prompting further examination of the patient. However, it was a whole-body PET/CT scan utilized as a targeted diagnostic tool, which ultimately proved vital in revealing an occult metastatic cancer of a completely different origin than expected. This raises the question of whether to implement whole-body ^{18}F-FDG PET/CT scan as a standard screening tool to detect or at least exclude occult malignancy in patients presenting with otherwise unprovoked DVT.

Conflicts of interest

None.

Funding sources

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

Ethical approval

Not applicable.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Author contribution

Joachim Mikkelsen: conception and design of the study, acquisition of data, analysis and interpretation of data, drafting the article, revising the article critically for important intellectual content, final approval of the version to be submitted.

Steen Henrik Matzen: conception and design of the study, analysis and interpretation of data, revising the article critically for important intellectual content, final approval of the version to be submitted.

Registration of research studies

Not applicable.

Guarantor

Joachim Mikkelsen.
Steen Henrik Matzen.

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