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What lies beneath a deep vein thrombosis

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Abstract

Presentation
We describe a case of non-small cell lung carcinoma (NSCLC) initially presenting with migratory VTE in a previously healthy never smoker. This case demonstrated unexpected wisespread metastatic spread to a variety of unusual sites which have only been rarely reported in the literature.

Diagnosis
Initial doppler ultrasound confirmed lower limb deep vein thrombosis. Subsequent CTPA revealed pulmonary embolism and a suspicious lung lesion which was later confirmed as NSCLS on histology. PET CT revealed extensive metastatic disease.

Treatment
Therapeutic anticoagulation was the mainstay of therapy along with symptom management.

Discussion
Malignancy is linked with venous thromboembolism (VTE) by a two way clinical association[1]. Trousseau Syndrome, which is inconsistently defined in the literature, is considered a paraneoplastic phenomenon manifesting as hypercoagulability in the context of underlying malignancy[2]. Our patient was previously well with no identifiable risk factors for venous thromboembolism or lung cancer. This highlights the importance of high clinical suspicion for an underlying cause even in the most benign appearing cases of venous thromboembolism.

Introduction

Malignancy is linked with venous thromboembolism (VTE) by a two way clinical association[1]. Trousseau syndrome which is inconsistently described in the literature is considered a

paraneoplastic phenomenon manifesting as hypercoagulability in the context of underlying malignancy[2]. Lung cancer often presents late with significant symptom burden and advanced disease. Contrary to this, herein we describe a case of non-small cell lung carcinoma (NSCLC) initially presenting with VTE in a previously healthy, never smoker, demonstrating widespread metastatic disease to sites rarely reported in the literature.

Case Report

A previously well 60 year old amateur athlete and lifelong non-smoker presented with unexplained right lower limb swelling. Notably he had a history of a right quadricep tendon surgical repair eight months earlier. A doppler ultrasound confirmed a deep vein thrombosis (DVT), without any provoking risk factors identified. Despite appropriate therapeutic anticoagulation he developed a contralateral lower limb DVT later that month. A report of persistent chest pain over the following fortnight prompted a Computed Tomography Pulmonary Angiogram (CTPA) that identified a pulmonary embolism and suspicious consolidation of the left lower lobe requiring further investigation. In the intervening two weeks he presented with a TIA like episode complaining of transient diplopia. He was discharged following a normal Magnetic Resonance Imaging (MRI) Brain scan. A scheduled bronchoscopy and endobronchial biopsy of the proximal left main bronchus was performed. Histology and immunohistochemical studies showed a poorly differentiated non-small cell carcinoma with TTF-1 and Napsin A positivity, consistent with an adenocarcinoma. Molecular studies did not identify any targetable mutations. Two weeks later further radiological staging with Position Emission Tomography (PET) demonstrated diffuse metastatic disease with mediastinal, pleural, bone, adrenal, pancreatic, splenic, peritoneal, thyroid and widespread intramuscular metastases. He was admitted under the oncology team that week for further work up and consideration of systemic treatment. On day two of his admission he developed an acute onset right sided hemiparesis followed by a drop in Glasgow Coma Scale (GCS). A contrast enhanced CT Brain revealed a large left frontal metastatic lesion with haemorrhagic transformation. Ongoing clinical deterioration led to the involvement of the palliative care and he died two days later, within three months of his initial ‘unprovoked’ DVT diagnosis.

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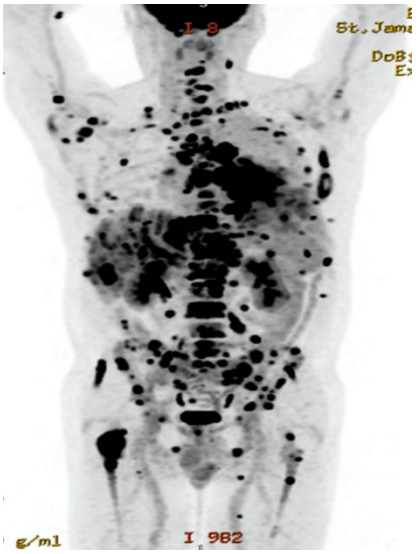

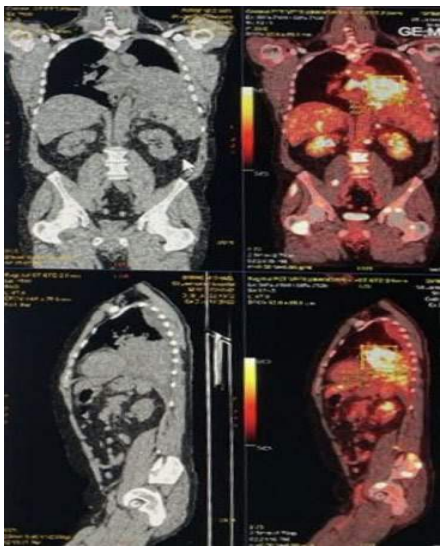

PET/CT images of metabolically active primary lung tumour and widespread metastases including liver, bone, peritoneum and soft tissue.

Discussion

After initially presenting with an unexplained deep vein thrombosis our patient had an incidental finding of aggressive widely metastatic lung cancer that rapidly led to his death. He was previously systemically well with no identifiable risk factors for venous thromboembolism or lung cancer. This highlights the importance of high clinical suspicion for an underlying cause even in the most benign appearing cases of venous thromboembolism.

Cancer related thrombosis is the second most common cause of death in this population, after cancer itself[3]. With a four to seven fold increased risk of venous thromboembolism in a patient with

a diagnosis of cancer, clinicians should have a low threshold to empirically treat and investigate this cohort[4]. Conversely, venous thromboembolism as the first clinical manifestation of an underlying malignancy is less frequently considered, yet up to 20% of patients presenting with a deep vein thrombosis have an underlying active cancer which has not yet been identified[5]. Those with an unprovoked deep vein thrombosis have a five percent rate of occult cancer diagnosis within the following year[6], often with a diagnosis made during the initial treatment period suggesting cause not correlation. Trousseau syndrome described as recurrent or migratory venous thromboembolism, most commonly presents with lower limb deep vein thrombosis or pulmonary embolism[7] and should prompt investigation of an occult visceral neoplasm[8].

Guidelines regarding screening for malignancy in those presenting with venous thromboembolism are lacking with investigations left to the clinician's discretion[9,10]. Interestingly as in our case this can lead to missed or delayed diagnosis of underlying malignancy. More recently age and gender specific screening utilises widely available established and validated screening programmes to investigate for breast, cervical, colon and prostate cancer in the first instance[11]. Studies into patient related outcomes such as quality of life, morbidity and mortality however, have repeatedly failed to show consistent improvement with an aggressive approach to screening[10,11]. While a recent Cochrane review suggests that intensive screening may result in an earlier cancer diagnosis that is potentially more amenable to treatment, it remains uncertain as to whether this corresponds to improved patient outcomes, specifically cancer and venous thromboembolism related deaths[12].

Lung cancer spreads most commonly to the mediastinum, brain, bone, liver and adrenal glands with distant metastases in over half of patients at the time of diagnoses[1314]. Less common sites of metastatic disease in lung cancer include the pancreas, spleen, thyroid and soft tissue and account for less than five percent of metastases in this cohort. Their presence is associated with a more aggressive disease and subsequently a poorer outcome[13].

While thought of as a rare clinical event pancreatic metastases have recently been recognised as more common than originally thought following a retrospective analysis of varying tumour types[15]. Post mortem rates of twelve percent have been reported in the literature[14]. Renal cell carcinoma, followed by lung, colorectal and gastric were the most common primary sites[16–19]. Previous reviews indicate that lung adenocarcinoma is the least commonly associated with pancreatic metastases[20,21]. Our case of diffuse disease across both the head and body of the pancreas has not previously been described in a case of lung cancer.

Metastatic spread to the spleen is often again diagnosed post mortem, with a varying rate of 2-7% in an autopsy series. Due to its anti-angiogenesis properties it is thought of as a poor microenvironment for tumour cells and is another rarely encountered site for metastatic disease in clinical practice[22]. Such as in our case, left sided primary lung cancer is more commonly reported in those with malignant infiltration of the spleen[23]. This radiological pattern of disease can help differentiate between primary and secondary disease if the lesion is not amenable to biopsy.

Considered a rare occurrence due its high iodine content and vascularity, metastases to the thyroid gland are rare accounting for less than five percent of tumours in the thyroid gland [24]. An autopsy review reports a prevalence of up to quarter in cancer patients suggesting this is potentially overlooked during the radiological staging process. Adenocarcinoma of the lung is the most common subtype to metastasise to the thyroid[25]. When assessing for primary site of origin, Thyroid Transcription Factor-1 (TTF-1) immunohistochemistry is not always helpful as it can be expressed in both lung adenocarcinoma and thyroid carcinoma[26]. Napsin A is a useful marker for lung adenocarcinoma however, poorly differentiated thyroid cancers may also be Napsin A positive[27,28]. Thyroglobulin immunohistochemistry can help distinguish in cases such as this[29]. Our patient had a planned biopsy of his thyroid for further characterisation however this was not feasible prior to his death.

Peritoneal carcinomatosis is usually seen in the context of other intra-abdominal deposits in patients with metastatic disease. Metastatic peritoneal spread from lung cancer is rare but so too is primary peritoneal adenocarcinoma. Less than five percent of lung cancer will have peritoneal involvement documented[30]. Case reports have identified synchronous malignancies of the lung and peritoneum and so this must remain a differential[31,32].

Despite the large surface area and proportion of muscle mass, soft tissue metastasis is extremely uncommon with an autopsy detection rate of 0.8%[33]. Muscle metabolism generates a hostile environment acting as a deterrent for cancer cells despite its vascularity[34]. Intramuscular metastases usually occur after widespread organ involvement and typically present with painful and palpable mass-like lesions[35]. Interestingly CT imaging is not as sensitive as PET/CT for their detection and may be missed on initial staging. Multiple bilateral thigh, gluteal, paraspinal, psoas, iliac vessel and chest wall FDG avid foci represent widespread disease to such a degree that has not been previously documented in the literature.

This is the first described case of such widely disseminated metastatic disease found incidentally in a patient presenting with unprovoked deep vein thrombosis. Clinicians should have a high level of suspicion in patients presenting with venous thromboembolism even in those without overt risks, signs or symptoms for malignancy. Screening should be considered with atypical features and recurrent thrombosis should prompt investigation for occult disease. The evolution of imaging with increased sensitivity for subclinical metastases may identify less commonly encountered disease with increasing incidence and this may influence patient counselling, treatment strategies and surveillance programmes going forward.

Declarations of Conflicts of Interest:
None declared.

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