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Unprovoked Bilateral Deep Vein Thrombosis – Ignore at Your Own Peril

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Abstract

Bilateral lower limb deep vein thrombosis as a sole presenting symptom is a rare but documented manifestation of Hon Hodgkin lymphoma. We present the case of a 51 year old otherwise healthy and active male with no recent trauma or travel history who presented to the hospital with bilateral lower limb swelling of 12 days duration. Lower extremity Doppler revealed extensive bilateral deep vein thrombosis extending upto the level of the common iliac veins. CT contrast studies of abdomen, pelvis and chest revealed mediastinal and chest lymphadenopathy with occlusion of Inferior Vena Cava. Thrombophilia and collagen vascular disease workup was negative. In view of enlarged supraclavicular lymph nodes as confirmed by ultrasound neck, excision biopsy of left supraclavicular lymph node was performed which showed a high grade non-Hodgkin large cell lymphoma. Patient was started on anticoagulation and referred to Oncology services for further management. Clinicians should exercise due care and diligence and appropriately investigate otherwise healthy active adults presenting with unprovoked bilateral DVT and no other apparent cause as it could be the harbinger of asymptomatic or occult malignancy.

Keywords: Bilateral unprovoked; Deep vein thrombosis; Occult malignancy; Non-Hodgkin's lymphoma

Introduction

Malignancy is a known risk factor for deep vein thrombosis. This relation, first described by Trousseau in relation to tumors of the gastrointestinal tract [1], has been the subject of much study. Synthesis of procoagulatory factors by the malignancy, chemotherapy employed, endothelial abnormalities, abnormal blood flow and stasis due to extrinsic compression are some of the physiological reasons for this relation [2]. In light of the above, unprovoked deep vein thrombosis can be a tell-tale presenting sign of hitherto hidden malignancy of various organ systems. When considering Non-Hodgkin's lymphoma the presentation is quite varied ranging from the common B symptoms, to the less common oncological emergencies and paraneoplastic syndromes [3]. Literature review has mentioned deep vein thrombosis of upper limb veins as a presenting symptom in Non-Hodgkin's Lymphoma [4]. Such deep vein thrombosis may be an atypical presentation of occult cancer [5]. We present here a case of bilateral unprovoked lower limb deep vein thrombosis in an otherwise healthy male who on investigation was found to have high grade diffuse Non-Hodgkin's Lymphoma. Therefore, appropriate investigations by clinicians to exclude such hidden malignancies is advisable in cases of unprovoked lower limb deep vein thrombosis especially when no obvious cause is present.

Case Description

We report a case of a 51 year old active man of Asian origin working as an outdoor security guard with no other medical comorbidities who presented to the hospital with a 12 day history of lower limb swelling. He had no similar prior episodes. General examination revealed bilateral, extensive lower limb edema and some calf tenderness. System examination was unremarkable. He was also found to have left supraclavicular lymph node enlargement which was non tender, mobile and rubbery in consistency. A doppler ultrasound of his lower extremities revealed extensive sub-acute DVT of bilateral external iliac veins

as well as bilateral Common femoral vein, Sapheno-femoral vein and popliteal veins extending through the saphenofemoral junction bilaterally down to the level of the proximal long saphenous veins (Figure 1).

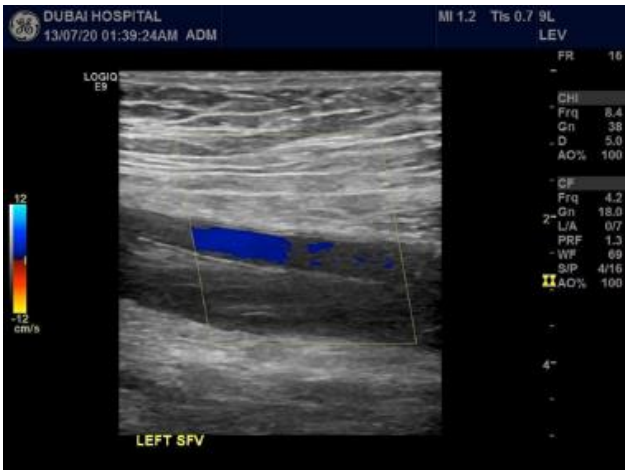

***Figure 1**: Doppler ultrasound of left lower extremity showing thrombosis.*

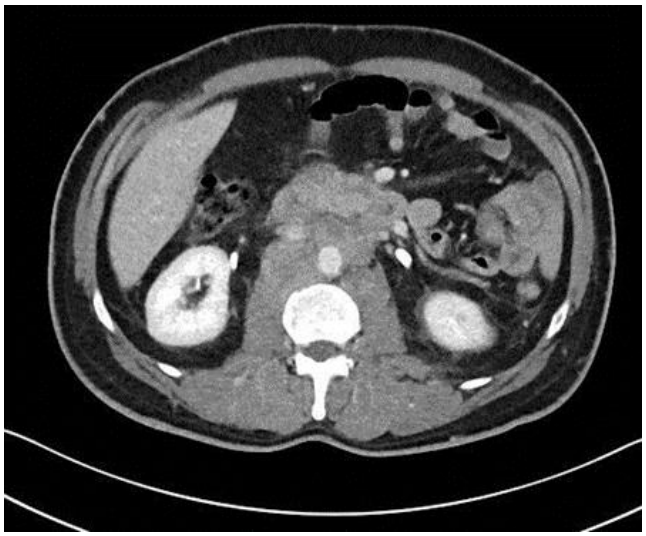

***Figure 2**: Contrast Enhanced CT abdomen displaying enlarged paraaortic lymph nodes.*

Contrast Enhanced CT abdomen and pelvis showed multiple enlarged hypodense, necrotic retroperitoneal lobulated para aortic, paracaval and periportal masses with few showing calcifications suggestive of abdominal lymphadenopathy (Figure 2). Common femoral vein, common iliac and inferior vena cava (IVC) were distended and showed no filling of contrast in the vein. IVC was partially visualized proximal to the renal vein in the intrahepatic part. Multiple collateral vessels were seen in the pelvis (Figure 3). CT Pulmonary Angiogram to rule out possible Pulmonary Embolism showed multiple enlarged lymph nodes in the paratracheal, pretracheal, sub carinal, supraclavicular region the largest measuring 33mm x 30mm. with no evidence of pulmonary embolism (Figure 4).

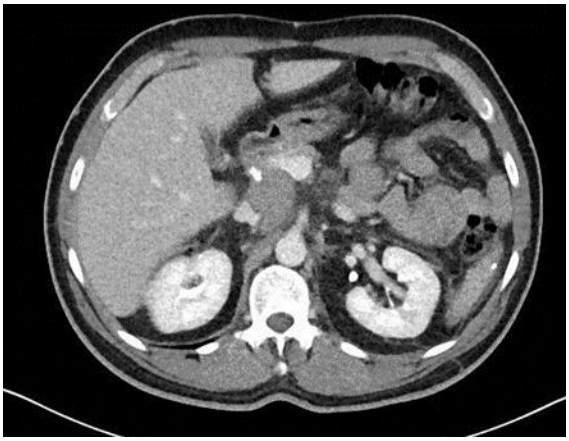

***Figure 3**: Contrast Enhanced CT abdomen displaying thrombosed Inferior vena cava.*

***Figure 4**: CT pulmonary angiogram showing mediastinal lymphadenopathy.*

Thrombophilia workup all returned negative. Coagulation parameters (PT, aPTT) were also with normal limits with the exception of elevated D-Dimer levels. Treatment was initiated with appropriate anticoagulation. An excisional lymph node biopsy of the palpable left supraclavicular node was performed. USS neck performed prior to biopsy showed left supraclavicular lymphadenopathy with most of these nodes displaying loss of fatty hilum, central necrosis and intralesional vascularity. Histopathology performed on lymph node specimen showed high grade large cell non-hodgkin lymphoma with mixed diffuse to nodular/follicular growth patterns. No extranodal extension or necrosis was seen (Figure 5). Immunohistochemistry (IHC) of the specimen was consistent with diffuse large B-cell lymphoma of non-germinal center origin. IHC was performed for CD20, CD3, bcl2, bcl6, CD10, myc, MUM1, PAX5 and Ki67. The neoplastic lymphoid cells were diffusely and strongly positive for CD20, PAX5 and bcl2, moderately for MUM1, with weakly to moderate focal patchy staining for myc (i.e. most cells were myc-negative). Ki67 showed 60-65% proliferation index in the neoplastic lymphoid cells. The neoplastic lymphoid cells were negative for

the remaining markers. The patient was informed about his diagnosis and referred to appropriate oncology services for further management.

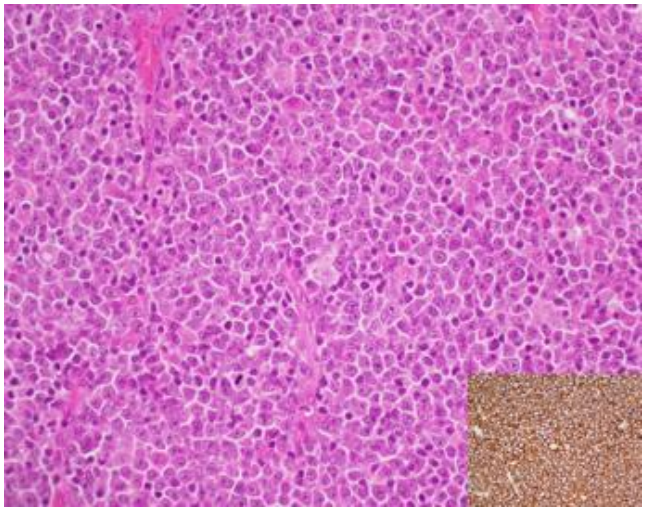

Figure 5*: Hematoxylin & Eosin stained section of the lymph node showed a diffuse solid sheet composed of large neoplastic lymphoid cells with large vesicular nuclei and prominent nucleoli, with frequent mitotic figures and scattered apoptotic bodies. Inset: The neoplastic lymphoid cells are diffusely and strongly positive for CD20 (B-cell) immunomarker).*

Discussion

Malignancy is a known risk factor for thrombosis through a variety of mechanisms. The estimated incidence of venous or arterial thrombosis per annum is 0.1% in the general population while compared to 0.5% in cancer patients [6]. In the first retrospective study evaluating idiopathic bilateral DVT by Rance and coworkers, it was seen that the prevalence of subsequent diagnosis of malignancy approached 30% [7]. In previous studies looking at thrombotic events in lymphoma, the incidence rate of thrombosis observed in subjects with non-Hodgkin lymphoma (NHL) was 6.5%. More importantly, during the course of that study it was seen that 95% of thrombotic events occur during the treatment of the disease, with only 3.8% occurring as sole presenting symptom of a hitherto unknown malignancy [8]. Other studies, both clinical and with automated analysis, have helped develop a clinical predictive score to accurately assess the risk of patients developing cancer following a DVT, helping to differentiate low - risk populations from high- risk ones who could benefit from extensive investigation [9,10]. More such studies and tools along with clearly established guidelines are required to help physicians determine which patient populations presenting with DVT require extensive and appropriate investigations.

Conclusion

DVT is a common clinical condition with several predisposing factors. In most cases, a readily identifiable precipitating cause is present. In certain cases, however, the DVT appears to be unprovoked with no apparent cause. This case presented to the hospital with an unprovoked bilateral lower limb DVT. Further workup eventually revealed the presence of previously undetected high grade diffuse Non-Hodgkin's Lymphoma. To our knowledge, there has not been any previous reporting of diffuse high grade Non-Hodgkin's Lymphoma presenting as unprovoked bilateral lower limb deep vein thrombosis. Physicians should maintain a high degree of suspicion for malignancy in any unusual or unprovoked presentations of venous thrombosis with no contributing risk factors. The deep vein thrombosis, in such scenarios, actually provides a window of opportunity to detect underlying hidden malignancies if present, at an early stage and prevent possible delays in management.

List of Abbreviations

DVT: Deep Vein Thrombosis; CT: Computed Tomography; IVC: Inferior Vena Cava; PT: Prothrombin Time; aPTT: Activated Partial Thromboplastin Time; NHL: Non-Hodgkin's Lymphoma

Ethics approval and consent to participate

Not applicable.

Human and animal rights

Not applicable.

Consent for publication

Not applicable.

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Conflicts of interest

The authors declare no conflict of interest, financial or otherwise.

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