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Case Report

Distal deep vein thrombosis as a presenting manifestation of tropical hyper-eosinophilia

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ABSTRACT

A young woman with swelling and pain in her left leg was diagnosed with deep vein thrombosis (DVT) confirmed by Doppler study. However, she also had hypereosinophilia (HE), which led to investigations for possible underlying causes. Positive serologic testing for Filariasis suggested it as the likely cause, highlighting DVT as a presenting manifestation of tropical HE. Treatment with rivaroxaban for DVT and antiparasitic medication led to normalization of eosinophil counts and complete resolution of DVT on follow-up. This case presents a rare occurrence of DVT seen as a presentation with tropical HE.

Keywords: HE, DVT, Filariasis, Tropical eosinophilia, Rivaroxaban

INTRODUCTION

Eosinophilia is a systemic condition characterized by peripheral blood eosinophil count more than 500/mm^3. It can be divided into mild (500-1500/mm^3), moderate (1500-5000/mm^3) and severe (>5000/mm^3) eosinophilia. The moderate and severe category encompasses the spectrum of HE. Causes of HE can be familial, primary (clonal), secondary (parasitic infections, drug allergies, allergy, skin diseases, respiratory and gastrointestinal tract diseases) and idiopathic.[1]

HE can also manifest in the context of hematologic malignancies like myeloproliferative neoplasm, Myeloproliferative syndrome/chronic eosinophilic leukaemia, not otherwise categorised, myeloid neoplasm associated with eosinophilia and abnormalities of PDGFRA/PDGFRB, or fibroblast growth factor receptor 1 (FGFR1), or T-cell neoplasm/lymphoma, unclassifiable.[2]

The most common clinical manifestation of HE was dermatological involvement (69%), followed by pulmonary (44%) and gastrointestinal (38%), with low cardiac involvement (20%).[3]

DVT (deep venous thrombosis) is an obstructive disease occurring in the deep veins due to abnormal blood clot formation, impeding circulation in the lower limbs. Environmental factors like surgery, trauma or fracture, immobilisation, cancer, acute infection, oral contraceptive or hormone therapy use, physical activity, and obesity increases incidence. Genetic factors causing hypercoagulable state also predispose to DVT.[4] Symptoms include edema, pain/tenderness, changes in skin colour, temperature or perfusion.[5] National Institute for clinical excellence (NICE) guidelines suggest D-Dimer assay, coagulation profile and proximal leg vein ultrasound for investigation of DVT.

Lymphatic filariasis is a vector-borne disease, caused by infection with the nematode species *Wuchereria bancrofti*, *Brugia malayi* or *B. timori* filarial parasites, with Wuchereria causing 90% of the infections.[6,7] Filariasis can manifest as elephantiasis, lymphoedema or hydrocele. 50% of these infections are asymptomatic.

However, acute infections may present with fever, inflammation, tender red streaks, malaise or tropical pulmonary eosinophilia. They may also occasionally disseminate into the breast, testicles or the subcutaneous tissues. Lymphatic filariasis can be diagnosed by multitude of tests: Serology testing (for peripheral microfilariae), skin biopsy (for tissue nematodes), ultrasonography (visualize movements), PCR, lymphoscintigraphy, filariasis antigen detection and immunochromatographic tests. Diethylcarbamazine (DEC), ivermectin and albendazole are being used as multidrug therapy, as advised by WHO, to prevent filariasis and reduce the spread of infection.[7]

CASE REPORT

A female in her early 20s, hailing from a rural background presented to our tertiary specialist unit with a 1 month history of swelling and pain in her left leg. Patient reported having no past history of infection, no history of atopy and no significant family history. General physical examination and complete systemic examination barring the presenting symptoms as mentioned above. Based on the clinical presentation, DVT was suspected and patient was sent for a Doppler study of the affected leg which confirmed the same. No predisposing factors for DVT such as immobilization, obesity or any recent trauma/surgery was noted. Treatment was started for the DVT, although a noteworthy finding in the patient's blood workup was, HE (Table 1). Extensive workup was done to screen for maximum possible causes of HE in the patient. Physical examination was unremarkable with no lymphedema or any dermatological finding.

Doppler showed acute DVT in mid and distal femoral vein and popliteal vein. Liver and kidney function were within normal limits and thyroid function tests as well. Chest X-ray, Doppler echocardiography, abdominal and pelvic ultrasound as well as an eye examination excluded thoracic, abdominal or pelvic lesions and eosinophilic organ infiltration.

Table 1: Patient's blood investigations.

Parameters	Result	Normal
Hemoglobin (in %)	10.9	12-15
Total leukocyte count (per mm^3)	16240	4000-10000
Total platelet count (per mm^3)	403000	150000-410000
Neutrophils (in %)	18	38-70
Lymphocytes (in %)	27	20-45
Monocytes (in %)	1	2-8
Eosinophils (in %)	54	1-4
Basophils (in %)	0	0-1
D-dimer level	1212 ng/mL	<500 ng/ml
IgE	438.18 IU/ml	1.5-144 IU/ml

Examination of fresh stool, examination of urine, and serologic testing (*Echinococcus, Toxocaracanis, Cysticercus and Trichinella* sp). Stool test results for liver fluke eggs, fungi, and infectious diseases tests were all negative. Serologic testing for Filariasis was positive (antibody titre-424**).**

On peripheral blood smear examination, normocytic and normochromic RBCs and eosinophilic leukocytosis was seen with no microfilariae. Bone marrow aspirate and biopsy showed preponderance of eosinophilic precursors in the absence of blasts.

ANCA (antineutrophil cytoplasmic antibodies), ANA (antinuclear antibody spectrum), anticardiolipin antibodies, and direct Coombs test results were all negative. APLA was found to be absent on investigation.

RT-PCR excluded the presence of leukemia-associated molecular mutations, and lymphocyte subpopulations, when analyzed by flow cytometry, were normal. Normal serum tryptase and vitamin B12 levels were seen.

Multiple diagnoses associated with HE were considered and systematically tested to ascertain the cause in the patient. These included secondaries HE due to parasitic and helminth infections, allergies (none reported by history), connective tissue disorders, and other autoimmune disorders but were ruled out. Secondary non-clonal HE in hematological and non-hematological malignancies, lymphocytic variant hypereosinophilic syndrome (LHES), and clonal HE due to PDGFRA, PDGFRB, FGFR1, PCM1-JAK2 rearrangements, and core binding factor leukemias were also evaluated but came out to be negative. A positive serologic test for filariasis, combined with the patient's residence in a filariasis-endemic region, led to the conclusion that filariasis was the cause of HE in this patient.

Patient was started on rivaroxaban for the DVT and Diethylcarbamazine, albendazole and ivermectin for filariasis which was the likely cause of eosinophilia. Her eosinophil counts normalized after 3 weeks of antihelminthic/antiparasitic medications. She was continued on anticoagulation for 6 months. Repeat Doppler after 3 months of anticoagulation revealed complete resolution of DVT.

DISCUSSION

There are 3 factors determining thrombosis, namely, Vessel wall damage, Stasis of blood and a Hypercoagulable state. There are various mechanisms that explain thrombus formation due to HE. Eosinophils control activation and regulation of blood coagulation. Previous research confirmed the expression of tissue factor (TF) and autonomous TF-dependent generation of thrombin by eosinophils.[8-10] Eosinophils, when active, can induce release of platelet-activating factor, which in

turn activates leukocytes, endothelial cells, and platelets and releases Tissue factor.[11]

Eosinophils support TF mediated thrombin generation by providing procoagulant phospholipid surface. Protein particle is present in the eosinophils called eosinophilic cationic protein which stimulates thrombosis by neutralizing anticoagulant effects of heparin by binding to it.[11] Major basic protein which is another protein present in the eosinophills induce direct toxic damage to microvascular endothelial cells may cause microthrombi in patients with HE.[12,13] Activated eosinophils can also express CD40 Ligand (CD40L), and the CD40/CD40L system plays a role in inflammation, endothelial cell dysfunction, platelet activation and coagulation activation.[14]

The limited available literature indicates that approximately one-fourth of hypereosinophilic syndrome (HES) patients develop thromboembolic complications, with a mortality rate ranging from 5% to 10%.[15] Most earlier reports focus on venous thromboembolism (VTE) associated with idiopathic HES. For instance, Micco et al reported a case of a patient with idiopathic hypereosinophilic syndrome who developed DVT in both lower limbs.[16] Similarly, Su et al described a 32-year-old patient with widespread thrombosis leading to brain death due to HE.[14] Another study by Gao et al involved a patient with extensive DVT and multi-organ damage attributed to hypereosinophilic syndrome.[17]

Hayashida et al also highlighted a correlation between eosinophilia and DVT, where the patient developed DVT and was started on anticoagulants, which subsequently led to eosinophilia, although establishing a clear temporal relationship was challenging.[18]

Diagnosing eosinophilia involves several modalities, including complete blood count (CBC), peripheral smear, or histopathological evaluation if specific tissues are involved. In our patient, an extensive investigative panel was conducted to determine the cause of HE.

Notably, in most of the aforementioned studies, HE was idiopathic, and patients presented with DVT. Consequently, the time interval between the onset of HE and DVT formation cannot be determined. To the best of our knowledge, this is the first reported case of a patient presenting with DVT due to HE secondary to a tropical infection, specifically filariasis. This connection between filariasis-induced HE and DVT is significant and warrants further research.

Rivaroxaban can be used for treatment in low-risk VTE settings.[19]

CONCLUSION

In conclusion, this case illustrates the rare but significant association between distal DVT and tropical hyper-eosinophilia due to filariasis. Our findings underscore the need for clinicians to consider underlying parasitic infections in patients with unexplained eosinophilia and thrombotic events. Early diagnosis and appropriate treatment can lead to favorable outcomes, highlighting the importance of comprehensive evaluation in similar cases.

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