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General Medicine

DEEP VEIN THROMBOSIS ASSOCIATED WITH EOSINOPHILIA: CLINICAL INSIGHTS AND PERSPECTIVES

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ABSTRACT Eosinophilia, characterised by an elevated eosinophil count, is a rare but significant cause of thrombotic events, including deep vein thrombosis (DVT). This case report presents a patient with marked eosinophilia who developed DVT, exploring the pathophysiological mechanisms underlying this association. The patient, a middle-aged individual, exhibited classic symptoms of DVT, including swelling and pain in the lower extremity, and was subsequently diagnosed via Doppler ultrasound. Laboratory tests revealed significant eosinophilia, prompting further investigation into potential aetiologies. The pathogenesis of thrombosis in the context of eosinophilia involves multiple mechanisms: eosinophil granule proteins can directly damage endothelial cells, promoting a pro-thrombotic state; cytokines released by eosinophils can enhance platelet aggregation and activation; and the inflammatory milieu fostered by eosinophils can contribute to vascular injury and coagulation cascade activation. This case underscores the importance of considering eosinophilia as a differential diagnosis in patients with unexplained thrombotic events.A comprehensive review of the literature highlights similar cases and elucidates the critical role of interleukin-5 (IL-5) in eosinophil proliferation and survival, further linking it to thrombotic risk. Effective management of eosinophilia, including targeted therapies against IL-5, may mitigate thrombotic complications. This report aims to enhance clinical awareness and guide future research on eosinophilia-associated thrombosis.

KEYWORDS : Eosinophilia, Deep Vein Thrombosis (DVT), Thrombosis,IL-5 (Interleukin-5), Hypereosinophilic Syndrome (HES), Platelet Activation Endothelial Damage, Inflammation and Thrombosis, Thromboembolic Events, Eosinophil-Related Thrombosis,Vascular Injury,Coagulation Cascade Activation.

INTRODUCTION

Eosinophilia, defined by an elevated eosinophil count of more than 0.5 x 10^9/L in the peripheral blood,[1] can be attributed to a variety of underlying conditions, including allergic reactions, parasitic infections, autoimmune diseases, and certain malignancies. While primarily known for its role in combating parasitic infections and participating in allergic responses, eosinophilia has also been implicated in thrombotic events, a connection that remains under recognised in clinical practice .[2]

Deep vein thrombosis (DVT) is a condition characterized by the formation of a blood clot within a deep vein, commonly in the lower extremities. It poses significant morbidity and can lead to serious complications such as pulmonary embolism if the clot dislodges and travels to the lungs. The pathogenesis of DVT is multifactorial, involving alterations in blood flow, endothelial injury, and hypercoagulability—collectively known as Virchow's triad.

In the context of eosinophilia, the pathogenesis of thrombosis involves several mechanisms. Eosinophils release cytotoxic granules and cytokines that can damage the endothelium, activate platelets, and promote a pro-inflammatory environment, all of which contribute to a hyper coagulable state[3]. Interleukin-5 (IL-5), a cytokine crucial for eosinophil proliferation and survival, plays a significant role in these processes by enhancing the activation and persistence of eosinophils in the bloodstream .

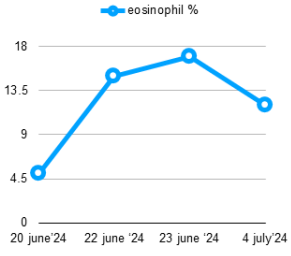


Figure 1: Change curve of the eosinophil %

This case report presents a patient with marked eosinophilia who developed DVT, exploring the clinical presentation, diagnostic challenges, and therapeutic interventions. By reviewing the literature on eosinophilia-associated thrombosis, this report aims to elucidate the underlying mechanisms and highlight the importance of considering eosinophilia in patients with unexplained thrombotic events. This case underscores the need for heightened clinical awareness and further research into targeted therapies that may mitigate the thrombotic risks associated with eosinophilia.

CASE PRESENTATION

Patient History And Initial Presentation

A 32-year-old male presented to the general medicine department with a one-week history of progressive swelling and pain in the left lower extremity. He also reported a dry cough for one week and low-grade fever in the evening for two days .The patient reported no history of recent trauma, prolonged immobilization, or prior thrombotic events. His medical history was not notable for seasonal allergies, he had no known history of parasitic infections or autoimmune diseases. The patient had no history of similar complaints, and his family history was unremarkable

Physical Examination and Initial Workup

On physical examination, the patient had marked swelling and tenderness in the left calf, with no erythema or local rise of temperature .his vital signs were stable with a blood pressure of 110/70 mmHg and a pulse rate of 80 bpm.The pulsations of bilateral dorsal foot arteries were maintained.There were no signs of systemic illness or infection. There were palpable lymph nodes in the left inguinal region,firm in consistency,non tender . Cardiovascular , respiratory and abdominal examinations were unremarkable. Initial laboratory investigations, including a complete blood count, revealed a significant eosinophilia with an absolute eosinophil count of 2.0 x 10^9/L (normal range: 0.0-0.5 x 10^9/L). With an eosinophil percentage of up to 17% during hospitalization (normal range: 1-6%) (figure 1) . The total leukocyte count on the day of admission was 7,700 cells/cumm(normal range: 4000-11000 cells/cumm). Coagulation Profiles revealed elevated D-Dimer levels(>10). Other blood counts and basic metabolic panels were within normal limits.

Diagnostic Imaging

A Doppler ultrasound and a CT venogram of the left lower extremity confirmed the presence of a thrombus in the common iliac, left external iliac , common femoral, left popliteal vein, anterior tibial and posterior tibial vein consistent with a diagnosis of deep vein thrombosis (DVT). There was no evidence of concurrent pulmonary embolism on a subsequent CT Chest. Even. Though it showed a few areas of focal ground glass opacities in bilateral upper lobes. Superficial inguinal ultrasound revealed 2 enlarged

left suprainguinal lymph nodes, the largest measuring approximately 24mmx7mm with maintained fatty hilum.

Further Investigations
Given the significant eosinophilia, further investigations were undertaken to determine the underlying cause. Stool samples were negative for parasitic infections. Serologic tests for autoimmune conditions, including rheumatoid factor and antinuclear antibody, were negative. Despite extensive work up,no secondary cause of eosinophilia such as parasitic infection or malignancy was identified . The patient was thus diagnosed with idiopathic hypereosinophilic syndrome (HES)**.** Bone marrow biopsy could not be performed as the patient was on anti coagulation.

Treatment and Follow-up
The patient was started on anticoagulation therapy with low molecular weight heparin followed by warfarin. Additionally, he was initiated on corticosteroids to manage the eosinophilia. . The patient remained symptom-free on a maintenance dose of corticosteroids**.**

After one dose of low molecular weight heparin was administered a panel of tests was sent in which serum homocysteine was found to be elevated ,27.7 umol/L (normal range : 6-15 umol/L)

DISCUSSION
This case illustrates the complex interplay between eosinophilia and thrombosis. The high eosinophil count likely contributed to endothelial damage and a pro-thrombotic state through the release of toxic granules and cytokines. The role of IL-5 in promoting eosinophil proliferation and survival was evident, highlighting the potential for targeted therapies in managing similar cases. This report underscores the need for clinicians to consider eosinophilia in patients with unexplained DVT and to explore comprehensive diagnostic approaches to identify and treat the underlying cause**.**

Detailed Pathogenesis of Deep Vein Thrombosis (DVT)
Deep vein thrombosis (DVT) occurs when a blood clot forms in a deep vein, usually in the legs. The pathogenesis of DVT is complex and involves a combination of factors described by Virchow's triad: endothelial injury, hypercoagulability, and stasis of blood flow.

1. **Endothelial Injury:**
- **Mechanical Trauma:** Physical damage to the endothelium, such as from surgery or injury, can expose subendothelial tissues, promoting platelet adhesion and clot formation.

- **Inflammatory Processes:** Inflammatory conditions can lead to endothelial activation and dysfunction, increasing the expression of pro-coagulant factors and adhesion molecules that facilitate clot formation. In the context of eosinophilia, eosinophils release cytotoxic granules (e.g., major basic protein and eosinophil cationic protein) that can damage the endothelium and create a pro-thrombotic environment .

2. **Hypercoagulability:**
- **Genetic Factors:** Inherited thrombophilias, such as Factor V Leiden mutation or prothrombin gene mutation, increase the tendency of blood to clot.

- **Acquired Conditions:** Conditions like cancer, pregnancy, and use of hormone replacement therapy or oral contraceptives can enhance the blood's coagulability. In this case, the patient's eosinophilia contributes to hypercoagulability. Eosinophils release cytokines and pro-inflammatory mediators (e.g., interleukin-5) that promote platelet aggregation and coagulation cascade activation

- **Autoimmune Disorders:** Conditions such as antiphospholipid syndrome can create a hypercoagulable state, although this was not present in this case.

3. **Venous Stasis:**
- **Immobility:** Prolonged bed rest or immobility slows blood flow in the veins, which can lead to stasis and increase the risk of clot formation.

-Obstruction: External pressure from tumors, cysts, or even during pregnancy can obstruct venous return, contributing to stasis.

Significance Of Other Tests
About 50% of patients with unprovoked VTE have lab evidence of inherited thrombophilic disorder.

◦ Work-up during acute thrombosis leads to false positivity (↓protein C, ↓protein S, ↓antithrombin, ↑anticardiolipin Abs, ↑lupus anticoagulants, ↑Factor VIII)

◦ Work-up during heparin and warfarin treatment leads to false results (↓protein C, ↓protein S, ↓antithrombin, ↔lupus anticoagulants)

◦ Therefore, given the recommendations for treatment duration and rates of false values, testing is not likely to change management and should be deferred in most cases! As a reminder, in all cases, acute testing will not be helpful.

◦ Consider thrombophilia work-up if patient has 1st-degree relatives with VTE, clot at young age (<40) ,has plan for pregnancy or plan for OCPs; may be part of miscarriage work-up (>3 miscarriages per guidelines).

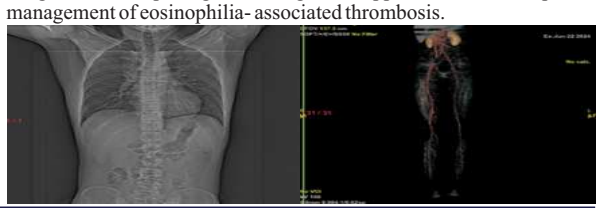
◦ Consider thrombophilia workup in young patient if high suspicion for AntiPhosphoLipid Syndrome
▪ Wait 30 days from clot: send Lupus Anticoagulant and Anticardiolipin Antibody IgG and IgM.
▪ If one is +, resend in 90 days to confirm, while continuing anticoagulation.

◦ Consider thrombophilia work-up if mesenteric clot or other unusual location: if considering myeloproliferative disorder, send CBC and JAK2.

Comparison With Other Cases
In comparison to other reported cases of eosinophilia-associated thrombosis, this case is unique due to the absence of common secondary causes such as parasitic infections or hematologic malignancies, thus categorizing it as idiopathic hypereosinophilic syndrome (HES). For example, a study by Ames et al. (2009)[4] highlights various parasitic diseases that can lead to eosinophilia and subsequent thrombosis . Unlike these cases, our patient had no identifiable secondary cause despite comprehensive investigations, making it a rare and idiopathic presentation.

Unique Aspects and Learning Points
1. Idiopathic Nature: The idiopathic nature of eosinophilia in this case is notable, emphasizing the need for extensive diagnostic workup to exclude secondary causes.
2. Comprehensive Evaluation: The detailed investigations,including a range of serological tests,imaging studies and coagulation profiles underline the importance of a thorough and systematic approach in diagnosing the underlying etiology of thrombosis
3. Therapeutic Management : The combination of anti coagulation therapy and corticosteroids effectively managed both the thrombotic event and the eosinophilia, highlighting the dual approach needed in such cases.
4. Clinical Vigilance : this case highlights the need for clinicians to maintain a high level of suspicion for eosinophilia as a potential cause of thrombosis,particularly in the absence of common risk factors like immobilisation and recent surgery.
5. Limitations and Future Directions : Further research into targeted therapies, such as anti -IL 5 treatments,could provide new avenues for managing patients with eosinophilia associated with thrombosis, potentially improving outcomes and reducing thrombotic risks.

CONCLUSIONS
This case of eosinophilia- induced DVT in a young, otherwise healthy individual underscores the complexity and diagnostic challenges associated with hypereosinophilic syndromes. It also highlights the importance of considering eosinophilia in the differential diagnosis of unexplained thrombotic events . Through a detailed review and comparison with existing literature, this report contributes valuable insights into the pathogenesis,diagnostic approach , and therapeutic management of eosinophilia- associated thrombosis.



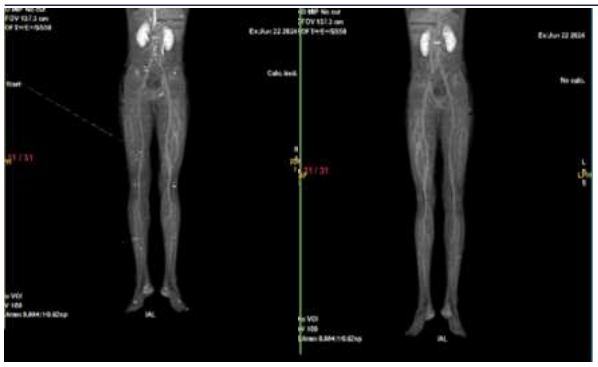


Figure 2: CT Venogram of the abdomen,pelvis,lower limbs: multiplanar reformatted images showing inferior vena cava with normal patency with near complete filling defect with enhancing wall noted in left common iliac vein extending to the left external and internal iliac vein,common femoral vein,extending into Great Saphenous Vein,superficial and deep femoral vein,popliteal vein,anterior tibial vein, posterior tibial veins.

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