Eosinophilic Vasculitis: Time for Recognition of a New Entity?

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Abstract Hypereosinophilia is part of a group of complex disorders with multisystem involvement. A 23 year old male was admitted to our centre with bilateral popliteal artery and venous thrombosis and impending gangrene of the left forefoot along with deep venous thrombosis of the right lower extremity. Investigations revealed marked peripheral blood eosinophilia (27,669/ μ L). Bone marrow showed increased eosinophils & eosinophil precursors and no evidence of a clonal disorder. Skin biopsy from the ulcerated lesions showed small vessel vasculitis with intense eosinophilic infiltration. Investigations to look for secondary causes of hypereosinophilia in the form of Antinuclear Antibody, P-Anti Neutrophil Cytoplasmic Antibody (ANCA) and C-ANCA and FIP1L1-PDGFR α , Bcr-Abl and JAK2V617F mutations were negative. The arterial and venous thrombosis and cutaneous vasculitis were linked to the presence of hypereosinophilic syndrome. The patient's illness responded to high dose corticosteroids leading to complete resolution of symptoms. We reviewed the literature on the lesser known entity of eosinophilic vasculitis and its association with thrombosis.

Keywords Eosinophilia · Vasculitis · Thrombosis

Introduction

Hypereosinophilia is defined as an absolute eosinophil count greater than 1,500/ μ L. Hypereosinophilia may be reactive to infections and parasitic infestations, part of clonal disorders (acute and chronic leukaemia) or due to unknown causes defined as idiopathic hypereosinophilic syndrome. Vasculitis and hypereosinophilia have been associated with each other both in cause as well as in effect. Certain forms of vasculitis such as Eosinophilic Granulomatosis and Polyangiitis (EGPA) have been associated with hypereosinophilia, although the end organ damage in these cases is not related to the hypereosinophilia itself. The term eosinophilic vasculitis has been described in literature however it is not accepted by many as a distinct entity. Eosinophilic vasculitis is a condition wherein the vascular injury may occur due to an underlying connective tissue disease or as an idiopathic form designated as primary eosinophilic vasculitis, both of which may be associated with hypereosinophilic syndrome. Both states have been associated with a prothrombotic state causing venous and arterial thrombosis that may be life threatening. Fortunately, both EGPA and the Idiopathic Hypereosinophilic Syndrome are responsive to therapy with corticosteroids.

Case Report

A 23-year-old male developed swelling and pain in both legs after a 10 h bus journey. Attributing this to fatigue, he sought no treatment for the same. After 5 days, he developed painful ulcers on both legs. The ulcers were initially small and painful but over the next few days coalesced to form large confluent lesions with the overlying skin

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Fig. 1 Gangrenous changes affecting left lower extremity. Bullous lesions are also seen

Fig. 2 Extensive cutaneous necrosis with punched out and confluent ulcerated lesions on both lower extremities

developing a necrotic appearance. The patient was admitted to a local hospital for these complaints where a diagnosis of deep venous thrombosis of both popliteal and common femoral veins was made and therapeutic anticoagulation started. However, in hospital this patient developed pain and discoloration of the left foot along with progression of the ulcerated lesions to involve the upper limbs as well. Arterial Doppler and CT angiography revealed bilateral popliteal artery thrombosis and impending gangrene of the left forefoot. He was referred to our centre with the above complaints. On examination, the patient was tachypnoeic at rest with an oxygen saturation of 95 % on room air. He had multiple confluent punched out ulcerated lesions on both legs with gangrenous changes affecting the left foot (Figs. 1, 2). At admission the patient had a haemoglobin of 12.1 g/dL, a total white cell count of 40,100/ μ L with an absolute eosinophil count of 27,669/ μ L and a platelet count of 396,000/ μ L. Renal and liver serum chemistries were normal. Baseline prothrombin time and activated partial thromboplastin time were within normal limits. D-dimer was elevated. Doppler ultrasonography revealed the presence of deep venous thrombosis affecting both lower limbs and the left upper limb, as well as arterial thrombosis affecting both popliteal arteries, which was confirmed by CT angiography (Fig. 3). Pulmonary CT angiography showed a small sub-segmental pulmonary thromboembolism. A bone marrow examination was performed and showed a marked increase in eosinophils and

Fig. 3 Bilateral Popliteal artery cut off on CT angiography

Fig. 4 Healing ulcers on lower extremity (after steroid therapy)

eosinophil precursors. Skin biopsy showed the presence of small vessel vasculitis with intense eosinophil infiltration into the perivascular areas but no granulomas. The patient was extensively worked up for secondary causes of hypereosinophilia. Anti nuclear antibody, P-ANCA and C-ANCA were negative. Total Immunoglobulin E levels were $>10,000$ units/L. Serum tryptase levels were normal. Polymerase Chain Reaction (PCR) for the FIP1L1-PDG-FRA, Bcr-Abl and JAK2V617F mutations were negative. Pulmonary function test was suggestive of mild restriction and there was no history suggestive of reactive airway disease. Stool examination for parasites and a filarial serology were both negative. A procoagulant workup did not reveal any abnormal findings however protein C and S levels could not be assessed in the presence of thrombosis. Transthoracic echocardiography was normal.

A diagnosis of Hypereosinophilic Syndrome with medium vessel vasculitis was made. The patient was given intravenous methylprednisolone (1 gm per day for 3 days) followed by oral prednisolone (1 mg/kg/day) resulting in a rapid response. Peripheral blood eosinophilia and skin ulcers resolved after the initiation of the above therapy (Fig. 4). In addition the patient was treated for hospital acquired pneumonia with intravenous piperacillin-tazobactam and teicoplanin. Anticoagulation was initiated with

an infusion of unfractionated heparin which was then changed to oral warfarin after a 5 day overlap. Aspirin (150 mg/day) and atorvastatin (20 mg/day) were also given in view of arterial thrombosis. Despite these measures the area affected with gangrene could not be salvaged and the patient underwent a below knee amputation.

Discussion

The Hypereosinophilic Syndromes (HES) are a heterogeneous group of disorders that are characterised by overproduction of eosinophils and clinical manifestations related to organ infiltration and damage by circulating eosinophils and cytokines. The defining criteria included the persistence of eosinophilia $>1,500/\mu\text{L}$ for 6 months or more, the existence of eosinophil mediated end organ damage and the absence of other aetiologies for hypereosinophilia [1]. These criteria have invited criticism as most patients may require treatment before the onset of end organ damage or 6 months. The current criteria for the diagnosis of hypereosinophilia include the presence of $>1.5 \times 10^9/\text{L}$ eosinophils in the peripheral blood on two occasions >1 month apart and the presence of tissue or bone marrow eosinophilia or marked deposition of eosinophil granule contents [2]. The current definition of HES includes the above criteria and the presence of end organ damage attributable to eosinophils in the absence of other aetiologies. The clinical manifestations of HES are dependent on the organs affected. Vasculitis has been associated with the hypereosinophilic syndrome as a separate entity, distinct from that seen in EGPA [3]. Two forms of eosinophilic vasculitis have been described. One form has been associated with some peculiar skin lesions including pruritic papules, urticaria and angioedema with mild eosinophilia. Another form has been described in conjunction with the hypereosinophilic syndrome but no features suggestive of EGPA [4]. Both forms of vasculitis have been associated with the development of arterial and venous thrombosis.

Thrombosis in the hypereosinophilic syndrome may be caused by a number of factors. These include the activity of eosinophil granule contents. Eosinophils are a source of tissue factor production and storage, and this may influence the prothrombotic state in hypereosinophilic syndrome [5]. Eosinophilic Cationic Protein (ECP) has been implicated in thrombogenesis by enhancing factor XII activity and binding endogenous heparanoids [6, 7]. Another granule content, Major Basic Protein (MBP) may also damage endothelium directly and thereby expose collagen leading to thrombosis [8, 9]. Although widespread vasculitis and microthrombosis results in the characteristic multiple organ dysfunction typical of the vasculitides, some cases may

Table 1 Characteristics of patients with eosinophilic vasculitis and thrombotic complications

Source	Age/ Sex	Site of thrombosis	Other complications	AEC	Treatment given	Outcome
Ishii [18]	30/M	Thrombosis demonstrated in small arterioles in nearly all organs on autopsy	Endomyocardial Fibrosis	119,040/ μ L	Busulfan and Prednisolone	Death (Cardiac Failure)
Parker [19]	44/M	Small-bowel necrosis with vasculitis and thrombosis	Asthma, cutaneous blisters	5,040/ μ L	Prednisolone	Bowel resection, survived
Schulman [20]	11/M	Cerebral Venous Thrombosis	Cutaneous erythematous lesions	8,589/ μ L	Prednisolone	Died
Jang [21]	34/M	Digital gangrene, Raynaud's phenomenon	Cutaneous brownish plaques, Mononeuritis multiplex	7,385/ μ L	Prednisolone	Survived
	24/M	Digital gangrene	Cutaneous erythematous and purpuric lesions	8,580/ μ L	Prednisolone	Survived
Narayan [22]	29/M	Cutaneous infarction	Fever	9,282/ μ L	Prednisolone,	Survived
Liao [4]	58/M	DVT of both lower limbs	Pulmonary thromboembolism, Renal vein thrombosis, congestive heart failure, Cerebral infarction, Cutaneous lesions	4,018/ μ L	Prednisolone, hydroxyurea	Died
	21/M	DVT of right lower extremity	Pulmonary Embolism, Mitral insufficiency, Cutaneous erythematous lesions	3,655/ μ L	Prednisolone,	Survived
Kim [23]	32/F	Digital gangrene affecting all four limbs	Multiple arterial thrombosis demonstrated on angiography	16,358/ μ L	Prednisolone, Oral Cyclophosphamide	Survived
Aslan [24]	29/M	DVT of left lower extremity	Factor V Leiden mutation was positive	10,788/ μ L	Prednisolone, Hydroxyurea	Survived
Abdulwahab [10]	13/M	Thrombosis of the main portal and superior mesenteric and hepatic veins	Splenic infarction	5,883/ μ L	Methylprednisolone pulse, prednisolone, oral cyclophosphamide, azathioprine	Survived
Song [12]	48/M	DVT of the left lower extremity	Acute Cholecystitis, Mononeuritis multiplex	3,629/ μ L	Prednisolone	Survived
	21/M	Pulmonary artery and right portal vein	Erythematous papules with skin necrosis	2,990/ μ L	Prednisolone	Survived
Nakajima [25]	93/F	Digital Gangrene	Indurated purpuric lesions on extremities	1,072/ μ L	Prednisolone, Oral Cyclophosphamide	Died of unrelated causes (Heart Failure)
Jandus [26]	55/F	Digital Gangrene, Raynaud's phenomenon	Four prior episodes of deep venous thrombosis in both lower extremities	12 % eosinophils in peripheral blood	Prednisolone, Methotrexate	Survived
Present Study	23/M	DVT of right lower extremity, bilateral popliteal artery thrombosis	Cutaneous blisters and infarction, pulmonary thromboembolism, gangrene of left foot	27,669/ μ L	Prednisolone	Survived, Amputation of left foot

DVT Deep venous thrombosis, AEC Absolute eosinophil count

present only with thrombotic complications involving larger vessels. Such patients may present with mesenteric ischaemia [10], stroke [11], deep venous thrombosis [12] and pulmonary thromboembolism [13].

The hypereosinophilic syndrome needs to be recognised early and after exclusion of precipitating causes, should be treated aggressively. Patients with hypereosinophilia as a part of a myeloproliferative neoplasm may benefit from imatinib therapy if the FIP1L1-PDG-FRA rearrangement was present [14]. Patients with other forms of HES should receive treatment with corticosteroids as initial therapy and may require further immunosuppressive therapy with cyclosporine, tacrolimus or cyclophosphamide [15]. Anti Interleukin-5 directed therapy with the monoclonal antibody Mepolizumab has also been used [16].

A review of literature (Table 1) revealed a number of similar cases presenting with thrombotic complications. Many of these cases were males of Asian ethnicity. Cutaneous findings were seen in most cases and all received some form of steroid therapy.

Previously published experience with hypereosinophilia from our institute consisted of four cases, two of which were related to myeloproliferative neoplasms [17]. None of these patients had any evidence of thrombotic complications or vasculitis.

Conclusion

Eosinophilic Vasculitis is a rare association of the spectrum of Hypereosinophilic Syndromes. It may be associated with thrombotic complications involving both arterial and venous circulations. Containment of the pathogenic mechanism by steroids and other forms of immune suppression may lead to control of the prothrombotic state.

Conflict of interest The authors declare that they have no conflict of interest.

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