

## Case Report

# Arterial and Venous Thrombosis in a Chinese Boy with Hypereosinophilic Syndrome

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### Abstract

A 16-year-old Chinese boy presented with multiple tender subcutaneous nodules and erythematous pruritic rashes over bilateral lower limbs. Investigation showed markedly elevated circulating eosinophils ( $7.35 \times 10^9/L$ ) and positive lupus anticoagulant. Doppler ultrasound and positron emission tomography scan revealed extensive venous thromboses and arterial insufficiency. The diagnosis of idiopathic hypereosinophilic syndrome with multiple end-organ involvement was established after exclusion of possible infectious, allergic and oncologic causes. Symptoms resolved after treatment that included low-molecular-weight heparin, corticosteroid and azathioprine. Here we describe the variable manifestations of hypereosinophilic syndrome and its associated features.

### Key words

Hypereosinophilia; Lupus anticoagulant; Thrombosis; Vasculitis

### Introduction

Hypereosinophilic syndrome is notorious for its heterogeneous manifestations and any organ system can be involved. Vasculitis and thrombosis, if they occur, can be life-threatening. The presence of lupus anticoagulant may further increase the risk of thrombotic events. Here we describe a case involving a Chinese child who developed

this rare disease entity complicated by vasculitis and thrombosis, which was managed with anticoagulation therapy, corticosteroid and then azathioprine.

### Case Presentation

A 16-year-old Chinese boy from Hong Kong with a past history of childhood allergic rhinitis and asthma presented with 3 months of bilateral ankle swelling and multiple indurated lesions under the skin of his thigh, with overlying erythema. There was no travel history and he denied consumption of exotic foods, unsanitary water, over-the-counter medications or herbal supplements. This was treated as cellulitis with several courses of antibiotics consisting of oral amoxicillin-clavulanate, ceftriaxone and ceftazidime. Subsequently, he developed tingling and numbness at his left middle fingertip.

The patient was admitted for progressive symptoms and a low-grade fever of  $38.1^\circ\text{C}$ . Physical examination revealed multiple tender, erythematous indurations over bilateral calves and thighs and increased warmth. The largest induration was up to 3 cm x 3 cm. Additionally, there was increased warmth, tenderness and effusion of his left knee. Bilateral inguinal lymph nodes were enlarged.

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Laboratory results revealed leukocytosis ( $14.6 \times 10^9/L$ ) with marked eosinophilia ( $7.35 \times 10^9/L$ ), and normal haemoglobin concentration and platelet count. Liver and renal function was normal. Inflammatory markers were elevated (C-reactive protein: 13.4 mg/L, or 127.6 nmol/L; erythrocyte sedimentation rate: 12 mm/hr). Cultures from the blood and knee synovial fluid were negative, and the knee aspirate had white cells of 1+. Immunoglobulin E (IgE) was markedly elevated at 10,100 IU/ml. Autoimmune markers including C3, C4, rheumatoid factor, anti-cyclic citrullinated peptide, anti-cardiolipin, antinuclear antibodies and antineutrophil cytoplasmic antibodies were within the normal ranges, but lupus anticoagulant was detectable. His clotting profile was slightly deranged (prothrombin time 15.5 sec N: 10-12.3 sec; APTT 41.6 sec N: 28.2-38.2 sec). Levels of protein C, protein S, anti-thrombin III, and tryptase ( $3.2 \mu\text{g/L}$  N:  $<11.4 \mu\text{g/L}$ ) and urinalysis were unremarkable.

The patient began to have spikes of high fever and night sweats. Numbness over his fingertips became more apparent and gangrene later developed over multiple fingertips. The right radial, bilateral posterior tibial and right dorsalis pedis pulses became non-palpable. There was also superficial thrombophlebitis of his left great saphenous vein and left small saphenous vein, which presented as hardened and tender veins (Figure 1).

To assess the extent of end-organ involvement, biopsy of an inguinal lymph node showed reactive lymphoid hyperplasia with a component of dermatopathic lymphadenopathy. Skin biopsies of the left calf and thigh lesions showed dermal, subcutaneous peri-vascular and



**Figure 1** Superficial thrombophlebitis of the patient's left great saphenous vein: a non-tender, non-collapsible and hardened left great saphenous vein (red arrow).

peri-adnexal mature eosinophilic infiltration, with focal micro-thrombus and angiitis. There was no evidence of malignancy, flame figures or granuloma.

Positron emission tomography scan showed vasculitis involving both lower extremities. There were subcutaneous oedema and skin thickening with increased fludeoxyglucose-F-18 activity, probably inflammatory in nature. There were also multiple mildly active lymph nodes in the lower limbs and increased bone marrow activity. An artery duplex scan of the lower limbs revealed thromboses of the bilateral ulnar and right radial arteries, and very limited flow to both tibial arteries. Ultrasound of the lower limbs showed deep vein thrombosis (DVT) in one of the peroneal veins in the left mid-calf and superficial thrombophlebitis of the left great and small saphenous veins.

A comprehensive microbiological investigation was negative, including stool examination for ova and cyst, serum microfilaria culture and antibodies against *Penicillium marneffeii*, *Aspergillus*, *Coccidioides*, *Histoplasma*, *Blastomyces* and *Cryptococcus* spp. Viral serologies for human immunodeficiency virus, cytomegalovirus, parvovirus, Epstein-Barr virus, hepatitis B virus and hepatitis C virus were negative. Acid-fast bacillus smear and culture in the stool and urine were negative. Bone marrow examination revealed megakaryocytic hyperplasia with marrow eosinophilia (the eosinophil and their precursors counts were up to 19%) and a blast count of up to 1.2%. Trepine biopsy demonstrated slight marrow eosinophilia but no abnormal cellular infiltration. Fluorescence in situ hybridisation of the bone marrow showed an absence of FIP1L1 and platelet-derived growth factor receptor (PDGFR) A and B rearrangement. Flow cytometry showed no clonal expansion of lymphocytes.

For his vasculitis and venous thromboses, the patient was started on oral prednisolone 30 mg twice daily and subcutaneous tinzaparin 11,000 IU daily, which was later tapered to 9,000 IU daily according to serum anti-Xa level monitoring. Nifedipine 5 mg four times daily and dipyridamole 100 mg three times daily were given for his arterial insufficiency.

After commencement of corticosteroid therapy, his eosinophilia resolved the next day, followed by a fall in IgE levels. Lupus anticoagulant became negative. His arterial insufficiency gradually improved, and ultrasound of his lower limbs showed recanalisation of the previous thrombosed veins. Oral azathioprine 100 mg daily was added as a steroid-sparing agent one month later while the

corticosteroid was tapered down slowly, and he is currently on prednisolone 5 mg on alternate days. Tinzaparin was discontinued after 6 months. The child is followed up regularly with monitoring of his eosinophil counts, IgE levels and inflammatory markers.

## Discussion

### *Manifestations of Hypereosinophilic Syndrome*

In 2012, a consensus on the criteria of eosinophilic disorders was made, and hypereosinophilic syndrome (HES) was defined by 1) persistent peripheral blood eosinophilia of  $\geq 1.5 \times 10^9/L$  ( $1500/mm^3$ ) on 2 examinations (with an interval of  $\geq 1$  month apart) and/or tissue hypereosinophilia, 2) with the absence of a secondary cause 3) and evidence of eosinophil-associated end-organ damage.<sup>1</sup> This disorder rarely occurs in children, and the cause is often secondary. Atopic dermatitis and graft-versus-host disease are the two most commonly associated conditions.<sup>2</sup> Our patient fulfilled these criteria based on peripheral eosinophilia and vascular infiltration of eosinophils, complicated by vasculitis and thrombosis. Secondary causes were ruled out after workup by multiple paediatric subspecialists.

The manifestations of HES can be heterogeneous and any organ system can be involved. Ogbogu and colleagues reviewed 188 patients from 11 institutions who met the criteria for HES and they found a male predominance of 55%, with a median age at diagnosis of 45 years old (range: 6-85 years).<sup>3</sup> There was a mean peak eosinophil count of  $6.6 \times 10^9/L$ . The most common presentation of HES involves the dermatologic (37%), followed by pulmonary (25%) and gastrointestinal (14%) systems. Other systems include rheumatologic, cardiac, neurologic and hematologic (including DVT and superficial thrombophlebitis), while <6% of patients were asymptomatic. However, only occasional cases of peripheral vascular involvement and/or thrombotic complication have been reported.<sup>4,5</sup>

### *Eosinophilia, Lupus Anticoagulant and Thrombosis*

The precise mechanism underlying thrombosis associated with eosinophilia is unclear. It is known that eosinophils secrete tissue factor (TF) and major basic protein (MBP). TF activates the clotting cascade, and MBP stimulates platelet aggregation and inhibit vascular endothelial thrombomodulin.<sup>6</sup> Recently, two groups reviewed HES-related arterial vasculitis.<sup>4,5</sup> Male predominance was a common finding. Complications

included limb ischaemia requiring amputation, mesenteric ischaemia, stroke, DVT and pulmonary thromboembolism. As such, prompt anticoagulation treatment is paramount.

In addition to his significant eosinophilia, our patient had circulating lupus anticoagulant that likely further contributed to thrombosis. Lupus anticoagulants are thrombogenic autoantibodies and act via several pathways that may ultimately result in increased tissue factor expression by monocytes and endothelial cells, platelet activation, thromboxane release, fibrin polymerization, a decrease in fibrinolysis and inhibition of natural anticoagulants.<sup>7</sup> Ames et al reviewed 12 cases of different disease identities including infective causes, anti-phospholipid syndrome, eosinophilic granulomatosis with polyangiitis and HES with co-existing eosinophilia and anti-phospholipid antibodies.<sup>8</sup> Ten patients suffered from vascular occlusions and ischaemic stroke. The exact mechanism of this phenomenon and the association between HES and elevated lupus anticoagulants are not yet fully understood. We speculate that our patient's lupus anticoagulants became absent due to the immunosuppressive effects of corticosteroids and azathioprine.

## Management

The World Health Organization revised the classification of eosinophilic disorders in 2017.<sup>9</sup> After ruling out reactive causes of eosinophilia, treatment is primarily dependent on the type of eosinophilic disorder according to the classification scheme (Figure 2). In the case of clonal eosinophilia with FIP1L1-PDGFR $\alpha$  (FP-positive) or PDGFR $\alpha$ /PDGFR $\beta$  rearrangements, imatinib is the first-line option and corticosteroid should also be added for patients with cardiac involvement.<sup>9</sup> Corticosteroid therapy is the mainstay treatment for hypereosinophilia in FP-negative clonal eosinophilia, lymphocyte variant and idiopathic HES. Hydroxyurea may be used in conjunction with corticosteroid for non-responders. The most appropriate dose and the duration of treatment remain controversial. The novel anti-IL-5 therapy (benralizumab) has recently completed a phase 2 trial for PDGFR $\alpha$ -negative HES with promising results.<sup>10</sup>

Prednisolone was started for our patient and tapered down according to his decreasing eosinophil counts, while an anticoagulant was given for 6 months until complete resolution of his thrombosis. Azathioprine was added as a

steroid-sparing agent. Anti-IL-5 therapy was reserved as a second-line treatment if his symptoms remained refractory.

treatment for FP-negative HES. Our patient's disease is currently in remission with sustained resolution of his eosinophilia and thrombosis.

### Conclusion

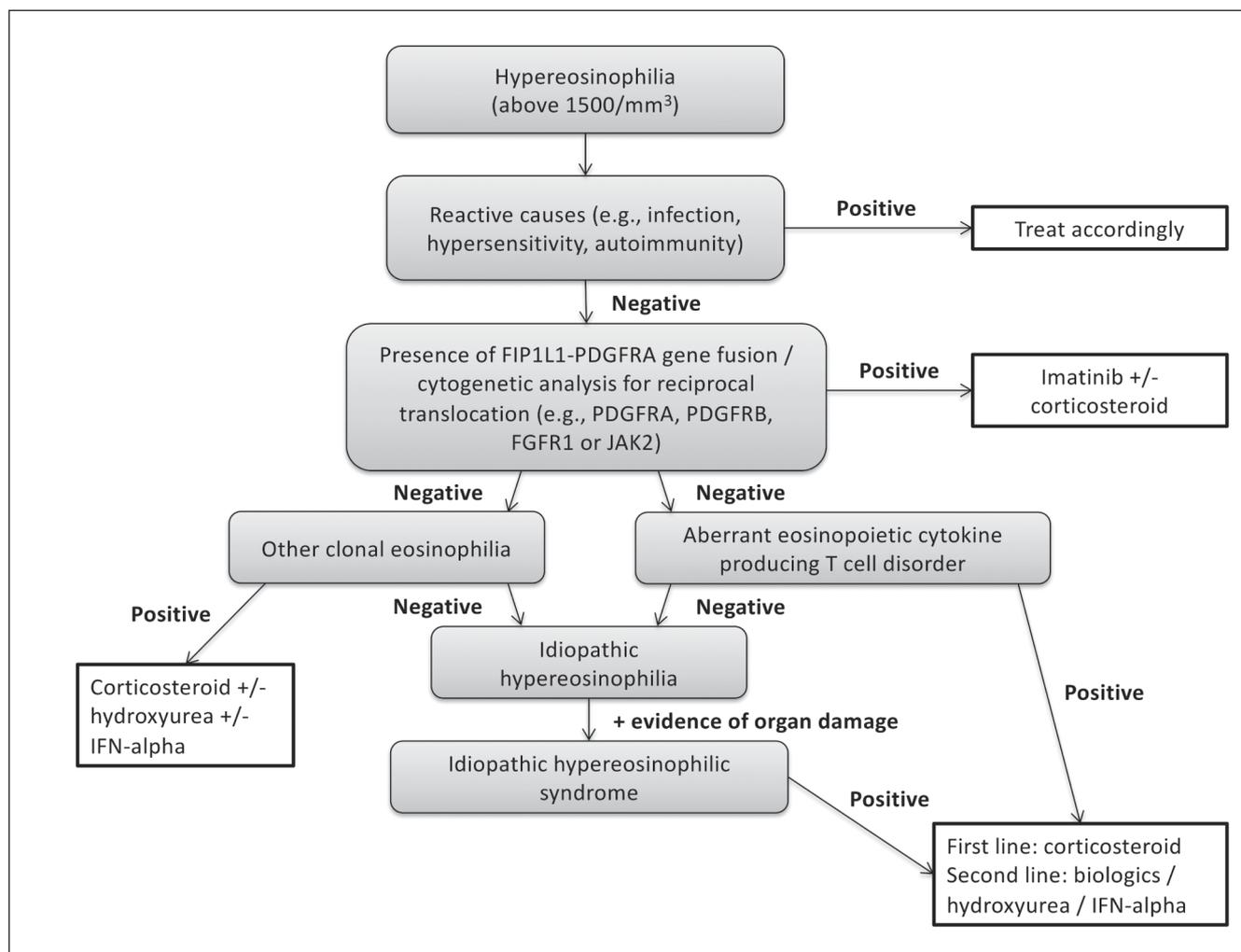
Hyper eosinophilia can lead to vasculitis and the presence of lupus anticoagulant may further aggravate the associated thrombosis. This combination, although rare, can occur such as for our patient and may result in significant morbidity or mortality. Early identification and treatment can prevent loss of limb(s) and life-threatening complications. Corticosteroid therapy is the mainstay

### Ethical Approval

Consent has been obtained and no approval was required for this case report.

### Conflicts of Interest

None



**Figure 2** The recommended therapies for hyper eosinophilia are dependent on results from following the diagnostic algorithm (PDGFRA, platelet-derived growth factor receptor alpha gene; PDGFRB, platelet-derived growth factor receptor beta gene; FGFR1, fibroblast growth factor receptor 1; JAK2, Janus kinase 2; IFN-alpha, interferon-alpha).

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