

## Acute Pulmonary Embolism in A Patient with Hypereosinophilia and Psoriasis

Jui-Hung Ko, MD; Jheng-Wei Lin, MD; Rosaline Chung-Yee Hui, MD, PhD

Peripheral blood hypereosinophilia reflects various underlying disorders. However, its thromboembolic consequences are not often highlighted. We report a case of acute pulmonary embolism in a 42 year-old male prisoner hospitalized for erythrodermic psoriasis who presented with generalized edema and shortness of breath. Severe eosinophilia (absolute eosinophil count 6232/ $\mu\text{L}$ ) was also noted. Although severe psoriasis can be associated with eosinophilia and metabolic syndrome, acute pulmonary embolism is very rare in these patients. Immobilization secondary to severe psoriatic arthritis and prolonged use of leg cuffs can exacerbate the formation of thromboembolism. Although investigating the underlying causes of eosinophilia is important, we would like to highlight the importance of being aware of thromboembolic events, especially in patients with other thrombotic risk factors. (*Chang Gung Med J 2011;34(6 Suppl):17-23*)

**Key words:** hyper-eosinophilia, thrombo-embolic disease, psoriasis

**B**lood eosinophilia is an integral phenotype of an underlying hematologic neoplasm or cytokine-mediated reactive phenomenon.<sup>(1)</sup> Its identifying causes have been emphasized in the English literature, but discussion of related complications, such as thromboembolic disease, is limited.<sup>(2-4)</sup> We herein report a patient with marked eosinophilia and psoriatic arthropathy who developed pulmonary embolism caused by deep vein thrombosis (DVT) of the lower extremity. For clinicians, hypereosinophilia could be a clue to thromboembolic disease.<sup>(3)</sup>

### CASE REPORT

A 42 year-old male prisoner with a history of severe psoriasis vulgaris and psoriatic arthritis for 20 years was hospitalized because of intermittent fever, chills, general malaise, and acute exacerbation of psoriatic erythroderma for one week. Exertional dys-

pnea was also noted for a few days. He has been treated with acitretin 25 to 35 mg per day for the last 20 years.

Physical examination showed an overweight, bedridden man (76.9 kg, with body mass index of 26.22) with generalized scaly erythematous papuloplaques on the scalp, trunk, and extremities (Fig. 1). Because of bilateral knee flexion contractures secondary to psoriatic arthritis, he had been unable to walk for at least a year. His feet had also been placed in leg cuffs for 3.5 months because of imprisonment. The range of motion on knee flexion was 30 degrees (normal range, 135 degrees) on the right side and 45 degrees on the left side, while knee extension was completely limited (normal range, 0-10 degree). No evidence of varicose veins was observed.

Laboratory data showed leukocytosis with eosinophilia with white blood cells: 15200/ $\mu\text{L}$  (normal range, 3900-10600); segments: 35% (normal,

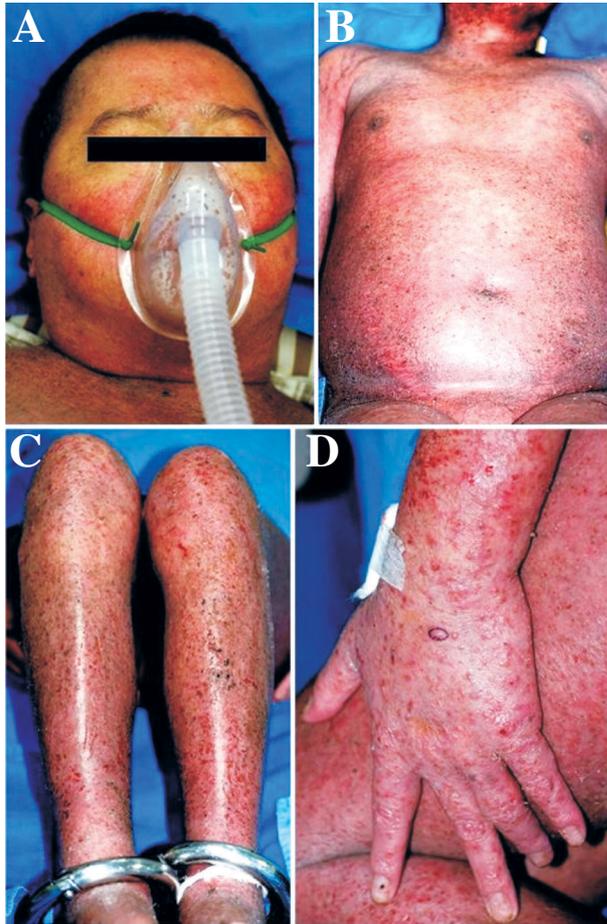
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From the Department of Dermatology, Chang Gung Memorial Hospital at Taipei, Chang Gung University College of Medicine, Taoyuan, Taiwan.

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Correspondence to: Dr. Rosaline Chung-Yee Hui, Department of Dermatology, Chang Gung Memorial Hospital at Taipei, 199, Dunhua N. Rd., Songshan District, Taipei City 105, Taiwan (R.O.C.) Tel: 886-2-27135211 ext. 3397; Fax: 886-2-27191623;

E-mail: rosaline.hui@gmail.com



**Fig. 1** A 42-year-old bedridden dyspneic man with generalized swelling and scaly erythematous papulo-plaques. (A) Swelling and flushing of the face. (B) Erythematous and scaly papulo-plaques on the trunk. (C) Severe excoriation on the legs, with flexion contractures and heavy leg cuffs on the feet. (D) Scaly papulo-squamous eruption on the dorsum of the left hand.

42-74) and eosinophils: 41% (normal, 0-5); platelets: 131000/ $\mu$ L (normal, 150000-400000); absolute eosinophil count (AEC): 6232/ $\mu$ L (normal, 50-350) and elevated IgE 36800 IU/mL. He also had a high C-reactive protein [CRP: 185.05 mg/L (normal,  $\leq$  5)], and lactate dehydrogenase (LDH): 708 U/L (normal, 125-215) and low albumin: 2.1 mg/dl (normal, 3.5-5.5). Other biochemistry data were within normal limits. Our patient had a penicillin allergy with a positive result on a penicillin skin test. He denied using other medications aside from acitretin in the past 20 years. He also denied having allergic

rhinitis, asthma, or body weight loss. There was no evidence of parasitic infestation from concentrated stool ova examination. He tested negative for human immunodeficiency virus 1 + 2 antibodies and rapid plasma reagin.

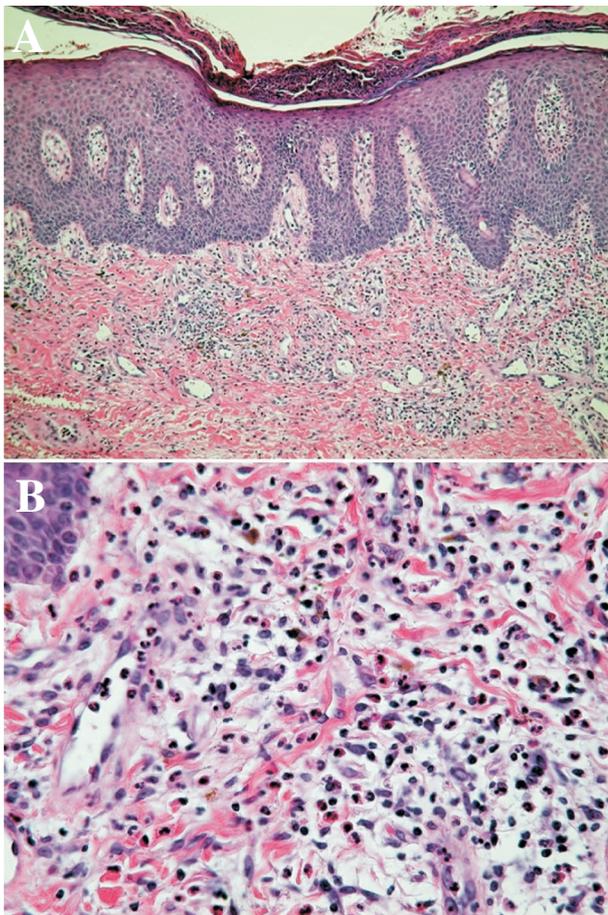
However, fungemia (*Candida albicans*) was detected from two sets of blood cultures 17 days later. There was no evidence of adrenal insufficiency [cortisol (06:00): 3.8  $\mu$ g/dl (normal range, 4.2-38.4); cortisol (16:00): 3.3  $\mu$ g/dl (normal, 1.7-16.6)], or malignancies from plasma electrophoresis and tumor markers although he had an elevated cancer antigen-125 (CA-125) [265.6 U/ml (normal < 35)] and squamous cell carcinoma antigen 11.8 ng/mL (< 1.5). A peripheral blood smear revealed increased eosinophils with normal morphology. Perinuclear antineutrophil cytoplasmic autoantibody was negative on enzyme-linked immunosorbent assay.

Histopathologic examination of an abdominal skin biopsy showed parakeratosis with Munro's microabscess, absence of the granular layer, marked acanthosis, exocytosis, and perivascular mononuclear cell infiltrates with neutrophils and eosinophils in the dermis (Fig. 2). These findings were consistent with psoriasis vulgaris.

Intermittent shortness of breath with occasional drops in oxygen saturation was noted during hospitalization. Chest radiography disclosed mild infiltration of the right lower lobe. No microorganisms were cultured from the blood or sputum initially. Fifteen days of empirical antibiotics (amoxicillin clavulanate 1.2 g 8 h, vancomycin 1 g q 12 h, imipenem 500 mg q 6 h, and ceftazidime 2 g q 12 h) were given for suspected pneumonia without a response. Systemic methylprednisolone 20 mg q 8 h was then tried for three days, resulting in resolution of eosinophilia but it rebounded to 6760/ $\mu$ L one day after discontinuation of the drug.

However, his dyspnea did not improve. Chest computed tomography (CT) to investigate the lung lesion unexpectedly showed a filling defect in the right pulmonary artery (Fig. 3A) and the anterior branch with several wedge-shaped opacities in the bilateral upper lung lobes. This was suggestive of pulmonary embolism. There was also bilateral pleural effusion with passive and partial atelectasis of the bilateral lower lobes.

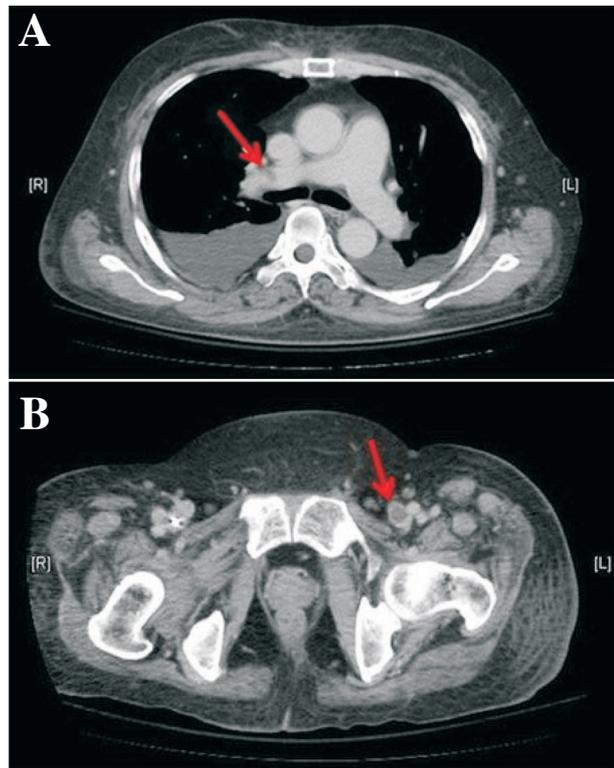
Further CT imaging of the lower abdomen and lower extremities demonstrated filling defects in the



**Fig. 2** Histopathology of a skin biopsy from the abdomen suggests psoriasis. (A) Low power magnification shows Munro microabscess, absence of the granular layer, marked acanthosis and perivascular infiltrates in the dermis (H & E, original magnification  $\times 100$ ). (B) Marked perivascular and interstitial infiltrates of eosinophils and neutrophils in the dermis (H & E, original magnification  $\times 400$ ).

inferior vena cava, and left iliac and femoral veins (Fig. 3B). In addition, diffuse subcutaneous edema and mild ascites with stranding of the mesentery were also noted. Pulmonary embolism resulting from DVT was impressed.

Whole body CT did not reveal any other tumor mass. Peripheral venous Doppler ultrasonography revealed poor recanalization in the left common femoral vein, long segmental vein and proximal long saphenous vein. Results of autoimmune antibodies such as antinuclear antibody and antinuclear antibody were negative, while levels of protein C, protein S and antithrombin III were all within normal



**Fig. 3** Chest and abdominal computed tomography (CT) is consistent with pulmonary embolism with deep vein thrombosis. (A) Chest CT shows a filling defect in the right pulmonary artery. (B) Abdominal CT shows a filling defect in the left femoral vein.

limits.

After a definite diagnosis of pulmonary embolism, our patient was treated with enoxaparin 60 mg q 12 h for two weeks and the intermittent shortness of breath improved. Upon discharge, his absolute eosinophil count had dropped to 2470/ $\mu\text{L}$  and IgE 9980 IU/ $\mu\text{L}$  with the use of fluconazole 400 mg q1d for 12 days. Prophylactic warfarin 2 mg daily was also prescribed for one month. Because of imprisonment, he was unable to return to the cardiology department for monitoring of sustained oral anti-coagulant therapy.

At the 8-month follow-up, the patient's absolute eosinophil count had returned to 57/ $\mu\text{L}$  and IgE 4960 IU/mL. There was no recurrence of exertional dyspnea or local tenderness in the right leg. The levels of fibrin degradation products, D-dimer, and fibrinogen were also within normal limits. Chest radiography revealed no active lesions. By the 18-month follow-

up, this man's absolute eosinophil count was mostly normal with occasional elevations.

## DISCUSSION

Acquired eosinophilia is not rare and usually signifies underlying disease. In healthy people, the upper limit of the AEC and the percentage of eosinophils in white blood cell count on a peripheral blood smear do not exceed 500/ $\mu$ L and 5%, respectively.<sup>(5)</sup> Eosinophilia can be categorized as mild (AEC 600-1500 cells/ $\mu$ L), moderate (AEC 1500-5000 cells/ $\mu$ L), or severe (AEC > 5000 cells/ $\mu$ L). The reported patient had severe eosinophilia with an initial AEC of 6232/ $\mu$ L on admission and 14630/ $\mu$ L after 13 days.

Etiologically, eosinophilia can be classified into primary (clonal), secondary, or idiopathic.<sup>(1)</sup> Primary eosinophilia is a clonal expansion of eosinophils, such as in acute myeloid leukemia, acute lymphoblastic leukemia, and chronic myeloid disorder. We found no myeloblasts in the peripheral blood smear or skin biopsy of our patient. Causes of secondary eosinophilia include allergy, infection, drugs, pulmonary eosinophilia, autoimmune disorder, inflammatory disorder, malignancy, and endocrinopathy. Although fungemia due to *Candida albicans* may be associated with eosinophilia, reported absolute eosinophil counts have ranged from 354-774/ $\mu$ L.<sup>(6,7)</sup> The presence of marked eosinophilia (47% of leukocytes) two weeks before detecting fungemia in our case suggested a second possible etiology such as a severe psoriasis flare. Indeed, an association with the severity of psoriasis has been documented.<sup>(8,9)</sup>

We incidentally found pulmonary embolism and DVT on chest CT in a survey for unexplained intermittent dyspnea irresponsive to systemic antibiotics. On hindsight, the dyspnea, generalized subcutaneous edema, and the elevated CRP, LDH, and CA-125 could all be accounted for by the extensive thrombosis.<sup>(10)</sup>

Acute pulmonary embolism is a life-threatening disease with significant morbidity and mortality. It is defined by obstructive thrombosis of the pulmonary artery. Although unilateral leg edema, pain, warmth and erythema are the clue symptoms, many patients with DVT are asymptomatic.<sup>(11)</sup> Even then, pain and tenderness do not correlate with the severity and

location of the thrombus.<sup>(12)</sup> Our patient demonstrated generalized anasarca secondary to hypoalbuminemia. Although his left leg swelling was slightly more severe, the extensive painful erythematous swelling on all limbs was regarded as a severe psoriasis flare with arthritis and obscured DVT in the differential diagnosis. Classically, DVT originates from the veins of the calf muscles.<sup>(12)</sup> Occasionally, DVT originates from the proximal veins, usually in response to a surgical procedure or trauma, which our patient denied. Long-term immobilization of the legs such as in bedridden patients in intensive care units, also induces DVT by slowing blood flow, but not from the large proximal veins.<sup>(13)</sup> Furthermore, the incidence of DVT in Asians is much lower than reported in Caucasians so thrombolytic therapy is not routinely prescribed for bedridden patients.<sup>(14)</sup> Base on the extensive thromboembolism originating from the inferior vena cava, left iliac vein and "Virchow's triad" theory in the pathogenesis of venous thrombosis, which includes damage to the endothelium, change in blood flow and hypercoagulability,<sup>(15)</sup> we hypothesized that both hypereosinophilia and long-term immobility contributed to this thromboembolic event.

A relationship between hypereosinophilia and thromboembolism has been increasingly reported in the English literature. Case reports of hypereosinophilia associated with thrombosis of the pulmonary artery,<sup>(3,16)</sup> femoral vein,<sup>(16)</sup> hepatic vein (Buddi-Chiari syndrome),<sup>(4)</sup> coronary artery,<sup>(17)</sup> renal vein,<sup>(18)</sup> and splenic vein<sup>(19)</sup> have been published. In a series of fifteen patients with the hypereosinophilic syndrome,<sup>(20)</sup> 66% suffered arterial and/or venous thrombosis at some stage of their disease. Another study found arterial occlusion ranging between 3.1% and 18.7% and a prevalence of venous occlusion between 5.8% and 30% in patients with Churg Strauss syndrome. Patients have thrombotic events when eosinophilia is at its highest.<sup>(21)</sup> Awareness of the pathogenetic link between eosinophils and thrombosis has implications in disease treatment.

Potential mechanisms for thrombosis in eosinophilic inflammatory states include direct endothelial damage by degranulation of activated eosinophils, inhibition of the natural anticoagulant pathways, and release of tissue factor with enhanced coagulation activation.<sup>(2)</sup> Toxins released by eosinophils include eosinophil-derived neurotoxin,

cationic protein, major basic protein, reactive oxygen species, eosinophil peroxidase product hypothiocyanous acid, and arachidonic acid derivatives. These are potent stimuli of platelet activation and aggregation that can initiate coagulation or inhibit natural anticoagulant activities of thrombomodulin, heparin, heparan sulphate, and antithrombin III.<sup>(22)</sup> Thrombomodulin is an anionic endothelial protein.<sup>(23)</sup> Normally, it forms a complex with thrombin and exerts anticoagulant ability by activating protein C and inactivating clot fibrinogen.<sup>(20)</sup> When eosinophilic cationic proteins bind to the thrombomodulin, they impair anticoagulant activities, resulting in excessive thrombin generation, which leads to vascular occlusion. Therefore, peripheral blood eosinophilia is directly linked to a thrombotic tendency by inducing inflammatory damage to the endothelium, and promoting a hypercoagulable state.<sup>(24)</sup>

In conclusion, numerous etiologies can result in hypereosinophilia so the underlying disease should be determined. At the same time, clinicians should be alert for possible associated thromboembolic events such as pulmonary embolism and stroke, especially when other risk factors are present. These include disease-associated metabolic syndrome as well as immobility from imprisonment,<sup>(25)</sup> a bedridden condition, or disabling psoriatic arthritis.<sup>(26)</sup> Although severe psoriasis can be associated with eosinophilia and metabolic syndrome, it is very rare for patients to develop acute pulmonary embolism. We would like to highlight that hypereosinophilia could be a clue to thromboembolic disease.

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# 在一位嗜伊紅性白血球過多症及乾癬的病人身上 發生急性肺栓塞

柯瑞宏 林政緯 許仲瑤

週邊血液嗜伊紅性白血球過多症是一種偶爾可見的臨床問題而且它象徵著有潛在性的疾病需要被找尋出來。關於嗜伊紅性白血球過多症與血栓栓塞疾病之間的關係通常很少被強調。我們在這裡報告一位四十二歲的乾癬病患，表現全身水腫、紅皮症、呼吸困難以及兩側膝關節因乾癬性關節炎而彎曲攣縮。抽血檢查發現非常明顯的嗜伊紅性白血球過多症（絕對嗜伊紅性白血球數目：6232/ $\mu$ L）。肺臟及下肢的電腦斷層發現右邊肺動脈及左邊股靜脈有填充缺陷徵象，意味著深層靜脈栓塞導致急性肺栓塞。除此之外，非常明顯的嗜伊紅性白血球過多症可能引發血栓栓塞性疾病。但是在乾癬病患身上發現急性肺栓塞是非常罕見的。對於臨床醫師來說，非常明顯的嗜伊紅性白血球過多症有可能和血栓栓塞性疾病有相關性，必須要小心。（長庚醫誌 2011;34(6 Suppl):17-23)

**關鍵詞：**嗜伊紅性白血球過多症，血栓栓塞疾病，乾癬

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長庚醫療財團法人台北長庚紀念醫院 皮膚科；長庚大學 醫學院

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通訊作者：許仲瑤醫師，長庚醫療財團法人台北長庚紀念醫院 皮膚科。台北市105敦化北路199號。

Tel: (02)27135211轉3397; Fax: (02)27191623; E-mail: roseline.hui@gmail.com