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Case report

Pulmonary embolism and deep vein thrombosis in eosinophilic granulomatosis with polyangiitis successfully treated with rivaroxaban

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A B S T R A C T

A 41-year-old woman presented complaining of cough and purpura for one month. On her first visit, a blood test demonstrated peripheral blood eosinophilia, but chest radiography showed no abnormalities. However, 2 days after the first visit, she went to the emergency room because of fever and right-sided chest pain. Contrast-enhanced computed tomography of the chest showed pulmonary embolism and air space consolidation. Thrombosis was present in the popliteal vein. Bronchoscopy revealed alveolar hemorrhage and increased eosinophils in the bronchoalveolar lavage fluid, and a skin biopsy demonstrated a perivascular eosinophilic infiltrate. The patient was diagnosed with eosinophilic granulomatosis with polyangiitis (EGPA). We started steroid therapy and low-molecular-weight heparin (LMWH). The chest pain and fever disappeared, and the peripheral eosinophil count normalized. However, the thrombosis in the leg worsened. It was dramatically improved by changing from LMWH to oral rivaroxaban. The thrombogenic risk of eosinophilia should be recognized. This case suggests that oral rivaroxaban is useful when thrombosis is uncontrolled by LMWH in a patient with EGPA.

1. Introduction

Eosinophilic granulomatosis with polyangiitis (EGPA), formerly called Churg-Strauss syndrome, was first described by Churg and Strauss in 1951. EGPA is a necrotizing vasculitis involving small and medium-sized vessels with granulomas and eosinophilic infiltration of vascular tissues [1]. Eosinophilia is also thought to increase the risk of thrombosis [2].

We report a case of deep vein thrombosis and pulmonary infarction in a patient with EGPA that was successfully treated with oral rivaroxaban.

2. Case presentation

A 41-year-old Japanese woman was referred to our hospital for evaluation of a one-month history of cough and purpura for 2 weeks. She had a history of allergic rhinitis. The family history was unremarkable. She did not smoke nor did she use drugs. There was no history of relevant occupational or environmental exposure. A blood test showed eosinophilia. There were no abnormalities on chest radiography. However, she went to the emergency room 2 days later because of the sudden onset of fever and right-sided chest pain. A chest radiograph demonstrated bilateral consolidation. She was hospitalized for further evaluation and management.

On admission, her vital signs were a temperature of 39.5 °C, pulse 127 bpm, blood pressure 134/94 mmHg, and O_2 saturation on room air 95%.

Physical examination revealed purpura on the fingertips, palms, and feet. The lungs were clear to auscultation. There were no neurologic abnormalities.

Laboratory test results included a white blood cell count of 16.0×10^9/L (eosinophils: 8.5%, 1.4×10^9/L), hemoglobin 138 g/L, platelet count 24×10^9/L, prothrombin time 16.9 s, prothrombin time international normalized ratio 1.45, activated partial thromboplastin time 32.1 s, fibrinogen 4.54 g/L, D-dimer 49.8 mg/L, fibrin degradation products 113.3 mg/L, antithrombin III 0.96, lactate dehydrogenase 4.7 μkat/L, C-reactive protein 636 nmol/L, and non-specific IgE 765 IU/mL. Levels of antineutrophil cytoplasmic antibody, anticardiolipin antibody, lupus anticoagulant, cryoglobulin, and β-d-glucan were all within the normal range.

Chest radiography revealed bilateral consolidation. Chest contrast-enhanced computed tomography showed wedge-shaped consolidation and ground-glass opacities in both lungs and emboli in both pulmonary arteries. Furthermore, a thrombus was observed partially occluding the

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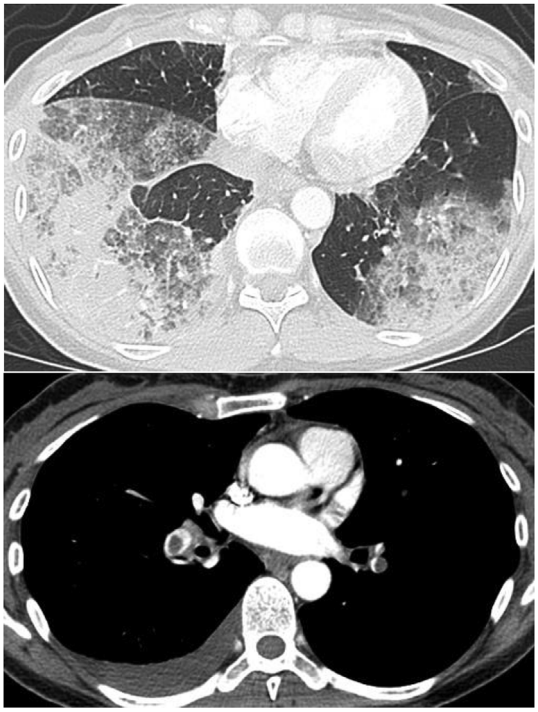

Fig. 1. Chest contrast-enhanced computed tomography on hospital day 2 demonstrates wedge-sharped consolidation and ground-glass opacity in both lungs and emboli in both pulmonary arteries. There is a thrombus partially occluding the left popliteal vein.

left popliteal vein (Fig. 1).

Bronchoscopy returned increasingly bloody fluid. On microscopy, the fluid contained hemosiderin-laden macrophages. The cell counts were 22% eosinophils, 7% lymphocytes, 20% macrophages, and 50% neutrophils.

A bone marrow biopsy showed normal cellularity with increased megakaryocytes. There was no Fip1-like1 and platelet-derived growth factor receptor alpha gene fusion. Antibody tests and stool examination for parasites were negative. Echocardiography and nerve conduction studies were normal.

The skin of the patient's fingertip was biopsied. Histologic examination showed an intravascular clot and a perivascular eosinophilic infiltrate (Fig. 2).

The patient's findings of cough, peripheral eosinophilia, history of

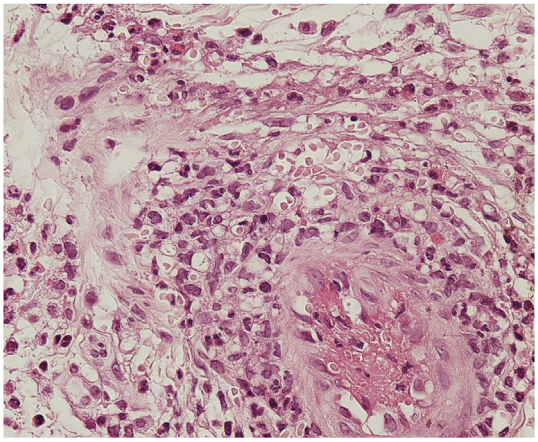

Fig. 2. Hematoxylin and eosin stain of a biopsy specimen from the fingertip skin shows a marked perivascular eosinophilic infiltrate and an intravascular clot (×100 magnification).

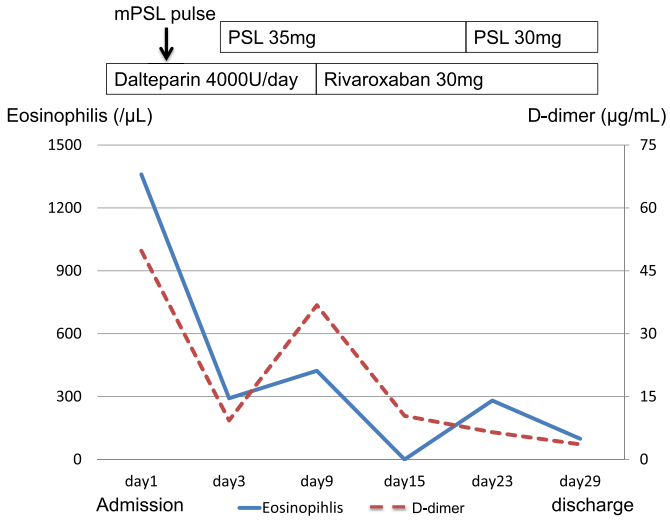

Fig. 3. Changes in absolute eosinophil count and D-dimer level over time in relation to the administration of steroids and anticoagulation therapy. mPSL methylprednisolone, PSL prednisolone.

allergic rhinitis, pulmonary infiltrates, and perivascular eosinophilic infiltrates were consistent with a diagnosis of EGPA based on the American College of Rheumatology (1990) criteria [3].

We assumed that the EGPA had induced disseminated intravascular coagulation, venous thromboembolism, and pulmonary embolism, thereby causing alveolar hemorrhage because the patient did not show the presence of any other primary cause of thrombotic disorders, such as the antiphospholipid antibody syndrome.

The patient was treated with methylprednisolone, 1 g/day for 3 days, followed by gradual tapering of prednisolone and with the low-molecular-weight heparin (LMWH) dalteparin, 4000 U/day (Fig. 3). We were concerned about exacerbating the alveolar hemorrhage, so we chose LMWH, as it has a lower bleeding risk than unfractionated heparin. The chest pain and fever disappeared within 1 day after beginning treatment, and the peripheral eosinophil count normalized within 3 days. However, on day 9, the patient complained of left pedal edema, and the D-dimer level was still elevated at 36.8 mg/L. We discontinued dalteparin and started oral rivaroxaban (30 mg/day) because the most recent American College of Clinical Pharmacy (ACCP) guidelines recommend rivaroxaban in VTE and non-cancer patients rather than vitamin K antagonist (VKA) therapy (Grade 2B) and VKA therapy rather than LMWH (Grade 2C) [3]. The signs of deep vein thrombosis in her left leg then resolved, and the chest X-ray abnormalities improved. She was discharged on day 29, still on prednisolone and rivaroxaban.

Four months later, the prednisolone was reduced to 5 mg/day and the rivaroxaban to 15 mg/day. She had no recurrence of symptoms or abnormal laboratory findings.

3. Discussion

This is the first case report of venous thromboembolism (VTE) with pulmonary infarction successfully treated with rivaroxaban in a patient with EGPA.

An association between eosinophilia and thrombosis had been noted in a number of studies. The reported incidence of VTE in EGPA ranges from 5.8% to 30.0% [4]. VTE therefore is not a rare complication in patients with EGPA.

The mechanisms underlying thrombosis in eosinophilia are not fully understood. However, several hypotheses have been proposed to link the two. Eosinophil cationic protein (ECP) promotes coagulation through a factor XII-dependent mechanism [5]. Major basic protein (MBP) inhibits the anticoagulant activities of the endothelial membrane

by binding to thrombomodulin. Eosinophil peroxidase (EPO) damages vascular endothelial cells. MBP and EPO activate platelets. Hypothiocyanous acid, the main oxidation product of EPO, promotes thrombosis by stimulating tissue factor expression [6]. ECP blocks heparin that fails to bind to antithrombin, resulting in unhindered factor X activation and thrombin generation [7].

Recently, oral rivaroxaban, a specific direct factor Xa (FXa) inhibitor, has been approved for use instead of warfarin. There is no directly comparable data on the effects of rivaroxaban versus LWMH in terms inducing thrombus regression. In the global EINSTEIN–PE trial involving patients with symptomatic pulmonary embolism, rivaroxaban (15 mg twice daily for 3 weeks, followed by 20 mg once daily) was not inferior to enoxaparin for the treatment of VTE [8]. In our case, rivaroxaban was effective for treating the patient's VTE when her leg symptoms worsened on LMWH treatment. The reason is not clear, but several mechanisms are possible. First, LMWH suppresses free FXa activity in plasma via antithrombin, but rivaroxaban inhibits not only free FXa but also FXa in the prothrombinase complex on platelets [9]. It therefore seems effective in suppressing thrombus formation. Second, as noted above, ECP derived from eosinophil granules has been shown to inactivate heparin. Third, FXa and one of its major receptors, protease activated recepror-2, are involved in chronic inflammation [10]. In this case, administration of rivaroxaban may have an anti-inflammatory effect.

Although we started the treatment using steroid pulse therapy, steroid therapy itself may exacerbate thrombosis. However, steroid therapy is indispensable for the treatment of vasculitis. Thus, another immunosuppressant (e.g. cyclophosphamide) with glucocorticoid-sparing effects can be prescribed if it is difficult to control the patient's disease activity [11].

In conclusion, EGPA can increase the risk of life-threatening VTE. In our patient, rivaroxaban was useful for treating thrombosis that was poorly controlled by LMWH. This direct FXa inhibitor has been widely used to treat VTE and may be worth selecting for prophylaxis against VTE in patients with disorders that include hypereosinophilia.

Disclosure statement

The authors have no conflict of interest to declare. Appropriate written informed consent was obtained for publication of this case report and accompanying images.

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