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【 CASE REPORT 】

Portal Vein Thrombosis as a Cause of Undetermined Thrombocytopenia with Liver Dysfunction in a Patient with Eosinophilic Granulomatosis with Polyangiitis

Naoya Oka, Yusuke Yoshida, Tomohiro Sugimoto, Ai Yorishima, Sho Masuda and Shintaro Hirata

Abstract:
We herein report a 20-year-old woman who developed eosinophilic granulomatosis with polyangiitis (EGPA) and portal vein thrombosis (PVT). EGPA was diagnosed based on the patient's history of asthma, hypereosinophilia, and mononeuritis complex. Thrombocytopenia and liver dysfunction were observed, necessitating contrast-enhanced computed tomography (CECT), which revealed PVT. Her symptoms soon improved with glucocorticoids and anticoagulation therapy. As patients with EGPA often suffer from asthma, they can be hesitant to undergo CECT. However, if patients with EGPA show uncertain thrombocytopenia with liver dysfunction, a further evaluation using CECT is warranted to detect PVT.

Key words: eosinophilic granulomatosis with polyangiitis, portal vein thrombosis, thrombocytopenia, liver dysfunction

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Introduction

Eosinophilic granulomatosis with polyangiitis (EGPA) was first reported in 1951 by Churg and Strauss as eosinophilic granulomatosis with necrotizing vasculitis in patients with asthma (1). In 2012, it was defined as antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) by the Chapel Hill Consensus Conference (2). Both vascular inflammation and eosinophilia contribute to organ damage in EGPA, and their manifestations are classified into three phases: a prodromal phase with asthma and rhinosinusitis, an eosinophilic phase with peripheral eosinophilia and organ involvement, and a vasculitic phase with organ damage associated with vasculitis (3).

The proliferation and activation of eosinophils cause their deposition in organs and the release of toxin-containing granule proteins, leading to tissue damage (4, 5). Eosinophil counts above 1,500/μL increase the risk of tissue damage, but lower eosinophil counts in affected organs can also cause it (6-8). Inflammation due to vasculitis also leads to elevated C-reactive protein (CRP) levels, high blood sedimentation rates, and platelet hyperplasia.

EGPA has been reported to cause venous thrombosis in 8.2% of patients and arterial thrombosis in 3.1% to 18.7% of patients (9, 10). Although cerebral vessels, coronary arteries, and deep veins are the main sites of thrombus formation, complications of the inferior vena cava and pulmonary embolism have also been reported (10). The incidence rate of thrombus formation is higher in EGPA than in other AAVs (9). This higher incidence rate may be due to increased eosinophil activation in EGPA, which promotes thrombus formation (10).

We herein report a rare case of EGPA complicated by undetermined thrombocytopenia and liver dysfunction that was finally diagnosed as portal vein thrombosis (PVT).

Case Report

A 20-year-old woman was admitted to our hospital in June 2021 with chief complaints of dyspnea and numbness in the extremities. She had a history of childhood asthma,

Department of Clinical Immunology and Rheumatology, Hiroshima University Hospital, Japan
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Correspondence to Dr. Yusuke Yoshida, fisher37@hiroshima-u.ac.jp

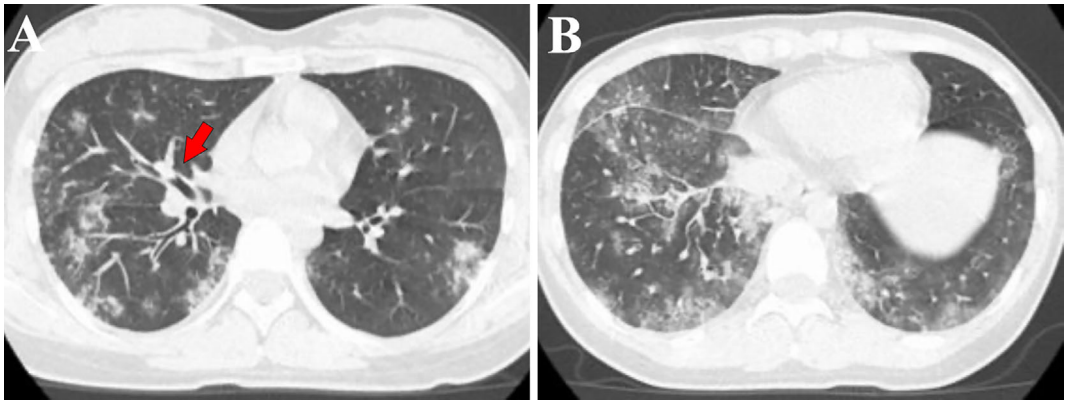

Figure 1. Ground-glass opacities with bronchial wall thickening (indicated by a red arrow). (A) Lobular central granular shadows and (B) computed tomography findings of the chest.

although her asthma-related symptoms had resolved over the past 15 years. She had no family history of rheumatoid arthritis or connective tissue diseases. She had been smoking six cigarettes daily for four years. Since three months before being transfered to our hospital, she had been experiencing a fever, cough, and respiratory distress; she visited a nearby hospital. She was clinically diagnosed with eosinophilic pneumonia due to findings of eosinophilia and diffuse ground-glass opacities with bronchial wall thickening and lobular central granular shadows on computed tomography (CT) (Fig. 1). She was administered prednisolone (PSL) at 40 mg/day, and the dose was tapered and then discontinued by two months ago. Thereafter, she did not return for a follow-up visit at her discretion because her subjective symptoms were relieved.

In mid-May, she experienced a fever and cough again. Petechial purpura and numbness were noted in her lower legs. 8 days ago, the patient developed a severe cough and dyspnea and was rushed to the nearby hospital. CT of the chest revealed ground-glass opacities in both lungs. Bronchoscopy was performed owing to the eosinophilia and relapsed pneumonia, revealing a high proportion of eosinophils (30%) in the bronchoalveolar lavage fluid. Although she restarted treatment with PSL at 20 mg/day 7 days ago, her symptoms did not improve. Thus, the dose of PSL was increased to 60 mg/day. She was transferred to our hospital under suspicion of EGPA based on the diagnosis of eosinophilia with organ involvement, including the lungs, skin, and peripheral nerves.

Her vital signs on admission were as follows: blood pressure (BP), 142/100 mmHg; pulse, 133 beats per minute; body temperature, 36.4°C; and oxygen saturation, 97% on room air. The patient's height and weight were 157.0 cm and 50.3 kg, respectively. The patient was conscious, oriented, and able to respond to verbal commands. A physical examination revealed fine crackles in both lungs and purpura in the upper abdomen and lower legs. She had left-side predominant leg edema (Fig. 2A) and pain with numbness on the lateral side of the left toe and sole. In addition, claw hand (left), indicative of radial nerve palsy, was also observed.

The results of the laboratory investigations performed upon admission are shown in Table. Thrombocytopenia, liver failure, and high D-dimer levels were observed. As steroids had already been started by a local hospital, the eosinophil counts and CRP levels on admission were already within the normal range; however, before the initiation of steroids, these levels had been 7,400 cells/μL and 0.64 mg/dL, respectively. ANCA of proteinase-3 (PR3) and myeloperoxidase (MPO), rheumatoid factor, and antiphospholipid antibodies were negative. A urine analysis revealed no microscopic hematuria or proteinuria.

Chest CT revealed recurrence of bronchial wall thickening and random patchy opacities in both lungs that resembled a galaxy sign. Short-tau inversion recovery on magnetic resonance imaging (MRI) of the left femoral and lower leg regions showed muscle hypertrophy and fascial thickening, consistent with eosinophilic fasciitis (Fig. 2B, C). Axonal damage to the peroneal and tibial nerves was confirmed by a nerve conduction study. Based on the above findings, a diagnosis of EGPA was made by fulfilling the Lanham criteria (11) and the criteria of the Ministry of Health, Labor, and Welfare of Japan for EGPA. Subsequently, contrast-enhanced CT (CECT) was performed to rule out complications of venous thrombosis as a cause of the high D-dimer levels with thrombocytopenia. Extensive areas of poor contrast were detected from the inferior vena cava to the left femoral vein, with thrombi noted in the deep veins (Fig. 3). In addition, multiple heterogeneous areas of poor contrast were observed in the liver, suggesting PVT (Fig. 4).

Anticoagulation therapy, started with low-molecular weight heparin and subsequently replaced with warfarin with a target prothrombin time-international normalized ratio of 2.0-3.0, was initiated in combination with steroid administration, leading to improvements in the platelet count, liver function, and D-dimer levels. Four weeks later, intravenous immunoglobulin therapy was administered to treat residual peripheral neuropathy, and her neurological symptoms gradually improved.

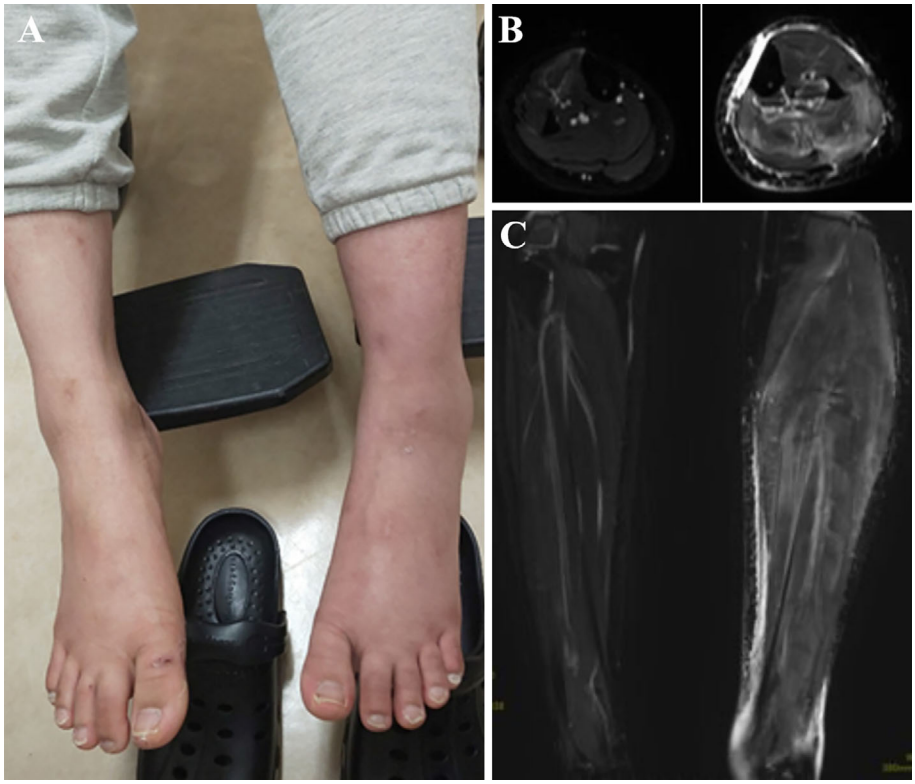

Figure 2. **(A) Left-sided predominant edema of the lower legs. Muscle hypertrophy and fascial thickening of the left lower leg region detected by an (B) axial and (C) coronal view of short-tau inversion recovery on magnetic resonance imaging (MRI).**

Table. **Laboratory Findings at the Time of Admission to Our Hospital.**

Complete blood count		***Biochemistry***	
White blood cells (3,300-8,600)	7,110 /μL	AST (13-30)	41 U/L
Neutrophils (38.3-71.1)	86.8 %	ALT (7-23)	145 U/L
Lymphocytes (21.3-50.2)	11.3 %	LDH (124-222)	287 U/L
Monocytes (2.7-7.6)	1.7 %	ALP (38-113)	125 U/L
Eosinophils (0.0-7.3)	0.1 %	γ-GTP (9-32)	108 U/L
Red blood cells (386-492)	447×10^4 /μL	CK (41-153)	52 U/L
Hemoglobin (11.6-14.8)	13.3 g/dL	BUN (8.0-22.0)	11.5 mg/dL
Platelets (15.8-34.8)	5.0×10^4 /μL	Cre (0.46-0.79)	0.64 mg/dL
Coagulation system tests		***Serological tests***	
PT (INR)	0.97	CRP (<0.14)	0.04 mg/dL
APTT (26.9-38.1)	25.9 s	IgE (170-232)	872 mg/dL
Fibrinogen (200-400)	171.7 mg/dL	Anti-nuclear antibody	(-)
FDP (0-5)	16.6 μg/mL	Rheumatoid factor	(-)
D-dimer (0-1)	11 μg/mL	MPO-ANCA	(-)
Protein C activity (64-146)	177 %	PR3-ANCA	(-)
Protein C antigen (70-150)	165 %	aCL-IgG	(-)
Protein S activity (56-126)	124 %	aCL-β2GPI	(-)
Protein S antigen (60-150)	89 %	LAC	(-)

PT: prothrombin time, INR: international normalized ratio, APTT: activated partial thromboplastin time, FDP: fibrin/fibrinogen degradation products, MPO: myeloperoxydase, ANCA: anti-neutrophil cytoplasmic antibody, PR3: proteinase-3, aCL anti-cardiolipin antibody, β2GPI: β2-glycoprotein I, LAC: lupus anticoagulant

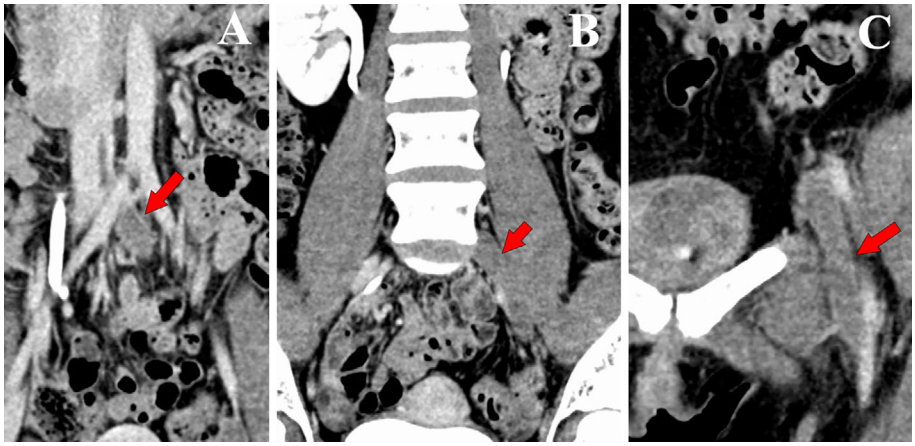

Figure 3. **Poor contrast from the inferior vena cava (A) to the left femoral vein (B, C) on contrast-enhanced computed tomography (CECT) (indicated by red arrows).**

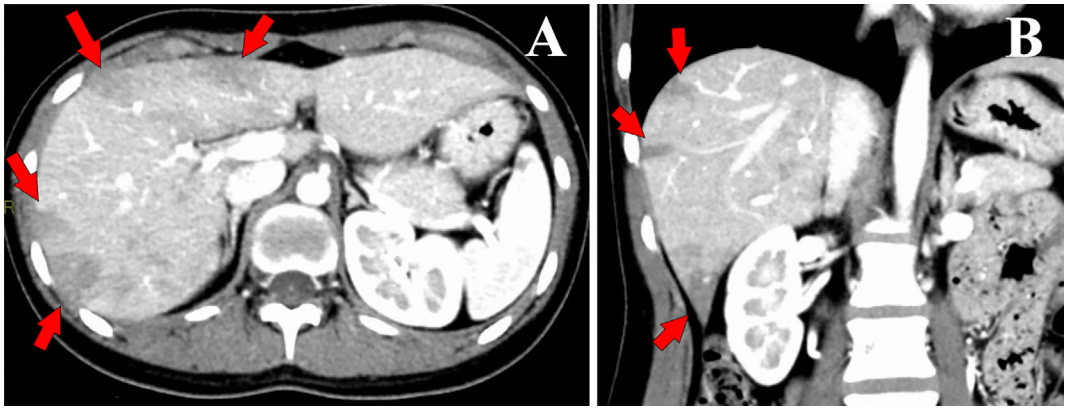

Figure 4. **Multiple areas of poor contrast in the liver with irregular margins on contrast-enhanced computed tomography (indicated by red arrows). (A) Axial and (B) coronal views.**

Discussion

We reported a case of EGPA complicated with thrombocytopenia and liver dysfunction due to an extensive venous thromboembolism (VTE), including PVT. This case was diagnosed with EGPA based on the patient's history of asthma, eosinophilia, polyneuritis, and purpura. Although thrombocytosis is frequently observed at the diagnosis of EGPA, the platelet count in this case had decreased to 5.0×10^4/μL. The differential diagnoses of thrombocytopenia include infection, drug use, thrombotic microangiopathy, congenital predisposition (protein C and S deficiency, antithrombin deficiency, and antiphospholipid antibodies), and pregnancy. However, all were ruled out in this case. High D-dimer levels enabled CECT to detect a wide range of VTE. The cause of thrombocytopenia seemed to be the excessive consumption of platelets due to thrombus formation.

The involvement of eosinophils has been identified as a mechanism for thrombus formation (10, 12, 13). Eosinophils contain a variety of granules, which, when activated, release granule proteins, such as major basic protein (MBP), eosinophilic cationic protein (ECP), and eosinophil peroxidase (EPOx). These proteins cause hypercoagulation. MBP binds to thrombomodulin and inhibits the anticoagulant activity of protein C. ECP binds to heparin which prevents the inhibitory effects of antithrombin on factor X and thrombin, whereby the activation of factor XII is prevented and down-regulation of the fibrinolytic system enabled. Hypothiocyanous acid produced by EPOx then stimulates endothelial cells to release tissue factors that activate factor VII. Eosinophils themselves then also release tissue factors that result in thrombosis. Thus, eosinophilia enhances the coagulation cascade and increases the risk of thrombus formation.

VTE is one of the complications observed in idiopathic hypereosinophilia (IHE) and hypereosinophilic syndrome (HES) as well as EGPA, thus providing support for the idea that eosinophils accelerate thrombus formation (14-16). It has been suggested that the longer the duration of hypereosinophilia, the greater the risk of thrombus formation (14, 15). In a study conducted by Liu et al., glucocorticoids and anticoagulants were shown to reduce the eosinophil count to below 500 with no recurrence of deep venous thrombosis within 6 months in patients with IHE and HES (14). Medium-to-high doses of glucocorticoids and anticoagulants are considered effective treatments for EGPA

complicated by thrombosis.

In the present case, liver dysfunction was observed at the same time as thrombocytopenia. CECT showed multiple poorly contrasted areas in the liver, suggesting multiple infarctions of the liver and the presence of PVT. These findings improved after combination therapy with steroids and anticoagulants. To date, only three cases of adult-onset EGPA with PVT have been reported. A 36-year-old woman with necrotic skin lesions and pulmonary infiltrate was diagnosed with PVT on abdominal echocardiography. She had an abnormal liver function and abdominal tenderness on a close examination for thrombocytopenia (12). In a 48-year-old man with eosinophilic peritonitis following an acute abdomen, CECT was performed because PVT was suspected on abdominal echography and revealed thrombi in the portal and superior mesenteric veins (17). A 36-year-old man was diagnosed with Budd-Chiari syndrome by MRI, hepatic venography, and a liver biopsy after a close examination for hematemesis and diarrhea revealed esophageal varices and hepatic vein obstruction on abdominal echocardiography (13). Two out of the 3 reported PVT cases (36-year-old woman and 48-year-old man) as well as our patient presented with eosinophilia and thrombocytopenia with hepatic dysfunction.

Although CECT is a useful tool for identifying the presence of a thrombus, it is often difficult to perform because EGPA usually presents with the complication of refractory asthma. Therefore, we believe that there may have been cases of EGPA with an undetectable thrombus. Thrombus manifestations can be found in fatal lesions of cerebral infarction, coronary artery occlusion, and pulmonary thromboembolism. Therefore, early detection and treatment are needed, and non-invasive echography may help screen for the presence of PVT if findings indicative of thrombi are observed. Although no abnormalities were detected by conventional B-mode ultrasonography in our case, color Doppler ultrasonography is reported to be more useful in detecting PVT (18).

In conclusion, thrombosis is a common complication of EGPA. In patients with EGPA with thrombocytopenia and hepatic dysfunction, the complication of multiple infarctions of the liver due to PVT should be considered, and thorough thrombus detection using CECT is necessary.

Author's disclosure of potential Conflicts of Interest (COI).
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