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【 CASE REPORT 】

Acute Pulmonary Hypertension Crisis after Adalimumab Reduction in Rheumatoid Vasculitis

Gentaro Yamasaki[1], Mitsumasa Okano[1], Kazuhiko Nakayama[1], Naoe Jimbo[2], Sho Sendo[3], Naoki Tamada[1], Kenta Misaki[4], Yuto Shinkura[1], Kenichi Yanaka[1], Hidekazu Tanaka[1], Kengo Akashi[3], Akio Morinobu[3], Hiroshi Yokozaki[5], Noriaki Emoto[1,6] and Ken-ichi Hirata[1]

Abstract:
Rheumatoid vasculitis is a rare etiology for pulmonary hypertension (PH) in patients with connective tissue disease. We encountered a case of acute PH crisis in a case with rheumatoid vasculitis eight months after undergoing adalimumab reduction. Since no repetition of arthralgia occurred after the adalimumab reduction, we decided to not increase the dose of adalimumab. However, hemodynamic collapse thereafter developed and even though steroid pulse therapy was administered, the patient nevertheless died. The autopsy showed clusters of acute and chronic inflammation around the remodeled pulmonary arteries along with microthrombi in the vessel lumen. We should consider the possibility of critical worsening of PH as a phenotype of vasculitis related to immunosuppressive therapy reduction.

Key words: rheumatoid arthritis, perivascular inflammation, connective tissue disease, tumor necrosis factor alpha, lymphocyte, cytotoxic T cells

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Introduction

Connective tissue disease-associated pulmonary arterial hypertension (CTD-PAH) is common in patients with systemic sclerosis (SSc) but rare in those with rheumatoid arthritis (RA) (1, 2). A cohort study in the United Kingdom reported the prevalence of CTD-PAH (n=343) as follows: SSc 76%, mixed connective tissue disease 8%, systemic lupus erythematosus 8%, RA 3%, dermatomyositis and polymyositis 2%, and Sjögren's syndrome 1% (3). CTD-PAH had a worse prognosis than idiopathic PAH, and SSc-PAH had a worse 1-year survival than any other connective tissue disease (4). However, the prognosis of PAH in RA has been rarely reported. In addition, there are very few cases of PAH in patients with rheumatoid vasculitis (5). The pathology of rheumatoid vasculitis is related to vascular injury by perivascular inflammation and autoimmunity, but the underlying mechanism of PAH development is not fully understood (6). In addition, the efficacy of immunosuppressive therapy in PAH remains unclear.

We herein report a case of acute pulmonary hypertension (PH) crisis in a patient with rheumatoid vasculitis after adalimumab (ADA) reduction.

Case Report

Background with RA

In 2008, a 56-year-old man presented with arthralgia. He was diagnosed with seropositive RA and mild interstitial lung disease (ILD). He had received prednisolone (PSL),

[1]Division of Cardiovascular Medicine, Department of Internal Medicine, Kobe University Graduate School of Medicine, Japan, [2]Department of Diagnostic Pathology, Kobe University Graduate School of Medicine, Japan, [3]Division of Rheumatology and Clinical Immunology, Department of Internal Medicine, Kobe University Graduate School of Medicine, Japan, [4]Department of Rheumatology, Kita-Harima Medical Center, Japan, [5]Division of Pathology, Department of Pathology, Kobe University Graduate School of Medicine, Japan and [6]Department of Clinical Pharmacy, Kobe Pharmaceutical University, Japan
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Correspondence to Dr. Kazuhiko Nakayama, nakayama@med.kobe-u.ac.jp

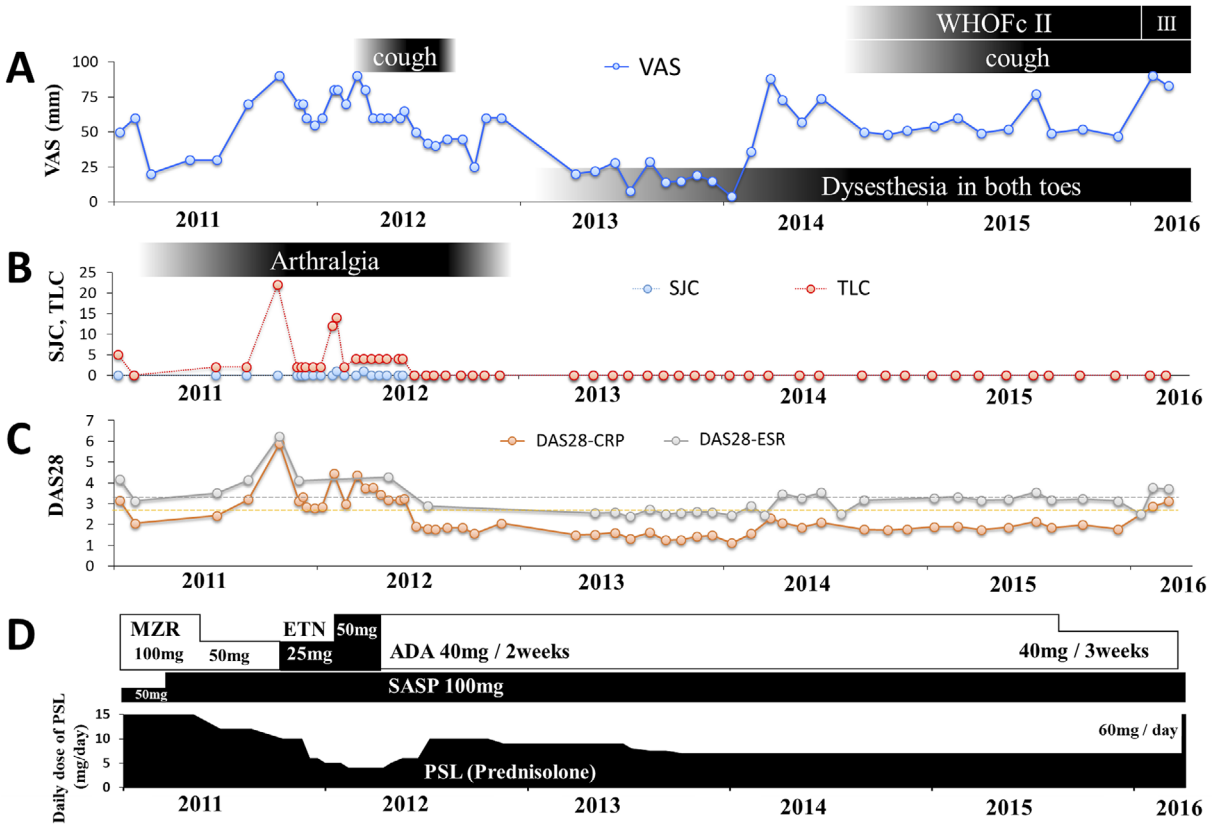

Figure 1. **The clinical course of rheumatoid vasculitis. Unstable arthralgia (B) under MZR, SASP, ETN, and PSL (D) was completely controlled by ADA, with no SJCs or TJCs (B) and a low DAS28 score (C). The high VAS score from 2014 (A) was due to dysesthesia of the toes, cough, and dyspnea, not arthralgia. Consequently, ADA was reduced from August 2015, as his arthritis was stable. ADA: adalimumab, DAS: disease activity score, ETN: etanercept, MZR: mizoribine, SASP: salazosulfapyridine, SJC: swollen joint count, TJC: tender joint count, VAS: visual analogue scale**

salazosulfapyridine, mizoribine, and etanercept treatments, which did not control his arthralgia effectively (Disease Activity Score 28-joint count using erythrocyte sedimentation rate: DAS28-ESR >3.2, moderate activity). In March 2012, the administration of ADA, an anti-tumor necrosis factor alpha (TNFα) monoclonal antibody, completely relieved his unstable arthralgia [Disease Activity Score 28-Erythrocyte sedimentation rate (DAS28-ESR) <2.0]. In 2014, he presented with dysesthesia of the toes, cough, and exertional dyspnea without arthralgia. Head magnetic resonance imaging showed multiple cerebral infarctions, but they were not related to the symptoms.

As his arthritis was stable, ADA was reduced from 40 mg/2 weeks to 40 mg/3 weeks in August 2015. Six months later, echocardiography detected a tricuspid regurgitation pressure gradient (TRPG) of 60 mmHg, indicating the onset of PH. The clinical course of the patient is shown in Fig. 1 and 2.

The investigation of PAH and diagnosis of rheumatoid vasculitis

In March, 2016 (Day 0), the patient was admitted to our hospital because of his progressive dyspnea (WHO functional class III) and dysesthesia of limbs over the previous eight months after ADA reduction. On admission, his vital signs were as follows: blood pressure 119/85 mmHg, heart rate 76 bpm, respiratory rate 24/min, and saturation 96% with 3 L/min O_2 flow. A clinical evaluation revealed jugular venous distension, fine crackles, and leg edema. No skin lesions or arthritis was noted. The laboratory results were as follows: C-reactive protein (CRP) 1.36 mg/dL, ESR 110 mm/h, D-dimer 11.7 μg/mL, serum brain natriuretic peptide 30.1 pg/mL, and Krebs von den Lungen 6 (KL-6) 781 U/mL. He had markedly elevated immunological markers of RA: rheumatoid factor (RF) 1,459 IU/mL, anti-cyclic citrullinated peptide antibody (ACPA) 777 U/mL, and matrix metalloprotenase-3 (MMP3) 226 ng/mL. Antinuclear antibodies were positive at 1:1,280, with homogenous and speckled patterns. No other specific antibodies, including anti-ribonucleoprotein, were positive (Table 1). Immune complexes assessed by a C1q-binding assay and complements were at normal levels.

Chest X-ray (Fig. 3A-C) and chest computed tomography (CT) (Fig. 3D and E) showed persistent ILD findings in the bilateral lower lobes. Ventilation perfusion lung scintigraphy showed no mismatch. Lung function testing revealed restrictive ventilator impairment (%Vital capacity: 59%) and decreased % diffusing capacity of the lung for carbon monox-

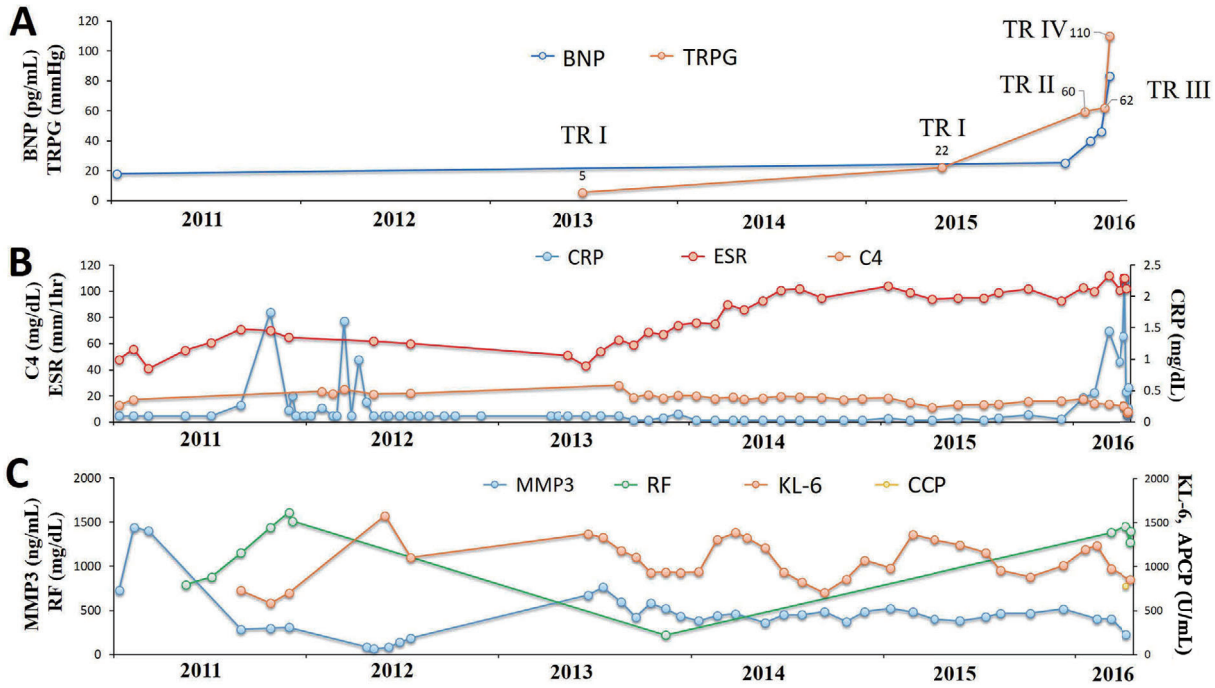

Figure 2. Activity of pulmonary hypertension and inflammatory markers. (A) Six months after ADA reduction in February 2016, the TRPG had increased to 60 mmHg, indicating the onset of PH crisis. The TRPG increased to 62 mmHg on day 8 and 110 mmHg on day 17 with elevation of the BNP level. (B) The CRP levels correlated well with the severity of PH, but the ESR gradually increased, and the C4 decreased from 2013. (C) The levels of RF and ACPA were extremely high at the time of PH crisis. KL-6 and MMP3 were not useful as predictors of worsening PH. BNP: brain natriuretic peptide, C4: complement C4, ACPA: anti-cyclic citrullinated peptide antibodies, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, KL-6: Krebs von den Lungen 6, MMP3: matrix metalloprotenase-3, RF: rheumatoid factor, TRPG: tricuspid regurgitation pressure gradient

ide (%DL_{CO}: 43%). Electrocardiogram (ECG) (Fig. 4) showed incomplete right bundle branch block. Echocardiography detected a D-shaped left ventricle (Fig. 3F and H) and elevated TRPG (70 mmHg). Right heart catheterization (RHC) showed an increased mean pulmonary arterial pressure (mPAP: 43 mmHg) with a normal pulmonary capillary wedge pressure (PCWP: 9 mmHg), normal cardiac index (CI 3.1 L/min/m^2), and elevated pulmonary vascular resistance (PVR: 456 dyne·sec/cm^5) (Table 2). He was diagnosed with rheumatoid vasculitis based on mononeuritis multiplex, ILD, asymptomatic cerebral infarctions (Fig. 3I and J), and a high level of RF on a background of chronic RA (7, 8). Based on the above findings, we diagnosed the patient with PAH associated with rheumatoid vasculitis.

Rapid progression to PH crisis

The patient had his dosage of PSL increased drastically (60 mg/day) without the introduction of a pulmonary vasodilator. However, despite this intensive steroid therapy, his desaturation and dyspnea progressed (WHO functional class IV). On day 17, follow-up RHC showed a worsening of the hemodynamics (mPAP: 52 mmHg, PCWP: 6 mmHg, CI: 3.3 L/min/m^2, PVR: 586 dyne·sec/cm^5) (Table 2). TRPG was elevated to 110 mmHg. Of note, the ILD had not worsened according to the time course of the KL-6 levels and the CT findings. The serum level of C_4 was decreased.

Our team, which included cardiologists and rheumatologists, suspected that the main pathology of vasoconstriction was inflammation in the pulmonary arteries due to the activated vasculitis. We judged the PH severity to be moderate and decided to change his drug treatment from oral PSL at 60 mg to intravenous methylprednisolone (M-PSL) at 1,000 mg as steroid pulse therapy on day 17. On day 18, he was intubated for intensive respiratory care. ECG revealed SIQIII-ITIII, severe right axis deviation, complete right bundle branch block, and negative T wave of V1-V4, indicating right ventricular load (Fig. 4). Chest X-ray (Fig. 3A-C) and CT (Fig. 3D and E) showed worsening of cardiomegaly and persistent mild ILD findings. Echocardiography showed progression of left ventricular compression forming a D-shape (Fig. 3F-H). Based on the time course of the above findings, further PH progression occurred from day 17-18 and became exacerbated beyond our estimation. We considered introducing pulmonary vasodilators, including epoprostenol, and the induction of intermittent pulse intravenous cyclophosphamide therapy (IVCY), based on the approaches adopted in previous studies (9), but a ventricular fibrillation storm occurred, and he died the same day.

The pathological findings from the autopsy revealed micro-thrombi (Fig. 5A and B) in pulmonary arteries with

Table 1. Serological Markers of Autoimmune Disease.

Serological markers	Values (Normal range)
Rheumatoid factor (IU/mL)	1,459 (~15)
ACPA (U/mL)	777 (~4.5)
MMP3 (ng/mL)	249 (37-121)
Anti-nuclear antibody	1:1,280 (~1:40)
dsDNA (IU/mL)	2.6 (~12)
ssDNA (AU/m)	7.8 (~25)
Sm (U/m)	2.5 (~10)
U1-RNP (U/mL)	0.8 (~10)
SS-A/Ro (U/mL)	0.6 (~10)
SS-B/La (U/mL)	0.3 (~10)
Scl-70 (U/mL)	<5 (~10)
Centromere (U/mL)	<5 (~10)
RNA polymerase III (index)	<5 (~28)
Jo-1 (U/mL)	<5 (~9)
ARS (index)	<5 (~25)
Cardiolipin (U/mL)	3.0 (~10)
CLβ2GPI complex (U/mL)	<0.7 (~3.5)
Lupus anticoagulant	0.8 (~1.3)
c-ANCA (U/mL)	0.1 (~5)
p-ANCA (U/mL)	0.1 (~5)

ACPA: anti-cyclic citrullinated peptide antibodies, ANCA: antineutrophil cytoplasmic antibodies, ARS: aminoacyl-tRNA synthetases antibodies, CLβ2GPI: cardiolipin β 2 -glycoprotein I, dsDNA: double-strand DNA, MMP3: matrix metalloproteinase-3, Scl-70: topoisomerase I, Sm: smith, SS-A: Sjögren's-syndrome-related antigen A, SS-B: Sjögren's-syndrome-related antigen B, ssDNA: single-strand DNA, U1-RNP: U1-ribonucleoprotein

perivascular inflammation, which was compatible with vasculitis. Around the mildly remodeled artery (Fig. 5C and D), indicative of acute inflammation, neutrophils with a few lymphocytes had infiltrated into the vessel wall (Fig. 5E and F). In contrast, around the progressive remodeled artery (Fig. 5G, 6A and B), indicative of chronic inflammation, the majority of the inflammation cells were lymphocytes (Fig. 5H). In addition, both T (Fig. 6C) and B (Fig. 6F) lymphocytes were observed in the perivascular space. CD8+ cytotoxic T cells (Fig. 6E) were more abundant than CD4+ helper T cells (Fig. 6D) on immunohistochemical staining.

Discussion

PAH in RA and rheumatoid vasculitis patients

PAH in RA is rare, and the prognosis is not well known. A cohort study reported that PAH in RA had a better outcome than idiopathic PAH (10). However, some studies have reported a poor response to therapy targeting inflammatory components, suggesting that early PH screening and the consideration of immunosuppressive therapy in conjunction with vasodilator therapy may be beneficial. Similar to this case, a previous case report described a case of fatal PAH due to rheumatoid vasculitis with mild arthralgia that was refractory to immunosuppressive therapy (5). There may be considerable differences in the severity of PH between RA and rheumatoid vasculitis. We should consider introducing combination therapy with intensive immunosuppressive therapy and pulmonary vasodilators at the early stage of PH, when the pathological changes are still reversible.

Predictors for PAH development in patients with RA

Appropriate monitoring for disease activity is an issue in RA patients. Inflammation and immunological markers, including the ESR, CRP, complement, RF, and ACPA levels, have some correlation with the RA disease activity. In the clinical setting, the RA disease activity is often assessed based on the articular involvement using the DAS28 score, with attempts later made to decrease the immunosuppressive therapy. Some patients develop PH, but how to predict these patients remains unclear, as is whether or not these markers work well as predictors of PH development. In the present case, the elevated levels of CRP, RF, and ACPA and the low levels of complement were correlated with the severity of PH. We should not dismiss complaints of dyspnea in patients with mild arthritis, which may indicate complications of PH or lung diseases. The early physiological evaluation of respiratory symptoms and screening tests for PH, such as echocardiography, are recommended (11). In the present RA patient, we should have suspected PH as a complication of vasculitis earlier. We need to monitor the status of PH with frequent ECG, chest X-ray, and echocardiography. On detecting PH, we should consider performing further examinations, including RHC, through good teamwork between cardiologists and rheumatologists.

PH crisis

We herein report an instructive case drawing attention to PH crisis related to immunosuppressive therapy reduction in a patient with rheumatoid vasculitis. Despite the presence of mild ILD, we diagnosed the patient with PAH due to vasculitis as the main pathology because of the time course of his symptoms, inflammation markers (CRP and ESR), KL-6 levels, CT findings, and pathological findings. The neurological symptoms and elevated ESR without worsening of arthritis indicated the presence of underlying vasculitis (12) in 2014. In addition, the ADA reduction in 2015 was unlikely to have triggered the PH crisis, as it was resistant to steroid therapy. We were able to eliminate acute massive pulmonary embolism as well, since it was deemed unlikely during the crisis based on the autopsy findings.

In this rheumatoid vasculitis patient, we should have been aware of the risk of rapid progression towards PH crisis. On day 17, the simultaneous introduction of pulmonary vasodilators, including epoprostenol, and inotropic agents was suspended due to the moderate severity of PH based on the result of the second RHC. In addition, another increase in the dose of ADA was also suspended due to previous concerns

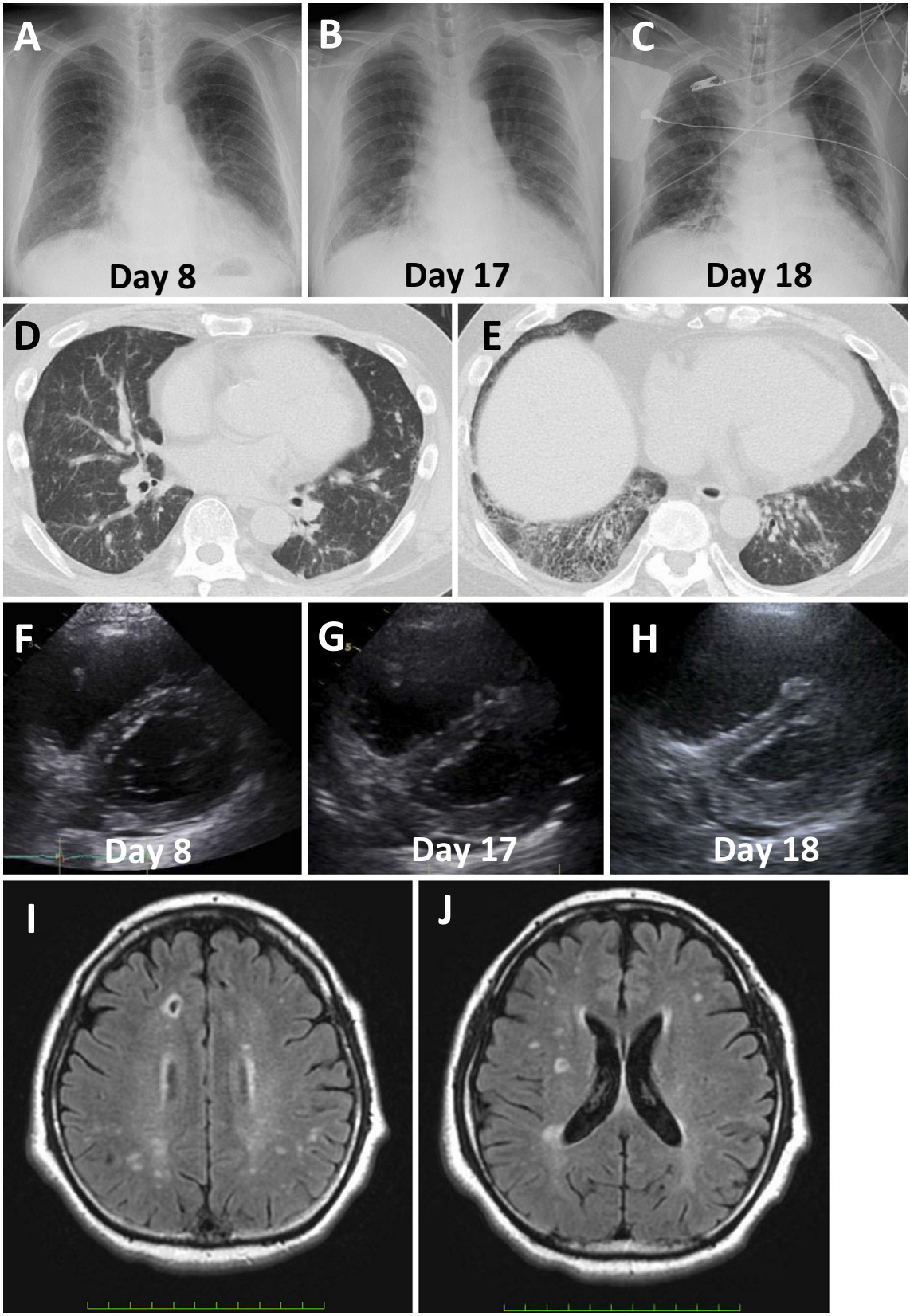

Figure 3. **Clinical images during PH worsening. Chest X-ray (A-C) shows worsening of cardiomegaly. Chest computed tomography shows dilated pulmonary arteries (D) and mild interstitial lung disease (E). Trans-thoracic echocardiography (F-H) detects a D-shaped left ventricle. Brain MRI (FLAIR) shows multiple old cerebral infarctions (I, J).**

about its adverse effects on chronic heart failure under TNFα pathway inhibition (13). Furthermore, we should have introduced inhaled nitric oxide as an additional pulmonary vasodilator and also considered performing percutaneous

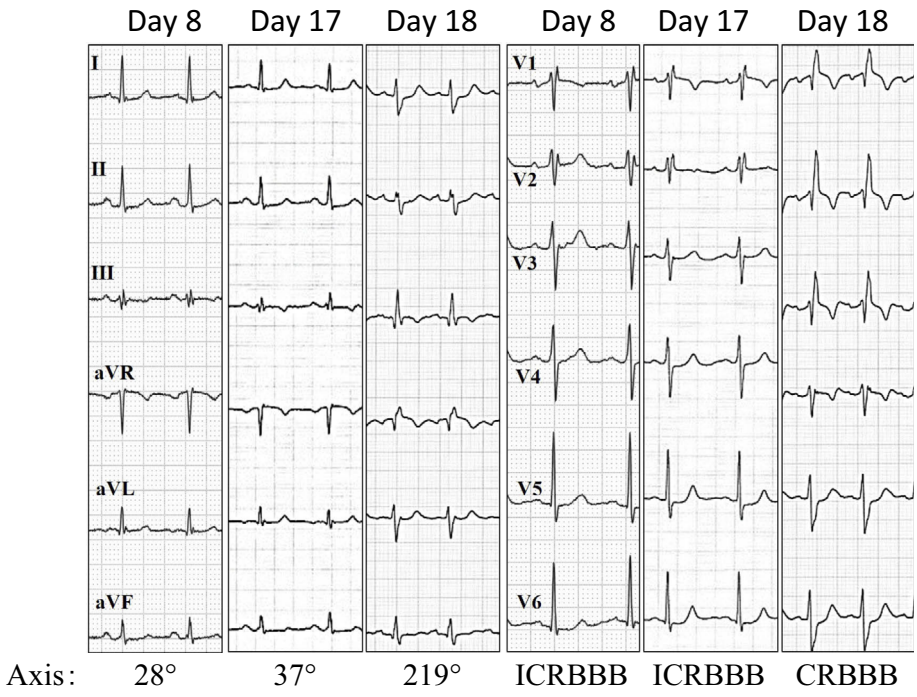

Figure 4. **Time course of ECG after PH development. Electrocardiography shows SIQIIITIII and severe right axis deviation on day 18. According to the time course, ICRBBB changed to CRBBB. The negative T wave of V1-V4 indicates right ventricular load. ICRBBB: incomplete right bundle branch block, CRBBB: complete right bundle branch block**

Table 2. **Time Course of Hemodynamics and Oxygenation.**

Variables	Day 8	Day 17
RAP (mmHg)	15	6
mPAP (mmHg)	43	52
PCWP (mmHg)	9	6
Cardiac index (L/min/m^2)	3.1	3.3
PVR (dyne*sec/cm^5)	456	586
SVR (dyne*sec/cm^5)	1,087	1,045
SBP (mmHg)	119	109
DBP (mmHg)	85	76
Heart rate (/min)	76	97
SaO_2 (%)	86.7	82.6
PaO_2 (%)	52.6	48.6
A-aDO_2 (mmHg)	60.3	272.7
PaO_2/FiO_2 (mmHg)	250.5	97.2
O_2 condition	room	FiO_2 50% NPPV
Dose of prednisolone after the RHC	60mg * 7days	1g * 1day

A-aDO_2: partial pressure difference of alveolar-arterial oxygen, DBP: diastolic blood pressure, FiO_2: fraction of inspired oxygen, NPPV: non-invasive positive pressure ventilation, mPAP: mean pulmonary arterial pressure, PaO_2: partial pressure of arterial oxygen, PCWP: pulmonary capillary wedge pressure, PVR: pulmonary vascular resistance, RAP: right atrial pressure, SaO_2: atrial saturation of oxygen, SBP: systolic blood pressure, SVR: systemic vascular resistance

cardiopulmonary support to manage the hemodynamics until the intensive drug administration sufficiently improved the pathology. However, our underestimation of the severity and progression of PAH ultimately let to the delayed introduction of intensive therapy, which thus failed to prevent hemodynamic collapse and the subsequent fatal events.

A previous case report of a patient with PH-associated systemic sclerosis described similar clinical worsening and death after the cessation of infliximab (14). In a rat model of monocrotaline-induced PAH, etanercept prevented PAH by reducing inflammatory cell infiltration (15). These reports suggest the critical involvement of the TNFα pathway

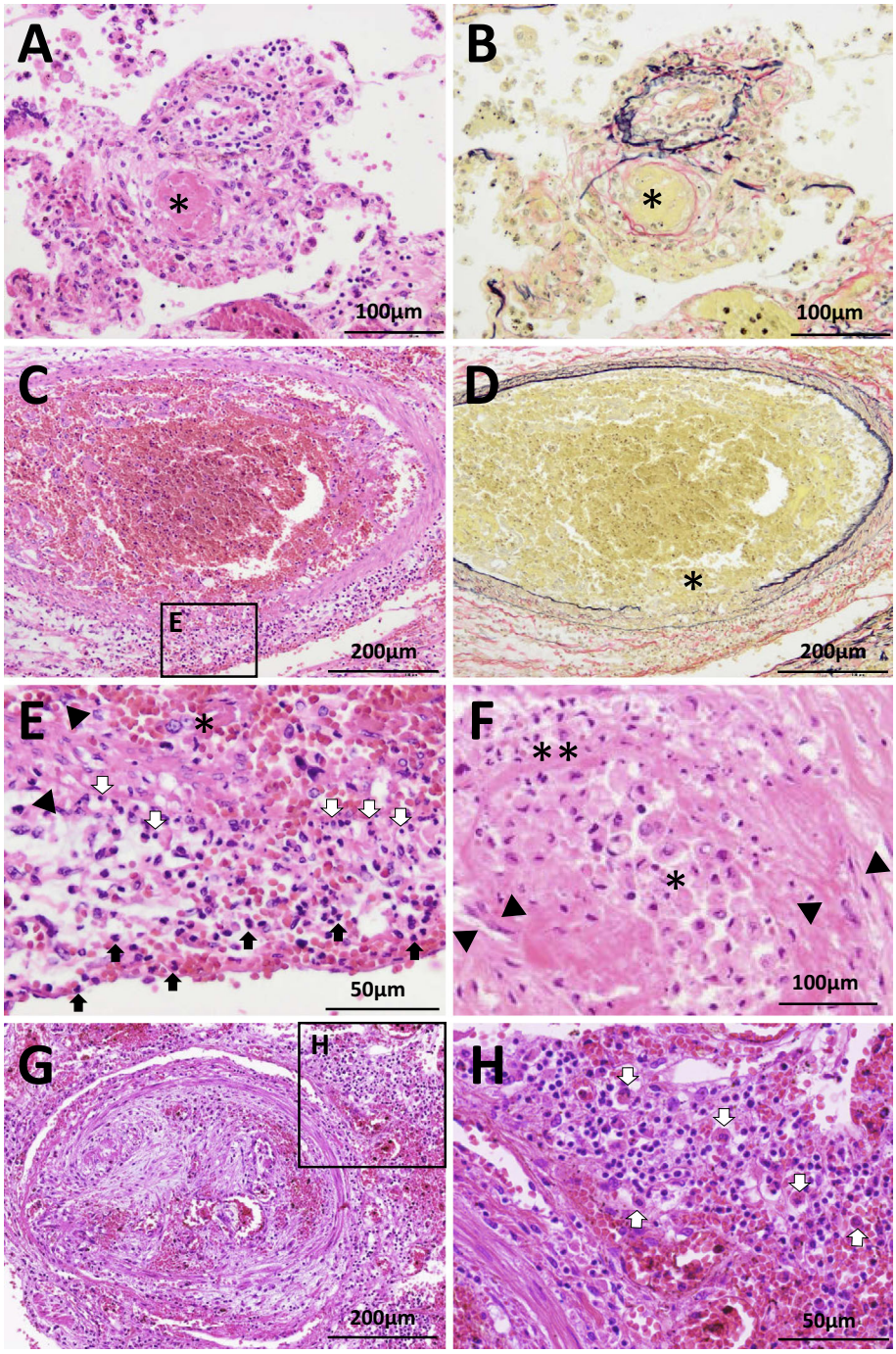

Figure 5. **Pathologic findings of pulmonary arteries in rheumatoid vasculitis. Micro-thrombi (A, B; *), perivascular inflammation (C), and degradation of the elastic lamina (D; *) are observed in the acute inflammatory area. In the adventitia, the majority of inflammatory cells are neutrophils (E; ↑) with a few lymphocytes (E; ⇩) infiltrating the vessel wall (E; ▶◀). Clusters of macrophages (E, F; *) and neutrophils (F; **) intersect in the vessel lumen (F; ▶◀). Around the progressively remodeled vessel (G), the majority of inflammatory cells are lymphocytes (H) with a few neutrophils (H; ⇩). Hematoxylin and Eosin (A, B, E-H) and Elastica van Gieson (B, D) staining.**

in the progression of PH.

Pathological features of the pulmonary arteries in rheumatoid vasculitis

In this case, we documented histologically proven pulmonary vasculitis, which may help improve our understanding of the mechanism underlying PAH development. A pathological examination revealed the multiple pathognomical features located in the pulmonary arteries including micro-thrombi, acute inflammation, chronic inflammation, and fibroelastic intimal proliferation. Nonspecific interstitial pneumonia was observed in the bilateral lower lobes without significant active inflammation. Neutrophils and macrophages with a few lymphocytes were found to have infiltrated into

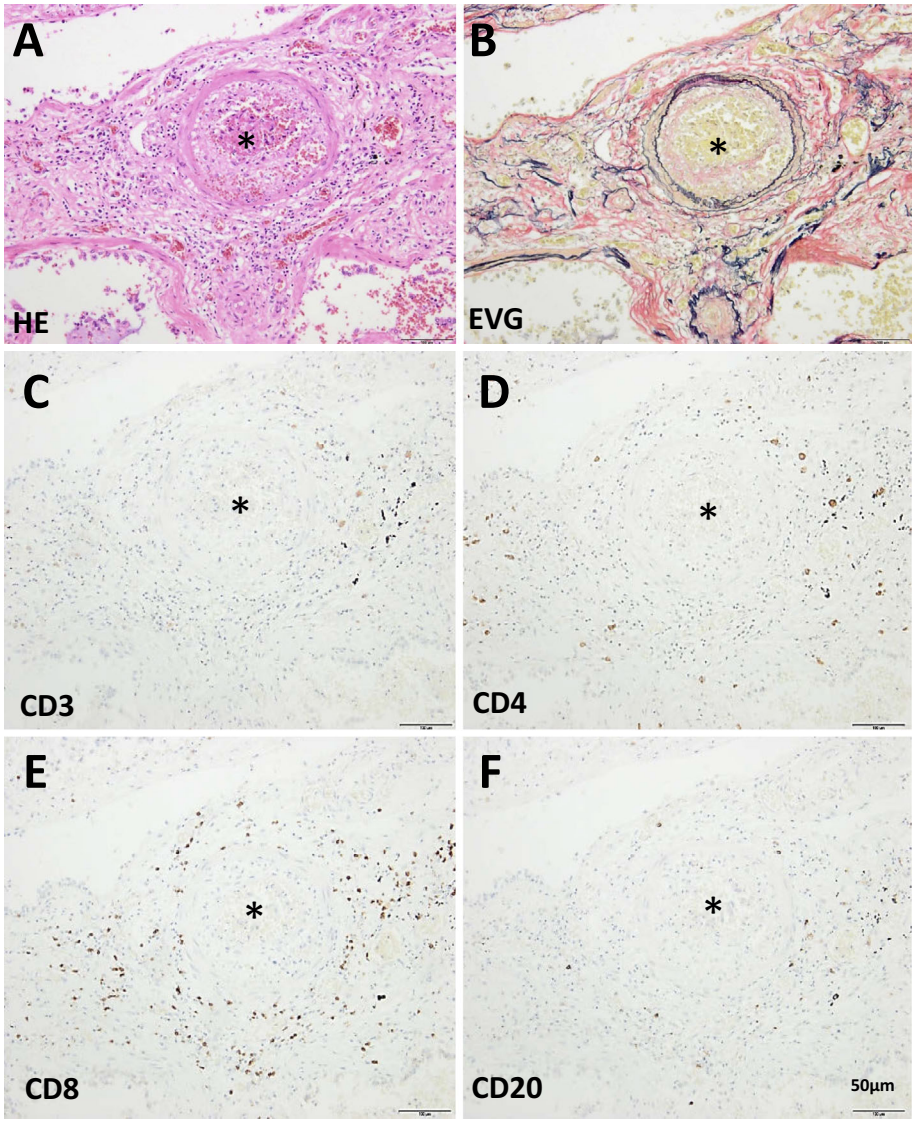

Figure 6. **The characterization of perivascular lymphocytes. Around the moderately remodeled pulmonary artery (A, B; *), both T (C) and B (F) lymphocytes are recognized in the perivascular space. In the T cell fraction, $CD8^+$ cytotoxic T cells (E) are more abundant than helper T cells (D). Hematoxylin and Eosin (A) and Elastica van Gieson (B) staining.**

the vessel wall around the mildly remodeled artery showing mild intimal thickening along with destruction of the elastic lamina, indicating an acute inflammation area. In contrast, around the progressively remodeled artery showing extensive fibroelastic proliferation of the intima and media to the point of luminal occlusion, the perivascular inflammation cells mainly consisted of lymphocytes, indicating a chronic inflammation area.

In systemic rheumatic diseases, imbalances in the numbers and fractions of T cell subsets are key pathogenic derangements (16). $CD8^+$ cytotoxic T cells were more abundant than other T cells in the present case, indicating that $CD8^+$ T cells had a role in the PAH progression. We are interested in the potential efficacy against PAH of abatacept, a cytotoxic T lymphocyte-associated antigen 4 immunoglobulin fusion protein that may reduce the number of cytotoxic T cells (17). Further studies exploring the efficacy of biologic disease modifying anti-rheumatic drugs against PAH, including TNF inhibitors and interleukin (IL)-6 receptor antagonists, are being conducted in the TRANSFORM-UK study, and clinical trials (18) are warranted.

Conclusion

We encountered a case of PH crisis associated with histologically proven rheumatoid vasculitis after ADA reduction. Physicians should be alert for the potential development of PAH in RA patients due to vasculitis. An appropriate monitoring system for PH development is needed. Although there are few cases of PAH associated with rheumatoid vasculitis, we should bear in mind the possibility of critical worsening of PH due to the reduction of immunosuppressive therapy in RA patients.

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

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Gentaro Yamasaki and Mitsumasa Okano contributed equally to this work.

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