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【 CASE REPORT 】

Anti-proteinase 3-positive Eosinophilic Granulomatosis with Polyangiitis Revealed by Cardiac Tamponade

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Abstract:
Eosinophilic granulomatosis with polyangiitis (EGPA) is a rare systemic vasculitis characterized by asthma, eosinophilia, and diffuse eosinophilic infiltration. Although cardiovascular involvement is common and a leading cause of EGPA-related mortality, severe pericarditis-led cardiac tamponade occurs rarely. We herein report a 72-year-old man with anti-proteinase 3 (anti-PR3) anti-neutrophil cytoplasmic antibody (ANCA)-positive EGPA diagnosed by the presence of cardiac tamponade, which responded quickly to pericardiocentesis and a single administration of prednisolone. This is the first case of anti-PR3 ANCA-positive EGPA with cardiac tamponade; the patient displayed clinical features of both ANCA-positive and ANCA-negative cases.

Key words: eosinophilic granulomatosis with polyangiitis, Churg-Strauss syndrome, anti-proteinase 3 anti-neutrophil cytoplasmic antibodies, pericarditis, cardiac tamponade

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Introduction

Eosinophilic granulomatosis with polyangiitis (EGPA), also known as Churg-Strauss syndrome, is a systemic vasculitis of small vessels. Although cardiovascular involvement is common in EGPA, pericarditis-led cardiac tamponade occurs rarely. In addition, anti-proteinase 3 (anti-PR3) anti-neutrophil cytoplasmic antibody (ANCA) is seldom positive in patients with EGPA, and its clinical and pathological roles in this disease remain unclear.

We herein report a 72-year-old man with anti-PR3 ANCA-positive EGPA revealed by cardiac tamponade.

Case Report

A 72-year-old man was admitted to our hospital with a high-grade fever, fatigue, and anorexia. The patient had had bronchial asthma for the past 26 years. His medical history comprised nonsustained ventricular tachycardia, atherothrombotic brain infarction caused by a stenosis of the left internal carotid artery, diabetes mellitus, and acute sinusitis. He was allergic to household dust and was not taking any anti-leukotriene agents. Although asthma was not quiescent with 2.5 mg of oral prednisolone, he discontinued its use without his physician's permission for 1 month.

Upon admission, his body temperature was 37.5℃, pulse was 110 beats/min, and blood pressure was 82/67 mmHg. He was in respiratory distress with scattered wheeze. In addition, he developed skin rashes on his chest, abdomen, and both insides of the femur. The neurological examination findings were normal, and no symptoms were observed in the ocular or gastroenterological systems.

Computed tomography (CT) suggested an opacification of the ethmoid sinuses, a large amount of pericardial and left pleural effusion, and pulmonary infiltrates in the right upper lobe (Fig. 1). Cardiac tamponade was diagnosed based on transthoracic echocardiography findings showing pericardial effusion and diastolic collapse of the right ventricular free wall (Fig. 2). Nearly 500 mL of turbid pericardial fluid was aspirated by pericardiocentesis, and continuous drainage was initiated. Posttreatment, his respiratory distress was relieved, and the blood pressure was elevated to 135/72 mmHg.

Blood tests findings were as follows: total leukocyte count, 8,600/mm^3, with 44.5% eosinophils on differential leukocyte count; platelet count, $29.5\times10^4/mm^3$; C-reactive

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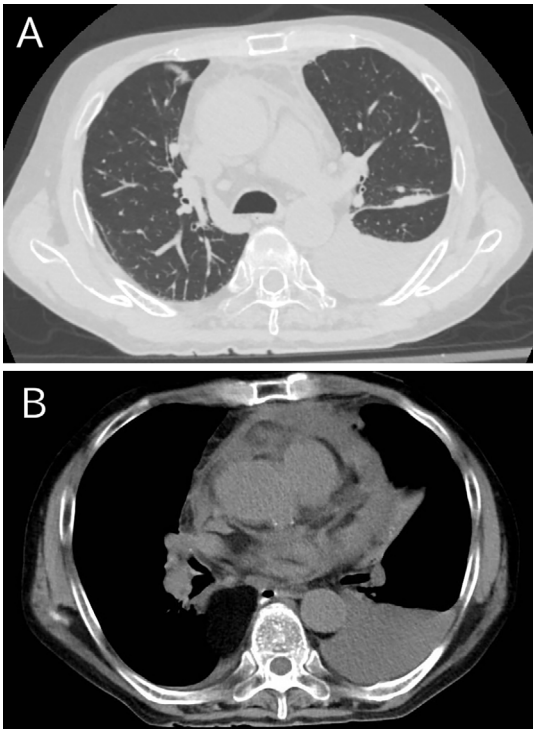

Figure 1. Chest computed tomography (CT) reveals pulmonary infiltrate in the right upper lobe and left pleural effusion (A). Chest CT reveals a large amount of pericardial and left pleural effusion (B).

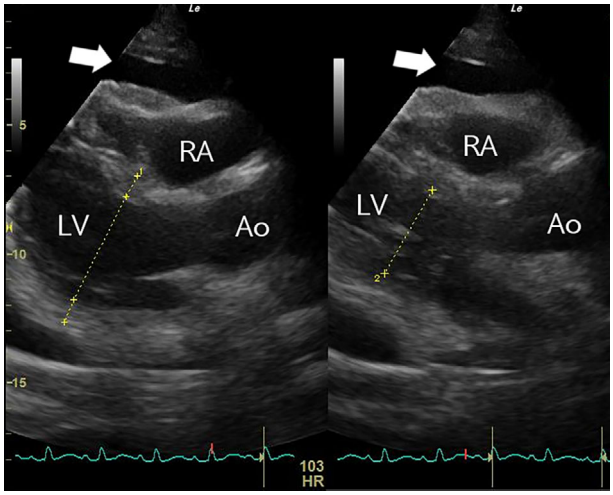

Figure 2. A transthoracic echocardiogram (TTE). Diastolic collapse of the right ventricular free wall and pericardial effusion (arrow) can be visualized. RV: right ventricle, LV: left ventricle, Ao: aorta

protein, 7.67 mg/dL; and brain natriuretic peptide 16.2 pg/mL. In addition, the serum creatinine (2.01 mg/dL, 178 μmol/L) and blood urea nitrogen levels (39 mg/dL) were elevated. A urinalysis revealed urine-specific gravity 1.030, occult blood 2+, and urine leukocyte 2+. The immunological workup revealed positive ANCA findings with an anti-PR3 level of 7.8 IU/L but negative findings for anti-myeloperoxidase (MPO). While serum IgE (2,000 IU/mL) and IgG4 (191 mg/dL) were elevated, IgG (1,115 mg/dL) was normal. In addition, rheumatoid factor (RF) and antinuclear antibody (ANA) were negative.

Table 1 shows the other findings of the blood tests and urinalysis. Laboratory tests of the pericardial fluid revealed the following: total leukocyte count, 45,600/mm^3, with 72.0% of eosinophils; total protein, 6.2 g/dL; adenosine deaminase (ADA), 79.4 IU/L; and lactate dehydrogenase (LDH), 1,742 IU/L. Furthermore, analyses of the left pleural fluid revealed the following: total leukocyte count, 32,400/mm^3, with 81.0% of eosinophils; total protein, 6.2 g/dL; ADA, 47.1 IU/L; and LDH, 906 IU/L (Table 2).

Cytological analyses of the aspirated pericardial and pleural fluid revealed numerous eosinophils but not malignant cells. Rhinoscopy failed to reach the ethmoid sinuses and detect nasal polyps; however, an excisional biopsy from the inferior nasal concha detected eosinophilic infiltration (15/high-power field). In addition, a skin biopsy on his femur showed the extravascular infiltration of eosinophils (Fig. 3). Based on the clinical, laboratory, and imaging findings, EGPA was diagnosed per the American College of Rheumatology (ACR) criteria (1).

Accordingly, the patient was treated with 40 mg of intravenous prednisolone alone for 9 days because he declined high-dose glucocorticoids and immunosuppressants. On day 7, continuous pericardial drainage was finished without a cardiac effusion replenishment. Eventually, the prednisolone dose was tapered to oral 30 mg daily on day 10. On day 13, his eosinophil count was depleted, and the serum creatinine was normalized. In addition, the urine occult blood and leukocytes were simultaneously negative. Given these changes in the blood test and urinalysis findings, vasculitis as well as cardiac insufficiency was deemed to have triggered the renal dysfunction upon admission. After the prednisolone dose was reduced to 25 mg on day 17 and 20 mg on day 24 without relapse, he was discharged on day 31. Fig. 4 shows the patient's clinical course during hospitalization.

Discussion

The ACR criteria for EGPA include asthma, eosinophilia, extravascular eosinophilic involvement, paranasal sinus abnormality, pulmonary infiltrate, and neuropathy (1). Our patient met the first five conditions with anti-PR3 ANCA positivity.

EGPA is an ANCA-associated vasculitis (2), and the serum IgG4 level correlates with the Birmingham vasculitis activity score (BVAS) (3). The BVAS evaluates the vasculitis activity, and a parallel decline in the serum IgG4 level and BVAS is observed in the course of remission in EGPA (3). Furthermore, the EGPA prognosis is assessed by the revised Five-Factor Score (FFS), which estimates a high risk of mortality and the need for cytotoxic agents besides systemic glucocorticoids (4).

The clinical manifestations and laboratory findings of EGPA could be collected into ANCA-positive and ANCA-

Table 1. Blood Test and Urinalysis Findings upon Admission.

Hematology		Immunology	
Leukocytes	8,600 /μL	IgG	1,115 mg/dL
Neutrophils	47.5 %	IgG4	191 mg/dL
Eosinophils	44.5 %	IgA	220 mg/dL
Basophils	0.5 %	IgM	30 mg/dL
Monocytes	1.0 %	IgE	2,000 IU/mL
Lymphocytes	6.5 %	CH50	31 U/mL
Erythrocytes	420 $\times 10^4$/μL	C3	110 mg/dL
Hemoglobin	10.6 g/dL	C4	29 mg/dL
Platelets	29.5 $\times 10^4$/μL	RF	5 IU/mL
Coagulation		ANA	<40
Prothrombin activity	70 %	anti-PR3 ANCA	7.8 IU/mL
PT-INR	1.2	anti-MPO ANCA	<0.5 IU/mL
APTT	32 s		
Fibrinogen	460 mg/dL	Urinalysis	
D-dimer	13.6 μg/mL	Leykocytes	2+
Biochemistry		Occult blood	2+
Total protein	5.9 g/dL	Specific gravity	>1.030
Albumin	2.8 g/dL	pH	5.5
AST	28 U/L	Protein	1+
ALT	14 U/L	Glucose	-
LDH	554 U/L	Ketone	2+
Total bilirubin	0.72 mg/dL	Bilirubin	-
Creatine kinase	201 U/L	Nitrite	-
Blood urea nitrogen	39 mg/dL	Bacteria	-
Creatinine	2.01 mg/dL		
Uric acid	12.7 mg/dL		
Sodium	138 mEq/L		
Potassium	4.9 mEq/L		
Chloride	107 mEq/L		
Glucose	94 mg/dL		
BNP	16.2 pg/mL		

PT-INR: international normalized ratio for prothrombin time, APTT: activated partial thromboplastin time, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, BNP: brain natriuretic peptide, CH50: 50% hemolytic unit of complement, RF: rheumatoid factor, ANA: anti-nuclear antibody, anti-PR3 ANCA: anti-proteinase 3 anti-neutrophil cytoplasmic antibodies, anti-MPO ANCA: anti-myeloperoxidase anti-neutrophil cytoplasmic antibodies.

negative EGPA, and only 40% of EGPA is ANCA-positive unlike other ANCA-associated vasculitides (AAVs), which are highly positive for ANCA. While ANCA positivity is known to be associated with the symptoms and prognosis of EGPA, it has no association with the serum IgG4 level in EGPA (3, 5); this contradiction may be attributed to cardiovascular events (myocardial infarction, cardiac insufficiency, or arrhythmia), which account for up to 50% of deaths in EGPA and often occur in ANCA-negative cases (5, 6). ANCA-positive EGPA is related to vasculitic syndrome, including renal, skin, and neural involvement; however, previous studies have primarily included patients with anti-MPO ANCA because anti-PR3 ANCA is rare among patients with EGPA. To our knowledge, this is the first case report of anti-PR3 ANCA-positive EGPA with cardiac tamponade. Our patient also exhibited overlapping manifestations of ANCA-positive and ANCA-negative EGPA, similar to a previously reported case with positive anti-PR3 ANCA and extensive cardiac involvement (7).

Cardiovascular involvement is common and it accounts for almost 50% of EGPA-related mortality. EGPA is characterized by myocardial infarction, myocarditis, and congestive heart disease. Especially, cardiac insufficiency is a common occurrence, and it is included in the revised FFS as a poor prognostic factor (4). Pericarditis is another major manifestation and it typically occurs with slight pericardial effusion; therefore, cardiac tamponade, as well as severe pericarditis, have rarely been reported in EGPA (8). Some studies have found no relationship between the anti-MPO ANCA positivity and pericarditis occurrence (5, 8). Nevertheless, the role of anti-PR3 ANCA in pericarditis remains unclear because of its rarity in EGPA.

However, recent studies have demonstrated the immunological mechanisms underlying the roles of ANCA and

Table 2. Results of Laboratory Tests of the Pericardial and Pleural Fluid upon Admission.

Pericardial fluid		Pleural fluid	
Leukocytes	45,600 /μL	Leukocytes	32,400 /μL
Neutrophils	24.5 %	Neutrophils	16.5 %
Eosinophils	72.0 %	Eosinophils	81.0 %
Basophils	0.0 %	Basophils	0.0 %
Lymphocytes	1.5 %	Lymphocytes	1.0 %
Histiocytes	2.0 %	Histiocytes	1.0 %
Erythrocytes	1 $\times 10^4$/μL	Erythrocytes	1 $\times 10^4$/μL
Hemoglobin	0.2 g/dL	Hemoglobin	0.1 g/dL
specific gravity	1.024	specific gravity	1.025
pH	7.6	pH	7.6
Total protein	6.2 g/dL	Total protein	6.4 g/dL
Albumin	2 g/dL	Albumin	2 g/dL
LDH	1,742 IU/L	LDH	906 IU/L
Glucose	2 mg/dL	Glucose	2 mg/dL
ADA	79.5 IU/L	ADA	47.1 IU/L

LDH: lactate dehydrogenase, ADA: adenosine deaminase

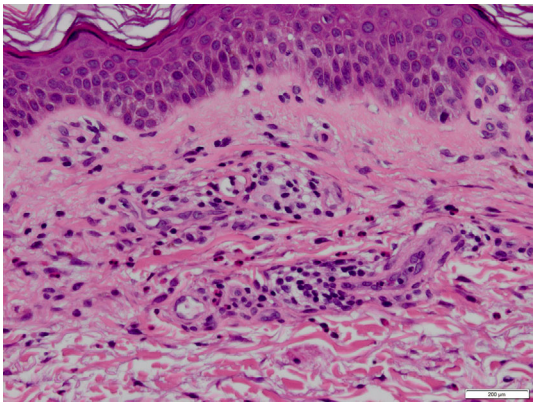

Figure 3. A skin biopsy on the patient's femur. Extravascular infiltration of eosinophils can be seen.

eosinophils in AAVs. Neutrophil extracellular traps (NETs) are reported to trap and kill bacteria, and increased levels of NETs contribute to the pathogenesis of AAVs as proinflammatory factors (9, 10). Similar cascades occur in eosinophils, called eosinophil extracellular traps (EETs) (11). Since eosinophils express PR3 on their surface, anti-PR3 ANCA may activate EETs in EGPA patients (12). However, despite the findings of these previous studies, the correlation between anti-PR3 ANCA and eosinophils in EGPA remains unknown. Further studies are warranted to elucidate the clinical and pathological role of anti-PR3 ANCA in EGPA.

Although most patients with EGPA respond quickly to glucocorticoid therapy, patients with a high FFS tend to be resistant to the treatment. The revised FFS includes age ≥65 years old, cardiac symptoms, gastrointestinal involvement, renal insufficiency (serum creatinine >150 μmol/L), and the absence of ear, nose, and throat manifestations (4). Notably, monotherapy with glucocorticoids is recommended only in patients with an FFS of 0 (13), while those with an FFS ≥1 are usually treated with glucocorticoids and immunosuppressants (14). Furthermore, while pericarditis with myocardial injury warrants immunosuppressive therapy, isolated pericarditis without other visceral involvement occasionally requires only glucocorticoids (15).

For patients with EGPA resistant to glucocorticoids and immunosuppressants, rituximab (RTX), mepolizumab, and omalizumab are permitted in remission induction therapy. RTX is a B-cell depletion monoclonal antibody directed against CD20, and anti-MPO ANCA-positive patients with EGPA probably respond better to RTX than anti-MPO ANCA-negative patients (16, 17). Mepolizumab is a monoclonal antibody against IL-5. IL-5 is a major survivor factor for eosinophils, and Mepolizumab is reportedly effective in reducing the frequency of relapses and doses of glucocorticoids in EGPA (18). Omalizumab, a monoclonal antibody targeting the high-affinity receptor-binding site on IgE, triggers eosinophilic apoptosis and exerts a glucocorticoid-sparing effect in EGPA patients with asthma and/or sinonasal manifestations (19). The outcomes of these agents based on the anti-PR3 ANCA status remain unclear; however, these drugs may be considered for refractory cases of anti-PR3 ANCA-positive EGPA.

Despite having a high FFS (i.e., age, cardiac symptoms and renal insufficiency) as well as elevated serum IgG4 levels and complications with other visceral involvements, our patient was treated with prednisolone alone because of his refusal to undergo intensive therapy. Fortunately, our medication succeeded, but the risk of relapse and steroid dependence remains as long as he is receiving glucocorticoid monotherapy. Thus, additional immunosuppressants, RTX, or mepolizumab might be necessary in the follow-up.

In conclusion, we herein report a case of anti-PR3 ANCA-positive EGPA revealed by cardiac tamponade that responded rapidly to treatment with pericardiocentesis and a single administration of prednisolone. However, we were unable to clarify the clinical or pathological role of anti-PR3

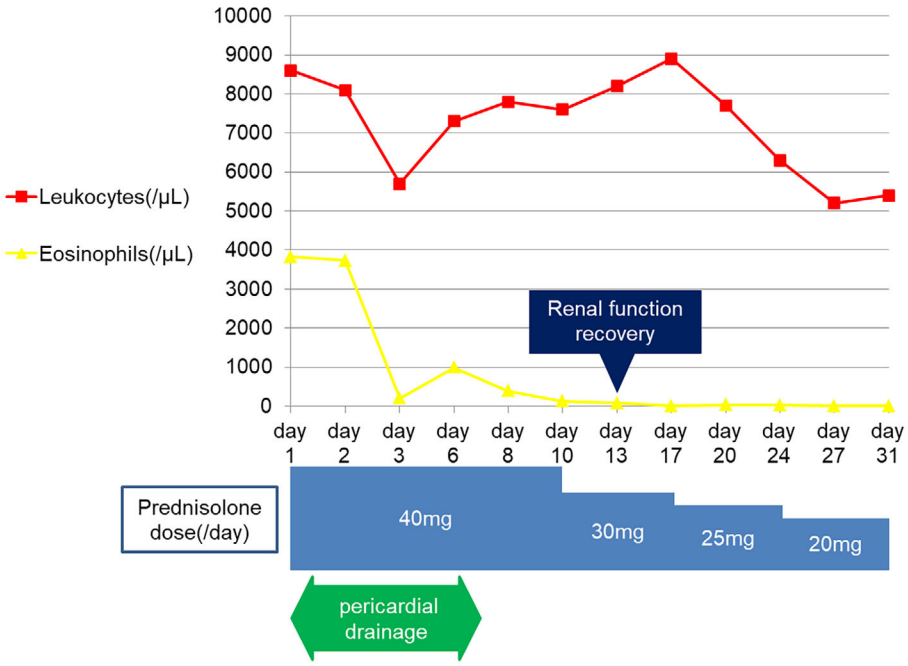

Figure 4. **The patient's clinical course during hospitalization. Pericardiocentesis was performed, and continuous pericardial drainage was initiated on day 1. After the patient was treated with prednisolone, pericardial drainage was finished without recurrence of pericarditis on day 7. Furthermore, his renal function recovered, resulting in the normalization of blood test and urinalysis findings on day 13.**

ANCA in EGPA, necessitating further investigations.

The authors state that they have no Conflict of Interest (COI).

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