CASE REPORT

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

Yuji Yamamoto, Yasushi Otani, Fukuko Okabe, Midori Yoneda, Osamu Morimura and Kinya Abe

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

(Intern Med 58: 3045-3050, 2019)
(DOI: 10.2169/internalmedicine.2937-19)

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°C, 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/mm³, with 44.5% eosinophils on differential leukocyte count; platelet count, 29.5×10⁹/mm³; C-reactive protein level, elevated; and anti-PR3 ANCA was positive. C-reactive protein level, elevated; and anti-PR3 ANCA was positive. The patient was promptly treated with pericardiocentesis and a single administration of prednisolone. He showed a favorable response to the treatment within a week, with resolution of pericardial effusion and improvement in pericardial tamponade.
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 IgG (1,115 mg/dL) were elevated, IgG4 (191 mg/dL) was 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 IgG (1,115 mg/dL) were elevated, IgG4 (191 mg/dL) was normal. In addition, rheumatoid factor (RF) and anti-nuclear 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, 32,400/mm³, 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/mm³, 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-negative.
Our patient also exhibited overlapping manifestations of anti-PR3 ANCA-positive EGPA with cardiac tamponade. To our knowledge, this is the first case report of ANCA because anti-PR3 ANCA is rare among patients with EGPA. 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 anti-PR3 ANCA in the pathogenesis of EGPA (8). Therefore, anti-PR3 ANCA positivity may be a significant factor in the pathogenesis of EGPA (8).

Table 1. Blood Test and Urinalysis Findings upon Admission.

| Hematology | Immunology |
|------------|------------|
| Leukocytes | IgG        |
| Neutrophils| IgG4       |
| Eosinophils| IgA        |
| Basophils  | IgM        |
| Monocytes  | IgE        |
| Lymphocytes| CH50       |
| Erythrocytes| C3        |
| Hemoglobin | C4         |
| Platelets  | RF         |
| Coagulation| ANA <40    |
| Prothrombin activity | anti-PR3 ANCA |
| PT-INR     | anti-MPO ANCA |
| APTT       |            |
| Fibrinogen |            |
| D-dimer    |            |
| Biochemistry| Occult blood |
| Total protein | Specific gravity |
| Albumin     | pH         |
| AST         | Protein    |
| ALT         | Glucose    |
| LDH         | Ketone     |
| Total bilirubin | Biliubin |
| Creatine kinase | Nitrite |
| Blood urea nitrogen | Bacteria |
| Creatinine  |            |
| Uric acid   |            |
| Sodium      |            |
| Potassium   |            |
| Chloride    |            |
| Glucose     |            |
| BNP         |            |

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).
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 ANCA.
ANCA in EGPA, necessitating further investigations.

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

References

1. Masi AT, Hunder GG, Lie JT, et al. The American College of Rheumatology 1990 criteria for the classification of Churg-Strauss syndrome (allergic granulomatosis and angiitis). Arthritis Rheum 33: 1094-1100, 1990.
2. Jennette JC, Falk RJ, Bacon PA, et al. 2012 Revised international Chapel Hill consensus conference nomenclature of vasculitides. Arthritis Rheum 65: 1-11, 2013.
3. Vaglio A, Strehl JD, Manger B, et al. IgG4 immune response in Churg-Strauss syndrome. Ann Rheum Dis 71: 390-393, 2012.
4. Gaillelin L, Pagnoux C, Seror R, Mahr A, Mouthon L, Le Toumelin P; French Vasculitis Study Group (FVSG). The Five-Factor Score revisited: assessment of prognoses of systemic necrotizing vasculitides based on the French Vasculitis Study Group (FVSG) cohort. Medicine (Baltimore) 90: 19-27, 2011.
5. Comarmond C, Pagnoux C, Khellaf M, et al. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss): clinical characteristics and long-term followup of the 383 patients enrolled in the French Vasculitis Study Group cohort. Arthritis Rheum 65: 270-281, 2013.
6. Sada KE, Amano K, Uehara R, et al. A nationwide survey on the epidemiology and clinical features of eosinophilic granulomatosis with polyangiitis (Churg-Strauss) in Japan. Mod Rheumatol 24: 640-644, 2014.
7. Zhu D, Luo Y, Liu X, Zu L. Antiproteinase 3 positive eosinophilic granulomatosis with polyangiitis presenting with heart failure and intraventricular thrombosis. Case Rep Rheumatol 2017: 2908185, 2017.
8. Yano T, Ishimura S, Furukawa T, et al. Cardiac tamponade leading to the diagnosis of eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome): a case report and review of the literature. Heart Vessels 30: 841-844, 2015.
9. Brinkmann V, Reichard U, Goosmann C, et al. Neutrophil extracellular traps kill bacteria. Science 303: 1532-1535, 2004.
10. Söderberg D, Segelmark M. Neutrophil extracellular traps in ANCA-associated vasculitis. Font Immunol 7: 256, 2016.
11. Ueki S, Melo RC, Ghiran I, Spencer LA, Dvorak AM, Weller PF. Eosinophil extracellular DNA trap cell death mediates lytic release of free secretion-competent eosinophil granules in humans. Blood 121: 2074-2083, 2013.
12. Wong CK, Dong J, Lam CW. Molecular mechanisms regulating the synergism between IL-32γ and NOD for the activation of eosinophils. J Leukoc Biol 95: 631-642, 2014.
13. Ribi C, Cohen P, Pagnoux C, et al. Treatment of Churg-Strauss syndrome without poor-prognosis factors: a multicenter, prospective, randomized, open-label study of seventy-two patients. Arthritis Rheum 58: 586-594, 2008.
14. Cohen P, Pagnoux C, Mahr A, et al. Churg-Strauss syndrome with poor-prognosis factors: a prospective multicenter trial comparing glucocorticoids and six or twelve cyclophosphamide pulses in forty-eight patients. Arthritis Rheum 57: 686-693, 2007.
15. Agard C, Rendu E, Leguern V, et al. Churg-Strauss syndrome revealed by granulomatous acute pericarditis: two case reports and a review of the literature. Semin Arthritis Rheum 36: 386-391, 2007.
16. Mohammad AJ, Hot A, Arndt F, et al. Rituximab for the treatment of eosinophilic granulomatosis with polyangiitis (Churg-Strauss). Ann Rheum Dis 75: 396-401, 2016.
17. Thiel J, Troilo A, Salzer U, et al. Rituximab as induction therapy in eosinophilic granulomatosis with polyangiitis refractory to conventional immunosuppressive treatment: a 36-month follow-up analysis. J Allergy Clin Immunol Pract 5: 1556-1563, 2017.
18. Wechsler ME, Akuthota P, Jayne D, et al. Mepolizumab or placebo for eosinophilic granulomatosis with polyangiitis. N Engl J Med 376: 1921-1932, 2017.

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.
19. Jachiet M, Samson M, Cottin V, et al. Anti-IgE monoclonal antibody (omalizumab) in refractory and relapsing eosinophilic granulomatosis with polyangiitis (Churg-Strauss): data on seventeen patients. Arthritis Rheum 68: 2274-2282, 2016.

© 2019 The Japanese Society of Internal Medicine

*Intern Med 58: 3045-3050, 2019*