Pulmonary Hypertension and Right Sided Heart Failure in a Patient with Eosinophilic Granulomatosis with Polyangiitis: A Case Report

RACHEL ANNE MONTECLARO, MD [1], CHERYL ANNE A. DELA CRUZ-TAN, MD, FPCP, FPRA, CCD [2]

Abstract

Introduction. Eosinophilic Granulomatosis Polyangiitis (EGPA) is the rarest among the ANCA-associated vasculitis with an incidence of seven per million individuals. Cardiac involvement occurs in 15-60% of patients and is the most severe manifestation associated with poor prognosis and mortality. EGPA typically affects the left side of the heart. There is only one published study to date that describes a case of right sided heart failure from pulmonary arterial hypertension.

Case. A 40-year-old, Filipino, female, complained of rash, wheezing and right sided heart failure symptoms. After a thorough work-up, she was managed as a case of EGPA based on palpable, erythematous, nonpruritic rash on the lower extremities, peripheral eosinophilia (54%), adult-onset asthma, mononeuritis multiplex, cardiac symptoms, (+) p-ANCA and leukocytoclastic vasculitis with eosinophils and early granuloma formation on skin punch biopsy. The 2D-echocardiography showed an elevated estimated pulmonary pressure with signs of right sided volume overload. Chest computed tomography with contrast revealed right atrial and biventricular enlargement, hepatomegaly and unremarkable pulmonary findings. Methylprednisolone along with intravenous cyclophosphamide pulse therapy were initiated which resulted in the resolution of symptoms with normalization of blood eosinophils. Repeat 2D-echocardiogram had unremarkable findings as well. With the improvement noted, she was then maintained on glucocorticoids and mycophenolate mofetil.

Discussion. Although EGPA commonly presents with symptoms of asthma, rhinosinusitis and/or peripheral eosinophilia, one uncommon presentation would be cardiac manifestations, specifically progressive pulmonary arterial hypertension with subsequent right sided heart failure. High dose glucocorticoids along with other immunosuppressants such as cyclophosphamide, are the treatment options in managing life-threatening conditions. Early detection is crucial in the prevention of grave outcomes

Keywords. EGPA, Filipino, Heart failure, Pulmonary hypertension, Vasculitis

Introduction

Eosinophilic granulomatosis with polyangiitis (EGPA) is the rarest among the ANCA associated vasculitis with an incidence of seven per million individuals [1]. This disease is characterized by adult-onset asthma, peripheral and tissue eosinophilia, extravascular granuloma formation and vasculitis of small and medium sized vessels in the different organs of the body [2].

Cardiac involvement is the most severe manifestation of EGPA and is the cause of mortality in most patients. This involvement may be a result of the direct activity of the disease affecting any part of the heart, and the usual presentations in many case reports were pericarditis, myocarditis, cardiomyopathy, heart failure, cardiogenic shock, myocardial infarction, and arrhythmia [3]. EGPA typically affects the left side of the heart. Unlike the other connective tissue diseases, ANCA vasculitis such as EGPA, are rarely associated with pulmonary artery hypertension [4]. This paper aims to present a case of EGPA characterized by pulmonary artery hypertension and right sided heart failure. To date, there is only one

[1] Department of Internal Medicine, Southern Philippines Medical Center JP Laurel Ave, Bajada, Davao City, Davao del Sur
[2]Department of Internal Medicine, Southern Philippines Medical Center, JP Laurel Ave, Bajada, Davao City, Davao del Sur
corresponding author: RACHEL ANNE MONTECLARO, Email: rachelannemonteclaro@gmail.com

published study that describes a case of right sided heart failure from pulmonary arterial hypertension

Case

A 40-year old female, Filipino, married, who works as a domestic helper in the Middle East, consulted at the Emergency Department of our institution due to rash and dyspnea.

Twenty-four weeks prior to admission, the patient noted new onset erythematous, smooth, slightly elevated and pruritic patches on bilateral lower extremities (Figure 1) which were not associated with dyspnea, wheezing, palpitations, gastrointestinal symptoms, fever nor body pains. She did not seek any consultation nor take or apply any medications, especially for her rash. She had no prior food or drug allergy. Within a week, the rash progressed to painful non-blanching purpuric lesions that were burning in character (PS 3/10) now involving the bilateral lower and upper extremities. She also had new onset non-migrating, left knee pain (pain scale 7-8/10) with swelling, warmth and pain on both active and passive movements, notable upon waking up and persisting throughout the day. She experienced fatigue and nighttime non-productive cough with occasional audible wheezing and frequent sneezing. She had no history of childhood asthma nor allergic rhinitis. There was no fever, body malaise, alopecia, oral ulcers, weight loss, and night sweats.

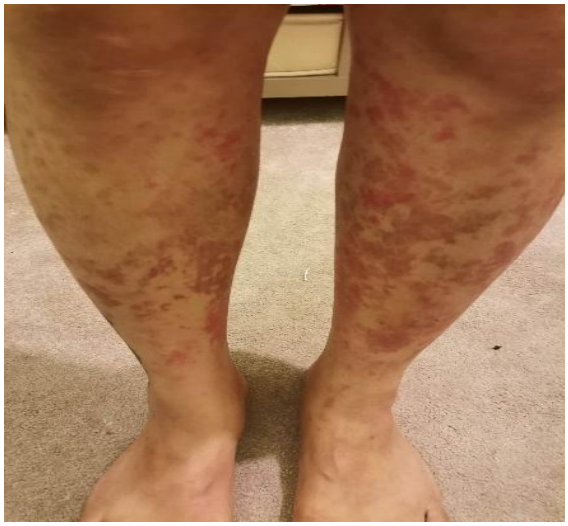


Figure 1: Palpable, nontender, non-blanching erythematous rash on bilateral lower extremities

Twenty-two weeks prior to admission, there was spontaneous resolution of knee pain, but the rash persisted. At this time, she noted new onset bipedal edema and occurrence of exertional dyspnea. She was unable to walk more than twenty steps on a flat surface. She sought consultation with a physician in Kuwait wherein unrecalled laboratory tests were done. She was diagnosed with an allergic reaction with concomitant rheumatoid arthritis and was only given cetirizine, which was taken with good compliance, but afforded no relief. The tests done nor the diagnosis were not completely explained to her, and she was just told to take the prescribed medication.

She noted progression of exertional dyspnea with three-pillow orthopnea and later on, she could only sleep sitting up because of orthopnea. She still had episodes of night time coughing and audible wheezing. The patient also complained of intermittent numbness of bilateral hands and left leg. There was no weakness and or limitation of movement as she was able to move around and do her activities albeit would take longer time to finish her work. The rashes were noted to wax and wane, usually over two days, and occurring in various areas all over her body. She had multiple consults but was given no additional medications nor workups.

Twelve weeks prior to admission, the patient returned to the Philippines, still with bipedal edema, marked orthopnea, dyspnea at rest, wheezing and sneezing, and recurring painful, erythematous rashes. She no longer complained of intermittent numbness of her hands and left leg during this time. She sought consultation with a private physician, and was managed as a case of asthma and allergic rhinitis. She was given prednisone 20mg twice a day for one week and salmeterol + fluticasone propionate inhaler, with resolution of symptoms. She subsequently returned to Kuwait clinically improved.

Four weeks prior to admission, the patient had recurrence of exertional dyspnea, bipedal edema, two-pillow orthopnea, generalized erythematous pruritic rashes, still spontaneously resolving and recurring every two days on average, and exertional dyspnea. She initially tolerated the condition, however within the next two weeks, the said symptoms were noted to persist and progress. She decided to return to the Philippines, and shortly after arrival, she became dyspneic even at rest, prompting consultation and subsequent admission in our institution.

She is hypertensive for three years but is not compliant with her medication (lisinopril 5mg daily) with highest systolic blood pressure (SBP) of 200mmHg and usual SBP of 130-140mmHg. She had no childhood asthma and has no food nor drug allergies. She is a gravida 3 para 3 mother, and her pregnancies were delivered via spontaneous vaginal delivery except for the last pregnancy wherein she underwent cesarean section for fetal malpresentation. All pregnancies had unremarkable outcomes. She has no history of oral contraceptive pill intake. She has no known vices and her family history is unremarkable with no known autoimmune diseases.

Clinical Findings

Upon arrival at the emergency room, she was noted to be tachypneic (24cpm), orthopneic, hypertensive (BP 140/90 mmHg) with desaturation (92%) at room air. She had pale skin with palpable, nontender, non-blanching erythematous rash on bilateral extremities with dusky discoloration of the left foot compared with the right foot (Figure 2). She had slightly icteric sclerae but has no alopecia, malar rash, nasal polyps, nor oral ulcers. The

jugular venous pressure was at five centimeters from the sternal line on 45 degrees head elevation. She had dynamic precordium with heaves and a displaced point of maximal impulse at sixth intercostal space anterior axillary line. The heart sounds were distinct with accentuated P2 but without S3, nor murmurs. Subcostal retraction was seen on chest inspection with bilateral crackles on both lung fields from mid to base. There was absent hepatojugular reflux but the liver edge was palpable in the right subcostal area suggesting hepatomegaly. She had grade two bipedal edema without ulceration and varicosities. The pulses were good on all extremities with ankle brachial index of 1.14 bilaterally.

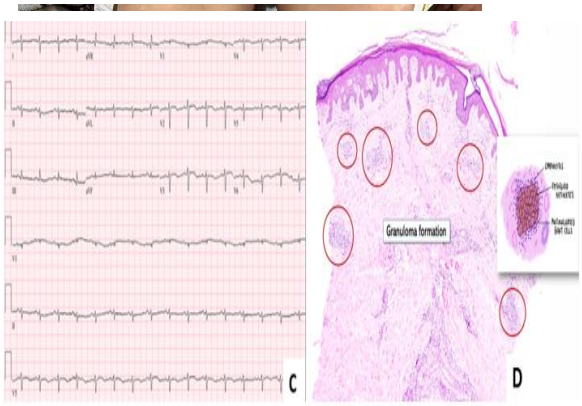
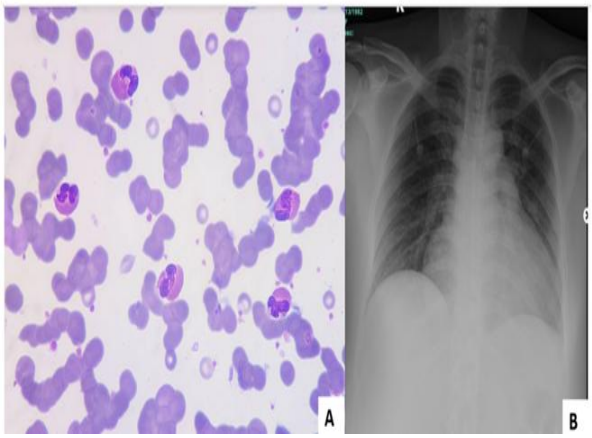


Figure 2: Palpable, nontender, non-blanching erythematous rash on bilateral lower extremities

Timeline

24 weeks PTA	Onset of erythematous, smooth, slightly elevated and pruritic patches on bilateral lower extremities without associated symptoms
23 weeks PTA	Rash progressed to painful non-blanching purpuric lesions that were burning in character involving all extremities associated with joint pains, fatigue, cough, wheezing and sneezing.
22 weeks PTA	Resolution of knee pain but rash persisted. She had new onset bipedal edema and exertional dyspnea. She had her first consult in the Middle East, was diagnosed with rheumatoid arthritis and allergy.
	rsisted and progressed.
	‹ to the Philippines, was diagnosed with bronchial ı short course high dose oral steroid and inhaler with ɔf symptoms. ‹ to Kuwait improved.
	waxing and waning rash, dyspnea, edema, orthopnea gressive.

Figure 3: A: Peripheral blood smear with eosinophilic predominance; **B:** Chest X-ray with unremarkable pulmonary findings and cardiomegaly; **C:** 12-L ECG was sinus rhythm, right axis deviation, poor R-wave progression, low voltage QRS complexes and persistent posterobasal forces; **D:** Leukocytoclastic vasculitis with eosinophils and early granuloma formation



Therapeutic Intervention Five factor score (FFS) is a validated tool to prognosticate and guide treatment in patients with EGPA. She was categorized as having severe active disease based on the validated Five Factor

Score (FFS) of two from cardiac involvement and absence of ear and nose abnormality. Cardiac involvement is a life-threatening condition which prompted the use of 1 gram methylprednisolone given intravenously for three consecutive days (pulse therapy), followed by high dose oral prednisone at 1mg/kg/day after the pulse therapy, as well as cyclophosphamide 1 gram intravenous pulse therapy. These managements were in accordance to the 2021 ACR/VFG recommendation on remission induction in severe active disease wherein a pulse therapy or high dose oral steroid should be combined with a non-glucocorticoid immunosuppressant such as cyclophosphamide or rituximab. Cyclophosphamide was preferred in the guideline for patients with active cardiac involvement.

After discharge, she underwent two more cyclophosphamide pulse therapy within a two weeks interval. There was marked improvement on her symptoms as the rash resolved, and she was able to walk approximately 3 meters without dyspnea. On CBC, her eosinophils also decreased, from a baseline of 54% to normal level of 5% on 2nd follow-up.

WBC (x 10^3/uL)	25.25	18.99	22.31	14.22	18.48
Neutrophils (%)	26	19	16	72	62
Lymphocytes (%)	15	9	11	12	26
Monocytes (%)	4	4	2	2	7
Eosinophils (%)	54	68	71	14	5
Basophils (%)	1	0	0	0	0
Platelet (x 10^3/uL)	335	100	207	236	276

The guideline stated that the optimum duration of remission induction is still not known for EGPA hence FFS could be used to guide treatment. When an FFS of 0 was maintained on subsequent follow-ups, her non-steroid immunosuppressant was switched to mycophenolate mofetil while her glucocorticoids was tapered subsequently.

Follow-up and Outcome The patient was closely followed-up post discharge and underwent a total of three cycles of cyclophosphamide infusions two weeks apart in line with the recommendation of the ACR/VFG 2021 treatment guidelines. There was no recurrence of symptoms after the first pulse therapy (FFS 0). Her heart failure symptoms, rashes (Figure 4) and abnormal breath sounds resolved. There were also improvements in the laboratory tests such as normalization of WBC and eosinophil counts (Table 1) and improvement of 2D-echo result with loss of the interventricular flattening, normalization of the right atrial and ventricular dimension and decrease in pulmonary hypertension to 44mmHg.

Table 1: Complete blood count trends

CBC	4/24/23	4/28/23	5/2/23	5/19/23 (1st follow- up)	6/5/23 (2nd follow-up)
Hb (g/L)	83	120	126	133	160
Hct	0.24	0.36	0.38	0.41	0.45
RBC (x 10^6/uL)	2.38	3.87	3.95	4.2	4.73

DiscussionEosinophilic granulomatosis with polyangiitis (EGPA) formerly called Churg Strauss Syndrome, is the rarest of the three anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides. Its incidence is approximately seven per million individuals [1]. It affects the small and medium-sized vessels and is characterized histologically by necrotizing vasculitis, extravascular granulomatous inflammation and tissue infiltration of eosinophils [2].

Patients with EGPA usually experience a spectrum of symptoms corresponding to three overlapping phases of this disease. These include the prodromal phase which typically starts as asthma in the second or third decade of life in continuum with the eosinophilic phase to the vasculitic phase [5]. According to the study of Vives et al. 2021, asthma precedes the diagnosis by a median of 97 months (36-240). Other organ involvement may be present in patients with EGPA but patients with cardiac involvement however, have a shorter duration of EGPA related symptoms. In this case, the adult onset of asthma was noted only six months prior to admission, with subsequent unfolding of the rest of her symptoms, thereafter, leading to admission.

Laboratory findings such as hypereosinophilia, leukocytosis and skin punch biopsy finding consistent with EGPA, confirmed the diagnosis. The patient also had hypocomplementemia (C3 of 34. 4 mg/dL). In some cases of vasculitis, C3 can be low because there is consumption and depletion in the blood when the inflammatory cells act on the blood vessel walls. There is a rapid breakdown of C3 turning it into active fragments that lead to further inflammation and damage. When the vasculitic flare is very active, C3 can be seen deposited within the inflamed blood vessel walls, diminishing the levels in the blood circulation, hence the hypocomplementemia. Low C3 levels are often associated with a more severe disease and poorer prognosis in some cases. In one study, serum C3 and C4 levels were noted to be low in 4.5% of cases of cutaneous small vessel vasculitis [7].

Involvement of the heart is the most severe complication that causes morbidity and comprises almost 50% of deaths [8]. Patients with predominantly cardiac symptoms are usually p-ANCA negative with negative skin biopsy findings, however these were both positive in our patient [9,10]. P-ANCA is present in only 48% of EGPA patients. One interesting finding in this case is that EGPA patients with predominant cardiac involvement are usually found to be ANCA negative. Our patient on the other hand, is P-ANCA positive. P-ANCA positivity is usually associated with the vasculitis phenotype than the cardiac phenotype suggesting that the cardiac involvement, specifically the right sided heart failure, could be due to the pulmonary hypertension from vasculitis. Predominant cardiac involvement can be seen in approximately 15-60% of EGPA patients and may manifest with myocarditis, pericarditis, arrhythmia, coronary arteritis, valvulopathy, intracavitary cardiac thrombosis and heart failure [3].

This patient was noted to have heart failure symptoms which is a common cardiac symptom, present in 51.6% of patients in the meta-analysis of 62 case reports of EGPA [3]. Left ventricular dysfunction is the most common reason for the heart failure symptoms in EGPA patients, however in our patient the heart failure symptoms were most likely from the right sided failure and pulmonary hypertension. These were based on the physical examination findings of distended neck veins and bipedal edema, supported by the presence of right axis deviation in the ECG and right sided overload and pulmonary hypertension in the 2D-echo.

The most common cause of right sided failure is one that is secondary to a left sided heart failure, however right sided failure can occur prior or after the development of left sided failure, if there is diffuse myocardial disease [13]. For this patient, it can be hypothesized that the right sided heart failure could be due to the effect of progressive pulmonary hypertension caused by pulmonary vasculitis, and the diffuse myocardial damage from eosinophilic infiltration [14].

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Pulmonary arterial hypertension is a common complication of some connective tissue diseases like systemic sclerosis and systemic lupus erythematosus, but it is a rare condition associated with systemic vasculitis [10]. Inflammation of the pulmonary artery may cause pulmonary hypertension in ANCA associated vasculitis [15, 16]. Studies have shown that eosinophilic vasculitis can induce vascular remodeling in mice leading to pulmonary muscularization and later on pulmonary hypertension while the use of anti-IL 5 treatments which are known to inhibit eosinophil migration attenuates this effect [17].

The diffuse myocardial damage is postulated to be caused by eosinophilic myocarditis on the basis of peripheral hypereosinophilia and fulfillment of the European Society of Cardiology (ESC) diagnostic criteria for clinically suspected myocarditis (subacute heart failure signs with poor r wave progression in the 12L ECG and unexplained LV, RV structural abnormalities) [18]. A cardiac magnetic resonance imaging showing hyperemia, edema or necrosis and endomyocardial biopsy if done, may have been an essential key to further confirm the diagnosis, however, it was not available in our institution.

The management of EGPA starts with determining the severity of the patient's symptoms based on the validated Five-Factor Scoring (FFS). The factors included are age > 65, cardiac insufficiency, renal insufficiency, gastrointestinal involvement and absence of ENT manifestations (presence is associated with better prognosis).

According to the 2021 ACR/VFG recommendation, patients with severe active disease should receive intravenous pulse glucocorticoid or high dose oral steroid combined with a non-glucocorticoid immunosuppressive agent such as cyclophosphamide or rituximab for remission induction. Cyclophosphamide is preferred for patients with cardiac involvement due to increased experience with cyclophosphamide. The duration of remission induction was not specified in the guideline and clinicians are encouraged to use the FFS to guide therapy when switching to remission maintenance medications. For patients with severe EGPA whose disease has entered remission, cyclophosphamide may be switched to either methotrexate, azathioprine or mycophenolate mofetil. Treatment of non-severe disease include glucocorticoids combined with either mepolizumab, methotrexate, azathioprine, mycophenolate mofetil or rituximab. The optimal duration of treatment for all ANCA associated vasculitis is still not known at the moment.

In this case, we can postulate that the eosinophilic inflammation may have contributed to the pulmonary vascular remodeling and myocardial damage, since she had marked clinical improvement after the initiation of intravenous methylprednisolone pulse therapy and IV-cyclophosphamide therapy.

ConclusionEosinophilic granulomatosis with polyangiitis can cause various life-threatening diseases, although pulmonary hypertension and right sided heart involvement may be seen, these can occur as uncommon presentations. Early recognition along with identification of an accurate diagnosis and its possible organ involvement, and prompt immunosuppressive therapy, are needed for this rare disorder, to ensure a good outcome.

Conflict of Interest No conflict of interest relevant to this article is reported.

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