

## Eosinophilic Granulomatous Polyangiitis with Renal Granulomatous Angitis and Interstitial Eosinophilic Infiltration without Lung Granuloma

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### Abstract

Eosinophilic granulomatous with polyangiitis (EGPA) is systemic vasculitis characterized by concomitant symptoms of asthma, allergic rhinitis, and marked increase in peripheral eosinophilia. It was previously known as Churg-Strauss syndrome. EGPA incidence in Japan is very low, with only approximately 1,800 cases reported. Renal involvement occurs in approximately 20-25% of EGPA patients, and the most typical expression is pauci-immune crescentic glomerulonephritis. We herein report a case of 69-year-old Japanese woman with fever and high titer of myeloperoxidase-antineutrophil cytoplasmic antibodies (MPO-ANCA) and eosinophilia. Her renal biopsy showed massive interstitial nephritis with granulomatous vasculitis like lesion without apparent active crescent formation in glomeruli.

Immediately after steroid treatment (prednisolone [PSL] 30 mg/day), she had symptomatic relief and was discharged with a reduction in MPO-ANCA.

**Keywords:** EGPA; Churg-Strauss syndrome; MPO-ANCA; Granulomatous angitis

### Introduction

Eosinophilic granulomatosis with polyangiitis (EGPA) is a multisystemic disorder involving small vessel antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, which is defined as an eosinophil-rich and necrotizing granulomatous inflammation often involving the respiratory tract, and necrotizing vasculitis predominantly affecting small to medium vessels, which is associated with asthma and eosinophilia. Formerly known as Churg-Strauss syndrome, this eponym was replaced during the 2012 Revised International Chapel Hill consensus conference (CHCC) with the aim of focusing on the histopathology of the disease [1,2]. Unlike the 1990 American College of Rheumatology classification criteria and the former CHCC classification criteria, the 2012 CHCC reported for the first time that ANCA is found in EGPA, especially in patients with glomerulonephritis.

EGPA incidence in Japan is reported to be approximately 100 new cases annually, and the total number of EGPA patients was approximately 1,886 cases in 2008 [3]. EGPA incidence in Europe is 0.5-6.8 new cases per year per 1 million of the population, whereas its prevalence is 10.7-13 cases per 1 million of the population. It mostly affects individuals between 40 and 60 years old, and the mean age at diagnosis is 48 years [4].

We report one case of EGPA with renal granulomatous lesion, which is less frequent than EGPA with crescentic glomerulonephritis.

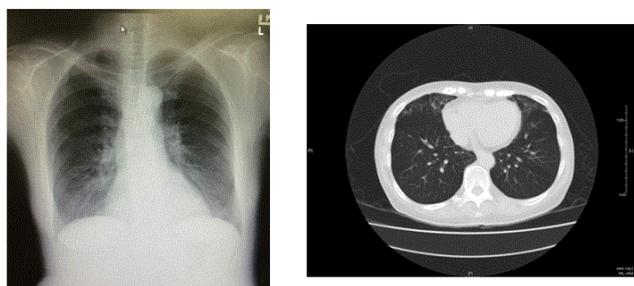
### Case Report

A 69-year-old woman had a more than 40-year history of chronic sinusitis, allergic rhinitis, and diabetes mellitus, a 14-year history of bronchiectasis, and a history of autoimmune hemolytic anemia treated with corticosteroids 10 years previously that remained in remission with 5 mg of prednisolone. She had no family history of renal disease or dialysis.

She had a fever 1 month previously and was treated with antibiotics (clarithromycin [CAM]) for infectious disease). However, her symptoms did not show any improvement with CAM, and she developed fever, arthralgia, and myalgia within 2 weeks prior to admission despite a change in antibiotics to levofloxacin (LVFX).

Test results for myeloperoxidase-antineutrophil cytoplasmic antibodies (MPO-ANCA) (288 U/ml), proteinuria, and urine occult blood were positive, and LVFX did not result in improvement; therefore, she was referred to our hospital for further evaluation and treatment. On physical examination, her temperature was 37.5°C and her blood pressure was 141/74 mmHg. Lower extremity edema without dyspnea was evident. She was prescribed bed rest without activity.

Chest radiography revealed mild cardiac enlargement, with a cardiothoracic ratio of 56% without pleural effusions; chest computed tomography revealed no granulomatous lesion (Figure 1).



**Figure 1:** X-ray and Computed tomography (CT) of the chest. Chest radiography revealed mild cardiac enlargement as CTR 56% without pleural effusions, and a chest computed tomography (CT) scan revealed no granulomatous lesion in lung.

The following laboratory results were obtained (Table 1): white blood cell (WBC) count, 14,100 WBC/ $\mu$ l eosinophil 1410/ $\mu$ l (10% of

WBC); red blood cell (RBC) count,  $328 \times 10^4$  RBC/ $\mu$ l; hemoglobin, 9.5 g/dl; hematocrit, 28.8%; platelet count (plt),  $37.3 \times 10^4$  plt/ $\mu$ l; total protein, 5.8 g/dl; albumin, 2.19 g/dl; blood urea nitrogen, 14 mg/dl; serum creatinine (Cr), 0.8 mg/dl; sodium, 130 mEq/L; potassium, 3.8 mEq/L; chloride, 96 mEq/L; C-reactive protein (CRP), 10.95 mg/dl; plasma glucose, 118 mg/dl; hemoglobin A1c, 8.1%; aspartate aminotransferase, 15 IU/L; alanine aminotransferase, 10 IU/L; alkaline phosphatase, 172 IU/L; gamma glutamyl transpeptidase, 24 IU/L; IgG, 1,490 mg/dl; IgM, 153 mg/dl; IgA, 227 mg/dl and IgE, 728 IU/ml. The third complement component (C3) level was 144 mg/dl (normal, 50-130 mg/dl); the fourth component (C4) level was 16.5 mg/dl (normal, 10-50 mg/dl). Hemolytic complement activity via the classical pathway (CH50) was 42.2 U/ml (normal, 25.0–48.0 U/ml) and test results for antinuclear antibody were negative. MPO antibodies were > 300 U/ml, and proteinase 3 antibodies (PR3), ANCA, and antiglomerular basement membrane (anti-GBM) antibodies were not detected. Urinalysis showed 0.65 g of protein per 1 gram of Cr and 10-29 RBC per high-power field (HPF). The urinary  $\beta$ -2 microglobulin level was 1,539 ng/ml.

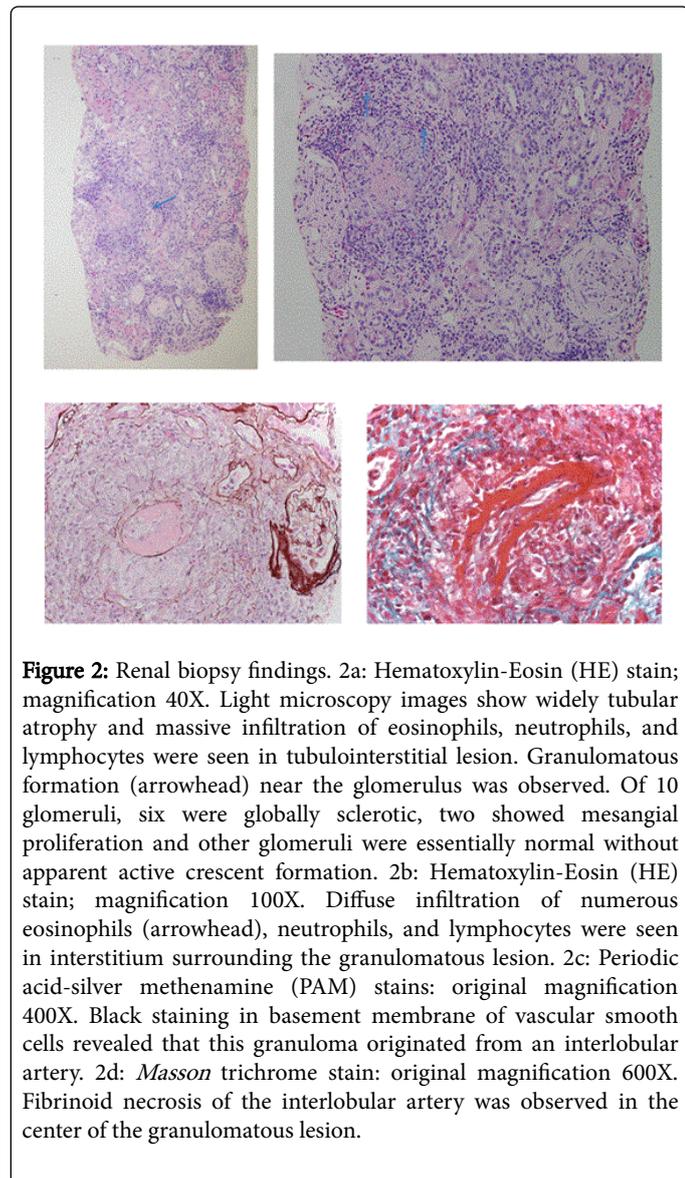
CBC		WBC differentiation		TP	5.8 mg/dl
WBC	14100 / $\mu$ l	Polys	77.50%	Alb	2.19 mg/dl
RBC	$328 \times 10^4$ / $\mu$ l	Lympho	7%	CRP	10.95 mg/dl
Hgb	9.5 g/dl	Mono	4.50%	Immunological findings	
Hct	28.80%	Eosino	10%	HBAg	
Plt	$37.3 \times 10^4$ / $\mu$ l	Baso	1%	HCV Ab	
Urine		Chemistry		TPHA	
pH	5.5	T-Bil	0.52 mg/dl	IgG	1490 mg/dl
SG	1.029	AST	15 mg/dl	IgA	227 mg/dl
Protein	3+	ALT	10 IU/l	IgM	153 mg/dl
	0.65 g/gCr	ALP	172 IU/l	IgE	728 mg/dl
Occult blood	3+	LDH	161 IU/l	C3	144 mg/dl
Glucose	1+	Na	130 IU/l	C4	16.5 mg/dl
Keton	-	K	3.8 mEq/l	CH50	42.2 IU/ml
$\beta$ 2MG	1539.3 ng/ml	Cl	96 mEq/l	P-ANCA	300 U/ml
Urine sediment		Ca	8.1 mEq/l	C-ANCA	1 U/ml
RBC	73	P	2.4 mg/dl	ANA	
WBC	52	BUN	14 mg/dl		
		Cre	0.8 mg/dl		
		UA	2.1 mg/dl		

**Table 1:** Laboratory findings on admission.

A percutaneous renal biopsy was performed on day 2 (Figures 2a-2d). Widely tubular atrophy and diffuse infiltration of numerous eosinophils (Figure 2b arrowhead), neutrophils and lymphocytes were noted in interstitium, surrounding the granulomatous lesion (Figure

2a arrowhead). Furthermore, granulomatous vasculitis like lesion with histiocytes and lymphocytes around the interlobular artery were also observed in Periodic acid-silver methenamine stain (PAM) stain and *Masson* trichrome stain (Figures 2c and 2d). Fibrinoid necrosis of the

interlobular artery was also observed in the center of granulomatous lesion and so this granuloma was originated from an interlobular artery (Figure 2d). Of 10 glomeruli, six were globally sclerotic, two showed mesangial proliferation and other glomeruli were essentially normal without apparent active crescent formation. This global sclerosis was thought to be consistent with her age and long term usage of corticosteroid.

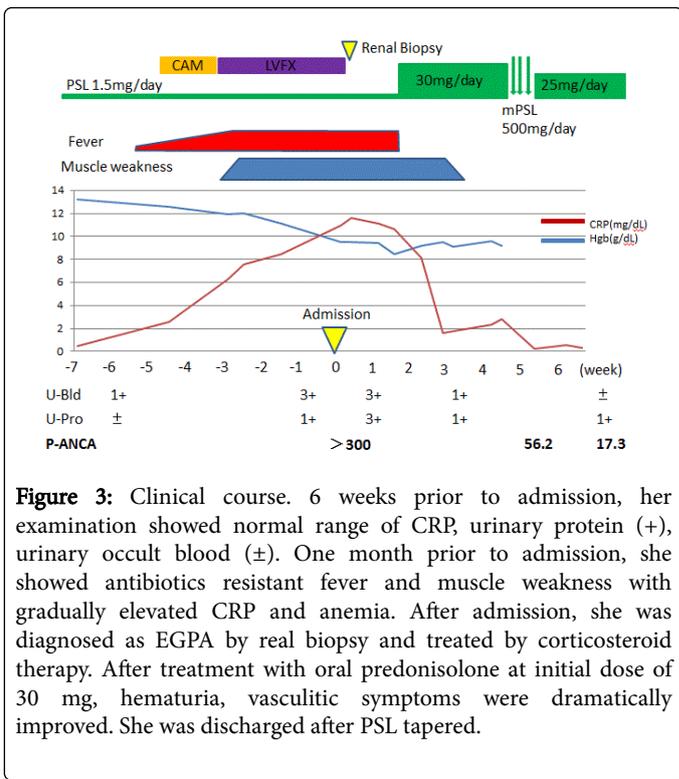


**Figure 2:** Renal biopsy findings. 2a: Hematoxylin-Eosin (HE) stain; magnification 40X. Light microscopy images show widely tubular atrophy and massive infiltration of eosinophils, neutrophils, and lymphocytes were seen in tubulointerstitial lesion. Granulomatous formation (arrowhead) near the glomerulus was observed. Of 10 glomeruli, six were globally sclerotic, two showed mesangial proliferation and other glomeruli were essentially normal without apparent active crescent formation. 2b: Hematoxylin-Eosin (HE) stain; magnification 100X. Diffuse infiltration of numerous eosinophils (arrowhead), neutrophils, and lymphocytes were seen in interstitium surrounding the granulomatous lesion. 2c: Periodic acid-silver methenamine (PAM) stains: original magnification 400X. Black staining in basement membrane of vascular smooth cells revealed that this granuloma originated from an interlobular artery. 2d: *Masson* trichrome stain: original magnification 600X. Fibrinoid necrosis of the interlobular artery was observed in the center of the granulomatous lesion.

There were no remarkable glomerular changes except for global sclerosis. Immuno-deposits of IgG, IgA, IgM, C1q, C3, and fibrinogen were absent.

Our patient was diagnosed as having definite EGPA because of the three main clinical findings (allergic rhinitis, eosinophilia and fever, myalgia and muscle weakness) and the histological finding (granulomatosis with eosinophilic infiltration around arteriole with fibrinoid necrosis) according to the diagnostic criteria of EGPA by Ministry of health and welfare in Japan.

She was treated with corticosteroids (PSL 30 mg/day) (Figure 3).



**Figure 3:** Clinical course. 6 weeks prior to admission, her examination showed normal range of CRP, urinary protein (+), urinary occult blood (±). One month prior to admission, she showed antibiotics resistant fever and muscle weakness with gradually elevated CRP and anemia. After admission, she was diagnosed as EGPA by renal biopsy and treated by corticosteroid therapy. After treatment with oral prednisolone at initial dose of 30 mg, hematuria, vasculitic symptoms were dramatically improved. She was discharged after PSL tapered.

Immediately after PSL administration, she had a normalized serum CRP level and showed dramatic symptomatic relief of her fever, arthralgia, muscle weakness, and myalgia. Anemia, proteinuria, and urine occult blood improved. PSL was tapered to 25 mg/day after 4 weeks, and she was discharged with a reduction in MPO-ANCA (17.3 U/ml).

**Discussion**

EGPA typically develops into three sequential phases marked by a progression of the main symptoms. The first phase, also called allergic, is most common during the second or third decade of life and is distinguished by asthma, allergic rhinitis, and sinusitis. Subsequently, the eosinophilic phase develops. The main pathological findings of this phase are increased peripheral eosinophilic count and eosinophilic organ infiltrations, especially in the lungs, heart, and gastrointestinal system. The third phase is vasculitic. During this last phase, the patient experiences the consequences of necrotizing vasculitis (e.g., peripheral neuropathy, crescentic glomerulonephritis), which is generally associated with vascular or extravascular granulomatosis, and constitutional symptoms like fever, malaise, and weight loss [5]. In this case, the woman had a history of allergic rhinitis since her second decade of life, which is a symptom of the first (allergic) phase.

ANCA is present in approximately 40-60% of patients; perinuclear ANCA is the prevalent pattern with antibody specificity for anti-MPO [5,6,7].

Recently, it was reported by Sablé-Fourtassou et al. [8] that ANCA-positive EGPA patients, compared with ANCA-negative patients, more frequently had kidney involvement (35% vs. 4%). Comarmond also reported the same results for a cohort of 383 in the French Vasculitis Study Group [9]. Although less frequent than the other two types of ANCA-associated vasculitis (AAVs) (microscopic polyangiitis [mPA]

and granulomatosis with polyangiitis), renal involvement occurs in approximately 25% of EGPA patients; the most typical expression is pauci-immune crescentic glomerulonephritis, which has clinical features ranging from isolated urinary abnormalities (proteinuria, hematuria) to rapidly progressive glomerulonephritis [6]. Moosig also reported that renal involvement occurred in 18% of 150 monocentric cases in Germany [10]. It is suspected that MPO-ANCA induces abundant proinflammatory cytokines in EGPA as well as in mPA [11]. Our patient had an extremely high P-ANCA titer (> 300 U/ml) and renal involvement, which is consistent with previous reports. Her renal involvement included urinary abnormalities (proteinuria, hematuria) without Cr level elevation (0.8 mg/dl). Renal biopsy results revealed granulomatous changes, histiocytes and lymphocytes around the necrotizing interlobular artery, and massive interstitial infiltration of eosinophils and lymphocytes without apparent active crescent formation in glomeruli, which could be explained by renal involvement. Regarding renal granulomatous changes in EGPA, these are less commonly accompanied by crescent formation. Bajema reported that only 16 out of 157 systemic vasculitis patients showed renal granulomatous lesions; among these 16 patients, only two had EGPA [12]. We found only one case report of renal granulomatous lesions in EGPA [13]. In EGPA, lung granuloma is well known, but it may be accompanied by granulomatous lesions in the kidney.

We report a rare case of EGPA with renal granulomatous lesions and eosinophilic infiltration without crescent formation, respiratory symptoms, or lung granuloma. Necrotizing vasculitis as the renal involvement and lung granuloma as the respiratory involvement in EGPA are well known, but EGPA may be accompanied by granulomatous lesions in the kidney.

### Compliance with Ethical Standards

This article does not include a research involving human participants which needs the informed consent or animal which needs the statement on welfare of animals.

### Conflict of Interest

All the authors have declared that no conflict of interest exists.

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