Received: 9 June 2021 | Revised: 23 June 2021 | Accepted: 7 July 2021

DOI: 10.1002/cia2.12194

Journal of Cutaneous Immunology and Allergy

WILEY

CASE STUDY

Relevance of cutaneous manifestations and antineutrophil cytoplasmic antibody status in eosinophilic granulomatosis with polyangiitis

Meiko Sone | Chie Miyabe | Ryujin Miyata | Yuko Takenaka | Naoko Ishiguro

Department of Dermatology, Tokyo Women's Medical University, Tokyo, Japan

Correspondence
Chie Miyabe, M.D., Ph.D., Department of Dermatology, Tokyo Women's Medical University, 8-1 Kawadacho, Shinjuku-ku, Tokyo 162-8666, Japan.
Email: cmderma.ak@twmu.ac.jp

Abstract

Eosinophilic granulomatosis with polyangiitis (EGPA) belongs to the family of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis syndromes. Although increasing evidence indicates the correlation of clinical and histological features with the presence or absence of ANCAs in EGPA, the variations in cutaneous features according to their ANCA status have not been fully described. Here, we retrospectively reviewed the clinical and histological findings of 9 cases of EGPA, who presented with cutaneous lesions. Our data indicate that ANCA-positive patients often present with blisters, systemic inflammatory symptoms, and are prone to receive a higher dose of oral prednisolone and additional immunosuppressive therapies.

1 | INTRODUCTION

Eosinophilic granulomatosis with polyangiitis (EGPA), previously known as Churg–Strauss syndrome, is a rare disease characterized by eosinophil-rich inflammation and systemic necrotizing vasculitis affecting small- to medium-sized vessels.[1] Approximately 50% of EGPA cases are associated with antineutrophil cytoplasmic antibodies (ANCAs), most commonly myeloperoxidase (MPO)-ANCA; therefore, EGPA has been categorized as one of the ANCA-associated systemic vasculitides (AAV).[2] EGPA can affect a wide variety of organs, including the skin, nerves, kidneys, lungs, ears, heart, and gastrointestinal tract.

Increasing evidence suggests clinical and histological differences between cases, in correlation with their ANCA status. It has been reported that a positive ANCA status at diagnosis is associated with the renal, peripheral nervous system, and skin involvement, whereas a negative ANCA status is associated with cardiac manifestations and fever.[3,4] A recent study also demonstrated that the serum levels of C-reactive protein (CRP) were higher in the MPO-ANCA-positive group than in the MPO-ANCA-negative group, whereas eosinophilic inflammation was more prominent in the MPO-ANCA-negative group.[5] A genome-wide association study revealed that ANCA-positive cases have an association with *HLA-DQ*, whereas ANCA-negative cases are postulated to have a mucosal/barrier dysfunction origin.[6]

Approximately half of the patients with EGPA show cutaneous manifestations, and these patients often have severe systemic manifestations of vasculitis, such as alveolar hemorrhage and glomerulonephritis.[7] The cutaneous manifestations of EGPA vary, reflecting the size of affected vessels, include purpura, nodules, livedo, blisters, ulcers, and urticarial lesions.[8] Easy accessibility of the skin lesions in EGPA facilitates its prompt diagnosis on the basis of histological findings. Histopathological examination of the skin lesions also serves as predictive factors of systemic disease, such as thromboses, in EGPA.[9] Nonetheless, the association between the histological features of cutaneous lesions and ANCA positivity has not been fully described.

In the present study, we reviewed the systemic and cutaneous manifestations of EGPA and their histological features in correlation with the presence or absence of ANCAs.

TABLE 1 Patient characteristics and clinical profile

Case	Sex	Age	MPO-ANCA (U/ml or EU)	Eosinophils (cells/μl)	CRP (mg/dl)	Fever	Asthma	Pulmonary infiltrates	Sinonasal symptoms	Peripheral neuropathy	Renal involvement	Skin first	PSL dose (mg/day)	Other therapy
1	M	53	189†	8303	7.64	+	+	–	+	+	–	No	50	mPSL pulse
2	F	57	587†	2342	3.40	–	+	–	–	+	+	No	50	mPSL pulse + MPZ
3	F	69	59†	8789	1.54	–	–	–	+	–	–	No	60	IVCY
4	F	46	36§	2343	2.66	–	+	–	–	–	–	Yes	50	
5	F	39	629§	6431	9.98	+	+	+	–	–	–	No	40	mPSL pulse
6	F	48	Negative	4449	2.71	–	+	+	+	+	–	No	45	
7	M	72	Negative	6312	1.98	–	+	+	+	+	–	No	30	
8	M	33	Negative	17016	3.45	–	+	–	+	–	–	Yes	40	
9	M	31	Negative	3200	0.06	–	–	–	–	–	–	Yes	30	

Abbreviations: CRP, C-reactive protein; IVCY, intravenous cyclophosphamide; MPO-ANCA, myeloperoxidase-antineutrophil cytoplasmic antibodies; mPSL, methylprednisolone; MPZ, mepolizumab; PSL dose, initial prednisolone dose; Skin first, Skin lesion(s) appeared first.

†U/ml (MPO-ANCA positivity was defined as 3.5 U/ml or higher).

§EU (MPO-ANCA positivity was defined as 20 EU or higher).

2 | CASE REPORT

We retrospectively investigated 9 patients with EGPA diagnosed at the Department of Dermatology of Tokyo Women's Medical University between 2005 and 2018. The presence of vasculitis had been confirmed by skin biopsies in all the patients. The baseline characteristics of the patients are shown in Table 1. The diagnosis of EGPA was made according to the criteria reported by the Research Group of Intractable Vasculitis, Ministry of Health, Labor, and Welfare of Japan.[10] All the patients were diagnosed as definite EGPA, except case 9. Case 9 was diagnosed as probable EGPA, and other eosinophilic disorders such as chronic eosinophilic leukemia and hypereosinophilic syndrome were ruled out. ANCA was measured using chemiluminescent enzyme immunoassay (CLEIA) (cases 1, 2, 3, 6, 7, and 9) or enzyme-linked immunosorbent assay (ELISA) (cases 4, 5, and 8). Of the 9 patients enrolled, 5 were MPO-ANCA-positive and 4 were MPO-ANCA-negative. All patients tested negative for ANCAs directed against proteinase 3 (PR3). There were no notable differences in age, eosinophil counts, or serum CRP titers among the patients. Although other organ involvement was almost equivalent between the ANCA-positive and ANCA-negative groups, fever (2 cases, 40%) and renal involvement (1 case, 20%) were exclusively observed in ANCA-positive patients. The mean daily dose of prednisolone administered for the initial therapy was 50.0 mg in ANCA-positive patients, whereas 36.25 mg in ANCA-negative patients ($p = 0.032$) (Figure 1a). Other treatment modalities such as methylprednisolone (mPSL) pulse, mepolizumab, and intravenous cyclophosphamide (IVCY) therapies were used only for ANCA-positive patients.

The cutaneous manifestations and histological features of EGPA that were observed in each patient are described in Table 2. Among the cutaneous lesions, erythema and purpura were common manifestations in both ANCA-positive and ANCA-negative patients. Notably, blisters were frequently observed in ANCA-positive patients (4 cases, 80%) but less prevalent in ANCA-negative patients (1 case, 25%). Histologically, dermal small-vessel vasculitis was observed in all cases, whereas subcutaneous muscular-vessel vasculitis was observed more commonly in ANCA-negative patients (2 cases, 50%) than in ANCA-positive patients (1 case, 20%). Neutrophil infiltration into the vessels was observed in both groups. In contrast, tissue eosinophilia and blisters were more prevalent in ANCA-positive patients than in ANCA-negative patients. Granulomatous inflammation mixed with histiocytes and eosinophils was present in 1 ANCA-positive patient.

Cited below are two contrasting cases from the case cohort. First, a 39-year-old female patient positive for MPO-ANCA presented with hemorrhagic vesicles in the lower leg. She also had fever and was diagnosed with eosinophilic pneumonia. Histopathological examination revealed dermal small-vessel vasculitis (Figure 1b, c). Second, a 33-year-old, ANCA-negative male patient presented with slightly indurated, erythematous lesions in the lower leg and vocal cord paralysis. Histopathological examination revealed subcutaneous muscular-vessel vasculitis (Figure 1d, e), in addition to dermal

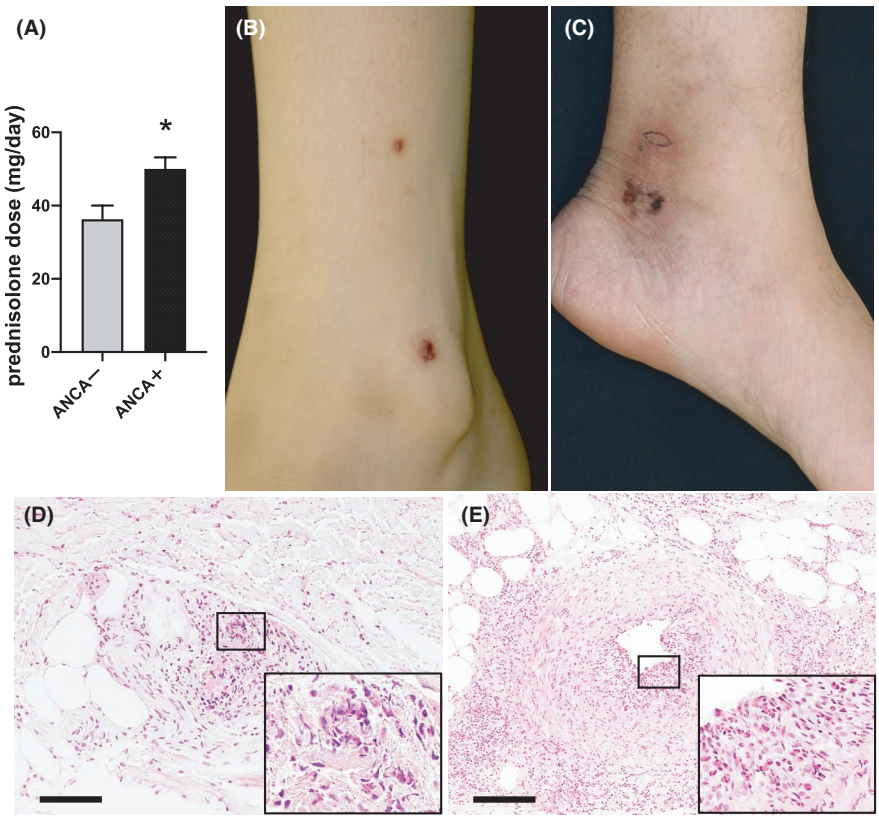

FIGURE 1 (A) The mean daily dose of prednisolone administered for the initial therapy. Data indicate mean ± SEM. $^{*}p < 0.05$ versus ANCA-negative patients with the Mann–Whitney *U*-test. (B) A 39-year-old woman positive for ANCA presented with hemorrhagic vesicles in the lower leg. (C) Histological examination showed small-vessel vasculitis in the dermis (hematoxylin-eosin, scale bar: 100 μm). High-power-field image shows leukocytoclastic vasculitis with slight extravasation of erythrocytes. (D) A 33-year-old man negative for ANCA showed erythematous lesions with a central crust in the lower leg. (E) Histological examination revealed medium-sized muscular-vessel vasculitis in the subcutaneous tissue (hematoxylin-eosin, scale bar: 200 μm). High-power-field image shows abundant eosinophilic infiltration in the hypertrophic intima

small-vessel vasculitis. It is speculated that the blisters observed in MPO-ANCA-positive patients might result from the involvement of relatively smaller vessels in the upper dermis.

3 | DISCUSSION

Antineutrophil cytoplasmic antibodies play a central role in the pathogenesis of AAV through ANCA-mediated excessive activation of neutrophils, which subsequently release inflammatory cytokines, reactive oxygen species, and lytic enzymes.[2] Infection is considered a trigger for ANCA production, which has a pathogenic potential by itself. However, previous studies have not fully explained why ANCA-negative cases also develop vasculitis.

Previous histological observations indicate that ANCA-positive cases are characterized by small-vessel vasculitis, whereas ANCA-negative cases are characterized by eosinophilic tissue damage.[11] In contrast to previous reports, all of our cases, regardless of their ANCA status, demonstrated dermal small-vessel vasculitis, while tissue eosinophilia was detected only in ANCA-positive cases. There have been several reports describing the cases that presented with vesicles and bullae in AAV including microscopic polyangiitis[12] and granulomatosis with polyangiitis,[13] as well as EGPA.[14] In our study, blisters were often observed in ANCA-positive cases, although the exact mechanisms for the blister formation by ANCAs remain unclear. It has been demonstrated that neutrophilic vasculitis commonly occurs in ANCA-positive patients, and eosinophilic vasculitis is often found in ANCA-negative patients with EGPA.[14] However, in our study, neutrophilic infiltration was not unique to ANCA-positive cases.

Although serum CRP titers were not significantly elevated in the ANCA-positive cases, systemic manifestations such as fever and renal insufficiency were exclusively observed. These manifestations are consistent with previous reports indicating marked inflammatory features in ANCA-positive patients with EGPA.[5,15]

Regarding treatment, ANCA-positive patients required a higher dose of oral prednisolone, in line with a previous study.[4] Furthermore, our study indicates that ANCA-positive patients often receive additional immunosuppressive therapies compared to ANCA-negative patients.

Few limitations of our study also need to be considered. The small sample size and retrospective and monocentric nature of the study could have influenced the results. In addition, some of the ANCA-negative cases might have had ANCAs that do not target MPO or PR3; many other antigens for ANCA have been identified, such as elastase, bactericidal protein, cathepsin G, lactoferrin, and lysozyme.[16] In our study, only MPO-ANCA and PR3-ANCA were routinely tested; therefore, we were unable to exclude the presence of other minor ANCAs in ANCA-negative cases.

In conclusion, our data suggest that ANCA-positive patients tend to present with blisters and systemic inflammatory symptoms. They also receive more intensive treatment during the initial therapy than ANCA-negative patients.

Our findings highlight the potential diagnostic importance of cutaneous manifestations and ANCA status in the evaluation and management of EGPA. Further studies are required to support our

TABLE 2 Cutaneous manifestations and histological features of the patients

Case	MPO-ANCA	Cutaneous Manifestations	Histological findings					
			Dermal Small-vessel vasculitis	Subcutaneous muscular-vessel vasculitis	Tissue eosinophilia	Neutrophil infiltration	Panniculitis	Blister
1	+	Erythema, blister, and petechiae	+	+	+			+
2	+	Erythema, blister, and purpura	+		+			+
3	+	Erythema and blister	+		+	+		+
4	+	Erythema, petechiae, and ulcer	+			+		
5	+	Purpura and blister	+			+		+
6	Negative	Erythema and blister	+					+
7	Negative	Palpable purpura	+			+		
8	Negative	Erythema and purpura	+	+		+	+	
9	Negative	Erythema	+	+				

Abbreviation: MPO-ANCA, myeloperoxidase-antineutrophil cytoplasmic antibodies.

theory and improve the understanding of the pathogenic roles of ANCAs in EGPA.

4 | DECLARATION SECTION

Approval of the research protocol: The study protocol was approved by the ethics committee of Tokyo Women's Medical University (#2020-0084). The study was conducted in compliance with the ethical principles of the Declaration of Helsinki.

Informed Consent: Since this study was a retrospective study, explanations and consents to patients were made by opting out on the Tokyo Women's Medical University website.

Registry and the Registration No. of the study/trial: N/A.

Animal Studies: N/A.

ACKNOWLEDGEMENT

We thank Mai Onuki for the technical assistance provided.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ORCID

Chie Miyabe https://orcid.org/0000-0003-3051-4179

REFERENCES

1. Fagni F, Bello F, Emmi G. Eosinophilic Granulomatosis With Polyangiitis: Dissecting the Pathophysiology. Front Med (Lausanne). 2021;8:627776.
2. Nakazawa D, Masuda S, Tomaru U, Ishizu A. Pathogenesis and therapeutic interventions for ANCA-associated vasculitis. Nat Rev Rheumatol. 2019;15(2):91–101.
3. Sablé-Fourtassou R, Cohen P, Mahr A, Pagnoux C, Mouthon L, Jayne D, et al. Antineutrophil cytoplasmic antibodies and the Churg-Strauss syndrome. Ann Intern Med. 2005;143(9):632–8.
4. Sokolowska BM, Szczeklik WK, Wludarczyk AA, Kuczia PP, Jakiela BA, Gasior JA, et al. ANCA-positive and ANCA-negative phenotypes of eosinophilic granulomatosis with polyangiitis (EGPA): outcome and long-term follow-up of 50 patients from a single Polish center. Clin Exp Rheumatol. 2014;32(3 Suppl 82):S41–7.
5. Nishi R, Koike H, Ohyama K, Fukami Y, Ikeda S, Kawagashira Y, et al. Differential clinicopathologic features of EGPA-associated neuropathy with and without ANCA. Neurology. 2020;94(16):e1726–e37.
6. Lyons PA, Peters JE, Alberici F, Liley J, Coulson RMR, Astle W, et al. Genome-wide association study of eosinophilic granulomatosis with polyangiitis reveals genomic loci stratified by ANCA status. Nat Commun. 2019;10(1):5120.
7. Micheletti RG. Cutaneous vasculitis in rheumatologic disease: Current concepts of skin and systemic manifestations. Clin Dermatol. 2018;36(4):561–6.
8. Frumholtz L, Laurent-Roussel S, Aumaître O, Maurier F, Le Guenno G, Carlotti A, et al. Clinical and pathological significance of cutaneous manifestations in ANCA-associated vasculitides. Autoimmun Rev. 2017;16(11):1138–46.
9. Kanno K, Minami-Hori M, Honma M, Ishida-Yamamoto A. Histopathological findings and increased D-dimer are predictive factors of systemic thromboses in eosinophilic granulomatosis with polyangiitis. Am J Dermatopathol. 2018;40(12):879–83.

10. Ozaki S. ANCA-associated vasculitis: diagnostic and therapeutic strategy. Allergol Int. 2007;56(2):87–96.
11. Kallenberg CG. Churg-Strauss syndrome: just one disease entity? Arthritis Rheum. 2005;52(9):2589–93.
12. Kawakami T, Kawanabe T, Saito C, Kannari M, Mizoguchi M, Nagafuchi H, et al. Clinical and histopathologic features of 8 patients with microscopic polyangiitis including two with a slowly progressive clinical course. J Am Acad Dermatol. 2007;57(5):840–8.
13. Rawn S, Miettunen P, Brown HA, Schmeling H. Purpura, petechiae, and bullae as first signs of juvenile granulomatosis with polyangiitis. Eur J Pediatr. 2014;173(12):1685–9.
14. Ishibashi M, Kawahara Y, Chen KR. Spectrum of cutaneous vasculitis in eosinophilic granulomatosis with polyangiitis (Churg-Strauss): a case series. Am J Dermatopathol. 2015;37(3):214–21.
15. Kawakami T, Kimura S, Takeuchi S, Soma Y. Relationship among antineutrophil cytoplasmic antibody, blood urea nitrogen and complement in patients with eosinophilic granulomatosis polyangiitis (Churg-Strauss syndrome). J Dermatol. 2013;40(7):511–5.
16. Tateyama K, Kodama S, Kishibe K, Harabuchi Y, Suzuki M. A novel strategy with combined assays for detection of anti-neutrophil cytoplasmic antibody (ANCA) in clinically ANCA-negative granulomatosis with polyangiitis patients. Auris Nasus Larynx. 2017;44(6):735–41.

How to cite this article: Sone M, Miyabe C, Miyata R, Takenaka Y, Ishiguro N. Relevance of cutaneous manifestations and antineutrophil cytoplasmic antibody status in eosinophilic granulomatosis with polyangiitis. J Cutan Immunol Allergy. 2022;5:12–16. https://doi.org/10.1002/cia2.12194