Dermatology Practical & Conceptual

# Eosinophilic Annular Erythema: Clinicopathologic Analysis and Therapeutic Outcomes from a Multicenter Cohort

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## ABSTRACT

**Introduction:** Eosinophilic annular erythema (EAE) is a rare dermatosis characterized by persistent pruritic erythematous annular plaques with dermal eosinophilic infiltrates. It typically has a chronic, relapsing course with variable treatment responses and frequent refractory cases.

**Objectives:** This retrospective multicenter study reports the clinical and histopathological features of EAE and the treatment outcomes in a case series of 10 patients.

**Methods:** Ten patients with a confirmed clinical and histopathological diagnosis of EAE were referred to the Dermatology Departments of the University of Brescia and the University San Raffaele of Milan for evaluation and treatment.

**Results:** The cohort included six females and four males, all Caucasian, with a median age of 56 years. Time from lesion onset to diagnosis ranged from two days to seven years. Patients exhibited annular,

figurate, or polycyclic plaques with erythematous borders—dashed in 80% and centrally pigmented in 70% of cases. Intense itching was reported by 90%. Histopathology displayed dermal infiltrate primarily composed of lymphocytes with various numbers of eosinophils, ranging from scattered (10%) to abundant (40%) and numerous (50%). Treatment responses were variable, oral corticosteroids, either alone or in combination with hydroxychloroquine, being the most used therapies. However, flares frequently occurred following discontinuation of treatment. Dupilumab has shown promise in achieving long-term remission.

**Conclusion:** Most patients exhibited pruritic lesions with dashed borders and central pigmentation, strongly suggesting a diagnosis of EAE. The positive response to dupilumab in refractory cases, along with long-term follow-up, reinforces the growing body of scientific evidence from case reports documented in the literature.

## Introduction

Eosinophilic annular erythema (EAE) is a rare condition of unknown etiology and pathogenesis characterized by persistent, pruritic, erythematous, annular, and gyrate plaques [1]. Histopathology shows inflammatory infiltrates with eosinophils in the dermis [2]. The course is usually chronic and relapsing. Several drug treatments are available, but the therapeutic response in individual patients is largely unpredictable, and refractory cases to one or more treatment options are common [1].

## Objectives

In the present retrospective multicenter study, we report the clinical and histopathological features and the clinical outcome of various treatment approaches in a case series of ten individuals.

## Methods

We reviewed medical records of 10 EAE patients referred to the outpatient clinics of the Dermatology Departments of the affiliated universities from January 2011 to December 2020. All patients had itching figurate or annular plaques and underwent a skin biopsy, which revealed dermal infiltrates with eosinophils. We looked at the medical files for information on age, sex, comorbidities, disease duration, clinical features, symptoms, prior treatments and their outcome, blood count with formula, and routine biochemistries. Histological samples were always available and were reviewed by expert dermopathologists. The study was approved by the local ethics committee (protocol number: 4017), and all participants provided written informed consent. It was conducted in strict adherence to the principles outlined in the Declaration of Helsinki, ensuring the confidentiality of participants' data and their absolute right to withdraw from the study at any point.

## Results

All enrolled patients (six females and four males) were Caucasian. The median age was 56 years (range: 35–85 years). The main personal, clinical, and histopathologic features are reported in Table 1. The duration from lesion onset to EAE diagnosis varied from between two days and 84 months (median: 10 months). All patients were suffering from annular, figurate, or polycyclic plaques with slightly elevated erythematous borders (Figures 1–3). The borders were dashed in eight (80%) patients, and lesions had a central pigmentation in seven (70%) patients. Lesions were located on the trunk (80%), lower limbs (70%), and upper limbs (60%). Chronically sun-exposed body areas, i.e., the face, neck, and hands, were never affected. All patients reported itching, which was intense in nine (90%). The histopathological examination revealed normal epidermis in eight patients and spongiosis in two (Table 2). All biopsies revealed a dermal infiltrate primarily composed of lymphocytes with various numbers of eosinophils, ranging from scattered (10%) to abundant (40%) and numerous (50%). Mucin deposits were found in three patients (33%). Flame Figures were detected only in the second biopsy of one patient. Skin samples from four patients were investigated with direct immunofluorescence, and granular C3 deposits at the dermal-epidermal junction were seen in one case (10%). Blood eosinophilia was observed in only two patients (20%). Regarding therapeutic approaches, the most common first-line treatment was oral corticosteroids alone (seven patients; 70%) or in combination with hydroxychloroquine (two; 20%). Among the patients treated with oral corticosteroids alone, three (30%) did not exhibit any clinical improvement. An additional three patients (30%) experienced relapses during follow-up, necessitating multiple treatment cycles. Only one patient (10%) achieved complete remission after a single course of corticosteroid therapy. Of the two patients who received the combination of oral corticosteroids and hydroxychloroquine, one required further treatment cycles due to

**Table 1. Baseline Characteristics, Previous Therapies, and Treatment Outcomes of the 10 Patients With Eosinophilic Annular Erythema (EAE).**

| Case | Sex, Age | Clinical Lesion | Dashed Borders | Central Pigmentation | Involved Site | Comorbidities | Associated Symptoms | Eosinophilia | Onset | Previous Treatments | Ongoing Treatment, Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | F, 56 | Erythematous, annular plaques | + | + | Trunk and extremities | Prior hepatitis B | Pruritus | no | 7 y | Cyclosporine, hydroxychloroquine, dapsone, methotrexate, thalidomide, UVA1 phototherapy, intravenous steroids + indomethacin, and oral steroids | Dupilumab Complete remission, no relapse |
| 2 | F, 68 | Annular, polycyclic, and gyrated lesions | + | + | Trunk and lower extremities | Major depressive disorder | Pruritus and limb arthralgia | no | 2 d | none | Oral steroids Complete remission, no relapse |
| 3 | F, 78 | Erythematous, annular plaques | + | + | Lower extremities | Chronic lymphocytic leukemia, arterial hypertension, type 2 diabetes, prior hepatitis B | Pruritus | no | 5 m | Fusidic acid cream, terbinafine gel, and topical and oral steroids | Dupilumab Complete remission, no relapses |
| 4 | F, 38 | Annular, polycyclic, and gyrated lesions | + | - | Trunk | None | Pruritus and burning sensation | no | 10 m | UVA1 phototherapy, cetirizine, and topical steroids | Oral steroids Complete remission, new flares after discontinuation |
| 5 | M, 35 | Annular, polycyclic, and gyrated lesions | - | + | Trunk and extremities | None | Pruritus | no | 4 m | None | Indomethacin Partially effective, new flares after discontinuation |
| 6 | M, 56 | Erythematous, annular plaques | + | - | Extremities | None | Pruritus | no | 8 m | PUVA phototherapy | Oral steroids and hydroxychloroquine Complete remission, new flares after discontinuation |

*Table1 continues*

**Table 1. Baseline Characteristics, Previous Therapies, and Treatment Outcomes of the 10 Patients With Eosinophilic Annular Erythema (EAE).**
*(continued)*

| Case | Sex, Age | Clinical Lesion | Dashed Borders | Central Pigmentation | Involved Site | Comorbidities | Associated Symptoms | Eosinophilia | Onset | Previous Treatments | Ongoing Treatment, Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 7 | M, 85 | Erythematous, annular plaques | - | + | Trunk and lower extremities | Clear cell carcinoma | Pruritus | no | 6 m | None | Oral steroids Complete remission, new flares after discontinuation |
| 8 | M, 49 | Annular, polycyclic, and gyrated lesions | + | + | Trunk and upper extremities | None | None | no | 1 y | None | Hydroxychloroquine Complete remission, new flares after discontinuation |
| 9 | F, 61 | Annular, polycyclic, and gyrated lesions | + | + | Trunk and upper extremities | None | Pruritus | yes | 1 y | Oral steroids | Oral steroids and hydroxychloroquine Complete remission, no relapse |
| 10 | F, 49 | Annular plaques and gyrated lesions | + | - | Trunk and upper and lower extremities | None | Pruritus | yes | 1 y | None | Oral steroids Complete remission, new flares after discontinuation |

y: years; m: months; d: days

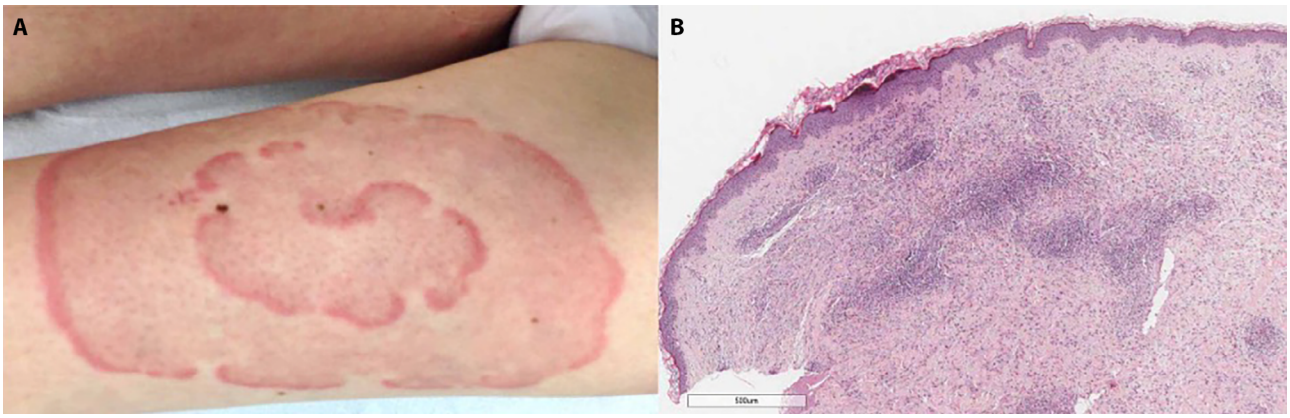


**Figure 1.** (A) Clinical eosinophilic annular erythema (EAE) with (B) corresponding histopathology (right side, H&E) of three patients on the left thigh, with superficial-deep, perivascular, and interstitial mixed infiltrate of lymphocytes with numerous eosinophils.

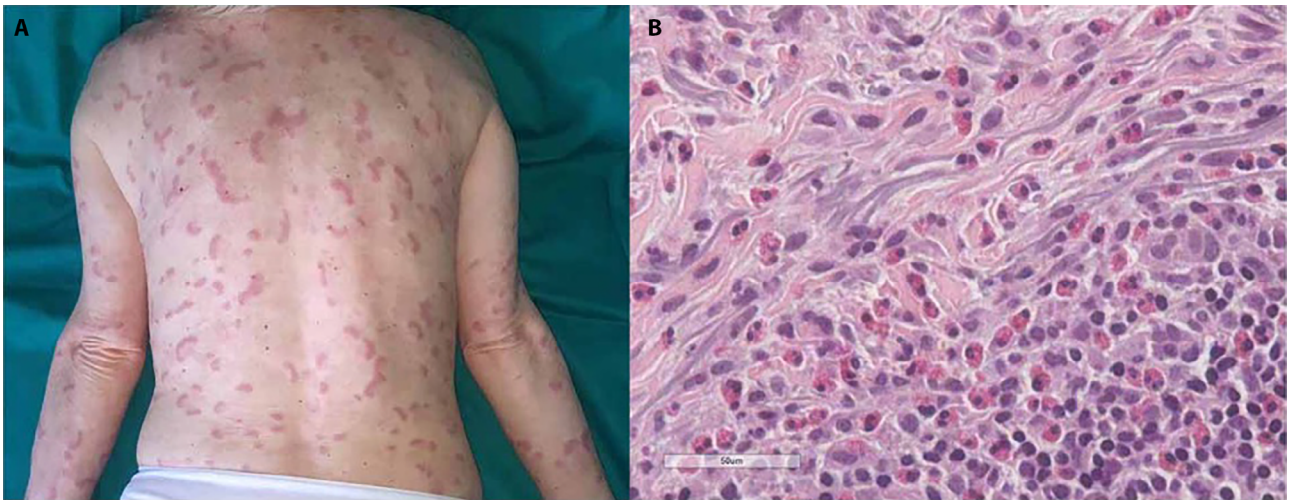


**Figure 2.** (A) annular plaques on the trunk and the upper arms and (B) histopathology displaying abundant eosinophilic infiltrate.

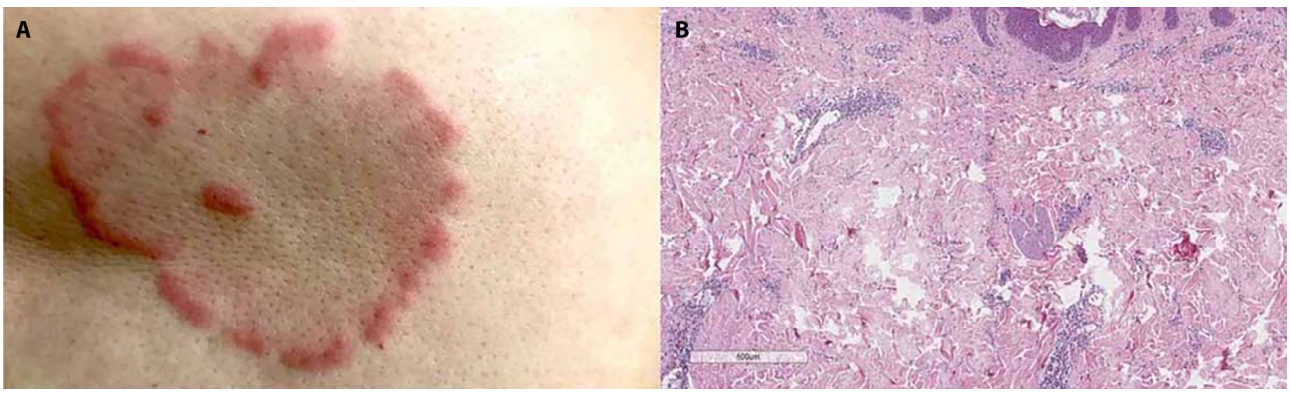


**Figure 3.** (A) EAE lesion of the trunk with dashed borders and central pigmentation, characterized with superficial-deep, perivascular, and (B) interstitial mixed infiltrate of lymphocytes and abundant eosinophils.

relapse, while the other experienced long-lasting remission following the discontinuation of therapy. UVA1 phototherapy and PUVA treatment were administered to one patient each, without any improvement. Indomethacin was partially effective in one patient, and hydroxychloroquine alone was completely effective in another, but relapses occurred after discontinuation in both patients, and continuous treatment cycles were administered. Two patients were treated with an initial subcutaneous dose of dupilumab (600 mg), followed by a maintenance dose of 300 mg every two weeks for 12 months. Subsequently, the dosing regimen was adjusted to 300 mg every month. Both patients achieved complete clinical

**Table 2. Histopathological Characteristics of the 10 Patients With Eosinophilic Annular Erythema (EAE).**

| Case | Sex, Age | Spongiosis | Inflammatory Infiltrate and Pattern of Eosinophilic Infiltration | Direct Immunofluorescence | Flame Figures | Mucin Deposit |
|---|---|---|---|---|---|---|
| 1 | F, 56 | - | Superficial-deep, perivascular, and interstitial mixed infiltrate of lymphocytes with numerous eosinophils | Not Tested | - | + |
| 2 | F, 68 | - | Superficial, perivascular, and interstitial mixed infiltrate of lymphocytes with numerous eosinophils | Not tested | - | - |
| 3 | F, 78 | + | Superficial, perivascular, and interstitial mixed infiltrate of lymphocytes with scattered eosinophils | Not tested | - | - |
| 4 | F, 38 | - | Superficial-deep, perivascular, and interstitial mixed infiltrate of lymphocytes with abundant eosinophils | Not tested | - | - |
| 5 | M, 35 | - | Dense dermal infiltrate with lymphocytes and abundant eosinophils | Not tested | - | + |
| 6 | M, 56 | - | Dense dermal infiltrate of lymphocytes, and numerous eosinophils | - | - | + |
| 6 | M, 56 | - | Dense dermal infiltrate of lymphocytes, and numerous eosinophils | - | + | + |
| 7 | M, 85 | - | Dense dermal infiltrate of lymphocytes, and numerous eosinophils | Granular C3 deposits at the dermal-epidermal junction | - | - |
| 8 | M, 49 | - | Dense dermal eosinophilic infiltrate with lymphocytes, and histiocytes | Not tested | - | - |
| 9 | F, 61 | + | Perivascular and interstitial infiltrate with lymphocytes and abundant eosinophils | - | - | - |
| 10 | F, 49 | - | Perivascular and interstitial infiltrate with lymphocytes and abundant eosinophils | Not tested | - | - |

response without any reported adverse events. Notably, no relapse was observed during a 4-year follow-up period.

## Conclusion

EAE is a rare clinical disorder, and the delay before diagnosis is considerable up to seven years in the present case series. Clinically, it manifests as annular plaques, which can sometimes be polycyclic or exhibit dashed borders or central pigmentation. Histologically, despite differences in clinical presentation, an inflammatory infiltrate composed of lymphocytes and variable numbers of eosinophils is observed. Mucin deposits may also be present at times. In one case, flame Figures were noted, although immunofluorescence findings were inconsistent. Regarding therapy, there is currently no established treatment approach for EAE. Several drugs, i.e., oral corticosteroids, cyclosporine, indomethacin, doxycycline, hydroxychloroquine, thalidomide, methotrexate, dapsone and nicotinamide, and phototherapies have been used, with variable outcomes in isolated case reports or small case series, ranging from none/partial to complete response [1]. Notably, relapse of EAE has been reported upon discontinuation of most of these therapies [1]. The broad range of treatments with very different mechanisms of action suggests a largely empirical therapeutic approach, given that the pathogenesis of EAE has not yet been clarified. Indeed, only recently has it been emphasized that eosinophils' dermal infiltration plays a key role [3]. The upregulation of the Th-2 response, triggered by unidentified stimuli, releases interleukin (IL)-5, prompting the migration of eosinophils from the bone marrow into the bloodstream. These mechanisms could explain why two cases showed complete resolution of EAE with the administration of anti-IL-5 mepolizumab [4] and benralizumab [5], respectively. Nakazato and colleagues [6] demonstrateed that central pigmentation reflects basal melanosis. Melanocytes express IL-5 at a low level, and it is conceivable that IL-5, which attracts eosinophils to the dermis, may also exert an effect on melanocytes, supporting the idea that dysregulated tissue eosinophilia act as a pivotal factor. Additionally, IL-4 and IL-13 contribute to their recruitment into tissues, sustaining the activation of the Th-2 response. However, these mechanisms remain unclear, warranting further research to improve therapies. Dupilumab is a fully human monoclonal antibody that has been approved for treating moderate-to-severe atopic dermatitis. It works by blocking the α subunit of the IL-4 receptor, which in turn prevents the signaling cascade of IL-4 and IL-13. This ultimately leads to a reduction in the Th2 immune response. Additionally, dupilumab prevents the migration of eosinophils into tissues by blocking the production of eotaxins and vascular cell adhesion molecules mediated by IL-4 and IL-13 [7,8]. This mechanism could be helpful in treating EAE, as previously reported in two cases [9,10] and in two patients of the present case series. Moreover, we report the cases of EAE treated with dupilumab with the longest follow-up period free of relapses. Furthermore, a maintenance dose of 300 mg every month post-remission did not demonstrate any flare. Additional studies are necessary to confirm and validate these findings. Beyond its efficacy in atopic dermatitis, dupilumab has been successfully used in other eosinophilic disorders, such as eosinophilic esophagitis [11] and chronic rhinosinusitis with nasal polyps [12]. The response of EAE to dupilumab observed in our case series is consistent with its efficacy in these conditions, suggesting a broader role of IL-4/IL-13 inhibition in eosinophil-mediated skin disorders. The relationship between Wells syndrome (WS) and EAE remains debated [2,13]. WS is most often characterized by cellulitis-like erythematous plaques accompanied by blood eosinophilia, and at histologic examination, dermal edema, eosinophilic dermal infiltration, and free eosinophilic granules coating collagen bundles (flame Figures) are seen. EAE presents with annular and figurate lesions with central pigmentation, normal blood level of eosinophils, and eosinophilic infiltrates without flame Figures. However, the clinical presentation of WS and EAE may be heterogeneous, and the differentiation may be difficult. In fact, both our study and the existing literature have reported the presence of flame Figures and blood eosinophilia in cases of EAE. It is noteworthy that, in our case series, the vast majority of the figurate lesions exhibited interrupted margins, defined as "dashed borders". Managing EAE is challenging due to the lack of standardized treatment guidelines[1]. The therapy typically begins with topical corticosteroids such as betamethasone or clobetasol, achieving none to partial and complete responses. For more severe or resistant cases, systemic corticosteroids and antimalarial drugs like hydroxychloroquine are effective. Dapsone serves as a second-line treatment, and combination therapies of systemic corticosteroids with hydroxychloroquine can be used for refractory patients. In cases associated with hematologic malignancies, appropriate cancer therapy combined with corticosteroids has been successful. Methotrexate and thalidomide have been used in anecdotal cases, with varying success [1]. Last-resort options include advanced biologics and JAK inhibitors, while some patients may experience spontaneous improvement without aggressive treatment.

This study has several limitations. First, its retrospective design may have introduced selection and reporting biases. Second, the small sample size limits the generalizability of our findings and precludes robust statistical analysis. Finally, the lack of standardized treatment protocols across centers may have influenced therapeutic outcomes.

In conclusion, EAE presents as a chronic, relapsing dermatologic condition characterized by pruritic lesions with central

pigmentation and dashed borders, which strongly raise suspicion for the diagnosis. Standard treatments, such as corticosteroids and hydroxychloroquine, often result in relapses upon discontinuation. However, dupilumab has demonstrated significant promise in refractory cases, achieving long-term remission with no relapse during extended follow-up. These findings support the growing evidence for dupilumab as an effective treatment for EAE, emphasizing the need for further studies to validate its long-term efficacy and safety.

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