



Title	Eosinophilic annular erythema is clinically characterized by central pigmentation reflecting basal melanosis : a clinicopathological study of 10 cases
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Original article

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Eosinophilic annular erythema is clinically characterized by central pigmentation
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ABSTRACT

BACKGROUND: Eosinophilic annular erythema (EAE) has been proposed as a clinical entity to describe annular skin lesions associated with tissue eosinophilia. However, systematic investigations on the histopathology of EAE have not been performed, and useful histopathological findings for diagnosis of EAE remain unknown.

OBJECTIVE: The aim of this study was to investigate the clinicopathological features of EAE.

METHODS: We retrospectively studied 10 patients at our hospital during a 5-year span who clinically showed annular or figurate lesions and histopathologically exhibited eosinophilic infiltration in the dermis.

RESULTS: Nine of the 10 cases had annular lesions with pigmentation on the interior side. Blood eosinophilia was found in only 1 patient. Histopathologically, basal melanosis was observed in 9 cases. Infiltration of eosinophils was confined to the dermis in 9 cases. Patients treated with systemic corticosteroid tended to show less recurrence than those treated with topical corticosteroid.

LIMITATIONS: The main limitation of our study is the small number of patients.

CONCLUSION: Skin biopsy should be performed when EAE is suspected, even in cases without blood eosinophilia. Basal melanosis and tissue eosinophilia confined to the dermis suggest the diagnosis of EAE. We recommend topical corticosteroids as the initial treatment for EAE.

Key words: eosinophilic annular erythema, figurate, pigmentation, basal melanosis, eosinophils, eosinophilia, corticosteroids

Introduction

As stated in the first report of eosinophilic annular erythema (EAE), the entity of EAE was proposed to describe annular skin lesions associated with tissue eosinophilia.¹ To date 25 cases of EAE have been reported in the English literature.¹⁻¹⁶ EAE is characterized by the appearance of persistent annular or figurate lesions, a chronic course with recurrent relapse and recalcitrance to various treatments.^{11,14} Typical EAE is histopathologically characterized by dense perivascular infiltrates with abundant eosinophils but without “flame figures.”¹⁵

Some EAE cases have been clinically documented as being accompanied by a dusky-toned area and pigmentation.^{10,14,16} However, the frequency of discoloration has not been elucidated, and there have been no descriptions of histopathological examinations corresponding to the clinical pigmentation. Furthermore, the pattern and depth of eosinophilic infiltration in EAE has not been well investigated, which leaves the clinicopathological distinction between EAE and Wells’ syndrome (WS) unclear. To address these issues, we conducted a single-center, retrospective clinicopathological review of 10 cases of EAE. Our study demonstrates that most cases of EAE clinically

show pigmentation, and that the histological localization of eosinophils is limited to the dermis, without peripheral eosinophilia.

Materials and methods

A single-center study of 10 patients diagnosed with EAE at Hokkaido University Hospital was performed. Their first visits were between 2011 and 2015. On the basis of the reports and studies in the past, we defined EAE as skin lesions that clinically show annular or figurate erythema and histopathologically exhibit abundant eosinophilic infiltration at least in the dermis. According to these criteria, we collected patients and retrospectively examined clinical features and histopathological findings. Data from the medical records included age, gender, past medical history, history of drug intake, disease duration, clinical features of lesions, symptoms, laboratory examination results (including whole blood cell count), and treatments and their responses.

Histopathological findings including epidermal changes, basal melanosis, vacuolar changes, melanin incontinence, patterns of eosinophilic infiltration, flame figures, coat

sleeve-like infiltration of lymphocytes around blood vessels, vasculitis and mucin deposition were reviewed.

Written consent for skin biopsy was obtained from each patient. All analyses in this study were performed in accordance with the ethical guidelines of Hokkaido University Hospital and the *Declaration of Helsinki* guidelines. The study was approved by the institutional review board of Hokkaido University Hospital (approval #015-0525; approval date: June 17, 2016).

Report of Cases

We highlight 2 representative cases of EAE from our 10 cases.

Case #2: A 42-year-old Japanese woman presented with a 1-year history of a pruritic rash on the four extremities. Treatment with systemic corticosteroid at the previous clinic brought temporary response. However, the rash recurred after the cessation of systemic corticosteroid. Physical examination revealed multiple annular erythema with peripheral infiltration on the extremities. Most of these lesions had brownish pigmentation (Fig. 1a). A biopsy specimen from the periphery of erythema on the left

thigh showed infiltration of inflammatory cells from the superficial to the mid dermis, including numerous eosinophils (Fig. 1b). The pattern of infiltration by the eosinophils was interstitial rather than perivascular (Fig. 1c). The epidermis presented basal melanosis and pigmentary incontinence (Fig. 1d). There were few inflammatory cells, including eosinophils, in the subcutis. Topical application of 0.05% difluprednate ointment was successful, and the rash had disappeared by the time of 5-week follow-up. However, the erythema relapsed and treatment with topical corticosteroid was restarted. The rash finally resolved 18 months after the first visit.

Case #8: A 31-year-old Japanese woman presented with a 2-month history of a pruritic eruption on the left lower leg. The eruption had gradually expanding before she visited our outpatient clinic. Examination revealed annular erythema with peripheral palpable infiltration and diffuse pigmentation on the left popliteal fossa and lower leg (Fig. 2a). Skin biopsy revealed perivascular and interstitial infiltration of inflammatory cells from the superficial to the mid dermis, including lymphocytes and eosinophils (Fig. 2b, c). Inflammatory cells, including eosinophils, did not extend to the subcutaneous tissue. The epidermis presented basal melanosis and mild focal spongiosis. There were mild

vacuolar changes and slight pigmentary incontinence (Fig. 2d). Mucin deposition was seen through the dermis. These annular erythema spontaneously regressed without treatment within 4 weeks, and no recurrence was noted.

Results

We present the clinical information of the patients in Table 1. There were 7 women and 3 men aged 27 - 82 years. Associated systemic disorders were recorded in 7 patients: asthma in 3 of these patients, and rheumatoid arthritis in 2 of these patients. Other items from the medical histories included cervical cancer, breast carcinoma, chronic gastritis, Hashimoto disease, hypertension and osteoporosis, in 1 patient for each. The duration of EAE from onset to first visit ranged from 2 weeks to several years. Itching was marked in all patients; however, tenderness of the lesion was not described. There was no history of preceding insect bite or contact dermatitis in any case. The descriptions and photographs of the lesions revealed that 9 cases had pigmentation mainly at the center of the lesions.

The histopathological findings of the skin biopsy are shown in Table 2. The skin biopsy specimens were taken from erythema in each case. Three specimens included flat, pigmented central areas with slight erythema. Basal melanosis was observed in 9 cases and melanin incontinence was noted in 3 cases. According to findings of flat pigmented central areas, basal melanosis was shown in all 3 specimens and pigment incontinence in 1 specimen. Vacuolar change was observed in 5 cases. Eosinophils infiltrated the superficial dermis in all cases and the deep dermis in 7 cases. Infiltration of eosinophils into the subcutis was noted in only 1 case. The pattern of eosinophilic infiltration was a mixture of perivascular and interstitial in 9 cases (Fig. 3a, b) and was exclusively perivascular in 1 case (Fig. 3c, d) (case #4). Inflammatory infiltrates including lymphocytes and eosinophils with coat-sleeve distribution were seen in 4 cases. Mucin deposition was observed in 2 cases. Flame figures and vasculitis were not seen.

Elevated blood eosinophilia ($>500/\mu\text{l}$) was observed in only 1 of the 10 cases.

The patient was associated with asthma and eosinophilic granulomatosis with polyangiitis, and showed marked blood eosinophilia of up to $2.3 \times 10^3/\mu\text{l}$ (case #10).

According to serologic tests, anti-BP180 antibodies, anti-SS-A antibodies and anti-SS-B antibodies were negative in all 4, 7 and 6 patients tested for them, respectively.

As for treatments, 4 patients were treated with systemic corticosteroid (prednisolone 20-40 mg/day), 4 patients with topical corticosteroid and 1 patient with topical tacrolimus. The 1 remaining patient spontaneously resolved without treatment. 5 of the 9 patients showed a favorable course with no recurrence after cessation of the intervention. The mean duration of these 5 patients from the start of initial treatment to significant response was 3.8 weeks. 3 of these 5 patients were treated with systemic corticosteroid (the mean duration to significant response was 2.0 weeks) and 2 others with topical corticosteroids (6.5 weeks). In contrast, 1 of 4 patients treated with systemic corticosteroid and 3 of 5 patients treated with topical corticosteroid relapsed. For the 1 patient whose initial treatment with topical corticosteroid was ineffective, the treatment was changed to topical tacrolimus with immediate effect and no relapse (case #4). The 2 remaining refractory patients treated with topical corticosteroid finally resolved with 1 or 2 repetitions of the same therapies. However, a male patient who was initially treated with systemic prednisolone at 40mg/day showed a persistent course of

the disease with remission and exacerbation (case #6). No cases were treated with hydroxychloroquine or other antimalarials.

Discussion

This study has elucidated the following. 1) Most cases clinically exhibited pigmentation that histopathologically resulted not from melanin incontinence but from basal melanosis. 2) Prominent eosinophilic infiltration was observed in the dermis, whereas eosinophils were scarce in the subcutis and peripheral blood. Flame figures were not shown in any of the cases. 3) EAE tends to respond more rapidly and relapse less frequently with systemic corticosteroid therapy than topical corticosteroid. 4) EAE tends to affect women more often than men.

Even though some case reports of EAE have noted a dusky tone or pigmentation,^{10,11,14} our study clearly demonstrates for the first time that EAE is clinically characterized by central pigmentation. Since several previous EAE cases noted the histopathological finding of vacuolar change,^{12,16} we expected melanin incontinence would be a predominant finding corresponding to clinical pigmentation.

However, our study unexpectedly demonstrated that basal melanosis (9 of 10) was observed more frequently than melanin incontinence (3 of 10), and vacuolar change was found in only 30% of EAE cases. Therefore, basal melanosis is considered to contribute mainly to clinical pigmentation. Since melanocytes were not increased in our study, some factors may exist to activate melanogenesis of melanocytes in the pathophysiology of EAE. Melanocytes express IL-5 at a low level,¹⁷ and it is possible that IL-5, which attracts eosinophils in the dermis, also acts on melanocytes. On the other hand, it can be also considered that melanogenesis of normal human melanocytes is inhibited by IL-4, which is produced by eosinophils (Fig. 4).¹⁸ Further studies are needed in order to clarify the relationship between melanocytes and eosinophilic infiltration.

In previous reports and studies of EAE, elevated levels of blood eosinophils tended to be found in cases without underlying disease.¹¹ However, except for 2 cases associated with underlying diseases, our cases showed no blood eosinophilia, despite there being active skin lesions. As for histological eosinophilic infiltration, El-Khawalany *et al.* reported that the dermal eosinophils extended into the subcutis in

well-developed and long-standing lesions.¹¹ Conversely, most cases of EAE in the literature did not show abundant eosinophilic infiltration into the subcutis.^{1-4,8,12-16} In our study, eosinophilic infiltration into the subcutaneous tissue was noted in only one in 10 cases. Some previous reports of EAE described the presence of flame figures^{9-11,14}, whereas our cases did not show flame figures in specimen tissues.

Although the predominant opinion is that EAE represents a variant of WS with an annular or figurate clinical appearance,^{11,14} the relationship between EAE and WS remains a matter to be discussed further. As WS is usually accompanied by blood eosinophilia,²⁰ the absence of blood eosinophilia can be crucial in distinguishing EAE from WS. Furthermore in WS, the inflammatory cells, including eosinophils, often involve the subcutis as well as the dermis, and flame figures can be found as characteristic features.¹⁹ The localization of eosinophils to the dermis and the absence of flame figures suggest EAE rather than WS (Fig. 4).

In previous reports, EAE patients frequently showed prolonged courses, resistance to various treatments and high relapse rates.¹¹ Contrary to these facts, however, our study demonstrated that 3 out of 4 cases treated with systemic

corticosteroids resolved without recurrence. In addition, although recurrence was observed in 3 out of 5 cases initially treated with topical corticosteroids, all 4 cases of EAE treated with long-term topical corticosteroids finally resolved in our study. As in one previous report,¹² 1 patient underwent spontaneous regression. From what has been discussed above, EAE has a moderate therapeutic response and is similar to WS in this respect; most WS patients have a benign course.²⁰ EAE should be treated with potent or superpotent topical corticosteroids as the initial treatment. If topical treatment for several months is ineffective, systemic corticosteroid could be administered for additional treatment. Antimalarials have been suggested as the drug of choice in EAE^{1,11,15}, although we did not choose them for treatment.

The male:female ratio of EAE was 3:7 in our cases and 13:15 in previous reports; there is a slight predominance in females¹⁻¹⁶. The reason is yet to be elucidated, but 3 EAE female cases had a history of autoimmune disorders in our study. Also, histories of thyroiditis were found in previous female cases^{1,3}. Therefore, autoimmunity might be involved in the pathophysiology and female predominance of EAE.

Conclusion

EAE should be included as a differential diagnosis of annular figurate erythema, in addition to major skin disorders such as erythema annulare centrifugum, drug eruption, subacute cutaneous lupus erythematosus and bullous pemphigoid, even if there is no blood eosinophilia. Skin biopsy is needed to confirm the diagnosis of EAE.

Eosinophilic infiltration confined to the dermis and basal melanosis suggest the diagnosis of EAE. Systemic corticosteroid is recommended for EAE if treatment with topical corticosteroid is ineffective.

Abbreviations used:

EAE: eosinophilic annular erythema WS: Wells' syndrome

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Figure legends

Fig 1. Clinical presentation and histopathological features of case #2.

A, Annular erythema with peripheral infiltration on the right shoulder. **B**, Inflammatory cells have infiltrated the superficial to mid dermis but do not extend to the subcutaneous tissue. **C**, Interstitial infiltration of inflammatory cells, including eosinophils, is seen in the dermis. Mucin deposition is also observed. **D**, The epidermis presents basal melanosis (arrows). Superficial perivascular infiltration is also observed. (**B**, **C**, and **D**, hematoxylin and eosin staining; original magnifications: **B**, x12.5; **C**, x400; **D**, x100)

Fig 2. Clinical presentation and histopathological features of case #8.

A, Annular erythema with peripheral palpable infiltration and diffuse pigmentation on the left popliteal fossa and lower leg. **B**, Inflammatory cells have infiltrated the superficial to mid dermis but do not extend to the subcutaneous tissue. **C**, The epidermis presents basal melanosis (arrows) and mild spongiosis. There are also mild vacuolar changes and slight pigmentary incontinence. **D**, Interstitial infiltration of inflammatory cells, including eosinophils, is seen in the dermis. Mucin deposition is also observed. (**B**,

C, and **D**, hematoxylin and eosin staining; original magnifications: **B**, x12.5; **C**, x400; **D**, x100)

Fig 3. Pattern of histopathological eosinophilic infiltration. **A** and **B**, Case #9 show a mixture of perivascular and interstitial patterns. **C** and **D**, Case #4 shows an exclusively perivascular pattern. (hematoxylin and eosin staining; original magnification: **A** and **C**, x40; **B** and **D**, x200)

Fig 4. An illustration of the pathophysiology of EAE and the differences between WS and EAE. In WS, the inflammatory cells, including eosinophils, often involve the subcutis as well as the dermis, and flame figures can be found as characteristic features. In EAE, eosinophils are limited to the dermis, and flame figures do not appear in specimen tissue. In the pathophysiology of EAE, IL-5 might activate the melanogenesis of melanocytes and attract eosinophils in the dermis. On the other hand, it could be also considered that IL-4 produced by eosinophils might inhibit the melanogenesis of melanocytes.

Table legends

Table 1 Clinical data and therapeutic responses of the 10 patients with EAE

Table 2 Histopathological profiles of the 10 patients with EAE

Fig. 1

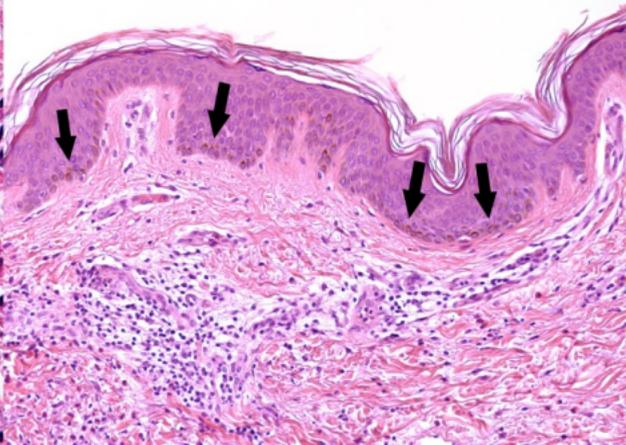
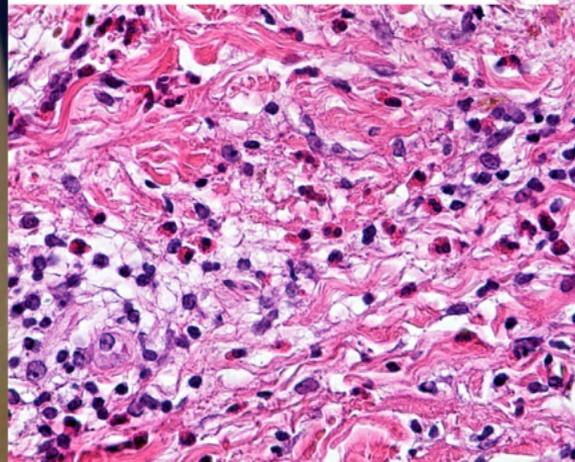
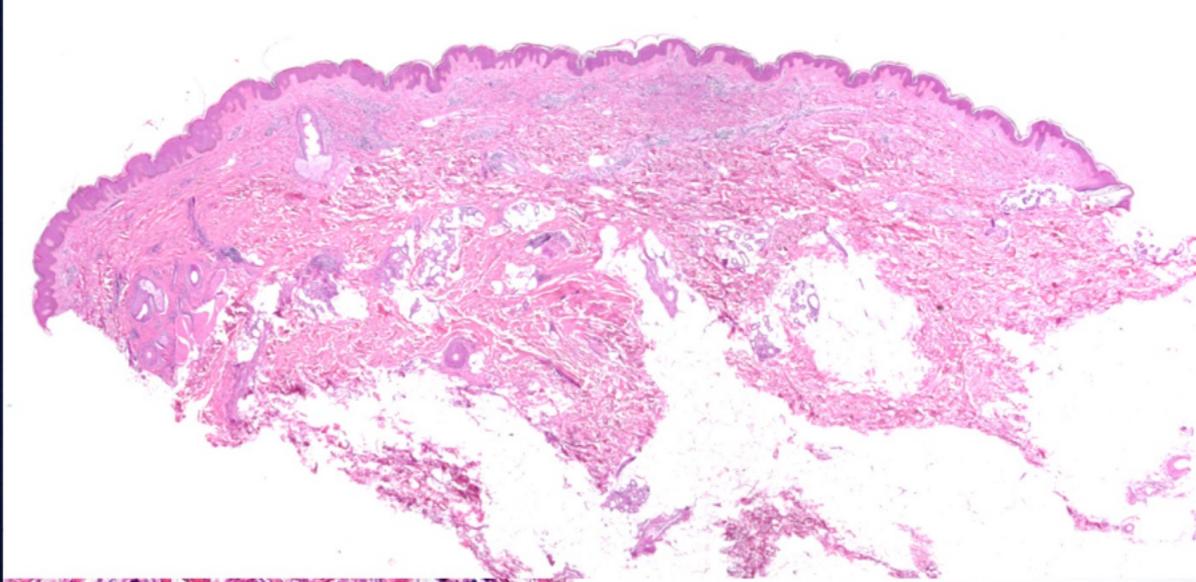


Fig. 2

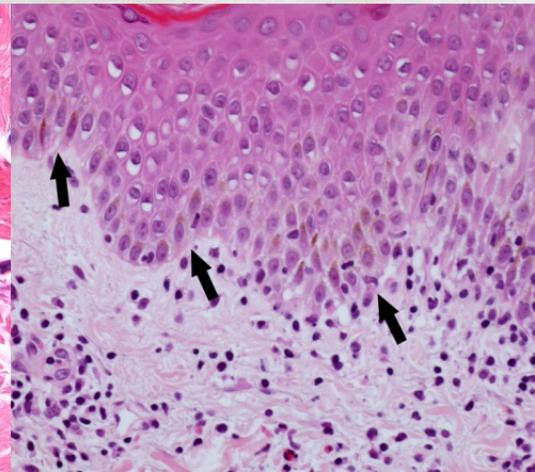
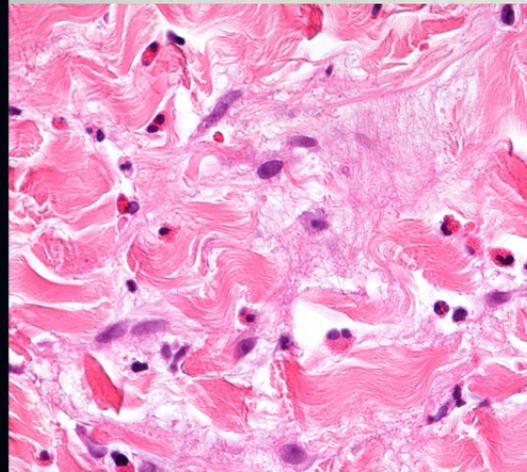
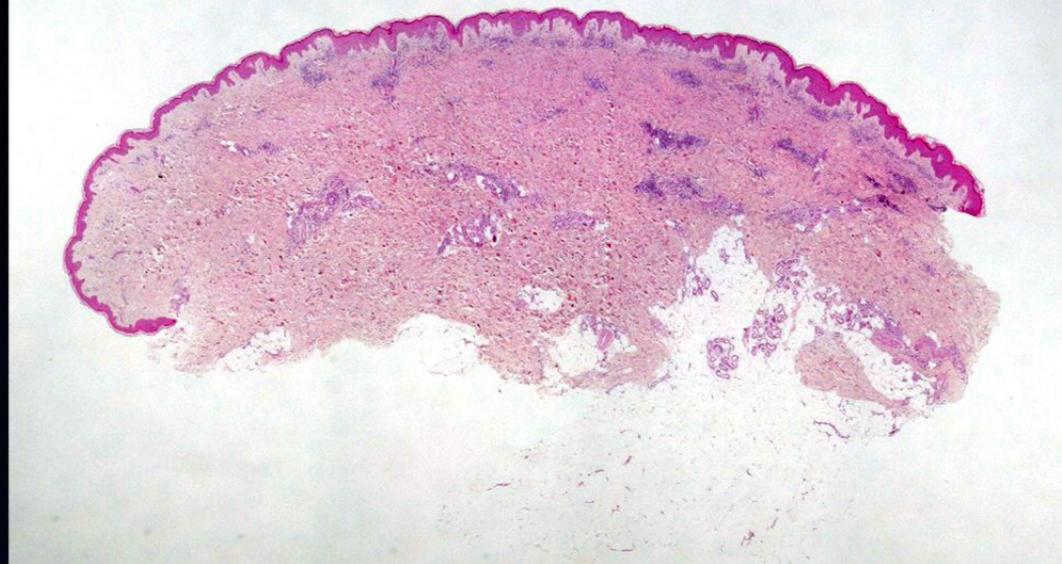
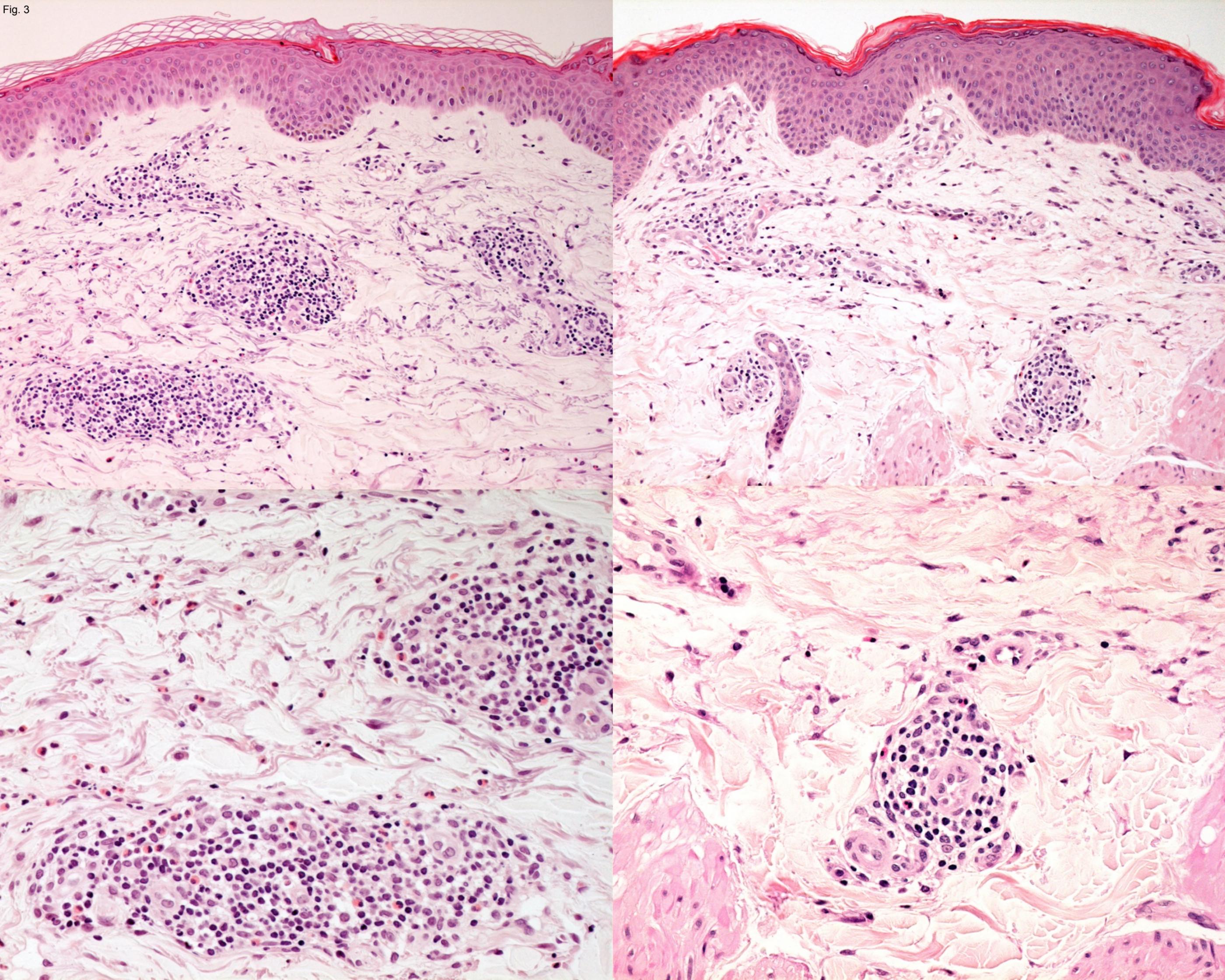
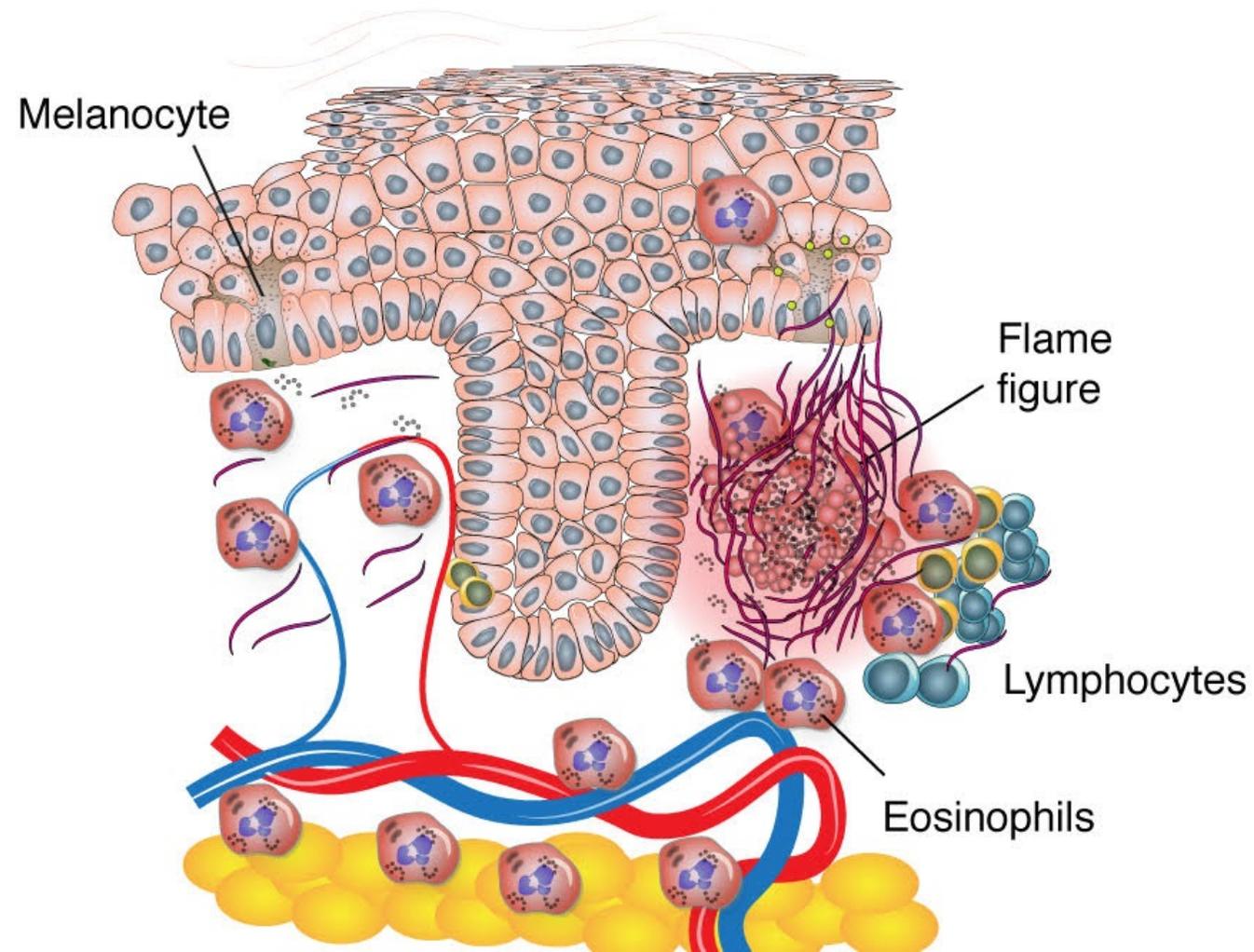


Fig. 3



Well's syndrome



Eosinophilic Annular Erythema (EAE)

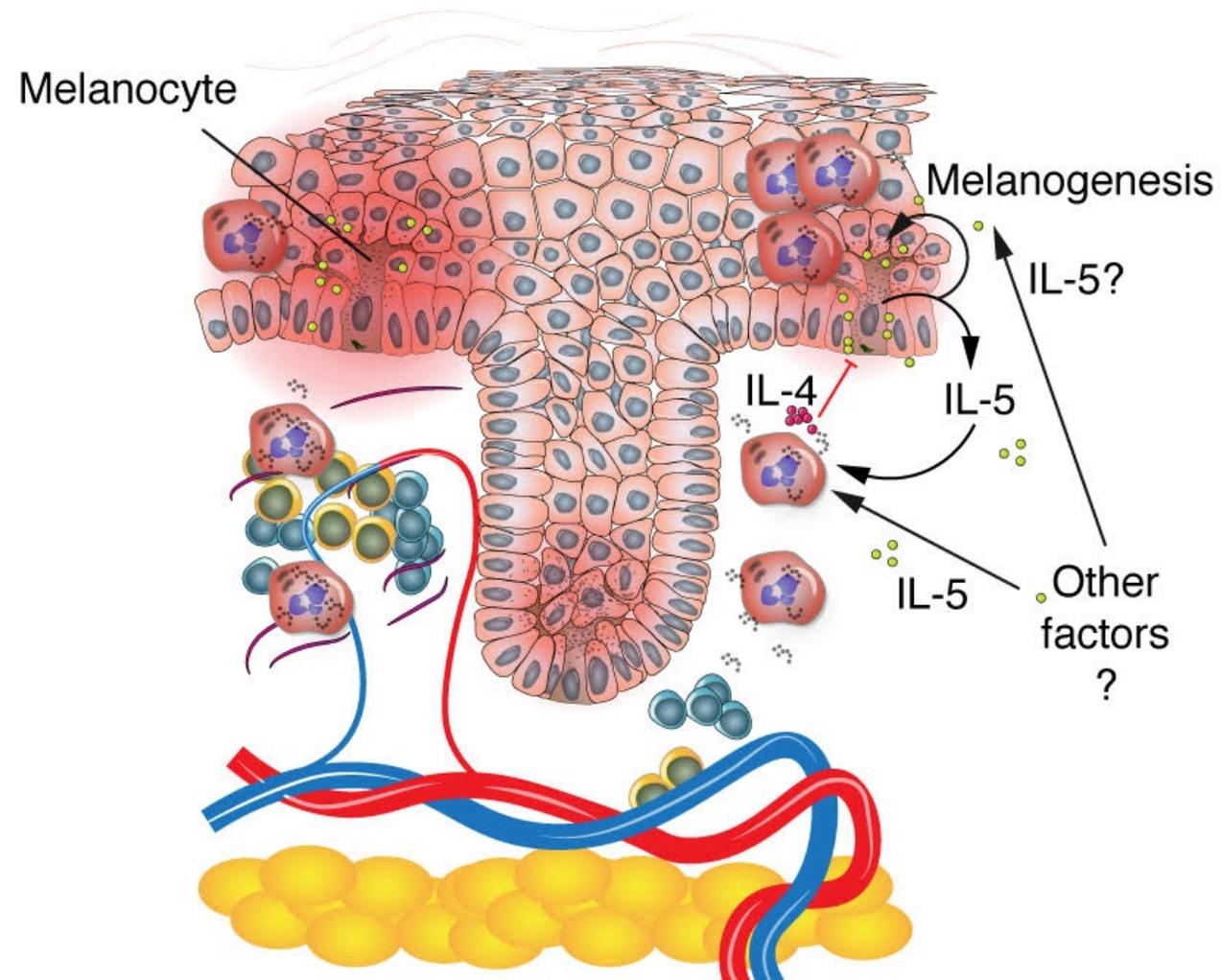


Table 1

Case	Age	Gender	Past medical history	Duration from onset to first visit	Initial location	Description of lesions	Peripheral blood eosinophils (%)	Peripheral blood eosinophil count	Initial treatment	Significant response (weeks)	Relapse	Follow-up period (weeks)	Duration from first visit to resolution (weeks)
1	27	M	nothing of note	2-3 months	face, palm, back, extremities, sole	edematous annular erythema with pigmentation	6.1	330	topical corticosteroid	4	+	23	23
2	42	F	asthma, cervical cancer, rheumatoid arthritis	1 year	extremities	annular erythema with pigmentation	0	0	topical corticosteroid	5	+	73	73
3	68	F	rheumatoid arthritis	2 weeks	scalp, hand, forearm, abdomen	annular erythema with central pigmentation	4.0	290	topical corticosteroid	4	—	8	4
4	47	M	nothing of note	2 months	trunk, extremities	annular erythema with central pigmentation	6.3	240	topical corticosteroid *	10	+	83	70
5	54	F	asthma, breast carcinoma	6 months	lower leg	light-brownish plaque encircled by erythematous papules	7.6	460	topical corticosteroid	9	—	9	9
6	31	M	chronic gastritis	2 years	whole body	edematous erythema enlarging in an annular pattern	0	0	systemic corticosteroid (PSL 40 mg)	2	+	126	over 126 **
7	82	F	Hashimoto disease	1 year	both upper legs	pigmented erythematous plaque with induration in an annular pattern	4.4	270	systemic corticosteroid (PSL 20 mg)	2	—	9	over 9 ***
8	31	F	nothing of note	several years	lower leg	annular erythema with central pigmentation	1.0	50	none	4	—	14	10
9	66	F	hypertension, osteoporosis	1 month	neck, forearm	edematous annular erythema with pigmentation	2.8	220	systemic corticosteroid (PSL 20 mg)	2	—	4	4
10	32	F	asthma, eosinophilic granulomatosis with polyangiitis	6 weeks	trunk, extremities	diffusely pigmented macules encircled by red papules	25.0	2300	systemic corticosteroid (PSL 30 mg)	2	—	10	over 10 ***

* In case 4, treatment with topical tacrolimus was followed by cessation of topical corticosteroid and was effective.

** In case 6, the patient showed a persistent course of the disease until the end of the research period.

*** In cases 7 and 10, the patients were referred to other clinics or hospitals for personal reasons.

PSL: prednisolone

Table 2

No	Age	Gender	Site of biopsy	Spongiosis	Basal melanosis	Vacuolar change	Melanin incontinence	Pattern of eosinophilic infiltration	Direct immunofluorescence	Inflammatory infiltrates with coat-sleeve distribution	Mucin deposition
1	27	M	P	—	—	+	—	superficial~deep, perivascular and interstitial	IgM deposition at the basement membrane zone	—	—
2	42	F	P	—	+	—	+	superficial, perivascular and interstitial	not tested	—	—
3	68	F	P	—	+	—	+	superficial~deep, perivascular and interstitial	not tested	+	—
4	47	M	P	+	+	+	—	superficial perivascular	not tested	—	—
5	54	F	P	—	+	—	—	superficial~deep, perivascular and interstitial	not tested	+	+
6	31	M	P	—	+	—	—	superficial~subcutis, perivascular and interstitial	not tested	+	—
7	82	F	C	—	+	+	—	superficial~deep, perivascular and interstitial	not tested	—	—
8	31	F	PC	+	+	+	+	superficial~mid, perivascular and interstitial	—	—	+
9	66	F	PC	—	+	—	—	superficial~deep, perivascular and interstitial	not tested	+	—
10	32	F	P	—	+	+	—	superficial~deep, perivascular and interstitial	IgM and C3 deposition in the dermal vessels	—	—

P: peripheral elevated erythema, C: central pigmentation with slight erythema, PC: an area including both P and C