ing the growth pattern of the tumoral lesions rather than being involved in their etiopathogenesis.

Thus, it has been confirmed that the main risk factor in the onset of KA may be represented by HPV infection, which explains its exophytic growth pattern and its high regression rate, similarly to HPV dependent warts.

On the other side, *in situ* and invasive SCCs share the UV mediated damage as the main risk factor, while the role of HPVs remains marginal, as a possible cofactor[2] determining probably only the tumor growth pattern.

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# Eosinophilic annular erythema successfully treated with cyclosporine

A 59-year-old woman presented with asymptomatic erythematous papules and plaques at the forehead and neck with an annular or polycyclic configuration. Lesions started seven months before and had a recurring course (Figure 1A-C). The patient was in good general health, and there was no history of any factor occurring before disease onset such as medications, insect bites, etc. Routine laboratory investigations as well as antinuclear antibodies were within normal range. Histopathological examination revealed a normal epidermis, with focal infundibular spongiosis and occasional eosinophils. In the dermis, a discrete perivascular lymphohistiocytic infiltrate with numerous eosinophils and scattered neutrophils was present (Figure 1D). Eosinophils single or in aggregates colonized also the interstitium, with signs of degranulation and initial damage of collagen fibers (Figure 1E). Search for hyphae and/or fungi with Alcian-PAS as for bacteria with Gram stain was negative. The patient was treated consecutively with topical corticosteroids, triamcinolone i.m. 40 mg every three weeks for two months, oral hydroxychloroquine 200 mg/b.i.d. for three months and then salazopyrin 500 mg/b.i.d. for two months without benefit. Thereafter, oral cyclosporine 2.5 mg/kg/day (200 mg/day) was started with complete resolution in two weeks. After additional two weeks, cyclosporine was reduced to 100 mg/day for one month and then stopped. At three-, six- and nine-month follow-up, no recurrence was noted.

Eosinophilic annular erythema (EAE) is a rare, benign eosinophilic dermatosis, first described in infants in 1981 by Peterson and Jarratt as annular erythema of infancy, and in adults in 2000 by Kahofer *et al.*[1] Clinically, EAE is characterized by annular erythematous papules and plaques at the trunk and extremities, with a centrifugal growth pattern and a central area of clearing, resolving

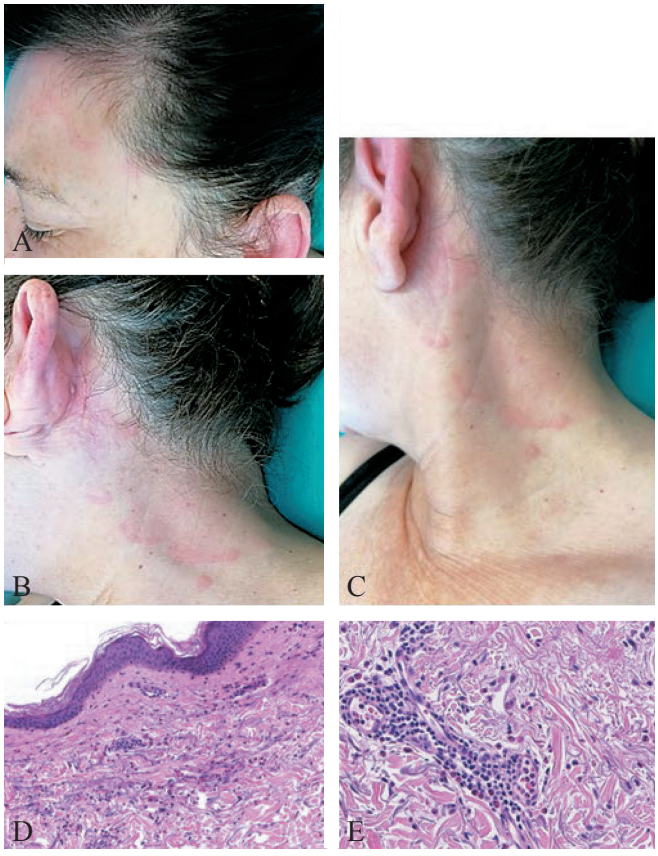


Figure 1.—Erythematous annular plaques, localized at the forehead and at the neck (A-C). Epidermis was normal with focal infundibular spongiosis and occasional eosinophils. In the dermis, perivascular lymphohistiocytic infiltrate mixed with numerous eosinophils and scattered neutrophils are present (D, 200x; H&E). Degranulation of the eosinophils, with initial damage of the collagen fibers (E, 400x, H&E).

without scarring or atrophy.[2] EAE has a chronic relapsing-remitting course, may resolve spontaneously in months-years but is typically resistant to multiple treatments.[3] A literature search revealed only 40 cases of EAE in adults, with a slight female preponderance of 1.14:1 and an age onset of 20-85 years.[3] EAE has been reported in association with autoimmune disorders, borreliosis, H. pylori, chronic hepatitis-C, diabetes mellitus, kidney disease and malignancy.[3] The nosology of EAE is not well elucidated. There is a discussion of whether EAE is a separate entity or related to Wells Syndrome. EAE may be differentiated from Wells Syndrome by the absence of 'flame figures', composed of eosinophilic major basic protein and degenerated collagen on histopathology and by a normal eosinophil count in peripheral blood. However, "flame figures" and peripheral blood eosinophilia may be present in well-developed and long-standing EAE; therefore, some authors considered EAE a subset of Wells syndrome.[2, 3] Other differential diagnoses include the deep form of *erythema annulare centrifugum*, *lupus erythematosus tumidus*, Jessner lymphocytic infiltrate, *erythema migrans*, granuloma annulare, interstitial granulomatous dermatitis, Sweet Syndrome rich in eosinophils and bullous pemphigoid.[2]

First-line treatments of EAE are topical corticosteroids (betamethasone or clobetasol for 4-8 weeks), followed by systemic corticosteroids (0.5-1 mg/kg/die for 2-3 months) and hydroxychloroquine (200-400 mg/die for 2-3 months), alone or in combination. In patients resistant to previous therapies, dapsone (50-100 mg/die for 2-3 months) is a third-line option. Other treatments include indomethacin, thalidomide, nicotinamide, methotrexate, mepolizumab, dupilumab, baricitinib and narrow-band UVB.[2-6] Combination therapy did not demonstrate greater benefit compared to monotherapy; however, anti-malarial with systemic corticosteroids are effective.[4] Furthermore, since most cases go into spontaneous remission, the first-line therapy should not be very aggressive. In one study, cyclosporine was used in combination with systemic corticosteroids, with partial improvement.[1] Cyclosporine is effective in hypereosinophilic dermatoses, acting on T-helper cells (CD4+) and suppressing the blood eosinophil counts and production of IL-5.[5] Our case showed a dramatic response to low-dose cyclosporine alone, with persistent remission, suggesting that immune mechanisms are important in EAE pathogenesis, and cyclosporine alone is a second-line treatment option.

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# Resolution of granuloma annulare during pregnancy

Granuloma annulare (GA) is a benign granulomatous skin disease that might be mediated by immunological mechanisms with mixed T-helper (Th)1/Th2 polarization and dysregulated Janus kinase/signal transducer and activator of transcription signalling.[1, 2] Various disorders and triggering conditions have been associated with GA.[1] Herein, we report two cases of GA improving during pregnancy with complete resolution maintained for several months after delivery. The first patient was a 38-year-old woman with asymptomatic erythematous annular plaques on both elbows since February 2017 (Figure 1A). Following histopathological confirmation of GA, only a modest and transient response was obtained with repeated courses of potent topical corticosteroids. The patient became pregnant in 2019 and noticed her lesions gradually improving after the first trimester and completely disappearing during the sixth month (Figure 1B). GA did not recur thereafter up to the last follow-up visit in June 2022. The second patient was a 48-year-old atopic woman with a 20-year history of histologically confirmed generalized GA, characterized by multiple asymptomatic erythematosus-to-flesh-colored papules and plaques on the trunk and extremities that were refractory to topical corticosteroid therapy. During her first pregnancy, GA spontaneously improved with complete resolution during the last trimester. Eight months after delivery, the patient experienced a recurrence of GA with scanty small lesions involving previously unaffected sites. Two years later, there were only two small superficial plaques with faint erythema on the dorsal aspect of the left hand and the right foot. Endocrine abnormalities, dyslipidemia and autoimmune disorders were absent in both women. Medical history revealed previous use of hormonal contraceptives only in the second patient for approximately 8 months with no effect on GA lesions. Both pregnancies were without any complications. Each patient received multivitamin-multimineral supplementation, including folic acid, and did not use any topical or systemic medications during pregnancy, apart from intramuscular progesterone administered in the latter patient to prevent adverse outcomes of her at-risk pregnancy. To our knowledge, data regarding the influence of pregnancy on GA are very limited. In contrast to our observation, de Guia *et al.* recently reported a case of generalized perforating GA appearing during the first trimester of pregnancy and resolving *postpartum*. The same authors mentioned a previous article documenting different course of GA in two pregnant women. Particularly, GA lesions resolved in a patient during pregnancy and recurred at six months after childbirth, whereas in the other patient GA lesions returned during pregnancy and involuted while she was still pregnant.[3] We cannot exclude that the favorable disease course in our patients might have been due to pregnancy-related hormonal and immunological changes. Modifications of maternal immunity during pregnancy can induce anti-inflammatory effects in Th1- and Th17-driven autoimmune diseases with possible *postpartum* disease flares.[4] Interestingly, in our patients, improvement of GA was durable, with persistent complete remission of localized GA in the first case and resolution of generalized GA for 8 months postdelivery followed by the development of very few localized lesions in the latter. Progesterone is essential for implantation and maintenance of gestation, as well as for immune modulation during pregnancy. This might be responsible for the pregnancy-related improvement in certain autoimmune diseases and, speculatively, for the disease course in our second case.[5] The amelioration of GA seemingly induced by pregnancy in our patients should be interpreted with caution, as GA can have a self-limiting course. Anyway, reports of pregnancy-associated changes of inflammatory skin disorders should be encouraged because such information can contribute to a better understanding of their pathomechanisms.

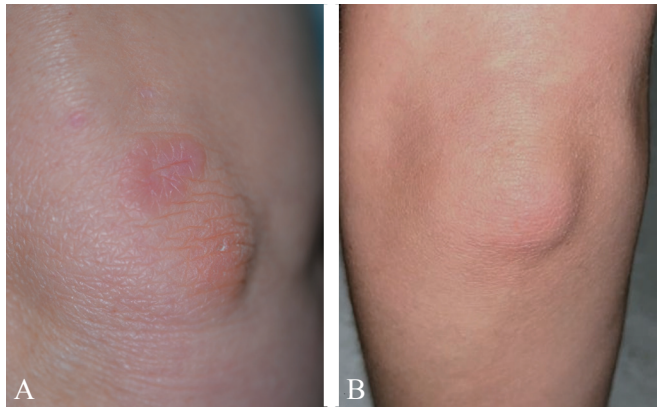


Figure 1.—Clinical appearance of the elbow of patient 1: A) before; and B) during pregnancy.

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