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Pathogenesis of annular lesions: Why a ring presentation?

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Abstract Annular lesions represent a distinct morphology which characterizes many well-known dermatologic conditions. Little is definitively known regarding the pathogenesis of annular lesions, however there a few well-regarded hypotheses. Lesions that clear centrally while enlarging peripherally may result from a local central tissue anergy, or tolerance. The central area in lesions due to dermatophyte infections or subacute cutaneous lupus erythematous may have a central immunity to the antigen that trigged the lesion. The peripheral spread of inflammatory mediators may also contribute to lesions that expand centrifugally. In a highly active immune response, some of the inflammatory mediators may spread to adjacent tissue, which can propagate the inflammatory reaction. The additional hypotheses regarding pathogenesis are disease specific with individual mechanisms having been proposed. This chapter will describe both general and disease specific mechanisms that may contribute to the formation of annular lesions.

Many common dermatologic conditions are known for their annular morphology; however, little is definitively known about the pathogenic factors that result in this presentation. One leading hypothesis is that morphologic patterns in cutaneous disease may be related to pathologic changes in constituent regional molecules. These changes may be induced by various etiologic factors:

1. genetic
2. immunologic
3. physical
4. chemical
5. infectious[1]

Localized physiologic changes affecting specific cutaneous neurovascular structures may also play a role.[2] Understanding the postulated pathogenesis of annular lesions in general and in specific conditions may provide clinicians additional insight about effective treatment. Iatrogenic or traumatically-induced annular lesions, such as post-inflammatory changes due to electrocardiogram leads, a *doughnut* verruca post cryosurgery or *paintball purpura* will not be considered.

Mechanism

Annular lesions that clear centrally as they expand and enlarge centrifugally have been postulated to form via two potential mechanisms: a central local tissue anergy or the peripheral spread of inflammatory mediators.

Lesions that clear centrally while enlarging peripherally are hypothesized to have a central local tissue anergy or tolerance. The central area may exhibit a local immunity to the antigen that caused the lesion to form.[3] For example, in dermatophyte infections, the cell mediated immune response that develops against fungal antigens may limit the growth of fungal organisms that were once present in the central, inactive area of the lesion. A similar hypothesis exists for the annular plaques characteristic of subacute cutaneous lupus erythematous. These lesions may form due to an autoimmune response to antigens in the basal cell layer. It is thought

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Table 1 Mechanisms of annular lesions

General mechanisms of annular lesions	Description
Central local tissue anergy	• A local immunity to the antigen that triggered the lesion
Peripheral spread of inflammatory mediators	• Excess inflammatory mediators spread into adjacent tissue, propagating the inflammatory reaction
Disease specific mechanisms	
Erythema annulare centrifugum	• T-cells and macrophages in the central area of the lesion lose their HLA histocompatibility, leading to central anergy • Linear spread of an inflammatory process along the grid network of the superficial dermal vasculature
Figurate erythemas (erythema gyratum repens)	• BZ reaction • Self-organized wave patterns due to high glutamine concentrations
Porokeratosis	• Peripheral expansion of a clonal mutant epidermal keratinocyte • Mutations of mevalonate kinase
Lichen planus	• High CD4/CD8 ratio in the border of lesions • Stronger ICAM-1expression in peripheral keratinocytes
Granuloma annulare	• Active collagen deposition • Local cutaneous production of IL-2 • Expression of IDO by myeloid dendritic cells and macrophages

BZ, Belousov-Zhabotinsky; HLA, human leukocyte antigens; ICAM, intercellular adhesion molecule; IDO, indoleamine 2,3-dioxygenase; IL, interleukin.

that the inflammatory response destroys the autoantigens that triggered the formation of the lesion, leading to an inactive central area.[4] This hypothesis is supported by the clinical observation that when two annular lesions grow towards each other, they do not invade each other's center and instead form an arciform lesion.[3,4]

The peripheral spread of inflammatory mediators is another potential contributory factor in the formation of annular lesions.[5] During an acute inflammatory reaction, connective tissue-active peptides are released, stimulating fibroblast production of glycosaminoglycans and glycoproteins. The secretion of these peptides is believed to aid in the containment of infection or tumor, preventing excess inflammatory mediators from diffusing into adjacent tissue. This process is referred to as the acute localized ground substance adaptive phenomenon. In a highly reactive immune response, the inflammatory reaction may be enhanced by the increased tissue viscosity or the dilution of tissue fluids. This may allow for peripheral spread of the inflammatory reaction and may explain the peripheral growth and central clearing of annular lesions. The formation of annular lesions is believed to be multifactorial, involving both the localized ground substance adaptive phenomenon as well as the cell mediated immunity of central tissue anergy.[5]

Understanding the pathogenesis of ring presentation according to disease

Erythema annulare centrifugum

Several studies have investigated annularity and the concept of central anergy in erythema annulare centrifugum (EAC). One case demonstrated the development of EAC as an id reaction to trichophyton antigens. The investigators injected trichophyton antigen at the center of an EAC lesion, at the inflammatory border, and at an area of uninvolved skin outside the lesion. A week later, a new lesion developed in the uninvolved skin, while the central area lacked an inflammatory reaction. The injection site at the inflammatory border was faintly discernable.[6] In a second case of EAC related to trichophyton antigens, the authors found that activated T-cells, macrophages, and Langerhans cells were present in the border of the cutaneous lesion, but these activated cells were absent at the center. As a result, the authors suggested that the T-cells and macrophages present in the center of the lesion had lost their human leukocyte antigens (HLA) histocompatibility. They proposed that the loss of HLA histocompatibility may be responsible for the central anergy, resulting in the annular morphology.[3]

Figurate erythemas

A proposed mechanism for the patterns seen in figurate erythemas involves the linear spread of an inflammatory process along vasculature in the superficial portion of the dermis. As the inflammation extends along dermal blood vessels, the inhibitory stages of the inflammatory process limit the spread of inflammation along the vasculature in the opposite direction. This mechanism is compared to the propagation of an impulse along an unmyelinated nerve.[7] The vasculature in the superficial dermis is arranged in conical vascular units that make up a grid-like pattern.[7,8] The propagation of the inflammatory front along these vessels may explain why lesions tend to expand centrifugally. Clinically, a "trailing scale" is characteristic of erythema gyratum repens (EGR) and EAC. The "trailing scale" has been proposed to result from the spread of inflammation into the superficial epidermis. The epidermal cells show changes as they progress to the surface, which clinically manifests as scale. The propagation of the inflammatory process along the superficial dermal blood vessels maintains the advancing edge of EGR and EAC lesions. If the inflammatory process spreads along vasculature in both the superficial and deep dermis, a "trailing scale" does not occur. Erythema chronicum migrans and the deep form of EAC both present without scale and are proposed to result from the spread of inflammation along deep dermal blood vessels.[7]

The specific patterns seen in EGR have also been studied using mathematic models. EGR has similar morphologic features to the patterns seen in the Belousov-Zhabotinsky reaction.[9] This chemical reaction involves spatial-temporal oscillations in chemical concentrations. In an oscillating reaction, there are periodic changes in the concentrations of one or more of the reactants. The reaction occurs due to alternating oxidations and reductions of cerium, an elemental metal.[9] It has been compared to the tricarboxylic acid or Krebs cycle.[10] When the reactants are combined, the solution spontaneously oscillates in color from red to blue.[9] If the solution is plated on a petri dish, patterns with traveling wave fronts and concentric rings are produced.[10] This pattern appears similar to the clinical lesions seen in EGR.[11] The mechanism of the Belousov-Zhabotinsky reaction can help explain biological oscillations.[9] For example, in a general immune response, there are exponential increases of mediators, followed by the dampening of the immune response due to a decrease in these mediators. An applied non-linear reaction-diffusion model describes the Belousov-Zhabotinsky reaction as a guide to explain the dynamic properties of EGR.[12] The inflammatory bands of EGR can propagate at a rate of 1 cm per day with a wavelength of 1 cm. The model was able to account for both the speed and wavelength of the inflammatory bands. It predicted that the rate of production of a small diffusible molecule plays an important role in the generation and maintenance of the pattern. The group hypothesized that interleukin-1 (IL-1) fits this prediction due to its size (17kDa) and ability to augment its own production. They also note that IL-1 may be produced by leukocytes and keratinocytes in the presence of antibody. Of note, one theory about the pathogenesis of EGR involves the deposition of tumor antigen-antibody complexes in the skin. Oscillating concentrations of immunoregulatory mediators, such as IL-1, might play a role in EGR. If these concentration gradients exist, the patterns seen in EGR may be due to successive waves of chemical concentrations propagating in the skin.[12]

Another theory pertaining to the patterns in EGR involves the amino acid L-glutamine.[13] The majority of EGR cases are paraneoplastic, and the lesions are hypothesized to be caused by an immune response to tumor antigens.[12] Glutamine is essential for the growth of both normal and malignant cells. As malignant cells proliferate, they require an increased amount of glutamine. A cutaneous reaction, such as EGR, may be the first physical sign of the accumulation of glutamine by malignant cells, with the patterns forming by high concentrations (>20mM) of glutamine in an aqueous solution. Glutamine is thought to move through an aqueous solution as a self-organized wave. The observed patterns then consist of concentric rings, similar to the morphology seen in EGR. As the glutamine concentration increases, crystals develop and concentric peripheral rings form. Increasing concentrations of glutamine might lead to crystal formation and inflammation in the skin. Similar crystal formations are seen in gout with the development of monosodium urate crystals, suggesting that glutamine crystal formation can also occur in EGR.[13] The similarity between EGR lesions and the wave patterns of glutamine, as well as the association of EGR with malignancy, suggests that glutamine may contribute to the mechanism of annularity in EGR.

Porokeratosis

Porokeratosis presents as a keratotic papule that expands peripherally in an annular pattern.[14] This annular lesion is characterized by a well-demarcated keratotic plaque, covered by a thread like scale; hence, porokeratotic. The primary histologic feature is the prominent cornoid lamella with underlying dyskeratotic cells. The pathogenesis of porokeratosis is unknown. One hypothesis suggests the peripheral expansion of a clonal mutant epidermal keratinocyte located at the base of the coronoid lamella.[14] Supporting studies point toward an euploid DNA plus an increased fraction of cells in the S and G2/M stages of the cell cycle in the keratinocytes near the coronoid lamella.[14] When a punch biopsy of normal skin and was autotransplanted to the periphery of a disseminated superficial actinic porokeratosis lesion,[15] the keratotic border reformed on the normal skin, but when a punch biopsy of a disseminated superficial actinic porokeratosis lesion was autotransplanted to normal skin, the border regressed.[15] The reformation of the keratotic border through normal skin suggests that the cells present in the border are important in the pathogenesis of the lesion. This research supports the concept of peripheral expansion in cutaneous lesions, where the peripheral expansion of a mutant keratinocyte may be an-

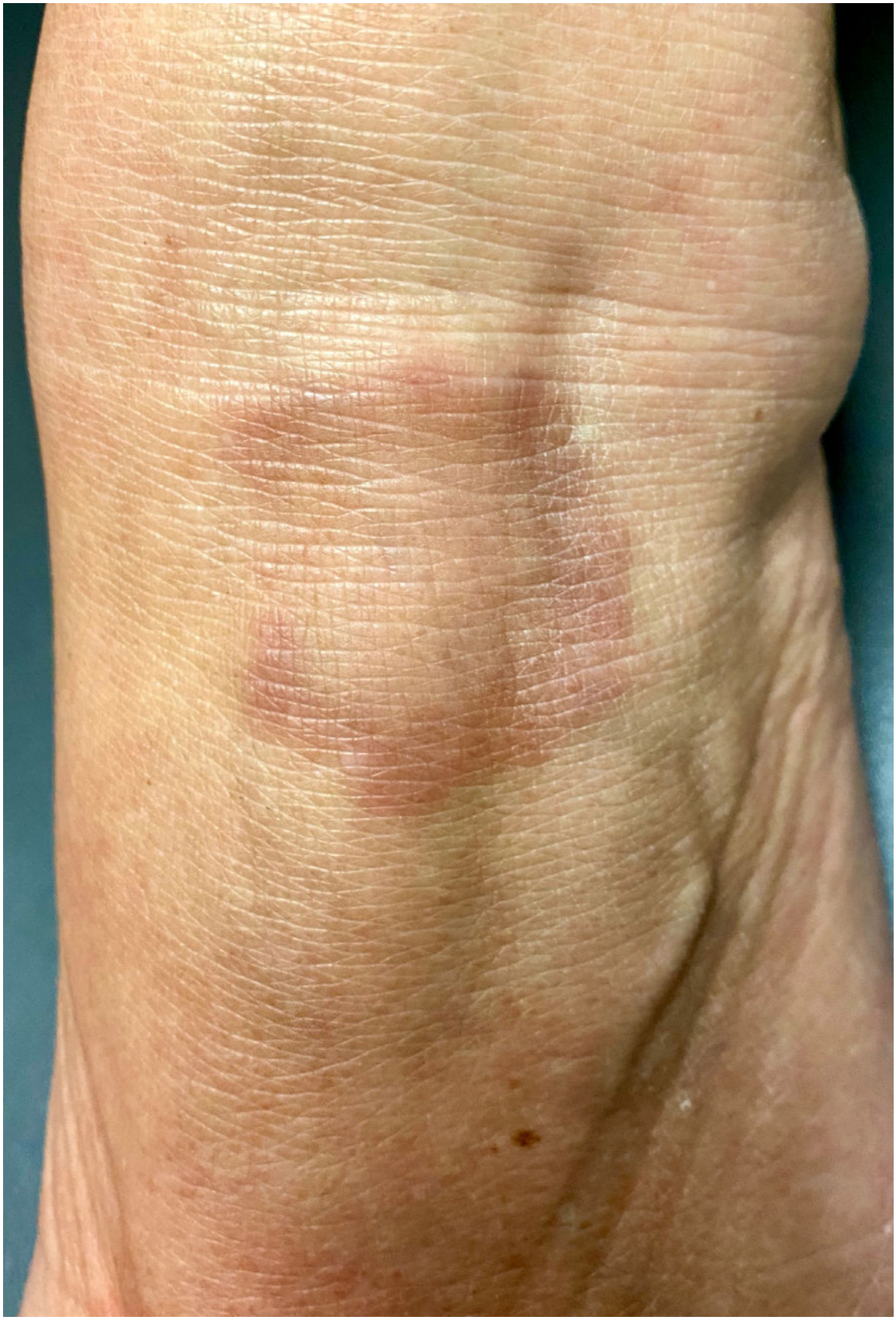

Fig. 1 Annular granulomatous plaque on the dorsal aspect of the foot in a patient with known granuloma annulare.

other mechanism for the formation of at least some annular lesions.

The mevalonate metabolic pathway, which uses acetyl-CoA to produce sterols and isoprenoid metabolites,[16] is essential for keratinocyte differentiation. Mutations of mevalonate kinase may inhibit keratinocyte differentiation to varying degrees and may be pathogenic in all variants of porokeratosis.[17] How this precisely contributes to the annular appearance of lesions is unknown.

Lichen planus

The possible mechanisms of annularity have also been studied in several cases of annular lichen planus,[18,19] a rare subtype of lichen planus that is usually found on the lips or genital area. One hypothesis for the annular morphology referenced specific immune patterns occurring in mucosal tissue.[18] The researchers examined the number of epidermal Langerhans cells and the characteristics of the dermal infiltrate in three different regions (the border, the central area, and the skin outside the lesion) of annular lichen planus. They found that dense infiltrates of CD3-positive cells with a high CD4/CD8 ratio were limited to the border zone. The density of the CD1a-postive and S-100 protein positive Langerhans cells in the epidermis was higher in the border zone than in the central portion of the lesion.[18] A second immunohistochemical study of annular lichen planus observe that intercellular adhesion molecule-1 expression was stronger in peripheral keratinocytes of active lesions. They hypothesize that intercellular adhesion molecule-1 expression might initiate the molecular event in the annular pattern by acting as an initiator of adhesion of lymphocytes to the epidermis.[19]

While I-CAM has been identified as a potential driving force behind peripheral extension, it is possible that the central, burned out areas in annular lichen planus is the result of lymphocyte mediated elastolysis. This theory was initially supported by the histologic loss of elastic fibers in the central portion of the lesion. Unfortunately, subsequent reports found similar loss of elastic fibers in the active borders of annular lesions.[20] Another group sought to assess the impact of metallothionein, a low-molecular-weight metal-binding protein found in basal keratinocytes, on lesion morphology. Metallothionein was undetectable at the center of the annular lesion; and they concluded that metallothionein expression was primarily affected by the inflammatory stage of the lesion.[21]

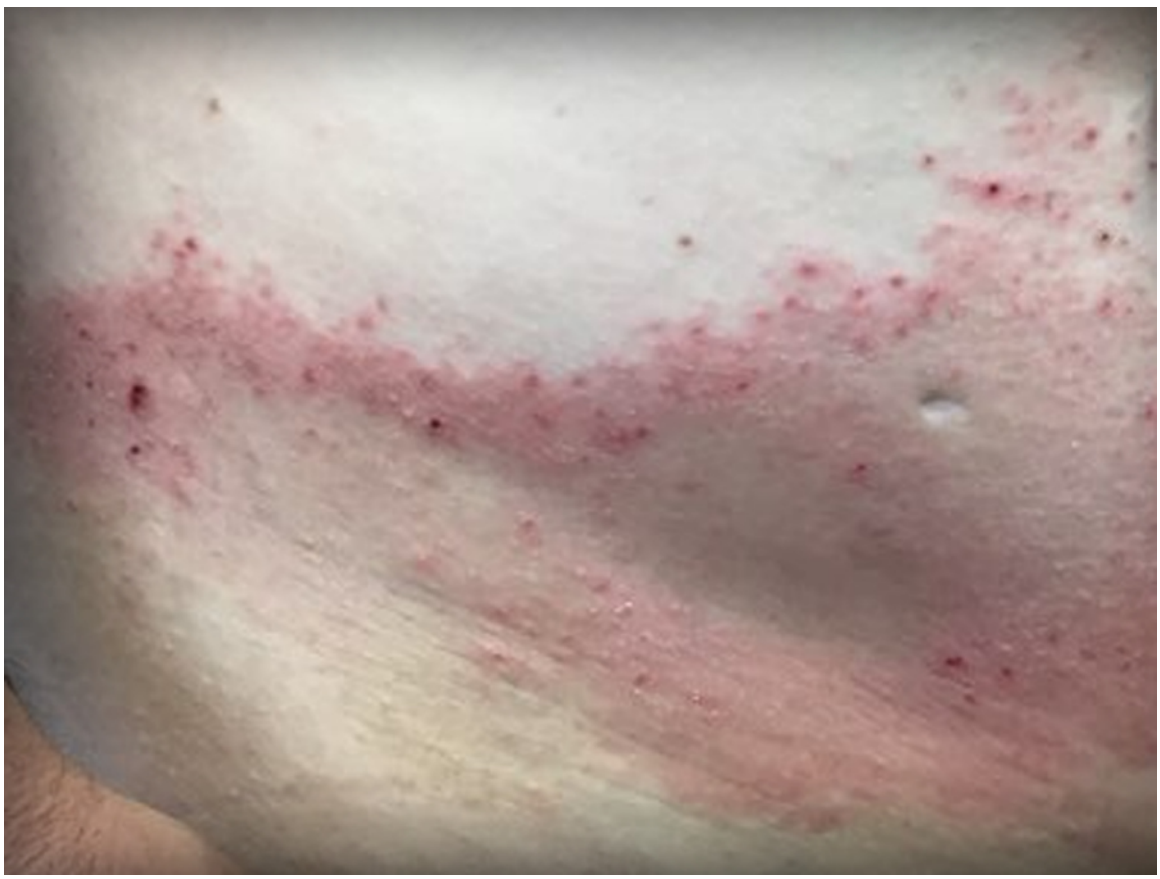

Fig. 2 Peripherally expanding annular plaque with scale and satellite erythematous papules consistent with erythema papulatum centrifugum.

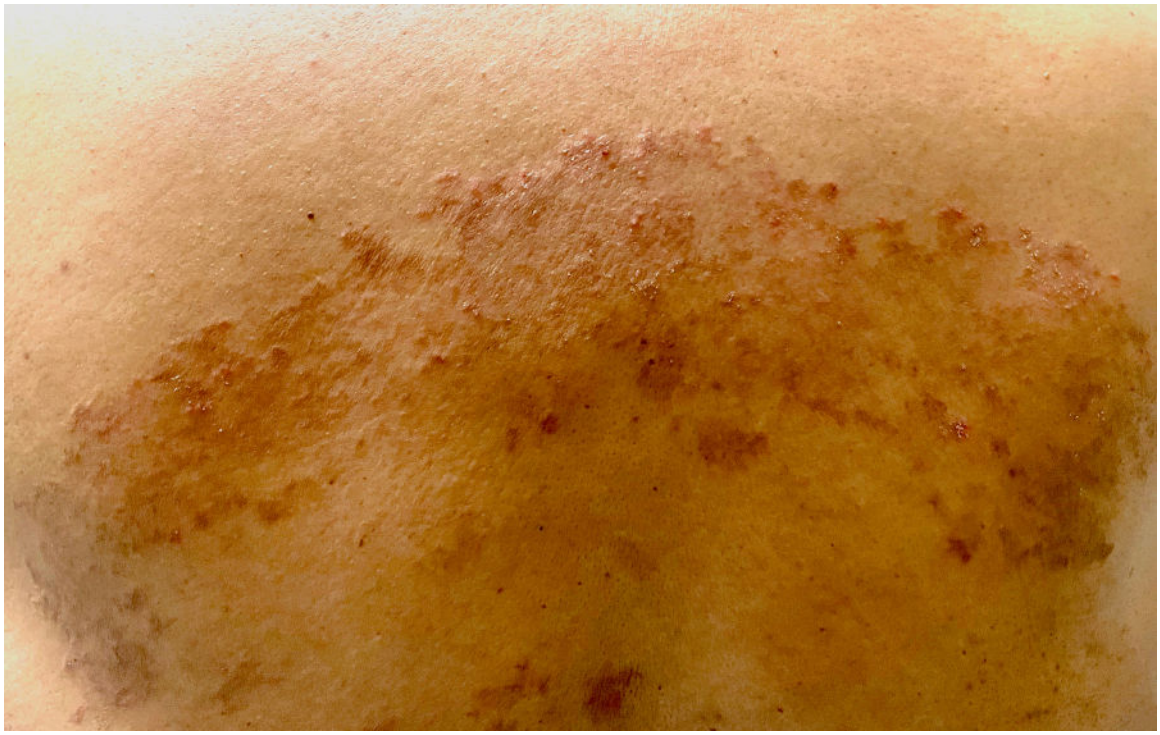

Fig. 3 Annular plaque with serpiginous border diagnosed as tinea corporis.

Granuloma annulare

Granuloma annulare (GA) is a non-infectious cutaneous granulomatous disease, where the most common presentation is an annular erythematous plaque, appearing as multiple pink to brown papules coalescing into the ring presentation (Figure 1).[22] A cell-mediated hypersensitivity reaction has been hypothesized,[23] where the cytokines involved include interferon-gamma, tumor necrosis factor–alpha, and matrix metalloproteinases, along with activated macrophages, Th1 subtype T-cells, and IL-2.[22] Unfortunately, the mechanism for the involvement for these cytokines to produce the GA lesions is unclear.

One group examined biopsies taken from the raised, active border of involved and uninvolved skin of five patients to investigate collagen synthesis in GA. The mRNA expression of pro-α1(I) was higher in the affected skin when compared with unaffected skin. The areas of collagen degeneration and necrobiosis were surrounded by active fibroblasts expressing pro-α1(I) and pro-α1(III) mRNA. They hypothesized that active collagen deposition contributes to the pathogenesis of GA lesions.[24]

Another group found high levels of IL-2 in GA lesions, although the increased IL-2 expression was not found in peripheral blood mononuclear cells. It seems that local cutaneous production of IL-2 may be responsible for maintaining local T-cell activation.[25]

An additional team investigated the expression of indoleamine 2,3-dioxygenase (IDO) by myeloid dendritic cells and macrophages in both infectious and non-infectious cutaneous granulomas. IDO degrades tryptophan, and its expression is considered to be an immunomodulatory signal. Expression of IDO can lead to the inhibition of T-cell proliferation, because T-cells are sensitive to low tryptophan concentrations. IDO is strongly expressed in the center and the ring wall of cutaneous granulomas. These investigators hypothesized that the expression of IDO by dendritic cells and macrophages induces a tolerogenic milieu. The expression of IDO is thought to be a signal that initiates the development of tolerance in adaptive immunity.[26] This results in a central tolerance, as a potential mechanism for the formation of annular lesions

Conclusions

There are several theories proposed to explain the development of annular lesions. These include a local zone of central tissue anergy, oscillations in inflammatory mediators, and the spread of inflammation along the cutaneous vascular network. These concepts are more applicable in defining the etiologies of EAC, figurate erythemas, porokeratosis, lichen planus and granuloma annular, but their applications in papulosquamous diseases, annular drug eruptions, and bullous diseases are not so accepted. Additional research is needed to further elucidate the pathophysiologic mechanisms that potentiate these entities.

Conflict of interest

The authors declare no conflict of interest.

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