# DIFFERENTIAL DIAGNOSIS OF ANNULAR SKIN LESIONS – A CLINICAL REVIEW

**[1]Wollina U., [2]Abdel-Naser Badawy M.**

*[1]Municipal Hospital of Dresden, Academic Teaching Hospital, Department of Dermatology and Allergology, Germany;*
*[2]Ain Shams University Hospital, Department of Dermatology, Andrology and STIs, Cairo, Egypt*

Annular lesions represent a particular macro-morphologic pattern of skin diseases. The word "annular" is derived from the Latin *annulus* – ring. An annular lesion represents a secondary efflorescence that develops from macules, papules or plaques. It is originally a sign of an enlargement of the skin lesion but may stabilize in size during the following course. Different subtypes of annular lesions can be distinguished. The lesions can be either asymptomatic or symptomatic.

*Asymptomatic annular lesions with papules*

A typical representative of this subtype is granuloma annulare. The disease presents with firm, shiny papules of different possible coloration with central involution. Hands are most commonly affected. Children most commonly present with the localized type [1] (Fig. 1).

In adults, lesions may be also generalized, perforating, patch-like and subcutaneous [2] (Fig. 2)

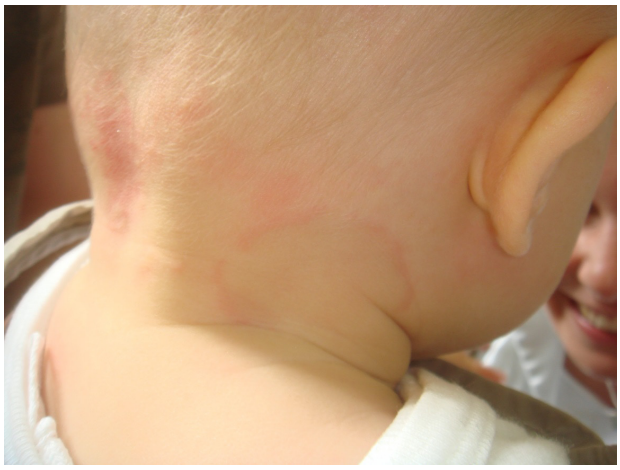

*Fig. 1. Granuloma annulare in a 5 months old toddler*

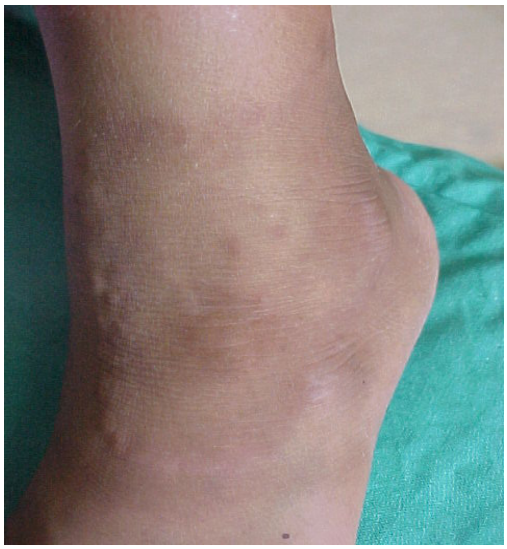

*Fig. 2. Granuloma annulare on the foot*

A rare differential diagnosis is annular elastolytic giant cell granuloma [3].

Erythema annulare centrifugum (EAC) describes a group of eruptions characterized by slowly migrating annular and well-configured erythematous lesions. The cause of the disease is unknown, but a number of precipitating factors such as infections or medical drugs have been reported. In rare cases EAC is associated with malignancies, mostly solid tumors. This subtype is known as PEAC (P stands for paraneoplastic) (Fig. 3) [4].

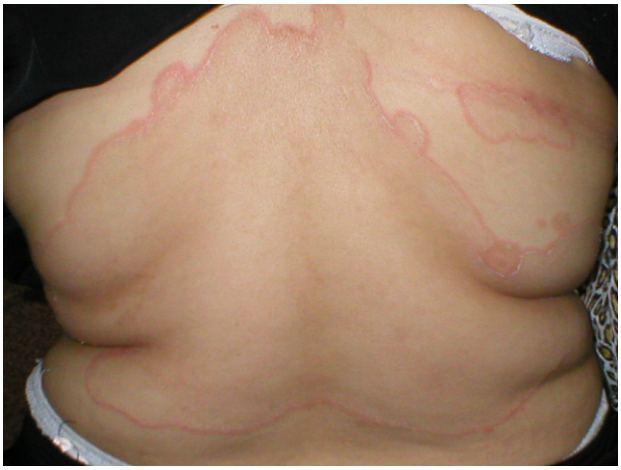

*Fig. 3. Erythema annulare centrifugum with central clearing*

*Asymptomatic annular lesions with papules and scaling*

In secondary syphilis annulo-papular lesions may occur symmetrically on palms and soles, extremities and trunk. The diagnosis is confirmed by Venereal disease testing laboratory (VDTL). Although the lesions themselves are asymptomatic, a temporary flu-like symptomatology may occur [5].

Slightly papular lesions may occur together with annular erythematous macules in secondary syphilis with exanthematous rash (Fig. 4).

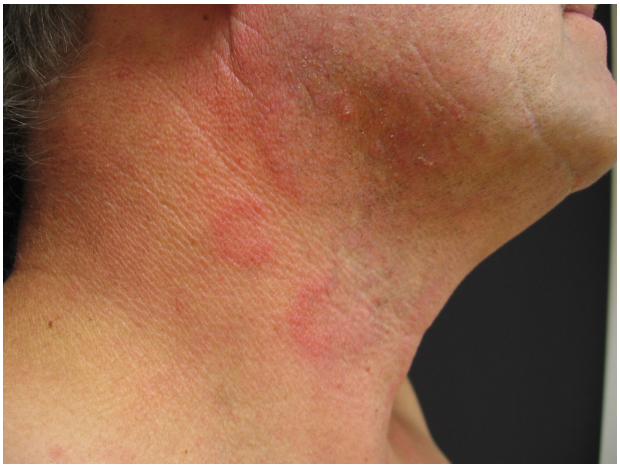

*Fig. 4. Annular, slightly papular erythematous neck lesions in secondary syphilis*

*Asymptomatic annular pustular lesions with or without scaling*

Annular pustular psoriasis may present with pruritus. The pustules are sterile. Children are affected more often than adults. The lesions can be combined with classical plaque type psoriasis [6]. Annular pustular lesions can occur in generalized pustular psoriasis (Fig. 5).

A very rare differential diagnosis is hereditary deficiency of lactate dehydrogenase M-subunit [7].

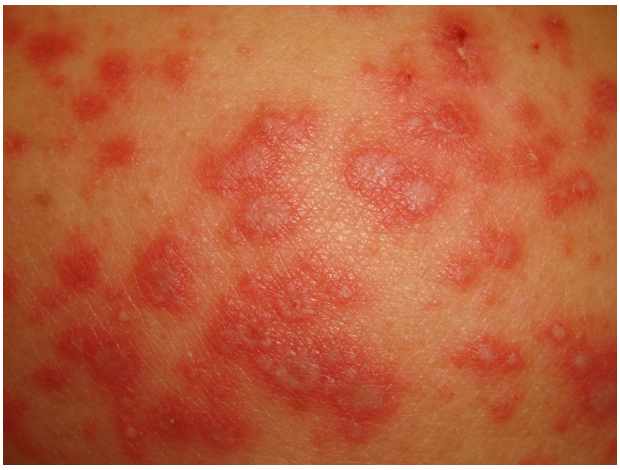

*Fig. 5. Annular pustular lesions in generalized pustular psoriasis*

*Asymptomatic annular urticarial lesions*

Eosinophilic annular erythema is characterized by recurrent episodes of annular urticarial, nonpruriginous erythematous plaques. The histopathological study shows a perivascular inflammatory infiltrate in the superficial and deep dermis, composed of lymphocytes and eosinophils. It was originally described in children but may be seen in adults occasionally [8].

*Annular lesions with peripheral blistering*

Among the highly variable skin lesions in early congenital syphilis, annular lesions with peripheral blistering develop rarely, resembling a "string-of-pearls." The diagnosis of congenital syphilis is made on the basis of radiologic evaluation and reactive testing by Venereal Disease Research Laboratory (VDRL) in both mother and child [9].

The "string-of-pearls" sign is not specific, since it can occur in localized pemphigoid as well (Fig. 6) [10].

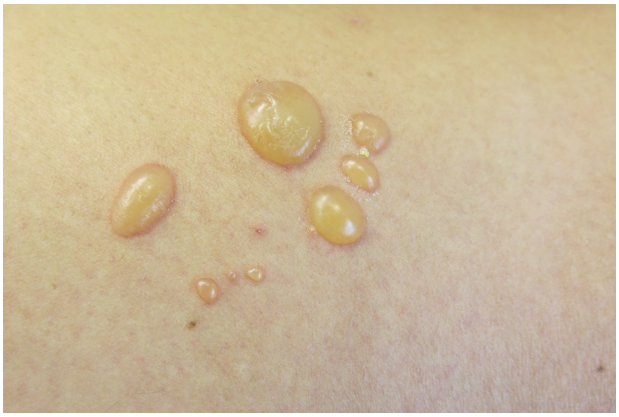

*Fig. 6. String-of-pearls-like appearance of bullous pemphigoid*

Chronic bullous disease of childhood, or linear IgA bullous dermatosis, is an autoimmune blistering disorder due to circulating IgA anti-glomerular basement membrane zone antibodies directed against the 97 kDa portion of bullous pemphigoid antigen in the lamina lucida. It occurs in all ages. It can also present as a "string-of-pearls" [11] (Fig. 7).

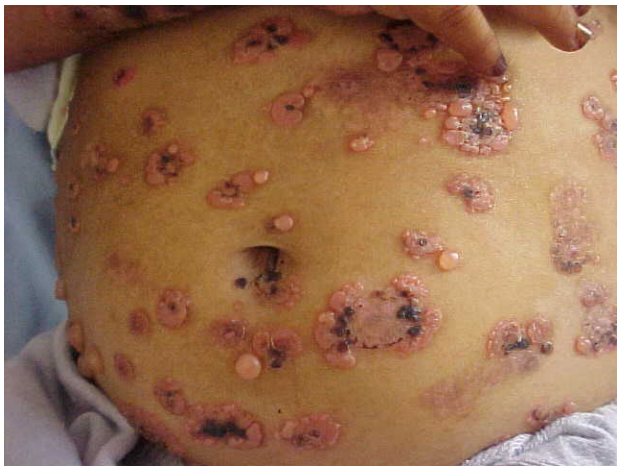

*Fig. 7. "String-of-pearls" appearance in chronic bullous disease of childhood*

Rarely, bullous lesions of type II have been reported in erythema nodosum leprosum (ENL) -an immune complex-mediated reaction that may complicate the course of multibacillary leprosy [12].

*Asymptomatic annular macular lesions without scaling*

Erythema migrans is characterized by an asymptomatic enlarging erythematous macule after a tick bite. The causative agents are Borrelia species. Sometimes multiple lesions develop. The clinical picture together with medical history of a tick bite are sufficient for diagnosis. Seroconversion usually occurs in 6-10 weeks after tick bite in a smaller percentage of patients. Serology is therefore not reliable for the diagnosis of erythema migrans [13].

Vitiligo has an estimated prevalence of 1% of the population worldwide. A rare observation is inflammatory vitiligo with slightly raised borders. Under Wood's light, the lesions appear bright [14].

*Asymptomatic annular macular lesions with scaling*

The most common representative of this subtype is tinea corporis due to infection with human pathogen dermatophytes. Anthropophilic, zoophilic and geophilic species can cause the disease. First step in diagnosis is a potassium hydroxide preparation of peripheral scale followed by mycologic culture. New molecular biologic technologies are available for rapid diagnosis [15] (Fig. 8).

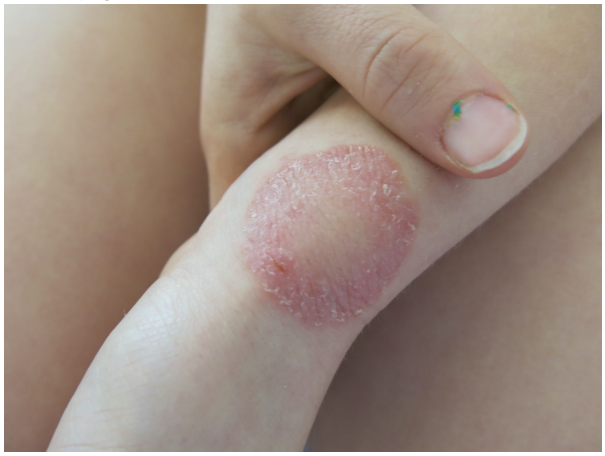

*Fig. 8. Scaling annular lesion due to tinea corporis in a 7-year-old girl (contracted from her pet ginuea pig)*

Annular scaling lesions can be seen in chronic discoid (CDLE) and subacute cutaneous lupus (SCLE). Histology shows a band-like subepidermal T cellular infiltrate and hydropic basal cell degeneration, which is more pronounced in CDLE. The lupus disease is photosensitive, what may be used in diagnostics [16].

Annular macular lesions like raccoon eyes and annular macules on other body parts are seen in the majority cases of neonatal lupus erythematosus [17].

*Burning and pruriginous annular macular lesions without scaling*

Fixed drug eruption is a localized erythematous or violaceous macule, sometimes with a central wheal, with itching and burning sensations. The inflammation can cause permanent hyperpigmentation. Thorogh anamnesis for medical drugs and intralesional scratch test with the identified compound will confirm the diagnosis [18] (Fig. 9).

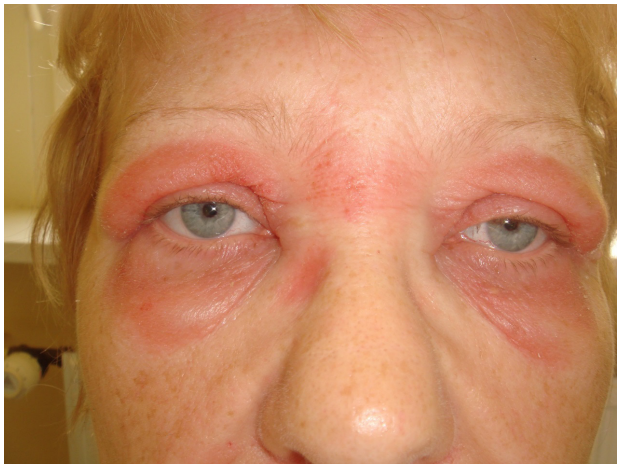

*Fig. 9. Fixed drug eruption due to oral sulfonamide therapy*

Erythema multiforme is a hypersensitivity reaction most commonly seen during the course of a herpes infection, but other infections or drugs may also trigger the disease. The lesions show a targetoid pattern. The occurrence of non-specific erythema multiforme-like lesions in systemic lupus erythematosus is known as Rowells's syndrome [19].

*Burning and pruriginous annular macular lesions with scaling*

Nummular eczema – a variant of atopic dermatitis – can be severely itching. The scaling is variable. The borders are ill-defined. Older lesions may show hyper- or hypopigmentation [20] (Fig. 10).

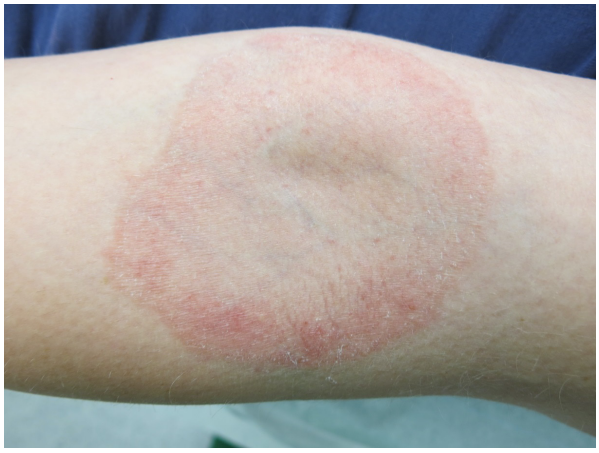

*Fig. 10. Annular macular lesion of atopic dermatitis with xerosis and scaling*

Tinea imbricata is a subtype of dermatophytosis with characteristic skin lesions consisting of scaly, concentric annular rings and overlapping plaques that are pruritic. It is more frequent in South-East Asia [21].

*Asymptomatic annular plaques without scaling*

Porokeratosis is characterized by erythematous, annular plaques with an atrophic center and hyperkeratotic ridge-like border. The most common actinic subtype is seen in sun-exposed skin of the extremities. The histopathological hallmark is the cornoid lamella, a thin column of parakeratotic corneocytes embedded within the stratum corneum [22] (Fig. 11).

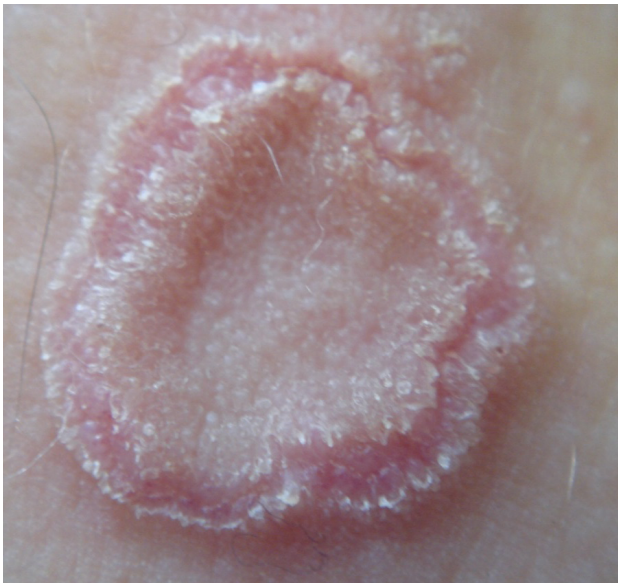

*Fig. 11. Annular plaque of porokeratosis Mibelli*

Rare differential diagnoses are the following two neutrophilic dermatoses: histiocytoid Sweet's syndrome presenting with erythematous annular plaques and chronic recurrent annular neutrophilic dermatosis (CRAND) [23,24].

*Asymptomatic annular plaques with scaling*

Such lesions may be seen in psoriasis with a silvery larger scaling or in pityriasis rosea herald patches with tiny scales. Psoriasis is a chronic inflammatory autoimmune-T-cell mediated disease affecting about 2% of the World population [25].

Pityriasis rosea is an acute, self-limiting exanthematous disease associated with the endogenous systemic reactivation of human herpesvirus (HHV)-6 and/or HHV-7. The distribution of lesions follows a Christmas-tree pattern [26].

Both diseases mentioned here, may in certain cases present with a mild itch. In most cases however, they remain asymptomatic.

*Annular plaques with hyposensitivity*

Annular plaques – with or without scaling – and decreased sensitivity to touch, temperature or pain are characteristic for leprosy caused by Mycobacterium leprae infection. The diagnosis can be confirmed by polymerase chain reaction to the infectious agent [27].

*Pruriginous annular papular lesions*

Lichen planus is a chronic inflammatory T-cell mediated autoimmune disorder. Various types of lichen planus are known. The disease is characterized by "six P", i.e. papules, plaques, polygonal, purple, pruritic. Hyperpigmentation is not uncommon in darker skin types (Fig. 12). Histology shows hypergranulation of the upper epidermis, a jig-saw epidermal acanthosis, and a lichenoid lymphocytic infiltrate [28].

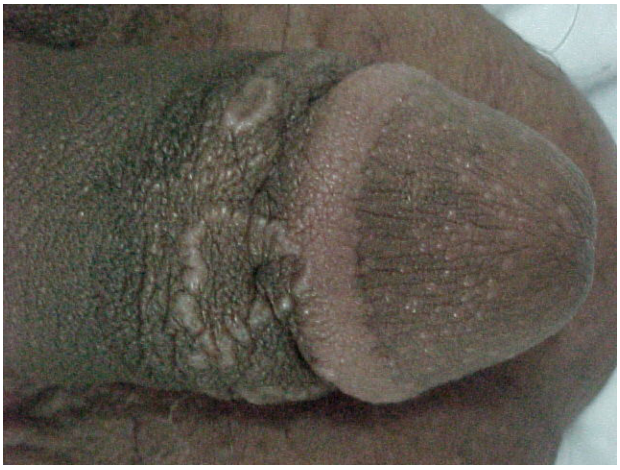

*Fig. 12. Genital lichen planus*

Mild to moderate itch may be associated with cutaneous sarcoidosis. Sarcoidosis is a granulomatous disease of unknown etiology that may affect various organs. Cutaneous involvement is present in 25% of patients. Annular papular lesions are a possible variant [29].

Severely pruriginous annular papules and generalized lichenification in combination with leukocytosis, peripheral blood eosinophilia and raised serum IgE levels are a hallmark of hypereosinophilic dermatitis. The most important differential diagnosis is systemic hypereosinophilic syndrome with bone marrow involvement [30].

*Annular patches with pain and secondary bullae formation*

In atypical cases with annular macular lesions, paraneoplastic skin reactions have to be ruled out. Painful annular erythematous macular lesions can be prodromi of hemophagocytic lymphohistiocytosis. Those patients may show secondary blistering with fever and malaise [31].

*Non-scaling annular plaques with fever, arthralgias, night sweats, and general malaise*

Interstitial granulomatous dermatitis (IGD) and palisaded neutrophilic granulomatous dermatitis (PNGD) are reactive skin diseases that exhibit annular plaques and may be associated with malignancies. A recent study investigated 37 cases of paraneoplastic PNGD/IGD and found that the most commonly associated neoplasia is myelodysplastic syndrome (MDS), but solid tumors may also be associated in rare cases [32].

*Pruritic annular urticae*

The most common condition presenting with pruritic urticae is urticaria with massive edema in the superficial dermis – well-circumscribed, erythematous lesions with raised borders and blanched centers. In case of deeper edema (subcutaneous urticaria), urticae may be missing but pruritus present (Fig. 13). Urticarial lesions can be caused by allergic or physical events, but the majority remains idiopathic. If individual lesions last longer than 24 hours, a biopsy should be considered to rule out urticarial vasculitis. In case of a typical acute idiopathic urticaria (lasting less than 6 weeks), no extensive laboratory investigations are recommended [33].

Urticarial drug reactions have to be considered for differential diagnosis.

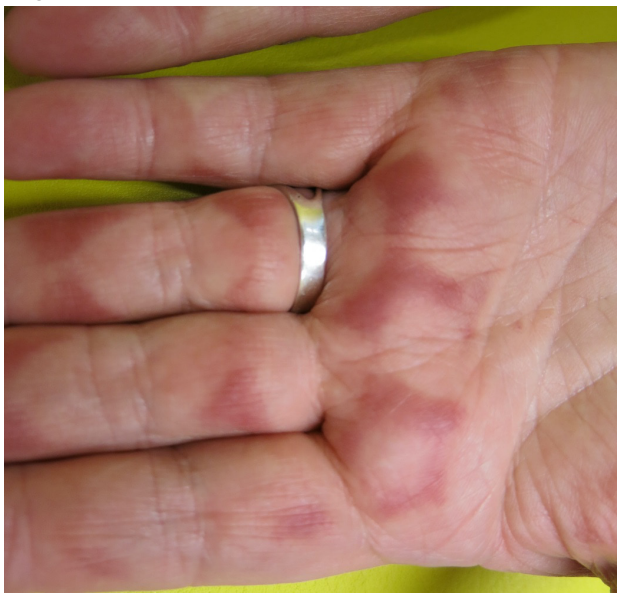

*Fig. 13. Pruritic annular urticaria lesions in delayed pressure urticarial*

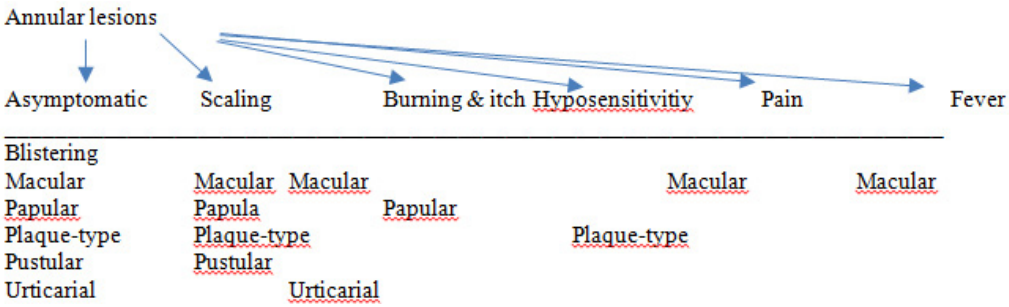


*Fig. 14. Differential diagnosis of annular lesions*

**Conclusions.** Annular lesions are common in clinical dermatology. Perception and visual recognition are part of the pathway to a correct diagnosis (Fig. 14). The use of other factors related to the dermatosis, like subjective symptoms or course, supports expertise in determining possible diagnoses. We present the clincial differential diagnosis of annular cutaneous lesions. Eventually the suspected diagnosis may need a confirmation by laboratory and/or histopathology findings [34].

**REFERENCES**

1. Patrizi A , Gurioli C, Neri I. Childhood granuloma annulare: a review. G Ital Dermatol Venereol. 2014;149:663-674.
2. Rubin CB, Rosenbach M. Granuloma annulare: a retrospective series of 133 patients. Cutis. 2019;103(2):102-106.
3. Kato H, Kitajima Y, Yaoita H. Annular elastolytic giant cell granuloma: an unusual case with papular lesions. J Dermatol. 1991;18:667-670.

4. McDaniel B, Cook C. Erythema annulare centrifugum. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2019 Jan-2019 Dec 17.
5. Ghafoor R, Anwar MI. A Young boy with persistent nodules and hoarseness: A rare presentation of nodular secondary syphilis. J Coll Physicians Surg Pak. 2018;28:S37-S38.
6. Liao PB, Rubinson R, Howard R, Sanchez G, Frieden IJ. Annular pustular psoriasis--most common form of pustular psoriasis in children: report of three cases and review of the literature. Pediatr Dermatol. 2002;19:19-25.
7. Takeo N, Fujiwara S, Sakai T, Saito-Shono T, Ishikawa K, Hatano Y. Hereditary lactate dehydrogenase M-subunit deficiency with late-developing pustular psoriasis-like lesions. J Dermatol. 2016;43:1429-1432.
8. Lobo MA, Gonzalo ES, Jiménez-Reyes J. Eosinophilic anular erythema in an adult. Dermatol Online J. 2017;23: pii: 13030/qt22c95125.
9. Mathews J, Naseem JA, Neupane N, Parameswaran N, Chandrashekar L. An unusual presentation of early congenital syphilis with annular configuration of blisters resembling "string-of-pearls". Pediatr Dermatol. 2019;36:735-736.
10. Raposo I, Machado S, Sampaio R, Selores M. Infantile bullous pemphigoid with "string of pearls sign". Dermatol Online J. 2017;23: pii: 13030/qt3fw4d2t2.
11. Tate C, Christian W, Newell L. Chronic Bullous Dermatosis of Childhood and the String of Pearls Sign. J Pediatr. 2018;202:325-325.e1.
12. Shah A, Mahajan R, Ninama K, Bilimoria F. Annular bullous lesions with atypical erythema multiforme in leprosy. Lepr Rev. 2014;85:201-207.
13. Nadelman RB. Erythema migrans. Infect Dis Clin North Am. 2015;29:211-239.
14. Olsavszky V, Géraud C. Slowly growing annular erythematous lesions on lightly pigmented skin: A quiz. Acta Derm Venereol. 2019; doi: 10.2340/00015555-3365. [Epub ahead of print].
15. Tchernev G, Penev PK, Nenoff P, et al. Onychomycosis: modern diagnostic and treatment approaches. Wien Med Wochenschr. 2013;163:1-12.
16. Wollina U, Hein G. Lupus erythematosus: uncommon presentations. Clin Dermatol. 2005;23:470-479.
17. Singalavanija S, Limpongsanurak W, Aoongern S. Neonatal lupus erythematosus: a 20-year retrospective study. J Med Assoc Thai. 2014;97:S74-S82.
18. Flowers H, Brodell R, Brents M, Wyatt JP. Fixed drug eruptions: presentation, diagnosis, and management. South Med J. 2014;107:724-727.
19. Akintayo RO, Olarinoye GM, Akintayo FC, Ilesanmi ON. Rowell syndrome in Nigeria: Systemic lupus erythematosus presenting as recurrent erythema multiforme in a young woman. Acta Dermatovenerol Croat. 2019;27:200-201.
20. Silverberg NB. Typical and atypical clinical appearance of atopic dermatitis. Clin Dermatol. 2017;35:354-359.
21. Leung AKC, Leong KF, Lam JM. Tinea imbricata: An overview. Curr Pediatr Rev. 2019;15:170-174.
22. Kanitakis J. Porokeratoses: an update of clinical, aetiopathogenic and therapeutic features. Eur J Dermatol. 2014;24:533-544.
23. Marcarini R, Araujo RN, Nóbrega MM, et al. Histiocytoid Sweet's syndrome presenting with annular erythematous plaques. An Bras Dermatol. 2016;91:154-156.
24. Croci-Torti A, Guillot B, Rigau V, Bessis D. Dermatose neutrophilique annulaire récurrente chronique. Ann Dermatol Venereol. 2017;144:362-367.
25. Boehncke WH, Schön MP. Psoriasis. Lancet. 2015;386:983-994.
26. Drago F, Ciccarese G, Rebora A, Broccolo F, Parodi A. Pityriasis rosea: A comprehensive classification. Dermatology. 2016;232:431-437.
27. Eichelmann K, González González SE, Salas-Alanis JC, Ocampo-Candiani J. Leprosy. An update: definition, pathogenesis, classification, diagnosis, and treatment. Actas Dermosifiliogr. 2013;104:554-563.
28. Weston G, Payette M. Update on lichen planus and its clinical variants. Int J Womens Dermatol. 2015;1:140-149.
29. Mishra AK, George AA, Peter D. Annular cutaneous sarcoidosis with systemic involvement. J Family Med Prim Care. 2017;6:660-662.
30. Yadav D, Sharma A, Agarwal S, Gupta V. Hypereosinophilic dermatitis: generalised lichenification and gyrate erythema as the sole manifestation of idiopathic hypereosinophilic syndrome. BMJ Case Rep. 2019;12: pii: e232142.
31. Jun HJ, Kim HO, Lee JY, Park YM. Preceding annular skin lesions in a patient with hemophagocytic lymphohistiocytosis. Ann Dermatol. 2015;27:608-611.
32. Pei S, Hinshaw MA. Palisaded neutrophilic granulomatous dermatitis leading to diagnosis of Hodgkin lymphoma: Report of rare case and literature review of paraneoplastic granulomatous dermatitides. Am J Dermatopathol. 2019;41:835-845.
33. Schadler ED, Kamat D. Common annular lesions in the pediatric population: Part 2. Pediatr Ann. 2019;48:e135-e138.
34. Lowenstein EJ, Sidlow R, Ko CJ. Visual perceptions, cognition, and error in dermatologic diagnosis: Diagnosis and error. J Am Acad Dermatol. 2029;81(6):1237-1245.

## SUMMARY

## DIFFERENTIAL DIAGNOSIS OF ANNULAR SKIN LESIONS – A CLINICAL REVIEW

**[1]Wollina U., [2]Abdel-Naser Badawy M**

*[1]Municipal Hospital of Dresden, Academic Teaching Hospital, Department of Dermatology and Allergology, Germany;*
*[2]Ain Shams University Hospital, Department of Dermatology, Andrology and STIs, Cairo, Egypt*

Annular lesions are a peculiar type of presentation of various skin disorders. The primary efflorescence can be either macule, papule, plaque, urticaria or vesicle. Depending on the primary efflorescence involved, the differential diagnoses can be delimited. It is important to identify secondary features such as scaling and discolorations. Additional symptoms may include pruritus, burning sensations or hypoesthesia. Depending on the clinical findings and medical history, confirmation of suspected working diagnosis is achieved by laboratory work-up, including histology and microbiology (mycology) studies.

**Keywords:** annular lesions, clinical dermatology, algorithm.

**РЕЗЮМЕ**

**ДИФФЕРЕНЦИАЛЬНАЯ ДИАГНОСТИКА КОЛЬЦЕВИДНЫХ КОЖНЫХ ПОРАЖЕНИЙ - КЛИНИЧЕСКИЙ ОБЗОР**

**[1]Воллина У., [2]Абдель-Насер Бадави М.**

*[1]Городская больница Дрездена, Академическая учебная больница, отделение дерматологии и аллергологии, Германия; [2]Университетская клиника Айн-Шамс, Отделение дерматологии, андрологии и венерических заболеваний, Каир, Египет*

Кольцевидные поражения являются своеобразным типом проявления различных кожных заболеваний. Первичное проявление такого поражения может быть либо в виде пятна, папулы, бляшки, крапивницы или пузырчатого волдыря. В связи с такой неоднородностью первичного проявления, дифференциальная диагностика довольно затруднена. Важно определить вторичные характеристики, такие как шелушение кожи и дисколорация. Дополнительные симптомы могут включать зуд, ощущение жжения или пониженную чувствительность - гипоэстезию. В зависимости от клинических данных и истории болезни, подтверждение рабочего диагноза достигается при помощи применения лабораторных методов исследования, в том числе гистологических и микробиологических (микологических).

რეზიუმე

კანის ბეჭდისებრი დაზიანებების დიფერენციული დიაგნოსტიკა – კლინიკური მიმოხილვა

[1]უ. ვოლინა, [2]მ.ბადავი აბდელ-ნასერი

[1]დერმატოლოგიისა და ალერგოლოგიის განყოფილება, დრეზდენის საქალაქო საავადმყოფო, აკადემიური საავადმყოფო, დრეზდენი, გერმანია; [2]დერმატოლოგიის, ამდროლოგიისა და ვენერიულ დაავადებათა განყოფილება,აინ-შამსის საუნივერსიტეტო კლინიკა,კაირო,ეგვიპტე

კანის ბეჭდისებრი დაზიანებები კანის სხვადასხვა დაავადების გამოვლინების თავისებურ ტიპს წარმოადგენს. ასეთი დაზიანება პირველადად შეიძლება გამოვლინდეს ლაქის, პაპულას, ფოლაქის, ჭინჭრის ცების ან ბუშტუკოვანი წყლულის სახით. პირველადი გამოვლინების ამგვარი არაერთგვაროვნებიდან გამომდინარე, დიფერენციული დიაგნოსტიკა საკმაოდ გართულებულია. მნიშვნელოვანია ისეთი მეორადი მახასიათებლების განსაზღვრა, როგორიცაა კანის აქერცვლა და დისკოლორაცია (ფერის შეცვლა). დამატებითი სიმპტომები აშეიძლება მოიცავდეს ქავილს, წვის შეგრძნებას ან მგრძნობელობის დაქვეითებას – ჰიპოესთეზიას. კლინიკურ მონაცემებსა და დაავადების ისტორიაზე დამოკიდებულებით, სამუშაო დიაგნოზის დადასტურება მიიღწევა კვლევის ლაბორატორიული, მათ შორის – ჰისტოლოგიური და მიკრობიოლოგიური (მიკოლოგიური) მეთოდების გამოყენებით.

## ПРОДУКЦИЯ АКТИВНЫХ ФОРМ КИСЛОРОДА И РАЗВИТИЕ АПОПТОЗА В ЛЕЙКОЦИТАХ КРОВИ ПРИ ЭКСПЕРИМЕНТАЛЬНОМ АНТИФОСФОЛИПИДНОМ СИНДРОМЕ

**[1]Яремчук О.З., [1]Посохова Е.А., [1]Лихацкий П.Г., [1]Летняк Н.Я., [1]Кулицкая М.И., [1]Кузьмак И.П., [1]Лисничук Н.Е., [2]Делибашвили Д.Г.**

*[1]Тернопольский национальный медицинский университет им. И.Я. Горбачевского, Украина; [2]Тбилисский государственный медицинский университет, Грузия*

Апоптоз – это запрограммированный и генетически регулируемый процесс гибели клеток, при котором отсутствует воспалительная реакция и не повреждаются соседние клетки [1]. Различные раздражители физиологического или патогенного характера могут спровоцировать апоптоз через внешние пути рецептора смерти или внутренние митохондриальные пути [9]. Индукция и реализация апоптоза требуют взаимодействия ряда молекул, включая сигнальные молекулы, рецепторы, ферменты и регуляторные белки. Важную роль в механизмах апоптоза играет сигнальная система каскада каспаз, которая регулируется различными молекулами, такими как ингибитор белка апоптоза, белки семейства Bcl-2 и кальпаин [19].

Антифосфолипидный синдром (АФС) – аутоиммунное нарушение, характеризующееся повышенным риском развития артериального и венозного тромбоза и патологией беременности. Со времени открытия заболевания в 1980-х годах проведены многочисленные исследования на культурах клеток, на моделях животных и на пациентах, которые привели к более глубокому пониманию патогенеза АФС. Эти исследования показали, что ведущим моментом патогенеза АФС является образование циркулирующих аутоантител, так называемых антифосфолипидных антител (aPL), большинство из которых распознают клеточные поверхностные белки, присоединенные к фосфолипидам плазматической мембраны. Связывание aPL с антигенами на клеточной поверхности вызывает взаимодействие комплекса с трансмембранными рецепторами с последующей инициацией внутриклеточной сигнализации в критических типах клеток, включая тромбоциты, моноциты, эндотелиальные клетки и трофобласты. Дальнейшее изменение различных клеточных функций приводит к развитию воспаления, об-