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Association of discoid lupus erythematosus with chronic granulomatous disease – a report of 2 cases and review of the literature

Running title

Discoid lupus in chronic granulomatous disease

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Conflict of interest

No conflict of interest.

Patient consent

Informed consent has been obtained from both patients for publication of their case notes and clinical photographs.

Abstract

Discoid lupus erythematosus (DLE) is known to be associated with chronic granulomatous disease (CGD), but most DLE occur in female carriers of X-linked CGD, with few reports of these lesions among CGD-affected individuals – this observation is unexplained. We describe two cases of DLE-like lesions in boys with CGD, one boy with partial neutrophil function, and another whose lesions were related to voriconazole use. Reviewing other previously reported cases, we conclude that the risk of developing DLE-like lesions appears to be increased primarily in two subsets of the CGD population: those with partial neutrophil function and those with near-absent neutrophil function where there is a second trigger. In the light of recent literature on the role of neutrophils in lupus pathogenesis, we propose that pathogenesis of DLE in CGD may indeed relate to NETosis, neutrophil dysfunction and deficiency of reactive oxygen species, influenced also by medications such as voriconazole.

Main text

Chronic granulomatous disease (CGD) is a rare hereditary primary immunodeficiency, caused by a defective nicotinamide dinucleotide phosphate (NADPH) oxidase complex, which is required for phagocytes to synthesize microbiocidal reactive oxygen species (ROS). This defect leads to recurrent bacterial and fungal infections, as well as granuloma formation. A number of gene defects have been identified, with the X-linked form comprising at least 70% of CGD cases, involving a deficiency in the gp91-phox (CYBB) protein of NADPH oxidase.[1] Four autosomal-recessive forms have been described, each involving different components of NADPH oxidase.[1, 2]

In addition to increased susceptibility to infection, patients with CGD are also predisposed to a variety of inflammatory and autoimmune conditions.[1] Discoid lupus erythematosus (DLE) without other organ involvement has been observed, mostly in female carriers of X-linked CGD,[3-7] with fewer reports of these lesions in affected individuals.[7, 8] This apparent increased risk of DLE in carriers and some affected individuals is unexplained. We describe two cases of DLE-like lesions in boys with CGD and refer to previous reports of similar cases, to identify people at higher risk of developing CGD-related DLE. We then explore implications, in the context of recent research findings, for a potential role of neutrophils in DLE pathogenesis.

Case reports

Patient 1

This Caucasian boy has the rare p40-phox (NCF4) deficient form of autosomal-recessive CGD confirmed on genetic testing, with only one other patient reported with this genotype.[2] He developed photosensitive erythematous plaques on his face from the age of 6 months (Figure 1), which later extended to his limbs and trunk. Recurrent mouth ulcers began at the age of 2. This was followed by lip swelling and anal fissures at age 3, which persisted into his teenage years. His medical history was also significant for recurrent staphylococcal

infections including styes and nasal crusting, as well as annual lower respiratory tract infections.

Skin biopsies taken from chest and lower leg plaques (Figure 2) showed epidermal thinning, hyper- and parakeratosis, with apoptotic keratinocytes and moderate focal vacuolar changes in the basal layer, with no basement membrane thickening. There were also dermal perivascular and periadnexal lymphocytic infiltrates, and mucin deposits between reticular dermal collagen bundles. Direct immunofluorescence (DIF) showed weakly positive staining for IgM and strongly positive staining for C3 along the basement membrane.

His discoid plaques resolved with hydroxychloroquine, topical corticosteroids and sun protection. Serial dihydrorhodamine oxidation (DHR) test performed between ages of 15 and 18 years, revealed between 23-90% functional neutrophils (control >90%). His ENA, ANA and dsDNA were consistently negative or weakly positive. No relatives had a history of similar skin changes.

Patient 2

This Caucasian boy had recurrent bacterial and fungal infections during his first two years of life, including recurrent otitis media, oral thrush, urinary tract infections, impetigo and osteomyelitis. He also suffered from recurrent esophagitis and esophageal strictures due to granulomata. DHR test showed 0.05% functional neutrophils, while his mother had 60% functional neutrophils on nitroblue tetrazolium test (NBT), consistent with X-linked CGD. He was commenced on prophylactic co-trimoxazole from the age of 18 months, subcutaneous gamma-interferon from the age of 3 years, and prophylactic itraconazole at age 12 years.

At age 15, he presented to the dermatology unit with a forearm plaque, with biopsy confirming aspergillus infection with granuloma. He was subsequently commenced on voriconazole, and within 3 weeks he developed erythematous plaques and pustules on his face, neck and upper chest (Figure 3). This eruption resolved a month after voriconazole was ceased, without further intervention. His ANA, ENA and dsDNA were negative. His mother and female relatives reported no history of skin eruptions.

Skin biopsies taken (Figure 4) showed prominent vacuolar change along the basal layer and apoptotic keratinocytes in the epidermis, without basement membrane thickening. There was perivascular and periadnexal lymphoid infiltration in the dermis. DIF showed minimal deposits of IgM and C3 along the basement membrane.

Discussion

Both our patients had lesions clinically resembling DLE, with histological features supporting but not entirely classical for DLE, and without ANA positivity or other evidence of systemic lupus erythematosus (SLE). Over the past 40 years, there have been reports of 51 other CGD patients or carriers with similar DLE-like lesions, most with some histological features of DLE but negative DIF.[3-11] We note that these lesions tend to occur in a subset of the CGD population – 40 were female carriers of X-linked CGD,[3-7] five were individuals with autosomal-recessive CGD,[7] three were related to voriconazole use (two of these patients had X-linked CGD).[9, 10] Despite X-linked being the commonest form of CGD, there have only been three reports of X-linked CGD patients developing DLE-like lesions without any identified trigger.[8, 11]

Whilst it has been contended that these dermatoses are pathologically separate from DLE due to predominantly negative DIF,[8] in the absence of definitive distinctions between the two skin conditions, they may still be considered to be in the same spectrum of disease, given their similar clinical presentation of erythematous plaques on sun-exposed skin. DLE is the most common form of cutaneous lupus erythematosus, and its pathogenesis is not fully understood. It is thought that stimuli such as ultraviolet (UV) light induce keratinocyte apoptosis, upregulating release of cytokines such as interferon, TNF-alpha, IL-6, IL-10 and IL-17 and increasing expression of autoantigens such as Ro52 and Ro60. This further encourages keratinocyte apoptosis, impairs phagocytosis and leads to formation of anti-Ro/SSA antibodies.[12] These circulating autoantibodies form immune complexes that deposit along the basement membrane, as well as inhibit macrophage clearance of apoptotic debris, further contributing to persistent inflammation, while dysregulation of T cells and dendritic cells have also been implicated.[12]

In CGD patients, abnormal neutrophil apoptosis and impaired clearance of apoptotic cells may play a role in the development of DLE. CGD neutrophils have diminished or delayed exposure of phosphatidyl serine (PS) on their surface, which results in *delayed apoptosis*, with release of apoptotic blebs containing immunogenic chromatin that in turn stimulate auto-antibody production via helper T cell and B cell activation.[13-15] Non-functional NADPH oxidase and consequent deficiency of ROS also impair clearance and degradation of immunogenic apoptotic material by phagocytes.[13, 16]

Anti-inflammatory mediator production is also reduced in CGD, with both neutrophils and macrophages found to have impaired production of prostaglandin D_2,while macrophages also have deficiencies in producing transforming growth factor-β.[15] Lack of ROS have also been hypothesized to alter cellular signaling among phagocytes and T cells, contributing to the hyperinflammatory response.[16]

However, factors discussed above do not explain the many reports of DLE among female X-linked CGD carriers, who have reduced numbers of functional neutrophils due to random X-chromosome inactivation, but no absolute deficiency, unlike most affected males.[1] With the abnormal apoptosis theory alone, one would expect carriers to have a lower incidence of DLE than affected males, due to lower proportions of dysfunctional neutrophils. Two authors have demonstrated correlation between worsening neutrophil impairment and increased DLE severity among female carriers of X-linked CGD.[4, 5] While this relationship was not as well established in another study,[6] overall there may be an association between DLE and having small, but not negligible, numbers of functional neutrophils.

More recently, the process of NETosis has been implicated in lupus pathogenesis. It has been shown that some activated neutrophils undergo NETosis, an alternative pathway of cell death where their nuclear, cytosolic and granular materials are released in long chromatin filaments, or neutrophil extracellular traps (NETs). In contrast to apoptosis, neutrophils undergoing NETosis do not display molecules such as PS before plasma membrane disruption, thus preventing early clearance by phagocytes.[17]

Several authors have proposed that NETs are highly immunogenic triggers for autoimmunity, serving as a source of autoantigens, activating dendritic cells, which in turn amplify

interferon-alpha production and stimulate T cells that subsequently activate B cells to produce autoantibodies.[14, 18, 19] It has been described that induction of autophagy and production of ROS by NADPH oxidase is the main pathway for initiating NETosis, and that neutrophils with non-functioning NADPH oxidase have impaired NETosis.[18, 20, 21] However, ROS-independent mechanisms of NETosis have been reported, and it is possible that CGD neutrophils release NETs in response to some stimuli.[17, 18]

Conversely, a report of lupus-prone mice showed similar lupus exacerbation associated with absolute and proportional deficiency in NADPH oxidase activity, which was interpreted by the authors as evidence against NETosis in lupus pathogenesis.[22] However, other consequences of ROS deficiency were not considered and the generalizability of their findings is unclear. In particular, it is worth noting that much of the data investigating the immunogenic role of NETs relates more to SLE and lupus nephritis, rather than DLE. The exact role of ROS on NETs formation requires clarification, as does their respective and combined roles in the complex pathways associated with apoptosis, autoantigen processing and autoantigen clearance.[23, 24] Furthermore, how each of these processes contribute to pathogenesis of CGD-associated DLE is unclear.

Our first case had a reduced proportion of functional neutrophils, but not an absolute deficiency. A much greater proportion of individuals with autosomal-recessive CGD have significant residual ROS production, compared to those with X-linked CGD, which is commonly associated with near-absent neutrophil function.[25] Development of DLE in this first case may be related to some functional neutrophils releasing NETs in the setting of many dysfunctional neutrophils, both contributing to the release and persistence of autoantigens, as well as ongoing inflammation (Figure 5).

Our second case had an absolute deficiency of functional neutrophils, but the development of DLE-like lesions was directly related to voriconazole, the fourth such case reported.[9, 10] Voriconazole-related DLE has only been reported once outside the CGD population.[26] The hepatic metabolite of voriconazole and its UVB photoproduct photosensitize keratinocytes to UVA (not UVB), induce ROS and so cause DNA damage.[27] Although voriconazole-induced photosensitivity in children is well described,[28] its role in triggering DLE in X-linked CGD and its effects on neutrophil function remain unknown.

In conclusion, these two CGD patients are amongst the few index cases to develop DLE-like lesions. We propose that the risk of developing DLE-like lesions is increased in two distinct subsets of the CGD population – individuals with a proportion of functional neutrophils, including many X-linked CGD carriers and autosomal-recessive CGD patients, and those with near-absent neutrophil function in the setting of a second trigger such as voriconazole. The pathogenesis of DLE in CGD may be critically related to NETosis, neutrophil dysfunction, ROS deficiency and in some cases, the use of medications such as voriconazole. Further work is required to clarify the pathogenic mechanisms.

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References

1. Winkelstein JA, Marino MC, Johnston RB, Jr., et al. Chronic granulomatous disease. Report on a national registry of 368 patients. Medicine. 2000; 79(3): 155-69.

2. Matute JD, Arias AA, Wright NAM, et al. A new genetic subgroup of chronic granulomatous disease with autosomal recessive mutations in p40 phox and selective defects in neutrophil NADPH oxidase activity. Blood. 2009; 114(15): 3309-15.

3. Cale CM, Morton L, Goldblatt D. Cutaneous and other lupus-like symptoms in carriers of X-linked chronic granulomatous disease: incidence and autoimmune serology. Clin Exp Immunol. 2007; 148(1): 79-84.

4. Garioch JJ, Sampson JR, Seywright M, et al. Dermatoses in five related female carriers of X-linked chronic granulomatous disease. Br J Dermatol. 1989; 121(3): 391-6.

5. Kragballe K, Borregaard N, Brandrup F, et al. Relation of monocyte and neutrophil oxidative metabolism to skin and oral lesions in carriers of chronic granulomatous disease. Clin Exp Immunol. 1981; 43(2): 390-8.

6. Sillevis Smitt JH, Weening RS, Krieg SR, et al. Discoid lupus erythematosus-like lesions in carriers of X-linked chronic granulomatous disease. Br J Dermatol. 1990; 122(5): 643-50.

7. Rupec RA, Petropoulou T, Belohradsky BH, et al. Lupus erythematosus tumidus and chronic discoid lupus erythematosus in carriers of X-linked chronic granulomatous disease. Eur J Dermatol. 2000; 10(3): 184-9.

8. Chowdhury MM, Anstey A, Matthews CN. The dermatosis of chronic granulomatous disease. Clin Exp Dermatol. 2000; 25(3): 190-4.

9. Gomez-Moyano E, Vera-Casano A, Moreno-Perez D, et al. Lupus erythematosus-like lesions by voriconazole in an infant with chronic granulomatous disease. Pediatr Dermatol. 2010; 27(1): 105-6.

10. Turegano MM, Lee C-CR, Malech HL, et al. Recurrent erythematous plaques on sun-exposed sites in an African American boy with chronic granulomatous disease. J Am Acad Dermatol. 2014; 70(3): 576-80.

11. Ortiz-Romero PL, Corell-Almuzara A, Lopez-Estebaranz JL, et al. Lupus like lesions in a patient with X-linked chronic granulomatous disease and recombinant X chromosome. Dermatology. 1997; 195(3): 280-3.

12. Yu C, Chang C, Zhang J. Immunologic and genetic considerations of cutaneous lupus erythematosus: a comprehensive review. J Autoimmun. 2013; 41: 34-45.

13. Sanford AN, Suriano AR, Herche D, et al. Abnormal apoptosis in chronic granulomatous disease and autoantibody production characteristic of lupus. Rheumatology (Oxford). 2006; 45(2): 178-81.

14. Bouts YM, Wolthuis DFGJ, Dirkx MFM, et al. Apoptosis and NET formation in the pathogenesis of SLE. Autoimmunity. 2012; 45(8): 597-601.

15. Brown JR. Diminished production of anti-inflammatory mediators during neutrophil apoptosis and macrophage phagocytosis in chronic granulomatous disease (CGD). J Leukoc Biol. 2003; 73(5): 591-9.

16. Schappi MG, Jaquet V, Belli DC, et al. Hyperinflammation in chronic granulomatous disease and anti-inflammatory role of the phagocyte NADPH oxidase. Semin Immunopathol. 2008; 30(3): 255-71.

17. Remijsen Q, Kuijpers TW, Wirawan E, et al. Dying for a cause: NETosis, mechanisms behind an antimicrobial cell death modality. Cell Death Differ. 2011; 18(4): 581-8.

18. Stephan A, Fabri M. The NET, the trap and the pathogen: neutrophil extracellular traps in cutaneous immunity. Exp Dermatol. 2015; 24(3): 161-6.

19. Garcia-Romo GS, Caielli S, Vega B, et al. Netting neutrophils are major inducers of type I IFN production in pediatric systemic lupus erythematosus. Sci Transl Med. 2011; 3(73): 73ra20.

20. Grayson PC, Kaplan MJ. At the Bench: Neutrophil extracellular traps (NETs) highlight novel aspects of innate immune system involvement in autoimmune diseases. J Leukoc Biol. 2015.

21. Bianchi M, Hakkim A, Brinkmann V, et al. Restoration of NET formation by gene therapy in CGD controls aspergillosis. Blood. 2009; 114(13): 2619-22.

22. Campbell AM, Kashgarian M, Shlomchik MJ. NADPH oxidase inhibits the pathogenesis of systemic lupus erythematosus. Sci Transl Med. 2012; 4(157): 157ra41.

23. Arazna M, Pruchniak MP, Demkow U. Reactive Oxygen Species, Granulocytes, and NETosis. Adv Exp Med Biol. 2015; 836: 1-7.

24. Radic M. Clearance of Apoptotic Bodies, NETs, and Biofilm DNA: Implications for Autoimmunity. Front Immunol. 2014; 5: 365.

25. Kuhns DB, Alvord WG, Heller T, et al. Residual NADPH oxidase and survival in chronic granulomatous disease. N Engl J Med. 2010; 363(27): 2600-10.

26. Denning DW, Griffiths CE. Muco-cutaneous retinoid-effects and facial erythema related to the novel triazole antifungal agent voriconazole. Clin Exp Dermatol. 2001; 26(8): 648-53.

27. Ona K, Oh DH. Voriconazole N-oxide and its ultraviolet B photoproduct sensitize keratinocytes to ultraviolet A. Br J Dermatol. 2015.

28. Rubenstein M, Levy ML, Metry D. Voriconazole-induced retinoid-like photosensitivity in children. Pediatr Dermatol. 2004; 21(6): 675-8.

Figure legends

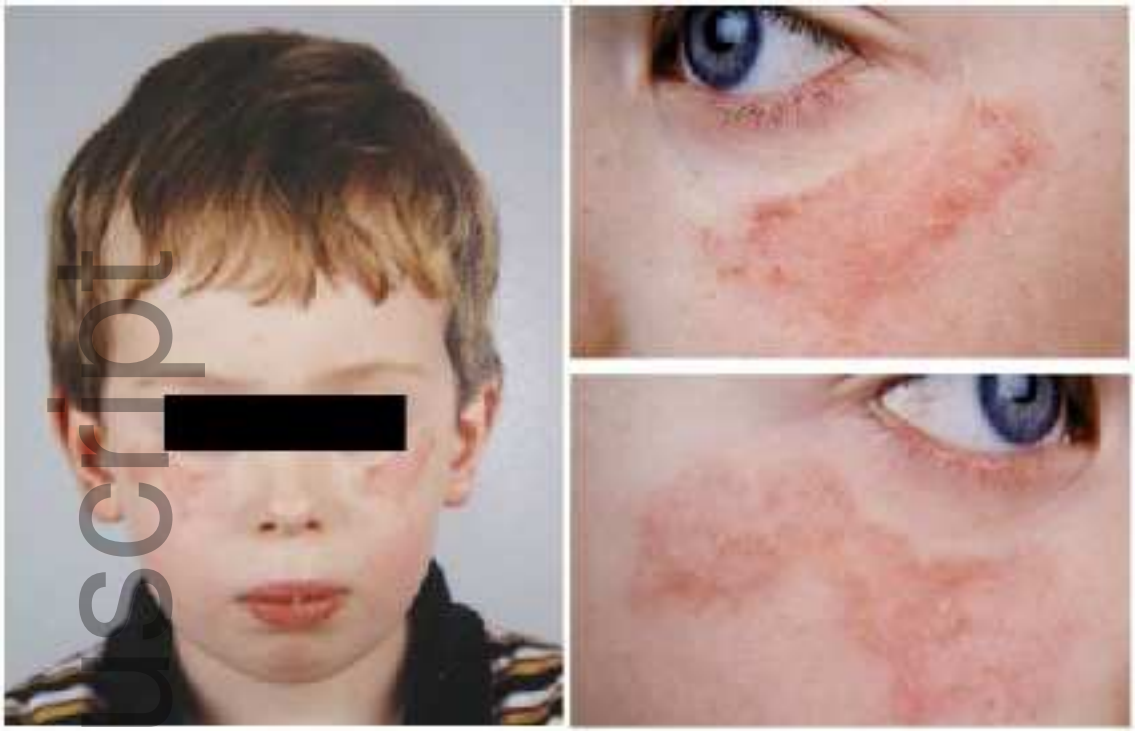
Fig 1. Photosensitive plaques on face of patient 1.

Fig 2. Histopathology of discoid lupus erythematosus-like lesions of patient 1. Haematoxylin and eosin stain, 200× magnification. a) epidermal parakeratosis, b) vacuolar changes in basal layer, c) perivascular lymphocytic infiltrate

Fig 3. Pustules and plaques on face, neck and chest of patient 2.

Fig 4. Histopathology of discoid lupus erythematosus-like lesions of patient 2. Haematoxylin and eosin stain, 200× magnification. a) vacuolar changes in basal layer, b) perivascular lymphocytic infiltrate

Fig 5. Hypothesized pathogenesis of discoid lupus erythematosus (DLE) in chronic granulomatous disease (CGD). Some CGD patients & carriers have a proportion of functional neutrophils that are capable of undergoing NETosis, while other non-functional neutrophils undergo delayed apoptosis – both processes contribute to release and persistence of autoantigens that activate the adaptive immune system, leading to formation of immune complexes. Impaired phagocytosis due to lack of reactive oxygen species (ROS) and reduced production of anti-inflammatory mediators by neutrophils and macrophages also play a role. The mechanism of voriconazole-related DLE in CGD is unclear, and may be related to its photosensitizing effects, induction of ROS and DNA damage.



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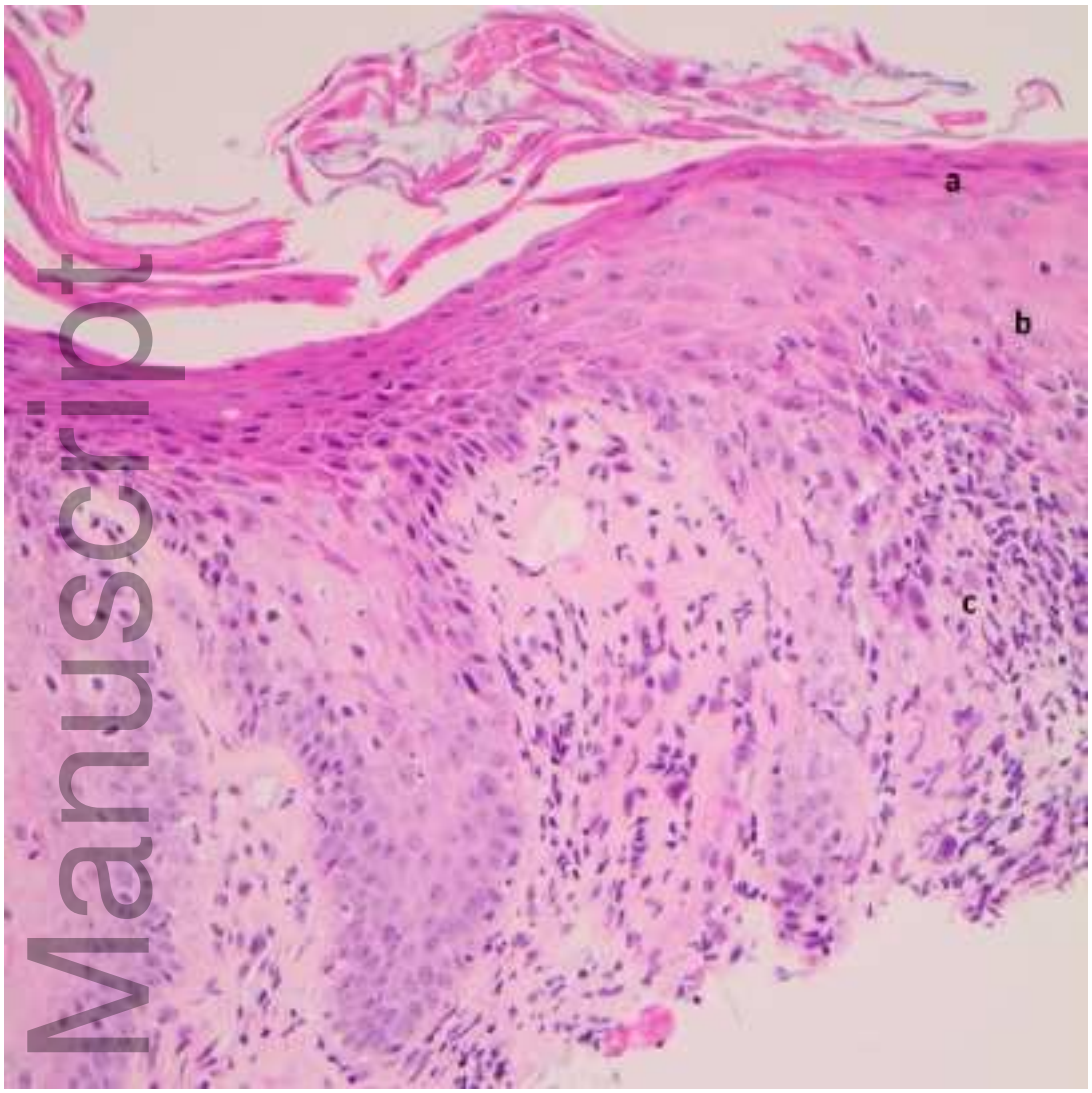

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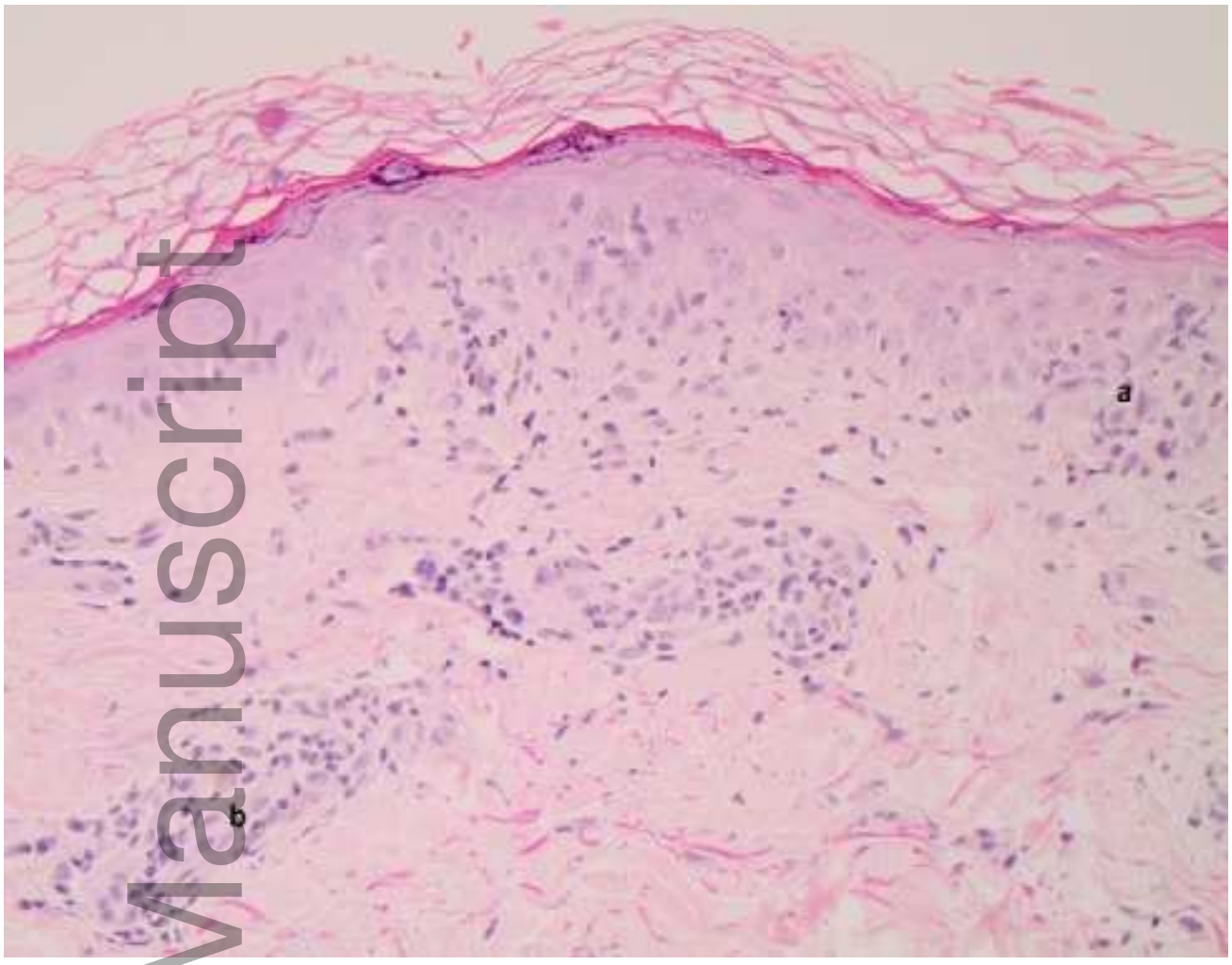

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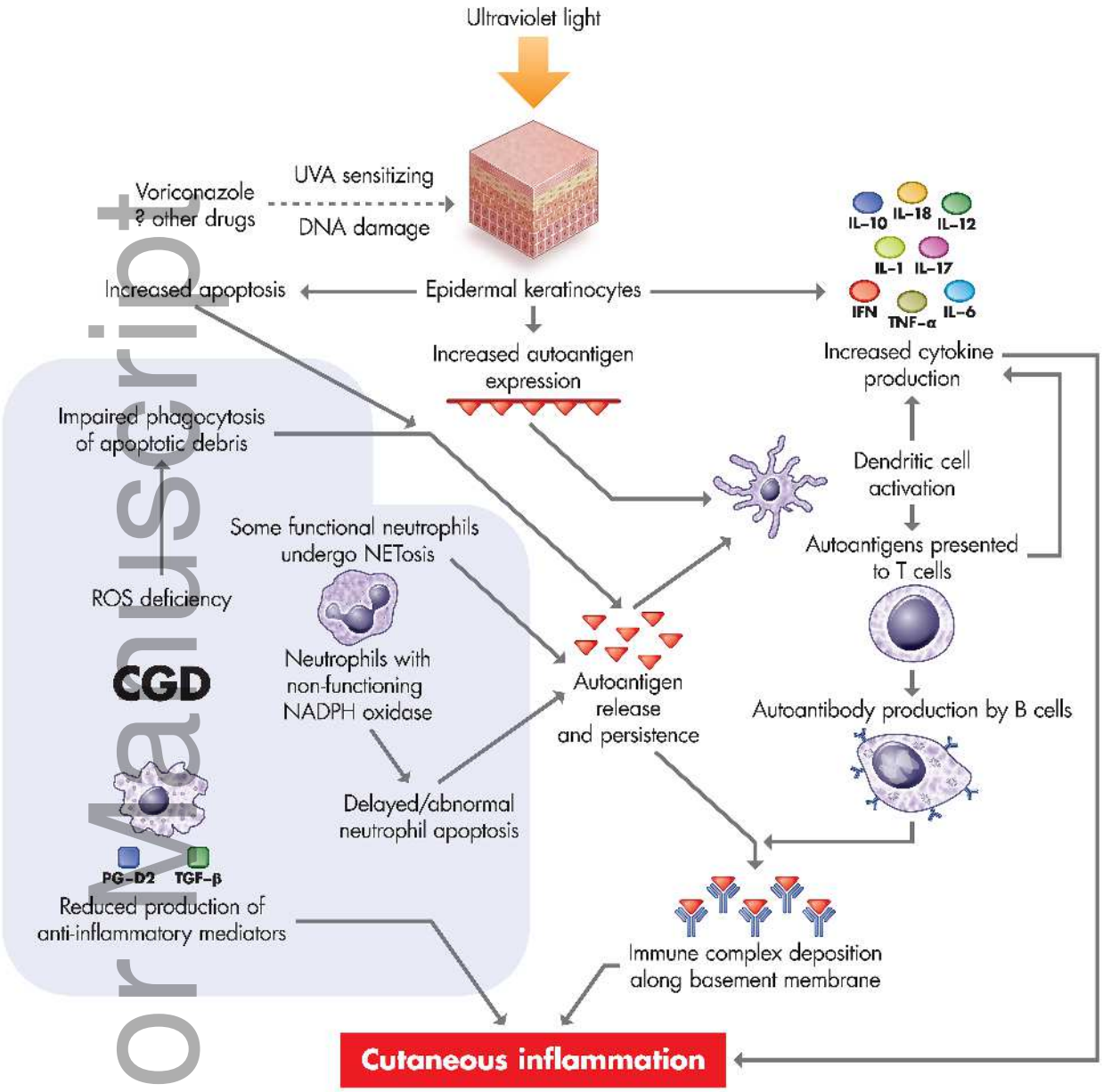

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