Paradoxes in dermatology

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ABSTRACT

Many paradoxical phenomena related to clinical, immunological, and therapeutic dermatology have been described. While some of them can be explained logically, the cause for others can only be speculated. Whenever encountered in clinical practice, background knowledge of such paradoxes may be useful to the clinician.

Key words: Granuloma paradox, paraben paradox, paradoxical hypertrichosis

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Diagnosing dermatological conditions has always been intriguing. Many unrelated conditions present with apparently similar morphology that often prove challenging to the untrained eyes. Furthermore, the existence of several complicated synonyms for apparently ordinary conditions do not help matters either. To add to this, several paradoxes and misnomers related to clinical, immunological, and therapeutic dermatology have also been described. A basic knowledge of such paradoxes, in addition to the usual, may be helpful when such situations are encountered in clinical practice.

A "paradox" is defined as a "*seemingly absurd or contradictory statement or proposition which when investigated may prove to be well founded or true.*"[1] In contrast, a "misnomer" is a completely inaccurate statement or assertion. There are some well-known paradoxes in dermatology, some of which can be explained logically or based on evidence, while for some, only assumptions or postulates are put forth. Furthermore, some of these paradoxes are yet to be ascertained any explanations. Following are some of such paradoxes in dermatology compiled under clinical, immunological, dermatopathological, and therapeutic categories.

PARADOXES IN CLINICAL DERMATOLOGY

Contact allergy

Paraben paradox

The "paraben paradox" is a well-known phenomenon in allergic contact dermatitis. Parabens are esters of *p*-hydroxybenzoic acid. Methyl, ethyl, propyl, and butyl *p*-hydroxybenzoates are most commonly used in medications, cosmetics, paste bandages, ultrasound gels, dentifrices, suppositories, and foodstuffs. The term "paraben paradox" was first coined by Fisher in 1973.[2] He described two paradoxical phenomena related to paraben:

- Paraben containing toiletries that are common causes of contact allergy often produce false negative results when patch tested on the back.
- Many individuals who are allergic (patch test positive) to parabens can continue using cosmetics containing them on normal skin without developing any dermatitis, but react to such topical medications when applied over compromised skin (e.g., venous ulcer).

Fisher attributed these phenomena to the insufficiently low concentration of parabens in such cosmetic preparations that fail to produce contact allergy on normal skin and the fact that patch testing is also carried over normal skin. Cashman, *et al*.,[3] in 2005, proposed the "esterase" and "microbial metabolite" hypotheses to explain the paraben paradox observed by Fisher.

- The esterases present in subcutaneous tissue hydrolyze the long chain parabens (butylparaben) that are least reactive, while the highly reactive short chain parabens (methyl and propylparaben) are metabolized by the esterases in epidermis. A compromised epidermis is therefore associated with altered metabolism and/or increased penetration of such short chain

highly reactive parabens into the subcutaneous tissue and consequent allergic reaction.

- According to the microbial metabolite hypothesis, repeated application of paraben containing topical preparations leads to selective proliferation of paraben-resistant microbial strains. These organisms hydrolyze parabens to hydroxybenzoic acid, which induce or accentuate sensitization.[3]

Lanolin paradox

Similar to paraben paradox, the "lanolin paradox" was described by Wolff in 1996.[4] Lanolin is a natural product obtained from sheep fleece that contains complex mixture of esters and polyesters of high molecular weight alcohols and fatty acids. Lanolin is mostly used in topical medications, emollients, and cosmetics. Lanolin-sensitive patients often are patch test negative to pure lanolin, which may be due to a low concentration of allergens and also the fact that when used "as is," pure lanolin is a weak sensitizer.[5,6]

Nail lacquers

Contact allergy to nail lacquers is quite frequent and mostly attributed to the resins included in the products intended to improve the gloss and adhesion of the lacquer film. Tosylamide/formaldehyde resins are most commonly used in laquers.[7] Allergic contact dermatitis to these resins may occur on any part that are accessible to the nails (commonly the eyelids, face, neck, and occasionally the thighs and genitalia) and paradoxically in many, no signs of dermatitis are seen at the periungal area.[8,9]

Nickel Allergy

Among the metals causing contact allergy, nickel is by far the most frequently encountered one, with sensitivity being more common in women than men. The commonest mode of primary nickel sensitization is by prolonged and direct skin contact with corroded nickel-releasing objects. Oral exposure to nickel was also shown to exacerbate the cutaneous dermatitis, and such patients were benefited after reduction of dietary nickel.[10] However, in some nickel insensitive individuals, oral exposure (e.g., drinking water, dental braces) may induce tolerance.[11,12] Reduced incidence of cutaneous eruption/exacerbation following low nickel diets in previously sensitized individuals has been reported.[13] Studies have also shown localized oral as well as cutaneous exacerbation with orthodontic implants in previously sensitized individuals.[14] On the other hand, lower incidence of oral contact reactions following dental brace implants in nickel-sensitive patients has also been described.[15] These phenomena of tolerance induction and reduced severity of the disease are attributed to selective induction of a suppressor T-cell mediated immunological tolerance or suppression of hypersensitivity following oral nickel exposure.[12]

Pigmentary derangements

Vitamin B12 deficiency

Mucocutaneous features of vitamin B12 deficiency include glossitis, angular chelitis, cutaneous hyperpigmentation, and hair depigmentation. Hyperpigmentation may be diffuse or mottled with predilection for dorsa of hands, palmar creases, knuckles, and flexures. The cause for hyperpigmentation is attributed to decreased levels of reduced glutathione that normally has an inhibitory effect on tyrosinase. Consequently, decreased reduced glutathione is associated with increased tyrosinase activity and melanin synthesis. Histopathology reveals increased number or melanocytes in the basal layer with melanin incontinence into the dermis. Associated hair depigmentation, which may be diffuse or localized, is considered to be a paradox, and Niiyama *et al*., proposed that the pigmentary incontinence in hair follicles might lead to cavities with resultant depigmentation as opposed to the skin where hyperpigmentation results.[16,17]

Chronic renal failure

Patients with chronic renal failure (CRF) and/or those on dialysis exhibit a variety of cutaneous pigmentary changes. Pallor of the skin attributed to decreased hematopoiesis and increased hemolysis is the earliest and commonest finding.[18] Hyperpigmentation, especially over the sun exposed areas, as a result of altered renal metabolism of β-melanocyte-stimulating hormone and yellowish discoloration due to retention of carotenoids and urochromes in the dermis are other cutaneous pigmentary changes associated with CRF and dialysis.[19] Hypopigmentation of the skin and hair has been described as a paradoxical phenomenon and has been attributed to altered phenylalnine metabolism generating tyrosinase-inhibiting metabolites.[20-22]

Exogenous ochronosis

Exogenous ochronosis is almost exclusively described in blacks, especially in African women. Although hydroquinone containing medications are widely used in the USA, the condition is very uncommon there. This paradoxical sparing of white skin is possibly due to the absence of factors seen in blacks such as a higher enzyme activity associated with melanin synthesis and intense ultraviolet (UV) exposure.[23]

Leucoderma in melanoma

Vitiligo-like leucoderma in melanoma is a well known, yet infrequent phenomenon and is especially seen in patients on immunotherapy.[24] Although vitiligo-like lesions are associated with an advanced stage of the disease with metastases, it is paradoxically associated with good prognosis.[25] Development of leucoderma in melanoma may be limited to the lesion, appear as a halo around the lesion, or be widespread and possibly indicates a T-cell mediated immunological response[26] that targets antigens present both on melanoma cells and on

normal melanocytes as well (e.g., MART-1, tyrosinase, gp100, tyrosinase-related protein 1 and 2),[27] thus resulting in melanoma regression and vitiligo.

Others

Hypothyroidism

Hair changes in acquired hypothyroidism are predominantly characterized by diffuse thinning and sparseness of body and scalp hair. Loss of lateral one-third of the eyebrows (Hertog's sign) is a characteristic finding as well. In some patients, especially among children, a paradoxical hypertrichosis characterized by growth of coarse terminal hair is seen over the shoulders, back, and outer surface of the lower limbs.[28,29] Although the exact mechanism is unclear, several hypotheses like associated hyperprolactinemia,[30] prolongation of the anagen,[31] and an associated keratinization abnormality[32] have been proposed.

Lichen planus

Itching is a consistent symptom of Lichen planus (LP) and may range from mild to obdurate. Itching is particularly present during the early eruptive stage and in hypertrophic LP. Paradoxically, excoriations are conspicuously absent as the patients rubs rather than scratches to gain relief and, hence, the pathognomonic lesional morphology and Wickham's striae all are well preserved.[33,34]

Bleeding diathesis in myeloproliferative disorders

The myeloproliferative disorders[35] including essential thrombocythemia, polycythemia vera, and primary myelofibrosis are associated with an abnormally increased platelet count that clinically manifests commonly with thrombotic episodes affecting various organs. Paradoxically, a bleeding diathesis may also be encountered, especially with higher platelet counts ($>1000 \times 10^9$/L)[36] that may range from ecchymoses or mucosal bleeds to dreadful internal hemorrhage. This is due to an acquired von Willebrand disease (loss of large von Willebrand factor multimers that results in its functional defect) and/or qualitative platelet defects (acquired storage pool disorder).[37]

Familial occurrence of sporadic diseases

Certain genodermatoses that almost exclusively occur sporadically have been unusually described to be occurring in a familial pattern affecting different generations. Several explanations like multifactorial etiology[38] or an autosomal dominant inheritance with variable expressivity[39] have been proposed for such paradoxical occurrence. In 1993, Happle described the concept of paradominant inheritance pattern to explain such observations.[40] Accordingly, individuals heterozygous for a "paradominant trait" transmit the mutated gene through several generations imperceptibly, and the condition manifests clinically only when an additional somatic mutation occurs in the early embryogenesis, which leads to loss of heterozygosity. Few examples for such paradominant traits include Becker's nevus syndrome,[41] Klippel-Trenaunay syndrome,[40,42] large congenital melanocytic nevi,[43] congenital triangular alopecia,[44] and some vascular malformations.

Melanoma and sun exposure

Sun exposure is undoubtedly a significant risk factor for the development of cutaneous melanoma. However, the incidence or risk of development of melanoma is determined by the type of sun exposure. Intermittent, recreational exposure, and a history of sunburns in childhood are perhaps more important in melanoma causation rather than continuous, occupational exposure without history of sunburn. Paradoxically, continuous exposure has been shown to be beneficial or be protective against melanoma development. Photoadaptation (increased melanization and epidermal thickening) and protective effects of vitamin D are possibly associated with continuous solar exposure that reduces melanoma risk.[45,46] The mortality in melanomas associated with chronic sun exposure is also paradoxically less as compared to those associated with no such exposure.[47]

Neuroblastoma

Although the stage IV-S neuroblastoma[48] is associated with distant metastases, the prognosis, however, is paradoxically favorable. The tumor may remit spontaneously[49] or transform into a benign ganglioneuroma.[50] Based on this biological behavior of the tumor, infants with stage IV-S disease are best observed carefully with minimal intervention. The mortality in these patients has been attributed to the complications secondary to the massive hepatomegaly leading to respiratory distress, and disseminated intravascular coagulation. It is only under these circumstances that an aggressive treatment approach is warranted.[51] Studies have also shown that complete resection of the primary tumor does not alter the overall outcome of the disease.[52]

IMMUNOLOGICAL PARADOXES

Human immunodeficiency virus (HIV) infection and AIDS

Target cell and viral load

The CD4+ T-lymphocytes are the target cells for the HIV. A paradoxical feature of long-term HIV-1 infection is the inverse relationship between the levels of these CD4 T-cells and the viral load in the blood.[53] With advancing depletion in the target CD4+ cells, there is increase in the plasma viral load. This paradox could be explained by increased viral production per infected CD4+ cell in the setting of a weaning (possibly CD8+ mediated) immune surveillance.[54] Also, the tissue macrophages serve as an alternate reservoir in which the HIV replicate even with declining CD4+ cell count.[55]

Hyperimmune conditions in AIDS

Various "AIDS defining" illnesses like oral hairy leukoplakia, giant molluscum contagiosum, bacillary angiomatosis, systemic mycoses, and atypical mycobacterial infections occur when the CD4+ T-cell count falls below 200/μL and are indicative of profound immunodeficiency. However, at this stage, several non-infectious inflammatory hyperimmune dermatoses including eosinophilic folliculitis, intense hypersensitivity to insect bites (manifesting as pruritic papular eruptions), seborrheic dermatitis, and drug hypersensitivity are also encountered.[56] The exact cause of this paradox has not been delineated, but a T-helper-2 (T_H2) immune response that predominates in progressive HIV disease might possibly facilitate the development of such disorders.[57,58]

HIV and human papilloma virus

Patients seropositive for HIV have more extensive and high-risk human papilloma virus (HPV) associated diseases. This is attributed to the progressive decline in the CD4+ T-cells that allow an increased prevalence of HPV-related infections, type-specific persistence, and an increase in HPV-associated malignancies. Although highly active anti-retroviral therapy (HAART) has a positive impact on patients' lives by reconstituting CD4+ T-cell count and decreasing the viral load, paradoxically however, the incidence of HPV-induced diseases has increased rather than decreased since the introduction of HAART.[59-62] This may partly be due to increased exposure to diverse HPV types, particularly high-risk types that persist longer in anogenital regions, to this upgrading immunity. Also, persistent or emergent HPV disease in HIV infection might represent persistent or modulated immune dysregulation after HAART initiation and, hence, may be viewed as a form of immune reconstitution associated disease.[63]

Psoriasis and HIV

Psoriasis, a T-cell mediated dermatosis that responds to T-cell immunosuppressants (e.g., cyclosporine), is seen to exacerbate or occur in severe or recalcitrant forms in HIV infected patients.[64] Furthermore, with advancing immunosuppression and declining CD4+ T-cell counts, psoriasis and psoriatic arthropathy worsen and improve with HAART initiation.[65] This paradoxical exacerbation is possibly due to loss of regulatory T-cells and increased activity of CD8+ T-cells.[66] Opportunistic infections, especially candidiasis and staphylococcal infections, or drugs may also contribute to the flare of psoriasis in HIV infected patients.[64]

Leprosy and HIV

Leprosy in HIV infected patients behaves no differently than in the non-infected individuals. In contrast to tuberculosis, the natural course leprosy is not altered with HIV co-infection. The clinical, immunological, and pathological features are the same even in progressive HIV disease and the granuloma formation, in contrast to tuberculosis, remains well-preserved even with declining T-cell mediated immunity—the so-called "granuloma paradox". This paradox may be due to the differences between the activation state and rates of cell turnover within leprosy and tuberculosis granulomas that differentially affect the susceptibility of the granulomas to HIV.[67-69]

Others

Leprosy and host T-cell immunity

After acquiring the infection, the pathogenesis of leprosy and the consequent clinical manifestations are largely determined by the extent of host T-cell mediated immunity mounted against *Mycobacterium leprae*. In children, the indeterminate, tuberculoid, and bordeline tuberculoid forms predominate and, paradoxically, multibacillary disease is rare even in those with poor cell-mediated immunity.[70]

Phenomenon of compartmentalization

Compartmentalization of inflammatory cells in the peripheral tissues is one of the proposed mechanisms for peripheral anergy seen in some immune-mediated disorders. In the following instances, although an intense immunological activity occurs in the involved tissues, there is however, a global reduction in immune response to antigens (anergy) or peripheral immune-cytopenia.

1. Sarcoidosis

Sarcoidosis is a multisystem disorder in which involved organs and tissues exhibit a common pathological change, the non-caseating granuloma, mediated by CD4 + helper T-cells of the T_H1 subtype. On the one hand, affected organs express intense immune response, while, on the other, there is a globally decreased delayed type hypersensitivity to common antigens (anergy). This paradox is particularly evident during the active phase of the disease. Compartmentalization of monocytes and T-lymphocytes in the peripheral tissues is one of the proposed mechanisms for peripheral lymphopenia and anergy.[71] A recent study showed that, in sarcoidosis, there is an expansion of regulatory T-cells (CD4+, $CD25^{bright}$) that suppress naïve T-cell proliferation, leading to anergy, but are unable to completely suppress tumor necrosis factor alfa (TNF-α), which is principally involved in the disease pathogenesis.[72]

2. Psoriasis

In similarity with the phenomenon of compartmentalization in sarcoidosis, psoriasis is characterized by reduced levels of circulating natural killer (NK) cells[73] as they are dedicated to in the pathogenesis of the disease, which is evidenced by increased levels of *perforin* (cytolytic product of the NK cells) in the epidermis of psoriatic plaques.[74] A similar phenomenon is also seen in other autoimmune diseases like rheumatoid arthritis.[73]

Androgens and hair growth

Hair growth in human beings is influenced by the circulating androgen levels. However, this influence is not uniform for all the hairs. At puberty, the beard and other secondary sexual hairs grow, the scalp hair is gradually lost, while the eyebrows and eyelashes remain unchanged.[75] This paradoxical effect of androgen at different hair bearing sites is attributed to the differential response of the follicular dermal papillae to androgen stimulation in these sites.[76] In response to androgen stimulation, the dermal papillae in the beard area secrete various autocrine growth factors, including the insulin-like growth factor 1 (IGF1), which has a stimulatory effect on the follicles.[77] On the scalp, however, these papillae secrete transformation growth factor beta1 (TGF-β1) that has an inhibitory effect on the hair follicles. This TGF-β1 mediated activity is maximum in the anterior aspect of the scalp, especially so, over the temples and hence, the development of "patterned" hair loss.[78]

Immune dysregulation in ataxia telangiectasia

Ataxia telangiectasia (AT) is a rare autosomal recessive disorder due to mutations in *ATM* (ataxia telangiectasia mutated) gene that encodes a phosphatidyl kinase involved in cell cycle control and DNA repair. AT is characterized by progressive neurodegeneration, oculocutaneous telangiectasia, variable immunodeficiency, and a high predisposition for lymphoreticular malignancies. Most common immunodeficiency profile, especially in those with complete absence of *ATM* gene activity, is that of IgA deficiency (especially IgA2) and lymphopenia (both T and B cells, except NK cells). Paradoxically, IgM, IgA, and IgG can be elevated in some patients, including monoclonal gammopathy in more than 10% of cases. The *ATM* gene also plays a role in immunoglobulin class switch recombination (Ig-CSR), which may be the cause for elevation of IgM. Concurrent infections may be also be related to such elevations.[79,80]

Psoriasis and pregnancy

Being a T-cell (T_H1) mediated disorder, psoriasis in general, has been shown to improve during pregnancy, which is associated with a shift of T_H1 to T_H2 cytokine profile.[81] This shift is attributed to elevated estrogen[82] and progesterone[81,83] individually (as both are known to have immunosuppressive functions) and to the altered estrogen progesterone ratio[84] in general as well. Paradoxically, some pregnancies are associated either with no change or even worsening of the disease, which has been postulated to be due to the achievement of lower levels of elevation in estrogen relative to progesterone as compared to those pregnancies in which psoriasis improves.[82] Also, impetigo herpetiformis, a type of pustular psoriasis is induced by pregnancy.

Lupus anticoagulant

Antiphospholipid syndrome (APS) is defined as per the international consensus statement preliminary criteria for antiphospholipid antibody syndrome.[36,85] The syndrome is mainly characterized by thrombotic events, recurrent pregnancy loss, and thrombocytopenia that are associated with antiphospholipid antibodies in the serum including anti-cardiolipin, anti-β2-glycoprotein I (β_2GPI) antibodies, and lupus anticoagulant (LA). Several mechanisms have been proposed for the development of thrombosis such as promotion of coagulation reactions, interference with anticoagulant or fibrinolytic pathways, and platelet activation.[36] The current consensus on the mechanism leading to the development of thrombosis in APS is the one mediated by anti-β_2GPI antibodies. Binding of anti-β_2GPI antibodies leads to the disruption of a crystal shield of *annexin V* that covers the platelet membrane and normally prevents binding of procoagulant molecules to its surface.[36,86] The LA however is associated with thrombosis *in vivo,* whereas, *in vitro*, is seen to prolong the coagulation tests that are employed to detect it and hence its name. The exact mechanism of this paradox as to how an "anticoagulant" promotes thrombosis *in vivo* remains to be clearly elucidated.[87]

PARADOXES IN DERMATOPATHOLOGY

Clinical-pathological disparities

Pauci-inflammatory photodermatitis

Polymorphic light eruption (PLE) is most common among the idiopathic photodermatoses. It is common in the first decades of life with females being more affected than males. As the name suggests, PLE manifests in different morphological patterns (papular, papulovsicular, erythematous, eczematous, or plaque like).[88] Prominent histopathological features include epidermal spongiosis and exocytosis with perivascular lymphoid infiltrate that is milder in early lesions and moderate-to-intense in late lesions. Mural and endothelial edema is also noted in the dermal vessels.[89] In some cases, clinically obvious lesions are discordantly associated with no or minimal histopathological changes. Such paradoxical photosensitive lesions are described under pauci-inflammatory photodermatitis.[90]

Sebaceous glands in aging skin

In the elderly, in spite of decreased output from sebaceous glands, which is attributed to decreased adrenal and gonadal androgen synthesis,[91] their sizehowever, is increased owing to decreased cell turnover.

Clinical course/picture versus histopathology

Certain conditions exhibit considerable discrepancy between their clinical behavior and histological features. A seemingly benign histological profile of a condition may be associated with a paradoxically aggressive clinical behavior or significant morbidity and vice-versa. Following are examples of such conditions:

Infantile fibromatosis

Infantile fibromatosis is one of the locally recurring fibromatoses that is histologically characterized by homogenous proliferation of bundles of spindle shaped cells with bland nuclei, indicating entirely banal nature of the lesion. The clinical behavior is however that of a rapidly growing tumor with potential to reach significant size and entrap vascular, neural, and articular structures, leading to morbidity. They are also persistent and promptly recur following excision. However, unlike fibrosarcoma, the lesions do not metastasize. Similarly, nodular fasciitis, a reactive myofibroblastic proliferation shows completely benign histopathological features, but paradoxically, it is a more rapidly growing lesion than any other potentially more aggressive process.[92]

Myofibromatosis

Myofibromatosis is characterized by multiple lesions affecting the subcutaneous tissue as well as the viscera that may be associated with a poor prognosis, not because of its clinical and pathological behavior (which is totally benign), but due to its sheer numbers in vital organs that compromise their function with possible fatality.[92]

Lymphomatoid papulosis

Lymphomatoid papulosis (LyP) is a condition characterized by a benign clinical picture, but, histopathologically shows features of cutaneous (CD30+) lymphoma. LyP is characterized by papules papulonecrotic or papulonodular lesions, affecting predominantly the upper trunk and proximal limbs of adult females, which are otherwise innocuous. The characteristic feature of Lyp is the occurrence of the lesions in recurrent crops that typically evolve rapidly within a few days and resolve spontaneously over few weeks to months, leaving behind atrophic scarring in many. Such crops recur every few months without any obvious inciting factors. Histopathologically, LyP is characterized by the presence of atypical lymphocytes with large nuclei and abnormal mitoses. Based on the predominant population of the cells, LyP is grouped into type A (Hodgkin's lymphoma like), type B (mycosis fungoides like), and type C (large anaplastic B cell lymphoma like).[93] Approximately, 5-10% of LyP progress to malignant lymphoma, mostly to mycosis fungoides.

Others

Basal cell carcinoma

Basal cell carcinoma (BCC) is the most common neoplasm occurring in humans. It is a neoplasm arising from the basal cells of the epidermis and also from outer root sheath of pilosebaceous units in a minority. Histopathologically, though numerous mitoses[94] are present, clinically the tumor is very slow growing. This paradox has been attributed to the correspondingly high apoptotic index with low expression of *survivin*, an apoptosis inhibitor in BCCs.[95]

Aging skin

In chronologically aging skin, the elastic fibers gradually lessen, most likely due to enzymatic degradation of elastin.[91] Together with decreased elastin, the skin becomes wrinkled, saggy, and inelastic, due to decreased collagen synthesis. Paradoxically, the photo-aged skin shows focally increased elastin owing to UV-induced transcriptional activation of the elastin gene[96] and lysozyme-induced reduction in leukocyte elastase activity.[97] Together with heliodermatitis,[91] photo-aged skin appears thick, dry, rough, deeply wrinkled, and inelastic owing to the disarrangement of collagen and elastic fibers.[98]

PARADOXES IN DERMATOLOGICAL THERAPY

Paradoxical induction/exacerbation of dermatoses

Antihistamine-induced urticaria

Antihistamines are the first-line treatment for urticaria, which are generally quite safe, allowing long-term administration. Paradoxically, antihistamine-induced urticaria, which, although uncommon, has been encountered, leading to confusion in the clinical setting. Lee, *et al*., reviewed 16 reports on antihistamine-induced urticaria that showed cetirizine being the most commonly reported culprit. The exact mechanism of this paradox is not clear. Type I and IV hypersensitivity reactions to antihistamines, non-immune mast cell activation-degranulation, and intolerance to antihistamines have been speculated.[99]

Anti-TNF-α biological induced psoriasis

The anti-TNF-α biologicals are being used to treat many inflammatory and autoimmune dermatoses. They (infliximab and etanercept) are especially used for recalcitrant extensive plaque psoriasis, generalized pustular psoriasis, and psoriatic arthritis. Cutaneous adverse effects of these agents include lichenoid, eczematous, urticarial, and other forms of lesions.[100] One of the perplexing side effects of these agents is the induction and/or exacerbation of psoriasis itself. There are many published reports of such anti-TNF biological induced (new-onset psoriasis in absence of past or family history) as well as exacerbated psoriasis (plaque and pustular types).[100-103] The exact pathophysiology of this paradox is unclear and, moreover, such psoriatic lesions are identical both clinically and histologically to idiopathic psoriasis. Unhindered interferon-α (IFN-α) release by plasmacytoid dendritic cells (PDC) in the background of TNF-α inhibition is one of the proposed mechanisms. Increased IFN-α also induces expression of CXCR-3 chemokine receptor on T-cells that facilitates their homing to the skin, which is also considered to be a mechanism of psoriasis induction or exacerbation in patients receiving anti-TNF-α biologicals.[104,105]

Anti-TNF-α biological-induced vasculitis

Infliximab has been used in the treatment of refractory

systemic vasculitis with great benefits.[106] However, anti-TNF-α biologicals have been paradoxically reported to induce vasculitis in patients with rheumatic diseases. In a recent study, cutaneous as well as systemic (renal vasculitis and peripheral neuropathy) vasculitis developed in equal number of patients treated with anti-TNF-α agents for rheumatoid arthritis and inflammatory bowel disease. As these diseases themselves may be associated with cutaneous vasculitis, the authors laid down criteria so as to attribute the development of vasculitis to the anti-TNF-α agents administered.[107] Although the exact cause of such vasculitis is unclear, development of auto-antibodies against these anti-TNF-α agents with subsequent immune complex deposition and inflammation is one of the proposed mechanisms.[108,109] Another hypothesis is the increased IFN-α (see above) mediated induction of autoimmune diseases like lupus erythematosus dermatomyositis including vasculitis.[110]

Anti-TNF-α agent-induced sarcoidosis

Similar to vasculitis, the anti-TNF-α agents are useful in refractory sarcoidosis and here as well, these agents may paradoxically induce sarcoid-like granulomas (cutaneous and pulmonary). The mechanism of such granuloma development has again been attributed to increased IFN-α, which mediates granuloma formation to the antigenic stimuli, possibly *M. tuberculosis* (pulmonary) and *P. acnes* (cutaneous).[111]

Isotretinoin and acne fulminans

Acne fulminans is a severe form of acne with systemic features, that may occur in some predisposed individuals as a hypersensitivity reaction to *P. acnes*.[112] The treatment of choice is a sequential therapy beginning with systemic corticosteroids to combat the early crisis followed by addition of low-dose oral isotretinoin for 3-4 months with the steroids being tapered off gradually. However, isotretinoin must be used with caution, as paradoxical induction/exacerbation of acne fulminans has been reported.[113-115]

Topical calcineurin inhibitors (TCIs)-induced rosacea

TheTCIs like tacrolimus and pimecrolimus are relatively newer topical treatment modalities used for the treatment of rosacea[116] and have been found to be both effective and safe. However, reports of rosaceiform dermatitis following long-term usage of these agents have also been documented. Topical immunosuppressive effects of the TCIs leading to overgrowth of *Demodex* mites in skin together with their inherent vasoactive properties possibly act synergistically leading to "iatrogenic rosacea."[117-119]

D-penicillamine-induced pseudoscleroderma

D-penicillamine is used as an antifibrotic agent in treatment of systemic sclerosis, as it is a known lathyrogen that acts by interfering with cross-linking of collagen. It is generally recommended in early disease with progressive skin changes, pulmonary compromise, or renal disease.[120] Paradoxically, morphea-like cutaneous lesions (pseudoscleroderma) have been reported in patients receiving D-penicillamine for other indications.[121,122]

Paradoxical antagonistic effects

H1-antihistamine-induced seizures

The H1-antihistamines are widely used for various pruritic conditions. These are traditionally grouped into first generation and second generation H1-antihistamines, based on their ability to produce sedation. The first generation H1-antihistamines cross the blood–brain barrier and hence, are sedative. In infants and children, these "sedative" first generation H1-antihistamines may paradoxically precipitate seizures, especially in known epileptics or cases of febrile convulsions.[123] In infants and children, the histaminergic system is probably a more important inhibitory system in the central nervous system than the γ-aminobutarate (GABA-nergic) system with regard to convulsions. Hence, the first generation H1-antihistamines may reduce the threshold for seizure precipitation by blocking the histamine activity.[124]

Q-switched laser-induced tattoo darkening

The Q-switched lasers are currently the lasers of choice for the treatment of tattoos. Although post-treatment hyperpigmentation is not infrequently encountered, it is generally transient. Paradoxical darkening of the tattoos, especially the red, white, or flesh-toned ones occur occasionally and the patients must be informed beforehand about this. These tattoo pigments often contain ferric oxide (rust-brown color) and titanium dioxide (white color). Following laser treatment, these pigments get reduced to ferrous oxide (black color) and blue-colored titanium dioxide respectively, resulting in immediate post-treatment darkening of such tattoos.[125]

Intense pulsed light (IPL)-induced hypertrichosis

Unwanted hair removal with lasers and IPL is becoming widely popular as it is both effective and safe. Choosing an appropriate treatment modality (laser or IPL), appropriate wavelength, and appropriate pulse width and fluence to deliver the wavelength at, are all imperative for optimal treatment outcome, as paradoxical hypertrichosis has been observed after laser treatment, especially in dark-skinned individuals. This occurrence has been attributed to the suboptimal fluences that possibly stimulate the follicles.[126]

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