Guest Editorial

Negative Evidence: Cutaneous Manifestations Associated with COVID-19 mRNA Vaccination

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Introduction

This article is part of an editorial series that addresses variety of vigorously debated issues in current medical, scientific, and political discourses.[1-16] These editorials utilize the **negative evidence method**, which involves critically examining the available information for unexpected gaps or inconsistencies. By asking why certain relevant data or viewpoints are absent, an objective investigator can gain deeper insight into the construction of misleading arguments produced to manipulate public opinions. The main goal is to encourage a more thorough analysis of complex topics, empowering readers to question official narratives and recognize biases contained in them.

This editorial focuses on the neglected dermatological side effects of the novel mRNA COVID-19 vaccine. Concerns about cutaneous manifestations have drawn much less attention from the public, regulatory agencies, and medical researchers than other more striking vaccine-related problems. While the significance of skin disorders remains obscure to most laymen, the neglect by regulators and medical experts was unexpected because they should know that skin disorders can cause much more serious problems than mere cosmetic issues.

Skin, in addition to being a barrier, plays numerous vital physiological roles as a part of the recently discovered **cutaneous-immuno-neuro-endocrine (CINE)** system.[17] Since skin is an immunological organ, studying those adverse effects could also provide valuable insights into the general immune mechanisms triggered by the mRNA vaccine. Counterintuitively, very little research has been done to address those issues. Only modest attempts were made to close the knowledge gaps through systematic reviews, registry analyses, clinical trials, and basic research.[18-32] Moreover those efforts were motivated by the desire to "decrease vaccine hesitancy," rather than to search for objective truth.[30] Thus, the true burden of cutaneous adverse reaction to mRNA vaccination remains undetermined.

The officially reported pooled prevalence of cutaneous adverse reactions to mRNA vaccination is approximately 6.9% (95% CI, 3.8%-12.3%).[33] That abstract number relates to "population" and does not reflect the clinical severity of cutaneous complications experienced by the individual patient. Even medical officialdom has reluctantly confirmed that mRNA vaccines are associated with greater risk of all adverse events than any other vaccine platforms.[34]

A thorough understanding of the significance of mRNA vaccine-induced disorders of the integumentary system requires at least basic knowledge of its functions and dysfunctions. Unfortunately, the physiology and pathology of human skin are often misunderstood by the general public and even by part of the medical community.

Significance of the Integumentary System

Laymen generally perceive skin function as limited to an "inert external wrapping of the body." They view skin disorders through the lenses of esthetics and common misconceptions: considering them to be mild, self-limiting "nuisances" resulting from "infections," "allergies," or "poor hygiene." Those misperceptions linger until they are affected by severe dermatological illness.

Physicians practicing outside of dermatology understand that skin and its appendages (hair, nails, sebaceous and sweat glands) are a part of the "integumentary system" that constitutes more than a mere passive barrier. Yet they may not fully grasp all its complex physiological roles and the serious impact of dysfunctions caused by dermatological disorders.

In fact, the integumentary system is the body's largest and most dynamic super-organ.[17] Skin is a crucial part of the CINE system: a sophisticated biological interface that keeps both local and systemic metabolic balance in response to environmental stressors.[17,35] Skin serves as a physical barrier, facilitates immune surveillance, thermoregulation, and chemical homeostasis. It enables sensory perception and carries out endocrine functions. Finally, skin can provide valuable diagnostic clues for numerous systemic diseases.[36-38]

Barrier Functions

Structurally, the skin is composed of three primary layers: the epidermis, the dermis and hypodermis. Each of them contributes to its defensive capabilities (see **Figure 1**).

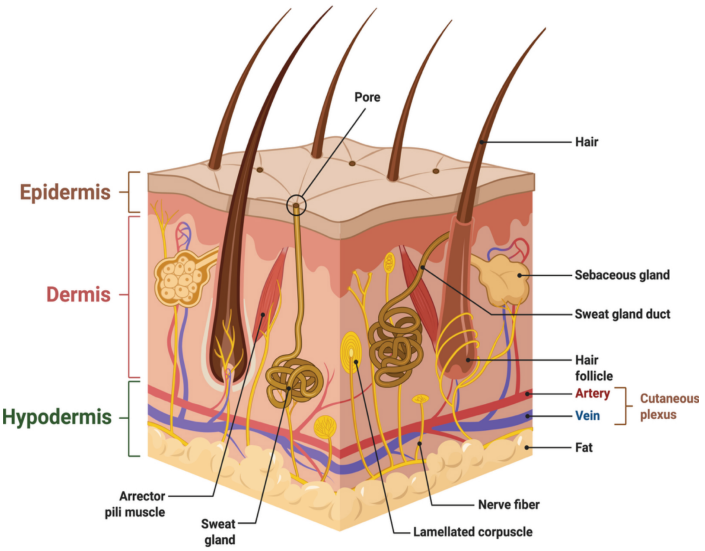

Figure 1. Detailed anatomy of the skin

The epidermis, the outermost stratified squamous epithelium, serves as the primary physical shield.[39] Central to this function are keratinocytes, which produce keratin, a fibrous protein that provides structural integrity and waterproofing. This layer effectively impedes the ingress of environmental toxins, particulate matter, and microbial pathogens, while simultaneously preventing the catastrophic loss of essential bodily fluids.[39] Beneath this lies **the dermis**, a thick layer of connective tissue rich in collagen and elastin fibers, which confers tensile strength and elasticity to the skin. This layer houses a complex network of blood vessels, nerve endings, and adnexal structures such as sweat and sebaceous glands.[39] The deepest layer, **the hypodermis** or subcutaneous tissue, is composed of loose connective tissue and adipose depots, functioning as a shock absorber, a thermal insulator, and a significant energy reservoir for the body.[39]

Table 1. Components and Physiological Functions of Three Layers of Skin

Layer	Primary Components	Key Physiological Functions
Epidermis	keratinocytes, melanocytes, Langerhans cells	Physical barrier, UV protection, vitamin D synthesis, innate immunity (antimicrobial peptides).
Dermis	fibroblasts, collagen, elastin, nerve endings, vasculature	Tensile strength, thermoregulation, sensory perception, adaptive immunity (SALT).
Hypodermis	adipocytes, connective tissue	Energy storage, insulation, cushioning of underlying organs.

Immunological Surveillance and Defense

Skin, in addition to serving as physical shield, serves the forward operating base of the immune system. The **skin-associated lymphoid tissue (SALT)**[39-41] contains strategically localized immune cell populations including keratinocytes, Langerhans cells, dermal dendritic cells, T cells, macrophages, and natural killer cells that provide continuous immunosurveillance. These components interact constantly to maintain the balance between immune tolerance and immune activation in response to environmental pathogens and stressors.

Our understanding of the complexity of SALT is expanding with new research. It is not a static anatomical structure but a dynamic system that constantly transforms in response to local immune stimuli.[42] Its most critical functional component is a lymphoid structure that forms during inflammatory responses: **inducible SALT (iSALT)**.[42] This consists of aggregations of dendritic cells, M2 macrophages, and high-endothelial postcapillary venules enabling efficient T-cell activation in situ.[42,43] Furthermore, this formation involves perivascular macrophages activated by IL-1α from keratinocytes, which then attract dendritic cells through CXCL2 signaling to facilitate memory T-cell activation.[42] Therefore, amazingly, SALT can enable local immune responses independent of lymph nodes.

In addition to those cellular mechanisms, skin produces a diverse array of humoral defenses, including antimicrobial peptides and cytokines, maintaining a delicate balance between tolerance of commensal skin microbiota and defense against pathogenic microbial invasion.[40]

This advanced immunological competence of skin is particularly relevant in the context of vaccination. Skin is either the site of administration of vaccines or is located close to it (as in case of mRNA vaccine). Therefore, skin serves as an initial point of interaction between the vaccine immunogen and the host immune system. Hence, it is surprising that to date so little basic research has focused on the potential changes within SALT occurring in response to novel mRNA vaccine.

Thermoregulation

The skin plays a pivotal role in maintaining the body's core temperature within the narrow physiological range required for enzymatic activity. This is achieved through the dynamic regulation of blood flow in the dermal vascular bed and the activity of sweat glands.[44,45] In response to heat, dermal vessels dilate to dissipate thermal energy, and sweat glands secrete fluids that cool the body through evaporation. Conversely, in cold environments, vasoconstriction and decreased sweating conserves heat.

Chemical Homeostasis

The skin contributes to systemic chemical homeostasis via metabolic waste excretion through eccrine sweat glands, which secrete urea, electrolytes (sodium, chloride, potassium), and other metabolites such as lactate and ammonia.[46-48] This represents only a minor pathway compared to renal excretion in patients with healthy kidneys. However, a phenomenon of kidney-skin crosstalk has been described to denote the existence of an integrated system for water and sodium homeostasis, with compensatory responses when either of those two organs is compromised.[49] Indeed, in case of renal failure the skin's capacity for excretion increases significantly. Dialysis patients show seasonal variation in blood urea levels, with lower values during summer months (mean difference 16 mg/dL), attributed to increased perspiration-mediated urea elimination.[50] While diaphoresis therapy using saunas or hot baths can substantially increase cutaneous losses of water, urea, and electrolytes, it is insufficient to fully replace dialysis. Yet it may supplement treatment in resource-limited settings.[51]

Sensory Perception

The skin is a vast depository of various neuro-receptors (see **Figure 2**). It serves as a sophisticated sensory organ that detects mechanical, thermal, chemical, vibrational, and nociceptive stimuli through a complex network of specialized nerve fibers, mechanoreceptors, and epidermal cells themselves that actively participate in sensory transduction.[52,53] This array of highly sensitive specialized sensors is essential to the body's intricate perception bio-mechanism, the **neuro-immuno-cutaneous (NIC) system**, which constitutes the pivotal part of the CINE system.[35,54] It can sense environmental dangers and communicate with the central nervous system, prompting protective actions and physiological responses to environmental challenges.[55,56] That integrated sensory network plays crucial roles in both physiological and pathological processes. The neuro-immuno-cutaneous interactions are central to common skin disorders including psoriasis, atopic dermatitis, chronic itch, and pain syndromes.[54,57] Understanding the factors that can disrupt these interactions is critical while assessing the dermatological side effects of mRNA vaccines.

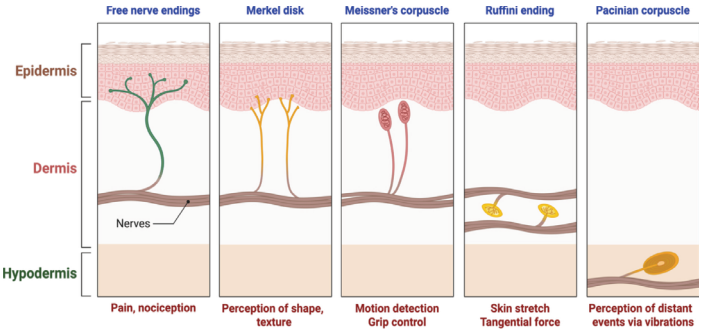

Figure 2. Types of skin neuroreceptors

The Endocrine Role

The skin is a neuroendocrine and steroidogenic organ that produces hormones, neuropeptides, and other signaling molecules that regulate both local cutaneous homeostasis and systemic endocrine functions.[58-60]

Skin makes significant contributions to circulating androgens and estrogens.[60,61] It participates in metabolism of glucocorticosteroids and is the main production site of vitamin D (see below).[58,60,62,63]

Skin expresses CYP11A1, the enzyme that initiates steroidogenesis by converting cholesterol to pregnenolone, enabling local production of glucocorticoids (corticosterone, cortisol), sex hormones (testosterone, dihydrotestosterone, estradiol), and novel secosteroids of as yet unknown function.[60,62] This steroidogenic activity varies by anatomical site and between sexes, with notable elevations in dehydroepiandrosterone in the axilla and androstenedione on the forehead.[61] Cutaneous glucocorticoid production can be regulated by locally produced CRH, ACTH, or cytokines, and is affected by UVB radiation.[62]

Vitamin D is a group of structurally related compounds. In humans, the most important forms of vitamin D are vitamin D_3 (cholecalciferol) and vitamin D_2 (ergocalciferol). Vitamin D is traditionally grouped with vitamins but should be recognized as a steroid (a secosteroid) hormone. The biologically active form 1,25-dihydroxyvitamin D_3 (calcitriol) functions as a true steroid hormone rather than a traditional vitamin.

Skin produces vitamin D_3 following UVB exposure, with subsequent metabolism by CYP11A1, generating several biologically active hydroxyderivatives that undergo further hydroxylation by CYP27B1, CYP27A1, and CYP24A.[58] CYP11A1 also acts on 7-dehydrocholesterol to produce several novel Δ7-steroids and vitamin D-like compounds with shortened side chains.[58]

While the public associates vitamin D primarily with bone health and calcium homeostasis, dermatological research has elucidated its profound systemic importance. Vitamin D receptors are ubiquitous, present in nearly every tissue including the brain, heart, muscles, and importantly, immune cells.[64] Within the skin itself, vitamin D exerts potent immunomodulatory effects. It regulates the differentiation of keratinocytes and dendritic cells, suppresses excessive T-helper 1 (Th1) and T-helper 17 (Th17) inflammatory responses, and promotes the development of regulatory T cells (Tregs) and the secretion of anti-inflammatory cytokines like interleukin-10.[64] Deficiency of this "sunshine vitamin" during the pandemic (due to lockdowns) has been implicated in the pathogenesis of various autoimmune and dermatological diseases, including psoriasis and atopic dermatitis.[64]

Hypothalamic-pituitary-adrenal axis mediators are expressed locally in skin, including CRH, urocortin, and pro-opiomelanocortin (POMC) with its products (ACTH, α-MSH, and β-endorphin).[59] These mediators are organized into dermal and epidermal regulatory units that allow field-restricted control and communicate with systemic levels through humoral and neural pathways.[59]

Neuropeptides and neurotransmitters produced by skin, which regulate responses to environmental stress,[59,65] include catecholamines, acetylcholine, and various neuropeptides that modulate immune function, pigmentation, and vascular responses.[17,59]

The CINE system, through release of hormones into the circulation and priming of immune cells, affects central neuroendocrine coordinating centers and global immune responses, allowing the body to adapt to environmental changes.[66] ***The potential interference of mRNA vaccine with those crucial functions of the skin may have very serious systemic consequences with grave implication for patient's general health status.***

Integumentary System as "Diagnostic Display"

The integumentary system provides crucial diagnostic clues for systemic diseases, often serving as the first and most accessible indicator of internal pathology.[36-38] The skin frequently manifests signs of systemic illness before other symptoms appear, making careful examination invaluable for early diagnosis.[36-38] The detailed discussion of this topic is beyond the scope of this text and is reviewed elsewhere.[36] However, the most essential aspects will be outlined below because the cutaneous signs in vaccinated patients may indicate not only presence of dermatological side effects of vaccine but may also signal the presence of systemic disorders that the mRNA vaccine could trigger such as vasculitis, malignancies, renal and endocrine disorders, systemic autoimmune syndromes, etc.

Cutaneous signs of systemic disorders include the butterfly rash, which suggests systemic lupus erythematosus, and Gottron's papules and heliotrope rash, which point to dermatomyositis, often appearing before muscular involvement becomes clinically evident.[36,38,67] Palpable purpura indicates leukocytoclastic vasculitis and is an early critical sign in rickettsial diseases like Rocky Mountain spotted fever, which require urgent diagnosis and treatment.[37] Perioral pigmented macules suggest Peutz-Jeghers syndrome, with its associated intestinal polyps.[37]

Cutaneous patterns of metabolic and endocrine disorders, if recognized, enable early intervention in severely debilitating conditions. Examples include hyperpigmentation of areolae and scars, characteristic of Addison disease, and the buffalo hump of Cushing's disease or corticosteroid toxicity.[36,68] Acanthosis nigricans is associated with metabolic syndrome and insulin resistance and can herald polycystic ovary syndrome.[36,68]

Cutaneous paraneoplastic syndromes are associated with internal malignancy that are not due to direct tumor invasion or metastasis. These syndromes can precede cancer invasion, making their recognition critical for early detection of underlying malignancy.[69,70] Acanthosis nigricans in addition to indicating metabolic syndrome may also signal internal malignancy, particularly gastric cancer.[37,71] Gastrointestinal malignancies are also associated with acrokeratosis paraneoplastica (Bazex syndrome), florid cutaneous papillomatosis, necrolytic migratory

erythema (glucagonoma syndrome) and palmoplantar keratoderma.[70] Hematologic malignancies are linked to acquired ichthyosis, exfoliative erythroderma, necrobiotic xanthogranuloma, paraneoplastic pemphigus, pyoderma gangrenosum, scleromyxedema, and Sweet syndrome.[69] Anatomically diverse malignancies can present with Leser-Trélat syndrome, dermatomyositis, erythema gyratum repens, hypertrichosis lanuginosa acquisita, tripe palms, and multicentric reticulohistiocytosis.[69,70]

Nail findings include Mees lines, suggesting arsenic poisoning; Terry nails, indicating liver disease; and half-and-half nails, pointing to point to uremia.[37] Nailfold capillary abnormalities help identify connective tissue diseases.[67]

Acral manifestations such as hand, foot, and nail findings may represent the first sign of undiagnosed malignancy or collagen vascular disease.[72] The pattern and distribution of skin lesions as well as the specific morphologies (annular, pustular, urticarial) can guide diagnosis of inflammatory rheumatic diseases.[67]

The Burden of Dermatological Disease: A Landscape of Morbidity

To contextualize the potential side effects of vaccines, it is imperative to understand the baseline prevalence and impact of dermatological conditions in the general population. Skin diseases are among the most common human afflictions, categorized broadly into non-malignant and malignant disorders.

Common Non-Malignant Skin Disorders

While termed "benign" or "non-malignant," these conditions are often chronic, incurable, and associated with significant physical and psychological burden.

Acne vulgaris is the most prevalent skin condition in the U.S., affecting approximately 50 million individuals annually.[73,74] It is a disease of the pilosebaceous unit involving follicular hyperkeratinization, increased sebum production, colonization by *Cutibacterium acnes*, and inflammation. While often dismissed as a transient adolescent phase, acne frequently persists into adulthood, affecting up to 15% of women in their 30s and 40s.[73] The condition manifests as comedones, papules, pustules, and nodules, which can lead to permanent scarring.

Atopic dermatitis (eczema, AD) is a chronic, relapsing inflammatory skin disease characterized by intense pruritus (itching) and eczematous lesions. It affects nearly 1 in 10 Americans and up to 20% of children.[73,74] The pathogenesis involves a complex interplay of genetic barrier defects (e.g., filaggrin mutations) and immune dysregulation, predominantly driven by Th2 cytokines such as interleukin-4 (IL-4) and interleukin-13 (IL-13).[75] AD is not merely "dry skin"; it is a systemic immune disorder often associated with asthma and allergic rhinitis. Its treatment is very difficult. It causes substantial physical and psychological and even financial burden. The associated pruritus interferes with sleep and rest. Skin lesions get infected, leading to serious complications.[75] Finally, most effective biological treatments are very expensive.

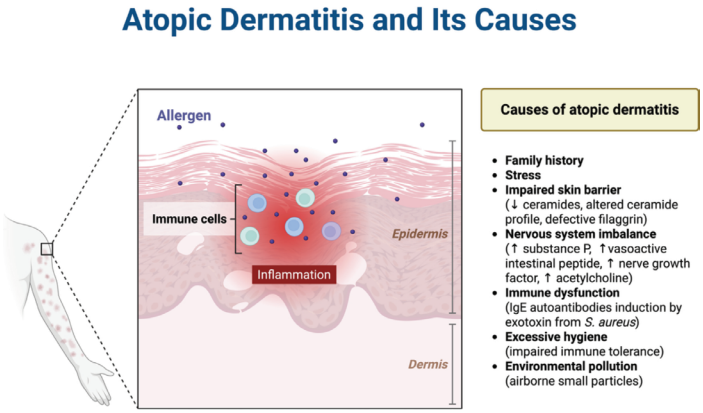

Figure 3. Causes of atopic dermatitis

Psoriasis is a chronic autoimmune disease mediated by the Th1 and Th17 immune pathways, leading to the rapid proliferation of keratinocytes and the formation of well-demarcated, scaly, erythematous plaques.[76] It affects millions globally and is associated with significant systemic comorbidities, including psoriatic arthritis, cardiovascular disease, and metabolic syndrome.[75]

Other common conditions include **rosacea**, a chronic inflammatory condition of the face; **alopecia areata**, an autoimmune form of hair loss; and **vitiligo**, characterized by the autoimmune destruction of melanocytes leading to depigmentation.[75]

Common Malignant Skin Disorders

Skin cancer is the ***most common form of malignancy*** in humans, surpassing all other cancers combined .[77]

Figure 4 summarizes most common types of skin cancer.

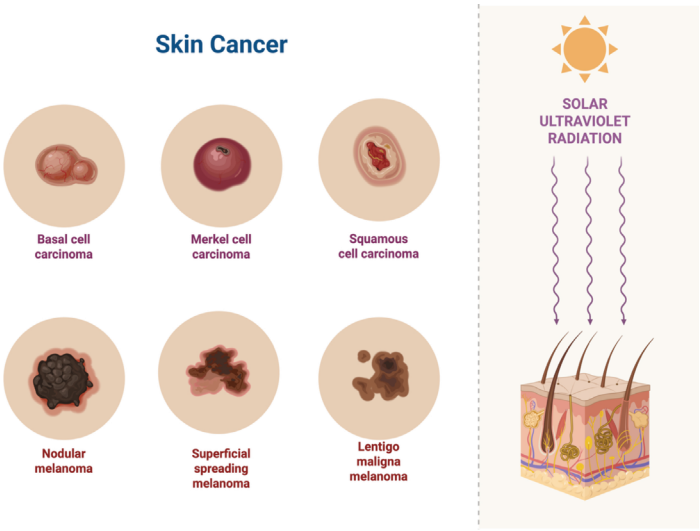

Figure 4. Skin cancer

Non-melanoma skin cancer (NMSC) includes basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). BCC arises from the basal cells of the epidermis and is locally destructive but rarely metastasizes.[78] SCC arises from keratinocytes and possesses a higher potential for metastatic spread if left untreated.[79] Both are primarily caused by cumulative UV radiation exposure.

Melanoma arises from melanocytes and is the most dangerous form of skin cancer. Although less common than NMSC, it accounts for the majority of skin cancer deaths due to its aggressive tendency to metastasize to vital organs such as the brain and liver.[80]

Psychosocial Impact and Secondary Morbidities

While many dermatological conditions are not lethal per se, they are associated with a substantial negative impact on patient quality of life and cause serious secondary morbidities. The skin is the most visible organ of the body; therefore, its pathology is immediately apparent to the self and others, leading to profound psychological consequences.

Studies utilizing the Dermatology Life Quality Index (DLQI) have demonstrated that nearly 95% of patients with chronic skin disorders experience a negative impact on their quality of life.[81] The impairment in QoL for patients with severe psoriasis or acne is comparable to that of patients with other major chronic diseases such as diabetes, heart failure, or epilepsy.[82]

The **"neurocutaneous axis"** describes the biological link between the skin and the brain, where skin disease can trigger mental health issues and vice versa.[83] Psychiatric comorbidities are strikingly common. Depression, anxiety, social phobia, and suicidal ideation are frequently observed in patients with visible dermatoses.[82] Stigmatization is a major driver of this distress. The erroneous public belief that skin lesions are contagious or the result of poor hygiene and sexually transmitted diseases leads to social isolation, shame, and low self-esteem.[82]

Secondary systemic morbidities can also be triggered or exacerbated by chronic skin inflammation, such as with psoriasis.[76] Thus, dermatological side effects, even if not immediately life-threatening, must be evaluated with a nuanced understanding of their potential to disrupt the fragile immune equilibrium.

Historical Perspective: Cutaneous Adverse Events in the Pre-mRNA Vaccine Era

To scientifically evaluate the safety profile of mRNA vaccines, it is essential to establish a baseline using historical data from traditional vaccines. Cutaneous adverse events (CAEs) following vaccination are a known phenomenon in medical history, observed long before the COVID-19 pandemic.

Local reactions include erythema, edema, and pain at the injection site. These are the most frequently reported side effects and are generally attributed to a nonspecific innate inflammatory response to the trauma of injection or the presence of adjuvants (e.g., aluminum salts).[84]

Systemic reactions include generalized rashes, urticaria, and more specific dermatoses, occurring through various immunological mechanisms.[85]

Specific Vaccine-Associated Dermatoses

- **Measles-Mumps-Rubella (MMR)**: Transient morbilliform (measles-like) rashes can occur in approximately 5% of recipients, often due to the replication of the attenuated vaccine virus. Rarely, idiopathic thrombocytopenic purpura (ITP), presenting as petechiae or bruising, has been reported.[86]
- **Tetanus Toxoid**: Arthus reactions (Type III hypersensitivity), characterized by localized vasculitis and necrosis due to immune complex deposition, have been documented, particularly in individuals with high preexisting antibody titers.[87]
- **Smallpox Vaccine**: This live vaccine was historically associated with significant dermatological complications, including eczema vaccinatum (a severe, disseminated viral infection in patients with atopic dermatitis) and generalized vaccinia (a secondary eruption due to blood-borne dissemination of vaccinia virus).[88]
- **Hepatitis B Vaccine**: There are reports linking this vaccine to lichen planus, a T-cell mediated autoimmune condition affecting the skin and mucous membranes, as well as erythema nodosum.[89]

Severe Cutaneous Adverse Reactions (SCARs)

Severe reactions such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) were reported following vaccination.[90] Systematic reviews of traditional vaccines like influenza or MMR have found several case reports; however, definitive causality was often difficult to establish due to confounding factors like concurrent infections or medication use.[90]

This historical context demonstrates that the skin is indeed a frequent site of vaccine-associated adverse events. In the past, before the recognition of the CINE system, these reactions have been dismissed as "transient, non-impactful, and manageable."

The mRNA Vaccine Platform: Theoretical Mechanisms of Dermatological Toxicity

The introduction of mRNA vaccines (Pfizer-BioNTech BNT162b2 and Moderna mRNA-1273) against SARS-CoV-2 represented a major paradigm shift in vaccinology. Unlike traditional vaccines that utilize inactivated viruses or protein subunits, mRNA vaccines deliver a genetic instruction set encoding the Spike (S) protein of SARS-CoV-2.[91] This novel mechanism introduces specific biochemical components and immunological pathways that predispose recipients to a unique spectrum of dermatological side effects.[91] Those known predispositions are outlined below. However, other as-yet-unknown mechanisms may cause various skin disorders that could lead to serious systemic issues. It is so because the details of mRNA vaccine's modus operandi are not fully known and the CINE system remains poorly understood.

Lipid Nanoparticles (LNPs) and PEGylation

The mRNA is fragile and must be encapsulated to enter host cells. This is achieved using lipid nanoparticles (LNPs), which typically consist of four lipid components: ionizable cationic lipids, phospholipids, cholesterol, and polyethylene glycol (PEG)-ylated lipids.[92]

- **Polyethylene Glycol (PEG)**: PEG is used to stabilize the nanoparticle and prevent early clearance. However, PEG is a known allergen. Pre-existing anti-PEG antibodies (IgG or IgM) can theoretically trigger hypersensitivity reactions. A proposed mechanism is **complement activation-related pseudo-allergy (CARPA)**, where anti-PEG antibodies activate the complement cascade, leading to the production of anaphylatoxins (C3a, C5a) and subsequent mast cell degranulation, manifesting as urticaria or anaphylaxis.[93]
- **Adjuvant Activity**: The LNPs themselves are not immunologically inert. They can act as adjuvants, stimulating innate immune sensors (e.g., Toll-like receptors) and creating a localized inflammatory milieu. This is likely the driver of the intense local injection site reactions and "COVID arm" phenomena.[92]

Spike Protein Translation and Molecular Mimicry

Once the mRNA enters the cell, it directs the synthesis of the

SARS-CoV-2 Spike protein. This protein is then presented to the immune system, eliciting a robust response.

- **Molecular Mimicry**: There is a serious concern that amino acid sequences within the Spike protein may share homology with human self-antigens. If the immune system cross-reacts, this "molecular mimicry" could potentially trigger autoimmune dermatoses such as pemphigus, lupus erythematosus, or vasculitis.[94]
- **ACE2 Receptor Interaction**: The Spike protein has a high affinity for the angiotensin-converting enzyme 2 (ACE2) receptor, which is expressed in cutaneous blood vessels. Although the vaccine-produced Spike protein is stabilized, theoretical interactions with ACE2 could contribute to endothelial activation and vascular side effects like chilblains.[93]

Th1 Immunological Polarization

The mRNA vaccines are specifically engineered to elicit a strong T-helper 1 (Th1) adaptive immune response, characterized by the production of cytokines such as Interferon-gamma (IFN-γ), tumor necrosis factor-alpha (TNF-α), and interleukin-2 (IL-2).[95] This has important implication for skin diseases. Many chronic inflammatory skin diseases, including psoriasis and lichen planus, are driven by Th1 and Th17 pathways. Therefore, there is a biologically plausible mechanism by which the robust Th1 polarization induced by the vaccine could exacerbate these pre-existing conditions, leading to flares.[94]

Pharmacovigilance of Dermatological Side Effects

Cutaneous adverse events of mRNA vaccine can be divided into two categories: vaccine-induced de novo dermatoses and vaccine-induced flares of preexisting dermatopathies. Global pharmacovigilance databases, such as the American Academy of Dermatology (AAD) COVID-19 Registry and the International League of Dermatological Societies (ILDS) have provided valuable insights into both types of cutaneous side effects of mRNA vaccines.[96,97] Unfortunately, the concerns that have been elicited by the information from those registries have been arrogantly dismissed by officialdom.[98]

Vaccine-induced De Novo Dermatoses

Table 2 provides the concise summary of dermatoses that can be induced by the mRNA vaccine in patients previously unaffected by skin conditions. The details are discussed below.

Table 2. Comparative Overview of Common De Novo Cutaneous Adverse Events (CAEs)

Reaction Pattern	Onset Time	Primary Mechanism	Clinical Features	Prognosis
Local injection site	< 24 hours	Innate inflammation, trauma	Pain, erythema, swelling	Resolves in 1-3 days
"COVID arm" (DLLR)	7-8 days (dose 1)	T-cell mediated (type IV)	Large erythematous, pruritic plaque	Resolves in 3-5 days; often milder on dose 2
Urticaria	1-3 days	Histamine release (type I/pseudo)	Itchy wheals, hives	Self-limiting; responsive to antihistamines
Chilblains	10-14 days	Type I interferonopathy	Acral swelling (toes/fingers), purple/red	Self-limiting
Filler reaction	Variable	Granulomatous inflammation	Swelling at filler sites	Temporary; treat with steroids/ antihistamines

Injection site reactions can appear immediately or with some delay. Data from clinical trials and real-world registries indicate that up to 88% of recipients experience pain, 20% experience erythema, and roughly 15% experience swelling at the injection site.[99] These typically begin within 24 hours of vaccination and resolve spontaneously within two to three days. They are mediated by the innate immune response to the physical trauma of injection and the immunostimulatory properties of the lipid nanoparticles.[100]

A delayed large local reaction (DLLR) or "COVID arm" is a unique and distinct phenomenon, which has been widely reported, particularly with the Moderna (mRNA-1273) vaccine. This manifests as a large, erythematous, edematous, and often pruritic plaque at the injection site. Unlike immediate reactions, it typically appears seven to eight days after the first dose.[99] Histopathological analysis suggests this is a T-cell-mediated delayed-type hypersensitivity (type IV) reaction to a vaccine component, likely the lipid nanoparticle.[94] The reaction is benign and self-limiting, usually resolving within three to five days. Importantly, it is not a contraindication to the second dose. While the reaction may recur after the second dose, it typically appears more rapidly (within two to three days) but presents with less severity.[100]

Urticaria (hives) and angioedema represent a spectrum of hypersensitivity reactions reported following mRNA vaccination. **Acute urticarial eruptions** are among the most frequently reported cutaneous reactions, often appearing within one to three days post-vaccination.[101] These pruritic wheals can be localized or generalized. While IgE-mediated allergy to PEG is a confirmed mechanism in rare anaphylactic cases, the majority of urticarial reactions are likely non-IgE mediated. Mechanisms such as CARPA (complement activation) or direct mast cell degranulation by LNPs are more probable drivers for the wider population.[93] Many cases are mild, self-limiting, and respond well to oral antihistamines.[91] Acute generalized urticaria secondary to mRNA vaccine may appear to be a mere cosmetic problem. However, if significant skin surface is affected it likely impacts the functions of the CINE system, potentially resulting in serious systemic consequences.

There are emerging reports of new-onset **chronic spontaneous urticaria (CSU)**, defined as wheals lasting longer than 6 weeks, or exacerbations of pre-existing CSU following vaccination.[102] Case series have documented patients developing persistent urticaria shortly after mRNA boosters.[103] Studies suggest that while vaccination can trigger flares in patients with controlled CSU, these flares are generally manageable with standard antihistamine therapy and do not require immunosuppression.[104] This reassurance may, however, be of little value for those patients who for variety of reasons may not tolerate antihistamine therapy.

Chilblains and vasculitis ("COVID toes") were one of the hallmark dermatological signs of COVID-19 infection. Interestingly, similar lesions have been observed following vaccination, highlighting the mimicry between the virus and the vaccine response. Chilblains (pernio) present as erythematous, violaceous, or purpuric swellings on the acral surfaces (toes, fingers), often accompanied by pain, burning, or itching.[99] The pathogenesis is linked to a robust type I interferon response. Interferons are critical for antiviral defense and are potently induced by mRNA vaccines. This "interferonopathy" can lead to lymphocytic inflammation and microangiopathy (small vessel disease) in the cutaneous vasculature.[94] Many authors opine that such reactions are typically mild and should resolve spontaneously without sequelae.[105]

Whether this opinion is factual or motivated by a desire to "decrease vaccine hesitancy" remains to be established.[30]

Leukocytoclastic vasculitis has been reported rarely.[106] Such cases likely result from immune complex deposition or molecular mimicry, but incidence is extremely low compared to the background rate in the population or even the rate associated with natural SARS-CoV-2 infection.[107]

Dermal filler reaction is a unique cosmetic procedure-related side effect identified early in the Moderna clinical trials. It is a delayed inflammatory reaction in patients with soft tissue fillers (e.g., hyaluronic acid).[108] Patients present with acute swelling, erythema, and tenderness at the precise sites of previous cosmetic filler injections, sometimes years after the cosmetic procedure.[108] The mechanism is believed to be that the vaccine-induced immune boost triggers a granulomatous inflammatory response to the "foreign body" (the filler) that was previously tolerated.[108] These reactions respond rapidly to oral corticosteroids or antihistamines.[108] While they are treatable, the increased use of soft-tissue fillers in cosmetic procedure should raise the question about the usefulness of mRNA mass vaccination policies.

Vaccine Induced Flares of Preexisting Dermatopathies

A major area of concern for dermatologists and patients alike is the potential for mRNA vaccines to destabilize pre-existing common chronic skin conditions. The vaccine induced flares may cause unnecessary severe physical, psychological, and iatrogenic burden (Table 3).

Table 3. Flare-Inducing Impact of mRNA Vaccination on Pre-existing Dermatological Conditions

Flares:	Theoretical Risk	Observed Outcome in Studies	Management Recommendation
Psoriasis	Th1/Th17 flare	Flares observed reported as mild	Continue biologic Tx; treat flares topically
Atopic dermatitis	Th2 shift / flare	Flares observed with various severity	Continue systemic/topical Tx
Bullous disease	Antibody induction	Very rare cases of BP/pemphigus	Treat with standard immunosuppression
Chronic urticaria	Autoimmune	Potential for transient flare	Pre-medicate with antihistamines if history warrants
Herpes zoster	Uncertain	High flare potential	Requires antiviral Tx; generally resolves
Pityriasis rosea	Uncertain	High flare potential	May resolve spontaneously

Psoriasis and atopic dermatitis can be controlled by continuous treatment. However, they are susceptible to extremely burdensome flares triggered by various factors. Recently mRNA vaccine became one such factor.

Because psoriasis is driven by the Th1/Th17 axis, and mRNA vaccines promote Th1 immunity, flares are not suspected but expected. Cases of new-onset psoriasis and exacerbations of existing plaque psoriasis have been documented following both the first and second doses.[109] Observational studies have found that psoriasis patients on biologic therapies (which target cytokines like TNF-alpha, IL-17, or IL-23) had a lower risk of flares compared to those not on biologics.[109] The problem is that biologics are extremely expensive and not covered by many insurance plans. That may make using them as a buffer against vaccine-induced inflammation impractical. Flares are said to be generally mild to moderate and can be managed with topical corticosteroids or a temporary adjustment in systemic therapy. However, the question remains: Why put patients through a virtually certain burden of flares?

Frequent flares of **atopic dermatitis** (AD) have been reported, and are expected due to nonspecific immune activation and a temporary shift in the Th1/Th2 balance.[91] Management of AD flares is extremely inconvenient and expensive for patients and their caregivers.[110,111] It is also frequently associated with iatrogenic reactions.[112] Since flares of AD are extremely arduous for patients and result in significant psychological and physical sequelae, the risk: benefit ratio of using mRNA vaccine in this population is unfavorable.

For **autoimmune bullous diseases** such as **bullous pemphigoid** (BP) and **pemphigus vulgaris** (PV), which are caused by autoantibodies against skin structural proteins, exposure to mRNA vaccine can be compared to introducing patients to a "perfect storm" of autoimmunity induction. Both flares and new onset of BP have been reported post vaccination.[26] Proposed mechanisms include "bystander activation" of autoreactive B-cells or molecular mimicry between the Spike protein and basement membrane components.[26] A scoping review of autoimmune sequelae emphasizes these conditions due to the significant hardship they cause.[113]

Viral Reactivation: Herpes Zoster and Pityriasis Rosea

The phenomenon of viral reactivation following mRNA vaccination has been a consistent signal in dermatological registries.

Reactivation of the **varicella zoster virus** (VZV) is one of the most common distant skin reactions reported.[94] The leading hypothesis is "immune distraction." The mRNA vaccine induces a massive mobilization of T-cells to respond to the Spike protein antigen. This may lead to a transient reduction in the T-cell surveillance required to keep latent VZV in check within the dorsal root ganglia, allowing the virus to reactivate and travel down the sensory nerve to the skin.[92] Herpes zoster is a very painful condition. It is treatable with antivirals and IV vitamin C administration.[114] However, both treatments are hard to obtain, and results may vary. The burden of pain and necessity for treatment raises questions about risk: benefit ratio of mass mRNA vaccinations.

Pityriasis rosea (PR) is widely believed to be associated with the reactivation of human herpesvirus 6 (HHV-6) or HHV-7. Vaccination has been observed to trigger PR-like eruptions, likely through similar immunomodulatory mechanisms of viral reactivation.[93] This acute, self-limiting papulosquamous eruption typically begins with a "herald patch" and spreads in a "Christmas tree" distribution.[115]

Comparative Analysis: Vaccine-induced vs. Infection-induced Cutaneous Manifestations

A rigorous safety assessment of any new modality, including mRNA vaccines, should compare all side effects of vaccine versus all outcomes of the disease it aims to prevent. The size of the population affected by the disease and of immunized population should also be considered.

It is well known that SARS-CoV-2 infection is itself a potent driver of dermatological pathology. COVID-19 infection is associ-

ated with a wide array of cutaneous findings, often grouped into five patterns: pseudo-chilblains ("COVID toes"), vesicular eruptions, urticarial lesions, maculopapular rashes, and livedo/necrosis.[107] It has been also recognized that the spectrum of vaccine reactions mimics the viral spectrum (chilblains, urticaria, morbilliform rash) but it also induces or worsens numerous skin disorders that are not part of the COVID-19 cutaneous manifestation.[91,107] Moreover, only a fraction of the population is affected by COVID-19-associated skin problems. In a contrast, mass COVID-19 vaccination schemes subject virtually all members of the population to the risk of very burdensome cutaneous side effects. Finally, the mRNA-induced skin pathologies are very likely to cause disruption of the CINE system, leading to serious morbidity and even mortality that may not be initially apparent.

Conclusions

A review of the positive and negative evidence related to dermatological side effects caused by mRNA vaccine shows that the harmful impact of those cutaneous reactions extend beyond mere cosmetic effects because skin, in addition to providing a mechanical barrier, is involved in regulation of metabolic processes crucial for survival, the cutaneous-immuno-neuro-endocrine (CINE) system.

Mechanisms such as LNP immunostimulation, Th1 polarization, molecular mimicry, and viral reactivation provide a scientifically plausible basis for clinically observed phenomena.

The fact that the mRNA platform was implemented despite those and other serious risks defies rational explanation. It should be removed from the market. The future research of detrimental effects of this and other vaccines should be driven by objectivity not by the desire to "decrease vaccine hesitancy."

Until that time physicians who encounter cutaneous signs in vaccinated patients should exert diagnostic due diligence. They should consider the possibility that those signs may indicate more than presence of dermatological side effects of vaccine but may also herald the presence of systemic disorders that the mRNA vaccine could trigger, including vasculitis, malignancies, renal and endocrine disorders, and systemic autoimmune syndromes.

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Acknowledgement: This text was created by a human author with limited support from advanced AI tools: licensed versions of Gemini, Co-Pilot, Grok, OpenEvidence. Those tools were used only for purposes of reference management, data visualization, and spelling and grammar refinement. All analyses, conclusions, and recommendations are solely those of the human author, who verified all sources.

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