Clinics in Dermatology (2019) **37**, 607–609

ELSEVIER

Clinics in Dermatology

Commentary

The skin as a target organ in multisystemic diseases III

> "The human skin is a screen on which all internal organs changes are projected."Bogomil Beron (1866-1936)[1]

This quotation comes from Professor Beron, who was the first president of the Bulgarian Dermatological Society.[1] His statement is accepted by most, if not all, dermatologists, but not by most patients nor even by some physicians. The skin, as the largest organ of the body, covers the surface; this results in skin diseases being called *superficial* and even dermatologists being so labeled.

Hopefully, this notion is being dispelled. For example, since the last decade of the 20th century, the concept that psoriasis is a systemic disease has been discussed and increasingly accepted; psoriasis is now considered part of the metabolic syndrome.

The advent of the biologics has provided support for the systemic nature of skin diseases. These "wonder drugs" are used to treat a variety of diseases ranging from non-Hodgkin lymphoma, chronic lymphocytic leukemia, rheumatoid arthritis, idiopathic thrombocytopenic purpura, ankylosing spondilitis, Crohn disease, ulcerative colitis, uveitis, and allergic asthma to many dermatologically oriented conditions. Diseases, like psoriasis, pemphigus vulgaris, hydrosadenitis suppurativa, and urticaria are now successfully controlled with identical biologic medications, thus pointing out possible similar pathogenetic mechanisms.

We present the third edition in *Clinics in Dermatology* of "Are Skin Diseases Systemic Ones?"[2,3] We have selected an international group of experts to illustrate the concept that there is parallel involvement of the skin with various internal organs and systems.

Supporting contributions

Gunther Burg gives philosophic and holistic approaches to changes in skin color in systemic and skin diseases in his paper "Color Changes of the Skin and Systemic Diseases."[4] Apart from ethnic factors, the various dermatoses comprise a rainbow of colors ranging from the most common red color to yellow, blue, brown, silver, green, black, and white. From the earliest days of the study of skin diseases, color has played a role, however erratic and incomplete.

Robert Willan (1757-1812) in "Description and Treatment of Cutaneous Diseases" uses the changes of color in his descriptions.[5] Looking for diseases of the skin is usually done in a holistic way and involves automatically and unconsciously recognizing localization, distribution, and appearance of the primary or secondary skin lesions. Changes in the structure and pigmentation of the epidermis, dermis, dermal constituents, and subcutis may provide a rainbow, which extends from the most common red to yellow, blue, brown, silver, green, black, and white. The author concludes that observing these changes is helpful in determining the comorbidities or extracutaneous involvement of many skin diseases and the extent of accompanying systemic diseases.

In their paper titled "Alopecia and Systemic Disease" Nanda et al[6] reveal the secondary alopecia that can affect the hair follicles in the setting of systemic diseases, medications, and external trauma. Connective tissue diseases, granulomatous diseases, bullous diseases, infections, and tumors are among the many reasons for alopecia. The authors note that, despite the fact that histopathologic examination is the gold standard in diagnosing alopecia, trichoscopy is a useful noninvasive tool and can guide the selection of the optimal site for the scalp biopsy.

The paper "Rosacea: A Systemic Disease" by Uwe Wollina[7] discloses the current understanding of the disease's clinical appearance and pathophysiology. Rosacea may develop as a manifestation of systemic diseases with significant morbidity and even mortality. Obesity, *Helicobacter pylori* infection, smoking, and inflammatory bowel disease bear a significant risk for the development of rosacea. Metabolic disorders, as well as psychiatric and neurologic disorders and certain types of cancer, show a significant association with rosacea. The possible link to cardiovascular events is debatable. Conditions, such as red scalp syndrome, ocular involvement, and migraine, can accompany rosacea, suggesting the systemic nature of the disease.

Kazandjieva and Christoff review systemic involvement in angioedema in their paper "Angioedema and Associated Systemic Diseases."[8] Angioedema, first reported by Heinrich Quincke (1842–1922), is a clinical entity defined as a self-limiting edema localized in the deeper layers of the skin and mucosa and lasting for several days. The disease can be mediated by bradykinin and/or mast cell mediators including histamine. The authors present the current classification and the pathophysiology of angioedema. The most common form of the disease associated with other systemic diseases is acquired angioedema (AAE) due to C1-inhibitor (C1-INH) deficiency. It is characterized by acquired consumption of C1-INH and various underlying disorders such as multiple myeloma, chronic lymphocytic leukemia, rectal carcinoma, and non-Hodgkin lymphoma.

The paper titled "The Rash that Becomes Purpuric, Petechial, Hemorrhagic, or Ecchymotic"[9] deals with specific causes and proposes a practical approach to a patient with a hemorrhagic eruption. Many conditions, including infectious diseases, coagulation and embolic disorders, vasculitides, and vasculopathies, can be the cause for such an eruption. Analyzing the distribution of the eruption and its symmetry can provide clues to the diagnosis. Another important characteristic is the size of the hemorrhagic lesions. The smallest lesions are the petechiae (punctiform hemorrhages with an arbitrary limit of up to 4 mm), followed by the purpura (sized up to a centimeter) and ecchymoses, which are larger. The size of the lesions corresponds to the amount of hemorrhaging in the tissues. A systematic approach with the help of certain laboratory methods are requested for the differential diagnosis of hemorrhagic eruptions.

Jacek Szepietowski et al reveal "Pruritus as a Sign of Systemic Disease."[10] The complex pathogenesis of pruritus may be regarded in several contexts. Exogenous and endogenous factors are released by immune cells, epithelial cells, and endothelial cells, resulting in the activation of signal cascades. Various interleukins (ILs), such as IL-2, IL-4, IL-13, IL-22, and IL-31, and cytokines, such as thymic stromal lymphopoietin, contribute to itching in different clinical entities. The authors provide an up-to-date summarizing table on the systemic diseases that may trigger skin itch. Uremic pruritus, chronic hepatobiliary diseases, neoplastic disorders, and hyperthyroidism are classic examples of systemically induced itch. The authors underline the importance of treating the systemic trigger of the itch.

In their review "Pityriasis Rubra Pilaris as a Systemic Disease,"[11] Kamarachev et al present the historical aspects and the evolution of the scientific understanding of the disease. First described in 1835, pityriasis rubra pilaris (PRP) is a rare inflammatory skin disorder of unknown etiology. Despite its clinical heterogeneity, PRP could be associated with a variety of rheumatologic, infectious, neoplastic, and other extracutaneous manifestations. These are the subject of the paper. The authors comment on the current classification and the clinical aspects, together with the histopathology pattern of PRP. The therapeutic approach to a patient with PRP is discussed. The application of alternative regimens such as therapy with penicillin and vitamin A as well as novel treatments, such as the application of biologics, are reviewed.

Systemic involvement in psoriasis is a widely discussed issue; psoriasis is now accepted as a systemic inflammatory disorder. The contribution by Demerdjieva et al focuses on "Ocular Changes in Patients with Psoriasis."[12] It reviews the current knowledge of eye involvement in psoriatic disease. The most common ocular changes in psoriasis include blepharitis, conjunctivitis, keratitis, iridocyclitis, UV induced cataracta, uveitis, and birdshot chorioretinitis. The common underlying mechanisms of psoriasis and inflammatory eye disorders are discussed. Providing an anamnesis for each ocular complaint of patients with severe arthropathic or pustular psoriasis is crucial. The absence of dedicated ophthalmic examinations can result in a misdiagnosed uveitis, which can evolve into a chronic disease.

Damevska et al review the novel *Insights in Adult-onset Still's Disease and the Role of Systemic Inflammation*."[13] Adult-onset Still disease (AOSD) is a rare systemic inflammatory disorder characterized by spiking fevers, rash, arthritis, and multiorgan involvement. It is a polygenic autoinflammatory disorder at the "crossroads" of autoinflammatory and autoimmune diseases. A clue to the diagnosis for the dermatologist is the salmon-colored eruption, which is a cutaneous manifestation of a generalized inflammatory reaction. The concept of AOSD has evolved and it is now considered a separate nosologic entity, with well-defined clinical features and specific diagnostic criteria; however, the diagnosis of AOSD remains challenging because many features overlap with other causes of severe illness including infectious, neoplastic, autoimmune, and other autoinflammatory diseases. The authors discuss *in extenso* the systemic involvement and manifestations of AOSD. Therapeutic options with an emphasis on novel treatments such as biologics are reviewed.

In their paper "Dupuytren's Contracture as a Sign of Systemic Disease,"[14] Ivan Bogdanov and Christopher Rowland Payne show that the prevalence of Dupuytren contracture (DC), first described in 1833, is highest in the North European population and in people of Viking descent, and its incidence is growing with age. The disease shares a common inheritance mode, predisposing factors, comorbidities, pathophysiology, and evolution with Ledderhose disease, Garrod knuckle pads, and Peyronie disease. The authors suggest a close relationship between DC, some skin malignancies, and psoriasis. Most of the comorbidities of DC, such as diabetes, epilepsy, hypertension, hyperlipidemia, and gout are well known. Other associations, such as different malignancies and AIDS, need further investigation. The authors conclude that skin diseases, such as psoriasis and

nonmelanoma skin cancer, appear to have a higher prevalence in patients with DC. Screening for such is important in patients with DC.

"Erythema Elevatum et Diutinum as a Systemic Disease"[15] by Sandhu and Tsoukas describes a rare disease first mentioned in the literature in 1894 and first coined in 1894 by Radcliffe-Crocker (1846–1909) and Campbell Williams. Erythema elevatum et diutinum (EED) is a disease of unknown origin, but the common pathogenetic mechanisms of EED and certain concomitant pathologies suggest the systemic nature of the disease. EED is associated with systemic infections that involve elevated levels of antigens or antibodies including streptococcal infections, HIV, Hepatitis B, tuberculosis, and syphilis. EED is also associated with IgA paraproteinemia, IgA myeloma, and various gammopathies (IgA, IgG, and IgM) as well as other hematologic diseases and malignancies, including hyperimmunoglobulin D, other plasma cell dyscrasias, non-Hodgkin lymphoma, myelodysplastic syndrome, hairy cell leukemia, B-cell lymphoma, and chronic lymphocytic leukemia. Other diseases that have been associated with EED include neutrophilic dermatoses like Sweet syndrome and pyogenic gangrenosum. A variety of autoimmune disorders have also been described in association with EED. In addition, arthralgias, scleritis, panuveitis, peripheral ulcerative keratitis, neuropathy, and ulcerations (oral, esophageal, and penile) have all been reported in patients with EED. The authors conclude that EED is a chronic leukocytoclastic vasculitis with systemic manifestations.

Recommendations

We hope that you, the reader, will agree with us that these conditions and diseases are more than "skin deep" and require a good deal of attention.

Nikolai Tsankov, MD, PhD, MSc
Department of Dermatology and Venereology, Tokuda Hospital-Sofia, Sofia, Bulgaria
E-mail address: tsankn@abv.bg

Jana Kazandjieva, MD, PhD
Department of Dermatology and Venereology, Medical University-Sofia, Sofia, Bulgaria

Razvigor Darlenski, MD, PhD
Department of Dermatology and Venereology, Trakia University-Stara Zagora, Bulgaria

https://doi.org/10.1016/j.clindermatol.2019.08.002

References

1. Beron B. *General Dermatology.* Fofia (Bulgaria): Medizina i fizkultura. 1926.
2. Tsankov N, Kazandjieva J, Darenski R. Are skin diseases systemic ones? I. *Clin Dermatol* 2014;32:341-456.
3. Tsankov N, Kazandjieva J, Darenski R. Are skin diseases systemic ones? *II Clin Dermatol* 2015;33:509-590.
4. Burg G. Changes in color of the skin and systemic disease. *Clin Dermatol.* 2019;37:610-617.
5. Willan R. *On Cutaneous Diseases.* Philadelphia: Kimber and Conrad. 1809.
6. Nanda S, De Bedout V, Miteva M. Alopecia and systemic disease. Clin Dermatol. 2019;37:618-628.
7. Wollina U. Is rosacea a systemic disease? *Clin Dermatol.* 2019;37:629-635.
8. Kazandjieva J, Christoff G. Angioedema as a systemic disease. *Clin Dermatol* 2019;37:636-643.
9. Antonov D, Kamarashev J, Kazandjieva J, Neykova T, Tsankov N. The rash that becomes purpuric, petechial, hemorrhagic, or ecchymotic. *Clin Dermatol.* https://doi.org/10.1016/j.clindermatol.2019.07.036
10. Welz-Kubiak K, Reszke R, Szepietowski J. Pruritus as a sign of systemic disease. *Clin Dermatol* 2019;37:644-656.
11. Kamarashev J, Grozdev I, Darlenski R, Tsankov N. Pityriasis rubra pilaris as a systemic disease. *Clin Dermatol* 2019;37:657-662
12. Demerjieva Z, Majdrakova I, Tsankov N, et al. Ocular changes in patients with psoriasis. *Clin Dermatol.* 2019;37:663-667.
13. Damevska K, Franca K, Nikolovska S, Gucey F. Adult-onset Still's disease as a cutaneous marker of systemic inflammation. *Clin Dermatol* 2019;37:668-674.
14. Bogdanov I, Rowland-Payne C. Dupuytren's contracture as a sign of systemic disease. *Clin Dermatol* 2019;37:675-678.
15. Sandju J, Tsoukas M. Erythema elevatum diutinum as a systemic disease. *Clin Dermatol* 2019;37:679-683.