"Sine Phenomenon" in Dermatology

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Abstract

Background: In dermatology, the term sine is often used in regard to any sign, symptom or finding whose absence would very likely mean uncommon variant of the target disease or condition. Sine phenomenon can be seen in different dermatological diseases such as scleroderma, polymorphic light eruption, dermatomyositis, pellagra, zona, psoriasis, necrobiosis lipoidica, lupus erythematosus, seborrheic keratosis, eccrine hidradenitis and acne fulminans.

Introduction

“Sine” means lacking or without especially in Latin phrases [1]. In dermatology, the term sine is often used in regard to any sign, symptom or finding whose absence would very likely mean uncommon variant of the target disease or condition [2]. The absence of such a sign, symptom or finding would thereby have very high sensitivity, and rarely miss the condition, so a negative result should be reassuring for sine phenomenon in dermatology. Sine phenomenon can be seen in different dermatological disease such as scleroderma, polymorphic light eruption, dermatomyositis, pellagra, zona, psoriasis, necrobiosis lipoidica, lupus erythematosus, seborrheic keratosis, eccrine hidradenitis and acne fulminans [3].

Dermatomyositis Sine Myositis

This is a historic term, which has now been replaced by the term amyopathic dermatomyositis, which is a variant of dermatomyositis. This terminology is used when there is a biopsy-proven hallmark skin lesion of cutaneous dermatomyositis without any presence of muscle involvement for 6 months or longer [4]. There should be neither clinical evidence of proximal muscle involvement nor any abnormalities in serum muscle enzymes. Other investigations for muscle involvement like electromyogram and muscle biopsy should be normal if done [5]. Sun et al. observed that the prevalence of interstitial lung disease in Chinese amyopathic dermatomyositis patients is strikingly high, and acute/subacute interstitial pneumonia is a major cause of death in amyopathic dermatomyositis patients. They recommend that laboratory findings combined with high-resolution computed tomography examination and pulmonary function tests can provide valuable predictive information of interstitial lung disease or acute/subacute interstitial pneumonia in amyopathic dermatomyositis patients [6]. Treatment with immunosuppressive drugs for 2 months or more within 6 months of onset of cutaneous lesions and use of drugs like hydroxyurea, and statins, which are capable of producing dermatomyositis like cutaneous changes, are exclusion criteria for amyopathic dermatomyositis [5]. There have been reports of typical skin lesions of dermatomyositis occurring without or with minimal evidence of myositis, the cases being labelled variously as dermatomyositis sine myositis, and amyopathic dermatomyositis.

However, the original classification of dermatomyositis by Bohan and Peter did not include such an entity [7]. Euser and Sontheimer have divided amyopathic dermatomyositis into 3 types: Type I: Pure amyopathic dermatomyositis patients who have only skin disease. Type II: Patients with skin disease who have subjective myalgias and weakness but not laboratory evidence of muscle disease. Type III: Patients with no muscle weakness clinically but who have evidence of abnormal laboratory tests at some time during their course [8]. Dermatomyositis sine myositis can occur as all types.
Systemic Sclerosis Sine Scleroderma

Scleroderma or systemic sclerosis is characterized by the presence of thickening and induration of the skin. Major organ involvement as part of systemic sclerosis without the characteristic skin changes of scleroderma, defined as systemic sclerosis sine scleroderma, was first described in 1954. The terminology “systemic sclerosis sine scleroderma” refers to those patients of systemic sclerosis who do not show cutaneous features of systemic sclerosis but exhibit vascular (like Raynaud’s phenomenon), immunologic findings and internal organ involvement as seen in systemic sclerosis. These comprise of nearly 1% of all systemic sclerosis patients. Pauling et al. observed a case of pulmonary artery hypertension as the presenting feature of systemic sclerosis sine scleroderma. They concluded this case highlights the importance of close monitoring of patients who present with Raynaud’s phenomenon and a strongly positive nucleolar ANA pattern, for further organ involvement such as pulmonary artery hypertension that can now be effectively treated if detected early enough. In addition, the presence of abnormal nail-fold capillaries at presentation could be another indicator of future risk. A strong case can be made for such patients having annual pulmonary function tests and echocardiography to estimate pulmonary artery pressures as is currently recommended for patients with scleroderma renal crisis (scleroderma renal crisis sine scleroderma sine hypertension) [10]. Korzets et al. observed a case of scleroderma renal crisis [scleroderma renal crisis sine scleroderma sine hypertension] [11]. Systemic sclerosis sine scleroderma should be included in the spectrum of systemic sclerosis with limited cutaneous involvement and should not be considered a distinct or separate disorder.

Linear Melorheostotic Scleroderma with Hypertrichosis Sine Melorheostosis

Linear melorheostotic scleroderma (LMS) is a condition, which is characterized by linear scleroderma like changes with cortical hyperostosis of the bones, exhibiting a dripping of burning candle-like appearance on radiography [12, 13]. However, the term LMS with hypertrichosis sine melorheostosis is used when the scleroderma like changes is seen with an increased growth of hair, but the characteristic bone changes are absent. Melorheostosis is a rare sclerosing dysplasia wherein the affected bone demonstrates a cortical or endosteal hyperostosis, characterized roentgenographically. Since its original description in 1922 by Leri & Joanny, more than 250 cases have been reported. In 1936, Dillehunt & Chuinard described a case in which a lesion defined as “linear scleroderma” was associated with melorheostosis. In one study, scleroderma-like skin changes and melorheostosis were reported to coexist in approximately 5% of 131 cases. In 1972, proposing a more appropriate term “linear melorheostotic scleroderma”, Wagers et al. described the clinical and histological features that distinguish the cutaneous changes of LMS from those of linear scleroderma [14, 15]. The pathogenesis of LMS is unknown. Wagers et al. proposed the possibility that the skin lesions were similar to the bone lesions in terms of the pathomechanism. As for its pathogenesis, inflammation and vascular abnormality have been proposed [14]. Mulier & Henderson postulated that the sclerosing changes in the skin of LMS should be derived from a primary mesenchymal defect that occasionally spills over into the skeletal tissues. However, many others favour the notion of a common developmental error both in the cutaneous and skeletal lesions. Fimiani et al. suggested the possibility that LMS is an integral part of a hamartoma that may affect one or more tissues, which was supported by the coexistence of hypertrichiosis with LMS, as noted in the present case. Hypertrichosis in LMS lesions is infrequent, but has been reported in five cases. There are three possible explanations for LMS that are not accompanied by bone alteration. First, there may be a difference in the onset of the pathogenic changes between the skin and bone. In fact, in a few previous cases melorheostosis became evident only several years after the appearance of the skin lesion. Secondly, it is possible that some cases of LMS without melorheostosis have been diagnosed as linear scleroderma. Thirdly, available instruments may overlook slight bone alterations in the early stage of melorheostosis. Although bone scintigraphy is often available to detect slight bone alterations, the patients of the present patient refused further study. No prophylaxis or therapy is effective to prevent the progression of melorheostosis [12, 13, 14, 15].

Psoriatic Arthritis Sine Psoriasis

This terminology refers to those patients who present with symptoms and signs of psoriatic arthritis but without any cutaneous psoriatic lesions, however, have a history of psoriasis in a first or second degree relative [16, 17]. In about 20% of patients with psoriatic arthritis the rheumatological manifestations precede the onset of the cutaneous lesions. If there is a family history of psoriasis these patients are diagnosed as having psoriatic arthritis sine psoriasis. In the past, they were also classified among patients with undifferentiated spondyloarthritides. The clinical spectrum of psoriatic arthritis sine psoriasis is wide and identified by dactylitis and/or distal interphalangeal arthritis, HLA-Cw6, and a family history of psoriasis. The Classification of Psoriatic Arthritis (CASPAR) criteria of psoriatic arthritis include psoriatic arthritis sine psoriasis [17]. Scorpa et al. think that a subset of patients with psoriatic arthritis “sine psoriasis” is identified by the occurrence of a spondyloarthropathy with dactylitis and/or distal interphalangeal arthritis, presence of HLA-Cw6, and familial psoriasis in first or second-degree relatives [16].

Polymorphic Light Eruption Sine Eruption

Polymorphic light eruption sine eruption is a variant of polymorphic light eruption (PLE), which is characterized by an intense pruritus on the sun-exposed areas without the development of any cutaneous lesions. The pruritus usually develops by 45 minutes to a day, and subsides by 1 to 5 days. Dower and Huuk describe seven patients, four female and three male, who developed intense pruritus on sun-exposed skin without visible change. The clinical features resembled those of polymorphic light eruption without rash. Four patients also occasionally developed typical polymorphic light eruption upon sun exposure, but sun-induced pruritus alone occurred most frequently. No patient was taking any drug therapy. One patient developed similar pruritus following solar simulated irradiation, and one following PUVA therapy. All other laboratory investigations were negative. Treatment with low dose UBV phototherapy or PUVA therapy was effective. The condition, which they have called polymorphic light eruption sine eruption (PLESE), appears

to be a variant of polymorphic light eruption [18, 19]. Commens also showed a case of polymorphic light eruption sine eruptione and brachioradial pruritus [19].

**Pellagra sine Pellagra**

Pellagra sine pellagra refers to those patients who manifest clinical features of pellagra in the absence of the classical cutaneous photosensitive dermatosis like Casal’s neckles, gauntlet of pellagra. This is seen in those patients of pellagra who do not go outdoors (thus avoiding photoexposure) and also among patients with riboflavin deficiency, rather than niacin deficiency [20]. Ishii N et al. showed that although patients with pellagra had presented with various mental, neurological and gastrointestinal symptoms, the diagnosis of pellagra had not been established clinically because, in the majority, there were no skin lesions. It is emphasised that whenever chronic alcoholics exhibit certain mental, neurological or gastrointestinal symptoms, one should strongly suspect pellagra sine pelle pelle even in the absence of skin lesions [21].

**Zoster Sine Herpete (Syn: Zoster sine eruptione)**

The term zoster sine herpete was coined by Weber in 1916 to describe herpes zoster without the classic rash. Herpes zoster is characterized by the occurrence of groups of vesicles on an erythematous base in a dermatomal pattern. The onset of the eruptions is preceded by sharp pain 2–4 days prior. However, in some patients, this pain is not followed by the occurrence of any cutaneous lesions. This is known as zoster sine herpete [22, 23, 24]. Javorsky reported a case of metastatic transitional cell carcinoma mimicking zoster sine herpete. They concluded that dermatomal pain could occur with neural metastases as well [22]. Vena reported a case of zoster “almost” sine herpete: diagnostic utility of real-time-polymerase chain reaction. This report describes the case of a female patient, presenting with intercostal pain associated with a single papulo-vesicular lesion localized within the same area [24]. Yaguchi reported a case of zoster sine herpete presenting with dysphagia diagnosed by polymerase chain reaction analysis of VZV DNA in aircular skin exudates [25]. Hon C et al. indicated a case of ophthalmic zoster sine herpete presenting as oculomotor palsy after marrow transplantation for acute myeloid leukemia [26]. Herpes zoster sine herpete can be also present as hyphema, trigeminal neuralgia, disciform keratitis, encephalomyelitis, facial palsy, uveitis, cranial and upper cervical nerves involvement, iridocyclitis, lateral sinus thrombosis, truncal sensory deficit, retinal periphlebitis and thoracic motor paralysis [27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39].

**Malignant Acanthosis Nigricans Sine Malignancy**

Malignant acanthosis nigricans is very similar to acanthosis nigricans in clinical appearance, but is usually sudden in onset, progressive, darker and extensive. It also involves the mucosal surfaces and palms. Malignant acanthosis nigricans may occur simultaneously, precede or follow occurrence of an internal malignancy and subsides with removal of the malignancy. The term malignant acanthosis nigricans sine malignancy is used when the patient presents with malignant acanthosis nigricans and extensive evaluation and investigations fail to reveal the presence of any malignancy [40].

**Acne Fulminans Sine Fulminans**

Acne fulminans was first described in 1959 and it is a rare form of acne, characterized by an acute onset of cystic acne, which tends to rupture leading to ulcerations, along with systemic manifestations like fever, malaise, myalgia, nausea, polyarthropathy, anorexia and osteolytic lesions [41, 42, 43]. Acne fulminans sine fulminans is a variant, which presents with cutaneous lesions, similar to acne fulminans but with minimum or nil systemic features [43]. Response to traditional acne therapies is poor. It is characteristically of sudden onset, most common in adolescent males and although response to isotretinoin is poor, patients usually respond to oral corticosteroids [44]. In a number of cases a familial association has been described. The aetiology of acne fulminans is not clearly established. In view of the familial associations, genetic susceptibility is likely. There is evidence of an altered immunological reaction to Propionibacterium acne in some patients, with previous demonstration of both type III and IV hypersensitivity to this organism. Another theory is that altered neutrophil function may result in severe acne flares. P. acnes destruction is thought to result in mediator release, inducing neutrophil chemotaxis, which may be responsible for the early flares seen on treatment with isotretinoin [45, 46]. Thomson et al. feel that it is important to identify patients of the acne fulminans ‘sine fulminans’ group so that modifications in treatment may be implemented [43]. These patients all showed a poor response to isotretinoin therapy, with resultant acne flares following the lowest dose. All patients developed scarring as a result of their acne lesions and the emphasis should therefore be on prevention of the severe flare. As has previously been identified, macrocomedones are a cause of flares in acne treated with isotretinoin. All but one of these patients had multiple macrocomedones and it is important that all acne patients are examined for these and treated with gentle cautery if necessary, allowing areas to heal (1–2 weeks) prior to commencing isotretinoin. In patients with macrocomedones, low dose isotretinoin (≤ 0.2 mg/kg/day) should be used. In patients who flare on low dose, the isotretinoin should be reduced further or stopped and the addition of a reducing dose of corticosteroids (0.5–1.0 mg/kg/day) should be considered. Patients who already show an acne fulminans ‘sine fulminans’ picture, should be treated in a similar fashion, with macrocomedones treated initially if present. Patients receiving isotretinoin should have this stopped or reduced to 0.2 mg/kg/day until the worst of the ulcerative fulminans lesions have resolved. Prednisolone should be given at a dose of 0.5–1.0 mg/kg/day with duration according to disease severity. This should be reduced gradually over weeks or months according to patient response, increasing the dose or reinstating prednisolone if disease flares occur. Patients not having received prior isotretinoin should be started on a low dose of this after 2 weeks treatment with prednisolone. Long-term low dose isotretinoin is frequently required, sometimes up to 2 years if necessary. In summary, authors have classified a group of patients with severe acne of sudden onset, as having acne fulminans ‘sine fulminans’ [41, 42, 43, 44, 45, 46, 47, 48]. Severity of disease is similar to that seen in acne fulminans but with no systemic features. This group sho-
uld be identified, as modification of acne therapy is required.

**Eruptive Seborrhoeic Keratosis Sine Malignancy**

The sudden eruptive onset or sudden increase in the size of existing seborrhoeic keratosis, often referred to as the *Leser-Trelat* sign, is associated with malignancy, especially adenocarcinomas of the gastro-intestinal system. Eruptive seborrhoeic keratosis sine malignancy or the false *Leser-Trelat* refers to the condition of eruptive seborrhoeic keratosis where extensive investigations fail to reveal the presence of any malignancy. *Rampen et al.* think that the sign of *Leser-Trelat* is usually regarded as a reliable cutaneous marker of internal malignancy. They have reviewed the literature and conclude that the evidence for a causal relation between eruptive seborrhoeic keratoses and cancer is meager. They have reviewed the literature and failed to reveal the presence of any malignancy.

**Pruritus Sine Materia**

The terminology pruritus sine materia is used to describe those conditions of pruritus, which occur on non-inflamed, non-diseased skin and includes pruritus secondary to systemic, neurological, psychosomatic or psychiatric origin and even pruritus that occurs in elderly people. Pruritus can be divided into several categories: pruritoceptive, neurogenic, neuropathic, and psychogenic. Neurpathic itch is caused by lesions of afferent neural pathways. Psychogenic itch is secondary to primary psychiatric disorders. Both of these types of pruritus present with no evidence of primary cutaneous lesions. The presentation of both conditions can be confusing and patients with no primary cutaneous lesions can be prematurely diagnosed as having a psychiatric disorder. Treatment of neuropathic and psychogenic pruritus can be divided into pharmacologic and nonpharmacologic therapies. Medications used include topical capsaicin and anesthetic agents, tricyclic antidepressants, selective serotonin reuptake inhibitors, and atypical antipsychotic agents. Nonpharmacologic therapies such as psychotherapy and hypnosis have been beneficial.

*Affif et al.* described the nature and the frequency of systemic diseases responsible for the pruritus sine materia. Value of this sign as a marker of malignancy. Prospective study undertaken over five years and 95 patients included. In 36 cases (40%), a systemic cause was found. The main conditions were: toxocariasis (8 cases), hematologic diseases (7 cases), chronic renal failure (6 cases), hypothyroidism (5 cases) and iron deficiency (5 cases). A neoplasm was found in eight cases (8.42%): seven hematologic malignancy (3 myeloma, 2 Hodkin’s diseases, 2 myeloproliferative syndromes) and one solid cancer (pulmonary adenocarcinoma). They concluded a systemic aetiology was observed in 38 cases (40%). The toxocariasis an underestimated disease comes at the first place. The pruritus sine materia can hide an hematologic malignancy. *Darsow et al.* reported a case of pruritus circumscriptus sine materia: a sequel of postzosteric neuralgia.

**Lupus Sine Lupo**

The cutaneous lesions of lupus erythematous are categorized into specific and non-specific on the basis of the *Gilliam* classification. The term lupus sine lupo is used when the patient fails to have any specific lesions of lupus erythematous.

**Eccrine Hidradenitis Sine Neutrophils**

Neutrophilic eccrine hidradenitis presents as tender erythematous papules and plaques and is often associated with chemotherapy for acute myeloid leukemia. Eccrine hidradenitis, often referred to as neutrophilic eccrine hidradenitis, is a condition, characterized histopathologically with eccrine degeneration and surrounding neutrophilic infiltrate often described post chemotherapy or associated with infectious agents. In eccrine hidradenitis sine neutrophils, the surrounding neutrophil infiltrate is deficient. *Yeh et al.* presented a case of hidradenitis occurring in a patient after chemotherapy for acute myeloid leukemia in the setting of profound neutropenia. Neutrophilic eccrine hidradenitis is postulated to be due to toxic injury to the sweat glands followed by neutrophilic inflammation. Alternatively, some hypothesize that neutrophilic eccrine hidradenitis represents a primary neutrophilic process. Neutrophil-poor variants of hidradenitis, both infectious and due to drug toxicity, should be considered diagnostically in neutropenic patients.

**Necrobiosis Lipoidica Sine Diabetes**

Necrobiosis lipoidica is closely associated with diabetes, with nearly 70% of the patients exhibiting diabetes. The term necrobiosis lipoidica sine diabetes is used to describe those patients of necrobiosis lipoidica who do not have diabetes. However, necrobiosis lipoidica can precede the onset of diabetes in nearly 15% of the patients.

**Keratosis Follicularis Sine Dyskeratosis**

*Diccio* reported a patients was seen in consultation in the clinic with an eruption that appeared to fulfill clinically all the diagnostic criteria of keratosis follicularis (Darier disease). However, further study of the case, including microscopic examination of a biopsy specimen, proved his tentative diagnosis to be incorrect. Since he has not been able to find a description of a similar case in the literature and since this hitherto unknown dermatosis mimics not only Darier’s disease but also other follicular disorders, he was tempted to report his case.

**References**


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