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REVIEW

Sweet Syndrome: A Review and Update

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Abstract Sweet syndrome is the most representative entity of febrile neutrophilic dermatoses. It typically presents in patients with pirexya, neutrophilia, painful tender erytomatous papules, nodules and plaques often distributed asymmetrically. Frequent sites include the face, neck and upper extremities. Affected sites show a characteristical neutrophilic infiltrate in the upper dermis. Its etiology remains elucidated, but it seems that can be mediated by a hypersensitivity reaction in which cytokines, followed by infiltration of neutrophils, may be involved. Systemic corticosteroids are the first-line of treatment in most cases. We present a concise review of the pathogenesis, classification, diagnosis and treatment update of this entity.

PALABRAS CLAVE
Síndrome de Sweet;
Dermatosis neutrofílicas;
Síndrome de Sweet asociado a malignidad;
Síndrome de Sweet inducido por medicamentos

Síndrome de Sweet: Revisión y puesta al día

Resumen El síndrome de Sweet es la entidad más representativa de las dermatosis neutrofílicas. Por lo general se presenta en pacientes con fiebre, neutrofilia, pápulas erytomatosas dolorosas, nódulos y placas. Los sitios frecuentemente afectados incluyen la cara, cuello y extremidades superiores los cuales característicamente presentan un infiltrado neutrofílico en la dermis superior. Su etiología no esta bien establecida, pero parece que puede estar mediada por una reacción de hipersensibilidad de las citocinas, seguido por un infiltrado de neutrófilos. Los corticosteroides sistémicos son la primera línea de tratamiento en la mayoría de los casos. Se presenta una revisión actual de la patogénesis, clasificación, diagnóstico y tratamiento de esta entidad.

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Introduction

Since it was first described by Dr. Robert Douglas Sweet, originally known as Gomm-Button disease (in reference to the first two patients), Sweet's syndrome, also referred to as febrile neutrophilic dermatosis, has been reported in hundreds of patients worldwide.[1] Neutrophilic dermatoses are a heterogeneous group of inflammatory skin disorders that include Sweet's syndrome, pyoderma gangrenosum, and subcorneal pustular dermatosis,[2] the former being the most represented and the focus of this review.

The purpose of this article is to make a review of Sweet syndrome, its clinical manifestations, definition, pathogenesis, diagnosis and management of this entity. It is essential for dermatologists to know the different aspects of Sweet's syndrome as well as its proper diagnosis, prevention and treatment.

Definition

Clinically, Sweet's syndrome presents in patients, all of which show characteristic neutrophilic infiltrate in the upper dermis.[3]

Sweet's syndrome can present as one of three clinical types: classical (or idiopathic) Sweet's syndrome, malignancy-associated Sweet's syndrome, or drug-induced Sweet's syndrome. Specific diagnostic criteria were proposed by Su and Liu[4] and subsequently revised and modified by von den Driesch.[5] Laboratory abnormalities may be found and are included in the diagnostic criteria, such as increased erythrocyte sedimentation rate (ESR), elevated C-reactive protein and leukocytosis (Table 1).

Etiology

Sweet's syndrome is an inflammatory skin disorder characterized by the extensive infiltration of neutrophils into the epidermis and dermis. For a dermatologist, understanding the pathophysiology of Sweet's syndrome is crucial for treatment.

The underlining biological pathways responsible for this cutaneous neutrophilic dermatosis have remained elusive. However, the association of this disease with infection, autoimmune diseases, neoplasms and drugs suggests an unusual hypersensitivity that may be mediated by cytokines, followed by infiltration of neutrophils that are probably activated by interleukin (IL)-1. Circulating autoantibodies, cytokines, dermal dendrocytes, HLA serotypes, immune complexes and leukotactic mechanisms have been suggested as factors that contribute to the pathogenesis of this syndrome. The presence of IL-1, IL-2 and IFN-γ but not IL-4, suggests that type 1T helper cells may play a role in the pathogenesis of idiopathic varieties of this syndrome.[6,7] Inflammatory cell markers, including CD3, CD163, myeloperoxidase, metalloproteinases and vascular endothelial growth factors, display significantly higher values in the lesioned skin of patients with Sweet's syndrome compared to non-Sweet's syndrome individuals or patients with other neutrophilic dermatoses.[8]

It has also been postulated that photosensitivity may play a role in the pathogenesis of Sweet's syndrome, although the pathomechanism is unknown, as Sweet's syndrome has been experimentally induced by phototesting.[9] One theory suggests that an isomorphic Koebner reaction is at work; another proposed mechanism associates ultraviolet B radiation with neutrophil activation and epidermal production of tumor necrosis factor-alpha and interleukin-8.[10]

In malignancy-associated Sweet's syndrome, the most accepted theory of mechanism of pathogenesis is the overproduction and inappropriate regulation of inflammatory cytokines, such as IL-1, IL-3, IL-6, IL-8, granulocyte colony stimulating factor (G-CSF) and granulocyte macrophage colony stimulating factor (GM-CSF).[11] This theory is supported by cases in which Sweet's syndrome patients received G-CSF/GM-CSF, interferon-γ and all-trans retinoic acid (ATRA) and subsequently developed Sweet's syndrome.[11]

Although there is no consistent evidence of a genetic predisposition for Sweet's syndrome, a higher frequency of HLA-Bw54 was reported in Japanese patients with Sweet's syndrome.[6] However, analysis of the HLA antigens in a Caucasian population showed no association between this syndrome and specific HLA-ABC antigens.[12] Recent evidence based on animal models suggest that an alteration in the gene encoding protein tyrosine phosphatase non-receptor type 6 (Ptpn6) could be involved in the pathogenesis of Sweet's syndrome,[13] as it encodes non-receptor protein tyrosine phosphatase Src homology region 2 (SH2) domain-containing phosphatase-1 (SHP-1). The malfunction of Ptpn6 results in unremitting footpad swelling, suppurative inflammation, and neutrophilia. More studies are required to better understand the etiology of this disease.

Clinical manifestations

Classical Sweet's syndrome has a worldwide distribution, usually presenting in middle age women with a 4:1 female to male ratio, no racial disparity, and recurrence in one-third of patients.[3] It presents as an acute febrile neutrophilic dermatosis characterized by a constellation of clinical symptoms, physical features, and pathological findings that include fever, neutrophilia, asymmetrically distributed painful tender erythematous skin lesions, consisting of papules, nodules and plaques, usually affecting face, neck and upper extremities (Fig. 1). Histology reveals a characteristic diffuse infiltrate predominantly consisting of mature neutrophils typically located in the upper dermis, which tend to promptly improve after the initiation of treatment.[7] Atypical lesions, characterized by erythematous plaques, vesicles and bullous lesions, have also been described.[14] Typically, classical or idiopathic Sweet's syndrome may be associated with infection, usually of the upper respiratory (streptococci) or gastrointestinal tract (salmonellosis and yersiniosis), and inflammatory bowel disease.[7] It can also occur during pregnancy,[15] possibly related to the vascular, cellular, microbiological, and immunological changes linked to increased estrogen and progestogen levels during pregnancy.[16] The symptoms and clinical manifestations typically respond promptly to systemic corticosteroid therapy and recurrence occurs in one-third of patients.[7]