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REVIEW ARTICLE

Drug-Hypersensitivity Syndrome: Diagnosis and Treatment

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Abstract Drug-induced hypersensitivity syndrome is a systemic autoimmune disorder that results in mucocutaneous symptoms ranging in severity from mild pruritus to life-threatening skin and mucosal loss, with different nomenclature depending on the severity of the symptoms. The purpose of this article is to review the recent advances in understanding the pathology of drug-induced hypersensitivity syndrome, as well as current recommendations for both medical and wound management.
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Introduction

Drug-induced hypersensitivity syndrome (DIHS) is a rare systemic autoimmune disorder that can cause mild to severe mucosal and cutaneous reactions. Discussion in the literature tends to focus on identifiable syndromes based on severity of symptoms (see Table 1); however, the underlying pathophysiology appears to be the same. The reported incidence varies: 0.4 per 1 million persons for drug reaction with eosinophilia and systemic symptoms (DRESS),[1] 1 to 1.4 per 1 million persons for toxic epidermal necrolysis (TEN),[2] and 2.9 to 6.1 per 1 million persons for Stevens-Johnson syndrome (SJS).[3-5] Predisposing factors include advanced age, polypharmacy, female sex, presence of infection (especially HIV), and genetic predisposition.[6] Mortality rates are approximately 5% for SJS, 30% to 50% for TEN,[7] and 10% for DRESS.

Pathophysiology

DIHS is an acute autoimmune reaction thought to be mediated by T cells and involving a variety of cytokines, inflammatory cells, and regulatory mechanisms, although not specifically understood. The mechanism appears to be activation of the immune system by the causative agents or their metabolites rather than a direct toxic effect on the keratinocytes.[8]

A study by Bellon et al. supported the T-cell–mediated hypothesis by identifying 85 genes that were differentially expressed during the acute phase of DIHS. Most of the genes upregulated in the acute phase were encoding proteins involved in cell cycle, apoptosis, and cell growth functions; 9 were involved in immune response and inflammation. Bellon et al. also found that histone messenger RNA levels were statistically significantly increased in severe and moderate reactions. Genes that were strongly upregulated in syndromes with both cutaneous and mucosal involvement were those involved in inflammation, now termed alarmins or endogenous damage-associated molecular patterns.[9]

Table 1   Drug-Induced Hypersensitivity Syndromes Based on Severity of Symptoms

Name of Syndrome	Identifying Characteristics
Maculopapular exanthemas	Generalized, widespread rash with red macular (not elevated) or papular (elevated) skin eruptions
Erythema multiforme (EM) minor	Localized skin eruptions, usually on the lower extremities, that begin to heal in 7 days
Fixed drug eruption	One or more local annular or oval erythematous patches; resolve with hyperpigmentation; recur at the same location
Drug rash with eosinophilia and systemic systems	Three of the following: fever, exanthema, eosinophilia, atypical circulating lymphocytes, lymphadenopathy, hepatitis
Stevens-Johnson syndrome; also called EM major	Cutaneous lesions of erythematous papules, vesicles, bullae, or iris lesions covering < 10% of the body surface area; mucosal lesions or conjunctivitis
Toxic epidermal necrolysis; also referred to as Lyell syndrome	Cutaneous lesions of erythematous papules, vesicles, bullae, or iris lesions covering > 30% of the body surface area; mucosal lesions or conjunctivitis
Chemotherapy-induced acral erythema	Painful, symmetrical swelling and erythema of the palms and soles of patients on high-dose chemotherapy[27]
Symmetrical drug-related intertriginous and flexural exanthema (Baboon's syndrome)	Bright-red, well-demarcated, anogenital lesions associated with a symmetrical eczematous eruption involving axillae, antecubital fossae, eyelids, and the sides of the neck[28]
Drug-induced lupus erythematosus	Typical lupus-like symptoms, including skin signs associated with long-term use of the putative drug; symptoms resolve with the withdrawal of the drug.[19]

In a study by Tohyama et al., immunostaining of cryosections from SJS and TEN lesions revealed CD14+ monocytes in the dermoepidermal junction, and CD14+ CD16+ cells present early in the disease process, before epidermal damage occurred, suggesting that the monocyte "infiltration is a cause, rather than a result, of epidermal damage."[10]

Merk discusses the role of xenobiotica-metabolizing enzymes and transport proteins as a biochemical barrier that serves, in addition to the epidermal stratum corneum, as a protection from toxic chemical compounds. He describes 3 phases of xenobiotica metabolism mediation: Phase 1 is the activation of the parent compound by oxidizing enzymes to highly reactive intermediates; in phase 2 the intermediates are metabolized by other enzymes, such as transferases, to create more water-soluble metabolites that can leave the cells; and phase 3 is mediated by the influx and efflux of transporter proteins in cutaneous cells. An imbalance in the 3 phases of xenobiotica metabolism results in binding of the highly reactive intermediates to high–molecular weight molecules (such as proteins) and a subsequent toxic response. Merk uses studies of contact dermatitis to relate this action to DIHS.[11]

Table 2   Drugs that have been reported to cause DIHS

Allipurinol
Antibiotics
  Betalactams (pediatrics)[29]
  Ceftriaxone (check)
  Cephalosporins
  Ciprofloxacin
  Clindamycin
  Fluoroquinolones
    Levofloxacin
  Penicillin
  Sulfanomides
    Trimethoprim-sulfamethoxazole[30]
  Tetracyclines
Anticonvulsants
  Carbamazepine
  Phenobarbitone
  Phenytoin
Anti-retroviral therapy
  Nevirapine[31]
Calcium-channel blockers
Dapsone
Oxicam NSAIDs
  Cyclooxygenase-2 (COX-2) inhibitors

Clinical Presentation

Symptoms of DIHS usually occur 1 to 3 weeks after the first ingestion of the causative medication (Table 2). SJS and TEN begin with fever, sore throat, and stinging eyes for 1 to 3 days, followed by mucosal lesions involving conjunctiva, oral and genital mucosa, trachea, bronchi, and gastrointestinal tract. Cutaneous lesions develop next with erythematous macules, progressing to flaccid blisters that easily tear.[12] The

initial lesions are sometimes referred to as targetoid lesions because of the target appearance, with 2 zones of color.[13] The rash usually involves the head, anterior and posterior torso, upper extremities, and lower extremities to above the knees and may progress to include lower back and gluteal area (see Figures 1 and 2).[8] The most important signs of an impending severe cutaneous reaction are skin pain, epidermolysis, and a positive Nikolsky's sign (slight rubbing of the skin causes separation of the epidermis and dermis).[14,15]

A retrospective study by Watanabe et al. suggested distinct differences between SJS and TEN and erythema multiforme major that can be helpful in making a definitive diagnosis. SJS and TEN patients were more likely to have mucous membrane involvement, higher C-reactive protein levels, and hepatic dysfunction. Erythema multiforme major patients had stronger mononuclear cell infiltration and required lower doses of systemic corticosteroids.[16]

The Score of Toxic Epidermal Necrosis (SCORTEN) scale is a severity-of-illness scale that can be used to determine the mortality rate of an individual patient.[17] Although it was initially developed for patients with SJS and TEN, it has been validated and used for patients with burns and other exfoliative disorders. Calculations are advised within the first 24 hours after admission and on day 3.[17] Tables 3 and 4 list the risk factors and mortality scores, showing that more risk factors result in a higher SCORTEN scale score, thereby indicating a higher mortality rate.

Diagnostic laboratory values can play a role in prognosis of the disease, especially TEN and SJS. Neutropenia and lymphopenia can occur and may be a negative prognostic factor.[18] The use of granulocyte colony-stimulating factor in the treatment of TEN has been shown to reverse the neutropenia with a corresponding increase in reepithelialization.[15] Hyperferritinemia as a result of acute liver failure can be a useful marker for the severity of DIHS.[19] Fujita and colleagues developed a rapid immunochromatographic test for detection of granulysin, a cytotoxic lipid-binding protein that causes apoptosis and is present in the blister fluid of patients with SJS and TEN. The granulysin was found to be elevated before skin and mucosal detachment occurred, suggesting that it may be a useful marker for detection of SJS and TEN in the early stages.[20]

Patch tests may be useful in most forms of DIHS, but not for SJS, TEN and vasculitis. The lymphocyte transformation test tends to test positive in maculopapular exanthemas, bullous exanthema, acute generalized exanthematous pustulosis, and DRESS, but rarely in TEN, cytopenias, and vasculitis.[21] Drug provocation tests may also be useful in diagnosing the drug allergy.[19]

Medical Management

The first and foremost medical strategy is identification and cessation of the causative agent, usually the last one the patient initiated 1 to 3 weeks prior to onset of symptoms.

Table 3   SCORTEN Scale Risk Factors for Determining Mortality Rates of Patients With Toxic Epidermal Necrolysis

Risk Factor	0	1
Age	<40 years	>40 years
Associated malignancy	No	Yes
Heart rate (beats per minute)	<120	>120
Serum urea nitrogen (mg/dL)	<27	>27
Detached or compromised body surface	<10%	>10%
Serum bicarbonate (mEq/L)	>20	<20
Serum glucose (mg/dL)	<250	>250

SCORTEN, score of toxic epidermal necrosis.

Thereafter, treatment is predicated on the severity of the symptoms, both cutaneous and systemic. Corticosteroids are used for both treatment of symptoms and prevention of progression. For milder cases, systemic corticosteroids dosed at 0.5 to 1 mg/kg/day and tapered over 6 to 8 weeks are recommended; for SJS, 1 mg/kg/day of prednisolone or 1 to 2 mg/kg/day of methylprednisolone is recommended.[21] Steroid therapy for TEN is reported as both controversial and no longer recommended; if used, it should be within the first 48 hours of treatment because of the increased risk of septic complications with an anti-inflammatory agent. Strict control of blood glucose levels is needed for patients with history of diabetes or on corticosteroids.[22]

For patients with extensive skin involvement, supportive care in an acute burn or intensive care unit is recommended for life support measures, pain management, and prevention of infection.[23] Mechanical ventilation, fluid resuscitation with IV fluids or Ringer's solution for electrolyte balance, anticoagulation with heparin to prevent thromboembolism, and supplemental nutrition via a nasogastric tube may be needed in severe cases.[2,12] Antibiotic therapy is not prophylactic but dependent on clinical symptoms, including positive skin cultures, sudden drop in temperature, or deterioration of patient's medical condition.[2] In order to prevent caloric loss and an increase in metabolic rate, a room temperature of 30 °C to 32 °C is also recommended.[2]

Clinical studies on the use of intravenous immunoglobulin for patients with SJS and TEN have shown mixed results. Successful treatment appears to be dose dependent (1 g/kg/day for 3 days with a total of 3 g/kg over 3

Table 4   Interpretation of the SCORTEN Scale

No. of risk factors	Mortality rate (%)
0-1	3.2
2	12.1
3	35.3
4	58.3
5 or more	>90

SCORTEN, score of toxic epidermal necrosis.
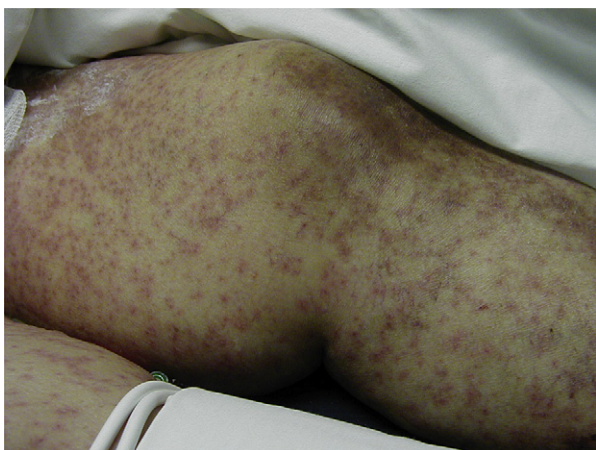
Figure 1   Skin Lesions on the Leg of a Patient With Toxic Epidermal Necrosis.

consecutive days), with early treatment recommended.[24] Other medications that have been studied and found beneficial include IV infliximab, cyclosporine, and IV N-acetylcysteine.[12] Acyclovir has been suggested for herpetic lesions in the oral cavity.[8]

Wound Management

For severe cases involving loss of epidermis, wound management goals are to prevent fluid loss, prevent infection, and facilitate reepithelialization. Although patients with SJS and TEN are best treated in an acute burn center, there are some definite differences in their clinical presentation that affect treatment. For example, SJS and TEN epidermal involvement may continue to spread after admission; subcutaneous necrosis is deeper in burns, thereby creating subcutaneous edema that is not observed in SJS and TEN; fluid requirements for SJS and TEN are usually two-thirds to three-fourths those of burn patients with the

Figure 2   Oral Lesions and Epidermal Necrolysis Visible on a Patient With Toxic Epidermal Necrosis.

same area involvement; and reepithelialization is usually faster in SJS and TEN because of more sparing of the hair follicles in the dermal layer.[2] Skin lesions can be expected to heal in an average of 15 days; oral and pharyngeal lesions may take approximately 4 weeks longer.[24]

Debridement of detached epidermal tissue is controversial and usually not advisable in patients who have a positive Nikolsky sign.[2] Collagen sheet dressings,[13] Biobrane (Dow B. Hickam, Inc, Sugarland, TX, USA),[8] and other occlusive nonadhesive wound coverings that prevent fluid loss and minimize pain with dressing changes have been recommended. These biological dressings create a physiological interface between the wound surface and the environment that is impermeable to bacteria, thus helping to prevent local wound infection.[25] In addition, the collagen sheets are noninflammatory, facilitate fibroblast migration to the wound site, assist in extracellular matrix synthesis, are nontoxic, and minimize scarring.[13]

Conformant (Smith & Nephew, Inc, Largo, FL, USA) is a nonadherent contact layer that comes in rolls and can be applied to large involved areas outside the operating room. Secondary absorbent layers are applied over the contact layer and changed as needed, thereby reducing the number of direct dressing changes. The mesh is released from the wound as healing occurs and thus is easily removed. Because Conformant has no antimicrobial properties, it is recommended only on uninfected skin early in the disease process.[8]

Oral topical anesthetic gel (lignocaine 2%) and chlorhexidine mouth rinse have been used for oral lesions, and dexamethasone (0.1%) eye drops for ocular lesions.[24] Post healing, artificial tears and lubricants may be needed.[2]

Skin care after full closure includes use of sunscreens and/or avoidance of sun exposure. Readministration of the causative medication should also be avoided. A second episode due to the same drug may have a shorter onset than did the first episode.[26]

Summary

In summary, DIHS usually occurs 2 to 6 weeks after initiation of the causative medication and can cause cutaneous and oral symptoms ranging from slight to life threatening. The most immediate care involves identification and cessation of the medication, followed by appropriate skin care and intensive medical care when indicated. A careful and thorough review of all medications, including start dates, is an integral component of the subjective and medical history of any patient presenting with dermatologic disorders.

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