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Abstract

Drug-induced delayed multi-organ hypersensitivity syndrome (DIDMOHS), also known as drug reaction (or rash) with eosinophilia and systemic symptoms (DRESS), drug-induced hypersensitivity syndrome (DIHS), or drug hypersensitivity syndrome (DHS) is a rare, potentially fatal, drug-induced hypersensitivity reaction characterized by cutaneous eruption, fever, lymphadenopathy, hematologic abnormalities, and visceral manifestations. Anticonvulsants such as carbamazepine, phenytoin, lamotrigine, and phenobarbital as well as allopurinol and sulfonamides, are the most common causes of DIDMOHS. Impaired drug detoxification and herpes virus reactivation play a key role in DIDMOHS pathogenesis. Human leukocyte antigen (HLA) haplotypes also contribute. Early cutaneous findings generally include a morbilliform eruption characterized by diffuse, erythematous, pruritic macules across the face, upper trunk, and upper extremities with later extension to the lower extremities. Rapid confluence and progression are characteristic. DIDMOHS frequently involves the lymphatic, hematologic, and hepatic systems. Renal, pulmonary, and cardiac dysfunction may also ensue.

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Early recognition and diagnosis with prompt withdrawal of the culprit drug is paramount. Corticosteroid therapy is widely accepted as the cornerstone of DIDMOHS management. Moving forward, haplotyping and assays such as the lymphocyte transformation test (LTT) will aid in the primary prevention and diagnosis of DIDMOHS. Novel steroid-sparing immunomodulatory agents also have significant therapeutic potential.

Keywords

Corticosteroids • Cytochrome P450 • Drug-induced delayed multi-organ hypersensitivity syndrome (DIDMOHS) • Drug reaction with eosinophilia and systemic symptoms (DRESS) • Drug allergy • Drug eruption • Drug-induced hypersensitivity syndrome (DIHS) • Eosinophilia • Erythroderma herpesvirus • Human leukocyte antigen (HLA) haplotype

Introduction

Drug-induced delayed multi-organ hypersensitivity syndrome (DIDMOHS) is a rare, potentially fatal, drug-induced hypersensitivity reaction characterized by cutaneous eruption, fever, lymphadenopathy, hematologic abnormalities and visceral manifestations.

A variety of other terms have been used to describe this condition, including drug reaction (or rash) with eosinophilia and systemic symptoms (DRESS), drug-induced hypersensitivity syndrome (DIHS), drug hypersensitivity syndrome (DHS), mononucleosis-like syndrome, anticonvulsant hypersensitivity syndrome (AHS), phenytoin syndrome and dapsone syndrome. The nosographic controversy surrounding DIDMOHS mirrors the absence of established diagnostic criteria for the disorder and its highly diverse clinical manifestations. We use the acronym DIDMOHS herein.

DIDMOHS was initially noted among patients treated with anti-epileptic agents in the 1930s when phenytoin was introduced. To this day, anti-epileptic agents (specifically carbamazepine, phenytoin, lamotrigine, and phenobarbital) and allopurinol are the most common causes of DIDMOHS. DIDMOHS is also induced by sulfonamides, especially sulfasalazine and dapsone, as well as vancomycin, minocycline, gold salts, and HIV medications such as abacavir.

Epidemiology

In the general population, DIDMOHS risk ranges between 1 in 1000 and 1 in 1,000 drug exposures. Immunocompromise predisposes individuals to DIDMOHS. Although DIDMOHS may occur in the pediatric population, the majority of cases occur in adults, with roughly equal distribution among males and females. African-Americans and individuals from the Caribbean basin may be at increased risk.

DIDMOHS frequency also varies based on drug types. Carbamazepine and phenytoin induce DIDMOHS at a rate ranging from 1 to 5 in 1,000 exposed individuals. Although relatively infrequently used, lamotrigine is associated with DIDMOHS in 1 in 300 adults undergoing treatment.

Pathophysiology

DIDMOHS pathogenesis is incompletely understood. However, it is widely accepted that immune-mediated phenomena are responsible. From a broad perspective, an immune diathesis is suggested by the increased risk with immunocompromise. Several attributes of DIDMOHS implicate a delayed-type cell mediated response in particular. These include its reproducibility with patch testing and obligatory sensitization interval between drug exposure and reaction onset. Rapid recrudescence

following drug re-challenge likewise insinuates cell-mediated immunopathogenesis.

HLA Haplotype

Strong associations exist between certain human leukocyte antigen (HLA) haplotypes and DIDMOHS. Interaction between the specific haplotype and culprit drug is thought to form a hapten. Subsequently, the hapten is presented to T-cells to generate the immune response. In the acute phase of DIDMOHS, expansion of both CD4⁺ and CD8⁺ T-cell populations occurs. These T-cells secrete proinflammatory cytokines such as interferon-gamma, interleukin-5 and others. In vitro and in vivo evidence in the form of lymphocyte proliferation analysis and patch testing demonstrates this response is drug-specific.

Heightened levels of interleukin-5 in conjunction with eotaxin evoke the eosinophilia of DIDMOHS. In turn, hypereosinophilia is thought to contribute to internal organ involvement, as eosinophil granule proteins are toxic to many tissues. Tumor necrosis factor is also involved, propagating tissue damage after secretion by macrophages.

The HLA-DR3, HLA-DQ2, and HLA-B*1502 haplotypes have been implicated in carbamazepine-induced DIDMOHS. Among individuals of Portuguese or Han Chinese descent, HLA-B*5801 is linked with severe allopurinol-induced drug hypersensitivity reactions, including DIDMOHS. White individuals with the HLA-B*5701 haplotype are predisposed to abacavir-induced DIDMOHS. In addition, the HLA-A*3101 haplotype is linked with higher frequency of DIDMOHS among European and Han Chinese populations.

The above associations notwithstanding, HLA haplotypes appear to be necessary but not sufficient for DIDMOHS initiation; these markers have high negative predictive value but low positive predictive value for drug hypersensitivity.

Drug Detoxification

Polymorphism of genes encoding enzymes responsible for the detoxification of drugs and

intermediate metabolites also contributes to DIDMOHS development. DIDMOHS cases often occur in a familial distribution, the basis for which appears to be autosomal dominant inheritance of detoxification genes.

In most individuals, anticonvulsants such as carbamazepine, phenytoin, and phenobarbital are metabolized by the cytochrome P450 (CYP-450) system, generating intermediate toxic arene oxides. These arene oxides are detoxified by the enzymes glutathione transferase and epoxide hydroxylase. However, mutations in these enzymes impair detoxification. Thus, toxic arene oxides thought to elicit the DIDMOHS response accumulate. Among patients recovering from DIDMOHS, defective detoxification of anticonvulsants and sulfonamides has been established. In addition, other processes inhibiting or inducing CYP-450 activity also modify DIDMOHS risk.

Sulfonamide-induced DIDMOHS susceptibility varies based on sensitivity of lymphocytes to hydroxylamine, a toxic intermediate generated by CYP-450. Patients with sulfonamide-induced DIDMOHS may develop antibodies that recognize microsomal proteins to which this reactive intermediate binds. Risk is also increased by specific acetylation polymorphisms which impede the conjugation phase of drug detoxification, particularly the slow N-acetylator phenotype.

Herpes Virus Reactivation

Reactivation of herpes viruses also contributes to DIDMOHS pathogenesis, principally human herpes virus (HHV)-6. DIDMOHS is also associated with HHV-7, cytomegalovirus (CMV), and Epstein-Barr virus (EBV) reactivation. Viral reactivation in DIDMOHS occurs sequentially. HHV-6 and EBV initiate the cascade of viral reactivation; with progression HHV-7 and finally CMV reactivation occur. Interestingly, the sequential order of viral reactivation in DIDMOHS parallels that of graft-versus-host disease (GVHD).

Approximately three out of five DIDMOHS patients demonstrate increasing anti-HHV-6 IgG antibodies and HHV-6 DNA titers in the weeks following the onset of cutaneous features. In situ

hybridization (ISH) and polymerase chain reaction (PCR) also confirm HHV-6 mRNA and DNA presence in lesional skin. In severe cases associated with hepatitis or encephalitis, HHV-6 may be detected in the liver and cerebrospinal fluid, respectively. In addition, recurrence of DIDMOHS manifestations such as fever and hepatitis appear to coincide with the presence of HHV-6 in sera.

Clinical Presentation

Prodrome

In most cases, DIDMOHS presents 2–6 weeks following exposure to the offending medication. This latency interval is substantially longer than the typical 4- to 9-day interval of exanthematous drug eruptions and 4- to 28-day interval of toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS). Latency varies based on the specific culprit drug; for instance, carbamazepine-induced DIDMOHS presents later than allopurinol-induced DIDMOHS. Malaise, pruritus, and pyrexia are often the initial manifestations of DIDMOHS. Typically, fever ranges between 38 and 40 °C and precedes dermatologic features by several days. In some cases, pyrexia lasts several weeks. Dysphagia may appear before skin lesions. Prodromal symptoms may also include lymphadenopathy.

Mucocutaneous Manifestations

Typically, DIDMOHS begins as a morbilliform eruption characterized by diffuse, erythematous, pruritic macules. The face, upper trunk, and upper extremities are often the first sites involved, with extension to the lower extremities. Follicular accentuation as well as sterile follicular or non-follicular-based pustules may be observed. Additional findings may include vesicles, bullae, and atypical target lesions.

Rapid confluence and progression of erythema is common in DIDMOHS. In half of cases, erythema encompasses over 50 % body surface area



Fig. 25.1 Exanthem over legs developing a violaceous hue before scaling. This patient had been on clindamycin for many weeks and developed this skin eruption, which generalized with time. He had renal disease that resolved after months of systemic corticosteroids and discontinuing the clindamycin. He was also noted to have eosinophilia

(BSA). Twenty to thirty percent of patients experience progression to exfoliative dermatitis or erythroderma, defined by generalized erythema and scale involving >90 % of BSA.

Lesions may become infiltrated and indurated with edema. Facial edema is present in half of cases, often with characteristic erythema, symmetry, and persistence. The periorbital and mid-facial regions are typically the most significantly affected. In some cases, facial edema is so prominent as to mimic angioedema.

The exanthem of DIDMOHS may assume a violaceous hue with generalized scale after initial presentation (Fig. 25.1). Even after withdrawal of the culprit drug, these findings may persist for weeks or months. Mucosal manifestations in the form of cheilitis, erosions, dysphagia, pharyngitis, pharyngeal erythema, and tonsillar enlargement may also be seen. In a recent prospective study, the oral mucosa was involved in 52 % of 117 cases.

Cutaneous Histopathology

Histopathology of skin lesions may aid in confirming the diagnosis of DIDMOHS, although the findings are relatively non-specific. There is an inflammatory infiltrate of lymphocytes, and often eosinophils in the dermis. There is also

interface dermatitis with variable degrees of spongiosis and keratinocyte dyskeratosis. In more severe cases, the dyskeratosis is widespread, and the interface vacuolization may lead to subepidermal vesiculation. These changes are evident clinically as epidermal necrosis and blistering.

Internal Manifestations

DIDMOHS may involve multiple organ systems, most commonly the lymphatic, hematologic, and hepatic systems. Renal, pulmonary, and cardiac dysfunction may also ensue. In rare cases, endocrine, gastrointestinal, musculoskeletal, and neurologic function may be impaired.

Lymphatic

Lymphadenopathy is prevalent in DIDMOHS, affecting 75 % of patients. Patients may experience limited lymph node involvement or generalized lymphadenopathy with enlargement (1–2 cm) and tenderness involving the cervical, axillary, and inguinal lymph nodal regions. Two distinct variants are present on histopathology: benign lymphoid hyperplasia and pseudolymphoma.

Hematologic

Hematologic abnormalities are common in DIDMOHS. Eosinophilia is prominent, with eosinophil counts above $>700/\mu\text{L}$ in 50–90 % of cases. Patients often demonstrate leukocytosis, up to 50×10^9 leukocytes/L. During the period between drug initiation and the onset of DIDMOHS symptoms, a period of leukopenia or lymphopenia frequently precedes leukocytosis. Atypical lymphocytosis with large activated lymphocytes, lymphoblasts, or mononucleosis-like cells may be observed. Atypical lymphocytes, often regarded as characteristic for DIDMOHS, are present in roughly two-thirds of patients.

Hematology may also reveal a decrease in hemoglobin and hematocrit, as well as thrombocytopenia. In rare, severe cases, hemophagocytic syndrome has been linked with DIDMOHS approximately 2 weeks following reaction onset.

Hepatic

The liver is the most frequent site of internal organ involvement in DIDMOHS. Hepatic features are associated with phenytoin, minocycline, and dapsone-induced DIDMOHS. Hepatomegaly and jaundice may be seen, often with concurrent hepatitis of varying severity. Hepatitis associated with DIDMOHS is generally anicteric. In most cases, hepatitis is asymptomatic and detected only after laboratory studies are obtained. Approximately 70 % of patients exhibit serum alanine aminotransferase (ALT) elevation. DIDMOHS with erythema multiforme (EM)-like cutaneous findings (purpura and atypical targets) correlates with significantly greater increase of liver enzymes. Liver enzyme levels frequently remain elevated for several days following culprit drug withdrawal. In some cases, ALT elevation may persist for months.

Severe acute hepatitis, defined by ALT elevation of >10 times the upper limit of normal and/or acute hepatic failure with coagulopathy and encephalopathy, may occur in conjunction with DIDMOHS. Sulfasalazine is the most frequently implicated drug in this instance. In severe cases, generalized hepatic necrosis may be observed. Liver failure with coagulopathy and sepsis may complicate hepatic necrosis. In fact, hepatic necrosis is the leading cause of mortality in DIDMOHS. Jaundice as well as profound elevation of aspartate aminotransferase (AST) and bilirubin are prognostic markers for incipient liver transplantation or death, as cases of life-saving emergency liver transplantation have been reported.

Renal

Renal manifestations occur in 10–30 % of DIDMOHS patients; most commonly acute interstitial nephritis. Those with comorbid kidney disease and the elderly are particularly susceptible. Allopurinol is most closely linked with renal involvement, though carbamazepine and dapsone are also associated. In most cases, patients are asymptomatic, though patients may rarely report hematuria. Laboratory studies reveal serum creatinine and blood urea nitrogen (BUN) elevation consistent with impaired clearance. Proteinuria

and eosinophilia may also be observed. Typically, renal dysfunction is mild and recovery occurs following withdrawal of the culprit drug.

Pulmonary

Pulmonary manifestations of DIDMOHS may also occur. Patients may experience dyspnea as well as nonproductive cough. Interstitial pneumonia may be observed, particularly in minocycline-induced DIDMOHS. In addition, pleuritis and impaired pulmonary function in association with DIDMOHS have been reported. DIDMOHS patients are also at risk for acute respiratory distress syndrome (ARDS) requiring emergent intubation and mechanical ventilation.

Cardiac

DIDMOHS may also involve the heart in the form of myocarditis. Minocycline and ampicillin are the most frequently implicated drugs. The onset of myocarditis is unpredictable, as it may occur early in the evolution of DIDMOHS or months following drug withdrawal.

Endocrine

Endocrine dysfunction may also be observed in association with DIDMOHS, more commonly as a long-term complication than during the acute phase of hypersensitivity. Thyroid abnormalities, most commonly thyroiditis and sick euthyroid syndrome, may be found, both of which may generate clinical hyperthyroidism, hypothyroidism, or both during their course. In addition, isolated elevation of free T4 or low thyrotropin (TSH) may be observed. Three to twelve months after DIDMOHS resolution, antithyroid antibodies may be detected. Correspondingly, symptoms of classical Graves' Disease ensue. In rare cases, overt thyrotoxicosis may develop. Hashimoto's Thyroiditis with antibodies directed to thyroid peroxidase (TPO) and thyroglobulin may also complicate DIDMOHS. Thus, routine assessment of thyroid function is recommended for at least 2 years in patients recovering from DIDMOHS.

Fulminant Type 1 diabetes mellitus (DMT1) may also present as a rare complication of DIDMOHS. Autoantibodies associated with classical DMT1 (i.e., islet cell and glutamic acid

decarboxylase autoantibodies, etc.) are characteristically absent. Instead, DMT1 associated with DIDMOHS is thought to be related to HHV-6 reactivation.

Gastrointestinal

DIDMOHS may also affect the gastrointestinal system. Gastroenteritis and associated dehydration are the most frequent findings. Acute gastrointestinal bleeding may also occur as a complication of ulcers, particularly in the setting of disseminated CMV infection. Arterial bleeding demonstrated via endoscopy may require emergent clipping and blood transfusion. In addition, colitis, pancreatitis, and even chronic enteropathy have also been reported.

Musculoskeletal

Musculoskeletal involvement in the form of arthralgia and/or arthritis, in addition to myositis, may also occur in the context of DIDMOHS.

Neurological

In rare cases, neurological manifestations evolve from DIDMOHS, namely meningitis and encephalitis. These complications develop roughly 2–4 weeks following reaction onset. Associated clinical findings include speech abnormalities, headache, seizure, muscle weakness, cranial nerve palsies, and coma.

Diagnosis

The protean manifestations of DIDMOHS complicate diagnosis. The diagnosis of DIDMOHS may be delayed or progress unrecognized due to its variable findings, evolution, severity, or similarity to alternative disorders. Disparate or fragmentary clinical features, for instance hepatitis without rash, or eosinophilia and pulmonary infiltrates in isolation may be enigmatic. Presently, no single set of diagnostic criteria has been widely accepted, adding to the challenge of diagnosis.

It is critical to exclude other serious processes when DIDMOHS is suspected. Viral and bacterial infections may present similar to

DIDMOHS. Hematologic disorders including various lymphomas, particularly angioimmunoblastic T-cell lymphoma as well as idiopathic hypereosinophilic syndrome, may share numerous clinical features with DIDMOHS but are distinguished via histologic analysis. Autoimmune/vasculitic processes including systemic lupus erythematosus, polyarteritis nodosa, granulomatosis with polyangiitis, and Churg-Strauss Syndrome, may present with cutaneous eruption, eosinophilia, and multiorgan manifestations. However, immunologic traits such as antineutrophil cytoplasmic antibody (ANCA) and antinuclear antibody (ANA) patterns aid in distinguishing these conditions from DIDMOHS.

It is also critical to distinguish DIDMOHS from other potentially fatal cutaneous drug eruptions because management differs among these conditions. Compared to TEN/SJS, acute generalized exanthematous pustulosis (AGEP) and drug-induced erythroderma, in DIDMOHS, the interval between culprit drug initiation and reaction onset is longer. DIDMOHS also takes longer to resolve. Histopathology differentiates TEN/SJS by its epidermal necrolysis and AGEP by its subcorneal pustules. In addition, eosinophilia, atypical lymphocytosis, and hepatitis are found with significantly greater frequency in DIDMOHS than other acute drug eruptions.

Favoring the term DRESS, Bocquet, Bagot and Roujeau proposed the first diagnostic criteria. According to Bocquet et al., the presence of three or more of the following is consistent with a diagnosis of DRESS: (1) drug rash; (2) eosinophilia $>1.5 \times 10^9/L$ or atypical lymphocytes present; (3) systemic manifestations (adenopathy [>2 cm in diameter], or hepatitis [transaminase elevation of at least two times upper limit], or interstitial nephritis, or pneumonitis, or carditis).

The European Registry of Severe Cutaneous Adverse Reaction (RegiSCAR) group later refined these initial criteria. According to RegiSCAR, the following three features must be present for diagnosis: (1) acute rash; (2) clinical suspicion of drug causality; (3) and hospitalization. In addition, three of the four following systemic features must be demonstrated: (1) fever >38 °C; (2) lymphadenopathy of two or more sites; (3)

involvement of at least one internal organ (liver, kidney, heart, pancreas, or other); and (4) hematologic involvement (lymphocyte count outside normal limit, eosinophil count higher than upper limit, or platelet count below lower limit). Points are allotted based on the extent of the above findings. A definite diagnosis is confirmed with a total score >5 . Scores of <2 , 2–3, or 4–5 are consistent with no case, a possible case, or probable case, respectively. Details of point assignment are available in prior publications.

Distinct criteria have been also proposed by the Japanese Research Committee on Severe Cutaneous Adverse Reaction (J-SCAR) group; the J-SCAR group uses the term DIHS. Their criteria are the first to incorporate contribution by HHV-6. J-SCAR criteria include the following: (1) maculopapular rash developing 3 weeks after culprit drug initiation; (2) persistent symptoms after withdrawal of culprit drug; (3) fever >38 °C; (4) hepatic abnormalities (ALT >100 units/L) or other organ involvement; (5) leukocyte abnormalities (one or more of the following: leukocytosis [$>11 \times 10^9/L$], atypical lymphocytes [>5 %], or eosinophilia [$>1.5 \times 10^9/L$]); (6) lymphadenopathy; and (7) HHV-6 reactivation. If all seven features are present, typical DIHS is confirmed. If the first five features are present, atypical DIHS is diagnosed. However, implementation of the J-SCAR criteria may be impaired by limited availability of serologies, such as HHV-6 IgG antibody titers.

No international consensus on the most suitable criteria for the diagnosis of DIDMOHS has been reached.

Treatment and Prognosis

Early recognition and diagnosis are paramount, as delay in diagnosis is detrimental to patient outcomes. Likewise, prompt withdrawal of the culprit drug is vital.

Corticosteroid therapy is widely accepted as the cornerstone of DIDMOHS management. Therapy should commence at a minimum dose of 1.0 mg/kg/day of prednisone or equivalent. In general, patients demonstrate rapid improvement

within several days of corticosteroid initiation. Further, corticosteroid therapy may preclude the development of late autoimmune sequelae. Following resolution of clinical and laboratory abnormalities, the induction dose may be gradually tapered over 3–6 months. Marked clinical deterioration may be observed with inadvertent discontinuation or overly rapid corticosteroid tapering. Immediate intervention to prevent organ failure is vital upon recognition of visceral dysfunction. The optimal approach is interdisciplinary, with involvement of specialists as indicated.

Patients with severe visceral manifestations may be treated with pulsed intravenous methylprednisolone at 30 mg/kg for 3 days. Pulsed methylprednisolone is also appropriate for patients who exhibit either no improvement or exacerbation on oral corticosteroids.

Steroid-sparing agents may provide additional treatment options, although no protocols exist. Intravenous immunoglobulin (IVIG) therapy has demonstrated therapeutic benefit in several cases. The impact of IVIG is thought to be related to its anti-inflammatory properties, support of anti-HHV-6 immunity, and repletion of immunoglobulins, which are often deficient in DIDMOHS. However, severe adverse effects or uncontrolled DIDMOHS occurred in five of six patients in one recent trial of single-agent IVIG treatment. Thus, IVIG is not recommended as monotherapy.

Treatment of DIDMOHS with cyclosporine and cyclophosphamide also appear in the literature. N-acetylcysteine (NAC) may also be a beneficial adjunct in anticonvulsant-induced DIDMOHS, as it moderates reactive intermediate toxicity and enhances drug metabolism. Antiviral interventions such as valganciclovir or ganciclovir may prevent or abrogate complications associated with HHV-6 reactivation. Consequently, a novel combination treatment regimen targeting distinct causative mechanisms has been proposed: prednisone, NAC, and valganciclovir.

Although corticosteroids have demonstrated efficacy in the acute setting, the long-term impact of corticosteroids on the course of DIDMOHS is unknown. Prolonged immunosuppression may facilitate viral reactivation. Moreover, a chronic,

steroid-dependent variant of DIDMOHS has been described.

In cases without severe organ involvement, for instance those devoid of renal or pulmonary involvement and limited hepatic enzyme elevation (e.g., <3 times upper limit of normal), symptomatic or supportive treatment may be appropriate. Supportive therapy should include antipyretics. Topical steroids and emollients as well as H1-antihistamines may be used for control of cutaneous symptoms such as pruritus. Non-steroidal anti-inflammatory agents should be avoided as these may complicate or exacerbate the clinical picture due to cross-reactivity. For the same reason, routine antibiotic prophylaxis is not recommended.

Transfer to a specialized intensive care or burn unit is appropriate for patients presenting with erythroderma. Similar to patients with extensive burns, individuals with erythroderma may require fluid resuscitation, correction of electrolyte abnormalities, elevated environmental temperatures, nutritional support, and vigilant skin care with emollient dressings. These patients are also at heightened risk for infection due to compromised epidermal barrier function. Erythroderma is particularly precarious in those with comorbid heart disease or the elderly, as the high-output state generated by cutaneous vasodilation may precipitate heart failure.

The consensus group of the French Society of Dermatology has proposed a decision tree for the management of DIDMOHS adapted to case-specific clinical manifestations. The foremost step is immediate withdrawal of the offending agent. They recommend supportive therapy for patients without signs of severity (hepatic enzymes <5 times normal, renal involvement, pneumonia, hemophagocytosis, cardiac involvement, etc.). Recommended supportive therapies include topical corticosteroids, emollients, and H1-antihistamines. One mg/kg/day of prednisone or equivalent as well as evaluation by appropriate specialists is advised for patients with the above signs of severity. In the presence of life-threatening conditions such as hemophagocytosis with bone marrow failure, encephalitis, renal failure, respiratory failure, or severe hepatitis,

combination therapy via addition of IVIG (2 g/kg over 5 days) is recommended. Patients with severe DIDMOHS and confirmed viral reactivation may be given antivirals such as ganciclovir in addition to steroids and/or IVIG.

Most patients experience full recovery from DIDMOHS, though symptoms may take many weeks to resolve; dermatologic sequelae such as dyschromia often persist for longer intervals. As in the acute setting, an interdisciplinary approach to follow-up is imperative for those with visceral involvement.

Retrospective studies have reported a mortality rate for DIDMOHS of 5–10 %, with most fatalities occurring outside the acute phase of illness. Children recover more readily from DIDMOHS, while the prognosis is more guarded in the elderly population.

Liver failure, multi-organ failure, fulminant myocarditis, hemophagocytosis, and sepsis are responsible for the majority of DIDMOHS-related deaths. Systemic inflammatory response syndrome (SIRS), tachycardia, tachypnea, leukocytosis, gastrointestinal bleeding, and coagulopathy portend heightened mortality risk in DIDMOHS.

Conclusions

Moving forward, DIDMOHS may prove an ideal setting for the practice of personalized medicine. For primary prevention of DIDMOHS, HLA haplotyping prior to drug administration will be beneficial. The FDA now recommends testing patients with Asian ancestry for HLA-B*1502 prior to initiating carbamazepine therapy.

The lymphocyte transformation test (LTT) will likely aid in determining the causative drug in DIDMOHS. The LTT quantifies T-cell proliferation in the presence of suspect drug(s). This test detects cross-reactivity and may also be used to distinguish reactions with distinct immunopathologic mechanisms. Accordingly, it may be used to select safe medication alternatives following adverse

reactions such as DIDMOHS. However, the false-negative rate of LTT is elevated during the acute phase of DIDMOHS. Thus, it is recommended that LTT be deferred until 5–8 weeks after DIDMOHS onset.

Novel immunomodulatory agents may be effective in the therapy of DIDMOHS, sparing patients the considerable morbidity of systemic corticosteroids. However, additional trials will be necessary to characterize the impact of these interventions on the course of DIDMOHS.

Suggested Reading

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