Piperacillin-Tazobactam–Induced Drug Hypersensitivity Syndrome

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GOAL

To understand drug hypersensitivity syndrome (DHS) to better manage patients with the condition

OBJECTIVES

Upon completion of this activity, dermatologists and general practitioners should be able to:

1. Recognize DHS.
2. Describe the pathogenesis of DHS.
3. Identify therapeutic options for DHS.

CME Test on page 368.

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The drug hypersensitivity syndrome (DHS) is a rare but serious and potentially life-threatening reaction to common drugs in predisposed individuals. The syndrome is a triad of fever, skin eruption, and internal organ involvement. Prompt identification and discontinuation of the offending drug with symptomatic treatment of toxic effects is the mainstay of therapy for DHS.

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Case Report

A 28-year-old paraplegic woman (secondary to spina bifida) was admitted to the hospital for vacuum-assisted closure of a chronic nonhealing left ankle ulcer of 21 months' duration. The patient was on oral ciprofloxacin 500 mg twice daily[1] and oral

clindamycin hydrochloride 300 mg 4 times daily for treatment of repeated bacterial infections. While in the hospital, a bone scan was performed and the results confirmed osteomyelitis of the left talonavicular region. The patient's oral therapeutic regimen was discontinued and she was given piperacillin-tazobactam (PT) 3.375 g by intravenous infusion every 6 hours. She responded well to this treatment, with a subsequent decrease in ulcer size. Two weeks following therapy, the patient developed fever, skin rash, nausea, and headache. The next day, the patient became anuric. There was no family history of renal or hepatic disease.

Results of a physical examination revealed the patient was febrile (temperature, 39.4°C); a widespread, symmetrical, morbilliform skin eruption was noted on her face, trunk, forearms, and legs. She had slight facial edema, with erythema and enlarged cervical lymph nodes bilaterally.

Results of laboratory investigations revealed the patient had an elevated white blood cell count of 18.4×10^9/L (reference range, 4.5–11.0×10^9/L), with a differential of 62% lymphocytes, 23% neutrophils, 5% bands, 2% monocytes, and 8% eosinophils (reference ranges, 34%, 56%, 3%, 4%, and 2.7%, respectively). The patient's liver enzyme levels were elevated including aspartate aminotransferase, 1545 U/L (reference range, 20–48 U/L); alanine aminotransferase, 383 U/L (reference range, 10–40 U/L); alkaline phosphatase, 297 U/L (reference range, 50–120 U/L); γ-glutamyltransferase, 235 U/L (reference range, 0–30 U/L); and lactate dehydrogenase, 5638 U/L (reference range, 50–200 U/L); synthetic liver function remained within reference range. The patient's serum creatinine (SCr) level was 212 μmol/L (reference range, 53–106 μmol/L), with a baseline of 45 μmol/L. Results of a urinalysis were within reference range; results of a urine culture were negative. An ultrasound of the abdomen did not reveal a cause for renal failure or liver dysfunction.

A diagnosis of PT-induced hypersensitivity reaction with acute toxic hepatitis and interstitial nephritis was made. The intravenous antibiotics were discontinued and the patient was given prednisone and hemodialysis 3 times weekly. Her SCr levels fluctuated during the treatment, reaching a peak of 461 μmol/L. The patient responded well to therapy, though her liver enzyme and SCr levels did not return to baseline at the time of hospital discharge (aspartate aminotransferase, 42 U/L; alanine aminotransferase, 72 U/L; alkaline phosphatase, 72 U/L; γ-glutamyltransferase, 122 U/L; lactate dehydrogenase, 300 U/L; SCr, 123 μmol/L). The patient was followed as an outpatient.

Comment

Drug hypersensitivity syndrome (DHS) is characterized by a triad of fever, skin eruption, and internal organ involvement.[2] DHS also is known as DRESS syndrome (drug rash with eosinophilia and systemic symptoms)[3] and DIDMOHS (drug-induced delayed multiorgan hypersensitivity syndrome).[4] DHS also has been described as multisystem hypersensitivity, pseudolymphoma, febrile mucocutaneous syndrome, Kawasakilike syndrome, mononucleosislike illness, and graft-versus-hostlike illness.[5]

DHS is a result of a specific, severe, idiosyncratic reaction. The incidence of DHS ranges between 1 in 1000 and 1 in 10,000 exposures. DHS occurs more often in women than in men.[5] A number of drugs have been reported to cause this syndrome, including sulfonamide antibiotics, trimethoprim, dapsone, and aromatic anticonvulsants (eg, phenytoin, phenobarbital, carbamazepine),[6-9] as well as lamotrigine,[10] minocycline,[11-12] and allopurinol.[13-14] Antiviral medications such as abacavir and nevirapine also have been reported.[15]

DHS occurs on the first exposure to the offending drug, with the symptoms starting 2 to 6 weeks after initiation of the medication. Reexposure to the same offending drug may cause symptoms to develop within 24 hours. The symptoms may last for weeks or even months after discontinuing the medication.

The most common presentations in patients with DHS are fever, which ranges from 38°C to 40°C and occurs in 85% of cases, malaise, pharyngitis, and cervical lymphadenopathy. A generalized exanthematous morbilliform rash develops in 75% of cases, either with or soon after the fever. Cutaneous manifestations can present in a number of ways including exfoliative erythroderma, follicular or nonfollicular pustules, purpuric lesions or blisters, and tense bullae induced by dermal edema.[5] The face, upper trunk, and extremities usually are involved. Facial edema is a common finding. Additionally, hypotension, bleeding, interstitial nephritis, arthralgia, arthritis, myositis, thyroiditis, pneumonitis, respiratory distress syndrome, pericarditis, myocarditis, pancreatitis, colitis, orchitis, encephalitis, and aseptic meningitis have been reported.[5] Hematologic involvement includes prominent eosinophilia, which occurs in 90% of cases; mononucleosislike atypical lymphocytosis, which occurs in 40% of cases; neutrophilia or neutropenia; thrombocytopenia; and hemolytic anemia. Elevated levels of liver transaminase, alkaline phosphatase, bilirubin, and prothrombin time are seen in 50% of cases. Fulminant hepatitis is the major cause of death associated with this syndrome, occurring in 5% to 10% of cases.[16]

Pathogenesis of DHS—The pathogenesis of DHS is unknown but likely is multifactorial. Exposure to a drug is the causal agent, but it is not enough to elicit DHS. It is postulated that a specific alteration in the metabolism and detoxification of a particular drug can occur in phenotypic susceptible individuals, which leads to an increased risk of toxic consequences of reactive oxidative drug metabolites.[2,5,17] Aromatic anticonvulsants are metabolized by cytochrome P450 to reactive metabolites that are detoxified by epoxide hydroxylase. If the detoxification process is defective, the toxic metabolite acts as a hapten, initiating an immune response. In 70% to 75% of DHS cases, cross-reactivity is shown between the different aromatic anticonvulsants. Lamotrigine has been reported to cause DHS, though it is not one of the aromatic anticonvulsants. The concurrent use of lamotrigine with valproic acid increases the risk of reaction because valproic acid prolongs the elimination half-life of lamotrigine.[5,18] There is a familial susceptibility of hypersensitivity to anticonvulsants, thus counseling of family members is essential.[2,19]

Sulfonamide antibiotics are metabolized by slow acetylators to reactive metabolites, mainly hydroxylamines and nitroso compounds, causing cytotoxicity. In patients with glutathione deficiency, detoxification of these toxic metabolites is not possible and can lead to DHS. There is an increased risk (25%) of first-degree relatives having a similar defect.[20] Aromatic amines (eg, dapsone, acebutolol, procainamide) are metabolized to the same compounds and hence there is a potential for cross-reactivity occurring in these individuals. There is no cross-reactivity between sulfonamides and other nonaromatic amines such as furosemide, thiazide diuretics, acetazolamide, celecoxib, and sulfonylureas.[21] The drugs associated with DHS are summarized in the Table.

The association of the human herpesvirus family—specifically, human herpesvirus 6—and DHS has been questioned. Descamps et al[22] explored the issues regarding viral infection and DHS. Hashimoto et al[23] suggested that the prolonged course, slow resolution, and/or relapse of cases of DHS may be attributed to human herpesvirus 6

Drugs Associated With Drug Hypersensitivity Syndrome

Drug	Clinical Features
Allopurinol	Fever, sore throat, facial edema, morbilliform rash, lymphadenopathy, hepatitis, atypical lymphocytes
Carbamazepine	Fever, facial edema, lymphadenopathy, eosinophilia, atypical lymphocytes, follicular skin eruption, erythroderma
Lamotrigine	Fever, morbilliform rash, hepatitis, eosinophilia, mucositis
Minocycline	Fever, sore throat, eosinophilia, arthralgia, lupuslike skin eruption, hypotension, pneumonitis
Phenobarbital	Fever, sore throat, facial edema, morbilliform rash, purpuric lesions, lymphadenopathy, hepatitis, eosinophilia, atypical lymphocytes
Phenytoin	Fever, purpuric lesions, hepatitis, eosinophilia, atypical lymphocytes, exanthem, renal dysfunction, disseminated intravascular coagulation
Piperacillin-tazobactam	Fever, sore throat, nausea, facial edema, morbilliform skin eruption, lymphadenopathy, nephritis, hepatitis, eosinophilia
Sulfasalazine	Fever, sore throat, nausea, vomiting, facial edema, lymphadenopathy, hepatitis, nephritis, atypical lymphocytes, maculopapular rash, petechiae
Trimethoprim	Fever, headache, backache, atypical lymphocytes, meningitis, thrombocytopenia
Valproic acid	Fever, facial edema, morbilliform skin eruption, lymphadenopathy, hepatitis, eosinophilia, encephalopathy

reactivation. Condat et al[24] have shown that reactivation of human herpesvirus 6 coincides with the course of DHS, but the direct causal effect of the virus is yet to be established.

Patients with human immunodeficiency virus are at a higher susceptibility to toxic drug metabolites.[25] This susceptibility could be explained by the reduced level of glutathione, selenium, and other antioxidants in these patients. Glutathione plays an important role in the antioxidant defense of cells. Immune mechanisms also are thought to contribute to the pathogenesis of DHS in these patients, though the immune mechanism of DHS still is not clear. The changes in DHS suggest both T_H1 and T_H2 cytokine production. Transient increase in the level of interleukin 5 has been demonstrated early in the disease process in some patients.[26] Interleukin 5 released by activated T lymphocytes contributes to the eosinophilia.

The differential diagnosis of DHS includes other drug eruptions, viral infection, idiopathic hypereosinophilic syndrome, pseudolymphoma, serum sicknesslike illness, and drug-induced vasculitis.

PT is an extended-spectrum synthetic penicillin combined with β-lactamase inhibitor. PT is effective against methicillin-sensitive, coagulase-negative staphylococci; *Streptococcus pyogenes;* and penicillin-sensitive *Streptococcus pneumoniae, Enterobacteriaceae, Haemophilus influenza, Moraxella catarrhalis, Pseudomonus aeruginosa, Enterococcus faecalis,* and anaerobes. The main indications of PT include nosocomial pneumonia, intra-abdominal infections, skin and soft tissue infections, pelvic inflammatory disease, septicemia, neutropenic fever, osteomyelitis, and septic arthritis.[27]

Multiple adverse effects with the administration of PT have been reported, including fever, leucopenia, thrombocytopenia, hemolytic anemia, hypercoagulopathy, and transient bone marrow suppression.[28-29] Acute interstitial nephritis,[30-31] encephalopathy,[32] recurrent paralysis,[33] allergic skin eruptions,[34] and hemorrhagic cystitis[35] have been documented after the administration of PT. There is only one reported case (a letter to the editor[36]) of hypersensitivity reaction during prolonged use of PT in the treatment of osteomyelitis; the patient developed rash, lymphadenopathy, and hematologic changes.

Our patient developed DHS after 2 weeks of initiating therapy with PT for osteomyelitis. The reaction caused severe parenchymal nephritis, leading to anuria that necessitated hemodialysis. Interestingly, our patient complained of numbness and paresthesia of the forearm during intravenous PT infusion 2 days prior to developing DHS; a similar symptom was reported by Behbahani and Kostman[36] with numbness of the patient's upper chest during intravenous infusion.

Treatment of DHS depends on discontinuation of the offending drug early in the course of the disease. Adding systemic corticosteroids (0.5–1.0 mg/kg/d) to the treatment regimen is essential, especially in life-threatening involvement of the lungs, heart, liver, or kidneys. Systemic corticosteroids should be slowly tapered to avoid a relapse of nephritis and skin eruption. Topical steroids have been used in milder cases of DHS to improve the cutaneous manifestations. Interferon-γ has been used in a few cases of long-standing DHS,[37] but studies are not available to establish the role of this drug in treatment.

Conclusion

DHA is an iatrogenic disease that affects multiple organs. The pathogenesis of DHS still is largely unclear. Multiple factors likely are responsible for DHS, such as the offending drug with a drug-drug interaction, susceptible individuals with impaired ability to detoxify toxic drug metabolites, immunologic factors, and viral infection. Identification and discontinuation of the offending drug is crucial, as is a multidisciplinary approach in managing affected patients.

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