Case report

DRESS: a rare adverse drug reaction of olanzapine

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Summary

A boy of 17 years was brought by his parents with the complaints of aggressive, violent and assaultive behavior towards parents, using abusive language, demanding money, restlessness, irritability, irrelevant talk and sleep disturbance. His urine test for cannabinoid was positive. He was diagnosed as substance use disorder and was treated with olanzapine along with psychotherapy. After few days, he developed fever followed by erythematous rash with pruritus and swelling of the face, eyelids, trunk and extremities with raised serum bilirubin, ALT and alkaline phosphatase. He was diagnosed as DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms), a rare complication of olanzapine. This is a dangerous and life threatening adverse effect. Early diagnosis can reduce its morbidity and mortality.

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Introduction

Adverse drug reaction is not uncommon, but some are very rare, dangerous and potentially life threatening. One of such reaction is DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms) syndrome. DRESS is one of several terms that have been used to describe a severe idiosyncratic reaction to a drug. It is characterized by a long latency of onset after exposure to the offending medication, rash, involvement of internal organs, hematologic abnormalities and systemic illness. Other synonymous names and acronyms include HSS (Hypersensitivity Syndrome), AHS (Anticonvulsant Hypersensitivity Syndrome), DIHS (Drug-Induced Hypersensitivity Syndrome), DIDMOHS (Drug-Induced Delayed Multiorgan Hypersensitivity Syndrome) and Drug-Induced Pseudolymphoma.[1] This adverse drug reaction can occur in both adults and children.[2] It was originally observed in patients treated with anticonvulsants in the early 1930s when phenytoin first became available.[3] In 1996 French dermatologist Bocquet proposed the term DRESS "to decreased the ambiguity of the denomination of hypersensitivity syndrome" and to give a more accurate description of this clinical entity.[4] Olanzapine is one of a commonly prescribed drug in psychiatry, causes this very rare, fatal and life threatening adverse effect. US FDA is adding a new warning to the drug labels for all olanzapine-containing products.[5]

Case summary

A boy of 17 years was brought by his parents with the complaints of aggressive, violent and assaultive behavior towards parents, using abusive language, demanding money, restlessness, irritability, irrelevant talk and sleep disturbance for about one month. He became hostile and abused his mother when he failed to get money from her. He became argumentative and irritable with silly matters. On mental state examination he was restless, annoyed, angry and agitated. His mood was irritable. He had grandiose delusion and auditory hallucination. On query, he confessed of taking ganja and his urine test for cannabinoid was positive. All other relevant investigations including complete blood picture and liver function tests were normal. He was diagnosed as substance use disorder and was advised to take olanzapine in oral form. On the 21st day of taking olanzapine, patient developed fever which rose up to 104^{o}F which was continuous and persisted for weeks. There was diffuse, morbilliform, erythematous rash with pruritus and swelling of the face, eyelids, trunk and extremities. His serum bilirubin (9.0 mg/dl), ALT (2793 U/L) and alkaline phosphatase (491 U/L) levels were raised. IgM for rubella and cytomegalovirus were positive. His total leukocyte count was high (21.30X10^{9}/L) and eosinophil count was significantly higher (raised up to 25%). Immediately patient was shifted to medical high dependency unit (Med HDU) and was evaluated also by dermatologist, gastroenterologist along with psychiatrist. He was then diagnosed as a case of DRESS. His olanzapine was discontinued. From the second day of discontinuation, his fever was gradually reducing and skin rash was disappearing. After 5 days of staying in Med HDU, he was shifted to ward with complete recovery.

Table 1: Diagnostic criteria for DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms)

Bocquet et al[10]	Regis CAR[11]	J-SCAR[12]
Cutaneous drug eruption	Acute rash	Maculopapular rash developing >3 weeks after starting offending drug
Hematologic abnormalities	Reaction suspected to be drug-related	Prolonged clinical symptoms after discontinuation of the causative drug
Eosinophils ≥ $1.5x10^9$/L Presence of atypical lymphocytes	Hospitalization Fever >38°C	Fever >38°C Liver abnormalities (ALT >100 U/L) or other organ involvement
Systemic involvement	Enlarged lymph nodes involving ≥2 sites	Leukocyte abnormalities (≥1)
Adenopathy: lymph nodes ≥2cm in diameter	Involvement of ≥1 internal organ	Leukocytosis (>$11x10^9$/L)
Hepatitis with liver transaminases ≥2times normal	Blood count abnormalities	Atypical lymphocytes (>5%)
Interstitial nephritis	Lymphocytes above or below normal limits	Eosinophilia (>$1.5x10^9$/L)
Interstitial pneumonitis Carditis	Eosinophils over laboratory limits Platelets under laboratory limits	Lymphadenopathy HHV-6 reactivation

Discussion

Drugs that commonly induce DRESS syndrome include phenobarbital, carbamazepine, phenytoin, valproic acid, lamotrigine, minocycline, sulfonamides, allopurinol, modafinil, dapsone, ziprasidone, fluoxetine, bupropion, vancomycin and most recently olanzapine.[5,6] The onset of symptoms typically occurs 2 to 6 weeks after drug administration.[4,7] The precise pathogenesis of DRESS syndrome remains elusive. Mechanisms that have been implicated in DRESS syndrome include drug detoxification enzyme abnormalities with subsequent accumulation of reactive drug metabolites, sequential reactivation of herpes viruses, such as cytomegalovirus, Epstein-Barr virus, human herpes virus -6 and-7, and genetic predisposition associated with certain human leukocyte antigen alleles.[6] Mutations of genes encoding drug detoxification enzymes lead to the accumulation of drug reactive metabolites, which can biochemically interact with and modify cellular proteins, trigger autoimmune response against skin or liver cells, alter immune responses, and induce the reactivation of viral infections.[8]

DRESS often begins with predominant symptoms of pruritus and fever. The fever generally precedes cutaneous eruptions by several days, with temperature ranging from 38°C to 40°C (100°F to 104°F), and may last for several weeks. Although there can be various cutaneous manifestations, morbilliform rash is the most common and is characterized by a diffuse, pruritic, macular and occasionally, erythrodermatous exanthema.[9] The classic cutaneous distribution involves the face, upper trunk, and upper and lower extremities, but it may encompass the entire surface of the skin. The liver is the most frequently affected visceral organ in DRESS syndrome, often with varying degrees of hepatitis and eosinophilia.[6] This patient developed diffuse, pruritic, morbilliform and erythrodermatous rash after three weeks of fever along with hepatitis and eosinophilia. This was not German measles, also called three-day measles, an infection caused by the rubella virus (as his IgM was positive). This rash may start around two weeks after exposure and last for three days. It usually starts on the face and spreads to the rest of the body, sometimes itchy, having swollen lymph nodes. [10]

Conclusion

Adverse drug reaction may occur following a single dose or prolonged administration of a drug or result from the combination of two or more drugs. Health care professionals and also caregivers should be aware as a part of after care of starting treatment to prevent such life threatening adverse reaction.

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