DRESS Syndrome Secondary to combined Oral Contraceptive Pills Presented by Acute Pancretitis (A case report and review of literature)

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Abstract: The life-threatening drug hypersensitivity syndrome (DHS), also known as DRESS (drug rash with eosinophilia and systemic symptoms) syndrome is characterized by the presence of at least three of the following findings: fever, exanthema, eosinophilia, atypical circulating lymphocytes, lymphadenopathy, and hepatitis. This syndrome is difficult to diagnose, as many of its clinical features mimic those found with other serious systemic disorders. This idiosyncratic reaction occurs most commonly after exposure to drugs such as allopurinol, sulfides, and aromatic anticonvulsants such as phenytoin, phenobarbital, and carbamazepine and very rarely oral contraceptive pills. We report a case of female patient, who was on oral contraceptive pills induced DRESS syndrome and presented with systemic symptoms as well as acute pancreatitis.
[Nouf T Mleeh. **DRESS Syndrome Presented by Acute Pancretitis Secondary to Oral Contraceptive Pills (A case report and review of literature).** *Life Sci J* 2014;11(12):1091-1094]. (ISSN:1097-8135). http://www.lifesciencesite.com. 186

Key Words: Drug hypersensitivity, Drug Reaction, Acute pancreatitis., DRESS syndrome .

1. Introduction

The drug hypersensitivity syndrome (DHS), also called Drug Reaction with Eosinophilia and Systemic Symptom (DRESS) is a severe adverse drug-induced reaction. The estimated incidence of this syndrome ranges from 1 in1000 to 1 in 10,000 drug exposures.

It is potentially life-threatening syndrome including a severe skin eruption, fever, hematologic abnormalities (eosinophilia or atypical lymphocytes), and internal organ involvement. Other features are a delayed onset, usually 2-6 weeks after the initiation of drug therapy, and the possible persistence or aggravation of symptoms despite the discontinuation of the offending drug. The diagnosis of DRESS is challenging because the pattern of cutaneous eruption and the types of organs involved is variable.

The purpose is to report oral contraceptive pill induced DRESS syndrome in patient who present with acute pancreatitis.

2. Case report:

A forty three years old Indonesian lady, presented to the emergency room in May 2012, complaining of, epigastric pain, nausea, vomiting and fever for three days. The patient also noticed skin rash on her trunk, extremities and face one day before the presentation. She was hypertensive for one year controlled with diet. She has not been taken any drugs except for combined birth controlled pills (contains drospirenone – ethinyl estradiol), which was started three weeks ago. She is married with 3 siblings. She is a housewife.

Physical Examination revealed ill looking patient, in pain. Vital signs showed high temperature of 39.2 ^{0}C, blood pressure was 132/85, heart rate was 102. Her weight was 64 kg. There were palpable left cervical lymph nodes. CNS exam was grossly intact. Eye, nose, mouth, were free. Lungs were clear to auscultation, cardiovascular exam were normal. Abdominal exam revealed tenderness on the right upper quadrant and epigastric area, no palpable masses and no organomegaly. The skin showed discrete erythematous non scaly macuolopapular rash over the trunk, extremities (Figure 1) and periorificial area, with mild facial edema, palms and soles were not involved.

The patient was admitted to the surgical ward and the provisional diagnosis was acute pancreatitis. Dermatology was consulted for the possibility of viral exanthema versus drug eruption.

Initial management at that time, included: intra Venus fluid, Naso gastric tube, frequent vital signs monitoring, and the patient kept nil per OS. The oral contraceptive pills was stopped due to suspicion of drug induced rash. Acetaminophen was given and blood was extracted for work up.

Laboratory tests showed neutrophilic leukocytosis with atypical circulating lymphocytes and mild eosinophilia (WBC: 12200/mmc, PMNn: 8580/mmc, and Eosinophil: 690/mmc), AST: 60 IU/L (normal value < 30 IU/L), ALT: 55 IU/L (nv < 30 IU/L), GGT: 38 IU/L (normal 5–36 IU/L), alkaline phosphatase: 259 IU/L (normal < 240 IU/L), total bilirubin: 0.9 mg/dL (normal < 1.0mg/dL), C-reactive protein 112mg/L, (normal < 5.0mg/L), and ERS 103 mm/1 hour; serum creatinine, glucose, calcium, Na, K were in normal range. Amylase was 930 U/L

(normal < 160 U/L) and lipase was 164 U/L (normal 7-58 U/L).

Blood, urine, and stool cultures resulted normal; serologic tests for an acute infection by EBV, parvovirus B19, CMV, HCV, HBV, HAV, HIV, syphilis, Salmonella and herpes simplex 1and 2, Chlamydia and mycoplasma were negative.

Among autoantibodies, rheumatoid factor, antinuclear antibodies, anti-DNA, ANCA, anti-cardiolipin, and lupus anticoagulants were negative.

Skin biopsy showed superficial perivascular lymphocytic infiltration with eosionophils. interface dermatitis ,exocytosis of inflammatory cells and dermal edema are observed.
(Figure 2)

Abdominal x-ray was unremarkable. CT scan with contrast showed nonenhancing pancreatic body anterior to the splenic vein. Peripancreatic fluid extending anteriorly from the pancreatic head was also noted. This finding consistent with acute pancreatitis.

Based on the diagnostic scoring system for DRESS proposed by RegiSCAR-group , the patient got more than 5 scores which met definite diagnosis of DRESS syndrome.

Further management included imipenem 500 mg IV every 6 hours and oral prednisolone 60 mg orally per day. During her 3rd day of hospitalization, the fever and abdominal pain started to subside. Serum amylase and lipase, started to return to normal values. The hepatic transaminases as well as the rash persisted for several days. Antibiotic was stopped on the 6th day of admission and prednisone was continued on the same dose. Seven days later, the liver enzymes returned to normal and the skin rash started to improve. Later the patient was discharged in good condition and planned to gradually reduce corticosteroid dosage.

Our patient presented with fever, exanthema, eosinophilia, atypical circulating lymphocytes, lymphadenopathy and pancreatitis suggestive of DRESS syndrome. There was a history of oral contraceptive pill consumption, suggestive of a rare and unusual oral contraceptive pill induced DRESS syndrome presented with acute pancreatitis. She was successfully treated by supportive measures, intravenous antibiotic, systemic steroid and education about future avoidance of corresponding drug. Patient was discharge home in a good condition.

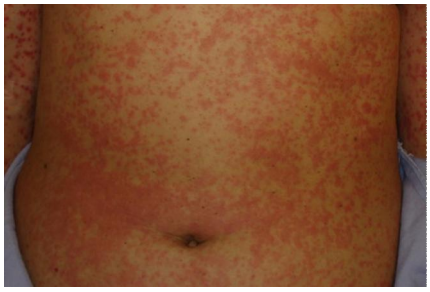

Figure (1)

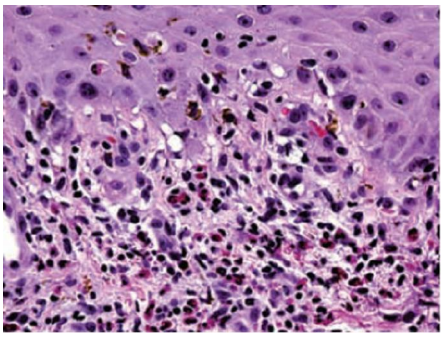

Figure (2)

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3. Discussion

Drug-induced hypersensitivity syndrome was first described in 1936 during treatment with anticonvulsant drugs. Later on, the association with other drugs was established and the name 'DRESS syndrome' was suggested to describe this entity. The syndrome is characterized by rash, fever, lymphadenopathy and internal organ involvement (single or multiple). (1,2)

The pathogenesis is not fully understood. It has been suggested that certain drugs may cause a hypersensitivity reaction as a result of abnormalities in the production and detoxification of its active metabolites in patients with genetic or acquired variations in drug metabolism pathways. Its incidence ranges between 1 in 1000 and 1 in 10 000 exposures. (3,4)

The aromatic anti-convulsions (phenytoin, phenobarbital, carbamazepine) and sulphonamides are the most common drugs described in this syndrome, but a variety of other drugs have been associated such as dapsone, allopurinol, captopril, calcium- channel blockers, ranitidine, thalidomide, minocycline, sulfasalazine, cefatoxime, non-steroidal anti-inflammatory drugs, tuberculostatics, α-metildope and antiretroviral drugs (zalcitabine, neviparine). (5,6)

The onset of the disease usually ranges from 2 to 6 weeks after the initiation of the therapy. The first symptoms are usually fever and rash. The skin involvement is characterized by a morbilliform macular rash that appears first in the face, abdomen and upper limbs, becoming purpuric later on, especially in lower limbs. An exfoliative dermatitis appears when the lesions tend to vanish. (7,8)

Facial oedema can also occur, as well conjunctivitis and pharyngeal mucosa erythema. The systemic involvement, that is thought to be the result of the eosinophilia, is not associated with the severity of skin lesions. Lymphadenopathy are present in 75% of the cases. The liver is the most common affected organ in DRESS syndrome. The findings may range from a transitory increase in liver enzymes to liver necrosis with fulminant hepatic failure, that is thought to be mediated by infiltration of oenophiles, resulting in death or liver transplantation. (9). These last two features are more frequently seen in women between the second and fourth decade of life with the outcome being independent of the use or dose of immunosuppressive therapy. A cholestatic injury pattern is seen in a minority of patients. The kidney, lung and heart are other sites that can be affected with interstitial nephropathy, pneumonitis, pericarditis and myocarditis being described in the literature (10,11). Arthritis, pancreatitis, encephalitis and thyroid involvement, with thyroiditis and hypothyroidism, have been reported to develop in a small subset of patients.

Diagnostic criteria for DRESS syndrome, published in 1996 by Bocquet *et al.,* include the simultaneous presence of three conditions, Drug-induced skin eruption, Eosinophilia ≥ 1500/mm3 and at least one of the following systemic abnormalities: Lymphadenopathy, or Hepatitis (transaminases >2 ULN) or Interstitial nephropathy, or Interstitial lung disease or Myocardial involvement. (12)

There are a minimum of laboratory data that will help to differentiate DRESS syndrome from other severe drug reactions and to identify asymptomatic internal organ involvement. These data include complete blood cell count that usually shows eosinophilia and mononucleosis-like atypical lymphocytosis, liver function parameters, serum creatinine levels and urinalysis. Thyroid stimulating hormone levels should also be measured and repeated after 2–3 months as hypothyroidism can emerge as a late complication. (13)

The lymphocyte-stimulation test (LST) is a routinely available test that measures the proliferation of T cells to a drug in vitro. The test is considered positive if a certain stimulation index is achieved. Overall, a stimulation index more than 2 is needed to classify the test as positive. During the acute phase of drug hypersensitivity, the immune system, in particular T cells, is strongly activated and for this reason the test should be performed after clinical and analytical remission to avoid false positive results. The test has a sensitivity of 60–70%. A positive LST is often a valuable contribution to the diagnosis (with only 2% of false positive results) but, due to its sensitivity, a negative test cannot exclude a drug hypersensitivity and therefore its performance is not mandatory in the presence of diagnostic criteria mentioned above. (14)

The skin biopsy may help to confirm the diagnosis but is usually not specific. It shows a lymphocytic infiltrate of the papillary dermis, which may contain eosinophils and is generally denser than in other drug reactions. The most common differential diagnoses include Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), hyper-eosinophilic syndrome and Kawasaki disease (Table 1). So far, prompt withdrawal of the offending drug is the only undisputed way to treat drug hypersensitivity reactions. Supportive therapy includes antipyretics and the use of topical steroids to improve symptoms. Systemic corticosteroids can reduce symptoms of delayed hypersensitivity reactions. They are known to inhibit the effect of interleukin-5 on eosinophils accumulation occurring in this syndrome, which may explain their benefit in the treatment. Dramatic improvement in clinical symptoms and laboratory

findings has been observed soon after the beginning of corticoid therapy in independent case reports. (15)

Our patient's case illustrates the difficulty in diagnosing the DRESS syndrome, which, due to its multitude of clinical features, mimics a number of serious systemic disorders. Our patient's initial presentation was with acute pancreatitis in which the patient was on oral contraceptive pills. No such association with oral contraceptive pills has been reported in the literature and up to our knowledge.

4. Conclusion

Our case report highlights the difficulty in diagnosing the DRESS syndrome. Clinicians should have a high index of suspicion for the DRESS syndrome in patients being treated with aromatic anticonvulsants and antibiotics. Based on the history of oral contraceptive pills consumption by our patient, this drug can be one of the rare causes of DRESS syndrome. Furthermore, DRESS syndrome should be considered in the differential diagnosis of patients presenting with pancreatitis, hepatitis and maculopapular skin rash in the setting of new medications.

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12/11/2014