DRESS and Ischemic Stroke

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ABSTRAK

Sindrom hipersensitivitas obat (SHO) adalah suatu kondisi yang mengancam nyawa yang ditandai oleh ruam kulit, demam, leukositosis dengan eosinofilia atau limfositosis atipik, pembesaran kelenjar getah bening, serta gangguan pada hati atau ginjal. Laporan kasus berikut akan mendeskripsikan koinsidensi kasus DRESS dengan strok iskemik.

Wanita 38 tahun datang ke rumah sakit dengan ruam kulit dan demam sejak empat hari sebelumnya. Satu bulan sebelumnya pasien memperoleh antibiotic dan multivitamin selama satu minggu. Pasien terlihat sakit dengan suhu tubuh mencapai 38,0°C. Temuan klinis yang bermakna adalah limfadenopati serta hepatomegali. Pemeriksaan dermatologikus memperlihatkan eksantema generalitasa. Hasil laboratorium memperlihatkan leukositosis, eosinofilia, serta peningkatan SGOT dan SGPT. Selama perawatan di RS pasien juga mengalami strok.

Terapi yang diberikan adalah oksigen, cairan intravena dan nutirisi adekuat, metil prednisolon, dan antihistamin.Terapi antibiotik yang diberikan didahului dengan graded challenge test atau test dosing.

Kata kunci: *DRESS, strok iskemik, test dosing.*

ABSTRACT

DRESS (drug rash eosinophilia and systemic symptomps) is a life threatening condition characterized by skin rash, fever, leucocytosis with eosinophilia or atypical lymphocytosis, lymphadenopathy, and internal organ involvement. This case report would like to describe an interesting case of DRESS coincidence with ischemic stroke.

A 38 year old woman had been admitted with skin rash and fever since four days before. Four weeks before admission she received antibiotic and multivitamin for one week. The patient looked ill, with body temperature 38.0°C. Marked physical findings were cervical lymphadenopathy and hepatomegaly. Dermatological examination finding was generalized exanthema. Laboratory evaluation showed leucocytosis, eosinophilia, and increased level of ALT and AST. During hospitalization the patient also suffered from ischemic stroke.

Treatments administered in this patient were oxygen, adequate intravenous fluid, parenteral nutrition, methyl prednisolone, cethirizin bid, ranitidin bid, and antibiotic. The antibiotic treatment in this case was performed with graded challenge or test dosing.

Key words: *DRESS, ischemic stroke, test dosing.*

INTRODUCTION

The incidence of adverse drug reaction is increased with the introduction of many drugs for diagnosis and treatment purpose. Adverse drug reaction is a response unwanted from drug administration within doses range.[1] Most of the adverse drug reaction did not have allergic component. It is estimated that 6-10% of adverse drug reaction was allergic reaction. Drug allergy is an adverse drug reaction that has immunologic mechanism.[1,2]

Stroke is a non-communicable disease

of increasing socioeconomic importance in ageing population. Cerebrovascular diseases are classified into four major types: ischemic stroke, primary intracerebral haemorrhage, subarachnoid haemorrhage, and transient ischemic attack. There are three subtypes of ischemic stroke: thrombosis, embolism, and systemic hypoperfusion. In young patient (16 to 49 years) the etiologies are cardioembolic disease (24%), small vessel disease (17%), and large vessel disease (16%).[3,4]

Drug hypersensitivity syndrome or also known as drug rash eosinophilia and systemic symptoms (DRESS) is a life threatening condition characterized by skin rash, fever, leucocytosis with eosinophilia or atypical lymphocytosis, lymphadenopathy, and internal organ (liver or kidney) involvement.[5,6]

The incidence of DRESS was 1:1000 up to 1:10.000 persons exposed with anti convulsant or sulfonamide antibiotic. The mortality rate was estimated 10% of cases, usually caused by systemic involvement.[5,6] Drugs frequently associated with DRESS are anticonvulsant, sulfonamide, dapsone, minoxycline, and allupurinol.[7,8]

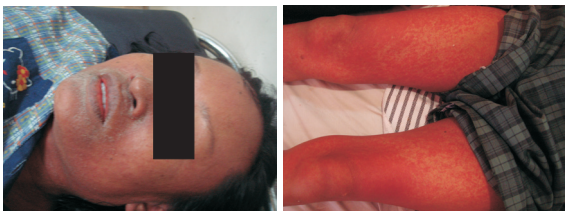
There was no report that stated the association between DRESS and ischemic stroke. This case report would like to describe the interesting case of DRESS coincidences with ischemic stroke.

CASE ILLUSTRATION

A 38 year old woman came to Cipto Mangunkusumo General Hospital with skin rash and fever since four days. The skin rash was developed from upper extrimities to all over the body and face. Patient then went to midwives and doctor and she got dexteem®, licodexon®, otopen®, and orphan®. After she took the medication the symptoms did not improve. One day before admission her condition deterioratied, so she was taken to local hospital and then referred to our hospital with diagnosis drug allergy. She also was having dysuria.

One month before she gave birth to her third child with caesarean section. After that she received antibiotics and multivitamins for one week. But the patient did not remember the brand or name of drug given. There was no history of allergy against drug or food. Asthma, allergic rhinitis, and atophy were absent. She already had three healthy children without any history of spontaneous abortion before.

At the emergency room the patient look ill, fully alert, with blood pressure 110/70 mmHg, heart rate 110 x/m, respiratory rate 28 x/m, and body temperature 38,0^{o}C. Marked physical findings were cervical lymphadenopathy and hepatomegaly. Dermatological examination finding was generalized exanthema (**Figure 1**).



(a) facial region (b) lower extremities

Figure 1. (a) and (b) There were multiple erythematose papul with numular size in facial and lower extremities region.

The initial laboratory evaluation showed leucocytosis, eosinophilia, and increased level of ALT and AST. There was increased level of serum bilirubin (**Table 1**). Urinalysis shows cloudy urine, leucocyte, and positive nitrite. Chest X-ray and electrocardiograph didn't show any abnormalities. The result of blood culture was sterile. Hepatitis viral marker, HIV, dsDNA, ANA were negative. The abdominal ultrasound revealed hepatomegaly with chronic hepatitis appearence. The IgE and C-reactive protein level was increased. The C-3 level was decreased. This patient we assessed as urosepsis and DRESS.

Treatment administered in this patient was oxygen, adequate intravenous fluid, parenteral nutrition, methyl prednisolone, cethirizin bid, ranitidin bid, and antibiotic. The antibiotic treatment in this case was performed with graded challenge or test dosing. This patient initially was given Cefpirom and Levofloxacin. During test dosing with both drugs the patient showed positive reactions, therefore the provocation test was stopped. The patient then tested with gentamicyn and did not showed any reaction. The methyl prednisolone dose was tappering down and switch from intravenous into oral administration after several weeks.

During hospitalization the patient complained of left hemipharesis. Brain CT scan was then performed and demonstrated right parietal lobe

Table 1. Laboratory result

Parameter	Results	Normal Value
Hb	12,0	12,0-14,0 g/dL
Ht	36,0	37,0-43,0 %
Leucocyte	21.900	5.000 – 10.000 /ml
Basofil	1,7	0,0-1,0
Eosinophil	12,2	1,0-3,0
Neutrophil	53	52-76
Lymphocyte	19,7	20,0-40,0
Monocyte	13,2	2,0-8,0
Ureum	31	10-15 mg/dL
Creatinin	0,9	0,5-1,3 mg/dL
AST	236	1-35 U/L
ALT	306	1-36 U/L
Blood glucose	161	70-200 mg/d
Protein total	4,2	6,4-8,7 g/dL
Albumin	3,2	3,40-4,80g/dL
Globulin	2	1,80-3,90 g/dL
Total bilirubin	2,6	0,20-1,00 mg/dL
Direct bilirubin	0,7	0,10-0,30 mg/dL
Indirect Bilirubin	1,9	0,10-0,70 mg/dL

infarction. The diagnosis of ischemic stroke was made. Further diagnostic evaluations were performed to find out the underlying condition associated with stroke. Transesophageal echocardiography, carotid ultrasound did not show any abnormalities. The lipid profiles showed low levels of HDL and increase of LDL level. Hemostatic evaluation was within normal value. The IgM Anti-ß2 glycoprotein-I level increased. The patient got additional treatment with antiplatelet, folic acid, vitamin B. The physical rehabilitation also started.

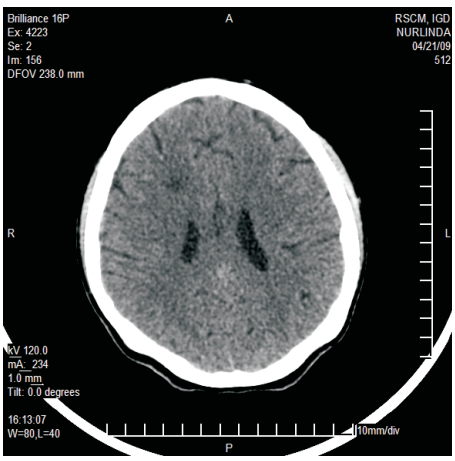


Figure 2. Hyperdens lesion in right parietal lobe.

After several days of the treatment the patient condition improved. Laboratory examination showed positive trend toward recovery condition. The patient was then discharged from hospital, with oral methyl prednisolone, vitamin, and antiplatelet therapy. The patient was planned for control in the policlinic. Unfortunately the patient was lost to follow up.

DISCUSSION

Diagnosis of DRESS in this case was based on the patient history, physical examination, and laboratory results. The triad of DRESS: fever, drug eruption, and internal organ involvement were present in this case.[6-8] The patient was coming with fever and generalized exanthema over her body. There was a history of drug administration four weeks before admission for a week period. The onset of DRESS was 2 to 6 weeks after drug administration.[7] The fever was usually high up to 38-40^{o}C and lasted for several weeks after the drug was stopped.[7,9] The physical examination of the patient revealed exanthema with erythematous macula, papule, and pustule that distributed generalized in the face, trunk, and extremities. The skin manifestations of drug allergy are varying from macula, papule, pustule, and vasculitis. The lesion was firstly noted from face, upper body trunk, and proximal of the extremities that spread into whole of the body.[10,11] In this case there was not involvement of mucous membrane that differ from Steven-Johnson syndrome (SSJ) and toxic epidermal neurolysis (TEN).[7]

The general physical examination revealed cervical lymphadenopathy and hepatomegaly. The internal organ involvement in this case was liver. The involvement of the liver was found in 51% of DRESS cases.[7,9] The cervical lymphadenopathy that frequently found was in the cervical region.[7,9] In the laboratory evaluation showed a marked lecocytosis and eosinophilia (>1500/ml). There were also increases in ALT and AST level, which confirmed the involvement of the liver.

The patient in this case also suffered from ischemic stroke. That was based on left hemipharesis, and brain CT scan that demonstrated infarct in right parietal lobe. Further evaluation to find out the risk for developing stroke in this case were low HDL and high HDL level. The imaging with carotid doppler and transesofagheal

ecochardiography did not show any abnormalities that could be related with stroke in this case, like atheroschlelorosis, carotid artery stenosis, thrombus, embolic source, patent foramen ovale, or atrial septal defect.[3,4,12] Since in this case the patient was still young with unknown etiology, we also performed antiphospholipid antibody evaluation. The titre of IgM Anti-ß2 glycoprotein-I was increased. The increased level of IgM Anti-ß2 glycoprotein-I could be sequele of the stroke or part of drug reaction.[4,13] The antiphospolypid syndrome diagnosis in this case could not be established, since the titre of anti-ß2 glycoprotein-I should be repeated in 12 weeks apart.[14] Unfortunately this could not be conducted in this case. Literature stated that internal organ involvements in DRESS cases are kidney, lung, heart, thyroid, and brain. The involvement of brain in DRESS case is a rare finding.[7] We did not find any correlation between DRESS and ischemic stroke, so the two happenings in this case, we think, were coincidental case.

The urinary tract infection in this case was treated with antibiotic. The administration of antibiotic in this case with test dosing or graded challenge.[1] During test dosing with Cefpirome and Levofloxacin the patient showed reaction with increased skin rash and pruritus. The reaction that happened during test dosing could be caused by cross reaction with other similar drugs. Other possible explanation that the reaction was a flare up reactions, that reaction happened caused by high activity state in patient immune system.[8,15] Gentamycin finally is chosen as alternatives, because the hypersensitivity reaction against aminoglycocydes is rare and only minor reaction.[1] After test dosing there was not any reaction against gentamycin.

Supportive and symptomatic treatments were given for DRESS case. Adequate nutrition, intravenous fluid, and skin care were conducted. The role of corticosteroid in the treatment of DRESS case is still controversial.[16] Prednison could be given 1-2 mg/kg/daily in severe condition. In this case, methylprednisolone was given but subsequently tappered down in several weeks. The corticosteroid dose should not be quickly reduced, since there is a chance for relapse.[17] Methyl prednisolon given 1.3 mg/kg/day until improvement achieved. The dosage then is tappered down within four weeks.[17] Anti-histamin also given to relieve symptoms.[16]

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