Original Research Paper

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Drug Rash, Eosinophilia and Systemic Symptoms Syndrome of Att Induced – A Rare Case Report.

MEDICAL SCIENCE

KEYWORDS :

V.Chandra Sekhar	M.B.B.S., DNB – Internal Medicine, CARE Hospital, Nampally, Hyderabad.
Madhusudan R. Jaju	DNB, EDIC, Director of Critical Care, CARE Hospital, Nampally, Hyderabad.
Shashank Kumar Srivastav	M.B.B.S., Resident, CARE Hospital, Nampally, Hyderabad

ABSTRACT

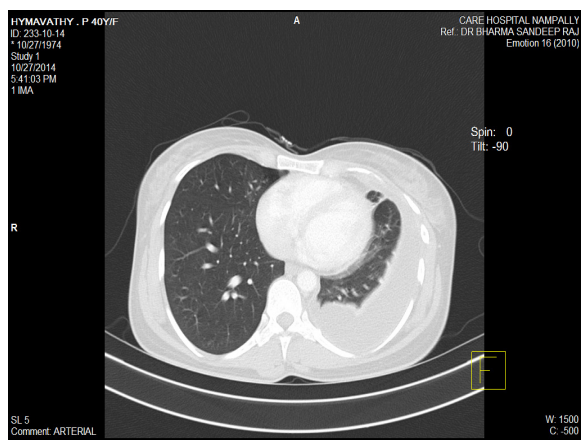
DRESS syndrome (Drug Rash, Eosinophilia and Systemic Symptoms) is a potentially life-threatening syndrome including severe eruption, fever, hypereosinophilia and internal organ involvement. We report a case of this syndrome in a 40-year old female with pulmonary Koch's, Lt pleural biopsy-Granulomata with small necrotic foci and was started on ATT, on which she developed skin rash, eosinophilia, liver injury after about six weeks of ATT which lead us to finding of DRESS Syndrome-ATT induced (ethambutol/rifampicin). This case resolved with ATT withdrawal. Rapid diagnosis is crucial as prompt withdrawal of offending drug is the key to treatment, while the potential role of corticosteroids remains controversial.

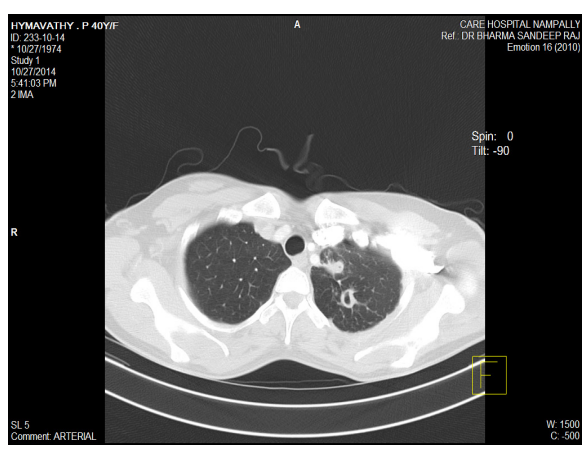
Introduction:

Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome is a severe adverse drug reaction presenting with rash, fever, lymphadenopathy and single or multiple organ involvement. Cholestasis can occur although it is rare. Many drugs have been associated with this clinical entity, including allopurinol. The pathogenesis is not fully understood and may be multifactorial, involving immunological mechanisms and particular drug detoxification pathways.

Case Report:

A 40-year old female patient came with chief complaints of cough with scanty expectorations, shortness of breath and fever of 4-weeks duration. She was evaluated at Government Hospital for left pleural effusion and was referred to our hospital for further management. Thoracocentesis and pleural fluid analysis done. The exudates (4.7gm/dl protein), 4,730 cells, 95% lymphocytes, ADA: 101 U/L. She was started on Anti-Tuberculosis Therapy(HREZ). There was no significant previous medical illness, no history of any surgery, drug allergy or bronchial asthma. On examination – patient conscious, coherent and sound to people around with pallor positive. No icterus, clubbing, cyanosis, lymphadenopathy, edema or skin rash. Temperature- 102^0F with vitals stable. On ausculatation, Lungs-decreased breath sounds on left infra scapular area with no crepts or rhonchi. Other systemic examinations were normal. Investigation showed Hb: 7.5gm/dl, TLC: 5,600, (N:60,L:20,E:5,M:5), Platelets:6.61, ESR: 40. Peripheral smear-microcytic and hypochromic RBC, with thrombocytosis. LFT-Sr.Bilirubin: 1.1, ALP: 118, SGPT: 170, SGOT: 178, Albumin: 3.6, Globulin: 3.4. RBS: 84mg/. Sr.Creatinine: 0.64. HIV, HBsAg, Anti HCV-negative. PCT 0.12ng/ml. Ultrasound Abdomen- Left pleural effusion. CT scan – Chest : Left pleural effusion, multiple tiny nodules, few showing central cavitations in left apico-posterior lobe. adjacent interlobular septal thickening, patchy areas of consolidation.





Images showing - CT scan Chest : Left pleural effusion, multiple tiny nodules, few showing central cavitations in left apico-posterior lobe. adjacent interlobular septal thickening, patchy areas of consolidation.

Thoracocentesis(250ml) - PFA: PH 8.0, 4130 cells (L:95%, P:5%), sugar: 41 mg/dl, protein: 5.4gm/dl, Albumin: 2.9. ADA: 26. LDH: 691, negative for malignant cells.

Further we stopped ATT and started Inj. Piperacillin + Tazobactam 4.5 gm I.V., 8^{th} hourly. We repeated thoracocentesis(100ml) after 2-days. In vivo multiple loculations, VATS was done on 5^{th} day of admission.

Sputum- Plenty of polymorphs, few gram positive cocci, AFB: negative. Culture/sensitivity –sterile.

Pleural fluid- AFB: negative. Culture/sensitivity –sterile.

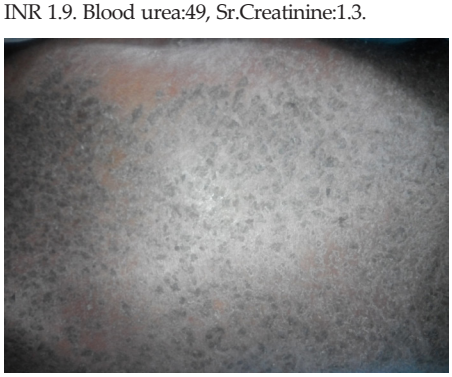
Pleural tissue- Plenty polymorphs, negative for AFB with Gram positive cocci.

Pleural biopsy showed thickened pleura with surface fibro purulent material, multiple granulomata noted, composed of epithelioid cells and langhans type giant cells, small foci of central necrosis.

We Restarted on ATT and discharged the patient in stable condition. LFT at time of discharge- Sr.bilirubin:0.9, SGPT :47, SGOT:19. In the course we transfused 2-units of PRBC.

The patient after 20-days was readmitted with complaints of vomiting since 10 days, skin rash of 5-6 days duration and with intermittent fever. On examination- Temperature: 99F, erythematous rash over back and both forearms. On evaluation found to have deranged LFT, ATT were stopped and started on Antihistamines and UDCA, Tab Levoflox 500 mg and Inj Streptomycin 0.75gm IM once daily. CBP- Hb: 9.6gm/dl, TLC: 10,900 (N:74,L:14,E:1,M:1), platelets: 2.95, ESR: 20. LFT- Sr.bilirubin: 8.3, ALP:152, SGPT:228, SGOT:216, Albumin: 2.7. INR: 1.2. On Day-3, she developed facial puffiness, arthralgia, bilateral edema of feet, high grade fever (103F), extensive maculopapular rash involving almost whole body (scalp, palms and soles spared), oral mucosa and conjunctiva-not involved, no lymphadenopathy. CBP- Hb:9.3gm/dl, TLC:16,200(N:60,L:20,E:20). Peripheral smear-microcytic and hypochromic RBC with anisopoikilocytosis and few elliptical cells, eosinophilic leucocytosis, no atypical lymphocytes. We stopped Levofloxacin and Streptomycin (after two doses each) and started on Inj Cefipime + Tazobactam after sending cultures. On Day-4, Persisting fever, hypotension(BP 80/60mm Hg) and decreased urine output. TLC-38,700 (N:60,L:15,E:20,B:5), PCT-3.15. Dengue, leptospirosis: negative. We started Inj Meropenem 1gm IV thrice daily, Inj Hydrocortisone 100mg IV 8th hourly. Progressive worsening of LFT and increasing TLC. On Day-6 Hb:9.2gm/dl, TLC:47,000 (N:60,L:5,E:15,B:15)-Eosinophilia,neutrophilic leucocytosis with left shift and band forms. We added N-Acetyl cysteine. The patient was having High grade fever, Extensive morbiliform skin rash, Eosinophilia, Liver injury which was diagnosed to be DRESS -Drug Reaction with Eosinophilia and Systemic Symptoms. Stopped Meropenem after five days, Inj Hydrocortisone tapered over one week, Fever,skin rash and nausea improved and discharged with Anti histamines, UDCA and NAC.

Patient readmitted after five days with bilateral edema feet, exfoliative dermatitis, decreased urine output. CBP- Hb:8.7gm/dl, TLC:23,380 (N:45,L:10,E:26,M:4,B:10), ESR:20.LFT- Sr.bilirubin: 11.6, ALP: 137, SGPT:52, SGOT:36, Albumin:2.4, Globulin: 2.6. INR 1.9. Blood urea:49, Sr.Creatinine:1.3.



Improved with antihistamines, antiemetics and supportive treatment. FIP1L1 PDGFRA mutation, Bone marrow biopsy: myeloid hyperplasia of marrow with eosinophilic prominence-17%.

Discussion:

Drug-induced hypersensitivity syndrome was first described in 1936 during treatment with anticonvulsant drugs.1 Later on, the association with other drugs was established and the name 'DRESS syndrome' was suggested to describe this entity. The syndrome is characterised by rash, fever, lymphadenopathy and internal organ involvement (single or multiple). 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. The aromatic anti-convulsants (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, minocicline, sulfasalazine, non-steroidal anti-inflammatory drugs, tuberculostatics, α-metildope and antiretroviral drugs (zalcitabine, neviparine).2–4 The onset of the disease usually ranges from 2 to 6 weeks after the initiation of the therapy.5 The first symptoms are usually fever and rash. The skin involvement is characterised 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.6 In our patient, after weeks of ATT she developed rashes all over body sparing scalp and soles for which she was readmitted. 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 eosinophils, resulting in death or liver transplantation.2–4 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. Arthritis, pancreatitis, encephalitis and thyroid involvement, with thyroiditis and hypothyroidism, have been reported to develop in a small subset of patients.7 8

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
- Hepatitis (transaminases >2 ULN)
- Interstitial nephropathy
- Interstitial lung disease
- Myocardial involvement.9

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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.10

Allopurinol is one of the drugs that have been implied. The accumulation of one of allopurinol metabolites, oxypurinol, is the mechanism responsible for the syndrome appearance, especially in the setting of decreased renal clearance and the use of thiazide diuretics.11

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 clini- cal 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.12

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.13 The most common differential diagnoses include Stevens–Johnson

syndrome (SJS), toxic epidermal necrolysis (TEN), hypereosinophilic syndrome and Kawasaki disease (table 1).14

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.15 16 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 find- ings has been observed soon after the beginning of corticoid therapy in independent case reports. Several authors suggest their use when internal organ involvement exists, although the ideal dosage and the length of therapy are unknown. However, randomised controlled trials are lacking, and whether steroids should be administered remains controversial.17 18 Relapses have also been described after tapering or withdrawal of systemic steroids. Death rate in DRESS syndrome is about 10%, mostly due to liver failure.2–4

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