IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 19, Issue 7 Ser.7 (July. 2020), PP 06-09
www.iosrjournals.org

Phenytoin-induced drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), a raredrugreaction complicated by auto-immune hypothyroidism.

Thabuna Sivaprakasam[1], Deepan Panneerselvam[2], Muthamil Arulselvan[3]
[1](Intern, Department of Internal Medicine, Kilpauk Medical College and Hospital, Chennai, Tamil Nadu, India)
[2](Intern, Department of Internal Medicine, Kilpauk Medical College and Hospital, Chennai, Tamil Nadu, India)
[3](PGY1, Department of Internal Medicine, Kilpauk Medical College and Hospital, Chennai, Tamil Nadu, India)

***Abstract*:**
Background: *A 22 year old female presented with the chief complaints of fever for 5 days, rashes since 15 days and yellowish discoloration of eyes and high-colored urine since 20 days. She also complained of arthralgia, myalgia, facial puffiness, itching and loss of weight and appetite. Her past history was significant for a new-onset seizure episode around two months back for which she was started on regular treatment with Tablet Phenytoin 300mg/day, for the past 45 days. Following an asymptomatic period of around 25 days, she initially developed the yellowish discoloration of eyes and urine followed by the generalized rash and finally high-grade fever with which she came to the hospital. General examination revealed a high temperature, icterus, pallor and significant cervical, axillary and inguinal lymphadenopathy. There was also facial puffiness and exfoliative rashes all over the body.*
Investigations: *Investigations were done and complete blood count revealed leucocytosis, anemia and thrombocytopenia. The liver function tests were grossly altered with elevated bilirubin, elevated liver enzymes and an abnormal coagulation profile. The peripheral blood smear showed eosinophilia and the ESR was raised. Having ruled out viral hepatitis after a negative viral markers panel, she was found to be positive for ANA antibodies. USG abdomen showed hepatomegaly. Liver biopsy was suggestive of auto-immune hepatitis and skin biopsy revealed the characteristics of a morbilliform drug eruption.*
Diagnosis and management: *Taking into account all the relevant clinical manifestations and investigations and using the RegiSCAR Diagnostic Score, the diagnosis of Phenytoin-induced Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome was made. Following phenytoin withdrawal, the patient was started on treatment with Tablet Prednisolone at 50mg/day and the dose was gradually tapered. After just one week of steroid therapy, patient showed marked improvement with regression of the rashes and gradual improvement of the LFTs. She was discharged after 22 days and advised routine follow-up. She presented 2 months later with symptoms suggesting hypothyroidism which was confirmed by a thyroid function profile and an elevated anti-TPO antibodies revealed an auto-immune cause. She was started on Tablet Levothyroxine 50 micrograms/day, advised to continue the steroids as per prescription and adhere to regular follow-up.*
Keywords: *DRESS syndrome, phenytoin, autoimmune hypothyroidism, prednisolone, regiSCAR, eosinophilia*

Date of Submission: 30-06-2020 Date of Acceptance: 16-07-2020

I. Introduction

DRESS Syndrome is an idiosyncratic adverse drug reaction that is estimated to occur in 1 in 1000 to 1 in 10000 drug exposures [1]. It is a type IV hypersensitivity reaction elicited by drug metabolites that activates T cells and initiates auto-immune processes. It is typically observed after the first exposure to the drug. DRESS Syndrome has been observed following the intake of many other drugs notably allopurinol, dapsone, carbamazepine etc.

Symptoms now recognized as DRESS was observed with phenytoin as early as 1950 but it was only after 1996, the term DRESS was coined to depict these severe drug reactions[2].

Hallmarks of DRESS Syndrome include a long latency period between the exposure to the causative medication and the development of the first symptom (2-3 weeks), fever, rash, hematologic abnormalities, lymphadenopathy and involvement of at least one organ system[3].

DRESS Syndrome can extend over a prolonged course despite discontinuation of the inciting drug and can frequently present with auto-immune sequalae.

II. Case report

A 22-year-old female presented to us with the chief complaints of fever since 5 days, rashes since 15 days and yellowish discoloration of the eyes and high-coloured urine since 20 days. On eliciting further history, the fever was reported to be high-grade and intermittent, not associated with any chills or rigors. The rash started peri-orally and then extended to the trunk, groin, upper and lower extremities. The rashes were initially maculo-papular and associated with itching and later turned into dry scaly lesions. Though the high fever motivated the patient to seek medical care, the initial symptom was the yellowish discoloration of the eyes which was eventually accompanied by the dark-colored urine. She also complained of oral ulcers, arthralgia, myalgia, facial puffiness, loss of weight and appetite and generalized pruritus. There was no history of abdominal symptoms such as vomiting, diarrhea,abdominal pain, hematemesis or melena. There was also no history of leg swelling/reduced urine outputaccompanying the facial puffiness. Past medical history was significant for the new-onset seizures 2 months back and correspondingly the treatment history revealed that she had been started on **Tablet Phenytoin** 300 g/day for the same and had been on the treatment since 45 days. She had no other co-morbidities and was not on any other drug.

On general examination, the patient was conscious, oriented, moderately built and nourished. She was **febrile** with a temperature of 101 degrees F, was **icteric** and had pallor. **The cervical, axillary and inguinal group of lymph nodes were enlarged.** And she also showed **facial puffiness** and **dry, exfoliative rashes** were observed diffusely over her body and peri-orally. Her vitals were normal except for the temperature of 101 degrees and her systemic examination revealed no abnormal findings.

Investigations : A complete blood count showed anemia (Hb – 7.8 g/dl), leucocytosis (WBC – 20,000 cells/mm^3) and thrombocytopenia (Platelets – 70,000/mm^3). The renal function tests were normal but there were **altered liver function tests** (S. Bilirubin – 27.8 mg/dl, D. bilirubin – 24.2 mg/dl, SGOT – 415 U/L, SGPT – 364 U/L, ALP – 361 U/L, Albumin – 3.2 g/dl and Globulin – 2.9g/dl). There was an **abnormal coagulation profile** with a raised Prothrombin Time (36.1 seconds), raised aPTT (51.8 seconds) with an INR of 3.5. The peripheral smear showed a dimorphic picture with thrombocytopenia and **eosinophilia with an absolute eosinophil count of 1250 cells.** The smear was negative for malarial parasites and microfilaria. The ESR was elevated (80/110 mm) and the CRP was normal (0.6 mg/l). She also tested **positive for ANA antibodies (1:60).**

The viral markers, direct Coomb's test, IgM dengue, MSAT were found to be negative. The serum amylase, serum lipase, serum ceruloplasmin were within normal limits. Routine X-ray chest, ECG and echo were also a normal study. USG abdomen showed minimal ascites and mild hepatomegaly and MRCP showed hepatosplenomegaly and hepatitis.

Finally, the **liver biopsy** was suggestive of **auto-immune hepatitis** and the **skin biopsy** was suggestive of findings consistent with **morbilliform drug eruption.**

Applying the relevant clinical findings and investigations to the **RegiSCAR Diagnosis Score for DRESS**[4], we came to a definite diagnosis of the **DRESS syndrome.**

RegiSCAR diagnostic score for DRESS			
Features	**No**	**Yes**	**Unknown**
Fever (38.5℃)	-1	0	-1
Enlarged lymph nodes (≥2 sites, ≥1cm)	0	1	0
Atypical lymphocytes	0	1	0
Eosinophilia	0		0
700-1499 or 10%-19.9%		1	
≥1500 or ≥20%		2	
Skin rash	0		0
Extent > 50%	0	1	0
Atleast 2: edema, infiltratoin, purpura, scaling	-1	1	0
Biopsy suggesting DRESS	-1	0	0
Internal organ involvement	0		0
One		1	
Two or more		2	
Resolution in more than 15 days	-1	0	-1
Atleast 3 biological investigations done and negative to excludealternate diagnosis	0	1	0
Final score: <2 = no 2-3 = possible 4-5 = probable >5= definite			

The positive clinical findings/investigations are highlighted by the arrows.

Following immediate withdrawal upon suspicion of DRESS, after the confirmation of diagnosis the patient was started on Tablet Prednisolone 50 mg/day (1 mg/kg/day) along with the supportive management.

After one week of steroid therapy, there was progressive decrease in the rash and the liver enzymes started reducing gradually. The patient was discharged home after 22 days with a prescription gradually reducing the steroid therapy and was advised routine follow-up.

After 2 months, during the routine follow-up, she was found to have history of excessive hair fall, constipation, heavy menstrual bleeding and history of cold intolerability. She was admitted again and evaluated.

Her CBC was normal except for anemia with a hemoglobin of 9.8 g/dl. Other routine tests were unremarkable for any abnormalities. The thyroid profile though, revealed **hypothyroidism** with a TSH of 28.7 mIU/L, a free T4 of 0.2 ng/dl and a free T3 of 215 pg/dl. She was **positive for anti-TPOantibodies** (65 IU/L) confirming the diagnosis of an **auto-immunehypothyroidism**. Patient was then started on Tablet Levothyroxine 50 micrograms/day and continued on steroids.

III. Discussion

Arriving at the final diagnosis of DRESS in our patient based on meticulous clinical examination and extensive work-up helped to identify the causative agent and stop it immediately, which resulted in a rapid regression of symptoms in the patient. DRESS Syndrome usually presents with cutaneous manifestations ranging from maculo-papular eruptions to exfoliative erythroderma[5]. And the visceral involvement can present as hepatitis, pneumonitis, nephritis, pericarditis or even colitis[6]. Apart from the prominence of the widespread rashes and the hepatic dysfunction, the association with lymphadenopathy and facial puffiness made us almost confirm a clinical diagnosis of DRESS. Now the next step was to rule out the other differential diagnoses we had in mind through appropriate investigations. Two other conditions that seemed possible were viral hepatitis and SLE, which were subsequently ruled out after the lab results came in. The laboratory investigations only further confirmed the diagnosis of DRESS through hematological abnormalities notably eosinophilia, elevated LFTs, positive ANA antibodies and most importantly a liver biopsy and skin biopsy revealing an auto-immune hepatitis and morbilliform drug eruption respectively. Having acquired a score of>5 on the RegiSCAR Diagnosis Score, tremendous improvement was seen upon stopping the drug and starting the patient on steroids.

With a mortality rate of 10%[7], the prognosis of DRESS can be worsened by the occurrence of severe organ damage or the complications of prolonged steroid therapy. Another cause of concern following the resolution of acute symptoms would be the development of long-term sequalae that are attributed to many mechanisms including auto-immunity. The regular follow-up of our patient helped us to give importance to her ensuing complaints, investigate accordingly and find out such auto-immune sequelae. DRESS has been reported to have been associated with endocrine abnormalities (mostly etiology unknown) such as Type I Diabetes, Hashimoto's thyroiditis, Grave's disease and painless thyroiditis which form a major part of the sequelae experienced[8]. Other less common non-endocrine sequalae such as auto-immune hemolytic anemia, SLE etc have also been observed [9.]In compliance with this, our patient with the hypothyroid symptoms, elevated TSH and positive anti-TPO antibodies only proved the same by the final diagnosis of auto-immune thyroiditis following Phenytoin-induced DRESS Syndrome.

IV. Conclusion

The precise pathogenesis of anti-convulsant induced DRESS remains elusive. However, the complex interplay between three factors may be considered : the deficiency of the epoxide hydroxylase enzyme responsible for detoxifying the metabolites, the sequential reactivation of the herpes virus family (HHV-6 and HHV-7) and also predisposition with certain Human Leucocyte Antigens[10]. Apart from the case with Phenytoin described here, DRESS has also been described with other drugs such as Allopurinol, Dapsone, Carbamazepine, Sulfasalazine etc[10].

In conclusion, DRESS Syndrome is a severe drug reaction and has the immense potential to turn into a cause of life-threatening morbidity if not diagnosed in time and the inciting drug, withdrawed. The later occurrence of permanent long-term sequelae can be overlooked because of the asymptomatic interval that occurs after the resolution of the acute severe drug reaction. Thus, the patients of DRESS must undergo long-term monitoring to detect early signs and symptoms that might be suggestive of auto-immune and more commonly, life-long sequelae.

References

[1]. Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome in two young children: the importance of an early diagnosis. **Massimo Luca Castellazzi, Susanna Esposito,Laura Elisabetta Claut,Valeria Daccò and Carla Colombo**

[2]. Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) Syndrome. Sonal Choudhary, MD, Michael McLeod, MS, Daniele Torchia, MD, and Paolo Romanelli, MD

[3]. Drug Reaction with Eosinophilia and Systemic Symptoms Shilpa Khetarpal MD, Anthony Fernandez MD, PhD.

[4]. Ashish Gupta et al (2018) 'Drug rash with Eosinophilia and Systemic Symptoms Syndrome Due to anti-tb Medication', International Journal of Current Advanced Research, 07(10), pp. 15878-15880. DOI: http://dx.doi.org/10.24327/ijcar.2018.15880.2912

[5]. Recent Advances in Drug-Induced Hypersensitivity Syndrome/Drug Reaction with Eosinophilia and Systemic Symptoms. Hideaki Watanabe, Hindawi Journal Of Immunology Research, Volume 2018 |Article ID 5163129 | 10 pages | https://doi.org/10.1155/2018/5163129.
[6]. Acute Hepatitis and Colitis in DRESS Syndrome in a Patient Taking Carbamazepine Pikeshkumar Patel, MD, Tomas Rodriguez, MD, and Simeon Carvajal, MD, Bronx Lebanon Hospital Center.
[7]. Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS): An Interplay among Drugs, Viruses, and Immune System **Yung-Tsu Cho, Che-Wen Yang, and Chia-Yu Chu***
[8]. A case of DRESS syndrome associated with autoimmune type 1 diabetes. Isabella Mattei, Elena García Fernandez, Gema Villa López, Irene Hoyas Rodriguez, Guillermo Martinez Díaz Guerra & Miguel León Sanz
[9]. Drug reaction with eosinophilia and systemic symptoms (DRESS) and its relation with autoimmunity in a reference center in Mexico* **Juan Manuel Ruiz Matta, Silvia Méndez Flores, and Judith Domínguez Cherit.**
[10]. Drug Reaction with Eosinophilia and Systemic Symptoms: An Update and Review of Recent Literature **Abhishek De, Murlidhar Rajagopalan, Aarti Sarda, Sudip Das, and Projna Biswas.**

Thabuna Sivaprakasam, et. al. "Phenytoin-induced drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), a raredrugreaction complicated by auto-immune hypothyroidism." *IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)*, 19(7), 2020, pp. 06-09.