International Journal of Healthcare Sciences ISSN 2348-5728 (Online)
Vol. 2, Issue 1, pp: (156-158), Month: April 2014 - September 2014, Available at: www.researchpublish.com

CLINICAL COURSE AND MANAGEMENT OF IATROGENIC CUSHING'S SYNDROME IN A POST SPLENECTOMY EVANS SYNDROME PATIENT

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***Abstract*: Evans syndrome (ES) is anecdotal and incidental combination of autoimmune hemolytic anemia (AIHA) and immune thrombocytopenia (ITP); occurrence may be simultaneous and sequential. Cushing's syndrome along with ES is just a co-existence and very rare combination. We report a case of Cushing's syndrome with ES in a 26 years old female who has undergone splenectomy for AIHA treatment. She was diagnosed with ITP and AIHA remission after splenectomy. Simultaneously the patient presented with Cushing's syndrome probably due to long term steroids use. Due to its rarity, this report shed light on clinical features, investigational procedures, management and outcomes in this particular combin ation.**

Keywords: **Immune thrombocytopenia, Autoimmune hemolytic anemia, CUSHINGOID, Transfusion, Immuno globulins**

I. INTRODUCTION

Evans syndrome (ES) is the contemporaneous or sequential occurrence of autoimmune hemolytic anemia (AIHA) and immune thrombocytopenia (ITP). Generally patients with ES show anemic and bleeding manifestations. Corticosteroids and/or intravenous immunoglobulin are the first line therapy supported with blood transfusions if necessary. Splenectomy also had seen as an effective option for AIHA or ITP management when medicinal therapy fails.[1] Occurrence of ES with Cushing's syndrome (CS) is very rare; we present a case of 26 years old female diagnosed to have ES along with CS (due to long term use of Prednisolone for AIHA). This case presents the occurrence of ITP after splenectomy (has been done for AIHA management) with AIHA remission. ITP after splenectomy with AIHA remission and CS is an uncommon combination; it would be interesting to know about clinical presentations, investigational procedures, management and outcomes for noted conditions. Hereby we present all for the particular case.

II. CASE PRESENTATION

A 26 year old female patient came to our hospital in January, 2014 with low backache and the pain radiating to both lower limbs for 2 days. Physical finding showed buffalo hump and puffiness of face with some of 'CUSHINGOID' symptoms; skin thinning, obesity, hyperglycemia and infections (fever with cough for 4 days with Erythrocyte Sedimentation Rate 96 mm/hour; suspected); pallor and icterus also shown . Adrenocorticotropic hormone (ACTH) level in blood was low; 3.2 pg/mL. She has gained 18 kg weight over past 2 years (according to her that was 48 kg in March, 2012 and now it is 66 kg in January, 2014). Patient medical history revealed that the patient is a known case of AIHA first diagnosed in 2008 and started on steroids (Prednisolone 60 mg daily) since. Splenectomy was performed in February, 2010 as a treatment of AIHA. In January, 2013 she was re-admitted and diagnosed to have Evans's Syndrome (AIHA remission with ITP) for

which Azathioprine 50 mg daily was added to continuous steroid therapy. On recent admission lab parameters shown hemoglobin 5.2 g/dL, hematocrit 17.4%; MCH 37.5 pg/cell, MCHC 30.1 g/dL, MCV 124 fL; RBC count $1.39*10^6$ cells/microL, total leukocyte count $28*10^3$ cells/microL and platelet count was 21000 cells/mm^3; with post prendial blood sugar level of 210 mg/dL. Peripheral smear reports showed the normocytic, normochromic RBCs with anisocytosis, polychromatophils, spherocytes and Howell-Jolly body inclusions and platelet had low count with giant forms; smear consistent with AIHA with evidence of hemolysis. Direct Coomb's test was positive for AIHA. Normal levels of Folate and Cyanocobalmin (Vitamin B12) ruled out thrombocytopenia secondary to folate/B12 deficiency. Anti-nuclear Antibody (ANA) serologies were negative, but serology for anti-platelet antibody was highly positive. Bone marrow biopsy was performed which revealed erythroid hyperplasia and thrombocytopenia due to peripheral destruction. On the basis of subjective and objective evidences patient was diagnosed to have steroids induced Cushing's syndrome (iatrogenic) with ES post splenectomy. Now she was started on injectable Prednisolone 50 mg daily instead of oral therapy and 1 pint RBCs transfused on 2nd day of admission. Azathioprine 50 mg daily has to be continued with folic acid 5 mg daily. Amoxicillin 500 mg and clavulanic acid 125 mg in combination were given for 4 days with paracetamol 500 mg daily on SOS basis and patient improved symptomatically from fever and cough. Metformin 500 mg daily was given for 1 month for the indication of elevated blood sugar levels. On 7th day after admission injectable Prednisolone switched to oral and patient been discharged with Prednisolone tapering therapy (50 mg daily for first 2 weeks; 40 mg daily for next two weeks and 30 mg daily for continue as maintenance dose) with Azathioprine 50 mg daily and folic acid 5 mg daily for continue. On discharge day lab reports had shown hemoglobin 7.4 g/dL, hematocrit 25.4% and platelet counts $118*10^3$ cells/mm^3. Patient improved symptomatically and backache has subsided. After 2 month on follow up she shown improvement in hematology; hemoglobin 8.6 g/dL and platelet counts $132*10^3$ cells/mm^3. Puffiness of face, buffalo hump and other 'CUSHINGOID' symptoms are subsiding leisurely.

III. DISCUSSION

Evans Syndrome (ES) is a rare disorder characterized by co-existence of AIHA and immune thrombocytopenia (ITP), first described by Evans et al in 1951.[1] The frequency of ES is less than 0.8-3.7 % of all patients with AIHA & ITP. The occurrence of AIHA and ITP may be simultaneous or sequential; considered as an anecdotal and incidental combination.[2] Although dysfunction of the body's immune system plays a role in, due to the rarity of the disease, pathophysiology of the disease still remains unclear. A recent study by Teachey *et al* revealed that Autoimmune Lymphoproliferative Syndrome (ALPS) may be involved in the pathophysiology of Evans.[3]

Clinical presentation of ES is varied and is dependent on the severity of anemia and thrombocytopenia. In general, the patient presents with anemic signs and symptoms such as lethargy, shortness of breath, pallor. In this patient, anemic signs were already prominent due to pre-existing AIHA. Although ITP was diagnosed by laboratory investigations; bleeding and bruising were not observed. Treatment of ES is complex as the disease is interspersed with periods of exacerbation and remission. The treatment is thus highly individualized and even the response varies within the same patient. Coombs' positive AIHA along with thrombocytopenia are the "gold" diagnosis of ES.[4] Corticosteroids and/or intravenous immunoglobulins are considered as the first line therapy for Evans management. Danazol, Cyclosporine, Azathioprine, Cyclophosphamide, rituximab, are some drugs used for Evans management.[5] Splenectomy in AIHA patients is safe and effective with excellent results; according to Parray &Wani 2004, approx 88% patients shown improvement by the procedure. Splenectomy is mainly performed when corticosteroids and immunomodulating agents failed to treat AIHA and/or ITP.[6,7] Although there is no evidence which may indicate that our patient has ITP due to splenectomy, the temporal sequence of occurrence of ITP after splenectomy is interesting and hasn't been reported before. Further study needs to be performed in this domain to ascertain the etiology of ES so that a more targeted approach can be followed.

The combination of Evans syndrome and Cushing's syndrome (CS) is unusual; we haven't found a single case of this combination in literature. In this case we considered both as co-existence, CS has evaluated due to long term use of Prednisolone for AIHA. CS shows the symptoms of hypercortisolism or prolongs exposure to high level of corticosteroids. CS is differentiated into exogenous and endogenous. When symptoms occurs because of over use of corticosteroids for any other complications it is considered as exogenous or iatrogenic CS, endogenous occurs because of overproduction of ACTH in own body. This patient was evaluated to have iatrogenic Cushing's syndrome.[8] Standard stigmata of CS includes classic moon face, buffalo hump and rapid weight gain with other clinical manifestations show "CUSHINGOID" symptoms; 'C' cataracts, 'U' ulcers, 'S' skin brushing or thinning, 'H' hyperglycemia/ hirsutism

/hypertension, 'I' infections, 'N' necrosis, 'G' glycosuria, 'O' osteoporosis/obesity, 'I' immunosuppression, 'D' diabetes. Dexamethasone suppression test, 24-hour urinary or saliva cortisol level and ACTH blood levels are the diagnostic tests for CS.

In iatrogenic CS corticosteroids shows the same effects as cortisol does in our body. Here in this case Prednisolone mimics the cortisol mechanism and developed CS symptoms. Reduction of corticosteroid use is the mainstay of the therapy of CS. Mifepristone can be used when patient has type 2 diabetes along with CS.[9] Sudden stoppage or withdrawal of corticosteroids often shows severe side effects and hence the doses are gradually tapered off.[10] In this case clinician has prescribed Prednisolone tapering therapy to reduce the dose. After 2 month on follow up the patient showed improvement from CS and ES both.

IV. AUTHORSHIP CONTRIBUTION

All authors are contributed equally in preparing of manuscript and eligible for authorship.

V. ACKNOWLEDGMENT

We are very thankful to Dr. Manjunath Hande, Department Of Medicine, Kasturba Medical College & Hospital, India for his valuable guidance.

VI. CONFLICTS OF INTEREST

All authors have declared no conflicts of interest.

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