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A case report on multiple effects of drugs in steroid dependent chronic ITP

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Abstract

The first line treatment for chronic Immune Thrombocytopenic Purpura (ITP) includes steroids. Immunomodulatory drugs for refractory cases include azathioprine, cyclosporine A, mycophenolate mofetil, dapsone, danazol and cytotoxic agents. Here, we report a case of a 26-year-old female, with ITP who showed a dose-dependent variation in the platelet count. On long term administration of steroids, she developed hyperglycemia, weight gain, acne, striae distensae and hair loss. Dapsone induced agranulocytosis is also another striking feature of this case.

Keywords

Immune Thrombtocytopenic Purpura (ITP); splenectomy; weight gain; hyperglycemia; agranulocytosis

Introduction

Immune thrombocytopenic purpura (ITP) is an auto-immune disease with low platelet count (thrombocytopenia) and the absence of other causes of thrombocytopenia. It causes a characteristic purpuric rash and an increased tendency to bleed. The etiology of ITP is poorly understood. The estimated annual incidence of adult ITP ranges from 0.6 to 6.6 cases per 100,000 adults. Women are affected disproportionately, with a female to male ratio of nearly two to one. ITP remits spontaneously, but if it is not appropriately managed, it can become fatal [1].

Corticosteroids are the drugs of choice for the initial management of acute ITP. Steroids have various physiological effects like metabolic control, regulation of water and electrolyte balance, regulation of body's response to stress, anti-inflammatory, anti-allergic and immunosuppressive action. Based on these effects, steroids can be used in a wide range of conditions like arthritis, collagen diseases, severe allergic reactions, auto-immune disorders, bronchial asthma, infective diseases, eye diseases, skin diseases and intestinal diseases. But steroids also carry a risk of multiple adverse effects like glaucoma, fluid retention, hypertension, cognitive problems, weight gain with fat deposits in abdomen, face and the back of neck, cataracts, hyperglycemia, increased risk of infections, osteoporosis and fractures, suppression of adrenal gland hormone production and skin allergic conditions.

Glucocorticoids increase hepatic glucose production and inhibits insulin-stimulated glucose uptake in peripheral tissues, thereby hyperglycemia accounts for one of the well known adverse effects of steroids.

Another well-recognized and documented adverse effect is weight gain, which is usually manifested in patients as central obesity with redistribution of body fat to truncal areas , appearance of dorsocervical and supraclavicular fat pads, classic moon face and striae [3].

Despite the high initial therapeutic efficacy, in many cases, steroids tapering or withdrawal is followed by a drop in platelet count and the need for additional treatment. The additional treatment includes azathioprine, cyclosporine A, cyclophosphamide, danazol, dapsone, mycophenolate mofetil, rituximab, and thrombopoietin receptor agonists like eltrombopag and romiplostim.

Dapsone is an antibacterial sulphonamide with anti-inflammatory property, which has shown therapeutic activity in patients with immune thrombocytopenia [6]. It can also cause a variety of adverse effects including hemolytic anemia, methemoglobinemia, exanthematous eruption, Steven –Johnsons Syndrome, toxic epidermal necrolysis, agranulocytosis, nephritis, pneumonitis, and hypothyroidism. Agranulocytosis is an acute condition where there is a sudden drop in white blood cell production, leaving the body susceptible to bacterial invasion and septicemia. It is a rare complication but exhibits very serious toxic effect of the sulfones [8].

Patients who do not respond to medical therapies, who relapse after response to therapies, or who require potentially intolerable doses of medical therapies to achieve platelet counts high enough to prevent bleeding usually undergo splenectomy, if the patient is a suitable candidate [1].

Case Report

A 26 yr old female patient presented with a history of excessive bleeding during menstruation and bleeding from the gums.

Past history revealed that in 2010 (6 years back), she had developed menorrhagia and passing large blood clots, purpuric spots on the skin and bleeding from gums. Her platelet counts were very low (4000 cells/cumm) and was diagnosed to have ITP. She was transfused with 14 units of platelets and started on prednisolone 40mg after which her platelet levels increased to 11000 cells/cumm. Her blood sugar levels were also elevated for which managed with insulin. General physical examination revealed a weight gain from 45kg to 70kg and puffiness of the face.

On follow-up in a private hospital in 2011, the dose of tablet prednisolone was tapered from 20mg OD for one week to 10 mg OD the next week followed by 5mg after which it was stopped with a platelet count of 80,000cells/cumm. Tablet azathioprine 100mg was started and the platelet count started to decrease gradually. She developed heavy bleeding during menses for 16 days for which a biopsy of the endometrium was done and she was found to have tuberculous endometritis. She was started on anti tuberculoar therapy, norethisterone 5mg and with vitamins B complex.

Azathioprine was continued for 2.5 years after which she became symptom free. She was off medications because she was symptom free till 2015. Suddenly, she developed bleeding, purpura and melaena for which she was admitted in a government hospital. Her platelet count was found to be 3000 cells/cumm and was managed with 2 units of platelets, 5mg of prednisolone and 50mg of azathioprine. She followed-up in the same private hospital she was admitted in 2011 where they treated her with 40mg of prednisolone and 50mg of azathioprine. After 1 month, azathioprine was stopped and changed to dapsone. The platelet count was improved to 218,000 cells/cumm. After a week, she presented with

loose stools, vomiting and fever. She was investigated to have dapsone induced agranulocytosis, thereby dapsone was stopped and the condition was managed with injection filgastrim and other supportive measures. She continued with 40mg of prednisolone for which there was an eventual elevation of blood sugar, body weight along with supraclavical fat pads, buffalo hump, hair loss, acne and striae distensae (Fig: 1). The dose was then tapered to 20mg for 5 days and then to 10mg which resulted in a consistent fall in the platelet count (Table 2).

She was shifted to a Multi-specialty hospital where she was managed with prednisolone 30mg and azathioprine 50mg.Finally, she underwent splenectomy whereby her platelets levels were elevated (339000 cells/cumm).

Discussion

The goal of medical care for immune thrombocytopenic purpura is to increase the platelet count to a normal level. Treatment with corticosteroids may not only reduce the rate of platelet destruction but may also rapidly alter endothelial cell integrity to facilitate primary hemostasis and to reduce bleeding and bruising.

According to a study by Gonzalez-Gonzalez ,"Glucocorticoids for 2 to 3 months produced an elevated incidence of diabetes, usually with mild hyperglycemia occurring between the second and fourth week and hyperglycemia was more frequent with continuous doses"[2].

In a study done by Greenstone and Shaw, measuring blood glucose response to alternate day prednisone dosing, patients exhibited hyperglycemia in the afternoons of the days when the steroids were given. Blood glucose levels normalized throughout the next day (the day off of steroids)[12].

In another case report, a 39 year old female patient was reported to have Cushing syndrome caused by chronic use of prednisolone. She had complaints of moon face, backache, swelling of limbs, abdominal distension, muscle weakness and striaes since 3 weeks. The prednisolone dose was tapered [3].

After an estimated two to three months of treatment, 40-60% of patients will observe weight gain and/or a significant change in their physical appearance. The risk increases with a higher prescribed dose (e.g. the equivalent of 10 mg per day of prednisone or prednisolone).

A study suggests that dapsone is a safe and effective second-line agent for steroid-dependent or refractory ITP patients where, 20 patients of ITP were treated with dapsone among which 14(70%) of them showed a response and 9 (45%) showed a complete response [7]. But various fatal hematologic adverse effects have been reported with the use of dapsone, agranulocytosis being a rare one among them. It results in reduced immunity to infections. The metabolite of dapsone is toxic to bone marrow and may produce maturation arrest of neutrophils. It may also induce the formation of antibodies against neutrophils precursors in the marrow [8].

Splenectomy remains the best curative treatment for chronic symptomatic ITP and platelet counts $<30 \times 10^9$/L after failure of the first-line treatments. The risk of infection is highest in the first two years after splenectomy, Guidelines published by the British Committee for Standards in Hematology emphasized that most infections after splenectomy could be avoided through measures that include

offering patients appropriate and timely immunization, antibiotic prophylaxis, education, and prompt treatment of infection [9,10].

Tables

Table 1:

Date	Dose of prednisolone (mg)	Platelet count (cells/cumm)	Fasting blood sugar(mg/dL)
16/11/2010	40	4000	190
17/11/2010	40	5000	226
18/11/2010	40	5000	135
21/11/2010	40	13000	210
30/11/2010	40	11000	207

Table 2:

Date	Treatment	Platelet count (cells/cumm)	Fasting blood sugar(mg/dL)	Body weight (kg)
07/06/2015	5 mg prednisolone	3000		61.3
21/07/2015	40mg prednisolone	18000		
10/09/2015	40mg prednisolone	218000	106	
20/09/2015	20mg prednisolone	47000	93	
28/09/2015	10mg prednisolone	36000		63.3
12/10/2015	10mg prednisolone	22000	76	
30/11/2015	10mg prednisolone +50mg azathioprine	95000		68.4
14/12/2015	10mg prednisolone +100mg azathioprine	92000		71.4
28/12/2015	10mg prednisolone (AD) +100mg azathioprine	71000	92	
27/04/2015	10mg prednisolone (AD) +100mg azathioprine	58000		
07/05/2015	10mg prednisolone (AD) + 100mg azathioprine	15000		
14/05/2015	40mg prednisolone +100mg azathioprine	71000		72
28/05/2015	30mg prednisolone +50mg azathioprine	8000	85	

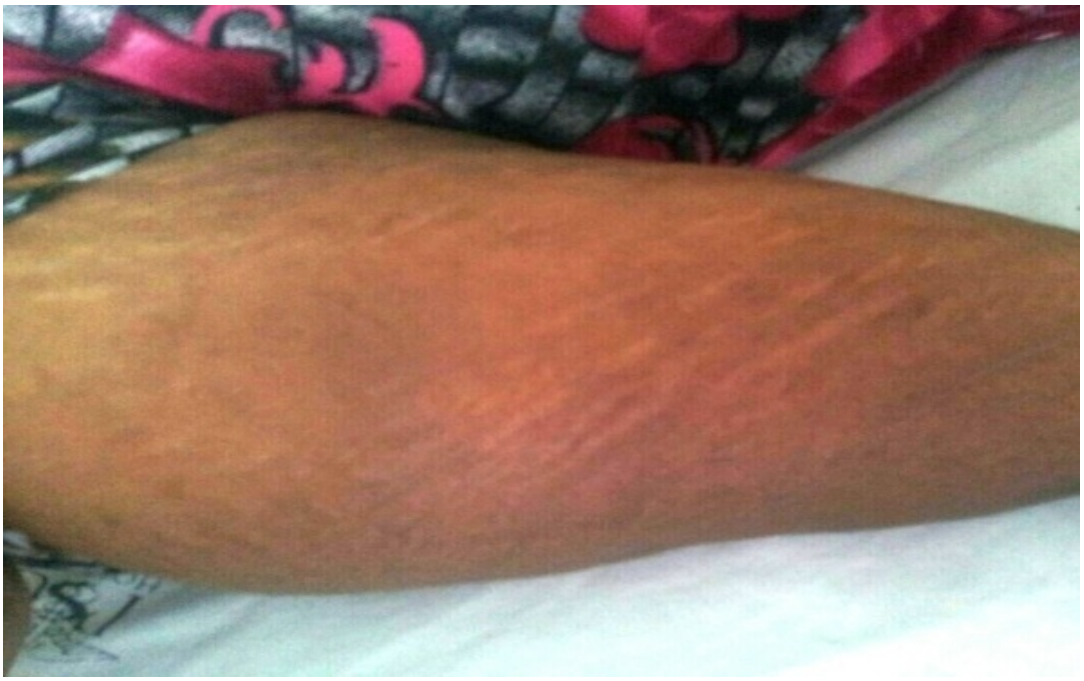
Conclusion

Our case of steroid dependent chronic ITP showed a dose –dependent variation in platelet count. The association of corticosteroid use and the development of the adverse effects, and their resolution after reduction of corticosteroid dose, suggest a causal relationship in this case. Agranulocytosis is a direct adverse reaction of dapsone though it showed a remarkable improvement in the platelet count.

This case report warns us the need for accurate dosing and tapering while administering oral corticosteroids. Patient education addressing the adverse effects and importance of follow up plays a vital role in minimizing such adverse effects.

Patients who develop adverse reactions like hyperglycemia and obesity should be given education regarding diabetic diet and measures to control weight. Patients should be emphasized the need for appropriate and timely immunization, antibiotic prophylaxis, and prompt treatment of infection. They should know the nature and likelihood of overwhelming post-splenectomy infection and that they should seek medical attention if they become ill and feverish.

Figures



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