**Case Report:**

**G-CSF Induced Posterior Reversible Leukoencephalopathy Syndrome and SLE flare up**

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**Abstract**

**Background:** Granulocyte-colony stimulating factor (G-CSF) is a glycoprotein which stimulates the survival, proliferation, differentiation and function of neutrophil, granulocyte progenitor cells and mature neutrophils. G-CSFs have been used to improve granulocyte count in neutropenic patients, reduce the incidence and duration of neutropenia in SLE patient. In general, side-effects are mild to moderate and life threatening side-effects like severe SLE flare up and posterior reversible leukoencephalopathy syndrome are very rare.

**Case Report:** We report a case of SLE patient who developed severe systemic lupus erythematosus (SLE) flare up and posterior reversible leukoencephalopathy syndrome (PRES) secondary to G-CSF. This case emphasizes the diagnostic and therapeutic challenges in the management of SLE.

**Key Words:** Posterior reversible leukoencephalopathy syndrome (PRES) — Systemic lupus erythematosus (SLE) — Granulocyte colony stimulating factor (G-CSF).

**Introduction**

**GRANULOCYTE** colony-stimulating factor (G-CSF) is a glycoprotein that controls production of functional neutrophils and their release into peripheral blood. It has been widely and frequently used for many conditions and disorders in the field of hematology and oncology ill. G-CSF is used to correct neutropenic state by promoting the growth, proliferation, differentiation and maturation of neutrophil precursors. In addition to recruiting more leukocytes, G-CSF promotes the functional capacity of peripheral white blood cells [1,2]. Side-effects are generally mild to moderate, including bone and joint pain, headache, fever, rhinitis, rashes, fatigue, thrombocytopenia and injection site reactions. Life-threatening complications such as stroke, myocardial infarction and splenic rupture, resulting from short-term or long-term use of these agents, however rare, can occur [3].

We present one such interesting systemic lupus erythematosus (SLE) patient who developed SLE flare up and posterior reversible leukoencephalopathy syndrome (PRES) secondary to G-CSF and was treated successfully with clinical improvement.

**Case Report**

A 20-year-old Saudi female presented to the Artificial Kidney Unit of Aseer Central Hospital, Abha, Saudi Arabia on 9/11/2009 for regular hemodialysis for her end stage renal disease with follow-up cell blood count which showed pancytopenia. She was admitted to the hospital for further workup of pancytopenia. There was no history of hemoptysis, productive cough, fever. Other systemic review was unremarkable. She was diagnosed with SLE 8 years earlier, and she was on prednisolone 10mg and azathioprine 50mg. Also, she developed lupus nephritis with kidney biopsy showed class IV glomerulonephritis four years earlier. She received full course of cyclophosphamide for 18 months and the last dose was a year back and also a high dose of steroid was given. She developed deep venous thrombosis, diagnosed to have antiphospholipid syndrome and was anticoagulated with warfarin. Her social history and family history were not significant.

On physical examination, she was conscious, oriented and not cyanosed or in respiratory distress. Vital signs were within normal range except here
blood pressure, which was 150/100 mmHg Cardiovascular, chest, abdominal and other examination findings were unremarkable.

Initial laboratory investigations revealed pancytopenia (leukocyte count of 1.8 x 10^3/L, platelet count of 81 x 10^3/L and hemoglobin level of 7.1 g/dL). Blood urea nitrogen was 140 mg/dL and serum creatinine was 6.3 mg/dL. Erythrocyte sedimentation rate was 48 mm/hour and C-reactive protein was negative. Coagulation profile and electrolytes were within normal ranges. The liver function test was normal apart from a serum albumin level of 2.2 g/dL. Hepatitis serology was negative. Postero-anterior chest X-ray taken on initial presentation was normal (Fig. 1).

A high dose of methylprednisolone 1 gm was given and azathioprin was discontinued. On the second day, cell blood count showed leukocyte count of 1.5 x 10^3/L, platelet count of 63 x 10^3/L and hemoglobin level of 6.7 g/dL. Peripheral blood smear showed pancytopenia with absolute neutrophil count (57%, 855 x 10^3/L), lymphocytes (36%), band (6%) and eosinophils (1%).

G-CSF (neupogen) was given because of leucopenia. Twelve hours after administration of G-CSF, the patient developed sudden bilateral visual loss and severe headache. Computed tomography of head was obtained immediately and showed symmetrical predominantly subcortical white matter hypodensities with mainly occipital distribution consistent with posterior reversible encephalopathy syndrome (Fig. 2).

Few hours after the sudden loss of vision, the patient started to have cough, hemoptysis and dyspnea with oxygen saturation 80% in room air. Chest examination revealed diffuse bilateral inspiratory crackles. Chest X-ray showed diffuse bilateral non-homogenous infiltration (Fig. 3A). Echocardiogram showed normal left side size and function with no effusion. Sputum Gram stain and culture were negative. Anti-Ds DNA showed high titer and low level of C3 and C4.

Fig. (1): Posterior-anterior chest X-ray shows normal.

Fig. (2): CT scan brain, showing symmetrical predominantly subcortical white matter hypodensities with mainly occipital distribution.

(A) (B)

Fig. (3): Diffuse bilateral non-homogenous infiltration (A) and clear improvement of the previous infiltration (B).
The patient was intubated. A high dose of steroid was continued with pulse dose of cyclophosphamide, intravenous antibiotics and G-CSF was discontinued.

On the sixth day, she was still on mechanical ventilator but she was conscious with improvement of saturation and she was able to count fingers.

Follow-up chest X-ray showed clear improvement of the previous infiltration (Fig. 3B). On the next day, the patient was extubated, vital signs were within the normal range, and she had normal visual acuity. Cell blood count revealed a white blood count of $7.14 \times 10^3 / L$, platelets count of $139 \times 10^3 / L$ and hemoglobin level of $9.1g/L$.

The patient was discharged after few days in a good condition with regular follow-up.

**Discussion**

SLE is a chronic inflammatory autoimmune disease. Although hematological anomalies are commonly found in SLE, neutropenia is uncommon. When it occurs, it is usually associated with severe infection or drug effect. G-CSF may be used to increase the neutrophil count [4].

G-CSF is a 175-amino acid, highly purified, nonglycosylated protein produced by recombinant technology in a laboratory strain of E. Coli by adding a gene expressing the granulocyte colony-stimulating factor [1-3]. G-CSF is a hematopoietic growth factor that acts selectively on the cells of the neutrophil lineage. It induces neutrophil production, differentiation, and release from the bone marrow [2,5]. It promotes the functional capacity of peripheral white blood cells. G-CSFs are generally regarded to be safe and mostly well tolerated. Clinical adverse effects are generally mild or moderate. Life-threatening complications such as PRES, SLE flare up are rare [1,5].

Our patient experienced severe SLE flare up in the form of pulmonary hemorrhage, low complement level and high titer of anti Ds-DNA as well as manifestations of PRES in the form of headache and visual loss after administration of G-CSF.

PRES is a clinico-radiological entity that was well described by Hinchey et al., as a clinical syndrome of insidious onset of headache, confusion or decreased level of consciousness, visual changes, and seizures, associated with characteristic neuroimaging findings of posterior cerebral white matter edema [6].

Several medical conditions have been associated with this syndrome, such as systemic hypertension, renal dysfunction, several chemotherapeutic and immunosuppressant agents, systemic lupus erythematosus or solid organ transplantation [7,8].

The pathogenesis of PRES is not fully understood. The presence of vasogenic edema is universal, but its origin remains controversial. The reversibility of the clinical and radiological changes seems to minimize the importance of cytotoxic edema in this syndrome, although there have been cases where both kinds of edema coexist [7,9].

In SLE, PRES can be a manifestation of lupus disease activity or a consequence of immunomodulatory therapy and management is dependent on the etiology [10]. Originally, PRES was described as a sub-cortical disease of the posterior cerebral [6,10], with symmetrical changes in both parietal and occipital lobes. More recently published series have shown different radiological findings and patterns, such as cortical involvement, as well as frontal, temporal, or, less commonly, cerebellum, brainstem, or basal ganglia lesions. Brain computed tomography imaging may be useful as a first examination, exhibiting hypodense areas in susceptible regions, but the diagnosis is more firmly established using brain magnetic resonance imaging [11-13].

In the setting of a possible manifestation of SLE activity, PRES is usually treated with immunosuppression, most commonly with intravenous methyleprednisolone and cyclophosphamide. If the cause is thought to be drug-induced, prompt cessation of the offending drug is necessary, together with supportive management of hypertension [10,13].

So, the final diagnosis of our case was reached as "G-CSF-induced PRES", since the patient developed visual loss and headache after the administration of G-CSF and the condition improved after its discontinuation, in addition to the supportive treatment and administration of methylprednisolone and cyclophosphamide.

Only few cases of G-CSF-induced SLE flare up without PRES have been reported [14,15]. Also, some cases of G-CSF induced PRES have been reported, but not in SLE patients [16,17].

In conclusion, this is the first reported case of G-CSF induced PRES and SLE flare up in the Kingdom of Saudi Arabia. Although regarded as safe and well tolerated, G-CSF administration could result in potentially fatal complications in
SLE patients. Therefore, G-CSF should be used with caution and close monitoring in SLE patients (including close monitoring of vital signs, visual examination, abdominal physical examination, daily complete blood count test) during and several days after G-CSF treatment is recommended.

References