CASE REPORT

Journal of Clinical Rheumatology and Immunology

OPEN ACCESS

Potentiation of Lupus Activity by Granulocyte Colony-Stimulating Factor

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ABSTRACT

Recombinant human granulocyte colony-stimulating factor (G-CSF) is commonly used to accelerate recovery of neutropenia in patients with marrow suppression. We hereby report a patient with systemic lupus erythematosus (SLE) who developed diffuse lupus nephritis and impending cytokine storm after G-CSF therapy. The exact mechanisms by which G-CSF leads to lupus flares remains enigmatic. Increased neutrophil apoptosis and release of cytokines have been postulated. The use of G-CSF in patients with autoimmune disease should be cautious.

Keywords: Granulocyte Colony-Stimulating Factor; Systemic Lupus Erythematosus; Leucopenia; Cytokine Storm Syndrome; Azathioprine.

INTRODUCTION

Patients with systemic lupus erythematosus (SLE) may have episodes of lupus flare from time to time. Lupus flare can be idiopathic or triggered by environmental factors, such as medications, infections, ultraviolet radiation, and so on [1]. Several types of drugs are well recognized to trigger SLE. Traditional drug-induced lupus agents include procainamide, hydralazine, and quinidine [2]. Some drugs are also shown to exacerbate idiopathic lupus include estrogen-containing contraceptives [3]. Cytokines like granulocyte colony-stimulating factor (G-CSF) is also postulated to be able to potentiate exacerbation of SLE [1].

This case report presents a patient with exacerbation of SLE, which was likely potentiated by G-CSF injection. The possible mechanisms of G-CSF potentiating lupus flare would be discussed, and cautious use of G-CSF injection in patients with autoimmune disease would be emphasized.

REPORT OF A PATIENT

A 46-year-old female patient with SLE, while on azathioprine (20 mg/day) and prednisolone (3 mg/day), was admitted to the medical ward due to a 2-week history of low-grade fever and generalized malaise.

Her SLE condition had been stable for 20 years with last relapse of lupus nephritis in 2001, presented as proteinuria. There was no previous use of G-CSF. Her anti-dsDNA and complements level had all along been static. The anti-dsDNA was 150 IU/mL (normal: <30.0 IU/mL) and C3, 70 mg/dL (normal: 90–180 mg/dL) C4, 18 mg/dL (normal: 10–40 mg/dL) before this admission. Hemoglobin (Hb) had also been static. The Hb before admission was 9 g/dL (normal: 11.5–14.8 g/dL). White cell count (WCC) and platelet count had been normal.

On the first day of admission, investigations revealed low WCC, 1.32×10^9/L (normal: 3.89–9.93 $\times$ 10^9/L); decreased neutrophil 0.75×10^9/L (normal: 2.01–7.42 $\times$ 10^9/L); low Hb 9.2 g/dL (normal: 11.5–14.8 g/dL); and elevated aspartate aminotransferase (AST), 60 U/L (normal: 35 U/L). Alanine transaminase (ALT) was normal. The erythrocyte sedimentation rate (ESR) was 49 mm/hr and the C-reactive protein (CRP) was <0.35 mg/dL (normal: <0.76 mg/dL). Complement levels were depressed (C3, 27 mg/dL; C4, <8 mg/dL) and anti-dsDNA was increased (>300 IU/mL;

Received 4 November 2020; Accepted 30 December 2020; Published 4 February 2021

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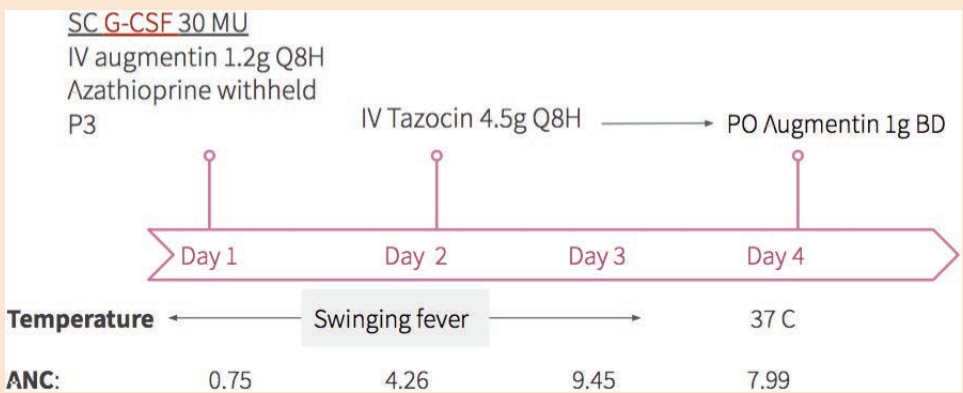
DOI: 10.1142/S2661341721720019

Table 1. Laboratory test results on day 1 of G-CSF injection.

Laboratory tests	Results	Reference ranges
White cell count (× 10^9/L)	1.32	N: 3.89–9.93
Absolute neutrophil count (× 10^9/L)	0.75	N: 2.01–7.42
Hemoglobin (g/dL)	9.2	N: 11.5–14.8
Platelet (× 10^9/L)	188	N: 167–396
Aspartate aminotransferase (U/L)	60	N: 35
Alanine transaminase (U/L)	30	
Erythrocyte sedimentation rate (mm/hr)	49	
C-reactive protein (mg/dL)	<0.35	N: <0.76
C3 (mg/dL)	27	N: 90–180
C4	<8	N: 10–40
Anti-dsDNA (IU/mL)	>300	N: <30.0
Ferritin (pmol/L)	Normal	

Figure 1. Change in ANC after admission.



normal: <30.0 IU/mL) (Table 1). Exacerbation of SLE was suspected given the elevated anti-dsDNA level and depressed complement levels. Nevertheless, in view of the fever and neutropenia possibly due to long term use of azathioprine, investigations were performed to exclude an underlying infection. Empirical intravenous amoxicillin and clavulanic acid and G-CSF were given to reduce the risk of potential devastating consequences of severe infection. Yet, blood, sputum, and urine cultures yielded no growth. Chest radiographs showed no consolidation. Cytomegalovirus (CMV) pp65 antigen was negative. The ferritin level was normal. Urinalysis showed no protein.

Azathioprine was withheld in view of the potential underlying infection. A dose of 30MU G-CSF was also given subcutaneously. Neutrophil counts normalized the next day (Figure 1) but fever persisted. The antibiotic was switched to intravenous piperacillin with the addition of a medium dose of steroid (prednisolone 30 mg/day). The fever subsided and she was discharged 4 days after admission.

However, she was rehospitalized on day 11 after G-CSF injection with a relapse of fever (up to 40°C) and malaise, in addition to persistent sinus tachycardia over 110 beats per minute. A new erythematous blanchable rash appeared on the head, neck, and trunk (Figures 2

Figure 2. Erythematous blanchable rash on head and neck.

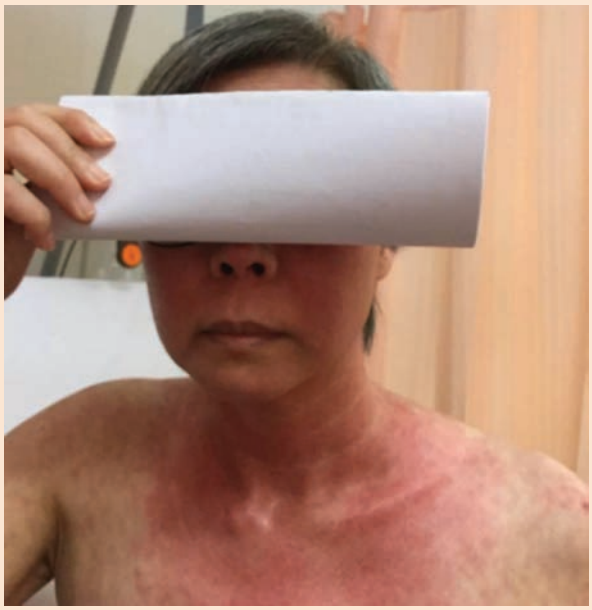
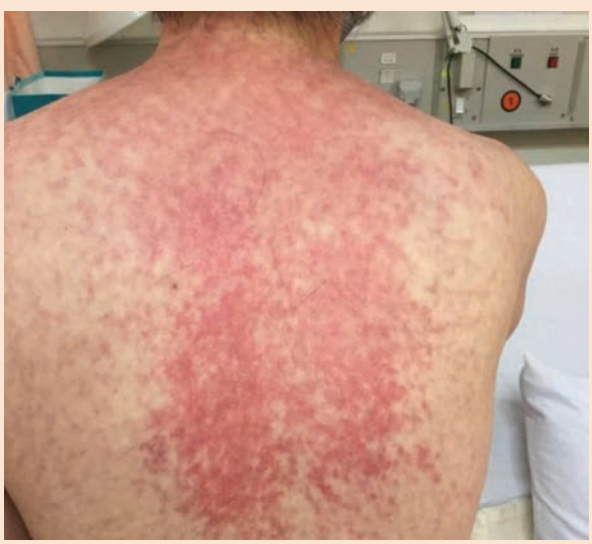


Figure 3. Erythematous blanchable rash on trunk.



and 3); and a vasculitic rash on bilateral palms. The WCC decreased further to 1.53 × 10^9/L (neutrophils 0.84 × 10^9/L), with concomitant elevation of liver enzymes (AST, 171 U/L; ALT 107 U/L). Thyroid function test was normal. The ESR increased to 73 mm/hr and CRP stayed less than 0.35 mg/dL. Complement levels remained low (C3, 27 mg/dL; C4, <8 mg/dL) and ferritin was markedly elevated on this admission (10,551 pmol/L) (Table 2). Blood, sputum, and urine cultures were negative. Repeated chest radiographs showed no consolidation.

Intravenous meropenem therapy was started but the fever persisted with progressive worsening of the liver function. The high fever, progressive cytopenia, worsened liver function, and elevated acute phase reactants (ESR and ferritin) were suggestive of impending cytokine storm syndrome. Urine protein creatinine ratio was 86 mg/mmol and 24 hour urine protein was 1.12 g/day. Bone marrow examination revealed very active granulopoiesis with megakaryocytic hyperplasia and reactive plasmacytosis (6%). Renal biopsy revealed Renal Pathology Society/International Society of Nephrology (RPS/ISN) class IV nephritis with the presence of a significant number of necrotizing crescents. Three intravenous pulses of methylprednisolone (1 g each) were given, followed by prednisolone 30 mg daily. The fever and skin rash gradually subsided. Combination of rituximab and mycophenolate mofetil (MMF) were added to the regimen for induction of this SLE flare. The overall clinical picture was compatible with rapidly worsened SLE after administration of G-CSF.

DISCUSSION

We report a case of acute exacerbation of SLE potentiated by G-CSF therapy, which resulted in severe lupus nephritis, cutaneous and vasculitic rash, and impending cytokine storm syndrome [4,5]. In this manuscript, we discussed the rationale of using G-CSF therapy, proposed mechanisms of potentiation of lupus flare by G-CSF, and cautious use of G-CSF therapy in SLE.

Exacerbation of SLE and infection was the possible diagnosis at the initial presentation. This was supported by the elevated anti-dsDNA level and depressed C3 and C4 levels. The presence of fever in an immunosuppressed patient with SLE made a coexisting infection possible. As a result, empirical board-spectrum antibiotics and G-CSF therapy were given, and azathioprine was withheld. Unfortunately, the administration of G-CSF therapy further potentiated the SLE exacerbation leading to a precytokine syndrome state.

Different mechanisms have been proposed for SLE exacerbation by G-CSF. G-CSF is a hematopoietic cytokine that increases neutrophil production, differentiation, and survival [6] by stimulating the growth of neutrophil bone marrow progenitors, and rate of maturation and release into the circulation. It also enhances adhesion and phagocytosis of mature neutrophils.

Table 2. Laboratory test results on day 11 of G-CSF injection.

Laboratory tests	Results	Reference ranges
White cell count ($\times 10^9$/L)	1.53	N: 3.89–9.93
Absolute neutrophil count ($\times 10^9$/L)	0.84	N: 2.01–7.42
Hemoglobin (g/dL)	9.5	N: 11.5–14.8
Platelet ($\times 10^9$/L)	148	N: 167–396
Aspartate aminotransferase (U/L)	171	N: 35
Alanine transaminase (U/L)	107	
Erythrocyte sedimentation rate (mm/hr)	73	
C-reactive protein (mg/dL)	<0.35	N: <0.76
C3 (mg/dL)	27	N: 90–180
C4	<8	N: 10–40
Ferritin (pmol/L)	10,551	

It is also the key cytokine that regulates neutrophils and neutrophil dysregulation is implicated in the pathogenesis of SLE [7]. Dramatic increases of neutrophils after G-CSF may lead to organ damage through tissue infiltration and release of pro-inflammatory cytokines [6]. In SLE, clearance of apoptotic material may be impaired as a result of primary (genetic) and/or secondary (via antibodies) effects [8]. G-CSF administration could additionally impair the inhibitory effect of neutrophil apoptosis, leading to a rapid surge of apoptotic material providing a rich source of lupus autoantigens [9] that further triggers autoantibody production [10]. Furthermore, G-CSF-induced upregulation of T cell-mediated pro-inflammatory cytokine production [11] may lead to a picture of cytokine storm syndrome as illustrated in our case.

No data exists for the treatment of cytokine storm syndrome in SLE. In this case, an attempt was made to remove the precipitating drug and aggressively treat the underlying SLE with mega-doses of corticosteroid and immunosuppressive therapy. This is in contrast to the cytokine storm syndrome in juvenile idiopathic arthritis (JIA), severe acute respiratory syndrome (SARS), or COVID-19 where interleukin (IL) 6 antagonists, IL-1 antagonists, and plasma exchange are the consensus treatments [12,13].

It remains arguable that our patient had an impending lupus flare with leukopenia, which might occur coincidentally with the application of G-CSF. However, the lack of SLE symptoms during the period of leukopenia and the rapid upsurge of the WCCs after G-CSF administration, the development of fever and other florid symptoms of active SLE suggested the flare could be temporally related to G-CSF therapy. Similar to our case, previous literature reported a severe flare up of autoimmune disease in hours to days after the therapy [14,15]. Nevertheless, other possible factors for lupus flare-up such as medications other than G-CSF, or certain kind of infections should not be overlooked [1].

Our experience raises concerns about potentially organ- or life-threatening SLE exacerbation after G-CSF administration. Although neutropenia may be due to myelosuppressive drugs [16] like azathioprine, it could also be a consequence of lupus disease activity due to antigranulocyte antibodies [17] and peripheral consumption. Careful history taking about the use of drugs, physical examination, genetic testing for the thiopurine methyltransferase (TPMT) gene, bone marrow examination, and a delicate balance between risk and benefits of G-CSF could help to prevent a potentially lethal exacerbation of SLE.

Apart from prescribing G-CSF with caution, attention should also be paid to the dose of G-CSF injection. Excessive doses of G-CSF may increase the risk of exacerbation of SLE, particularly if the absolute neutrophil count is increased to be much higher than 1×10^9/L [1]. Therefore, if G-CSF has to be given, the lowest effective dose should be used with close monitoring of the absolute neutrophil count after injection.

In summary, SLE could be exacerbated by G-CSF administration. We would recommend to use G-CSF

therapy with great caution in patients with autoimmune diseases.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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