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Case Report

Certolizumab Pegol is Effective for Granulocyte Colony-Stimulating Factor-Mediated Disease Exacerbation in Rheumatoid Arthritis

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Abstract

Granulocyte Colony-Stimulating Factor (G-CSF) is widely used for treating neutropenia. However, exacerbation of autoimmune diseases after G-CSF injection has been reported. We herein report a patient with Rheumatoid Arthritis (RA) who experienced disease flare after receiving G-CSF and was treated with Certolizumab Pegol (CZP). A 70-year-old woman who had RA with moderate disease activity developed drug-induced neutropenia and was treated with G-CSF. Five days after the start of G-CSF treatment, her neutrophil count increased and she developed severe arthritis in both wrists, suggesting of exacerbation of RA. Since discontinuation of G-CSF or nonsteroidal anti-inflammatory drugs did not improve her joint pain, she was finally treated with subcutaneous CZP injection, which led to a remarkable improvement of her arthritis. Our case demonstrates the potential efficacy of CZP for arthritis exacerbated by G-CSF therapy.

Keywords: Certolizumab Pegol; G-CSF; Neutropenia; Rheumatoid Arthritis; TNF-α

Introduction

Granulocyte Colony-Stimulating Factor (G-CSF) is widely used for treatment of neutropenia in the fields of hematology and oncology. G-CSF has been reported to cause autoimmune diseases including Rheumatoid Arthritis (RA) to flare up [1-4]. However, a therapeutic strategy for G-CSF-mediated exacerbation of arthritis in patients with RA is yet to be established. Here, we report the first case showing the effectiveness of Certolizumab Pegol (CZP), a novel Fc-free, PEGylated, anti-TNF-α monoclonal antibody, for acute aggravation of RA induced by G-CSF.

Case Presentation

A 70-year-old woman had been diagnosed with RA at the age of 52 years and had been treated with Prednisolone (PSL; 2 mg/day) and Methotrexate (MTX; 4 mg/week). She was admitted to our hospital because of RA-associated Interstitial Lung Disease (ILD), although the Disease Activity Score 28-joint count based on C-reactive protein (DAS28-CRP) was 2.14 (remission). After withdrawal of MTX, she was treated with oral PSL (20 mg/day) in combination with Intravenous Cyclophosphamide (IVCY). Sulfamethoxazole-Trimethoprim (ST) for prophylaxis of *Pneumocystis jirovecii* pneumonia, repaglinide for treatment of glucocorticoid-induced diabetes mellitus, and esomeprazole

magnesium hydrate for prophylaxis of gastrointestinal tract disturbance were orally administered. After the first session of IVCY therapy, her ILD improved and she was discharged.

Twelve days after the second session of IVCY therapy and dose tapering of PSL to 12.5 mg/day, she was again admitted to the hospital because of sudden onset of grade 4 neutropenia. Her body temperature was 35.5˚C, and she showed swollen joints, including the wrist, metacarpophalangeal, and proximal interphalangeal joints. DAS28-CRP was 2.9, which is suggestive of moderate disease activity of RA. Laboratory data showed leukocytopenia (1500/μL; reference range, 3300-8600/μL), neutropenia (345/μL; reference range, 1155-6278/μL), and elevated CRP level (2.04 mg/dL; reference range, 0.00-0.15 mg/dL). Her hemoglobin level, platelet count, renal and liver function test results, β-D-glucan level, cytomegalovirus antigenemia assay (C7-HRP) results, and urinalysis results were normal. Chest computed tomography revealed no evidence of infectious pneumonia or aggravation of ILD. After withdrawal of ST, repaglinide, and esomeprazole magnesium hydrate, which are known to cause agranulocytosis, she was treated with subcutaneous injection of the G-CSF filgrastim (75 mg/day) (Figure 1).

Two days after the beginning of treatment, the filgrastim injection dose was increased to 150 mg/day because the neutrophil count did not increase. Five days after the beginning of treatment, the neutrophil count increased to 10295/μL, and filgrastim injection was discontinued. However, 6 days after the beginning of treatment, she developed severe arthritis in both wrists and her serum CRP level was elevated to 13 mg/dL. Discontinuation of filgrastim injection or oral celecoxib did not improve her arthritis, and her joint pain deteriorated. DAS28-CRP worsened to 5.07, which is suggestive of high disease activity. We considered that the disease activity of RA was aggravated by the G-CSF-mediated elevation of granulocyte count and we started subcutaneous CZP injection with an initial loading dose of 400 mg at weeks 0, 2, and 4. After the CZP treatment, her joint pain immediately improved and she achieved remission (Figure 1). During the tapering of PSL dose to 5 mg/day, her physical examination results and laboratory data showed no evidence of RA and ILD relapse over a period of 16 months.

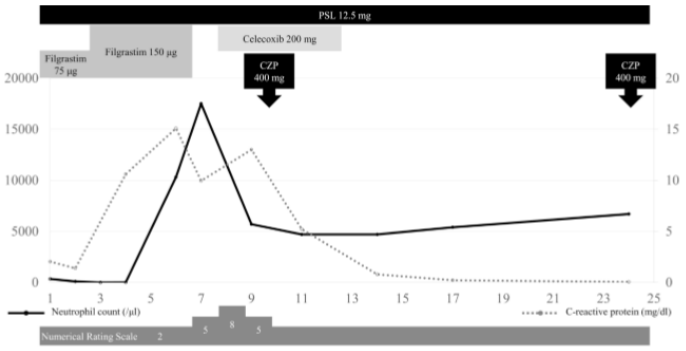

Figure 1: Clinical course and laboratory data during hospitalization.

Discussion

We report a previously undescribed case of G-CSF-mediated exacerbation of RA that was successfully treated with CZP injection. G-CSF is commonly used for treating neutropenia caused by chemotherapy, infection, and an abnormal immune system observed in patients with rheumatic diseases. Previous studies have shown an association between G-CSF during neutropenia and exacerbation of RA (Table 1) [5-9]. G-CSF is produced by various cells, including macrophages, endothelial cells and fibroblasts, and is involved in the process of inflammation [10]. In a mouse model of RA, G-CSF promoted macrophage-1 antigen-dependent migration of neutrophils and increased the severity of collagen-induced arthritis [11, 12]. G-CSF levels in serum and synovial fluid were reported to be elevated in a disease activity-dependent manner in RA patients [13]. However, a therapeutic strategy for G-CSF-mediated exacerbation of arthritis has not been established. In our case, arthritis caused by RA with moderate disease activity was exacerbated after G-CSF injection, and discontinuation of G-CSF injection or oral celecoxib did not improve the joint pain and swelling.

author	age, gender	dignosis	type of G-CSF	dosage	clinial features	laboratory data	therapy
Vidarsson B	56,F	Felty's syndrome	lenograstim	5.0μg/kg	arthritis (knees)	WBC 42,000/μL, Neut 32,000/μL, CRP 14.2mg/dl	increasing prednisolone
Schots R	47,F	Felty's syndrome	filgrstim	5.3μg/kg	arthritis (hands)	no data	discontinuing G-CSF
Quesnel B	16,F	juvenile arthritis	unknown	1.0-5.0μg/kg	hemophagocytosis	no data	discontinuing G-CSF
Priora M	54,F	RA	filgrstim	0.25MU	arthritis	WBC 4,200/μL, Neut 1,910/μL, CRP 10.0mg/dl	discontinuing G-CSF and administering abatacept
Nakashima H	38,F	RA	filgrstim	150μg	arthritis (elbows)	no data	increasing prednisolone
Present Case	**70,F**	**RA**	**filgrstim**	**1.9-3.8μg/kg**	**arthritis (hands)**	**WBC 22,530/μL, Neut 17,460/μL, CRP 13.0mg/dl**	**discontinuing G-CSF and administering CZP**

Table 1: Previous and present cases demonstrating an association between G-CSF and RA exacerbation.

On the contrary, the patient immediately achieved remission after the beginning of CZP injection. CZP differs from other TNF-α blockers in its lack of an Fc region, which minimizes Fc-mediated effects such as Antibody-Dependent Cell-Mediated Cytotoxicity (ADCC) or Complement-Dependent Cytotoxicity (CDC) [14, 15]. PEGylated certolizumab Fab' binds to and neutralizes both soluble and transmembrane TNF-α with high affinity [16]. It has been reported that treatment with CZP with its initial loading dose resulted in rapid and sustained improvements in disease activity and quality of life in patients with active RA in placebo-controlled, double-blind, randomized studies [17]. Those previous reports and our case suggest that G-CSF is involved in the pathogenesis of RA and that TNF-α may be the major cytokine required for G-CSF-mediated exacerbation of arthritis. TNF-α blockers, especially CZP, may be effective for acute aggravation of RA by G-CSF [9, 18].

G-CSF-mediated exacerbation of arthritis is difficult to distinguish from acute-onset arthritis, including gout, pseudogout, and infection. However, in the present case, we observed that arthritis in at least some joints that had been swollen before the G-CSF injection was aggravated with an increasing number of leukocytes, suggesting exacerbation of RA rather than development of gout, pseudogout, or infection, which generally occurs in a single joint. Analysis of synovial fluid obtained through arthrocentesis may be required to confirm the diagnosis.

Conclusion

Our case provides evidence showing that CZP is effective for exacerbation of arthritis mediated by G-CSF in RA patients.

Patient Consent

Written informed consent for this case report was obtained from the patient.

Conflict of Interest

None.

Funding

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