

[CASE REPORT]

Pseudogout Attack after Pegfilgrastim Administration in Anaplastic Large Cell Lymphoma

Mayumi Hatayama¹, Katsuya Ikuta¹, Masatomo Ishioh¹, Takeshi Saito¹, Yasumichi Toki¹, Masayo Yamamoto¹, Motohiro Shindo¹, Yoshihiro Torimoto² and Toshikatsu Okumura¹

Abstract:

A 67-year-old man with relapsed anaplastic large cell lymphoma received salvage chemotherapy, and pegfilgrastim was used to prevent febrile neutropenia. On day 18 of chemotherapy, he developed a pseudogout attack. Although the first symptoms improved, another pseudogout attack occurred when he received the second course of chemotherapy and pegfilgrastim. Filgrastim was then used for the third course of chemotherapy, and a pseudogout attack did not occur. The serum granulocyte-stimulating factor (G-CSF) level was extremely elevated only when pegfilgrastim was used, suggesting a relationship between pseudogout and G-CSF. Pseudogout should be recognized as an adverse effect of pegfilgrastim.

Key words: pseudogout, pegfilgrastim, granulocyte-stimulating factor (G-CSF), febrile neutropenia

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Introduction

Pseudogout is an arthralgia that can occur in all joints in the body, especially major joints that are more frequently used, such as the knee and wrist joints. The symptoms vary and include pain, swelling, redness of the joints and a fever. Radiographs have demonstrated chondro-calcinosis within articular joints. Aspiration of the joint fluid shows calcium pyrophosphate in the joint space and contributes to the diagnosis of pseudogout (1). The treatment for pseudogout is rest and aspiration of the joint fluid. It is important to distinguish pseudogout from other forms of septic arthritis to avoid administering too many analgesics and antibiotics. Pseudogout is not a rare disease in elderly people, but the etiology of pseudogout remains unclear. It is said that aging and metabolic disease, such as hemochromatosis, hyperparathyroidism and hypomagnesemia, are risk factors, but other risk factors for the disease are unknown (1).

Granulocyte-stimulating factor (G-CSF) has been clinically used in various situations, such as for the treatment of febrile neutropenia and drug-induced neutropenia and for the mobilization of hematopoietic stem cells. Pegylated filgras-

tim (pegfilgrastim) is a long-acting form of filgrastim. Pegylation increases the size of filgrastim so that it becomes too large for renal clearance. The median serum half-life of pegfilgrastim is approximately 10 times that of filgrastim (pegfilgrastim's half-life: 42 hours, filgrastim's half-life: approximately 3.5 hours) (2). As a result, the clearance of pegfilgrastim is decreased, inducing sustained serum concentrations throughout the duration of neutropenia. Pegfilgrastim requires only once-per-cycle administration for the management of chemotherapy-induced neutropenia. However, its effectiveness and side effects are not sufficiently understood.

We herein report a case of pseudogout attack caused by pegfilgrastim administration.

Case Report

A 67-year-old man noticed neck lymph node swelling and was diagnosed with anaplastic large cell lymphoma (ALCL) after a biopsy of the lymph node. Positron emission tomography (PET) revealed lymphoma lesions in both sides of the neck and the left axilla. A bone marrow examination revealed no infiltration of the lymphoma cells. Therefore, a diagnosis of clinical stage IIA disease was made, according to

¹Division of Gastroenterology and Hematology/Oncology, Department of Medicine, Asahikawa Medical University, Japan and ²Oncology Center, Asahikawa Medical University Hospital, Japan

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Correspondence to Dr. Katsuya Ikuta, ikuta@asahikawa-med.ac.jp

Table 1. Laboratory Findings at the Day19 of 1st Course of CHASE.

WBC	20,930 / μ L	TP	7.1 g/dL
Mono	83.5 %	Alb	3.2 g/dL
Lymph	4.5 %	T-Bil	0.6 mg/dL
Mono	11.5 %	D-Bil	0.3 mg/dL
Eos	0.5 %	AST	29 U/L
Baso	0.0 %	ALT	43 U/L
		LDH	201 U/L
RBC	340×10^4 / μ L	γ -GTP	104 U/L
Hb	9.6 g/dL	Na	137 mmol/dL
Ht	29.4 %	K	4.2 mmol/dL
MCV	86.5 fL	Cl	99 mmol/dL
MCH	28.2 pg	UA	3.5 mg/dL
MCHC	32.7 %	BUN	9.2 mg/dL
Plt	464×10^3 / μ L	Cre	0.52 mg/dL
		CRP	17.0 mg/dL

WBC: white blood cell, RBC: red blood cell, Hb: hemoglobin, Ht: hematocrit, MCV: mean cell volume, MCH: mean corpuscular hemoglobin, MCHC: mean corpuscular hemoglobin concentration, Plt: platelet, TP: total protein, Alb: albumin, T-Bil: total bilirubin, D-Bil: direct bilirubin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactic acid dehydrogenase, γ -GTP: gamma-glutamyl transpeptidase, Na: sodium, K: potassium, Cl: chloride, UA: uric acid, BUN: urea nitrogen, Cre: creatine, CRP: C-reactive protein, CHASE regimen: dexamethasone, cyclophosphamide, cytarabine, etoposide

the Ann-Arbor classification. He had chronic hypertension but no endocrine diseases or electrolyte disorders, such as calcium and magnesium disorders. A CHOP regimen [adriamycin 50 mg/m² (day 1), vincristine 1.4 mg/m² (day 1), cyclophosphamide 750 mg/m² (day 1) and prednisolone 100 mg/body (days 1-5)] was started on admission, and the sizes of the lymph nodes decreased; however, 3 weeks after chemotherapy, the lymphadenopathy worsened. A dexamethasone, cyclophosphamide, cytarabine, etoposide (CHASE) regimen [dexamethasone 40 mg/body (days 1-3), cyclophosphamide 1,200 mg/m² (day 1), cytarabine 2,000 mg/m² (days 2-3) and etoposide 100 mg/m² (days 1-3)] was then started as salvage chemotherapy, and pegfilgrastim (3.6 mg) was administered on day 5 of CHASE. There were no remarkable problems after the administration of pegfilgrastim, so he was discharged from the hospital. However, on day 18 of CHASE, both knee joints became swollen and were red and painful. The patient therefore had to be hospitalized again.

The patient's physical examination showed a high fever and knee joint swelling and reddening. The left knee joint showed more swelling than the right side. A patella ballottement test was positive for both knee joints. The laboratory data are shown in Table 1. The white blood cell (WBC) count, especially the neutrophil count, and the C-reactive protein level were increased. The other biochemical parameters were nearly normal.

X-ray showed line-shape calcification in the left knee joint cartilage (Fig. 1A). Joint fluid obtained by aspiration of the left knee was yellow and muddy (Fig. 1B). Micro-

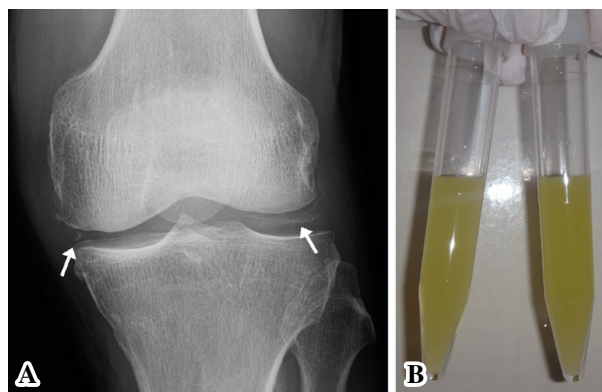


Figure 1. (A) X-ray photograph of the left knee. The white arrow indicates a crystal deposit in the left knee joint space. (B) Joint fluid obtained by aspiration from the left knee. The fluid was yellow and muddy.

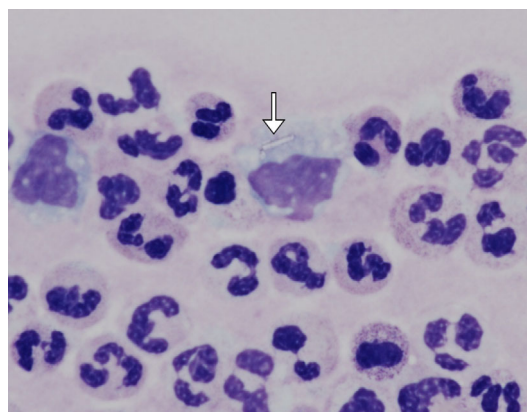


Figure 2. Microscopic findings of the joint fluid. The white blood cell was increased in the joint fluid, and calcium pyrophosphate dihydrate (CPPD) crystals were engulfed by neutrophils and macrophages. The white arrow indicates CPPD crystals.

scopic findings of the joint fluid demonstrated an increase in the WBC count and the presence of calcium pyrophosphate dihydrate (CPPD) crystals, but no uric acid crystals were observed. Phagocytosis of CPPD crystals by neutrophils and macrophages was also observed (Fig. 2).

A diagnosis of pseudogout was made, and the patient was instructed to rest the knee joints and received an analgesic. His pseudogout symptoms disappeared, and a second course of CHASE was started. Pegfilgrastim (3.6 mg) was administered on day 5 of the second course of CHASE. A pseudogout attack occurred again on day 15 of the second course of CHASE. Because the WBC count increased when both pseudogout attacks occurred, we suspected that there might be a relationship between the pseudogout and pegfilgrastim. Therefore, for the third course of CHASE, we used filgrastim (75 μ g) instead of pegfilgrastim on days 11 and 13. As a result, the WBC count did not increase as much as with pegfilgrastim, and no pseudogout attack occurred (Fig. 3).

We suspected that pegfilgrastim might have influenced the

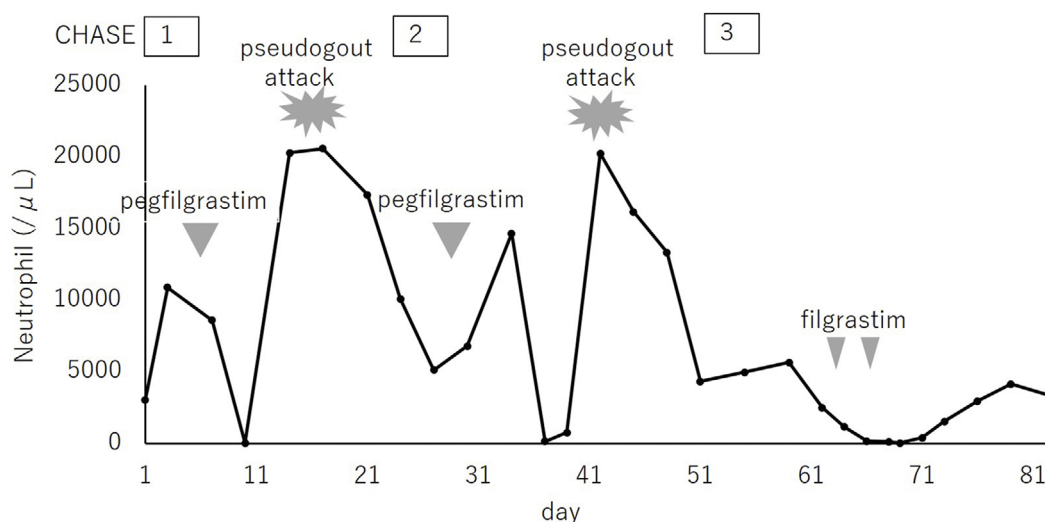


Figure 3. Clinical course. Changes of neutrophil during chemotherapy were shown. Pseudogout attack was occur when neutrophil increased after using pegfilgrastim. CHASE regimen: dexamethasone 40 mg/body (days 1-3), cyclophosphamide 1,200 mg/m² (day 1), cytarabine 2,000 mg/m² (days 2-3), etoposide 100 mg/m² (days 1-3).

Table 2. Measurement Results of Serum Cytokine Levels.

Cytokines (Reference range)	2nd CHASE day 18	3rd CHASE day -1	3rd CHASE day 18
IL-1 β (\leq 10.0 pg/mL)	\leq 10.0	\leq 10.0	\leq 10.0
IL-6 (\leq 4.0 pg/mL)	12.4	1.9	12.8
IL-8 (\leq 2.0 pg/mL)	\leq 2.0	5.4	13.3
TNF- α (0.6-2.8 pg/mL)	2.6	1.7	2.4
G-CSF (\leq 39.0 pg/mL)	289.0	47.0	40.6

IL-1 β : interleukin-1 β , IL-6: interleukin-6, IL-8: interleukin-8, TNF- α : tumor necrosis factor- α
CHASE regimen: dexamethasone, cyclophosphamide, cytarabine, etoposide

pseudogout attack, so we tried to measure the serum G-CSF levels and the levels of other cytokines. We obtained written informed consent from the patient as well as the approval of the ethics committee and measured the G-CSF, interleukin (IL)-6, IL-8, IL-1 β and tumor necrosis factor (TNF)- α levels in serum samples obtained at the following three time points: the time of the pseudogout attack (2nd CHASE day 18), the day before the 3rd course of chemotherapy (3rd CHASE day -1) and during the recovery from myelosuppression after the administration of filgrastim (3rd CHASE day 18). The G-CSF level was markedly elevated to 289.0 pg/mL (reference range: \leq 39.0 pg/mL) when the pseudogout attack occurred but then decreased to 47.0 pg/mL when the pseudogout attack resolved. The G-CSF level was not visibly increased (40.6 pg/mL) when filgrastim was used. The IL-1 β and TNF- α levels were within the reference ranges (IL-1 β : \leq 10.0 pg/mL, TNF- α : 0.6-2.8 pg/mL), regardless of whether or not a pseudogout attack had occurred. The IL-6 level seemed to increase slightly on both day 18 of the second course of CHASE (12.4 pg/mL) and the third course of CHASE (12.8 pg/mL) (reference range: \leq 4.0 pg/mL). The IL-8 level was elevated before chemotherapy (5.4 pg/mL) and on day 18 of the third course of CHASE (13.3 pg/mL) (reference range: \leq 2.0 pg/mL) (Ta-

ble 2).

Discussion

G-CSF stimulates the proliferation and differentiation of neutrophils. The present patient developed a pseudogout attack when pegfilgrastim was administered, and the neutrophil count was over 20,000/ μ L, but he did not suffer a pseudogout attack when filgrastim was administered. Some reports have suggested that filgrastim is related to pseudogout attacks (3), but there have been no reports about any attacks with pegfilgrastim. This is likely the first such report.

Sandor et al. reported a woman with ovarian cancer who received filgrastim after chemotherapy and developed pseudogout. In that case, the WBC count was over 20,000/ μ L when the pseudogout occurred, suggesting that a relationship exists between the WBC count and pseudogout (4). However, Teramoto et al. reported a pseudogout attack after the administration of filgrastim for a patient with drug-induced neutropenia. In that case, the WBC count was in the normal range (maximum of 4,200/ μ L) when the attack occurred. Those authors suggested that other factors might be involved in the development of pseudogout (5).

Teramoto et al. also reported that the WBC count and G-

CSF, IL-6 and IL-8 levels of the joint fluid were elevated during the pseudogout attack and considered that these changes contributed to pseudogout. *In vitro*, IL-6 and IL-8 production by synovial cells was elevated in the presence of calcium pyrophosphate when granulocyte macrophage colony-stimulating factor (GM-CSF) was administered. In the present case, the G-CSF level was markedly elevated to 289.0 pg/mL when the pseudogout attack occurred on day 18 of the second course of 2nd CHASE, but it subsequently decreased to 47.0 pg/mL. The G-CSF level at the pseudogout attack (13 days after the administration of pegfilgrastim) was very high. A prolonged high level of pegfilgrastim may have stimulated the proliferation and differentiation of neutrophil progenitor cells for an extended period of time, thereby resulting in excessive neutrophil production and finally contributing to the pseudogout attack. Teramoto et al. also reported that an elevated serum IL-6 level (77 pg/mL) might have contributed to the pseudogout attack in their patient, but changes in the level of IL-6 and other cytokines were not correlated with the pseudogout attack in our case; we therefore doubt that the changes in the levels of the cytokines (IL-1 β , IL-6, IL-8, and TNF- α) caused the pseudogout in our case.

In the present case, we were only able to measure the serum levels of cytokines and could not measure the cytokine levels in the joint fluid. The cytokine levels in the joint fluid might have been different from those in the serum, and it is important to measure the levels of cytokines in the joint fluid in addition to the serum. This may enable the elucidation of the pathophysiology of pseudogout during the administration of G-CSF and pegylated G-CSF.

The persistence of the effectiveness of pegfilgrastim for approximately 2 weeks makes this medication very valuable,

as it can prevent febrile neutropenia with only a once-per-regimen administration and reduce the need for hospitalization for patients receiving chemotherapy. However, the dosage of pegfilgrastim cannot be adjusted; there is therefore a possibility that pegfilgrastim stimulates cytokine production excessively and can cause an adverse effect with a different profile of G-CSF. Pseudogout must be recognized as an adverse effect of pegfilgrastim during its administration, and the frequency of this disease should be determined in the future.

The authors state that they have no Conflict of Interest (COI).

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