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Recurrent Pegfilgrastim-Associated Migratory Large Vessel Vasculitis in a Patient with Breast Cancer with Rare HLA Haplotype: A Case Report

Araki K[1*], Fujisawa T[2], Miyamoto T[2], Kawakami T[3], Anzai H[4], Horikoshi H[3] and Yanagita Y[2]

[1]Department of Medical Oncology, Gunma Prefectural Cancer Center, Ota, Gunma, Japan

[2]Department of Breast Oncology, Gunma Prefectural Cancer Center, Ota, Gunma, Japan

[3]Department of Diagnostic Radiology, Gunma Prefectural Cancer Center, Ota, Gunma, Japan

[4]Department of Cardiology, Gunma Prefectural Cancer Center, Ota, Gunma, Japan

[*]Corresponding author:

Kazuhiro Araki,
Department of Medical Oncology, Gunma Prefectural Cancer Center, 617-1 Takabayashi-Nishi-machi, Ota, Gunma 373-8550, Japan,
Tel/Fax: +81-276-38-0771/+81-276-38-8336;
E-mail: kaz-araki@gunma-cc.jp

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1. Abstract

Background: Granulocyte-Colony Stimulating Factor (G-CSF) rarely induces severe systemic vasculitis. However, diagnosing vasculitis can be challenging because clinical mani- festations in the early phase are non-specific. We report a case of pegfilgrastim-associated vasculitis in a patient with rare Human Leukocyte Antigen (HLA) genotype and multifactorial disorder during breast cancer chemotherapy.

Case Report: A 57-year-old woman with newly diagnosed invasive ductal breast carcinoma of the left breast came for con- sultation. She had undergone curative surgery for non-invasive ductal breast carcinoma of the right breast at 36 years old and had multiple comorbidities. We administered adriamycin plus cyclo- phosphamide adjuvant chemotherapy. She developed high fever, left anterior chest pain, insomnia, and surgical site inflammation after two cycles. High-resonance echography revealed concentric wall thickness of the right common carotid artery and brightness in the circumference tissue matrix of the artery. Magnetic resonance imaging showed wall thickness, as observed in large arteritis. Con- trast-enhanced dynamic computed tomography demonstrated dif- fuse arterial wall thickness of the brachiocephalic and common carotid arteries. All these indicated vasculitis-related inflammation

and edema. Culture of surgical site specimens revealed coagulase-negative Staphylococcus haemolyticus, for which she was treated; this delayed the diagnosis of recurrent pegfilgrastim-associated migratory vasculitis, as we initially thought that the vasculitis was sepsis-related. We examined the patient's specific HLAgenotype and determined that a multifactorial disorder may have been associated with the large vessel vasculitis.

Conclusion: Our findings suggest that G-CSF causes large vessel vasculitis in patients with communicable and non-commu- nicable environmental risk factors and in those with specific HLAgenotypes.

2. Introduction

Protection against chemotherapy-related Febrile Neutropenia (FN) is vital, and Granulocyte-Colony Stimulating Factor (G-CSF) is aprimary prophylactic option for standard supportive care [1]. How- ever, most oncologists are unaware that G-CSF can occasionally induce severe systemic vasculitis [2]. A Japanese post-marketing drug safety survey reported that the overall Adverse Event (AE) rate following the use of pegfilgrastim, a pegylated G-CSF-de- rived drug, was 7.47%, including the incidence rates of lumba-go (3.84%), fever (3.84%), and bone pain (0.61%) [3]. Most AEs were mild to moderate in intensity [3]. A recent Japanese adverse

drug event report revealed that G-CSF use is associated with a potential risk of vasculitis (adjusted odds ratio [OR], 45.87 [19.16, 109.8], $p < 0.001$) [2]. However, diagnosing vasculitis can be challenging due to the non-specificity of clinical manifestations in the early phase; vasculitis follows an insidious and chronic course without characteristic symptoms until ischemic clinical manifestations eventually lead the patient to seek medical attention [4].

Our patient developed recurrent pegfilgrastim-associated migratory vasculitis during adjuvant chemotherapy for breast cancer. We hypothesized that her large vessel vasculitis might have been induced by a multifactorial disorder. Moreover, we discussed a possible mechanism of G-CSF-associated vasculitis based on our experience with Human Leukocyte Antigen (HLA) genotyping.

3. Case Report

A 57-year-old Japanese woman visited our institute from a private outpatient clinic, where a category 5 abnormality had been detected on mammography, with a new diagnosis of invasive ductal breast carcinoma of the left breast. The patient had previously undergone curative surgery for non-invasive ductal breast carcinoma of the right breast at the age of 36 years. She had multiple lifestyle-related comorbidities, including obesity (body mass index > 38 kg/m2), hypertension, hyperlipidemia, type 2 diabetes mellitus, diabetic nephritis, hyper uric acidemia, cataracts, periodontitis, and gingivitis. She had total mastectomy for left breast carcinoma. The post-surgical staging was pT2N1M0, stage IIB, estrogen and progesterone receptor-positive, and without human epidermal growth factor receptor 2 overexpression or amplification. In addition, she had long consulted a private medical practitioner and an in-house dental clinic to manage these multiple comorbidities and was on numerous oral medications. The germline BRCA genetic test result was negative for mutations. Considering the recurrence risk for stage IIB breast cancer, we treated her with standard adjuvant chemotherapy, starting 3 weeks after surgery, once the surgical site wound had healed. Figure 1 shows the patient's clinical course.

Dental caries was treated to prevent FN related to chemotherapy-induced oral infection using empirical 7-day oral administration of amino-hydroxy benzylpenicillin. After 12 days of the first cycle of adriamycin plus cyclophosphamide (AC) and pegfilgrastim (3.6 mg/kg), she developed high fever (38.8°C), left anterior chest pain, and insomnia. The surgical site showed redness, swelling, and exudation. Evaluation of a specimen from the surgical site identified methicillin-sensitive Staphylococcus aureus, and symptoms were relieved by empirical oral treatment with levofloxacin for 2 weeks. Therefore, we initially considered that her postoperative surgical site infection might have induced these multiple symptoms. Considering the advantage of continuing adjuvant chemotherapy to reduce the risk of breast cancer recurrence, we continued treatment with the second and third cycles of AC combined with pegfilgrastim, levofloxacin, intermittent non-steroidal anti-inflammatory drugs (NSAIDs) (loxoprofen and/or acetaminophen), open surgical debridement, and drainage. Although the second cycle of AC and pegfilgrastim did not affect her systemic condition, she developed high-grade fever and increasing chest pain 11 days after the third cycle of AC, followed by pegfilgrastim. Her symptoms were more severe than those during the first AC cycle (Table 1 shows data from the patient's first admission). During the first emergency admission, the laboratory evaluation included full blood count and biochemical profile analysis, serodiagnosis, bacteriological analysis (Table 1), and imaging studies. These systemic, comprehensive evaluations could not support a diagnosis of autoimmune vasculitis but indicated systemic inflammatory disease suggestive of bacterial infection.

Analysis of blood and surgical site specimens identified coagulase-negative Staphylococcus haemolyticus. Treatment with empirical intravenous piperacillin (PIPC) for 10 days preceded the identification of the bacterial pathogen. The patient's symptoms improved, and we switched the antibiotic to intravenous cefazolin for 17 days based on her antibiogram. High-resonance ultrasound echography revealed concentric wall thickness of the right common carotid artery (5.7 mm) and brightness in the circumference tissue matrix of the artery. Magnetic resonance imaging (MRI) showed wall thickness, as observed in large arteritis. Furthermore, contrast-enhanced dynamic computed tomography (CT) demonstrated diffuse arterial wall thickness of the brachiocephalic and common carotid arteries. These imaging reports indicated inflammation and edema in vasculitis.

We initially attributed the diffuse vasculitis to septic vasculitis secondary to surgical site infection and managed it with antibiotics [5]. After completion of antibiotic therapies, 2-(F)-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET)/CT showed no abnormal Standardized Uptake Value (SUV) around the periaortic tissue matrix. After 3 weeks, we repeated both MRI and ultrasound echography examinations and found that the right common carotid artery wall thickness had slightly improved (wall thickness: 2.0 mm; surface: regular; intensity: still high). Concurrently, radiologists suggested Takayasu arteritis due to its broad distribution of age at onset [6] or another collagenous disease (e.g., a vasculitic type of Behçet's disease) from the time of her first emergency admission date. However, she had no symptoms related to Behçet's disease other than radiological vasculitis. Although we discussed the possibility of pathogenesis of vasculitis with the cardiologist, the differential diagnosis suggested by a radiologist (TK) provided instrumental information in making a definitive diagnosis.

After antibiotic therapy relieved the symptoms of vasculitis, we changed the adjuvant chemotherapy from AC to 12 doses of paclitaxel, administered weekly over 12 weeks. Persistent right anterior neck and chest discomfort since disease onset led to continued use of NSAIDs. During the 12-time weekly paclitaxel regimen, our patient did not experience symptoms other than chemotherapy-induced peripheral neuropathy. No vasculitis or infectious dis-

ease was observed in the absence of G-CSF administration. After careful discussion, the patient agreed to undergo a fourth cycle of AC to reduce the breast cancer recurrence risk. Considering her systemic condition, including vasculitis, we could not obtain information on the active aortic disease or any other uncontrolled disease; ultrasonography indicated inactive post-inflammation vasculitis of the right common carotid artery without stenosis (thickness: 1.4 mm; surface: irregular; intensity: high). MRI revealed that the aortic wall of the right common carotid artery had no abnormal characteristics. FDG-PET/CT showed no abnormal SUV uptake. Unfortunately, 13 days after the fourth AC cycle, followed by pegfilgrastim, she developed high fever (40°C) and experienced more severe bilateral anterior chest and neck pain than during the first and third cycles of AC. CT could not help determine any other cause of the fever. We initially considered the possibility of infectious disease. We started empirical PIPC to control the suspected infectious vasculitis during the second hospitalization. However, multiple bacterial evaluations did not detect any microorganisms. During empirical antibiotic therapy with PIPC, we believed that both antibiotics and acetaminophen would relieve pain and fever; unfortunately, these therapies had no noticeable effect on the patient's complicated systemic condition, and we decided to stop PIPC after 9 days of treatment.

Furthermore, because acetaminophen had a weak efficacy in controlling her symptoms, we switched to naproxen, another NSAID. Additional echography revealed a re-thickening of the right and left common carotid walls and the subclavian arteries. Enhanced dynamic CT revealed right wall thickness and thickening of the left common carotid artery and subclavian artery walls, contralateral to the side of the initial vasculitis (Figures 2 and 3).

Furthermore, we considered transient perivascular inflammation of the carotid artery (TIPIC) syndrome, which is a rare entity, as a differential diagnosis [7]. In our case, as the inflammation spread from the triple-branched aortic arch to both the left common cervical and brachiocephalic arteries and the right common carotid artery, our patient's multiple vasculitis differed from the typical presentation encountered in TIPIC syndrome. Finally, we considered that these clinical manifestations might be due to G-CSF-associated vasculitis rather than infectious vasculitis, as the initial onset occurred when she presented with symptoms during the first AC cycle; however, an unknown cause might have been present. After 2 weeks of naproxen therapy, the patient was discharged following symptom alleviation, and her laboratory data showed improvement compared with the values on admission.

After obtaining institutional review board approval (approval number: 405-03043) and written informed consent from the patient (in Japanese), we performed HLA typing. The HLA DNA typing results were A*02:01:01, A*26:01:01, B*35:01, B*67:01:02, DRB1*04:05, and DRB1*08:02 (Table 2). These allele frequencies are presented in Table 3 based on common, intermediate, and well-documented HLA alleles [8]. As commercial DNA typing could not confirm her HLA haplotype, we explored her possible HLA haplotype based on the Japanese version [9] and Allele Frequency Net Database (AFND) [10]. The HLA adverse drug reactions database in the AFND did not detect any relationship between G-CSF and vasculitis (data not shown). Interestingly, HLA-B*67:01 is strongly associated with Takayasu arteritis [11], and HLA-A*26 is closely associated with Behçet's disease in the Japanese population [12].

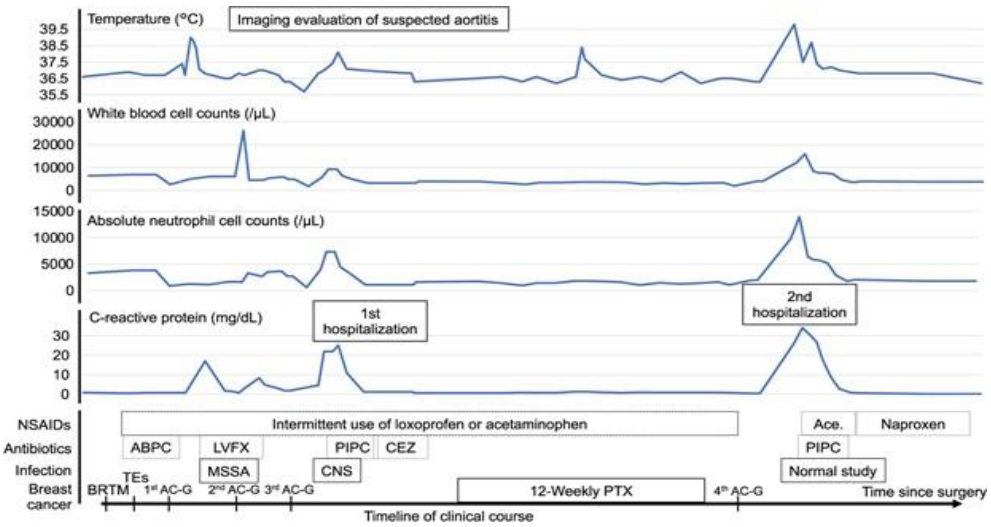

Figure 1: Timeline of the clinical course of vasculitis during treatment of early breast cancer for this case. The top row shows the trend in body temperature. The second, third, and fourth rows show the trends in white blood cell counts (/μL), absolute neutrophil counts (/μL), and concentrations of C-reactive protein (mg/dL), respectively. The fifth row shows the timeline of the clinical course of vasculitis treated with multiple modalities and evaluations. The X-axis shows the time since surgery.

AC, combination chemotherapy with adriamycin plus cyclophosphamide; Ace, acetaminophen; ABPC, amino-hydroxy benzylpenicillin; Breast cancer., Breast cancer-related events; BRTM, breast radical total mastectomy; CEZ, cefazolin; CNS, coagulase-negative Staphylococcus; G, pegfilgrastim injection; LVFX, levofloxacin; MSSA, methicillin-sensitive Staphylococcus aureus; NSAIDs, non-steroidal anti-inflammatory drugs; PIPC, piperacillin; PTX, weekly paclitaxel; TEs, teeth extractions for prevention of chemotherapy-induced adverse events.

Table 1: Laboratory data on admission

	First admission	Second admission	Normal range	Unit
Hematology				
White blood cell counts	6430	12140	3300–8600	/μL
Hemoglobin	7.7	8.1	13.7–16.8	g/dL
Platelet count	27.8	17.1	15.8–34.8	$\times 10^4/\mu L$
Neutrophils	4450	9880	1830–7250	/μL
Lymphocytes	820	830	1500–4000	/μL
Coagulation				
Fibrinogen degradation products	4.1	5.9	0.0–5.0	μg/mL
D-dimer	1.2	2.7	0.0–1.0	μg/mL
Fibrinogen	1005	881	200–400	mg/dL
APTT	28.4	26.4	25.0–37.0	sec.
PT-INR	1.05	1.05	0.90–1.10	
Antithrombin III	92	74	75–125	%
Procalcitonin	2+ (2–10)	3+ (≥10)	negative (< 0.5)	ng/mL
Biochemistry				
Total protein	6.6	6.1	6.6–8.1	g/dL
Albumin	2.6	2.9	4.1–5.1	g/dL
Total bilirubin	0.62	0.9	0.40–1.50	mg/dL
Blood urea nitrogen	11.3	10.6	8.0–20.0	mg/dL
Uric acid	3.9	3.5	3.7–7.8	mg/dL
Creatinine	1	1.28	0.65–1.07	mg/dL
Estimated glomerular filtration ratio	44.9	34.3		mL/min
Alkaline phosphatase	859	335	106–322	U/L
Aspartate aminotransferase	30	27	13–30	U/L
Alanine aminotransferase	37	32	10–42	U/L
Lactate dehydrogenase	157	221	124–222	U/L
Sodium	136	134	138–145	mol/L
Potassium	4.4	4.2	3.6–4.8	mol/L
Chloride	103	102	101–108	mol/L
C-reactive protein	25.14	26.21	0.00–0.14	mg/dL
Blood glucose level	191	105	73–109	mg/dL
Hemoglobin A1c	7.3	6.7	4.9–6.0	%
Urinalysis				
Color yellow	Yellow	Yellow		
Acidity (pH)	5	7	4.5–8.5	pH
Protein	(2+)	(2+)	(−)	
Sugar	(−)	(−)	(−)	
Blood	(2+)	(−)	(−)	
Concentration	1.02	1.01	1.005-1.030	
Leukocyte esterase	(−)	(±)	(−)	
Nitrites	(−)	(−)	(−)	
Red blood cell count	< 1	< 1	< 1	/HPF
White blood cell count	1–4	5–9	< 1	/HPF
Serology				
Immunoglobulins				
Immunoglobulin-G	1027	1313	861–1747	mg/dL

Immunoglobulin-A	369	435	93–393	mg/dL
Immunoglobulin-M	35	56	50–269	mg/dL
(1→3)β-D-glucan	< 4.0	< 4.0	< 20.0	pg/mL
IGRA	Negative	N/A	Negative	
Endotoxin	≤ 1.0	N/A	< 1.0	pg/mL
RF	5	N/A	< 15	IU/mL
ANA	< 40	N/A	< 40	Titer
Homogeneous	< 40	N/A	< 40	Titer
Speckled	< 40	N/A	< 40	Titer
Nucleolar	< 40	N/A	< 40	Titer
Centromere	< 40	N/A	< 40	Titer
Peripheral	< 40	N/A	< 40	Titer
MPO-ANCA	< 0.5	N/A	0.5–3.4	IU/mL

ANA, anti-nuclear antibody; HPF, high power field; IGRA, interferon-γ release assay; MPO-ANCA, myeloperoxidase-anti-neutrophil cytoplasmic antibody; N/A, not applicable; RF, rheumatoid factor

Table 2: Human leukocyte antigen (HLA) typing

HLA	HLA serological typing	HLA DNA typing allele
HLA-A	A2	*A*02:01:01*
	A26	*A*26:01:01*
HLA-B	B35	*B*35:01*
	B67	*B*67:01:02*
HLA-DR	DR4	*DRB1*04:05*
	DR8	*DRB1*08:02*

Table 3: HLA allele frequency based on CIWD version 3.0.0

HLA Allele	CWD v2.0	Prevalence in the Asian Pacific Islands	Prevalence worldwide
*HLA-A*01:02:01:01*	Common	Intermediate	Common
*HLA-A*26:01:01:01*	Common	Common	Common
*HLA-B*35:01:01:01*	Common	NA	WD
*HLA-B*67:01:02*	NA	Intermediate	Intermediate
*HLA-DRB1*04:05:01:01*	Common	NA	NA
*HLA-DRB1*04:05:02*	NA	NA	NA
*HLA-DRB1*08:02:01:01*	Common	NA	NA
*HLA-DRB1*08:02:02*	NA	NA	WD

Common: ≥ 1 in 10,000; Intermediate: ≥ 1 in 100,000; Well-documented (WD): ≥ 5 occurrences
CIWD, common, intermediate, and well-documented; NA: not applicable; WD, well-documented

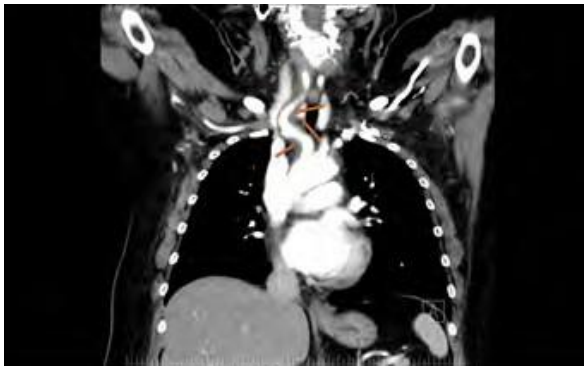

Figure 2: Chest CT during the second admission. Enhanced dynamic CT (coronal view) showing increased wall thickness of the arteries both on the right side and in the left common carotid and subclavian arteries on the contralateral side to the initial vasculitis.
CT, computed tomography

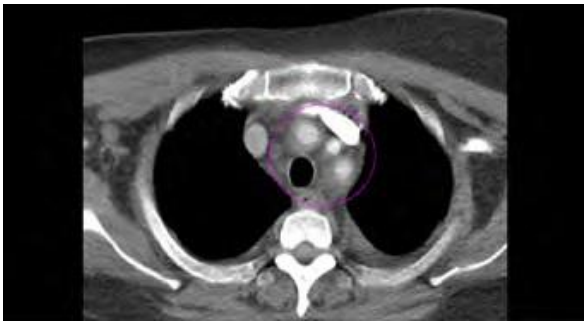

Figure 3: Chest CT during the second admission. Axial enhanced view at the level of the brachiocephalic artery showing inflammation extending from the triple-branched aortic arch to both the left common cervical artery and brachiocephalic artery, including the right common carotid artery.
CT, computed tomography

4. Discussion

We hypothesized that the reason for the multiple episodes of large vessel vasculitis was a multifactorial disorder. Four confounding factors that may cause large vessel vasculitis during migratory vasculitis of the common carotid artery (right side followed by left side) and the brachiocephalic artery were sequentially identified. These may include communicable infectious factors and three non-communicable factors as follows: baseline genetic predisposition, chronic systemic inflammation (i.e., metabolic syndrome), and use of pegfilgrastim to prevent chemotherapy-induced FN.

We expound on the four factors contributing to large vessel vasculitis. Systemic vasculitis is a multisystem blood vessel disorder, in which the size of the vessel is predominantly affected. The "large vessel" type is related to the aorta and its major branches [13]. Vasculitis is a general term that encompasses all conditions causing inflammation of the aortic wall. Vasculitis may involve the aortic root resulting in ostial coronary stenosis and/or valvulitis with aortic valve regurgitation; infectious arteritis usually affects patients with atherosclerotic and/or aneurysmal disease and/or infective endocarditis [4].

Infectious arteritis is more frequent in the elderly and men because of the higher incidence of aortic plaques and aneurysms that favor secondary infections [4].

Our patient was investigated for infectious and non-infectious vasculitis based on her clinical course. Staphylococcus, Salmonella, and Streptococcus infections are common pathogenic causes of vasculitis [5]. In addition, surgical site specimen evaluation indicated the presence of Staphylococcus strains. Therefore, Staphylococcus strains from the surgical site infection may have contributed to the large vessel vasculitis in this case.

Imaging indicated large vessel vasculitis related to non-infectious vasculitis, including Takayasu arteritis and/or Behçet's disease-related vasculitis. Based on the imaging results, HLA genotyping was performed. We found that the patient had the HLA-B*67 and HLA-A*26 alleles, which are associated with Takayasu arteritis [11] and Behçet's disease [12], respectively, in the Japanese population.

Takayasu arteritis, which is a rare chronic inflammatory disease, is the most common type of non-infectious arteritis. It is characterized by massive intima fibrosis and vascular narrowing that mainly involves the aorta, its major branches, and pulmonary arteries. Despite Takayasu arteritis primarily affecting young or middle-aged women largely from Asian countries, the disease is globally distributed and not age-specific [6]. A unique genetic factor consistently associated with Takayasu arteritis is the HLA allele HLA-B*52, as confirmed in various cohorts and several ethnicities [14]. A previous study suggested that the increased prevalence of Takayasu arteritis in Asians may reflect the predominance of the HLA-B*52 allele in this population [11].

In Japan, the prevalence of Takayasu arteritis is 40 cases per million people, and the occurrence of HLA-B*52 is 10% [11]. Conversely, in most European populations, where Takayasu arteritis is less prevalent, HLA-B*52 is recorded at < 2% [11]. Our patient did not have HLA-B*52, but she had HLA-B*67:01. HLA-B*67:01 is a novel HLA-B allele containing two amino acids associated with susceptibility to Takayasu arteritis in the Japanese population. In addition, HLA-B*67:01 is associated with Takayasu arteritis independent of HLA-B*52:01 [11].

Large vessel arteritis may also be associated with Behçet's disease, which is an autoinflammatory multisystemic neutrophilic perivasculitis characterized by recurrent inflammatory flares with diverse clinical manifestations. Behçet's disease is a chronic autoimmune disease resulting in mucous membrane ulceration. However, the diagnosis of Behçet's disease depends on combining clinical manifestations without genetic diagnostic biomarkers. Therefore, it may require several years to establish a definitive diagnosis after the initial manifestation of the disease. The HLA class I antigen HLA-B*51 has been identified as the predominant genetic susceptibility factor underlying Behçet's disease in many populations, particularly along the ancient Silk Road that ran from East Asia to the Middle East and the Mediterranean basin [15]. HLA-A*26 is another significant HLA type that is related to Behçet's disease. HLA-A*26 is significantly and independently associated with the risk of Behçet's disease, apart from HLA-B*51, in the Japanese population [16]. HLA-A*26 is related to the onset of Behçet's

disease, particularly in the HLA-B*51-negative Behçet's disease population [16]. Several genotyping studies have shown that the association between Behçet's disease and HLA-A*26 is geographically significant in Northeast Asia but not in the Middle East or Europe [16]. Recent evidence has indicated that polymorphisms in the HLA genes strongly influence autoimmune disease risk. HLA risk alleles could influence thymic selection to increase the frequency of T cell receptors (TCRs) reactive to autoantigens [17]. Some HLA haplotypes can induce an increase in the frequency of TCRs reactive to autoantigens [17]. Exogenous administration of G-CSF may induce stimulation of neutrophil precursors and enhance neutrophil chemotaxis [18]. Both G-CSF-induced inflammatory cells and HLA haplotype-related autoantigens could cause the development of multiple vessel vasculitis. Therefore, we conclude that a baseline genetic factor may influence large vessel vasculitis.

The third factor may be non-communicable systemic chronic inflammation. Furthermore, metabolic syndrome disturbs normal metabolic function and immune responses, which causes chronic systemic inflammation. Our patient had multiple lifestyle-related comorbidities. The clinical consequences of systemic chronic inflammation-driven damage can increase the risk of metabolic syndrome. These include hypertension, hyperglycemia, dyslipidemia, type 2 diabetes, non-alcoholic fatty liver disease, cardiovascular disease, chronic kidney disease, cancer, depression, neurodegenerative disease, autoimmune disease, osteoporosis, and sarcopenia, among others [19]. Therefore, we hypothesized that our patient's multiple comorbidities may have contributed to the vasculitis. Finally, we considered vasculitis that occurred in response to pegfilgrastim treatment. G-CSF-associated vasculitis is rare (0.47%), and a recent Japanese adverse drug event report revealed that G-CSF use was associated with a potential risk of vasculitis (adjusted OR: 45.87, 95% confidence interval: 19.16, 109.8) [2].

We do not believe that there is a strong, direct association between pegfilgrastim and vascular inflammation; however, there might be a weak association between them. The package insert of pegfilgrastim indicates a risk of vasculitis. However, little is known regarding the populations at risk for developing G-CSF-associated vasculitis. Therefore, we suggest that both the HLA haplotype and communicable and non-communicable environmental risk factors, including G-CSF, can induce various types of vasculitis. In addition, oncologists in charge of chemotherapy should consider that, although pegfilgrastim is a hematopoietic growth factor to prevent chemotherapy-induced FN, G-CSF has a valuable alternative role as an inflammatory cytokine [20]. In addition, the CSF family includes granulocyte/macrophage CSF and macrophage CSF. G-CSF can interact with the G-CSF receptors on neutrophils triggering inflammatory and autoimmune responses. Therapeutic G-CSF can induce the production of multiple cytokines, such as interleukin-1, interleukin-6, and tumor necrosis factor. Cytokine activation produces inflammatory reactions in surrounding cells (such as endothelial cells, epithelial cells, and fibroblasts) in conditions such as vasculitis [20]. Thus, we suggest that communicable and non-communicable risk factors induce the pathological mechanism of vasculitis. A single case may not be sufficient to draw definite conclusions regarding the causative factors for vasculitis. Moreover, there may be a weak association between the cause and effect because the patient received treatment considering both infectious and inflammatory causes, which led to ultimate improvement. Therefore, it might be challenging to confirm the association between the cause and effect. Our case simply delineates the possible culpable factors for the clinical course that our patient underwent, and further studies are warranted to reach a definitive inference.

5. Conclusions

Bacterial infection of the surgical site delayed the diagnosis of recurrent pegfilgrastim-associated migratory vasculitis during adjuvant chemotherapy for breast cancer in our patient. This may have been dependent on her specific HLA haplotype. Therefore, we conclude that G-CSF may be a risk factor for large vessel vasculitis in patients exposed to communicable and non-communicable environmental agents and with specific HLA allele genotypes, including HLA-B*67, associated with Takayasu arteritis, and HLA-A*26, associated with Behçet's disease. However, vasculitis is a communicable and/or non-communicable multifactorial disease and polygenic disease and not a monogenic Mendelian inheritance disease. Therefore, caution of vasculitis should be exercised while ruling out any G-CSF preparations due to the presence of the specific HLA haplotype.

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8. Ethics Approval and Consent to Participate

This study was approved by the local institutional review board of Gunma Prefectural Cancer Center (IRB#405-03043), and written informed consent was obtained from the patient.

9. Consent for Publication

The authors confirm that written consent for submission and pub-

lication of this case report, including the images and associated text, has been obtained from the patient, in line with the COPE guidelines.

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