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RESEARCH ARTICLE

Simultaneous Onset of Thrombocytopenia and Hypereosinophilia With Sars-Cov-2 Vaccine

Yoshiki Uemura*[1], Mitsuo Okada[2], Masayuki Ishida[3]

[1]Department of Hematology, Chikamori Hospital, 1-1-16, Okawasuzi, Kochi-shi, Kochi-ken 780-8522, Japan
[2]Department of Gastroenterology, Chikamori Hospital, 1-1-16, Okawasuzi, Kochi-shi, Kochi-ken 780-8522, Japan
[3]Department of Infectious Disease, Chikamori Hospital, 1-1-16, Okawasuzi, Kochi-shi, Kochi-ken 780-8522, Japan

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Corresponding Author: Yoshiki Uemura, Department of Hematology, Chikamori Hospital, 1-1-16, Okawasuzi, Kochi-shi, Kochi-ken 780-8522, Japan.

Abstract

Bleeding due to thrombocytopenia is a well-known side effect of the new SARS-Cov-2 vaccine. Moreover, the vaccine can induce eosinophilia with organ damage such as eosinophilic pneumonia. Thrombocytopenia or hypereosinophilia induced by the vaccine usually appears relatively early, within one to two weeks. However, as presented in our case, thrombocytopenia and hypereosinophilia simultaneously developed two months after vaccination. Our patient had simultaneous T-cell receptor (TCR) rearrangements of β-, γ-, and δ-chains. To the best of our knowledge, there has been no reported cases of the simultaneous onset of hypereosinophilia and thrombocytopenia after SARS-CoV-2 vaccination. We report an association between the simultaneous onset of thrombocytopenia and hypereosinophilia and the abnormal development of T cell clones, with some literature considerations.

Keywords: SARS-COV-2 mRNA vaccine, Eosinophilia, Thrombocytopenia, T-cell Receptor Rearrangement

1. Introduction

When a patient who died of intracranial bleeding several weeks after the administration of the Pfizer SARS-CoV-2 mRNA vaccine (BNT162b2) was reported in January 2021, thrombocytopenia that occurred after the vaccination became the center of attention [1]. Reports of an outbreak of thrombocytopenia or idiopathic thrombocytopenic purpura (ITP) occurred successively as a SARS-CoV2 mRNA vaccine induced harmful phenomenon. According to a report from the American Vaccine Adverse Event Reporting System (VAERS) data, the periods (median) from SARS-Cov-2 vaccination to ITP onset was 8 (0–38) days [2]. It has been reported that fever, pruritic eruption, and eosinophilia occurred within several hours after the Moderna coronavirus disease 2019 (Covid-19) vaccine [3]. We also reported that eosinophilia appeared 84 days after Pfizer Covid-19 vaccination [4]. Although we did not grasp the period of accurate onset of thrombocytopenia and eosinophilia because she did not have any blood examination just before the vaccination, these symptoms became apparent two months after the vaccination. As the mechanism of ITP onset induced by the SARS-CoV-2 mRNA vaccine, a cross-immune reaction by molecular homology of SARS-CoV-2 viral protein and platelets, and interference with the immune system, such as induction of the type I interferon peculiar to the mRNA vaccine, has been advocated [5, 6]. The mRNA vaccines of Pfizer Corporation and Moderna are enclosed with lipid molecules that are not degraded by human RNase. Polyethylene glycol (PEG) is used to maintain the solubility of the lipid bilayer, forming lipid nanomolecules. Anaphylaxis is thought to be induced by PEG [7].

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In our case, growth of the polyclonal T-cell clones was suggested because T-cell receptor (TCR) α, β, and γ rearrangements were detected. In ITP, γδ+T cells are important causes of immune-mediated thrombocytopenic purpura [8]. CD8+T cells increase platelet apoptosis and participate in thrombopenia [9]. Some groups have recently reported that the growth of CD3-CD4+ cells and CD3+ CD4-CD8 cells in peripheral blood is related to eosinophilia [10]. In our case, the possibility that the growth of some abnormal T cell clones simultaneously induced thrombocytopenia and eosinophilia is suggested. The SARS-Cov-2 mRNA vaccine derives strong antispike (S) antibodies and CD4+ T cells and establishes long-term immunity [11]. Considering her medical history, the third SARS-Cov-2 mRNA vaccination might have resulted in the growth of T-cell clones in our case.

We encountered a case in which bleeding symptoms with thrombocytopenia and eosinophilia with hepatic dysfunction developed simultaneously after the administration of the SARS-Cov-2 mRNA vaccine. The simultaneous onset of thrombocytopenia and hypereosinophilia induced by the SARS-CoV-2 mRNA vaccine has not yet been reported.

2. Case Presentation

An 84-year-old woman was admitted to our hospital with buccal (Fig. 1a) and tongue (Fig. 1b) hematoma and ecchymosis of the lower limbs. Our patient had an increased eosinophil count, mild abnormal liver function, and thrombocytopenia (Table 1). Computed tomography (CT) demonstrated slight hepatomegaly. Microscopic examination of the bone marrow smear showed a significant increase in the eosinophil count (Fig. 2a). In contrast, the megakaryocyte (MgK) cell count was normal (Fig. 2b). No dysplasia or tumor cell infiltration was detected in the bone marrow. She did not have skin allergy or respiratory symptoms, such as cough, sputum, and dyspnea. Fluorescence in situ hybridization (FISH) did not show the FIL1P1-PDGFRα fusion gene. Nonspecific IgE levels were high. However, the microbial ova - parasite examination results were negative. The patient had no history of bronchial asthma or allergic rhinitis. She had been taking benidipine because of hypertension a few years ago. However, she has not changed it to other agents and has not added any new agents. The value of the anti-Helicobacter pylori IgG level was within the normal range. She was diagnosed with ITP. Her complete blood count was normal until one year ago. After that, she did not undergo any blood tests until bleeding symptoms developed. She was inoculated with the third SARS-CoV-2 mRNA vaccine two months before hospitalization. The third SARS-Cov-2 mRNA vaccine was produced by Moderna; conversely, the first and second vaccines were made by Pfizer. In particular, fatigue following vaccination persisted for a long time. The patient also had hepatic dysfunction. We suspected that this was an organ disorder caused by eosinophil infiltration. After starting 40 mg prednisolone once daily, leukocytosis, eosinophilia, and abnormal liver function improved immediately (Fig. 3).

However, an increasing tendency in PLT was not observed. In addition, 100 mg of cyclosporine (CyA) was administered once a day because a tendency to re-increase eosinophils was recognized by the dose reduction of prednisolone. As a result, the eosinophil count decreased promptly, and PLT count increased immediately. Even after cancellation of prednisolone and decrease in CyA, the eosinophil count did not increase, IgE level was normalized, and PLT was maintained within normal levels. We suspected the presence of abnormal T-cell clones as a cause of thrombocytopenia and eosinophilia. Therefore, we examined TCR rearrangements. We detected multiple TCR rearrangements, such as Vβ/Jβ1, 2, Dβ/Jβ1, 2, Vγ1-8, 10/Jγ, Vγ9, 11/Jγ, and Vδ/Dδ/Jδ. When eosinophil and platelet counts were normalized with cyclosporin, the TCR rearrangements, except for Vβ/Jβ1, remained.

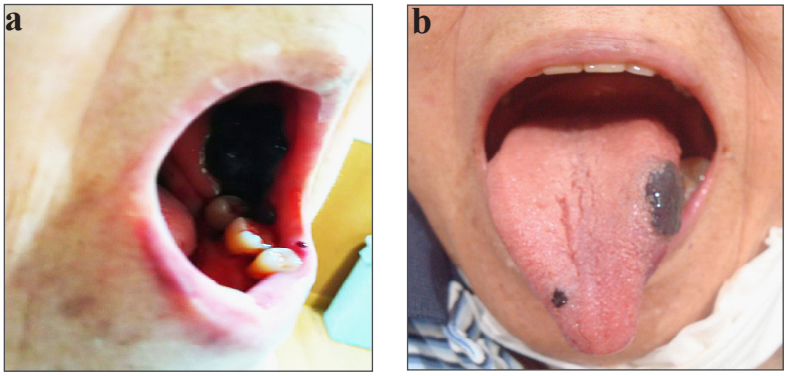

Figure 1. *Image of intraoral hematoma (a). Left buccal mucosa (b). Tongue*

Table 1. *Blood test on admission (June 27, 2022).*

Complete Blood Count		Biochemistry test		Serological test	
WBC	31,800 /μl	TP	6.5 g/dl	C3	102 mg/dl
Banded neutrophil	0.5%	Alb	3.2 g/dl	C4	31 mg/dl
Segmented neutrophil	11.0%	AST	41 U/l	ANA	<40 fold
lymphocyte	5.0%	ALT	189 U/l	RF	6 IU/ml
Monocyte	1.5%	ALP	301 IU/ml	BNP	73 pg/ml
Eosinophil	81.5%	-GTP	122 IU/l	HCV Ab	(-)
Aty-ly	0.5%	CHE	207 U/L	HBs Ag	(-)
RBC	366 x 10^4/μl	LDH	248 U/l	IgG	1233 mg/dl
Hb	11.2 g/dl	T-bil	0.7 mg/dl	IgA	187 mg/dl
Ht	33.6%	BUN	17.5 mg/dl	IgM	1272 mg/dl
MCV	91.8 fl	Cr	0.98 mg/dl	IgE	3550 mg/dl
Plt	.1 x 10^4/μl	UA	5.3 mg/dl	sIL-2R	3190 U/ml
Urinalysis		T-CHO	140 mg/dl	PA-IgG	1470 ng/10^7 cells
Color	yellow	TG	83 mg/dl	Ferritin	393 ng/ml
Protein	(-)	glu	88 mg/dl	Genetic test	
Glucose	(-)	HbA1c	5.9%	WT1mRNA	<5 x 10 copy/μg RNA
Occult blood	1(+)	Na	140 mEq/l	Coagulation	
RBC	5-9/HPF	K	3.4 mEq/l	PT-INR	1.15
WBC	50-99/HPF	Cl	107 mEq/l	APTT	36.0 sec
		CRP	2.31 mg/dl	Fibrinogen	331.3 mg/dl
				FDP	6.6 μg/ml
				D-dimer	1.2 μg/ml

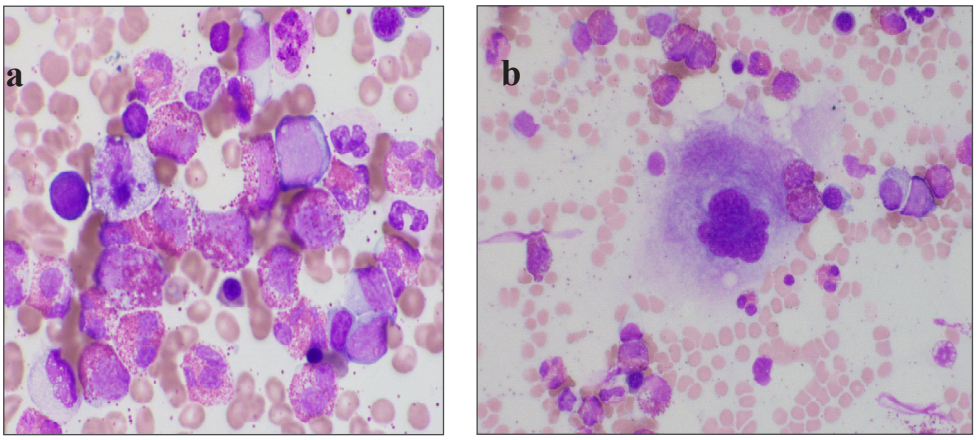

Figure 2. *May Grunwald-Giemsa staining of bone marrow (a) Marked increase in eosinophils. (X 400). (b) Moderate hyperplasia of megakaryocyte that lacks in the adhesion of platelete.(X 200).*

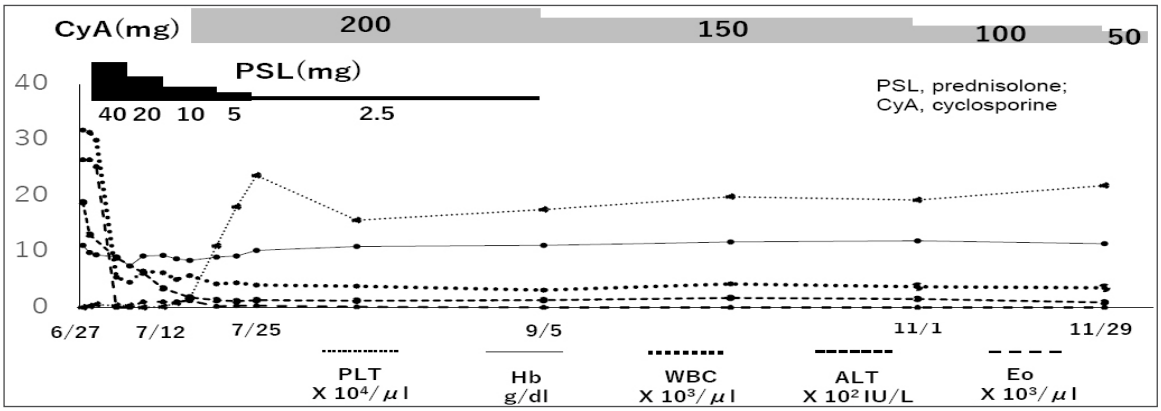

Figure 3. *Clinical course*

3. Discussion

We encountered a case of merged thrombocytopenia and eosinophilia. The patient also had hepatomegaly and hepatic dysfunction. This finding suggests an organ disorder caused by eosinophil infiltration. The bone marrow aspirate did not show any abnormal findings, except eosinophilia. It is well known that myelodysplastic syndrome (MDS) merges with eosinophilia [11]. However, the patient did not have cell dysplasia. The chromosome karyotype was normal and the WT1mRNA level was within normal limits. Therefore, the patient did not appear to have MDS. Parasites, autoimmune diseases, infectious diseases, and eosinophilia associated with malignant tumors were excluded. The FIP1L1-PDGFRA fused gene, PDGFRB 5q32 translocation gene, and BCR-ABL fused gene were not detected. Chronic eosinophilic leukemia and myeloproliferative neoplasm (MFN) were excluded. The radioallergosorbent test showed a positive reaction against several types of antigens, including cedar pollen and mites. However, she did not have a history of allergic diseases such as asthma and rhinitis. There is an existing case report of eosinophilic pneumonia and eosinophilia induced by SARS-CoV-2 vaccination [3]. She did not experience any side effects due to the first and second Pfizer vaccinations. However, she developed fever and fatigue immediately after the third vaccination. The intake of the third Moderna vaccine was strongly suspected as a cause of eosinophilia. Eosinophilic pneumonia after SARS-COV-2 vaccine inoculation is rare and severe, but corticosteroids are generally successful. Patients with poor management of asthma and allergies must consider the use of other vaccines that induce little allergic response. However, our patient had no history of allergic disease. Our patient did not have pneumonia but had a hepatic disorder caused by eosinophil invasion. The reaction to the steroids was good. Eosinophilia and abnormal liver function were immediately improved by steroids. Serum soluble IL-2 receptor (sIL-2R) levels increase in some cases of eosinophilia. This is significantly higher in malignant types of hypereosinophilic syndrome (HES) [12]. It is known that the eosinophil is a potential source of sIL-2R [12]. This can explain the high levels of sIL-2 observed in our case. As the eosinophil count decreased, IgE level, sIL-2R level, and liver function improved.

The number of MgKs was normal in the bone marrow, but immature small MgKs appeared. The underlying disease of thrombocytopenia, Helicobacter pylori infection, was not detected. Platelet-associated IgG levels were high. Therefore, the patient was diagnosed with ITP. The number of platelets before SARS-CoV-2 vaccination was normal. This suggests that ITP was also caused by SARS-CoV-2 vaccination, similar to eosinophilia. A property of ITP induced by the SARS-Cov2 vaccine is not inconsistent with that of general ITP. A general treatment such as high-dose immunoglobulin or corticosteroids is useful for both ITP types. However, in our case, corticosteroids, thrombopoietin receptor agonists, and rituximab (RIT) were ineffective for ITP. Gene rearrangements of each TCR β, γ, and δ were detected in our case. This suggests abnormal T-cell proliferation. In ITP, γδ+ T-cells induce immune-mediated thrombocytopenia and CD8+T cells participate in the induction of platelet apoptosis. In ITP cases lacking MgKs, as in our case, the possibility that a cytotoxic CD8 + T cell destroys a platelet and MgK as a target is suggested. A decrease in Th17 cell count is associated with steroid-resistant ITP [13]. The ITP in our case was resistant to corticosteroids and RIT but was immediately improved by CyA. CyA is used as 2nd line or 3rd line for ITP and HES treatment. CyA can inhibit T-cell activity. This supports the participation of abnormal T-cell clone growth in ITP in our case. After reducing the corticosteroid dose to moderate, the eosinophil count tended to increase again. However, the eosinophil count started to decrease with the combination of CyA and decreased to normal levels even after corticosteroid cancellation. Because our patient did not undergo a blood test until the appearance of this bleeding tendency from the third SARS-Cov-2 vaccination, the correct appearance time of eosinophilia was obscure. The participation of helper T-cells in delayed type IV allergy has also been suggested.

Concurrent occurrence of ITP and hypereosinophilia is rare. It has been reported that Helicobacter pylori (HP) eradication therapy simultaneously improves the merger of HP-associated ITP and HES [14], but our patient did not have HP infection. It has been reported that a case of HES with the FIP1L1-PDGFRA fusion gene was complicated by thrombotic thrombocytopenic purpura (TTP) [15], but our patient did not have the FIP1L1-PDGFRA fusion gene, and the findings suggested TTP.

4. Conclusion

It has been reported that SARS-Cov2 mRNA often induces ITP and eosinophilia, and the onset of these symptoms is relatively early. We report the first

case in which eosinophilia and ITP simultaneously developed through the abnormal growth of T-cell clones induced two months after SARS-Cov-2 mRNA vaccination. It is necessary to evaluate more cases to clarify whether the SARS-CoV-2 mRNA vaccine can induce eosinophilia and ITP concomitantly.

Data Availability

All data are available in the hospital's medical records.

Competing Interests

The authors declare that there are no competing interests regarding the publication of this paper.

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