World Journal of Clinical Cases

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World J Clin Cases 2022 November 26; 10(33): 12268-12277

DOI: 10.12998/wjcc.v10.i33.12268

ISSN 2307-8960 (online)

CASE REPORT

Case mistaken for leukemia after mRNA COVID-19 vaccine administration: A case report

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Specialty type: Hematology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Salim J, Indonesia; Zhang JX, China

Received: June 9, 2022
Peer-review started: June 9, 2022
First decision: July 29, 2022
Revised: September 6, 2022
Accepted: October 20, 2022
Article in press: October 20, 2022
Published online: November 26, 2022

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Abstract

BACKGROUND

Following the global outbreak of coronavirus disease 2019 (COVID-19), unlike other vaccines, COVID-19 vaccines were developed and commercialized in a relatively short period of time. The large-scale administration of this vaccine in a short time-period led to various unexpected side effects, including severe cytopenia and thrombosis with thrombocytopenia syndrome. Despite many reports on adverse reactions, vaccination was necessary to prevent the spread of COVID-19; thus, it is essential to understand and discuss various cases of adverse reactions after vaccination.

CASE SUMMARY

A 77-year-old woman was administered the second dose of Pfizer mRNA COVID-19 vaccine. After vaccination she experienced fever, myalgia, and weakness. Antibiotics were subsequently administered for several days, but there was no improvement in the symptoms. The patient showed severe thrombocytopenia and leukocytosis. Thoracic and abdominopelvic computed tomography showed no infection related findings, but splenomegaly and cirrhotic liver features were observed. A large number of immature cells were observed in the peripheral blood smear; thus, bone marrow examination was performed for acute leukemia. However, there were no abnormalities. The patient recovered after administration of hepatotoxins and transfusion treatment for cytopenia and was diagnosed with an adverse reaction to COVID-19 vaccination.

CONCLUSION

Adverse reactions of vaccination could be mistaken for hematologic malignancies including leukemia. We report a patient with leukocytosis following COVID-19 vaccination.

Key Words: COVID-19; Vaccine; mRNA; Leukocytosis; Adverse reaction; Case report

Core Tip: Cases of cytopenia or thrombosis with thrombocytopenia syndrome after coronavirus disease vaccination have been reported. We report a case of suspected hematologic malignancy, *i.e.*, leukemia after vaccination in a female patient. Adverse reactions of vaccination could be mistaken for hematologic malignancies.

Citation: Lee SB, Park CY, Park SG, Lee HJ. Case mistaken for leukemia after mRNA COVID-19 vaccine administration: A case report. *World J Clin Cases* 2022; 10(33): 12268-12277
URL: https://www.wjgnet.com/2307-8960/full/v10/i33/12268.htm
DOI: https://dx.doi.org/10.12998/wjcc.v10.i33.12268

INTRODUCTION

Since the coronavirus disease 2019 (COVID-19) outbreak at the end of 2019, there have been more than 200 million infections and over 4.5 million deaths worldwide. Several people suffer from COVID-19 complications following recovery. Autoimmune hematologic disorders such as immune thrombocytopenia (ITP) and autoimmune hemolytic anemia (AIHA), leukocytosis, thrombocytopenia, and eosinopenia have been reported as hematologic complications of COVID-19[1-5]. COVID-19 vaccination campaigns are conducted worldwide. Most adverse reactions after vaccination were mild and the vaccines are effective in the prevention of COVID-19. Severe adverse events include anaphylaxis, pericarditis, neurologic diseases such as Guillain-Barre syndrome, and hematologic diseases [hemolytic anemia, thrombosis with thrombocytopenic syndrome (TTS) such as cerebral sinus venous thrombosis, splanchnic vein thrombosis, and ITP][6-12]. Considering hematologic disorders, most cases are those of ITP or hemolysis in patients with underlying hematologic diseases[13-16]. Cases of blood-related adverse reactions have been reported even among individuals without underlying hematologic disease, and most of these cases were related to cytopenia[17-21].

Leukemoid reaction is a rare clinical condition defined as leukocytosis. This term was initially used by Krumbhaar[22] in 1926. Since then, it has been used to refer to reactive leukocytosis above 50×10^9/L with neutrophilia and a marked left shift (presence of immature neutrophilic forms) with non-hematologic malignancies[23].

We report a case with an adverse reaction that was mistaken for a hematologic malignancy due to an increased proportion of immature cells along with severe leukocytosis after COVID-19 vaccination.

CASE PRESENTATION

Chief complaints

A healthy 77-year-old woman with no known comorbidities and no medication use was transferred to the emergency room due to severe thrombocytopenia.

History of present illness

After the second dose of the BNT162b2 (Pfizer-BioNTech) vaccine, the patient visited a local clinic complaining of fever, myalgia, and weakness. The patient had no history of overseas travel, outdoor activity, or contact with wild animals. She was treated with antibiotics for a week due to elevated infection marker levels and fever. Despite continuous antibiotic administration, the patient's symptoms did not improve; this was followed by the occurrence of dyspnea along with thrombocytopenia. The patient was referred to our clinic for further evaluation of newly diagnosed thrombocytopenia and dyspnea.

History of past illness

Prior to vaccination, the patient had no history of disease, including malignancy, and there was no medication administration. There was no history of any infectious disease, including COVID-19.

Personal and family history

The patient is a housewife and has never been exposed to certain occupational risks. She denied tobacco smoking, alcohol drinking, and drug abuse. There was also no confirmed family history.

Physical examination

Except for fever, the patient's vital signs were stable. Despite dyspnea, there was no oxygen demand. Physical examination revealed splenomegaly of three-finger width.

Laboratory examinations

The complete blood count results were as follows (normal ranges are shown in parentheses): White blood cells, 11590 × 10^3/μL (4.0-10.0 × 10^3/μL); hemoglobin, 8.6 g/dL (12-16 g/dL); platelets, 38 × 10^3/μL (150-400 × 10^3/μL). The blood biochemistry results were as follows: Total bilirubin, 6.5 mg/dL (0.2-1.1 mg/dL); aspartate aminotransferase (AST), 242 U/L (5-40 U/L); alanine aminotransferase (ALT), 74 U/L (5-40 U/L); albumin, 2.06 g/dL (3.5-5.2 g/dL); blood urea nitrogen, 23.0 mg/dL (8-20 mg/dL); creatinine, 1.27 mg/dL (0.5-1.3 mg/dL); C-reactive protein (CRP), > 16 mg/dL (0-0.3 mg/dL). The coagulation profile results were as follows: Prothrombin time, 20.5 s (9.4-12.5 s); activated partial thromboplastin time, 41.3 s (28.0-44.0 s), fibrinogen 350 mg/dL (200-400 mg/dL), D-dimer 5830 (0-255 ng/mL) (Table 1). The real-time reverse transcription-polymerase chain reaction results were negative for COVID-19. The results were also negative for Hantavirus, *Letospira*, *Rickettsia*, and Scrub typhus. Further virological laboratory tests for human immunodeficiency virus and hepatitis B, C, and A were negative. Urine and blood cultures showed no bacterial growth (Table 2).

Imaging examinations

Thoracic and abdominopelvic computed tomography (CT) was performed to check for infection focus and the cause of dyspnea. Thoracic CT revealed mild pleural effusion, but no findings indicated infection, such as pneumonia or bronchitis (Figure 1). On abdominopelvic CT, liver cirrhosis was suspected with splenomegaly (16.5 cm) and moderate ascites (Figure 1).

FURTHER DIAGNOSTIC WORK-UP

Most infectious diseases were not considered to be the cause of the patient's symptoms; thus, the causes of cirrhosis and splenomegaly were evaluated. All tests for autoimmune hepatitis were negative (Table 3). Although no evidence of infectious disease was found, ceftriaxone administration was continued due to leukocytosis, CRP elevation, and persistent febrile symptoms. On day 2 of hospitalization, continuous renal replacement treatment (CCRT) was started due to decreased urine output accompanied by metabolic acidosis, and CCRT was stopped due to recovery of kidney function on day 5 of hospitalization. On day 4, the white blood cell count was elevated to 50790 × 10^3/μL (Figure 2) and immature cells were observed in the peripheral blood smear. To rule out acute leukemia, we performed bone marrow biopsy, but there were no abnormalities (Figure 3). On day 5 of hospitalization, the total bilirubin increased to 10.0 mg/dL and the LDH level also increased to 1053 mg/dL, with a low haptoglobin level. In the peripheral blood smear, schistocytes were observed in trace amounts, but both direct and indirect *Coombs'* test results were negative.

FINAL DIAGNOSIS

The patient was diagnosed with an adverse reaction to COVID-19 vaccination and not with a hematologic malignancy such as acute leukemia.

TREATMENT

Hepatotoxins, platelets and fresh-frozen plasma transfusion, and intravascular fluid were only administered due to liver cirrhosis, splenomegaly, changes in blood count, and CRP elevation observed at the time of hospitalization.

OUTCOME AND FOLLOW-UP

AST, ALT, and bilirubin levels decreased from day 7 of hospitalization, and the coagulation panel also started to improve. From day 5 of hospitalization, the leukocyte count started decreasing and recovered to the normal level on day 10; the platelet count also recovered to > 100000 showing a normal blood cell count profile from day 11. On day 13 of hospitalization, we performed abdomino-pelvic CT again and it was confirmed that the ascites had decreased and splenomegaly had improved. The patient was discharged in good condition on day 16 of hospitalization and is currently undergoing regular follow-up as an outpatient.

Table 1 Laboratory data at admission

Laboratory parameter	Result	Normal range
WBC (/μL)	11590	4000-10000
Neutrophil (%)	58.7	40-80
Lymphocyte (%)	31.2	25-50
Monocyte (%)	9.8	0-9
Eosinophil (%)	0.1	0-7
Basophil (%)	0.2	0-1.8
Platelet (/μL)	38000	150000-400000
AST (U/L)	242	5-40
ALT (U/L)	73.5	5-40
Total bilirubin (mg/dL)	6.5	0.2-1.2
CRP (mg/dL)	> 16	0.0-0.3

WBC: White blood cell; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; CRP: C-reactive protein.

Table 2 Infectious disease diagnostic test results

Diseases	Result
COVID-19	Negative
Ebstein-Barr virus	Negative
Cytomegalovirus	Negative
Hepatitis A	Negative
Hepatitis B	Negative
Hepatitis C	Negative
Hantavirus	Negative
HIV	Negative
Rickettsia tsutsugamushi	Negative
Leptospira	Negative
Blood bacterial culture	Negative
Urine bacterial culture	Negative

COVID-19: Coronavirus disease 2019; HIV: Human immunodeficiency virus.

DISCUSSION

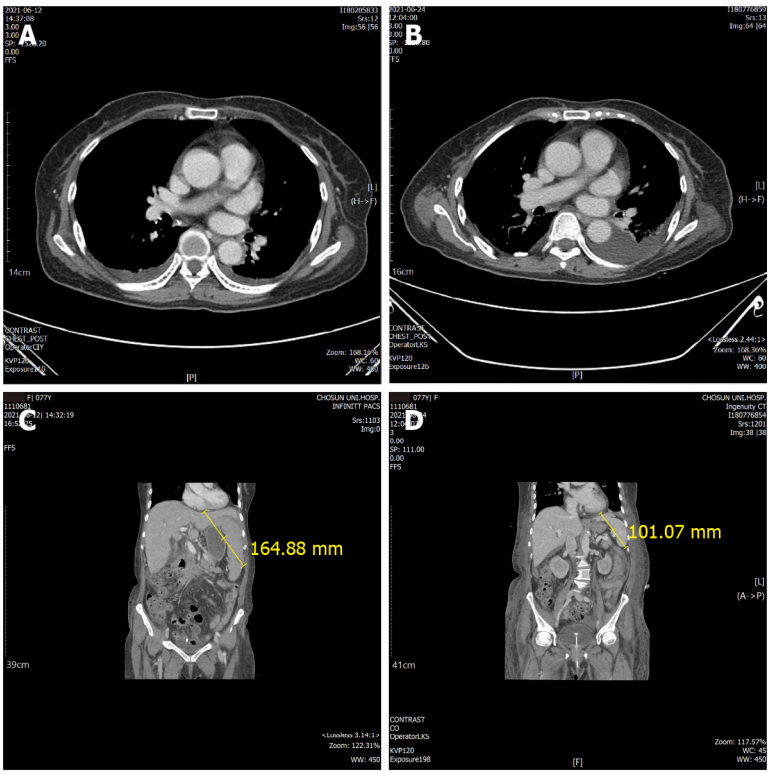
Various adverse events of COVID-19 vaccines like those of many other vaccines have been reported. There are mild adverse events such as fever, fatigue, headache, myalgia, and arthralgia, and more severe events such as anaphylactic shock, myocarditis, and TTS. Although one case of TTS related to mRNA-based vaccine has been reported, TTS is mainly reported in relation to adenoviral vector vaccines[17-20]. ITP and hemolytic anemia mainly occur in relation to mRNA-based vaccines[24-28].

Cases of ITP and one case of AIHA related to the mRNA-1273 (Moderna) vaccine have been reported [24]. One case of ITP was reported in a patient with Evans syndrome, and AIHA was observed in a healthy elderly man[13]. Adverse events related to the Pfizer-BionTech vaccine included several cases of ITP, one case of AIHA, and four cases of severe hemolysis in paroxysmal nocturnal hemoglobinuria (Table 4)[25-27]. Although the specific vaccine type is unknown, one case of hemolytic crisis in a patient with primary cold agglutinin disease and AIHA in a patient with clinically insignificant cryoglobulinemia have been reported[15]. However, to the best of our knowledge, there are no reports of severe leukocytosis. Cases of leukemoid reaction with COVID-19 have been reported, but there are no reports of similar cases related to vaccination[4,5]. The major causes of leukemoid reaction are severe infection,

Table 3 Evaluation of autoimmune hepatitis

Laboratory parameter	Results	Normal range
Anti LKM-1 Ab	Negative	Negative
Anti-mitochondria Ab	Negative	Negative
ANA (titer)	Centromere 1:1280	
Anti dsDNA antibody (IU/mL)	Negative < 10	10-15
p-ANCA (IU/mL)	Negative < 0.1	0-3.5

Anti LKM-1 Ab: Anti liver kidney microsomal antibody; ANA: Antinuclear antibody; ANCA: Anti neutrophil cytoplasmic antibody.



DOI: 10.12998/wjcc.v10.i33.12268

Figure 1 Computed tomography imaging. A: Initial thorax imaging; B: Day 13 thorax imaging; C: Initial hospitalization; D: Day 13 of hospitalization. Thorax computed tomography showed no findings indicating infection, but splenomegaly and liver cirrhosis were confirmed on abdomino-pelvic computed tomography. Splenomegaly improved on day 13 of hospitalization.

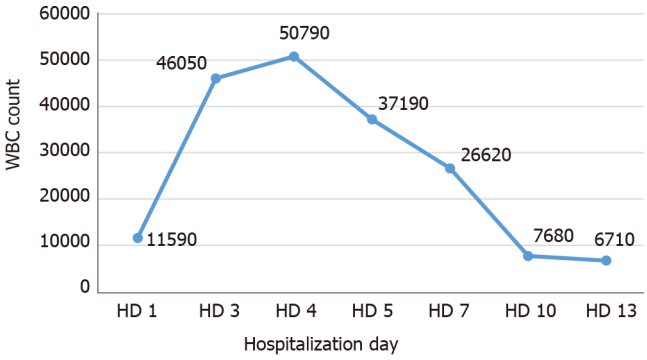
malignancies, intoxication, or hemorrhage. There were no findings that indicated malignancy or infection on CT performed at the time of admission when the patient was evaluated for all possible infectious diseases at the Department of Infectious Diseases; however, this was not confirmed. The patient showed negative real-time polymerase chain reaction test results for severe acute respiratory syndrome coronavirus 2, eliminating the possibility of COVID-19. With findings including thrombocytopenia, fever, dyspnea, and pleural effusion, a disease such as dengue fever can also be suspected. However, South Korea is not an endemic area of dengue fever and its residents have no history of travel to a country where the disease occurs; thus, this disease was excluded.

Our findings suggested the occurrence of cirrhosis from the early stage of hospitalization; all possible causes were evaluated, but the exact cause was not identified. There were no risk factors such as alcohol drinking history, drug abuse, or stick injury. The patient was transferred from the Department of Infectious Diseases to the Department of Hematology due to leukocytosis with immature cells that persisted without evidence of infection. Bone marrow examination was performed to differentiate malignant diseases such as acute leukemia; no abnormal cells including blasts were identified, and the Department of Laboratory Medicine reported that it was a reactive bone marrow according to the patient's disease state. The patient's condition improved with only supportive treatment, such as fluid therapy and blood transfusion, without any special treatment except for antibiotic administration. The

Table 4 Hematologic adverse events except for thrombocytopenic syndrome

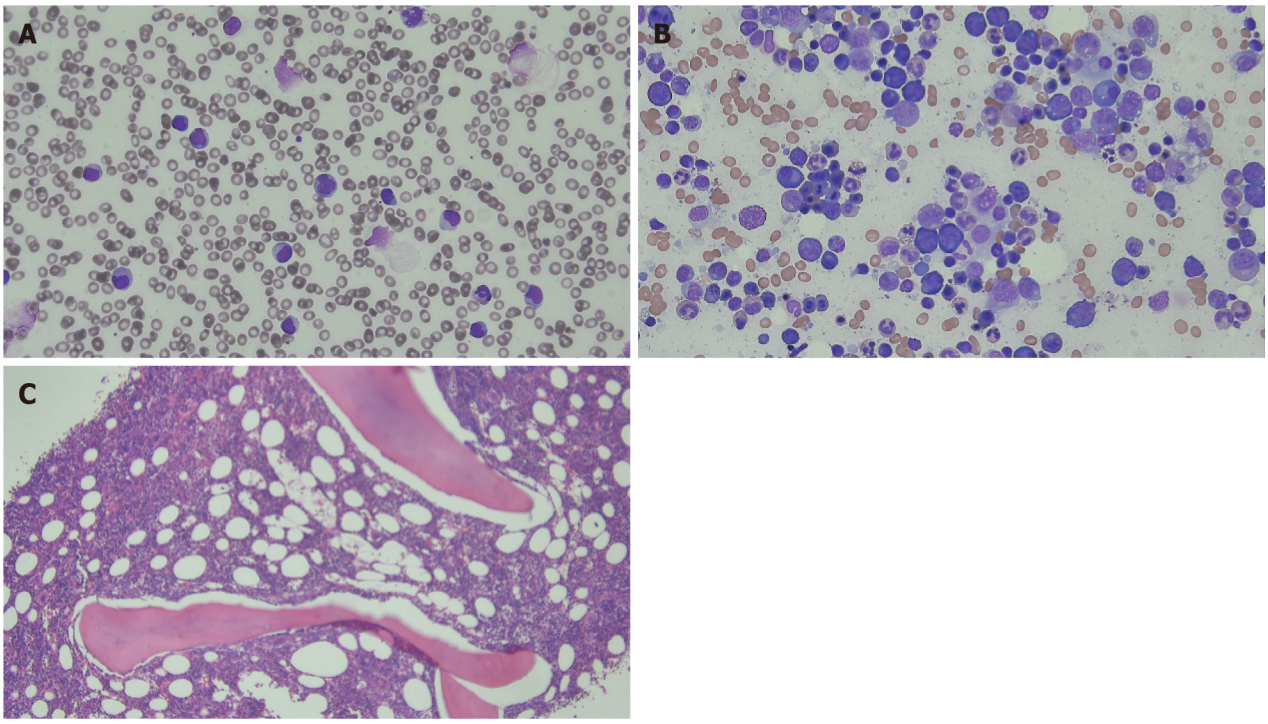
Types of hematologic adverse events	Patient No. and Ref.	Age, yr	Sex	Symptom onset (No. of days after vaccination)	Symptoms	Underlying diseases	Type of vaccine	Outcome
ITP	1, Tarawneh and Tarawneh [31]	22	M	3	Petechia, gum bleeding	None	Pfizer	Recovery
	2-9, Lee *et al* [26]	NA	NA	NA	NA	NA	Pfizer	NA
	10-20, Lee *et al*[26]	NA	NA	NA	NA	NA	Moderna	NA
	21, Shah *et al* [27]	53	M	8	Petechia rash, myalgia	Crohn's disease	Pfizer	Recovery
	22, Shah *et al* [27]	67	M	2	Melena	Chronic ITP	Pfizer	Recovery
	23, Shah *et al* [27]	59	F	2	Bloody diarrhea	SLE, chronic ITP	J&J	Recovery
	24, Ganzel and Ben-Chetrit[25]	53	M	14	Epistaxis	DM, HTN, otitis	Pfizer	Recovery
	25, Toom *et al*[32]	36	F	14	Petechia, bruising, gum bleeding, headache	ITP	Moderna	Recovery
	26, Paulsen *et al*[28]	72	M	11	Petechia, epistaxis, headache	Autoimmune thyroiditis	AZD1222	NA
	27 Paulsen *et al*[28]	71	F	11	Petechia, hyposphagma	Latent hyperthyroidism, breast cancer, stroke	AZD1222	NA
	28 Paulsen *et al*[28]	66	M	2	Petechia	HTN, mild thrombocytopenia	AZD1222	NA
	29 Paulsen *et al*[28]	64	F	15	None	HTN, COPD, steatosis hepatitis	AZD1222	NA
	30, Ghosh *et al*[33]	63	F	2	Bruise	COPD, Type 2 DM	Pfizer	Recovery
AIHA	30, Gaignard *et al*[13]	56	M	3	Painless petechia	Evans syndrome	Moderna	Recovery
	31, Gaignard *et al*[13]	77	M	5	Weakness, fatigue, shortness of breath	none	Moderna	Recovery
	32, Murdych [16]	84	M	19	Urinary frequency, dizziness	Prostate & colon cancer, CAD, HTN, trace cryoglobulinemia, emphysema, mild chronic anemia, major depression and/or anxiety	Pfizer	Recovery
	33, Brito *et al* [24]	88	F	2	Asthenia, jaundice	Insomnia	mRNA vaccine	Recovery
Hemolytic crisis	35, Pérez-Lamas *et al* [15]	57	F	2	Chills, weakness, exertional dyspnea, jaundice, mild hemoglobinurina	Cold agglutinin disease	mRNA vaccine	Recovery
Hemolysis	36, Gerber *et al*[14]	25	M	5	Abdominal pain	PNH	Pfizer	NA
	37, Gerber *et al*[14]	45	M	0	Fever, headache, myalgia, fatigue, hemoglobinuria	PNH	Pfizer	NA
	37, Gerber *et al*[14]	32	F	0	Fever, rigor	PNH	Moderna	NA
	38, Gerber *et al*[14]	63	M	0	Fatigue, darkening urine	PNH	Moderna	NA

ITP: Immune thrombocytopenia; AIHA: Autoimmune hemolytic anemia; M: Male; NA: Not available; F: Female; SLE: Systemic lupus erythematosus; DM: Diabetes mellitus; HTN: Hypertension; COPD: Chronic obstructive pulmonary disease; CAD: Coronary artery disease; PNH: Paroxysmal nocturnal hemoglobinuria.



DOI: 10.12998/wjcc.v10.i33.12268

Figure 2 White blood cell count during hospitalization. WBC: White blood cell; HD: Hospitalization day.



DOI: 10.12998/wjcc.v10.i33.12268

Figure 3 Peripheral blood smear and bone marrow examination. A: Peripheral blood smear; B: Bone marrow aspiration; C: Bone marrow biopsy. Peripheral blood smear showed leukocytosis with neutrophils and immature cells. Bone marrow aspiration and biopsy sample revealed reactive marrow.

detailed pathogenesis of leukocytosis and splenomegaly is unknown. The diagnosis of liver cirrhosis was presumed from initial CT findings such as splenomegaly with ascites; however, liver biopsy was not performed to rule out liver cirrhosis. Autoimmune hepatitis developing after COVID-19 vaccination has been reported. This report postulated that autoinflammatory dysregulation was the cause of tissue damage[29]. In our case, organ damage such as liver cirrhosis was observed by a similar mechanism. Further studies on the pathogenesis and confirmation in more cases are needed.

No case of severe leukocytosis after COVID-19 vaccination has been reported so far. There have been reports of leukocytosis after pneumococcal polysaccharide vaccine administration wherein it was hypothesized that the leukocytosis was the result of an inflammatory response due to increased cytokines in the body after vaccination. However, further studies on the pathogenesis have not yet been conducted[30]. An excessive inflammatory response can also be assumed in the present case, which could have been caused by increased cytokines after vaccination; however, additional research is

needed regarding this.

CONCLUSION

The patient was suspected to have infection due to fever, leukocytosis and CRP elevation. All infectious agents were excluded and immature cells were observed in the peripheral blood smear with leukocytosis; thus, other causes of leukemoid reaction were also investigated, but all results were negative. The patient had a history of COVID-19 vaccination prior to symptom onset, no specific underlying disease or medication history, and no special findings in the overall evaluation including bone marrow examination. The patient's symptoms were considered to be adverse events due to vaccination, and this is the first report of a leukemoid-like reaction that occurred after COVID-19 vaccination.

FOOTNOTES

Author contributions: Lee SB contributed mainly to the writing of the manuscript; Park SG and Park CY advised on manuscript drafting; Lee HJ proofread and revised the manuscript as a corresponding author; all authors have approved this version for publication.

Supported by Chosun University, 2020.

Informed consent statement: A written informed consent was obtained from the patient for publication of this case report.

Conflict-of-interest statement: The authors declare that they have no conflict of interest to disclose.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Country/Territory of origin: South Korea

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S-Editor: Wang DM
L-Editor: Webster JR
P-Editor: Wang DM

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