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WORD COUNT	2090	TIME SUBMITTED	19-SEP-2022 11:58AM
		PAPER ID	90644576

1
Name of Journal: *World Journal of Clinical Cases*

Manuscript NO: 77982

Manuscript Type: CASE REPORT

Case mistaken for leukemia after mRNA coronavirus disease 2019 vaccine administration: A case report

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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 feature 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 first reported leukocytosis following COVID-19 vaccination.

Key Words: Coronavirus disease 2019; Vaccine; mRNA; Leukocytosis; Adverse reaction; Case report

Lee SB, Park CY, Park SG, Lee HJ. Case mistaken for leukemia after mRNA coronavirus disease 2019 vaccine administration: A case report. *World J Clin Cases* 2022; In press

Core Tip: Cases of cytopenia or thrombosis with thrombocytopenia syndrome after coronavirus disease (COVID-19) vaccination have been reported. We reported 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.

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 infection[1-7]. COVID-19 vaccination campaigns are conducted worldwide. Most adverse reactions after vaccination were mild and effective in the prevention of COVID-19 infection. 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][8-26]. Considering hematologic disorders, most cases are those of ITP or hemolysis in patients with underlying hematologic diseases. 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[18-26].

Leukemoid reaction is a rare clinical condition defined as leukocytosis. This term was initially used by Krumbhaar in 1926[27]. 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[28].

We reported 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 for 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 [A1] 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 × 103/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, 242 U/L (5-40 U/L); alanine aminotransferase, 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 infection. The results were also negative for Hantan virus, *Letospira*, *Rickettsia*, and Scrub typhus. Further virological laboratory tests for human immunodeficiency virus and hepatitis B,

C, and A were negative. Owing to urine and blood cultures, bacterial growth was not confirmed (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 causes 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 because leukocytosis, CRP elevation, and febrile symptoms persisted. 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 hatoglobin 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 in case of 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 improving. From the day 5 of hospitalization, the leukocyte count started decreasing and it 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 decreased and the splenomegaly improved. The patient was discharged in good condition on day 16 of hospitalization and is currently undergoing regular follow-up as an outpatient.

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[12-15]. ITP and hemolytic anemia mainly occur in relation to mRNA-based vaccines[23-26].

Cases of ITP and one case of AIHA related to the mRNA-1273 (Morderna) vaccine have been reported[24]. One case of ITP was that of a patient with Evans syndrome, and AIHA was observed in a healthy old man[18]. 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)[23-25]. 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[20,22]. However, to the best of our knowledge, there are no reports on severe leukocytosis. Cases of leukemoid reaction with COVID-19 infection 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, 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 infection. 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 suggest 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 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. Autoimune hepatitis developing

after COVID-19 vaccination is reported[29]. This report postulated that autoinflammatory dysregulation is 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 on leukocytosis after pneumococcal polysaccharide vaccine administratiom wherein it was hypothesized that the leukocytosis was the result of an inflammatory reponse due to increased cytokines in the body after vaccination. However, further studies on the pathogenesis have not yet been conducted[30]. Excessive inflammatoy response can also be assumed in the present case, which could be caused by increased cytokines after vaccination; additional research is needed regarding this.

CONCLUSION

The patient was suspected with infection due to fever and 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 incuding 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 occured after COVID-19 vaccination.

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