CASE REPORT

Adult paroxysmal cold hemoglobinuria following mRNA COVID-19 vaccination

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Abstract
Paroxysmal cold hemoglobinuria (PCH) is an extremely rare subtype of autoimmune hemolytic anemia (AIHA) in adults. PCH is caused by the biphasic Donath–Landsteiner (DL) antibody which fixes complement to red blood cells at low temperatures and dissociates at warmer temperatures, leading to complement-mediated intravascular hemolysis. This biphasic antibody is known as the Donath–Landsteiner (DL) antibody and its presence is essential for the diagnosis of PCH.

Keywords
autoimmune disease, COVID-19 vaccination, paroxysmal cold hemoglobinuria

1 | INTRODUCTION

Autoimmune hemolytic anemia (AIHA) is a rare disorder and can be classified into five subtypes [1]. Three of the AIHA subtypes are cold-types of AIHA, which are cold agglutinin disease (CAD), secondary cold agglutinin syndrome (CAS), and paroxysmal cold hemoglobinuria (PCH).

PCH is caused by an autoantibody that fixes complement to red blood cells (RBCs) at low temperatures and dissociates at warmer temperatures, leading to complement-mediated intravascular hemolysis. This biphasic antibody is known as the Donath–Landsteiner (DL) antibody and its presence is essential for the diagnosis of PCH. There are many pediatric cases of PCH, while adult cases are extremely rare [2]. Most adult PCH cases were known to be caused by syphilis in the early 1900s. The numbers of PCH patients have drastically fallen with the decrease of untreated syphilis patients. Reports of PCH are scarce in recent years, and the causes of PCH were reported to be idiopathic or due to hematological malignancies including non-Hodgkin lymphoma (NHL), chronic lymphocytic leukemia, myelofibrosis, and myelodysplastic syndrome (MDS) [3–6].

Autoimmune hematological disorders including AIHA and immune thrombocytopenia have been reported in relation to COVID-19 infections and vaccinations [7–11]. However, PCH has not been previously reported in association with the mRNA COVID-19 vaccine.

2 | CASE REPORT

A 59-year-old Japanese male was admitted to our institution in early December, 2021 due to a two-week history of high fever, fatigue,
and shortness of breath. Onset of these symptoms appeared roughly four weeks after the second dose of BNT162b2 mRNA COVID-19 vaccination (Pfizer-Biotech). PCR tests for COVID-19 were negative, and peripheral blood tests showed severe anemia with hemoglobin of 5.1 g/dl, high total bilirubin levels of 6.7 mg/dl, and high lactate dehydrogenase levels of 1489 IU/L. Hemoglobinuria was present. Acute renal failure was also observed and creatinine (Cr) was 3.37 mg/dl. Peripheral blood smear showed agglutination of RBCs and active neutrophil erythrophagocytosis (Figure 1). Direct antiglobulin test (DAT) was positive for complement C3b/C3d, and negative for IgG (Ortho BioVue® System, DAT/IDAT Cassette). The direct DL test was negative, but the indirect DL test (done by mixing patient and donor serum and adding P-antigen-positive type O RBCs) was positive (Figure 2). Tests for Syphilis and cold agglutinin titers were negative, and bone marrow analysis showed no remarkable abnormalities. Whole body computed tomography (CT) scans were also unremarkable and showed no signs of malignant lymphoma. Blood and urine cultures were negative, and serological tests denied active infections of Epstein–Barr virus, cytomegalovirus, HIV, HTLV-1, and Mycoplasma pneumoniae. Thus, COVID-19 vaccination-related PCH was suspected. As for treatment, RBC transfusions and hydration were carried out, and the patient was kept warm. Anemia, LDH levels, and renal failure gradually improved, and the patient was discharged 10 days from admission. On his first outpatient visit, his general condition was well, and laboratory data showed improved hemoglobin levels and normalization of renal function. Two months after first outpatient visit, hemoglobin levels normalized but the indirect DL test remained positive (Figure 3).

3 | DISCUSSION

We encountered a case of adult onset PCH with no preceding infections or LPDs. PCH is a rare immunologic disorder often associated with infections and LPDs. Although syphilis and viral infections are known to trigger production of DL antibodies, the underlying mechanisms have not been fully elucidated. In general, the DL antibody targets the P-antigen on the RBC surface, but certain rare cases have reported targeting of the i-antigen [6]. Recently, certain autoimmune hematological disorders including warm-type AIHA, CAS, and PNH have been reported to be triggered by COVID-19 vaccinations [7–11]. Thus in theory, PCH is also a likely disorder to be triggered by COVID-19 vaccinations due to its autoimmune nature. Although there were two case reports of PCH onset following measles and seven-valent pneumococcal conjugate vaccination [12, 13], to the best of our knowledge, this is the first to report development of PCH subsequent to the mRNA COVID-19 vaccination. Symptoms of hemolysis were reported to develop a few days to a month after mRNA COVID-19 vaccinations in the aforementioned cases of AIHA, CAS, and PNH. Our case developed symptoms of hemolysis approximately 5 weeks after the second COVID-19 vaccination, which is relatively late as for timing of onset compared to most reported cases of autoimmune hematological disorders triggered by vaccination. However, the patient received his second COVID-19 vaccination in middle October, and symptom onset was in late November. We speculate that the patient may have developed DL antibodies earlier, but did not experience hemolysis until late...
FIGURE 3  Clinical course of the patient. Days are counted as the
days from first visit to our hospital. Abbreviations: Cre; creatine, Hb,
hemoglobin; LDH, lactate dehydrogenase; T-Bil, total bilirubin. Only
LDH values are dealing with the left axis

November because this is the time of the year when the temperature
usually starts to fall in Shizuoka prefecture, which is located in the
middle of main island Japan.

Due to the decline in number of patients with syphilis, adult cases
of PCH have become an extremely rare disorder, and thus PCH can
be overlooked by current day practitioners. Moreover, other than
hemolysis-associated manifestations such as hemoglobinuria and jaun-
dice, the symptoms of PCH are diverse and none are disease specific,
including myalgias, abdominal pain, back pain, anorexia, headaches,
rigors, nausea, and fever. Furthermore, although confirmation of the
direct DL antibody is essential for a diagnosis of PCH, the DL test requires
careful prewarmed sample collection and a highly skilled technician to
acquire accurate results. The direct DL test is prone to false-negative
results because the complement coated cells show resistance to lysis.
Therefore, when PCH is strongly suspected, the indirect DL test should
be additionally performed even when the direct DL test is negative.
Another important diagnostic clue is peripheral blood erythrophago-
cytosis, which is highly specific to PCH. In the presented case, DAT was
positive for complement C3b/C3d and negative for IgG, the indirect DL
test was positive, erythrophagocytosis was observed in the peripheral
blood smear, and thus a firm diagnosis of PCH was rendered.

Management of PCH is fundamentally supportive, constituted by
methods such as hydration, RBC transfusions, and avoiding cold expo-
sure. Use of infusion warmers should be considered when blood trans-
usions and fluid infusions are to be carried out. Although immune-
suppressive therapies including corticosteroid, rituximab, intravenous
immunoglobulin (IVIG), and azathioprine have been used for severe or
chronic hemolysis due to PCH, the true efficacy of these agents are
unclear. Eculizumab, a humanized anti-C5 monoclonal antibody which
blocks the complement pathway at the C5 stage, has been looked upon
as a promising treatment method for PCH [14]. In the presented case,
hemolysis promptly improved with warming alone and no recurrence
has been seen, and thus additional therapies were not necessary.

In conclusion, we report the first case of PCH developing subse-
cquent to the mRNA COVID-19 vaccination. Several autoimmune hema-
tologic disorders have been reported following the mRNA COVID-19
vaccination, and PCH may be an underrecognized adverse event.
Although we could only provide circumstantial evidence and no solid
proof that mRNA COVID-19 vaccination contributed to the develop-
ment of PCH, adult PCH in the current era is extremely rare and the
possibility of PCH developing coincidentally following vaccination can
be considered highly unlikely. Accumulation of cases and further etio-
logical studies are necessary for understanding the exact relationship
between mRNA COVID-19 vaccination and PCH.

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CONFLICT OF INTEREST
The authors declare that there is no conflict of interest that could be
perceived as prejudicing the impartiality of the research reported.

AUTHORS CONTRIBUTION
Kyohei Misawa: conceptualization, data collection and interpretation,
writing the original draft; Hajime Yasuda: investigation, writing the
original draft; Daisuke Koyama: supervision, data collection and inter-
pretation, revising the manuscript; Tadaaki Inano: conceptualization,
data collection and interpretation; Akemi Inoguchi: data interpretation
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tion and providing of technical support; Hina Takano: conceptualiza-
tion, data collection and interpretation, Noriaki Iwao: data collection
and interpretation, supervision; Miki Ando: supervision, revising the
manuscript; Michiaki Koike: supervision, revising the manuscript.

ETHICS STATEMENT
This study was approved by the ethics committee of Juntendo Shizuoka
Hospital. Written informed consent for this study was obtained from
the patient.

DATA AVAILABILITY STATEMENT
Not applicable as no datasets were generated for this study.

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