

Autoimmune Hemolytic Anemia After Inactivated Virus COVID-19 Vaccination: A Report of 2 Cases

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Very few cases of autoimmune hemolytic anemia (AIHA) have been reported after mRNA COVID-19 vaccinations. But herein we found 2 cases of AIHA after inactivated virus COVID-19 vaccination. Case 1: a 47-year-old Thai woman suffered from malaise, fatigue, and feverish feeling since the evening of the day of the first dose of inactivated virus COVID-19 vaccination (Sinopharm). She did not have any serious health problem prior this illness. Physical examination revealed marked pallor and body temperature was 38.1°C. Blood tests showed hemoglobin (Hb) 55 g/L, white blood cell (WBC) $12.2 \times 10^9/L$, platelet $310 \times 10^9/L$, nucleated red blood cell (RBC) 8/100 WBC, reticulocyte count 25.0%, direct antiglobulin test-4+ positive, indirect antiglobulin test-2+ positive. She was diagnosed with severe AIHA and well responsive to steroid therapy. Case 2: a 78-year-old Thai woman felt fatigue without fever 3 days after the second dose of inactivated virus COVID-19 vaccine (Sinopharm). Her underlying disease was anemia of the elderly with alpha thalassemia-1 heterozygosity. Her averaged Hb concentration before transfusion was 85 ± 3 g/L and she always needed transfusion every 2 months. Physical examination revealed only pallor. Blood test showed Hb 79 g/L, WBC $3.7 \times 10^9/L$, platelet $104 \times 10^9/L$, direct antiglobulin test-4+ positive, indirect antiglobulin test-4+ positive. She was diagnosed with AIHA and treated with cyclophosphamide and blood transfusion. Although the association between the inactivated virus COVID-19 vaccination and AIHA could not be simply concluded and the mix-and-match combination of different COVID-19 vaccines is promoted by Thai government, both of our patients chose to postpone the next dose of any kind of COVID-19 vaccine.

Keywords: Autoimmune hemolytic anemia, Inactivated virus COVID-19 vaccine, Shinopham

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Introduction

Autoimmune hemolytic anemia (AIHA) is a rare disease of acquired red blood cells (RBC) destruction due to the antibody against the autoantigen upon the surface of RBC. Patients with this disease have hemoglobin concentration ranging from less than 30 g/L to more than 90 g/L. Its onset can be abrupt or gradual meanwhile it may run acute or chronic course and few cases can be fatal. It is classified into primary or idiopathic if it occurs spontaneously that accounts for around 30% of cases, and secondary if it is found associated with various groups of disorders that include infections, lymphoproliferative disorders, systemic autoimmune diseases, malignancy, and drugs.¹

For vaccination, very few cases of AIHA were occasionally diagnosed after the influenza,^{2,3} oral polio, combination of mumps, measles, and rubella, and combination of diphtheria, pertussis, and tetanus vaccination.⁴ Likewise, secondary AIHA after COVID-19 vaccination has been reported. Very few cases of AIHA have exclusively been found after mRNA vaccine, in either previously healthy⁵⁻⁷ or few patients suffering from cancer or autoimmune disease.⁸⁻¹⁰

We herein found 2 cases of AIHA after receiving the inactivated virus COVID-19 vaccination in Thai women.

Report of Cases

Case 1

A 47-year-old Thai woman had exhaust, easy fainting, and palpitation for 3 days. Twenty days before presentation, she had been injected with the first dose of inactivated virus COVID-19 vaccine, Sinopharm injection, and she started experiencing malaise with feverish sensation in that evening. Her symptoms gradually progressed until she came to see the doctor. Before the vaccination, she had not serious health problem except for hysterectomy due to uncontrollable menorrhagia at 45 years of age without hormonal replacement.

Her physical examination revealed unremarkable, except for marked pallor, temperature of 38.1°C, pulse of

106 beats/min. Blood tests showed hemoglobin (Hb) 55 g/L, white blood cell (WBC) $12.2 \times 10^9/L$, platelet $310 \times 10^9/L$, nucleated red blood cell (RBC) 8/100 WBC, mean corpuscular volume (MCV) 115.0 fL, mean corpuscular hemoglobin (MCH) 35.9 pg/cell, frequent microspherocytes with polychromasia in peripheral blood smear, reticulocyte 25.0%, direct antiglobulin test-4+ positive, indirect antiglobulin test-2+ positive, erythrocyte sedimentation rate (ESR) 70 mm/h, antinuclear antibody (ANA)-positive, homogeneous type 1:320. Hb analysis showed A₂A, Hb A₂ 2.8%, albumin 43 g/L, globulin 35 g/L, aspartate aminotransferase (AST) 37 U/L, alanine aminotransferase (ALT) 41 U/L, total bilirubin 35.9 $\mu\text{mol/L}$, indirect bilirubin 30.8 $\mu\text{mol/L}$, alkaline phosphatase (ALP) 42 U/L, creatinine 70.7 $\mu\text{mol/L}$, real-time reverse transcription-polymerase chain reaction (RT-PCR) for COVID-19 virus-negative, and HIV antibody-negative, the chest film and the urinalysis-unremarkable.

She was diagnosed with severe AIHA and treated with intravenous dexamethasone 16 mg a day for 2 days and followed by oral prednisolone 60 mg a day. She could not be transfused due to the unavailability of the least incompatible blood. Her all symptoms were improved. Ten days later, her blood test showed Hb 88 g/L, WBC $13.7 \times 10^9/L$, platelet $310 \times 10^9/L$. She felt sick to her stomach, so prednisolone was replaced with oral cyclophosphamide 50 mg a day. Due to being afraid of recurrence of AIHA, she chose to defer the second dose of COVID-19 vaccine of any type. Eventually, her blood test results became normal within 3 months of therapy.

Case 2

A 78-year-old Thai woman felt fatigue and dizziness without fever 3 days after the second dose of inactivated virus COVID-19 vaccine, Sinopharm injection. The first dose of Sinopharm had been injected 3 weeks earlier without any serious untoward effect. Two years ago, she had been diagnosed with anemia of the elderly with the underlying alpha thalassemia-1 heterozygosity, Southeast Asian deletion type. Another concurrent disease was type 2 diabetes mellitus which had been well controlled with

oral hypoglycemic drugs for many years. Her averaged hematological parameters before transfusion were Hb 85 ± 3 g/L, hematocrit (Hct) 28.0 ± 1.0 %, WBC $3.9 \pm 0.4 \times 10^9$ /L, platelet $114 \pm 0.27 \times 10^9$ /L, MCV 65.7 ± 1.0 fL, MCH 19.9 ± 0.5 pg/cell, serum ferritin 1558.0 ± 110.0 µg/L and she always required 1 unit of blood transfusion every 2 months to combat her anemic symptom. The physical examination revealed only pallor without jaundice.

The present blood test showed Hb 79 g/L, WBC 3.7×10^9 /L, platelet 104×10^9 /L, MCV 70.1 fL, MCH 20.8 pg/cell, frequent polychromasia in peripheral blood smear, direct antiglobulin test-4+ positive, indirect antiglobulin test-4+ positive, autoagglutination-3+ positive, antibody screening-positive, antibody identification: C+, c+, Mia+, autoantibody+, normal thyroid, liver, and kidney function tests.

She was diagnosed with AIHA and treated with oral cyclophosphamide of 50 mg a day instead of corticosteroid which might aggravate the diabetes. One unit of the least incompatible packed red cells was slowly transfused. During transfusion, her anemic symptom did not deteriorate. She did not have fever or chill, and Hct concentration after the first 100 mL of the blood transfusion did not further diminish. She was discharged home after 2 days of admission with cyclophosphamide as home medication. She did not accept the booster dose of any kind of COVID-19 vaccination.

Discussion

Our cases had strongly positive direct antiglobulin test with increased polychromasia and/or nucleated RBCs found in the peripheral blood sample test. Hence, the diagnosis of AIHA could be concluded, and it was diagnosed a few days or weeks after inactivated virus COVID-19 vaccination. AIHA is the rare condition in either the general population¹¹ or post mRNA COVID-19 vaccination, and its incidence was 1:75 000 to 1:80 000 in general populations.¹² Our cases incidentally developed AIHA when the inactivated virus COVID-19 vaccine has been widely used in Thailand to promote “Herd Immunity” among the Thai people.

There are many reasons why the COVID-19 vaccine might associate with AIHA: 1) the COVID-19 vaccine can probably trigger the relapse of autoimmune diseases such as idiopathic thrombocytopenic purpura,^{5, 13} AIHA,¹⁴ Evans syndrome,¹⁵ rheumatoid arthritis,¹⁶ Still's disease¹⁷ and lupus nephritis;¹⁸ 2) common causes of AIHA such as hematologic disorders, solid malignancies, autoimmune diseases and infections¹¹ were not found in our cases; 3) a COVID-19 virus can trigger autoimmune inflammatory diseases;¹⁹ 4) the direct antiglobulin test was found positive in COVID-19 patients more than 2-fold the control,²⁰ and 5) the antibody against COVID-19 spike glycoprotein can cross-react with structurally similar host peptide sequences.²¹ All the facts mentioned above suggest that at least the association between AIHA and COVID-19 vaccine could not be definitely excluded.

Anemia can be found in 43% to 65% of adult patients with COVID-19 infection and 9% to 14.7% of these are AIHA. However, the degree of anemia is not severe: Hb 122 g/L with AIHA versus 130 g/L with negative direct antiglobulin group.²² Each COVID-19 vaccine is made of different parts of a COVID-19 virus, and it is possible that any sequel after COVID-19 infection may occur after some COVID-19 vaccinations.

The pathogenesis of AIHA in COVID-19 virus infection is probably the homology between the ankyrin-1 of RBC membrane and the COVID-19 spike glycoprotein that can lead to development of RBC autoantibodies and possibly AIHA. Both a COVID-19 virus and some COVID-19 vaccines also have similar spike protein, therefore, if AIHA can be found in the COVID-19 viral infection, it might possibly be found after COVID-19 vaccination.¹³

AIHA after COVID-19 vaccination can be found after either the first^{10, 22} or the second dose.⁶ For the patients who developed AIHA in a few weeks after the first dose of mRNA COVID-19 vaccine, the second dose were not advised.¹⁰ In Thailand, the mix-and-match policy of different COVID-19 vaccines is created particularly with the most popular program: to start with 1 or 2 doses of an inactivated virus vaccine followed by a viral vector or

mRNA vaccine. For the second or booster dose of COVID-19 vaccination, our cases were encouraged to weigh among the benefit of reduction of COVID-19 infection and its related death if the vaccination is repeated with Sinopharm or other types²³ and risk of reactivation of autoimmune disease by COVID-19 vaccination.²⁴ Although the odd ratios of adverse events after COVID-19 vaccination among numerous autoimmune diseases patients were similar to those of control,²⁵ and the US Advisory Committee on Immunization Practices (ACIP) concluded the benefit of vaccination outweighed the risk of serious side effects,²⁶ both of our patients chose to defer the next dose of all types COVID-19 vaccines.^{5, 10, 19}

As other cases of AIHA after COVID-19 vaccination,^{6, 10} our cases responded well to immunosuppressant therapy. Cyclophosphamide was chosen to replace prednisolone for avoidance of gastrointestinal discomfort in the first case

and it became the drug of choice in the second case for avoidance of disturbance of blood sugar control because of the diabetes. In fact, cyclophosphamide does not preclude them to receive the next dose of COVID-19 vaccination²⁷ if they would have liked.

Conclusions

Two Thai women were diagnosed with AIHA after the first and the second dose of inactivated virus COVID-19 vaccination. Neither of them had had AIHA before the vaccination. They both responded well to immunosuppressant therapy. Although the direct association between the COVID-19 vaccination and the AIHA could not be precisely concluded, the next dose of any type of COVID-19 vaccination was purposely postponed for avoidance of possible recurrence of AIHA.

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โลหิตจางเนื่องจากเม็ดเลือดแดงแตกโดยภูมิคุ้มกันต่อต้านตนเอง หลังจากฉีดวัคซีนโควิด 19 ชนิดเชื้อตาย: รายงานผู้ป่วย 2 ราย

สมชาย อินทศิริพงษ์¹, ธนากรณ์ อนันตะเศรษฐกุล¹, ลิขสิทธิ์ แสงลู่ทอง²

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โลหิตจางเนื่องจากเม็ดเลือดแดงแตกโดยภูมิคุ้มกันต่อต้านตนเอง หรือ Autoimmune hemolytic anemia (AIHA) หลังจากได้รับวัคซีนต่อต้านเชื้อโควิด 19 ชนิด mRNA มีรายงานน้อยมาก แต่เราพบผู้ป่วยที่มีภาวะดังกล่าวจำนวน 2 คน คนแรกเป็นหญิงไทย อายุ 47 ปี รู้สึกล้า อ่อนเพลีย และตัวอุ่นๆ ตั้งแต่ตอนเย็นของวันที่ได้รับวัคซีนโควิด 19 ชนิดเชื้อตายยี่ห้อซิโนฟาร์ม เข็มที่ 1 ก่อนหน้านี้นี้ผู้ป่วยไม่มีปัญหาสุขภาพรุนแรงใดๆ มาก่อน อาการเพิ่มขึ้นทีละเล็กละน้อยเป็นเวลา 20 วัน จึงมาพบแพทย์ ตรวจอุณหภูมิร่างกายเท่ากับ 38.1 องศาเซลเซียส ตรวจพบภาวะซีดชัดเจน ผลตรวจเลือดพบ Hemoglobin (Hb) 55 g/L, White blood cell (WBC) $12.2 \times 10^9/L$, Platelet $310 \times 10^9/L$, Nucleated red blood cell (RBC) 8/100 WBC, Reticulocyte count 25.0%, Direct antiglobulin test-4+ positive, Indirect antiglobulin test-2+ positive แพทย์ให้การวินิจฉัยว่าเป็นโลหิตจางเนื่องจากเม็ดเลือดแดงแตกโดยภูมิคุ้มกันต่อต้านตนเองแบบรุนแรง ผู้ป่วยตอบสนองดีต่อการรักษาด้วยยาสเตียรอยด์ คนที่ 2 เป็นหญิงไทย อายุ 78 ปี รู้สึกเพลีย 3 วัน หลังฉีดวัคซีนโควิด 19 ชนิดเชื้อตายยี่ห้อซิโนฟาร์ม เข็มที่ 2 ไม่มีไข้ เดิมผู้ป่วยเป็นโลหิตจางจากอายุมาก และพาหะของแอลฟาธาลัสซีเมีย-1 ก่อนเดิมเลือดมีค่า Hb เท่ากับ 85 ± 3 g/L ปกติต้องเติมเลือดทุก 2 เดือน ตรวจร่างกายพบเพียงซีด ผลตรวจเลือดพบ Hb 79 g/L, WBC $3.7 \times 10^9/L$, Platelet $104 \times 10^9/L$, Direct antiglobulin test-4+ positive, Indirect antiglobulin test-4+ positive แพทย์วินิจฉัยว่าเป็นโลหิตจางเนื่องจากเม็ดเลือดแดงแตกโดยภูมิคุ้มกันต่อต้านตนเองให้การรักษาด้วยยา Cyclophosphamide และเติมเลือด แม้ว่าความเกี่ยวข้องระหว่างวัคซีนโควิด 19 ชนิดเชื้อตายกับโลหิตจางเนื่องจากเม็ดเลือดแดงแตกโดยภูมิคุ้มกันต่อต้านตนเองจะยังไม่สามารถสรุปได้โดยง่าย และรัฐบาลไทยจะให้การสนับสนุนการไขว้วัคซีนโควิด 19 ต่างชนิดกัน ผู้ป่วยทั้งคู่เลือกที่จะเลื่อนการฉีดวัคซีนโควิด 19 เข็มต่อไป

คำสำคัญ: โลหิตจางเนื่องจากเม็ดเลือดแดงแตกโดยภูมิคุ้มกันต่อต้านตนเอง วัคซีนโควิด 19 ชนิดเชื้อตาย ซิโนฟาร์ม

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