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CASE REPORT

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Transfusion-Related acute lung injury (TRALI) caused by antibodies to HLA-DRB1* 07:01 and HLA-DQB1*02:02: A case report

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Key Clinical Message

Transfusion-related acute lung injury (TRALI) is characterized by non-cardiogenic pulmonary edema and acute hypoxemia. There are few reports of HLA-II antibodies causing TRALI in China.

KEYWORDS

blood transfusion, HLA class II antibodies, pulmonary edema, transfusion-related acute lung injury

1 | INTRODUCTION

The Food and Drug Administration (FDA) reports that transfusion-related acute lung injury (TRALI) contributes significantly to morbidity and mortality associated with transfusion.[1] This condition is characterized by the sudden appearance of non-cardiogenic pulmonary edema and hypoxemia within 6 h of blood transfusion.[2] According to data from the International Haemovigilance (HV) Network, the morbidity rate of TRALI is 0.0494 per 100,000 parts of blood transfused.[3] Additionally, the mortality rate of TRALI among the general patient population is approximately 10% to 15%, reaching nearly 40% in critically ill patients.[3,4] In Chinese populations, the morbidity and mortality rates of TRALI remain unclear due to insufficient disease awareness, incomplete reporting systems, and HV data. Here, we have attempted to raise awareness among clinicians by reviewing a patient who developed TRALI after receiving fresh frozen plasma (FFP) containing human lymphocyte antigen (HLA)-II antibodies. The successful treatment of this patient indicates the necessity of accurate management in TRALI cases.

2 | CASE REPORT WITH RESULTS

A 52-year-old man who had suffered for over a month from head and neck skin ulceration and purulent secretions was admitted to our hospital. The area of ulceration was about 3% of the total burn surface area (TBSA) with redness and swelling around the wound. The ulcer depth extended below the deep fascia and was thus diagnosed as necrotizing fasciitis. However, the primary cause of the severe infection was diabetes of which the patient was unaware. His temperature was 36.8°C, with a pulse of 67 bpm, blood pressure of 120/76 mmHg, respiration capacity of 20 times/min, and fasting plasma glucose (FPG) of 20 mmol/L. During the physical examination, clear bilateral lung sounds were observed without extensive dry or wet rales. No abnormal

findings were observed on the electrocardiography (ECG) or echocardiography. The laboratory test results were: a white blood cell (WBC) count of 14.36×10^9/L with 73.9% neutrophils, red blood cell (RBC) count of 3.03×10^{12}/L, hemoglobin of 84 g/L, C-reactive protein of 9.02 mg/L, and procalcitonin of 0.113 ng/mL. Culture of skin from the head and neck showed the presence of Gram-positive *Staphylococcus aureus* (3+) and *Serratia marcescens* (2+).

From Day 2 to 6 after admission, the patient received four packed red blood cell (PRBC) units with 2400 mL of FFP to counteract the effects of surgery and anemia, and to prevent coagulation disorder caused by necrotizing fasciitis. No adverse effects occurred during the transfusion, and arterial blood gas analysis indicated 99.8% arterial oxygen saturation (SpO_2), 130 mmHg partial pressure oxygen (PaO_2), and 43.9 mmHg carbon dioxide partial pressure ($PaCO_2$).

On the seventh day of hospitalization, the patient suddenly developed respiratory distress, dyspnea, and severe hypoxemia after receiving approximately 100 mL of FFP (SpO_2 64.1%; PaO_2 33.8 mmHg; $PaCO_2$ 39.6 mmHg). The plasma transfusion was immediately discontinued, and the patient was treated with facemask oxygen at 60 L/min. Additionally, 5 mg of dexamethasone was administered intravenously due to a suspected allergic reaction to the transfusion. However, the hypoxic symptoms did not improve. Coarse breathing sounds could be heard in both lungs upon auscultation, and a chest radiograph suggested bilateral pulmonary infiltrates (Figure 1A). A heart rate of 136 beats/min was observed when performing an urgent echocardiogram, with the ventricle and atrium presenting regular silhouettes. The patient was intubated, mechanically ventilated, and subsequently transferred to the intensive care unit (ICU) due to his worsening condition. The ventilator settings were adjusted to the synchronous intermittent mandatory ventilation (SIMV) mode using 10 cm H_2O positive end-expiratory pressure (PEEP) and a 90% fraction of inspired oxygen (FiO_2). After 1 day, the patient's blood SpO_2 improved and the PaO_2 increased. The FiO_2 was, therefore, decreased to 40%, and the PEEP was gradually lowered to 6 cm H_2O. The following day, the lung condition showed gradual improvement with fewer wet rales in bilateral lungs than on the previous day. The FiO_2 was adjusted to 30%, and the PEEP was maintained at a level of 6 cm H_2O. After 3 days of oxygen support, the patient's condition gradually improved, and PaO_2 level became normal. He was transferred to the burn and orthopedics department for the treatment of the infected wound. Chest computed tomography (CT) on Day 22 after the transfusion indicated that the bilateral lung infiltrates had been absorbed (Figure 1B).

We conducted high-resolution HLA genotyping to evaluate the development of TRALI. The NGSgo-AmpX kit (GenDx, Utrecht, the Netherlands) was used to amplify the HLA-A, B, C, DRB1, DQB1 and DPB1 loci. The amplicons were pooled and fragmented enzymatically using an NGSgo-LibrX kit (GenDx). Then "barcode" adapters were ligated using an NGSgo-IndX kit (GenDx), according to the NGSgo workflow. The pooled library was sequenced by a MiniSEQ instrument (Illumina, San Diego, CA, USA), using paired-end sequencing. FASTQ files were assembled and analyzed with NGSengine (version 2.30, GenDx). The HLA types of the recipient were identified as HLA-A* 24:02, 30:01; HLA-B* 13:02, 35:03; HLA-C* 06:02, 12:03; DRB1* 07:01, 07:01; DQB1* 02:02, 03:03; and DPB1* 04:01, 13:01. The recipient had received blood transfusions from a female plasma donor. Plasma samples were first tested with the screening assay LIFECODES LifeScreen Deluxe-LMX (Gen-Probe-Immucor, Stamford, CT, USA) according to the manufacturer's instructions. Test interpretation was performed using MATCH IT Antibody software (LIFECODES) on raw data obtained with a LABScan 200TM flow cytometer (Luminex Inc., Austin, TX, USA). High-definition single-antigen bead assays LIFECODES

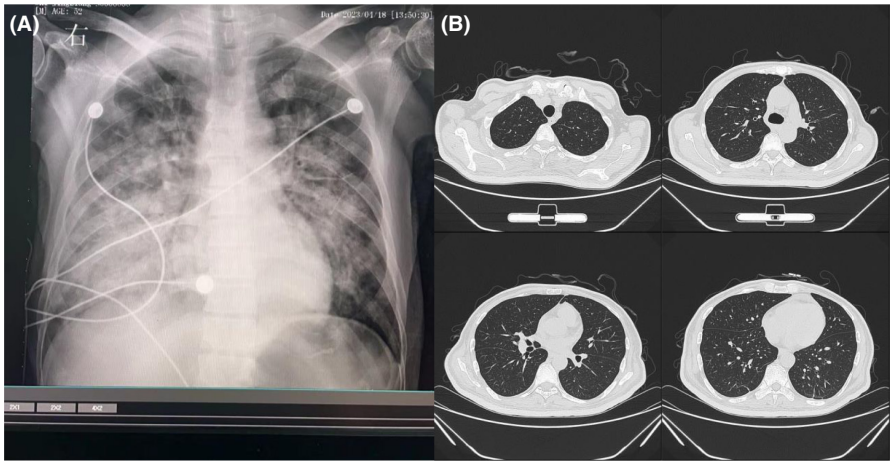

FIGURE 1 Lung images. (A) Chest X-ray is taken approximately 1 h after transfusion showing bilateral lung infiltrates, bilateral pulmonary oedema, and cardiac shadow with standard size and normal morphology. (B) Chest computed tomography (CT) 22 days after transfusion showing obvious absorption of bilateral lung infiltrates.

LSATM Class I and Class II (LIFECODES) were then performed on the donor plasma that tested positive on the LMX assay. A positive result was defined as a mean fluorescence intensity (MFI) of over 1000. The specific antibodies HLA-DRB1* 07:01 (MFI 17322) and HLA-DQB1*02:02 (MFI 1366–1475) were detected by testing of the donor plasma and were considered responsible for the development of TRALI. Furthermore, antibodies against HNA can also cause TRALI.[5,6] However, testing for these antibodies was difficult to perform as there is no laboratory in China that can perform such tests, so it is impossible to assess the possible contribution of HNA antibodies.

3 | DISCUSSION

According to the symptoms, laboratory test results and clinical course of the patient, the present case satisfied the criteria of the TRALI Type I category diagnostic assessment.[2] Specifically, symptom onset occurred within 6 hours of blood transfusion, including hypoxemia ($SpO_2 < 90\%$ on room air) with new bilateral lung infiltrates observed on chest radiography (Figure 1A) and no evidence of the risk factors for pulmonary vascular overload or acute respiratory distress syndrome (ARDS).

It has been shown that the total amount of HLAII antibodies (MFI > 1500) is a risk factor for TRALI.[7] In this case, a total of 54 specific antibodies against HLA-I and HLA-II were detected in the blood donor plasma. HLA-DRB1* 07:01 (MFI 17322) and HLA-DQB1*02:02 (MFI 1366–1475) were found to be the specific antibodies that caused TRALI in the recipient, whose HLA genotyping was HLA-A* 24:02, 30:01; HLA-B* 13:02, 35:03; HLA-C* 06:02, 12:03; DRB1* 07:01, 07:01; DQB1* 02:02, 03:03; and DPB1* 04:01, 13:01. In Chinese donors, the most frequent HLA-A-B-C-DRB1-DQB1 haplotype is A*30:01-B*13:02-C*06:02-DRB1*07:01-DQB1*02:02 (37‰), with the frequency of this haplotype varying in different regions of China, decreasing gradually from northeast to southwest.[8] For example, in populations living in latitudes higher than that of Shanghai, the A*30-B*13-DRB1*07 frequency was found to be higher than that of A*02-B*46-DRB1*09; the converse was seen in populations living in lower latitudes.[9] In this case, the patient was a native of Beijing which lies at a higher latitude than Shanghai, and his HLA haplotype was consistent with the above regional distribution. Although the positivity rates of HLA-DRB1*07:01 and HLA-DQB1*02:02 antibodies in Chinese donors do not classify them as high-frequency antibodies (about 0.2%),[10] the risk of TRALI is high due to the high proportion of corresponding HLA genotypes; the Chinese Common Allele (CWD) catalog lists the frequencies of the HLA-DRB1*07:01 and HLA-DQB1*02:02 genotypes as 9.3% and 7.4%, respectively.

The pathogenesis of TRALI remains complex and controversial. Most reports suggest that the pathophysiological process of TRALI can be viewed as a "two-hit" hypothesis. The first hit occurs when the underlying clinical condition of the patient (e.g., inflammation or sepsis) activates pulmonary endothelial cells (ECs), leading to increased expression of intercellular adhesion molecule 1 (ICAM-1) and the release of a large number of cytokines, which cause neutrophil activation, accumulation and adhesion to the activated pulmonary microvascular endothelium.[11,12] The second hit is represented by two TRALI types, namely, non-antibody-mediated and antibody-mediated types.[2,13] Non-antibody-mediated TRALI is thought to be caused by proinflammatory mediators, and bioactive lipids, among other factors.[4,14] Antibody-mediated TRALI, the most prevalent type, is thought to be caused by the passive transfusion of antibodies from donors, which usually contain HLA I or II or human neutrophil antigen (HNA) antibodies.[13,15] Monocytes represent a primary target in the induction of TRALI by HLA-II antibodies. The HLA-II antibodies bind to cognate antigens expressed on monocytes, leading to the release of proinflammatory mediators, including tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), IL-6, IL-8, and leukotriene B4. These monocyte-derived inflammatory mediators recruit and activate neutrophil reactive oxygen species (ROS) release, damaging pulmonary vascular endothelial cells, and inducing capillary permeability, which, in turn, induces TRALI.[2,14,16] Several studies, have also suggested a neutrophil-independent pathway, in which activated monocytes produce proinflammatory mediators and ROS that damage the pulmonary endothelium and cause TRALI.[16–18]

The lack of routine testing for HLA class II antibodies prior to 2001 led to missed cases involving these antibodies, resulting in earlier suggestions that TRALI was primarily caused by antibodies to HLA-I and HNA, while HLA-II antibodies were less common.[5,19] Currently, however, there are increasing reports of HLA-II antibodies and their association with severe cases.[19–22] We collected case reports on TRALI cases caused by HLA-II only from the PubMed and CNKI databases between January 2001 and June 2023. HLA-II antibodies were exclusively identified in 25 cases (Table S1). The 20 blood donors in the 25 cases with blood donor information were all female, including 9 parous female blood donors with one or more pregnancies. The triggering blood component in 14 of 25

TRALI cases was shown to be FFP. Hence, most studies indicate that HLA-II antibodies in the plasma of parous women are a major cause of TRALI.[20,23,24] After the inclusion of plasma from male donors in several countries, such as the USA, the UK, Germany, and Australia, to mitigate the risk of TRALI, the incidence of TRALI decreased significantly.[25–30]

The blood donor, in the present case, was identified as female. Her history of fertility and blood transfusions was unknown, making it impossible to further identify the source of the HLA antibodies in her body. She had donated blood six times without any transfusion-associated adverse events other than this. This could have been due to insufficient awareness of TRALI among clinicians and an imperfect reporting system for such adverse reactions in China.[31] A study evaluating the clinical outcomes of TRALI in a Chinese population revealed that 34.5% (20 out of 58) led to death. Moreover, logistic regression analysis indicated that misdiagnosis affected patient outcomes.[31] The primary factor behind the successful recovery of this case could be attributed to the timely identification and provision of effective oxygen therapy by the clinician coupled with supportive care. Therefore, improving TRALI awareness among clinicians would ensure the well-being of patients. The diagnosis and management of TRALI still need to be fully developed in China. Consequently, several proactive measures should be implemented to minimize the occurrence and mortality rates associated with TRALI.

AUTHOR CONTRIBUTIONS

Menggentuya Huang: Writing – original draft. **Xingtong Wang:** Investigation. **Li Wang:** Investigation. **Guanyi Chen:** Writing – review and editing.

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None.

CONFLICT OF INTEREST STATEMENT

All authors declare that they have no conflict of interests.

DATA AVAILABILITY STATEMENT

Data available on request due to privacy/ethical restrictions.

CONSENT

Written, informed consent was obtained from the patient for publication of this case report.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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