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Allergic blood Transfusion reaction: A Review

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Abstract

Non-haemolytic transfusion reactions are the most common type of transfusion reactions, including acute lung injury related to blood transfusion, circulatory overload related to blood transfusion, allergic reactions, febrile reactions, purpura after transfusion, and graft-versus-host disease. Although life-threatening allergic reactions occur rarely, allergic reactions occur more frequently. It has been proposed that immunologically active undigested or digested food allergens in the donor's blood can be transferred to recipients allergic to these antigens, thereby causing allergic reactions. Washed platelets have been shown to be effective in preventing allergic reactions caused by blood transfusion, although a large number of platelets will be lost during the washing process, and the recovery of platelets after transfusion may be different from that of unwashed platelets.

Keywords: allergic reaction, transfusion, washed platelets, allergens

Introduction

Allergic transfusion reaction refers to an allergic reaction caused by blood transfusion. This is one of the most common transfusion reactions. The reporting rate depends on the degree of active monitoring of the transmission of reports to the blood bank. (Savage *et al.*, 2014) In general, they are estimated to complicate 3% of all blood transfusions. The incidence of blood transfusion allergic reactions is related to the amount of plasma in the product. More than 90% of these reactions occur during a blood transfusion.

Allergic reactions caused by blood transfusion may be due to the presence of sensitizing antigens in the donor's blood, or the transfusion of allergic donor antibodies and then exposure to the antigen. Allergic transfusion reaction is a reaction to blood transfusion, which is defined by the Centers for Disease Control (CDC) (Ching *et al.*, 2015) as:

Diagnosis

If two or more of the following conditions, the diagnosis is to stop anaphylaxis In the 4 hours after the blood transfusion, the following will occur:

- Conjunctival edema
- Edema of lips, tongue and uvula
- Erythema and edema in the periorbital area

- Redness of whole body
- Hypotension
- Local angioedema Macular papules (Pruritus)
- Shortness of breath; bronchospasm
- Urticaria (urticaria)

If any of the following occurs within 4 hours of stopping the blood transfusion, possible diagnosis:

- Conjunctival edema
- Lips, tongue and uvula Hypophisema
- Erythema and periorbital edema
- Periorbital edema Local angioedema
- Maculopapular
- Pruritus (pruritus)
- Urticaria (urticaria)

The British Blood Alert Notification System (SHOT) classifies allergic reactions as mild, moderate and severe. Reactions characteristic of allergic and febrile reactions may occur.

Mild

Rash, hives or redness

Moderate

Wheezing (bronchospasm) or angioedema, but normal blood pressure and no respiratory damage. There may or may not be a related rash or hives.

Severe

This may be due to:

• Severe breathing problems (bronchospasm, wheezing), angioedema, or circulatory problems (such as low blood pressure) require immediate medical attention or hospitalization or prolonged hospital stay.

• Allergic reactions

Treatment

The treatment of allergic transfusion reactions involves stopping the blood transfusion immediately. If there are only mild symptoms (ie, urticaria and itching), the patient can be treated with antihistamines, and if the symptoms disappear completely and the patient feels well, the blood transfusion can be restarted. After the infusion of other products in the same unit, a mild transfusion reaction during the infusion usually does not develop into a more severe allergic reaction. (Ching, et, al, 2015) If symptoms are mild, blood transfusion should not be restarted.

Prevention

There is no evidence that preoperative antihistamines can prevent allergic reactions to transfusions, although these medications may reduce symptoms once they occur.

Transfusion reaction

Haemolysis reaction

The haemolysis reaction occurs when the recipient's serum contains antibodies against the corresponding antigen on the donor's red blood cells. This can be an ABO blood group incompatibility or a related incompatibility with different blood group antigens (Ching *et al.*, 2015)

Disseminated intravascular coagulation (DIC), kidney failure, and death are not uncommon after such reactions.

The most common cause of major hemolytic transfusion reactions is administrative errors, such as incorrectly labeled specimens sent to the blood bank or incorrect identification of the patient to whom you provided blood. Don't think that verification is the responsibility of another person!

Allergic reactions

Allergic reactions to plasma proteins range from urticaria and itching to allergic reactions. These reactions may occur in 1 in 200 red blood cell transfusions and 1 in 30 platelet transfusions(Ching *et*, *al.*, 2015).

Fever response

White blood cell response (fever response) is caused by the patient's antibodies, which are directed against antigens present on the imported lymphocytes or granulocytes. The risk of febrile reaction ranges from one in a thousand to one in ten thousand.

Symptoms usually include chills and an increase in body temperature> 1 degree Celsius.

Transfusion-related Acute Lung Injury (TRALI)

TRALI is now the leading cause of transfusionrelated deaths. It occurs most often when the donor plasma contains HLA or leukocyte-specific antibodies (usually granulocytes). Recipient leukocytes may be "stimulated" by the underlying disease to become more adherent to the alveolar epithelium. The introduction of donor antibodies into the recipient's body will cause the release of granulocyte enzymes, which will increase permeability capillary and cause sudden respiratory distress due to pulmonary edema, usually within 6 hours after blood transfusion. Leukopenia can occur temporarily. Most conditions will improve in 2 days. (Savage WJ et al., 2014)

TRALI occurs most frequently when using plasma-based blood products (such as FFP). The use of male plasma may reduce the incidence of TRALI, because pregnant women are more likely to have higher HLA antibody titers.

Circulatory overload

Circulatory overload can occur in the blood or any intravenous fluid, especially in patients with weakened cardiac function. The incidence of

Although the report shows that the incidence of allergic reactions to platelets (PLT) and red blood cells (RBC) is $3 \cdot 7\%$ and 0.15%, respectively, a review of the literature shows that the incidence has changed more than 100 times, which may be due to differences in pre-medication use, patient characteristics, product manufacture, storage time,

reporting rate, response definitions, and standards of follow-up (Geiger and Howard, 2007). A team in Canada showed that the incidence of allergic reactions between PLT and red blood cells was similar, and the incidence of allergic reactions to plasma infusion was 0 • 19% (Kleinman et al., 2003). Therefore, compared with other components, PLT transfusion is clearly associated with a higher risk, although it is not clear whether these differences are due to the nature of each component or patient factors. including underlying diseases and previous blood transfusion history.

Allergen-dependent pathways

Plasma proteins as allergens

The allergens that cause allergic transfusion reactions are plasma proteins, such as IgA (Vyas et al., 1968; Schmidt et al., 1969; Sandler et al., 1995) and haptoglobin (Hp) (Koda et al., 2000; et al., 2002). Although there have been reports of allergic reactions, many of which are severe (Vyas et al., 1968; Schmidt et al., 1969; Sandler et al., 1995; Koda et al., 2000; Shimada et al., 2002), there are no reliable data. Estimates of the incidence of allergic transfusion reactions mediated by IgA and Hp. The number of patients who lack IgA or Hp and specific antibodies but have never been diagnosed because they have no symptoms after blood transfusion is unknown. Therefore, at least for IgA deficiency, there is generally no reaction, and allergic reactions seem to be relatively rare (Sandler, 2006).

Although most IgA-related allergic reactions occur in people with IgA deficiency (serum IgA <0 • 5 mg/L) and detectable serum class-specific IgA antibodies, some patients have normal serum IgA levels. Subclass (IgA1 or IgA2) or allotypespecific IgA antibodies [IgA2m (1) or IgA2m (2)] have severe acute reactions to blood transfusion (Sandler et al., 1995).

Plasma Hp levels must be measured carefully because they are known to fall below detectable levels in certain pathological conditions, such as hemolysis and liver dysfunction (Rougemont et al., 1980). In these cases, the DNA diagnosis of Hp deficiency is helpful (Kodaetal, 2000).

It is worth noting that significant racial differences have been observed in the incidence of IgA and Hp deficiencies and resulting racial differences in the prevalence of anaphylactic shock mediated by these antibodies. The frequency of HP alleles in East and Southeast Asian populations is 1.5-3%. Therefore, the incidence of its deficiency is 1 / 1,000 to 1 / 4,000. However, this allele has not been detected in African, West Asian, and South Asian or European populations (Koda et al., 2000; Shimada et al., 2007; Soejima et al., 2007). In contrast, the reported incidence of IgA deficiency in Japanese is approximately 1 / 30,000, which is lower than that reported by Europeans (1/2 500)(Ropars et al., 1982; Kanoh et al., 1986). Therefore, East Asians should consider deficiency of Hp and Hp antibodies, while Europeans should consider deficiency of IgA and IgA antibodies as the cause of transfusion-related allergic reactions, respectively.

Although a rare anaphylactic shock has been reported after blood transfusion in patients with complement C4 deficiency (Lambin et al., 1984; Westhoff et al., 1992) and von Willebrand factor deficiency (Bergamaschini et al., nineteen ninety five). Factor IX inhibitors in hemophilia B patients occasionally induce anaphylactic shock after a factor IX transfusion (Warrier and Lusher, 1998).

Chemical allergens

In addition to plasma proteins, it is reported that methylene blue is a reagent for virus inactivation in fresh frozen plasma, which is reported to cause anaphylactic shock after blood transfusion (Dewachter et al., 2011; Nubret et al., 2011). Although the risk seems extremely low given the widespread use of this blood component, preventive measures should be taken in countries and regions with methylene blue inactivation systems.

Food Allergens

Recently, an interesting case report showed that blood transfusion-related allergic reactions occur after peanut allergens are passively transferred to sensitive people (Jacobs et al., 2011). In short, a 6-year-old boy developed an allergic reaction during a PLT transfusion, with a rash, angioedema, hypotension, and shortness of breath. Laboratory tests rule out possible defects in IgA, Hp, and C4; drug or latex allergies; human leukocyte antigen (HLA) antibodies and the presence of transfusion-related acute lung injury (TRALI). However, the patient had a history of severe peanut allergy at the age of 1 year and his serum contained specific IgE antibodies against the major peanut allergen, Ara h2, which had a resistance to pepsin digestion. strong Additionally, three of the five blood donors recalled eating a few handfuls of peanuts the night before the blood donation. This indirect evidence suggests that allergic reactions will occur after passive transfer of allergens from peanuts. This is consistent with the fact that a large number of food antigens are absorbed into the bloodstream in digested form, but retain a certain molecular size and antigenicity (Untersmayr and Jensen Jarolim, 2008). The direct way to test this hypothesis is to show these allergens in blood transfusions. However, no data was provided to prove the presence of peanut allergen in the donor's blood. The author only referred to a previous report that showed that the antidigestible Ara h2 peptide was detected in serum up to 24 hours after ingestion (Baumert et al., 2010). In addition, other researchers tried to detect the circulating peanut protein in volunteers after a large amount of intake, but failed (Vickery et al., 2011). When three-fifths of blood donors consumed a few handfuls of peanuts the night before blood donation, the hypothesis that physiologically related contamination occurred was suspected (Vickery et al., 2011). The true incidence of these reactions is unclear. Therefore, before providing more concrete evidence, we must take a cautious approach to this issue.

IgE-, Fc R-, mast cell- and histamine-mediated sub-pathway versus IgG-, Fc Rs-, basophiland platelet-activating factor (PAF)-mediated sub-pathway

IgG antibodies are usually detected in IgA and Hp-mediated allergic reactions, while IgE antibodies have also been detected in several studies (Burks et al., 1986; Harper et al., 1995; Dioun et al., 1998; Shimada et al., 2002). Therefore, IgG and IgE-mediated mechanisms are possible. In allergic reactions, it is important to check IgG antibodies and, if possible, check the IgE category. Although IgE, Fc R, mast cells, and histamine are thought to play important roles in allergic reactions, it has recently been demonstrated that IgG-mediated systemic allergic reactions are the main ones in mouse systems involving Fc R, basophils, and PAF. Participant. In this reaction, PAF instead of histamine is the main chemical mediator that causes systemic allergic reactions (Tsujimura et al., 2008). Although it is uncertain whether this pathway exists in humans, there is evidence to support this mechanism.

For example, an allergen-specific IgG antibody instead of an IgE antibody was detected in individuals who showed a systemic allergic reaction to medical reagents (such as protamine, dextran, and recombinant IgG, including antitumor necrosis factor-) (Kraft et al., 1982; Weiss et al., 1989; Adourian et al., 1993; Cheifetz et al., 2003). Vadas et al. (2008) studied the role of PAF and PAF acetylhydrolase (enzymes that inactivate PAF) in human allergic reactions. Based on the following observations, they concluded that the failure of PAF acetylhydrolase to inactivate PAF may lead to the severity of allergic reactions: (i) serum PAF levels are directly related to the severity of allergic reactions, (ii) serum PAF acetylhydrolysis Enzyme activity is negatively correlated (iii) PAF acetylhydrolase activity in patients with fatal allergic reactions to peanuts was significantly lower than that in the control group (Vadas et al., 2008).

In addition to basophils, neutrophils (Jönsson et al., 2011, 2012) and monocytes (Strait et al., 2002) have also been reported to play a key role in the development of allergic reactions in the murine system. Among these pathways, Fc R, IgG and PAF are involved. However, the exact participants, antibody classes, and chemical mediators in the human system remain to be determined. However, before a final conclusion can be drawn about the IgG, Fc R, and PAFmediated pathways in the human system, extensive research is needed.

Allergen-dependent pathway

Another hypothetical mechanism of transfusion allergic reactions is biological response modifiers (BRM), such as inflammatory cytokines and accumulate chemokines, which in blood components during storage and are transfused together with transfusions of blood and cause allergic reactions (Figure 1)). The stored PLT concentrate supernatant (PCSN) accumulated surprising levels of BRM during storage, including vascular endothelial growth factor, soluble CD40 ligand, histamine, transforming growth factor 1, and RANTES (Wadhwa et al., 1996; Edvardsen et al., 1998; Phipps et al., 2001; Wakamoto et al., 2003; Garrud et al., 2012). There is reason to believe that the infusion dose of these molecules may have clinical significance and may alter the immune function of the recipient. Although the role of these BRMs in the development of allergic reactions is still unknown, these or other substances may induce or modulate allergic reactions.

Patient factors other than allergens and antibodies

Serum from some patients with chronic idiopathic urticaria is known to have detectable histamine releasing activity (HRA). Based on this fact, Azuma et al. (2009a) published a unique report on patient factors in allergic reactions. They observed an activity similar to HRA in the pretransfusion serum of patients with transfusion reactions, that is, the ability to induce Ca influx in cultured mast cells (CaIA). This suggests that CaIA may be attributable to adverse reactions, especially urticaria-like manifestations (Azuma *et al.*, 2009). Since the influx of calcium is known to precede the release of histamine from mast cells (Ozawa *et al.*, 1993; Baba *et al.*, 2008), they speculated that serum samples showing CaIA activity might induce histamine release. Mast cells can be pre-activated to a certain extent. When allergic blood components are infused, mast cells tend to degranulate.

The team also found another blood transfusion reaction, indicating the presence of patient factors. This is a life-threatening hypotension after infusion of fresh frozen plasma containing CD36 (Nak) alloantibodies (Morishita et al., 2005). These CD36 antibodies showed the ability activate PLT mediated by Fc RIIa. to Interestingly, PLT from healthy human subjects showed considerable heterogeneity in reactivity to this plasma. The level of surface expression of CD36 and Fc RIIa of PLT and the degree of binding to these antibodies are obviously related to the significant difference in plasma PLT reactivity (Wakamoto et al., 2005). Passive Transfer of

Antibody and Passive Sensitization Passive Transfer of Antibody

In a study of 73,569 IgA-deficient blood donors, Vyas et al. (1975) found that 113 blood donors were IgA deficient. Of these, 13 have classspecific or high-titer IgA antibodies. However, no obvious adverse reactions were observed (Vyas et al., 1975). In another study, Winters et al. (2004) reviewed 22 apheresis PC transfusions from four IgA-deficient donors, in which no allergic reactions were observed with IgA antibodies. Therefore, passive transfer of IgA antibodies may not cause transfusion reactions. To date, there has been no report on the impact of passive transfer of antibodies to Hp. Therefore, the risk of immediate allergic reactions caused by passive transfusion of plasma protein antibodies appears to be very low.

Passive sensitization

The mast cells of patients and basophils are expressed in these cells when the patient is injected into the patient as part of the blood transfusion, generally a particular allergen and an IgE antibody against an inhalant allergen or a medicament. An IgE antibody injected through FC R will be captured. surface. This was the soft sensitization. Allergic reactions can occur after the patient ingests or inhaled these allergens. In one study, it was found that 23% of donors had significant levels of IgE antibodies against general allergens (Johansson et al, 2005). Therefore, the risk of passive sensitization due to blood and transfusion of plasma blood probably is not low.

Researchers in the same group then have two units containing known concentrations of IgE antibody (approximately 300 ml, each of the units of 8 to 205 km of antigen (kua) / L) and transfusion in living studies was. Patient (Johansson et al, 2005b). The IGE in translation, the plasma could be detected in the circulation of the recipient within 3 hours after blood transfusion. The half-life of IgE was $1 \cdot 13$ D. Axiction based on the base was obvious in samples of 3 h, and rapidly increased to the peaks after $3 \cdot 4$ D and then decreased for several weeks. This indicated that the IGE antibody against an allergen in particular could sensitize the patient's basophils.

Real examples of passive sensitization have also been reported. The branches and Gifford (1979) reported widespread urticaria of the recipients who received 2D cephalotin after all the blood transfusion of 4 donors. One of these donors was allergic to cephalotin and developed antibodies against antibiotics. Cephalotin antibodies were identified in blood after blood transfusion, but not before blood transfusion. Recently, a patented passive transfer case of allergy to the nut after blood transfusion was reported (Arnold et al, 2007). A non-active female patient received a blood transfusion in two FFP units. Two days later, ate muffin and peanut butter and had a sore throat, dyspnea, dysphagia and eruption in a few minutes. A week later, the skin irritation test of the peanut protein is positive and Peanut's specific

IgE level was 2 • 7 ku / l (normal level: 100 ku / l.

Plasma protein test

Test Plasma and IgA and HP proteins If the plasma protein antibodies can be performed first, IgG classes and IgE classes must be proven first. The road along the way is typically used to detect these defects and antibodies, and recently IgA was available to detect IGA deficiency and antibody (Palmer et al, 2012). Even if there is a transfusion blood product without identifying allergens and antibodies, the reaction is below, it is possible to investigate if it is essentially allergic based on a test.

Tripase test

Triputase is the serine proteinase based on more abundant secretory grain contained in obese cells. Increasing levels of whey triptase, plasma and other biological liquids consistent with the activation of the mast cell in general anaphylaxis and other immediate irritable allergic reactions (Schwartz et al., 1987, 1995). In the case of anaphylaxis mentioned above that occurred after the sensory transplantation of the peanut allergens, the level of serum triptase after this reaction was significantly higher, suggesting the ratio of cause between the reaction and blood transfusion (Jacobs et Al, 2011). Serum levels of Tryptasa were resurrected and supported by diagnosis (Dewachter et al, 2011.nubret et al, 2011 .nubret et al, 2011.nubret et al, 2011.nubret et al. In Japan, if the allergic reaction is suspected and the patient's serum sample is available, the Serum tripetarian levels are measured in patients suffering from non-enzymatic blood transfusion reactions. It has been shown that triptase tests are useful in the diagnosis of allergic transfusion reactions (Hirayama, 2010). But that has some inconveniences. Initially, it is often difficult to

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obtain a sample of a patient's serum for Tryptase tests for the middle life of short Tryptase, which only 2 hours after the release to circulation, and this is 2 hours after release to the circulation (Schwartz, 1990). Second, only small quantities of triptase produced by basophils, which are other mediators of allergic reactions (Castells et al, 1987, Foster et al, 2002). In contrast, the Basophilic activation test (BAT) is not limited with respect to the time of the patient samples collection, but can evaluate the activation of nebolic cells.

Basophil activation test (BAT)

BAT has recently been developed for the management of allergic diseases. In this test, a patient's whole blood sample is incubated with the allergen. Flow cytometry was then used to assess the activation of basophils, based on the upregulation of the cell degranulation/activation markers CD63 or CD203c (Bühring et al., 1999; Boumiza et al., 2005). This test has recently been applied to blood transfusion medicine. In the above three cases of allergic reactions after infusion of methylene blue-treated plasma, BAT was positive (Dewachter et al., 2011; Nubret et al., 2011). All three patients showed positive reactions to methylene blue and / or patent blue (a dye related to methylene blue that is more antigenic than methylene blue). One patient also tested positive for FFP-infused BAT.

We evaluated whether BAT can be used in 9 cases with allergic transfusion reactions and 12 cases without transfusion reactions using PCSN (Matsuyama et al., 2009). Since the patient's blood was not available, basophils were obtained from whole blood samples from healthy subjects. Three out of nine PCSN with allergic reactions activated basophils in at least one of the five blood samples. The degree of activation of basophils varies greatly between blood groups, indicating that patient factors are involved in the occurrence of allergic reactions. In contrast, only one of the 12 PCSNs without an allergic reaction caused basophil activation; this may be a false positive result for BAT because the PCSN was positive for BAT in only one of the five blood samples. Furthermore, the CD203c upregulation

is very small, close to the cutoff point. These data indicate that BAT may be a useful tool for managing allergic reactions to transfusions.

Allergic transfusion reactions are generally diagnosed based on symptoms and when they occur (ie, after a blood transfusion or after a blood transfusion). Plasma protein and antibody deficiency tests are not always performed. Even after completing these tests, they are usually negative. Therefore, in many cases of allergic reactions, there is no evidence other than that these reactions are essentially allergies and blood transfusions are the cause. If the residual blood from the transfusion is used for MTD and the patient's blood is positive, it can be concluded that transfusion caused a reaction. blood the Unfortunately, BAT has only just begun to be used in blood transfusion medicine. Therefore, its usefulness has not been fully evaluated. Furthermore, its sensitivity and specificity have not yet been determined (Hirayama, 2010). Therefore, a similar but larger study is needed to make a final assessment of BAT.

Prevention

Pre-transfusion medications

Paracetamol (a representative antipyretic) and diphenhydramine (a known antihistamine) are widely used as pre-transfusion medications to prevent transfusion reactions, although they lack evidence of their preventive effects.

Kennedy et al. (2008) conducted a large prospective, randomized, double-blind, controlled compared acetaminophen trial that and diphenhydramine as pre-transfusion drugs with placebo to prevent transfusion reactions, and focused on two main types of reactions: fever and allergy. The study drug was administered 30 minutes before the blood transfusion. Monitor the patient's reaction symptoms within 4 hours after the blood transfusion. A total of 315 eligible hematology / oncology patients were recruited. Among them, 62 people had reactions to blood transfusions and a total of 4199 blood transfusions occurred. Patients receiving active drug treatment received a total of blood transfusions in 2008 (1 •

44/100 blood transfusions) and 29 reactions occurred, while patients receiving placebo received a total of 2,191 blood transfusions (1 • 44/100 blood transfusions) .33 reactions. 51/100 blood transfusions). Most of these reactions (36/62) were urticaria in nature and occurred at the same rate between the active drug group and the placebo group. However, this study has limitations. Since patients with a history of allergic reactions are excluded, it is unclear whether diphenhydramine helps prevent recurrent reactions.

Sanders et al. (2005) conducted a retrospective study of 7,900 blood transfusions on 385 pediatric patients with cancer or in need of hematopoietic stem cell transplantation. The incidence of allergic reactions is 0 75%. In patients treated with diphenhydramine, allergic reactions were associated with $0 \cdot 9\%$ of blood transfusions, compared with $0 \cdot 56\%$ of patients who were not treated with this drug.

These two reports slightly support the common practice of pre-transfusion medication, especially for chronic blood transfusion patients. One disadvantage is that diphenhydramine may not be sufficient to prevent allergic reactions. However, this hypothesis has not yet been confirmed because the effects of more potent pre-drugs such as steroids are still unknown.

Conclusion

Although life-threatening allergic reactions occur rarely, allergic reactions occur more frequently. Washed platelets have been shown to be effective in preventing allergic reactions caused by blood transfusion, although a large number of platelets will be lost during the washing process, and the recovery of platelets after transfusion may be different from that of unwashed platelets.

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