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*Aleksandra Janusz, Joanna Janusz, Anna Grajewska, Krystyna Wieczorek, Joanna Józwa, Joanna Toborek, Maria Czachura, Joanna Skowrońska, Grażyna Domagała, Bożena Drybańska

Transfusion-associated mast cell activation syndrome (TA-MCAS) with course including EAR phase or EAR and LAR phases – hypothesis of a new complication upon transfusion of blood components

Poprzetoczeniowy zespół aktywacji mastocytów (TA-MCAS) przebiegający z fazą EAR lub fazami EAR i LAR – hipoteza nowego powikłania po przetoczeniu składników krwi

Regional Blood Donation and Blood Treatment Centre in Katowice
Director of Center: Stanisław Dyląg, MD, PhD

Keywords

MCAS, IgE, EAR, LAR class antibodies, transfusion-associated complication

Słowa kluczowe

MCAS, przeciwciała klasy IgE, EAR, LAR, powikłanie poprzetoczeniowe

Summary

Introduction. The global epidemiological data indicate an increase in the number of patients suffering from anaphylactic and anaphylactoid reactions. Both the anaphylactic and anaphylactoid reactions are connected with activation of mast cells (mastocytes).

Aim. The objective of the paper was explanation of the causes of occurrence of recurring allergic complication in patients upon blood component transfusion.

Material and methods. The analysis was conducted on results of laboratory tests and medical documentation of three patients with recurring transfusion-associated reaction.

Results. The following results were obtained: 1) despite the occurrence in patients of transfusion-associated complication in the form of allergy to plasma protein ingredients and antihistamine premedication recommended in such a case, another allergic reaction occurred in those patients after another transfusion; 2) transfusion of blood ingredients maximally deprived of plasma proteins, i.e. irradiated leukocyte-poor packed red blood cells washed and suspended in SAGM and irradiated leukocyte-poor blood platelet concentrate washed and suspended in SSP+, to patients did not result in any adverse clinical symptoms during and after the transfusion.

Conclusions. On the basis of the data from the literature and after the analysis of the studied cases, a hypothesis may be formed that the reason for reoccurrence of allergic complication following the transfusion of blood ingredients might be the LAR phase connected with the activation of mastocytes. Perhaps it would contribute to determine a new reaction in the group of transfusion-associated complications, i.e. TA-MCAS with the EAR and LAR phases. Understanding its mechanism and preventing its occurrence will increase the safety of transfusions carried out in patients.

Streszczenie

Wstęp. Światowe dane epidemiologiczne wskazują na wzrost liczby pacjentów z reakcjami anafilaktycznymi i anafilaktoidalnymi. Intensywność, charakter oraz zakres anafilaksji i reakcji anafilaktoidalnej może być lokalny, np. ograniczona pokrzywka i świąd mogą mieć charakter ogólnoustrojowy, czego wyrazem może być wstrząs anafilaktyczny stanowiący bezpośrednie zagrożenie życia. Zarówno reakcja anafilaktyczna, jak i anafilaktoidalna jest związana z aktywacją mastocytów (komórek tucznych).

Cel pracy. Celem pracy było wyjaśnienie przyczyn wystąpienia ponownego powikłania alergicznego, które stwierdzono u pacjentów po przetoczeniu składników krwi.

Materiał i metody. Analizie poddano wyniki badań laboratoryjnych oraz dokumentację medyczną trzech pacjentów z ponownym odczynem poprzetoczeniowym, które wpłynęły do Pracowni Konsultacyjnej Regionalnego Centrum Krwiodawstwa i Krwiolecznictwa w Katowicach.

Address/adres:

*Aleksandra Janusz
Regional Blood Donation and Blood Treatment Centre in Katowice
ul. Raciborska 15, 40-074 Katowice
tel. +48 (32) 208-73-32
ola.janusz@vp.pl

Wyniki. Uzyskano następujące wyniki: 1) pomimo wystąpienia u pacjentów powikłania poprzetoczeniowego o charakterze alergicznym na składniki białkowe osocza i zalecanej w takim przypadku premedykacji antyhistaminowej, u pacjentów tych po kolejnej transfuzji wystąpił ponowny odczyn o charakterze alergicznym; 2) przetoczenie pacjentom składników krwi maksymalnie zubożonych w białka osocza, tzn. NUKKCz przemywany i zawieszony w płynie SAGM oraz NUKKP przemywany i zawieszony w płynie SSP+, nie spowodowało podczas i po transfuzji żadnych niepożądanych objawów klinicznych.

Wnioski. W oparciu o dane piśmiennictwa oraz po przeanalizowaniu opisanych przypadków, można wysunąć hipotezę, iż powodem wystąpienia ponownego powikłania alergicznego po przetoczeniu składników krwi mogła być faza LAR związana z aktywacją mastocytów. Potwierdzenie tej hipotezy wymaga jednak wieloośrodkowych obserwacji klinicznych oraz specjalistycznych badań. Być może przyczyniłoby się to do wyłonienia w grupie powikłań poprzetoczeniowych nowego odczynu: TA-MCAS z fazą EAR i LAR. Poznanie jego mechanizmu i zapobieganie jego wystąpieniu zwiększy bezpieczeństwo przeprowadzanych transfuzji u pacjentów.

INTRODUCTION

The global epidemiological data indicate an increase in the number of patients suffering from anaphylactic and anaphylactoid reactions. They are becoming a significant social and medical problem. The intensity, nature and scope of anaphylaxis and anaphylactoid reaction can be local, e.g. limited urticaria and itch, or they can be of systemic nature, expressed by, for instance, anaphylactic shock posing a direct life hazard.

Both the anaphylactic and anaphylactoid reactions are connected with activation of mast cells (mastocytes). In the case of anaphylaxis, mastocytes are activated in the immunological mechanism in the IgE pathway, i.e. with the participation of IgE antibodies. This type of anaphylactic reaction is defined as type 1 hypersensitivity. Such anaphylaxis may also occur with participation of antibodies other than IgE, e.g. IgG antibodies. However, in such a case it is not connected with mastocyte activation and is defined as type 2 or 3 hypersensitivity. The activation of mastocytes through a non-immunological mechanism results in the development of an anaphylactoid reaction, or a pseudo-allergic reaction (1, 2).

The immunological-related activation of mastocytes is accompanied by two types of receptors binding IgE antibodies. These are:

- high-affinity receptor: FcεRI,
- low-affinity receptor: FcεRII.

The FcεRI receptor occurs in mastocytes, basophiles and antigen presenting cells (i.e. APCs), such as Langerhans cells and dendritic cells in the peripheral blood. The FcεRII receptor occurs in B and T lymphocytes, eosinophils, monocytes/macrophages, dendritic cells and thrombocytes. A receptor-mediated binding of a mastocyte with an IgE antigen-antibody complex induces its degranulation and results in *de novo* production of mediators of inflammation.

In the course of the anaphylactoid (pseudo-allergic) reaction, the degranulation of mastocytes occurs in a non-specific pathway which is not connected with antibodies directly. The factors triggering this type of reaction may be activated C3a and C5a complement fragments, known as anaphylatoxins, or chemicals and physical factor, e.g. mannitol, known as “releasers” (3).

The activation of mastocytes results in the following:

- secretion of mediators of inflammation, such as histamine, tryptase, platelet activating factor (i.e. PAF) and heparin,
- *de novo* synthesis of membrane lipids and arachidonic acid metabolites of the cyclooxygenase pathway (prostaglandins: PGD2, PGF2a, thromboxanes: TXA2) and the lipoxygenase pathway (leukotrienes: LTC4, LTB4, LTD4),
- secretion of chemokines, cytokines and growth factors, such as interleukins 1, 3, 4, 5, 6, 8, 10, 13, 16, TNF-alfa (tumour necrosis factor-alpha), TGF-beta (transforming growth factor-beta), GM-CSF (granulocyte-macrophage colony-stimulating factor), bFGF (basic fibroblast growth factor), FGF-2 (fibroblast growth factor-2), PDGF (platelet-derived growth factor), VEGF (vascular endothelial growth factor) and MIP-1 alpha (macrophage inflammatory proteins-1 alpha) (1).

In 2010 the specialist participating in Training Conference on Mastocyte Pathology proposed the name of Mast Cell Activation Syndrome (i.e. MCAS) for a syndrome of clinical symptoms occurring with the activation and degranulation of mastocytes (4). There are three variants of that syndrome, i.e.:

1. Primary MCAS – induced by monoclonal proliferation of mastocytes with the KITD816V genotype, occurring in the course of mastocytosis or of monoclonal mast cell activation syndrome (MMAS).
2. Secondary MCAS – characteristic of allergic diseases and atopy, occurring without monoclonal proliferation of mast cells.
3. Idiopathic MCAS – including the cases without:
   - clonal proliferation of mast cells,
   - occurrence of diseases with activation of mast cells,
   - presence of allergen-specific IgE antibodies (5).

Anaphylaxis may be induced by primary, secondary or idiopathic MCAS. The clinical symptoms of anaphylaxis are commonly associated with a clinical picture characterised by an IgE early allergic reaction (i.e. EAR). Depending on the organ exposed to the antigen, a patient may experience: pruritus, oedema and erythema of the skin, discharge of watery secretion from

the nose, sneezing or non-productive cough, wheezing breath and dyspnoea, developing within 10 to 20 minutes after the exposure to the antigen and subsiding usually after 1 to 3 hours. EAR symptoms are a consequence of the biological activity of mediators of inflammation, secreted after the degranulation of mast cells or produced *de novo* (6).

The latest studies have revealed that in 50% of patients, another phase of type 1 anaphylaxis may develop after the EAR phase, known as late allergic reaction (i.e. LAR). The risk of LAR increases along with the level of the antigen and the titre of specific IgE directed against that antigen. Clinically, between the EAR and LAR phases there may be an asymptomatic period of 1.3 to 28.4 hours on average. Most frequently, the initial symptoms of LAR develop 3 to 4 hours after exposure to the antigen. In the world literature, cases are however reported of LAR occurring even 48 hours after the EAR phase (6).

The pathogenesis of LAR is not understood fully. Nevertheless, it has been learnt that the mechanism of LAR is cellular infiltration, most probably induced by cytokines (i.e. IL-1, -4 and -5) and chemokines (eotaxin-1 and -2 and RANTES), secreted in mast cells, epithelial cells and other cells participating in EAR. The secreted mediators are a strong impulse resulting in an increased expression of adhesive particles located in the endothelium and leukocytes. The increased expression of adhesive particles facilitates the binding of intercellular adhesion molecule-1 (i.e. ICAM-1) on the endothelium with lymphocyte function-associated antigen-1 (i.e. LFA-1) and of vascular cell adhesion molecule-1 (i.e. VCAM-1) occurring on the endothelium with its ligand, very late antigen-4 (i.e. VLA-4), on leukocytes. This results in close adhesion and permeation of leukocytes through endothelium and chemokine-mediated migration to tissue. This phase is mainly accompanied by neutrophils, monocytes/macrophages, eosinophils, basophils and T lymphocytes. The neutrophils showed already 1 hour from exposure to the antigen. The activity of factors released from their cellular granules, e.g. lactoferrin and elastase, starts within 24 hours from provocation. The highest inflow of eosinophils to tissues occurs about 6 and 24 hours from the moment of the stimulation with the antigen. Eosinophils secrete mediators of inflammation, such as Major basic proteins (i.e. MBPs), eosinophil cationic proteins (i.e. ECPs), leukotrienes, LTC4 in particular, and cytokines (i.e. GM-CSF, IL-4 and IL-5). Their activity results in damage to tissues and organs, disorders of their functioning and further inflow of eosinophils to tissues.

Other cells present in the course of LAR are macrophages, Th2 helper cells, APCs, basophils and mast cells. The produce cytokines, including IL-4 and TNF-alpha, which result in intensification of the inflammatory reaction in the tissue microenvironment exposed to the antigen. The clinical symptoms of EAR and LAR are similar. Nevertheless, they differ in intensity. LAR is most frequently accompanied by cutaneous oedema in the form of infiltration, reddening of skin and its tenderness, contraction of bronchi of the bronchospastic type and oedema of nasal mucosa (7).

Figure 1 shows the mechanism and clinical symptoms of early phase EAR (A) and late phase LAR (B) of anaphylaxis with participation of IgE antibodies and the so-called “releaser” (chemical compound or physical factor).

The reason for MCAS and initiation of EAR and then LAR of anaphylaxis may be the transfusion of blood elements as it is connected with transfusion of large amounts of antigens. The binding of a mast cell with an immune complex, built of the donor’s antigen present in the transfused blood ingredient and the recipient’s IgE antibody, may induce the activation of those cells. Mediators of inflammation, released following the degranulation of mastocytes and synthesised *de novo*, may lead to the development of transfusion-associated complication in the recipient’s body. Transfusion-associated complications constitute a diverse group of adverse reactions to transfusion of blood ingredients (PRBCs – packed red blood cells, FFP – fresh frozen plasma), which generally occur during transfusion or shortly after it is completed. All adverse symptoms developing during transfusion of blood should evoke suspicion of a transfusion-associated reaction if there is no evidence that they are of other origin (8).

According to the current regulations, transfusion-related reactions in the form of anaphylaxis are classified due to the level of clinical symptom severity to allergic and pseudo-allergic reactions and anaphylactic shocks. Allergic reactions are frequent transfusion-associated complications. Their incidence ranges from 1:100 to 1:33 cases of blood ingredient transfusion. Transfusion-associated anaphylactic reactions are rather rare and occur in 1:20,000 to 1: 50,000 cases (8).

The etiology of allergic reactions is most often connected with IgE, IgM or IgG antibodies in the patient’s plasma, which can react with proper antigens present in the transfused blood element. Anaphylaxis in the allergic patient may be induced by any antigen able to react with specific antibodies directed against that antigen. The clinical symptoms usually occur after transfusion of FFP and blood platelet concentrate, which are a rich source of the donor’s plasma proteins, and PRBCs, the preserving and enriching fluid of which may be the source of the “releaser” and plasma proteins, to a lesser extent. Among the plasma proteins, IgA antibodies, haptoglobin and the C4 ingredient are the most frequent antigens present in the transfused blood element and reacting with proper specific antibodies detected in the recipient’s plasma (8).

If the recipient develops an anaphylactic reaction, the transfusion is to be immediately stopped, anaphylaxis controlled and the patient’s pulmonary function maintained. Adrenalin and anti-allergic medication are to be administered intravenously. After the symptoms subside, the transfusion of the blood element must

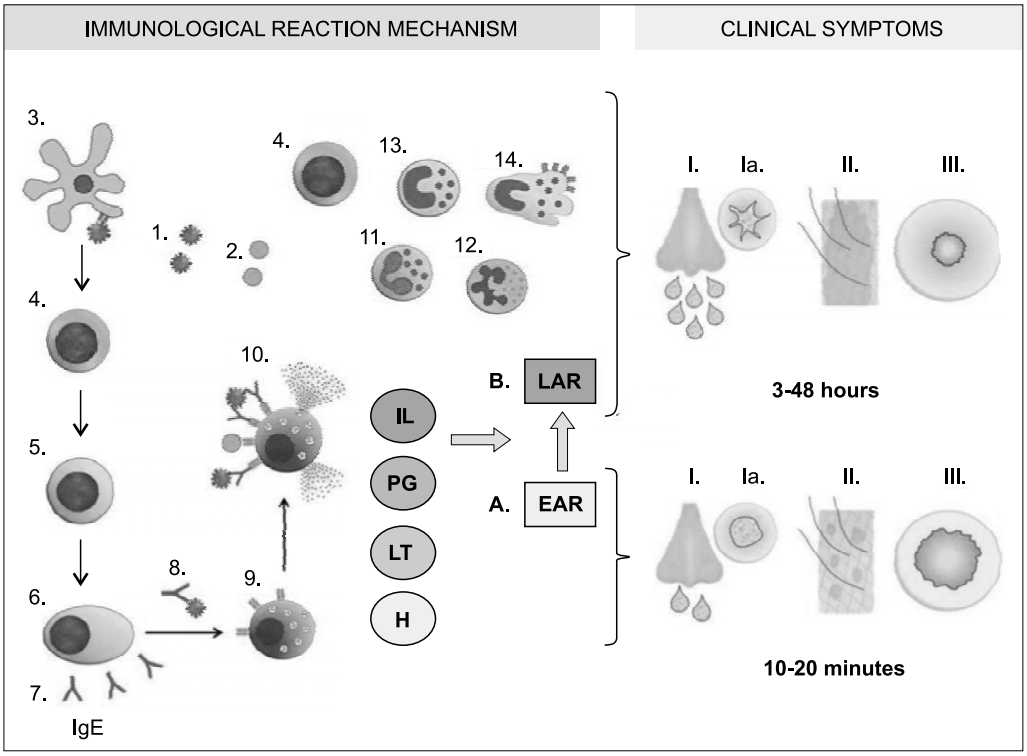

Fig. 1. Immunological reaction mechanism and clinical symptoms of early phase EAR (A) and late phase LAR (B) of anaphylaxis with participation of IgE class antibodies and the so-called "releaser" (chemical compound or physical factor)
The antigen (1) or "releaser" (2) is presented by the APC cell (3) to the Th2 lymphocyte (4) which, by means of glycoproteins and cytokines, exerts impact on lymphocyte B (5) undergoing specific activation and proliferation as well as transforming into a plasmatic cell (6), producing IgE class antibodies (7) that bind the antigen specifically forming an immunological antigen-antibody complex (8). The mast cell (9), having bound the immunological complex consisting of the IgE antibody combined bound with the antigen on its surface or having bound the so--called "releaser", undergoes degranulation (10), releasing the inflammatory process mediators: histamine (H) and, leukotrienes (LT: LTC4, LTB4), prostaglandins (PG: PGD4), interleukins (IL: IL-4, -5, -8) responsible for onset upon 10-20 minutes of such symptoms as: excessive mucous secretion (Ia) and oedema of the nasal mucosa (IIa), allergic hives (IIa) and bronchoconstriction (IVa)
(B) interleukins (IL: TNF-α, IL-4, -5, -6, -10, -13, GM-CSF) secret by mast cells (10) have a direct impact on revealing of the late phase (LAR) and stimulation of migration of inflammatory cells to tissues, such as: lymphocyte T (4), eosinophil (11), neutrophil (12), monocyte (13) transforming into a macrophage (14). The inflammatory condition is exacerbated and maintained by the inflammatory process mediators released by these cells, causing aggravation of clinical symptoms occurring in EAR upon 3-48 hours: intensive mucous secretion (Ib) and increased nasal mucosa oedema (IIb), redness and infiltration type skin oedema (IIIb), bronchospastic type bronchoconstriction (IVb)

not be continued. In the future, plasma (FFP) must not be transfused to the patient. Such transfusion may be carried out exclusively for life saving indications under intensive medical surveillance only. Plasma may be substituted with prothrombin complex factor concentrate. The used cellular blood elements should be entirely deprived of plasma, e.g. washed and suspended in 0.9% normal saline (0.9% NaCl). The following may also be transfused: PRBCs washed and suspended in plasma-replacement fluid, e.g. SAGM, and blood platelet concentrate washed and suspended in SSP+ (9).

Treatment of anaphylaxis includes the stopping of the transfusion and intramuscular or intravenous administration of anti-allergic medication. In the case of further transfusions, it is advisable to administer premedication 1 hour before the planned transfusion of blood element. Nonetheless, prevention of anaphylaxis in the recipient is not always effective (9).

AIM

The objective of the paper was explanation of the causes of occurrence of recurring allergic complication in patients upon blood component transfusion.

MATERIAL AND METHODS

The analysis covered medical documentation and laboratory test results of 3 patients, provided to the Consultation Centre of the Regional Blood Donation and Blood Treatment Centre in Katowice. The aim was to explain the causes of allergic transfusion-associated complications and to select adequate packed red blood cells (PRBCs).

First patient

A patient with acute myeloid leukaemia (i.e. AML) underwent transfusion of 300 ml of decanted irradiated leukocyte-poor blood platelet concentrate and did not develop any transfusion-associated complications.

5 days later the patient was transfused with 185 ml of irradiated leukocyte-poor blood platelet concentrate. 5 minutes after the transfusion the patient showed the following clinical symptoms: decreased pulse (from 114 BPM before the transfusion to 98 BPM after), anxiety, nausea and vomiting. Blood samples, medical documentation and residues of transfused blood were sent to the Regional Blood Donation and Blood Treatment Centre in Katowice to explain the causes of the transfusion-asso-

ciated complication. It was determined that the cause of the complication may have been an allergic reaction to protein elements in the plasma. No antibodies against red and white blood cell antigens were found. It was advised to administer antihistamine medication to the patient prior to the planned transfusion if it is necessary to treat them with blood elements.

Two days later, the patient was transfused with two units of FFP and 300 ml of irradiated leukocyte-poor blood platelet concentrate following the administration of antihistamine premedication (i.e. 0.75 mg of Clemastin). 10 minutes after the transfusion the patient developed a transfusion-associated complication again. Rash and reddening of skin were observed, which exacerbated two hours after the transfusion was completed. As a result of explanatory proceedings, it was indicated to continue premedication and transfuse irradiated and leukocyte-poor cellular blood elements.

48 hours later the patient was again in need for transfusion of irradiated leukocyte-poor blood platelet concentrate. Therefore, transfusion of 300 ml of such blood platelets was carried out with prior administration of 0.75 mg of Clemastin. 5 minutes after the transfusion, the patient's body temperature rose to 37°C, headache, abdominal pain appeared and there was a decrease in arterial blood pressure (from 120/80 before the transfusion to 100/60 after it was completed). It was advised to transfuse irradiated leukocyte-poor PRBCs and blood platelet concentrate, maximally deprived of plasma protein elements, i.e. irradiated leukocyte-poor PRBCs washed and suspended in SAGM and irradiated leukocyte-poor blood platelet concentrate washed and suspended in SSP+.

Within 2 subsequent months the patients was transfused with 9 units of irradiated leukocyte-poor PRBCs suspended in SAGM. During and after transfusions, the patient did not show any adverse clinical reactions.

Second patient

A patient with Ewing's sarcoma was transfused with PRBCs and no transfusion-associated complications followed.

6 days later the patient was transfused with 300 ml of decanted irradiated leukocyte-poor blood platelet concentrate and within 1 minute from transfusion the following symptoms occured: cutaneous pruritus, nausea and abdominal pain. Blood samples, medical documentation and residues of transfused blood were sent to the Regional Blood Donation and Blood Treatment Centre in Katowice to explain the causes of the transfusion-associated complication. On explanatory proceedings it was determined that the cause of the complication may have been an allergic reaction to protein elements in the plasma. No antibodies against red and white blood cell antigens were found. It was advised to administer antihistamine medication to the patient 1 hour before the planned transfusion.

Two days later, the patient was transfused with 180 ml of irradiated leukocyte-poor blood platelet concentrate following the administration of antihistamine premedication. 25 minutes after the transfusion the patient developed rash and reddening of skin. Another transfusion-associated complication was reported to the Regional Blood Donation and Blood Treatment Centre in Katowice. It was advised to continue transfusion irradiated and leukocyte-poor cellular blood elements and premedication prior to the planned transfusion.

The patient was not treated with blood elements again.

Third patient

A patient with acute lymphoblastic leukaemia (i.e. ALL) was transfused with PRBCs and blood platelet concentrate, upon which a rash of minimal severity was observed. No transfusion-associated complication was reported.

5 days later, the patient was transfused with 250 ml of irradiated leukocyte-poor blood platelet concentrate from apheresis following the administration of antihistamine premedication. 20 minutes after the transfusion the patient developed wheals from urticaria. Blood samples, medical documentation and residues of transfused blood were sent to the Regional Blood Donation and Blood Treatment Centre in Katowice to explain the causes of the transfusion-associated complication. No antibodies against red and white blood cell antigens were found in the serum of the patient. IgG antibodies not meeting the criteria for autoantibodies were found on the red blood cells of the patient. It was determined that the cause of the complication may have been an allergic reaction to protein elements in the plasma. Prior to subsequent transfusions, it was advised to administer antihistamine medication to the patient 1 hour before the planned procedure.

6 months later, the patient was transfused with 125-130 ml of irradiated leukocyte-poor PRBCs following the administration of antihistamine premedication. 80 minutes after the transfusion, the patient developed a spread macular and red rash and then reddening of skin. The transfusion-associated complication was reported to the Regional Blood Donation and Blood Treatment Centre in Katowice. It was advised to transfuse irradiated leukocyte-poor PRBCs and blood platelet concentrate maximally deprived of plasma protein elements, i.e. irradiated leukocyte-poor PRBCs washed and suspended in SAGM and irradiated leukocyte-poor blood platelet concentrate washed and suspended in SSP+.

In the subsequent days the patient was transfused with 3 units of irradiated leukocyte-poor PRBCs washed and suspended in SAGM. During and after transfusions, the patient did not show any adverse clinical reactions.

RESULTS

The analysis of laboratory test results, medical documentation and issued indications in the proceedings explaining transfusion-associated complications gave the following results:

1. After the transfusion of blood elements non-deprived of plasma proteins, patients developed an allergic reaction. Therefore, it was advised to administer antihistamine medication to the patients 1 hour before the planned transfusion.
2. Despite the occurrence of transfusion-associated complication in the form of allergy to plasma protein ingredients and administration antihistamine premedication indicated in such a case, the patients investigated in this study developed another allergic reaction after another transfusion.
3. Transfusion of blood elements maximally deprived of plasma proteins, i.e. irradiated leukocyte-poor PRBCs washed and suspended in SAGM and irradiated leukocyte-poor blood platelet concentrate washed in SSP+, to patients did not result in any adverse clinical symptoms during and after the transfusion.

DISCUSSION

So far, there are no reports on cases of LAR occurrence after transfusion of blood elements in the world literature. The time of occurrence of first clinical symptoms and duration of LAR after such transfusion is not known. The illustrated cases of LAR were concerned solely with inhalation and skin exposure to the allergen/antigen and occurred 3 to 4 hours following the exposure to that antigen on average, and the clinical symptoms may persist even for several days from the antigen stimulation, compared to EAR.

In the cases where anaphylaxis developed and antihistamine premedication proved ineffective, it would be advisable to extend medical observation to 48 hours after exposure to the antigen. It may be that it would make it possible to determine the occurrence point of transfusion-associated late phase of mast cell activation syndrome, which would allow for safer transfusion of blood elements. It is also justifiable as the occurrence of LAR is not prevented through administration of antihistamine medication. It was determined that antihistamine drugs influence EAR only while corticosteroids inhibit both EAR and LAR.

The patients in the case of whom antihistamine premedication proved ineffective are additionally offered the transfusion of washed and leukocyte-poor cellular blood elements maximally deprived of plasma proteins, e.g. irradiated leukocyte-poor PRBCs washed and suspended in SAGM. In the case of blood platelets concentrates, it is indicated to administer antihistamine medication and transfusion of irradiated leukocyte-poor blood platelet concentrate from apheresis washed and suspended in plasma-replacement fluid, e.g. SSP+.

So far, no complication occurring with late allergic reaction (i.e. LAR) and related to mast cell activation syndrome (i.e. MCAS) has been distinguished in the world literature. Non-treated LAR may result in lethal complications.

As in the studied cases the factors triggering MCAS were antigens present in a transfused blood element, most probably such as: plasma protein elements and elements of preserving or enriching fluid, the following name for the new transfusion-associated reaction may be suggested: Transfusion-associated mast cell activation syndrome (i.e. TA-MCAS). Its course may consist of one phase, i.e. EAR, or two phases, i.e. EAR and LAR. Therefore, "one-phase TA-MCAS" is suggested for the cases with EAR only and "two-phase TA-MCAS" for the cases with both EAR and LAR.

CONCLUSIONS

On the basis of the data from the literature and after the analysis of the studied cases, a hypothesis may be formed that the reason for reoccurrence of allergic complication following the transfusion of blood ingredients might be the LAR phase connected with the activation of mastocytes. Nevertheless, this hypothesis may be proved only upon multicentre clinical observations and specialised examinations. Perhaps it would contribute to determine a new reaction in the group of transfusion-associated complications, i.e. TA-MCAS with the EAR and LAR phases. Understanding its mechanism and preventing its occurrence will increase the safety of transfusions carried out in patients.

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received/otrzymano: 04.12.2015
accepted/zaakceptowano: 29.12.2015