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Perspective

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Transfusion reaction: A blind spot in autopsy

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Abstract

Although blood transfusion is generally safe, there are adverse events with varying severity even that can lead to death including Acute Haemolytic Transfusion Reaction (AHTR), anaphylaxis, bacterial sepsis, Transfusion Related Acute Lung Injury (TRALI) and Transfusion Associated Circulatory Overload (TACO). Transfusion Associated Graft vs Host Disease (TAGVHD) is a delayed type of reaction that can lead to death. Ascertaining the cause of death is complicated in such situations and multidisciplinary investigations are needed.
Serological investigations should be performed in the transfusion laboratory to detect haemolysis, immunological incompatibility, and bacterial contamination. In the postmortem examination AHTR can be diagnosed with serological investigations and presence of incompatible red cells can be identified in postmortem tissue samples by immune-histochemical methods. Detection of HLA antibodies in the respiratory tract tissues and intended donor investigations can confirm the diagnosis of TRALI. In a case of suspected bacterial contamination isolation of same organism in the postmortem blood and in the intended pack can conclude the diagnosis. In anaphylaxis, inflammation of the respiratory tract with eosinophilia can be seen and measuring the serum tryptase level is useful. In TAGVHD host tissue necrosis and lymphocyte infiltration are +seen and that can be confirmed by showing the DNA chimerism by PCR analysis.
Further studies are recommended to establish protocols and guidelines for postmortem examination following a transfusion reaction.

Keywords: *Blood transfusion, Transfusion reactions, Postmortem findings, Autopsy*

INTRODUCTION

Blood transfusion is a standard treatment in clinical practice. In some situations, clinical use of blood is essential as it cannot be replaced by any pharmacological agent (1). Blood transfusion is generally safe, but adverse effects can occur (2). Minor or less severe transfusion reactions are more common and significant or major transfusion reactions are rare (1). Among major transfusion reactions, there are reactions that can lead to death of the recipient (3). Therefore, proper documentation is important in blood transfusion and always informed consent must be taken from the patient (4).

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In case of a death following a transfusion of a blood component, it is necessary to rule out the transfusion reaction in ascertaining the cause of death. All documents and pre-transfusion and post transfusion samples together with the remainder of the intended blood unit must be preserved to arrange postmortem investigations. Diagnosing the exact reaction following the death may be difficult as reaction can affect more than one system of the body. Furthermore, a patient's underlying disease condition can also affect the outcome. Thorough examination and specific investigations need to establish a cause of death. Multidisciplinary approach would be helpful (5).

Acute transfusion reactions

Transfusion reaction is defined as any adverse outcome attributable to transfusion of a blood or blood components, occurring during or after transfusion. Depending on the time of presentation, transfusion reactions are categorized as acute or delayed (2). Acute transfusion reaction is a reaction that occurs during the transfusion or occurs within 24 hours after transfusion. Delayed transfusion occurs after 24 hours of completion of the transfusion. Based on pathophysiology, reactions can be classified as immunological and non-immunological. (Figure 1)

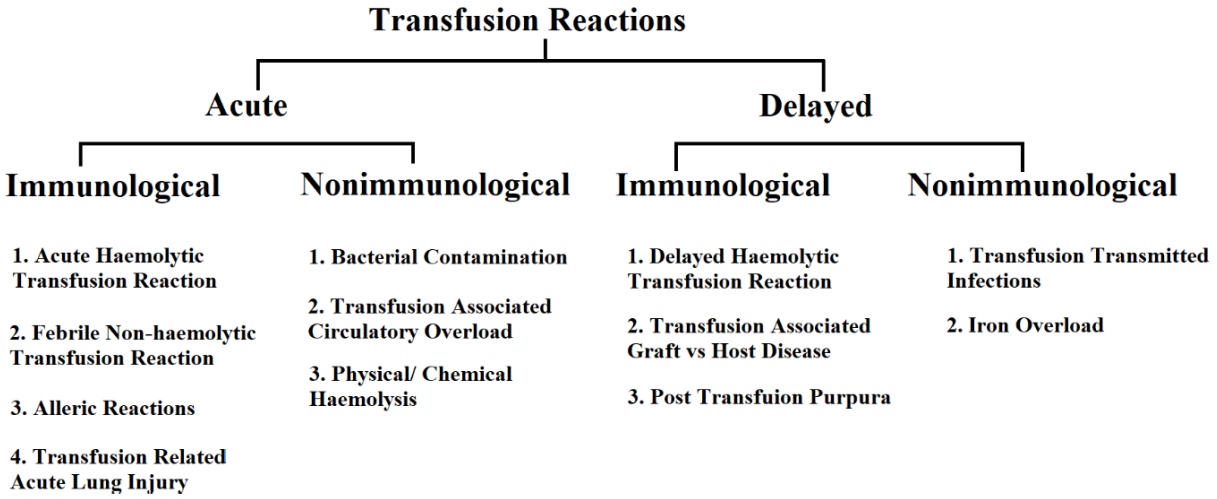

Figure 1

Among the acute transfusion reactions, reactions that can cause death are Acute Haemolytic Transfusion Reaction (AHTR) due to immunological or non-immunological causes, anaphylaxis, Transfusion Related Acute Lung Injury (TRALI), bacterial contamination and Transfusion Associated Circulatory Overload (TACO) (6). Transfusion Associated Graft Versus Host Disease (TAGVHD) is a rare but highly fatal adverse outcome of transfusion which usually occurs 1-6 weeks following transfusion.

According to the annual haemovigillance report, 2017 of National Blood Transfusion Service of Sri Lanka 3493 transfusion reactions are reported. Out of them only 231 were major events and 2 deaths were reported due to TACO.

Investigation of an acute transfusion reaction at the transfusion laboratory

Among the discovered blood group systems ABO grouping is the most important blood group system as ABO incompatibility can cause AHTR which may lead to death (7). Therefore, ABO incompatibility must be avoided always. But the majority of immune mediated AHTR occurs due to transfusion of ABO incompatible red cells due to clerical or administrative errors (1). A comprehensive documental check is essential following a suspected transfusion reaction (3). Guidelines on the investigation and management of acute transfusion reactions prepared by the Blood Transfusion Task Force of British Committee in Standards in Haematology recommends investigating all moderate to severe transfusion

reactions with laboratory investigations (8). This should include full blood count, renal and liver function tests, LDH and assessment of urine for haemoglobin and haptoglobin.

Direct Antiglobulin Test must be done and compatibility testing with blood grouping and antibody screening can be repeated in the transfusion laboratory with a new sample (6). Direct antiglobulin test is also indicated in the post transfusion sample. These serological investigations are useful in postmortem investigations also (5). Therefore, pre-transfusion sample, post-transfusion sample and the intended pack should be preserved for the investigations performed at the transfusion laboratory. But in serological investigations, Direct Antiglobulin Test (DAT) may be negative due to haemolysis of incompatible red cells; hence absorption elution test would be more practical (9). Urine sample is useful to identify haemolysis by examination for haemoglobinuria.

When bacterial contamination is suspected bacteriological investigations should be performed in the intended blood packs. Samples should be taken for cultures under sterile conditions. If available other products produced from the intended donation also can be used for those investigations. TRALI investigation should include antibody screening against Human Leucocyte Antigens (HLA) of the intended donor. HLA typing is also indicated. For those investigations tracing the intended donor and reviewing the relevant history is important.

Post-mortem autopsy findings

If AHTR has occurred due to ABO incompatibility, incompatible red cells can be identified in the tissues in the postmortem examination. Formaldehyde fixed paraffin embedded samples from the liver, kidney, spleen, and lung can be used for immuno-histochemical identification of transfused ABO incompatible red cells (10). Various techniques have been described for this. In 1986 Pedal I. et al have performed the indirect immunoperoxidase technique using monoclonal antibodies in paraffin embedded tissues (11). They have identified group A1 red cells in vessels and other organs of deceased group O recipients in which postmortem serology did not reveal evidence of incompatible transfusion. This method was published in another study as a highly sensitive test by Klír P in 1993 (12). Frontela Carreras L and coworkers have revealed that using immunofluorescence technique and counter-staining with p-phenylenediamine in tissues taken from the pharynx is helpful in making the diagnosis of ABO incompatibility in an autopsy (13). In autopsy examination mixed cell agglutination reaction can detect intravascular changes such as hyepreamia, stagnation and haemorrhage occurred in incompatible transfusion (14).

TRALI is a clinical syndrome that is characterized by acute onset of respiratory distress occurring during or within six hours after completion of transfusion without evidence of circulatory overload. 10% of cases are fatal (1). This is caused by the transfer of HLA and HNA antibodies and biologically active lipids with transfusion, and they can activate granulocytes leading to aggregation in the pulmonary microvasculature. A published autopsy case report has revealed massive pulmonary oedema and granulocyte aggregation in the pulmonary vasculature with extravasation into alveoli (15). But another case report has revealed bilateral pleural effusions and patchy areas of alveoli filled with fluid, without granulocyte aggregation and diffuse alveolar damage (16). When HLA antibodies are identified in the intended donor, an eluate from lung parenchymal tissue can be used to test to check the presence of the corresponding antibody in the recipient (17).
Anaphylaxis is also a potential adverse event which can cause death. In blood transfusion anaphylaxis can occur within 45 minutes after starting the transfusion (1). This can be caused by presence of antibodies to plasma components of the donor or passive transfer of antibodies from the donor. Diagnosis of anaphylaxis due to transfusion is same as for anaphylaxis caused by other substances. Serological investigations performed in the transfusion laboratory will be negative. In autopsy examination history will reveal variable combinations of symptoms including generalized flushing, urticaria, angio-oedema, vomiting, diarrhoea, conjunctivitis, rhinorrhoea, sneezing, and coughing; there may be loss of consciousness as a result of shock, or breathing difficulty caused by increased upper or lower airways resistance

leading to Asphyxia. More severe reactions can lead to respiratory or cardiac arrest resulting in sudden collapse and death (18). Macroscopic findings included signs of asthma (mucous plugging and/or hyper-inflated lungs), petechial haemorrhages, pharyngeal/laryngeal oedema, but for significant number of patients there will be nothing indicative of an allergic death (18). There will be airway obstruction by oedema and mucus. Microscopic examination of respiratory mucosa may show the evidence of inflammation with eosinophilia (19).

In blood investigations serum tryptase, which is a mast cell protease, level would be helpful (20) and they have revealed a value of 49.0 ng/mL in the published case report. But a five-year retrospective study done in autopsies of deceased due to anaphylaxis have identified a cut of level of 53µg/l for postmortem blood samples with a sensitivity of 89% and specificity of 93% (21). They have suggested this test should be performed with femoral blood and the test does not vary with other parameters. In another study it was found that high serum tryptase is a promising diagnostic biomarker for deaths due to anaphylactic shock, especially when it is higher than 30.4 µg/L (22). Expression of tryptase and chymase in mast cells in human lung tissue by immunofluorescence found that they were greatly increased in anaphylactic shock. It may provide morphological evidence and reference for the diagnosis of anaphylactic shock (23).

Bacterial contamination can occur in blood products. This is commoner in platelet concentrates as they are stored in room temperature to optimize their function during the storage. Transfusion of contaminated products can lead to fatal septic shock. There are fatal cases published due to transfusion of various blood products. In an autopsy carried out in a case of septic shock following platelet transfusion, rhabdomyolysis and neutrophil infiltration were identified (24). Autopsy materials contained the causative organism, Streptococcus pneumoniae, and it was isolated from the frozen plasma pack of the intended donation. In autopsy blood for microbiological investigations should be taken from cavities of the heart (25). For confirmation of the presence of the same organism in the body as well as in the intended pack, Polymerase Chain Reaction (PCR) can be useful (25). Sepsis can also lead to multiorgan failure.

TAGVHD, which is a delayed type of adverse event of transfusion, occurs due to inability to reject donor lymphocytes which leads to proliferation of donor lymphocytes resulting in host cell death and tissue destruction (1). Therefore, it is a multi-systemic condition. In an autopsy case report Otori K et al has demonstrated CD8+ lymphocyte infiltration of skin and liver lesions in a patient who died after 32days following transfusion (26). In the gastrointestinal tract there was crypt cell necrosis and degeneration of small bile ducts. Bone marrow hypoplasia was also noted. Definitive diagnosis of TAGVHD can be made with PCR analysis of DNA at microsatellite loci which shows DNA chimerism (27).

CONCLUSION

When a death occurs following blood transfusion, a transfusion reaction could be a cause of death. For ascertaining the cause of death reviewing the documented clinical history, examination findings and laboratory investigations are helpful. Serological investigations of the transfusion reactions should be performed in the transfusion laboratory. In autopsy depending on the circumstantial evidence thorough histological examination is suggested to rule out the diagnosis of the reaction. Established guidelines and protocols should be available to investigate for a transfusion reaction in a deceased. Further studies are recommended to establish protocols and guidelines.

Author declaration
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Conflicts of Interest:
The authors declare that there is no conflict of interest regarding the publication of this paper.

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