Delayed Hemolytic Transfusion Reaction - A Case Report

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Abstract

Blood transfusion is the process of receiving blood products into one's circulation intravenously. Transfusions are used in a variety of medical conditions to replace lost components of the blood .Transfusions of blood products are associated with several complications, many of which can be grouped as immunological or infection. *Acute hemolytic reactions* occur with transfusion of red blood cells and are due to destruction of donor erythrocytes by preformed recipient antibodies. Most often this occurs due to clerical errors or improper typing and cross matching. *Delayed hemolytic reactions* occur more frequently and are due to the same mechanism as in acute hemolytic reactions. However, the consequences are generally mild and a great proportion of patients may not have symptoms. However, evidence of hemolysis and falling hemoglobin levels may still occur. Treatment is generally not needed, but due to the presence of recipient antibodies, future compatibility may be affected. Hereby we share our experience of such a case of delayed hemolytic transfusion reaction and discussing the various measures to be taken during any such incidence and the biochemical and hematological tests to confirm the diagnosis.

Introduction

An ounce of prevention is better than a pound of cure as the anecdote goes, but, in certain situations, sometimes it's no use crying over spilt milk. It's beyond doubt that every medical procedure bears potential benefits as well as risks to patients, even in cases where transfusion of blood or blood products is contemplated. Blood transfusions, when indicated and performed correctly, can improve health and save lives. According to the American Society of Anesthesiologists, half of all the blood transfusions are done by anesthesiologists.[1] Blood transfusions are given to increase oxygen-carrying capacity and intravascular volume.

Theoretically, increasing intravascular volume is not an indication for blood transfusions because volume can be augmented with administration of crystalloids or some colloids. Practically, however, in acute hemorrhage, blood is given not only to increase oxygen-carrying capacity but also the intravascular volume.[3] Though infrequent, there are numerous adverse effects of transfusion; minor transfusion reactions such as fever and urticaria occur in approximately 1 in 100 transfusions. Major reactions are known to occur as well and have been well-documented in the literature, most common of which are hepatitis B or HIV infection, ABO hemolytic transfusion reactions and bacterial contamination.[2]

Case report

A 50-year old female patient (Mrs. Jayamma) reported to the oral & maxillofacial surgery outpatient clinic on September 9th 2011 with a right-sided painful swelling in the upper jaw in relation to the molars. Pain was dull, continuous and gnawing and increased on mastication of food and brushing teeth but relieved with analgesics. Before reporting to the outpatient clinic, the patient had undergone some dental treatment (details unknown) at a local clinic, from where she was referred to our unit for definitive management. The patient is married, and has one son. Her medical history was not contributory. On detailed local examination, a diffuse extra-oral swelling was noted over right maxillary sinus region; the overlying skin was normal. On palpation, it was tender. Intra orally, an ulcero-proliferative lesion, measuring about 3x2cm, was noted in relation to the right upper molars. The margins were everted and the lesion including its floor was covered with a pseudo-membranous slough; it was fixed to underlying structures

and bled on palpation. Mild right infraorbital nerve parasthesia was evident on objective evaluation. Regional cervical lymph node evaluation revealed palpable, non-tender, freely mobile right level 1B and 2B nodes. With all signs and symptoms included, a provisional diagnosis of a malignant epithelial tumor was arrived at.

Routine investigations included a hemogram and chest x-ray. A peripheral blood smear revealed normocytic hypochromic anemia. In view of the relatively low hemoglobin level i.e. 8gms/100ml, the patient was transfused three units of whole blood in order to attain optimum levels, preoperatively. However, no adverse events following transfusion were noted and, as a consequence, her hemoglobin levels were elevated to 10.6gm%. Conventional radiography that included an Orthopantomogram (OPG), a digital paranasal sinus (PNS) and maxillary occlusal views, demonstrated no more than periradicluar bone loss confined to the right upper permanent first molar, possibly leading to right maxillary sinusitis. Ultrasonography revealed a normal neck-node status and mild spleenomegaly. Computed tomography demonstrated a well-defined soft tissue mass (mean 55 HU) showing moderate enhancement (72-76 HU) in the right pre-maxillary area along the lateral wall of right maxillary sinus. Irregular cortical destruction of the infero-lateral wall of maxillary sinus and adjacent alveolar ridge including the anterior table of the right maxilla was also evident. Histopathological analysis of the excised specimen suggested moderately-differentiated squamous cell carcinoma, as per Broder's grading system.

Under general anesthesia, the patient underwent wide excision of the tumor (partial maxillectomy) and a right functional neck dissection (eradicating levels 1A, 1B, 2A, 2B & 3). The defect was reconstructed using a palatal transposition (rotation) flap. Intraoperatively, around 4 hours after commencement of surgery, the estimated blood loss was 350ml, and in view of patient's anemic condition, blood transfusion was started. But after 10minutes of transfusion, clear blood-tinged urine was noted and so transfusion was stopped immediately. The transfused blood sample was returned to the blood bank for incompatibility and direct antiglobulin test (Direct Coomb's test); both the test results were negative. Post-operatively, again, the same blood was transfused and, after 10 minutes, the same phenomenon (clear blood-tinged urine) was observed. Though in immediate hemolytic transfusion reactions, signs and symptoms such as fever with or without chills, anxiety, chest/back pain, flushing, dyspnoea, tachycardia and hypotension are noted, the patient did elaborate some of them despite the reaction being a delayed one. The concerned surgeon, anesthesiologist and physician then decided not to continue with the transfusion or transfuse any other blood product. Since the patient's hemoglobin levels post operatively had dropped to 7.4gm%, the patient was put on hematinics. However, despite undesirable hemolytic events, the patient's vital parameters were closely monitored and maintained within normal limits.

Table 1 :

Laboratory investigations:

INVESTIGATIONS	PRE-OPERATIVE	POST-OPERATIVE
Hemoglobin	10.6 gm%	7.4 gm%
Hematocrit	31%	21%
Total Leucocyte Count	7900 cells/mm^3	4900 cells/mm^3
Erythrocyte Count	4 million cells/mm^3	3.11 million cells/mm^3
Platelet Count	1.8 lakhs/mm^3	1.17 lakhs/mm^3
Erythrocyte Sedimentation Rate	45 mm at the end of 1hour	30 mm at the end of 1 hour
Serum Urea	35 mg%	44 mg%
Serum Creatinine	1.1 mg%	0.7 mg%
Prothrombin Time	18 sec	15 sec
INR	1.63	1.24

Activated Partial Thromboplastin Time	38 sec	36 sec
Serum Calcium	8.3 mg%	7.8 mg%
SGOT	34 IU/L	70.0 IU/L
SGPT	38 IU/L	20.0 IU/L
Serum Alkaline Phosphatase	149 IU/L	59.0 IU/L
Albumin	3.0 mg%	3.1 mg%
Globulin	2.6 mg%	2.7 mg%
Total Bilirubin	0.6 mg%	2.3 mg%

Discussion

Transfusion reaction may be defined as 'any unfavorable transfusion related event occurring in patient during or after transfusion of blood and blood components'.[3] Adverse transfusion effects can be either of immunologic or non-immunologic origin, depending on the presence or absence of antibody production.

Immunologic caused by stimulation of antibody production by foreign alloantigens present on transfused red cells, leucocytes, platelets, plasma proteins.

- ✓ Alloimmunization
- ✓ Hemolytic transfusion reaction
  - Immediate hemolytic transfusion reaction (IHTR)
  - **Delayed hemolytic transfusion reaction (DHTR)**
- ✓ Febrile transfusion reaction
- ✓ Transfusion related acute lung injury
- ✓ Allergic
- ✓ Graft-versus-host disease

Non Immunologic not caused by stimulation of antibody production by foreign alloantigens present on transfused red cells, leucocytes, platelets, plasma proteins but by:

- ✓ Volume overload
- ✓ Massive transfusion
- ✓ Infections -
  - Hepatitis A, B, C
    - HTLV-1
    - CMV
    - EBV

Hemolytic transfusion reaction

The most serious complication of blood transfusion results from interactions between antibodies in the recipient's plasma and surface antigens on donor's RBCs. Blood group antibodies are either naturally occurring or immune in origin. Naturally occurring antibodies are present in the plasma of individuals who lack corresponding antigens. The most important are anti-A and anti-B, and they are usually if IgM class. [4] Immune antibodies develop after a subject's exposure to RBCs expressing antigens which they lack. This results from previous blood transfusion or transplacental passage during pregnancy (commonly IgG in origin). [5] Hemolysis can occur immediately within the circulation or more slowly within the reticuloendothelial system.

Immediate Hemolytic Transfusion Reaction (IHTR)

IHTR are most typically associated with ABO incompatibility because anti-A and anti-B antibody are predominantly IgM and are capable of binding complement with immediate destruction of cells. [4] An IHTR caused by ABO incompatibility is rare and is usually caused by clerical error.

Pathophysiology

Primary event is the interaction between antibody and red cell stroma resulting in the development of immune complexes and the activation of complement system (leading to release of C3a and C5a) and the coagulation mechanism via cytokines and factor XII. Renal failure may occur mostly due to the obstruction of renal tubules by free hemoglobin. [6]

Signs and symptoms

Hemolytic reaction occurs soon after the incompatible transfusions.

Fever with or without chills

Anxiety

Chest/back pain

Flushing

Dyspnoea

Tachycardia

Hypotension

If the patient is under general anesthesia these symptoms will not be present, only severe hypotension and evidence of oozing or hemoglobinuria will serve as clues to the presence of hemolytic reaction. This can lead to acute renal failure and intravascular coagulation. [1,5]

Management

- Transfusion must be discontinued.
- Post-transfusion sample and the discontinued bag of blood should be sent to blood bank for investigations.
- Intravenous normal saline should be started to maintain blood pressure and to increase urine flow.
- Diuretics like furosemide (20-100mg I/V) can be given.[6]
- If oliguric renal failure is present then Dopamine may be effective against hypotension and impaired renal perfusion. Once renal failure is established the usual supportive measures including fluid resuscitation, management of electrolyte balance, dialysis is required.

Delayed Hemolytic Transfusion Reaction (DHTR)

This condition is milder and is predominantly extra vascular and involves the destruction of red cells after an interval of time, usually 3 to 21 days following transfusion, with most occurring about 7 days post-transfusion.[4]

Delayed hemolytic transfusion reaction occur when an alloantibody that are undetected in pre-transfusion antibody screening test increase in strength following secondary antibody response to transfused red cells processing the corresponding antigen. Antibodies of several blood group systems may cause delayed hemolytic transfusion reaction with antibody in the Rh (anti-D), Kidd (anti-Jk^a), Kell (anti-K) and Duffy (anti-Fy^a) system.[2]

Pathophysiology

Restimulation by red cells positive for the corresponding antigen to patients weak undetectable alloantibody cause the memory B cells to differentiate to antibody producing plasma cells. As new IgG antibody is produced it sensitizes transfused donor cells with antigen .The IgG sensitized donor cells are removed by extra vascular hemolysis mainly in spleen. [1,5,6]

Clinical presentation

Fever with or without chills.

Unexplained dropping in hemoglobin and hematocrit. [4]

Transient jaundice due to increase in bilirubin. [4]

Treatment

No specific therapy.

Alternatives to transfusion.

Investigation into hemolytic transfusion reactions as per the American Association of Blood Banks norms: [7]

If there are symptoms or findings suggestive of a hemolytic transfusion reaction, transfusion must be stopped and following must be performed:

- Check all labeling on blood containers and documentation
- Properly labeled blood sample must be obtained from patient and sent to transfusion laboratory along with the original transfusion bag and infusion set.
- Post reaction serum must be inspected for evidence of hemoglobinuria.A direct antiglobulin test must be performed and if positive must be compared with pre reaction sample
- Visual inspection of the urine for hemoglobinuria.
- Repeat ABO and Rh testing on pre and post transfusion samples and on donor units.
- Repeat the cross-matches pre and post transfusion samples.
- Repeat antibody screen on pre and post transfusion samples.

Hematology tests for confirming hemolysis:

- Red cell osmotic fragility.

- Peripheral blood film.
- Reticulocyte count.

Biochemical tests to confirm hemolysis:

- Haptoglobins.
- Methemalbimin.
- Lactate dehydrogenase.
- Bilirubin
- Tests for hemoglobinuria and hemosiderinuria

Conclusion

Since the transfusion reaction occurred without any serious clinical complications such as hypotension, cardiac arrest or acute renal failure after the fourth blood transfusion (no adverse events were noted during and after transfusion of the first 3 units), it can be concluded that the hemolytic transfusion reaction is of the delayed type, manifested by hemoglobinuria, a significant drop in hemoglobin (7.4gm%) and hematocrit (21%) levels accompanied by raised bilirubin (2.3mg%) levels. Delayed hemolytic transfusion reactions often manifest by a decrease in post-transfusion hematocrit only and not with any serious effects that could entail patient death. [1]

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