Case Report

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Is it an acute pain transfusion reaction?

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Abstract:

A 40-year-old male patient presented to the emergency department with complaints of anasarca, mild dyspnea, orthopnea, vomiting, and decreased urine output. A provisional diagnosis of chronic kidney disease was made and planned for hemodialysis. In view of severe anemia, 1 packed red blood cell (PRBC) was requested and after pretransfusion testing one unit of buffy coat-poor, nonleucofiltered, coombs cross-match compatible, fresh (<7-days old) saline-adenine-glucose-mannitol PRBC unit was issued. After transfusion of around 20 ml of red cells patient developed sudden onset of excruciating pain in the lower back and hip joints, tachypnea, and breathlessness with oxygen saturation dropping to 82%. Vitals were normal and patient remained afebrile. After stopping transfusion, supplemental oxygen and opioid analgesic were given. Once the symptoms subsided, transfusion was completed. A complete work-up was done to rule out other adverse reactions. Thus, this patient experienced what is known as an acute pain transfusion reaction.

Keywords:

Acute pain transfusion reaction, cytokines, pain, transfusion reaction

Introduction

Adverse reactions to transfusion of PRBCs is not uncommon. Reactions may occur immediately during transfusion to hours or days after completion of transfusion. These include allergic reactions, febrile non-haemolytic reactions (FNHTR), haemolytic transfusion reaction (HTR), transfusion-associated circulatory overload (TACO), transfusion-related acute lung injury (TRALI), transfusion-associated sepsis (TAS), acute hypotensive transfusion reaction (AHTR), transfusion-associated dyspnoea (TAD) and post transfusion purpura (PTP). Acute pain transfusion reaction is characterised by acute, severe pain involving joints, particularly in the back and trunk seen immediately after transfusion when other causes of transfusion reactions are ruled out. Other clinical features may include hypertension, tachycardia, and dyspnoea and some patients may experience pain located only in the limb used for transfusion.[1]

Case Report

A 40-year-old male presented with complaints of anasarca, dyspnea, anuria, and left-sided pleural effusion was admitted with provisional diagnosis of chronic kidney disease. He also had history of headache, loss of appetite, fatigue, orthopnea, and on and off chest pain and occasional vomiting after food intake. He had a history of hypertension since 3 months but was not on any medication. His blood pressure at presentation was 170/100 mm of Hg but all other vitals were stable. His initial investigations showed hemoglobin - 6.6 gm%, white blood cell (WBC) - 7370/uL, platelet count - 60,000, red blood cell - 124 mg/dL, blood urea nitrogen - 142 mg/dL, creatinine - 8.0 mg/dL, serum K^+ - 5.6 mEq/L, chest X-ray showed mild left-sided pleural effusion, arterial

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blood gas showed metabolic acidosis with respiratory compensation and electrocardiogram was normal. Ultrasonography kidneys, ureters, and bladder showed poor corticomedullary differentiation and decreased size of bilateral kidneys suggestive of chronic kidney disease. The patient was taken up for hemodialysis. The patient had no history of previous transfusions. After pretransfusion testing one unit of buffy coat-poor, nonleucofiltered, coombs cross-match compatible, fresh (<7-days old) saline-adenine-glucose-mannitol (SAGM) packed red blood cell (PRBC) unit was issued but transfusion was started almost 4 h after the issue of PRBC with no cold chain maintenance during this period. After around 20 ml of transfusion, the patient developed sudden onset of excruciating pain in the lower back and hip joints, tachypnea, and shortness of breath with oxygen saturation dropping to 82%. Patient's vitals did not vary much from the predialysis levels and remained afebrile throughout. Transfusion was stopped immediately and supplemental oxygen and injection tramadol 50 mg and injection diphenhydramine 25 mg were given intravenously. Hemodialysis was completed uneventfully after the reaction subsided. A complete posttransfusion reaction work-up was initiated as per blood bank protocol beginning with bedside confirmation of correct product and patient identification. Clerical errors were ruled out. Hemolysis check in the returned PRBC unit (3 days old) was done. No hemolysis in the returned PRBC unit was obvious as well as in the posttransfusion sample. The postreaction patient grouping was matching with the patient's pretransfusion sample with a negative direct antiglobulin test. Repeat grouping of the PRBC unit matched the unit label. Repeat testing of the full-cross match to both the patient's prereaction sample and postreaction sample confirmed compatibility of the unit. Peripheral blood smear did not show any schistocytes and serum indirect bilirubin was in normal range. Thus, hemolytic transfusion reaction was ruled out. Culture of the PRBC unit causing the reaction and posttransfusion reaction blood sample from the patient was also sterile. Chest X-ray showed no features suggestive of pulmonary edema. Second session of hemodialysis was completed uneventfully after an interval of 48 h without blood transfusion which rules out the pain manifestation and the reaction occurring due to hemodialysis-related factors. Other causes of lower back pain including spinal disorders/nerve compression, blood clots, varicose veins, and poor circulation had been ruled out before admitting the patient in the hospital as well as soon after the reaction by the concerned treating physician.

Discussion

Acute pain transfusion reaction (APTR) is a very rare and poorly understood transfusion reaction which can occur during or after the transfusion of blood products. The few published case reports on APTR also describe clinical manifestations similar to those experienced by our patient. The diagnosis of APTR should be made after all other causes of transfusion reactions are ruled out based upon negative immunohematological and other laboratory work-up.[1] Orton *et al*. in their multi-center retrospective analysis of over 29,000 medical records of patients receiving blood transfusion found 8% (12 reports) of transfusion reactions that were attributable to APTR. The clinical manifestations that were observed in those 12 reports were severe chest, back, or proximal extremity pain, tachypnea and/or dyspnea, hypertension, and tachycardia.[2] Review of the few published case reports reveals no underlying mechanism regarding the pathophysiology of this reaction. Similarly, in this case study, posttransfusion reaction laboratory workups were negative for any other causes of acute transfusion reaction. The review of few published case reports on APTR reveals this type of reaction occurs in patients with any underlying diagnoses. However, there seems an association between prestorage leukocyte-reduced blood products and APTR as evident in the published case reports.[1-3] However, in our case, the PRBC unit which caused the reaction was a nonleukoreduced buffy-coat poor SAGM PRBC unit.

It is well known from evidences that majority of transfusion reactions are mediated by cytokines (mainly interleukin [IL]-1β, IL-6, IL-8, tumor necrosis factor [TNF]-α and regulated on activation, normal T cells expressed and secreted) released from contaminating WBCs in stored blood. This has also been proven by the fact that leukoreduction significantly decreases febrile nonhemolytic transfusion reaction and may decrease cardiopulmonary transfusion reactions (transfusion-related acute lung injury and transfusion-associated circulatory overload) by reducing leukocyte-mediated cytokine release in stored blood.[4] The role of cytokines in APTR has not been studied and established. Interestingly, most published case reports of APTR have occurred after transfusion of leukoreduced blood products. This indicates the etiology of APTR may be due to factors other than cytokines. However, Weisbach *et al*. in their study demonstrated that there was no reduction in IL-8 levels by leukoreduction but IL-1 β and TNF-α levels were significantly reduced by leukoreduction until the end of storage period of RBC. This basal accumulation of IL-8 in PRBCs could not be prevented by leukoreduction because Fya and Fyb antigens present on RBCs are receptors for IL-8 which bind IL-8 and thus this previously bound IL-8 gets released from these receptors during storage of PRBCs which explains why IL-8 accumulation could not be prevented by leukoreduction.[5] IL-8 has been demonstrated to be a mediator of sympathetic pain in rat models by Cunha *et al*. in their study.[6] Proinflammatory cytokines mainly

IL-1 β, TNF-α, and IL-6 have been described to have an association with inflammatory and pathological pain in humans. IL-8 have also been implicated in inflammatory hyper nociception in cancers.[7] The accumulation of cytokines in the PRBC unit which caused the reaction cannot be explained in this case as the PRBC unit was very fresh (<3 days old). However, Weisbach *et al*. also demonstrated in their study that temporary warming caused an increase in IL-8 concentrations in PRBCs whereas there was no effect on IL-β and IL-6 but TNF-α was slightly elevated. Temporary warming of PRBCs allows greater metabolic activity of cytokine-producing WBCs and gives them the opportunity to synthesize and secrete cytokines at higher rates.[5] In our case, the PRBC unit was lying unattended in the hemodialysis room for around 4 h in room temperature that may have caused WBCs to secrete cytokines. However, this kind of clinical scenarios where PRBC units not being under cold chain maintenance after being issued from the blood bank may be common in hospital like ours where there is 100% bed occupancy and >50,000 blood products being transfused to patients annually and not all of these transfused patients get acute pain transfusion reaction. In this scenario, cytokine levels in the blood bag could not be measured as the entire bag was eventually transfused to the patient. Hence, additional investigational studies are needed to establish the etiology of this severe acute transfusion reaction.

Conclusion

APTR is a rarely reported event as clinicians are not aware of this transfusion reaction, particularly when pain manifestations are delayed after the completion of transfusion of blood products. Thus, an increase in awareness regarding this transfusion reaction phenomenon is needed for its recognition and reporting to take place.

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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