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Acute exacerbation of subclinical pulmonary fibrosis following red cell transfusion: a case report

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Abstract

Background—Red cell transfusion is associated with lung injury in susceptible hosts, although many cases do not meet criteria for transfusion related acute lung injury. Patients with underlying pulmonary fibrosis can exhibit precipitous deteriorations in respiratory status of unknown etiology defined as acute exacerbations due to superimposed lung injury syndrome. It is unclear whether red cell transfusion is associated with acute exacerbation of underlying pulmonary fibrosis.

Case Report—We describe a patient who underwent an uneventful elective left total hip replacement but developed anemia post-operatively. Twenty-four hours following transfusion of her fifth non-leukoreduced AS-5 red cell unit, she developed new bilateral airspace infiltrates associated with progressive hypoxemia. These RBC units were 35-38 days old. Despite supportive care and diuresis, patient remained profoundly hypoxemic with infiltrates that progressed to fibrosis.

Results—The patient had mild sub-clinical lower-lobe predominant interstitial pulmonary fibrosis but developed diffuse bilateral ground glass opacities with areas of consolidation 24 h after receiving her last RBC unit. Transbronchial biopsy of the right lower lobe showed active organizing pneumonia and underlying interstitial fibrosis, supporting the clinical diagnosis of acute exacerbation of pulmonary fibrosis. The bronchoalveolar lavage showed progressive bloody effluent, consistent with diffuse alveolar hemorrhage, a marker of lung injury. There was no evidence of viral inclusions, fungal elements, pneumocystis, or bacterial organisms.

Conclusion—Transfusion of multiple units of aged RBCs was temporally associated with an acute exacerbation and rapid progression of underlying sub-clinical pulmonary fibrosis.

Keywords

transfusion; acute exacerbation; pulmonary fibrosis; lung injury; red blood cells

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Introduction

Acute exacerbation of idiopathic pulmonary fibrosis is a well-recognized entity that is defined by a precipitous decline in respiratory status that is not explained by any identifiable cause, associated with histologic evidence of acute lung injury superimposed upon underlying interstitial fibrosis, and generally portends a poor outcome¹⁻². The diagnostic criteria for an acute exacerbation includes: (1) a clinically significant increase in dyspnea or cough within days (< 30 days) requiring additional medical care; (2) worsening gas exchange (decline $\geq 5\%$ in resting room air oxygen saturations or decline of ≥ 8 mmHg in resting room air partial pressure of oxygen in arterial blood (PaO₂) from last recorded level); (3) new airspace infiltrates on chest radiograph or new, ground glass opacities or consolidative processes by computed tomography (CT) scan; (4) absence of identifiable cause for the respiratory decompensation such as infection, pulmonary thromboembolism, cardiac events, or pneumothorax. Red blood cell (RBC) transfusion as a possible trigger for acute exacerbation has not been reported.

Case Report

A 62 year-old woman underwent an elective left minimally invasive total hip replacement with structural femoral head autograft and internal fixation to acetabulum under spinal anesthesia. The patient had a history of psoriasis and a remote episode of paroxysmal atrial fibrillation 14 years prior to admission for which she was treated with amiodarone, digoxin, coumadin, and metoprolol for approximately 2 years. Patient was currently taking a diclofenac 75 mg/misoprostol 200 mg tablet twice a day, used a fentanyl 25 microgram transdermal patch every 72 hours, and Tylenol with codeine #3 tablet every 4 hours as needed for her osteoarthritis pain. She was allergic to oxycodone, sulfadiazine, and penicillin. The patient did not drink alcohol, had no history of illicit drugs, and quit cigarette smoking 23 years ago. She lived alone with her 2 dogs and 1 parrot. She has lived with her parrot for 18 years. The patient's pre-operative chest radiograph 3 months prior was interpreted as without infiltrates but showed blunted right costophrenic angle (Figure 1). As the patient had no respiratory complaints, no further evaluation was performed pre-operatively. The patient's pre-operative hemoglobin concentration was 14 g/dL.

The patient's operative case was uneventful, lasting 105 minutes. The patient received 3000 mL of crystalloid, 500 mL of the colloid Hextend, and 135 mL of cell saver. The patient's estimated blood loss was 400 mL and the urine output was recorded as 600 mL intra-operatively. Her initial post-operative course was uneventful except for an episode of paroxysmal atrial fibrillation with heart rate of 113 treated with metoprolol. She was slowly weaned down to 2L of oxygen by nasal cannula throughout the day of surgery (hospital day 1).

Twelve hours following surgery, her hemoglobin was noted to be 6.2 g/dL. There was no evidence of hemorrhage at the surgical site or from gastrointestinal sources. The patient was transfused with a total of 5 units of RBCs over the course of the next 2 days (hospital days 2-3). All 5 units were non-leukoreduced and were between 35-38 days old. Immediately following the 5th RBC unit, her oxygen saturation was 95% on room air and her post-transfusion Hb was 10.2 g/dL. She was scheduled to be released 24 hours after the 5th RBC transfusion (hospital day 4), however at that time she complained of increasing dyspnea. Her room air saturation was recorded at 92% and she was placed on nasal cannula. Intravenous heparin was empirically initiated while awaiting evaluation for an acute thromboembolism. A CT angiography of the chest with intravenous contrast was performed which showed no evidence of pulmonary thromboembolism, and the heparin was discontinued. A mild usual interstitial pneumonia (UIP) pattern of pulmonary fibrosis was found on the chest CT, as

evidenced by lower lobe juxtapleural honeycombing and traction bronchiectasis (Figure 2C). There was superimposed diffuse multi-focal ground glass opacity and consolidation bilaterally (Figure 2A-B).

An echocardiogram was performed showing normal left ventricle size, normal systolic and diastolic function, moderate pulmonary hypertension, and dilated inferior vena cava consistent with increased right atrial pressure. A brain natriuretic peptide level was 583 pg/mL (normal level < 100 pg/mL). On hospital day 6, the patient developed progressively worsening hypoxemia with oxygen saturations at 80%, requiring 15 L oxygen by non-rebreather mask, and paroxysmal atrial fibrillation with rapid ventricular response. The patient was transferred to the intensive care unit and her heart rate was controlled with intravenous diltiazem and metoprolol.

She received 40 mg of intravenous furosemide for possible volume overload and voided 1.5 liters of urine upon admission to the intensive care unit without significant improvement in her respiratory status. Intravenous methylprednisolone at 40 mg every 12 h and broad-spectrum antibiotics were initiated given the chest radiograph findings of diffuse bilateral opacities of unclear etiology and severe hypoxemia.

The patient's respiratory status failed to improve following diuresis and empiric treatment with antibiotics. She underwent fiberoptic bronchoscopy on hospital day 19 due to persistent diffuse infiltrates on chest x-ray and hypoxemia. Bronchoalveolar lavage showed progressively bloody effluent, indicative of diffuse alveolar hemorrhage, a marker of lung injury. There was mild to moderate acute inflammation and a few macrophages on cytologic exam. There was no evidence of viral inclusions, pneumocystis, or fungal elements. Transbronchial biopsy of the right lower lobe showed acute organizing pneumonia with reactive pneumocytes and interstitial fibrosis. There was mild acute and chronic lymphocytic bronchitis and bronchiolitis.

The patient remained on 8-10 L oxygen with oximizer and 15 L facemask when performing any physical activity throughout her hospital course. She was maintained on corticosteroids, as attempts to taper them resulted in clinical deterioration. The patient was evaluated for lung transplantation. The patient's culture from the initial bronchoalveolar lavage on hospital day 19 grew *Mycobacterium gordonae* by hospital day 46. Both Infectious Disease and Transplant Infectious Disease consultation services felt the growth of this organism to be a contaminant and did not recommend treatment. A right heart catheterization was performed on hospital day 55 and showed normal mean pulmonary artery pressure of 23 mmHg. Pulmonary artery capillary wedge pressure was normal at 9 mmHg. A left heart catheterization showed normal coronary arteries throughout. A subsequent CT of the chest on hospital day 57 showed rapidly progressive interstitial lung disease with fibrosis (Figure 3), findings compatible with acute interstitial pneumonitis, a form of lung injury. Patient continued to do poorly, and on hospital day 125, she was intubated for progressive hypoxemic respiratory failure. A subsequent bronchoalveolar lavage showed no evidence of nosocomial pneumonia. The patient was treated with broad-spectrum antibiotics, the addition of mycophenolate mofetil 750 mg twice a day, and increases in her corticosteroid to 60 mg IV every 8 hours. The patient's condition continued to deteriorate with more difficult oxygenation requiring chemical paralysis. The patient died on hospital day 131. An autopsy was declined by the power of attorney.

Discussion

In this patient who underwent elective left hip replacement surgery, multiple RBC transfusions were temporally associated with the development of dyspnea, hypoxemia, and

radiographic evidence of diffuse airspace opacities. The patient had underlying mild pulmonary fibrosis that was not recognized until her respiratory decompensation occurred and a CT of the chest was performed. Acute lung injury syndrome superimposed upon underlying pulmonary fibrosis is a well-described clinical entity termed “acute exacerbation”, the etiology of which is unknown. This is the first report of multiple red cell transfusions temporally associated with the development of lung injury and progression of unremitting pulmonary fibrosis. We speculate that her unrecognized interstitial lung disease provided the first insult or predisposition, and the RBC transfusions served as the second “hit” to produce the acute exacerbation. Indeed, more than one insult compounds the risk of developing lung injury³⁻⁴, and this “two-hit” process has been increasingly recognized.

No other risk factors for the development of acute lung injury could be identified in this patient. The patient underwent spinal anesthesia rather than general anesthesia. Post-operatively, there was no witnessed aspiration, cough, sputum production, difficulty handling secretions, difficulty chewing, difficulty eating or swallowing, choking, or altered sensorium to suggest aspiration. There was no fever or leukocytosis to suggest sepsis or pneumonia. Fat embolism syndrome following elective orthopedic surgery as the cause of acute lung injury was not suspected as there was no documentation of neurologic abnormalities or petechial rash to support the diagnosis, and the symptoms presented > 72 h following the procedure. Thromboembolism and pneumothorax were effectively ruled out by imaging studies. While “acute exacerbation”, defined by the development of an acute lung injury syndrome, has been reported in patients with pulmonary fibrosis following surgeries, these patients underwent thoracic operations where lung biopsies were performed. It is speculated that surgical lung biopsies may precipitate lung injury either due to intra-operative respiratory management or direct manipulation of the lung⁵⁻⁷. We are unaware of any prior report describing acute exacerbation of pulmonary fibrosis following elective orthopedic surgery.

It is notable that the patient’s presentation does not meet the criteria for transfusion related acute lung injury (TRALI) based upon the consensus definition of 2004, given the >24 h time lag between the transfusion and development of new bilateral airspace opacities⁸. Hence, the patient’s presentation would not normally be reported to the transfusion medicine service as a transfusion reaction. The patient’s presentation is also not suggestive of transfusion associated circulatory overload (TACO) as her respiratory status did not improve following a significant diuresis⁹. While both dilated inferior vena cava and elevated brain natriuretic peptide level are indicative of increased right atrial pressures, forced diuresis did not improve the patient’s hypoxemia or radiographic infiltrates.

The etiology of this patient’s underlying subclinical pulmonary fibrosis is still undetermined. Possibilities include amiodarone exposure of approximately two years duration ten years prior to presentation, or more probably, chronic hypersensitivity pneumonitis given her continued, daily bird exposure of eighteen years. Indeed, others have also reported “acute exacerbation” characterized histologically by patterns of lung injury in patients with chronic, fibrosing hypersensitivity pneumonitis¹⁰. Transbronchial biopsy of the patient’s right lower lobe showed active organizing pneumonia, interstitial fibrosis, with mild acute and chronic lymphocytic bronchitis and bronchiolitis. This histopathology supports the concept that acute lung injury may have led to the acceleration of the patient’s underlying fibroproliferative process. An acute event triggering the acceleration of abnormal fibroproliferation has been previously set forth by others as a potential explanation for the underlying biology of acute exacerbations in pulmonary fibrosis¹.

The patient was transfused with five units of RBCs that were non-leukoreduced and between 35-38 days old. This is based upon standard practice at the institution that provides non-

leukoreduced RBCs for orthopedic surgery patients using a “first in, first out” protocol. The Food and Drug Administration permits the storage of additive solution-preserved packed red cell units for up to 42 days, and the mean calculated age at transfusion is 19.5 days in the U.S.¹¹. Whether or not the age of the transfused RBCs contributed to the patient’s acute exacerbation remains unclear, but soluble mediators with neutrophil activating potential are known to accumulate with increased storage duration¹² and to a greater degree in non-leukoreduced versus pre-storage leukoreduced RBC units¹³⁻¹⁵. Storage also promotes the loss of RBC chemokine scavenging property¹⁶, and the accumulation of free hemoglobin which can scavenge nitric oxide, mediate cytotoxic and pro-oxidant effects in vivo through its breakdown products heme and free iron¹⁷. In addition, storage induces the formation of microparticles with pro-coagulant¹⁸ and pro-inflammatory potential¹⁹.

We have previously shown that transfusion of aged red cells into endotoxemic mice augments existing lung inflammation and promotes injury, when compared to transfusion of newer red cells¹⁶. Our findings in the mouse model suggest that transfusion of aged red cells can promote lung injury in the setting of a predisposing condition, although a causal link between the age of the transfused RBCs and adverse outcomes in humans has not been conclusively demonstrated²⁰. Acute exacerbation of pulmonary fibrosis is characterized by airspace neutrophilia²¹ and diffuse alveolar damage, suggesting loss of alveolar epithelial cell integrity and injury¹. In this individual, we speculate that transfusion of a large volume of soluble mediators, RBC with the loss of chemokine scavenging potential, and RBC breakdown products might have triggered neutrophil activation and promoted cytotoxic and pro-oxidant effects in the lungs.

In summary, we report a case of an acute lung injury syndrome, or “acute exacerbation” in a patient with subclinical mild pulmonary fibrosis following transfusion of multiple units of packed red cells after elective total hip replacement. Multiple red cell transfusion has long been recognized as a risk factor for the development of acute lung injury^{3-4,22}. Red cell transfusion is associated with an increased risk of developing lung injury and mortality in acute respiratory distress syndrome (ARDS) in those with pre-existing risk factor(s) for acute lung injury²³. This is the first report noting the temporal relationship between red cell transfusion and the development of acute lung injury in a patient with underlying pulmonary fibrosis. In the absence of other identifiable risk factors, it is possible that the transfusion was a contributing factor to the patient’s respiratory deterioration. Based on our experience with this patient, we advise caution when transfusing individuals with interstitial lung disease, particularly transfusion of multiple RBC units. We also advocate the use of leukoreduced blood products, as many of these individuals are being considered for lung transplantation.

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Figure 1. Pre-operative chest radiograph taken 3 months prior to surgery. (A) Posterior-anterior chest radiograph interpreted as without infiltrates but showed blunting of the right costophrenic angle. (B) Lateral chest radiograph also shows the small pleural process anteriorly.

Figure 2. Computed tomography (CT) angiography of the chest with intravenous contrast taken on hospital day 4. (A) Diffuse multi-focal ground glass opacity and consolidation bilaterally at the level of the carina; (B) Prominence of consolidative pattern in the lingular region of the left lung observed at a level just below the carina; (C) Ground glass opacities bilaterally at a level just above the diaphragm; (D) A mild usual interstitial pneumonia (UIP) pattern of pulmonary fibrosis noted with lower lobe juxta-pleural honeycombing (right lower lobe) and traction bronchiectasis at the level of the liver.

Figure 3. High-resolution CT of the chest with radiographic findings compatible with acute interstitial pneumonitis, a form of lung injury taken on hospital day 57. (A) Rapid progression of interstitial lung disease with fibrosis at the level of the carina. (B) Traction bronchiectasis with areas of honeycombing at a level just above the diaphragm. A honeycomb cyst is noted in the right lower lung field that has increased in size over her hospital course.