Transfusion-related acute lung injury (TRALI) following platelet transfusion in a patient receiving high-dose interleukin-2 for treatment of metastatic renal cell carcinoma

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Abstract

Transfusion-related acute lung injury (TRALI) is an uncommon life-threatening complication of hemotherapy. It is hypothesized to be the result of two independent insults: the first related to the clinical status of the patient and the second to the infusion of biologic response modifiers within blood components. We present a case of TRALI in a patient who received high-dose Interleukin-2 (IL-2) as treatment for metastatic renal cell carcinoma, where IL-2 is speculated to have been the first insult and transfusion of platelet concentrate the second. This is the first reported case of TRALI complicating treatment with high-dose immunotherapy.

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1. Introduction

The transfusion of blood products is occasionally complicated by acute lung injury or adult respiratory distress syndrome (ARDS). This process is known as transfusion-related acute lung injury (TRALI) or a pulmonary leukoagglutinin reaction. Recent studies suggest that TRALI may require two sequential insults, where cytokine treatment may be the primary stimulus [1,2]. Renal cell carcinoma (RCC) is well recognized to evoke an immune response from the host, which has occasionally resulted in spontaneous and dramatic remission [3]. In an attempt to reproduce this response, various immunotherapeutic strategies have been attempted in the treatment of RCC. In 1992, the PDA approved high-dose bolus Interleukin-2 (IL-2) for the treatment of metastatic RCC based upon data from seven phase II trials involving 255 patients [3]. We report a case of TRALI following platelets transfusion in a patient who received high-dose IL-2 treatment for metastatic RCC. This potentially life-threatening association has never been described following immunotherapy modalities.
2. Case report

The patient is a 55-year-old gentleman with RCC diagnosed in 01/2001. At the time of diagnosis, the patient was felt to have localized disease (T1N0M0, stage I) and underwent a right radical nephrectomy. Pathological specimen showed a 5.5×5.0 cm mass consistent with RCC, sarcomatoid and papillary types with extensive necrosis and degeneration. No evidence of extra-capsular, renal vein or lymph node involvement was noted. Routine follow up chest X-ray performed on 03/2002 showed presence of new pulmonary nodules, which were biopsied and found to be consistent with metastatic RCC. Further work up demonstrated hepatic lesions suspicious for metastatic RCC. Patient was initially treated with an experimental protocol using PI-88 (heparanase inhibitor) with evidence of progressive disease after 3 months of therapy. On 12/2002, patient was admitted to the hospital for initiation of high-dose IL-2. He received 14 doses of high-dose IL2 therapy over the course of five days (600,000 IU/kg every eight hours over five consecutive days). He experienced the expected complications of IL-2 therapy including fever, tachycardia, confusion, weight gain due to capillary leak syndrome, chills, and rigors. Despite these complications, the patient tolerated the therapy relatively well. Approximately 24 h after his last dose of IL-2, patient was noted to have a platelet count of 24,000 l/L, and he was transfused with 10 units of platelets. The storage time of the unit of platelets was retrospectively estimated at 4.75 days. Within 2–3 h of his platelet transfusion, the patient developed hypoxia, cough, and bilateral rales. Chest X-ray showed diffuse interstitial infiltrates bilaterally consistent with either early pulmonary edema or acute lung injury. Due to persistent volume overload, aggressive diuresis with loop diuretics was initiated. Despite diuresis and correction of fluid excess, oxygen requirement remained elevated (up to FIO2 1.00 by facemask to maintain his O2 saturation >90%). Within 96 h, however, the patient’s oxygen requirement started to decrease and returned to baseline 8 days after the platelet transfusion. Laboratory tests showed, in addition to a small elevation of the total white blood cell count, an absolute eosinophilia (eosinophil count ~1200 μL⁻¹) 6 days after the platelet transfusion. The patient was successfully discharged from the hospital 8 days after his transfusion reaction.

3. Discussion

The incidence of TRALI is probably underestimated since many cases may go unrecognized or may be mistaken for other causes of pulmonary edema. In different reported series, the incidence varies between 1 in 1120 and 4 in 10,000 units of cellular blood components administered [2,4]. Recently, an epidemiological study of TRALI found that the relative prevalence of TRALI reactions being highest after transfusion of whole blood-platelets (2.4 per 1000) and lowest for plasma (1 per 19,000) [2]. Older reports demonstrate different results, where platelet transfusions are associated with the lowest incidence of TRALI [5].

Risk factors for TRALI have been poorly characterized, but longer storage of blood products prior to transfusion, and the presence of an underlying condition such as recent surgery, cytokine treatment, massive blood transfusion, or active infection have been implicated in the pathogenesis of TRALI [1,6]. Antileukocyte antibodies were initially implicated with the majority of cases of TRALI [1]. However, recent studies show that patients with underlying hematological malignancy and those with cardiac disease requiring coronary bypass surgery, longer storage period of blood products (4.5 vs 4.2 days) [2] and higher concentration of bioactive lipids (mostly neutral lipids and lysophosphatidylcholines) appeared to be risk factors for the development of TRALI [2]. In that same study, antileukocyte antibodies were found in only 3.6% of cases [2].

The pathogenesis of TRALI still remains obscure, but animal models and recent clinical observations suggest that it may be the result of at least two independent events [2,7]. The first event begins with activation of the pulmonary vascular endomelium, resulting in the release of chemokines and an increase in adhesion molecules on the endothelial surface [7,8]. These chemokines prime and attract polymorphonuclear leukocytes (PMNs)
to the endothelial surface, where they firmly adhere and undergo cytoskeletal changes that result in rigid nondistensible PMNs unable to traverse the pulmonary microcirculation [2,7,8]. This first event is then followed by a second event that causes activation of the microbicidal arsenal of these primed PMNs, which results in endothelial damage, capillary leak, and pulmonary damage [2,7]. In TRALI, the first event is likely the clinical status of the patient (active infection, traumatic injury, sepsis, recent surgery [specially cardiopulmonary bypass surgery], or as in our case, immunomodulatory treatment with IL-2), which systemically primes PMNs and activates a variety of endothelial tissue beds [8]. The second event is the transfusion of an “activator” for these primed, adherent PMNs (lipid-rich, cytokine-rich blood product) [2].

The characteristic clinical presentation of TRALI is very similar to our patient and includes sudden onset of respiratory distress during or shortly after the transfusion of blood products (<1–6 h following the infusion of blood products), which is manifested by severe dyspnea, hypoxia, and radiographic evidence of pulmonary edema with normal cardiac function. Chest radiographs revealed bilateral patchy alveolar infiltrates consistent with ARDS. Resolution often occurs rapidly; even when initial hypoxemia is severe [9]. Mortality is less than 5% and survivors usually recover to their baseline pulmonary function without apparent sequelae [9].

The management of the patient with TRALI is supportive, with the expectation that clinical improvement will occur spontaneously as the lung injury resolves. Milder cases can be managed with supplemental oxygen alone. Administration of a diuretic should be considered when pulmonary edema develops in association with blood product transfusion, because pulmonary edema may improve regardless of whether it is due to intravascular fluid overload or altered capillary permeability secondary to TRALI. Some authors advocate intravenous corticosteroids [10], but efficacy has not been tested in prospective clinical studies.

Even though individuals who have developed TRALI do not appear to be at increased risk for recurrent episodes, it is unclear whether these patients can safely receive further transfusion of blood components. If necessary, careful selection of components for transfusion in these patients should be considered, including the use of washed or fresh components. Physicians caring for patient receiving immunological based therapy should be aware of this potentially fatal complication.

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References