Early Tumor Regression Following Severe Lung Injury after Allogeneic Stem Cell Transplantation in a Patient with Renal Cell Carcinoma

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Abstract

We describe a 65-year-old man who had repeated lung injuries after reduced-intensity allogeneic stem cell transplantation (RIST) for renal cell carcinoma. Severe pneumonitis developed twice at the time of neutrophil recovery and acute graft-versus-host disease. Both episodes were successfully treated with steroid pulse therapy. Metastases regressed after the first episode and were stable during these lung disorders, but he died of tumor progression 6 months after RIST. This case suggests that certain local inflammatory reactions may be associated with an anti-tumor effect.

Key words: renal cell carcinoma, reduced-intensity stem cell transplantation, anti-tumor effect

Case Report

In 1991, a 65-year-old man was diagnosed as clear cell type renal cell carcinoma (RCC) of the right kidney and received right nephrectomy followed by interferon-α (IFN-α) therapy. He had been well until 2000, when a metastatic lesion was found in the left lung. He underwent a partial resection of the left lung and received IFN-α. However, in January 2003, new metastases appeared in the left chest wall, anterior mediastinum and paraaortic region. Despite the treatment with interleukin-2 (IL-2), the metastases progressed and he was referred to our hospital for reduced intensity allogeneic stem cell transplantation (RIST). The conditioning regimen consisted of intravenous fludarabine at 30 mg/m²/day for 6 days and oral busulfan at 4 mg/kg/day for 2 days. On April 17, 2003, he received granulocyte-colony stimulating factor (G-CSF) mobilized peripheral blood stem cells (2.58×10⁶ CD34+ cells/kg of patient’s weight) from his complete HLA matched sister. Graft-versus-host disease (GVHD) prophylaxis included intravenous cyclosporin A (CyA) (3 mg/kg/day starting on day-1), and methotrexate (10 mg on day 1 and 6 mg on day 3). Intravenous G-CSF (300 µg/day) was started on day 3. On day 13, as the computed tomography (CT) scan showed an enlargement of metastases (Fig. 1A), CyA was withdrawn. On day 15, he rapidly developed severe interstitial pneumonitis (Fig. 2A) requiring mechanical ventilatory support after the neutrophil recovery. There were neither signs of acute GVHD nor cardiac failure. We administered a broad spectrum antibiotic and an anti-fungal agent together with high doses of methylprednisolone (m-PRD, 1 g for 3 days and tapered). Serological tests and culture studies for blood and sputum showed no evidence of an infectious organism. Pulmonary disease showed a prompt improvement (Fig. 2B) and additionally his chest wall metastasis almost disappeared (Fig. 1B) on day 22. Complete donor T-cell chimerism was confirmed on day 28. After that, as he developed acute GVHD (skin, stage III; liver, stage II; intestine, stage I; grade III), CyA (3 mg/ kg/day) and PRD (120 mg/day) were resumed on day 31. Following this acute GVHD, he suffered from another pulmonary disease similar to the previous one. At this time, the mediastinal tumor regressed (Fig. 1C). On day 32, we began to treat him with high doses of m-PRD (1 g for 3 days and tapered) together with a broad spectrum antibiotic and an anti-fungal agent. Bronchoalveolar lavage showed no infec-
The pulmonary disorder gradually disappeared. As the CT scan on day 154 showed an enlargement of metastatic tumors, we discontinued CyA and did a rapid tapering of PRD. On day 170, he developed pneumonia again and metastases progressed (Fig. 1D). Intermediate doses of m-PRD (250 mg for 3 days and tapered) were used together with an antibiotic and an antifungal agent. At this time, he had no response to these treatments and died on day 190. Autopsy revealed an aspiration pneumonia and focal hemorrhage in both lungs and bacterial abscess formation in the left lung. No evidence of any fungal or viral infection was found. Metastatic lesions were identified in the anterior mediastinum and left chest wall and also in the both lungs, left ribs, left diaphragm and liver.

**Discussion**

Recently, a graft-versus-tumor (GVT) effect by RIST has been proven to work against some solid tumors including renal cell carcinoma (RCC) (1, 2). However, little is known about the relationship between RIST and its anti-tumor effect for solid cancer. We describe here a 65-year-old man with metastatic RCC who showed a transient tumor regression following a severe lung injury after RIST.
Acute non-infectious lung injury observed in the present patient is a major complication of allogeneic stem cell transplantation (3). This disease called “idiopathic pneumonia syndrome (IPS)” is defined as widespread alveolar injury following transplantation in the absence of an active lower respiratory tract infection and cardiogenic causes. It is postulated that the etiology of IPS includes toxic effects of preconditioning, immunologic cell-mediated injury, and inflammatory cytokine-induced lung damage (4,5). In this case, the first lung episode occurred on day 15 following the neutrophil recovery and the second occurred on day 32 after the onset of acute GVHD. Both episodes subsided following steroid pulse therapies, suggesting the causal role of inflammatory or immunologic factors (6). Of interest is that the metastases regressed after the first episode and were stable during these lung disorders. It is unlikely that preconditioning fludarabine and busulfan administration had an anti-tumor effect for RCC. Childs et al (1) described that tumor regression is delayed and occurred a median of 129 days after RIST. Compared to this, the time to regression was considerably short (day 22) in the present case. Early tumor response without accompanying acute GVHD has not been reported in the literature. RCC is known to be sensitive to inflammatory cytokines such as IFN-α or IL-2 (7,8), and our case had initially responded well to IFN-α. This allows us to speculate that local inflammatory cytokines associated with lung injuries might contribute to the tumor regression. On the other hand, the production of such cytokines is known to be easily suppressed by steroid hormone (9). Accordingly, certain suppressive action on local cytokine storm or alloimmunity by a prolonged steroid treatment might lead to the tumor progression. Since the mechanism of GVT effect for solid tumor still remains unclear, detailed investigations into more cases like ours are necessary to better understand the precise anti-tumor effect after RIST for RCC.

References