



A Pediatric Case of Very Late Onset Non-infectious Pulmonary Complication (LONIPC) after Allogeneic Hematopoietic Stem Cell Transplantation

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Abstract

17-months old infant with Wiskott-Aldrich syndrome was transplanted with genetically two-locus mismatched unrelated cord blood cells under the conditioning regimen of busulfan, cyclophosphamide and anti-thymocyte globulin. GVHD prophylaxis was cyclosporine (CSP) plus short-term methotrexate with prednisolone (1 mg/kg). Acute and chronic GVHD were not observed during the course. About six years later, he suffered from severe cough and dyspnea with no fever, and diagnosed as late onset non-infectious pulmonary complications (LONIPC). We have to be careful for LONIPC after SCT even in the absence of chronic GVHD for younger children because the sign of insidious obstructive pulmonary symptoms is difficult to monitor. To avoid the unexpected LONIPC, introduction of RIC regimen should be considered for younger children, although it has been reported that RIC regimen may increase the risk for GVHD and graft rejection.

Keywords: Non-infectious pulmonary complication; Chronic GVHD; Allogeneic hematopoietic stem cell transplantation

Introduction

Late onset non-infectious pulmonary complications (LONIPC) consist of major causes of morbidity and mortality after allogeneic hematopoietic stem cell transplantation (allo-HSCT). These include bronchiolitis obliterans (BO), bronchiolitis obliterans with organizing pneumonia (BOOP), and idiopathic pneumonia syndrome (IPS), and usually occur three months after HSCT. According to the literature, the incidence has been reported to be 10-25% [1]. Not well elucidated, it is speculated that allo-immune reactions play a major role in the pathogenesis, because they are closely associated with the presence of chronic GVHD. Concerning to LONIPC among the pediatric patients, few reports are available. Kojima et al have reported as a single institutional experience that the incidence of LONIPC in the pediatric patients was 10.3%, the median onset was 187 days (123-826 days), and it was also related with chronic GVHD as in the cases of adults [2].

Case Report

17-months old infant with Wiskott-Aldrich syndrome was transplanted with genetically two-locus mismatched unrelated cord blood cells. Major clinical symptoms were eczema and thrombocytopenia ($<1 \times 10^4/\mu\text{l}$) and he had no significant infection episodes before SCT. No expression of WASP protein was found in T-lymphocytes, and genetic analysis revealed splicing anomaly due to point mutation in intron2. Conditioning regimen consisted of busulfan (4 mg/kg/day for 4 days), cyclophosphamide (50 mg/kg/day for 4 days) and horse anti-thymocyte globulin (10 mg/kg/day for 4 days), and GVHD prophylaxis was cyclosporine (CSP) plus short-term methotrexate with prednisolone (1 mg/kg). Dose of oral busulfan was determined by the prior test dose and pharmacokinetic analysis. Methotrexate on day 6 and day 11 was omitted because of elevated serum transaminase. Neutrophil engraftment was on day 19, platelet engraftment on day 71 and complete chimerism was determined on day 21.

Because no GVHD was observed, CSP was stopped on day 95, and prednisolone on day 251. He became free of immunoglobulin supplementation one year after CBT. There were no significant infection episodes after CBT.

5 and 1/2 years after CBT, he began to complain of occasional dry cough, which resolved easily under cough remedy. A couple of months later, he suffered from severe cough and dyspnea with no fever. Auscultation revealed fine crackles on both lungs, and his oxygen saturation was 92% in room air. Chest X-ray presented marked consolidation of bronchioles (Figure 1). Under the suspicion of LONIPC, prednisolone (1 mg/kg/day) was started, which ameliorated his symptoms rapidly. Serum soluble IL-2R was slightly elevated to 937 U/ml (normal value: 145-519), and serum KL-6 was 458 U/ml (normal value: 0-500). Involvement of pathogens including RSV, CMV and fungi was excluded from the later examinations. He has been placed on oral prednisolone with clarithromycin (5 mg/kg/day) and fluticasone inhalation (twice daily). Three years later, he has been placed on home oxygen therapy and lung transplantation has been scheduled.

Discussion

Between 2001 and 2011, 72 pediatric patients (7m-22y8m; 7y3m \pm 6y8m [mean \pm SD]) have received 77 allogeneic stem cell transplantations in our institute. 9 patients (13.4%) in 67 patients who survived more than 3 months after SCT developed LONIPC (Table 1: observation period; 1155-5145 days). Multivariate analysis revealed myeloablative conditioning regimen and chronic GVHD as significant risk factors of LONIPC (data not shown). Unexpectedly, two patients developed LONIPC more than five years after HSCT and one patient died of respiratory failure 30 months after diagnosis of LONIPC.

As shown in Table 1, LONIPC was closely related with chronic GVHD also in our experience. Unexpectedly, two patients had no

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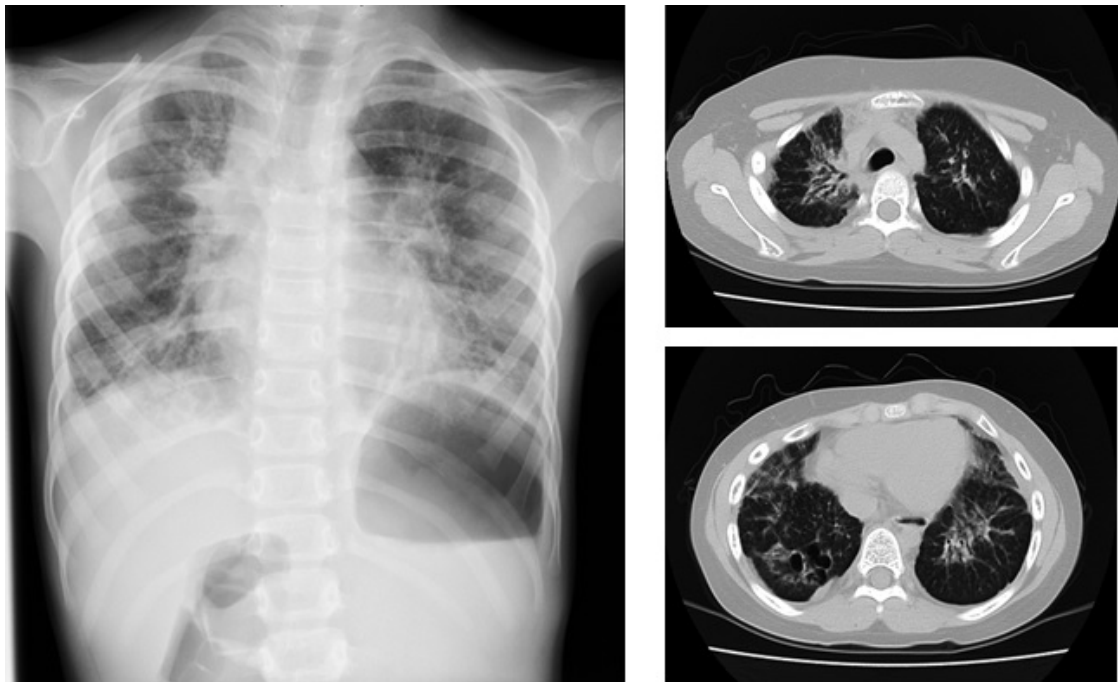


Figure 1: Chest X-ray and CT scan of the patient at the diagnosis of LONIPC.

S.No		Age at SCT	Source of SCT	Conditioning regimen	GVHD prophylaxis	aGVHD	cGVHD	Onset NIPC	Outcome	Cause of death
1	CAEBV	18y8M	UBMT	TBI+CY+VP	CSP + sMTX	II	(+)	126	Dead (631)	Respiratory failure
2	AML	14y4M	UBMT	BU+LPAM+CY	CSP + sMTX	III	(+)	90	Dead (335)	Respiratory failure pneumoniae
3	WAS	11y7M	UBMT	BU+CY+ATG	TAC + sMTX	IV	(+)	234	Dead (373)	Respiratory failure pneumoniae
4	AML	13y4M	Mismatched-related (mother)	TBI+CY	TAC + sMTX	III	(+)	107	Dead (374)	AML
5	AML	1y10M	MSB	iBU+LPAM	CSP + sMTX	IV	(+)	98	Alive (>2065)	-
6	ALL	7y	Mismatched-related (mother)	TBI+CY+VP+ATG	TAC + sMTX + PSL	I	(+)	131	Alive (>1582)	-
7	ALL	17y7M	MSB	TBI+CY+VP	CSP	II	(+)	345	Dead (720)	Subdral hemorrhage
8	WAS	8M	UBMT	BU+CY+ATG	TAC + sMTX	II	(-)	3578	Dead (4470)	Respiratory failure
9	WAS	1y5M	UCBT	BU+CY+ATG	CSP + sMTX + PSL	(-)	(-)	2118	Alive (>3821)	-

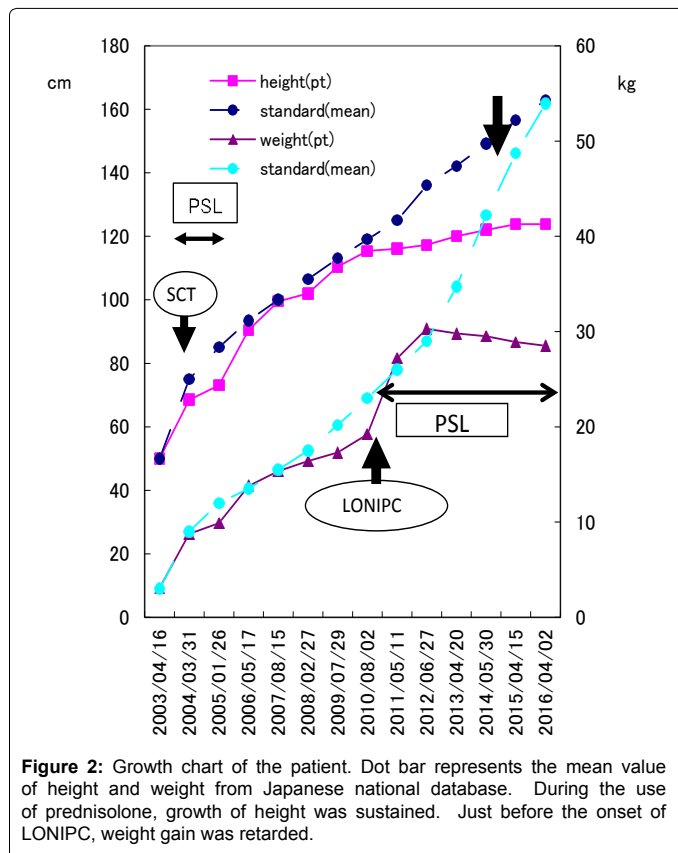
CAEBV: Chronic Active EB Virus Infection; MDS: Myelodysplastic Syndrome; WAS: Wiskott-Aldrich syndrome; AML: Acute Myelogenous Leukemia; ALL: Acute Lymphocytic Leukemia; UBMT: Unrelated Bone Marrow Transplantation; MSB: Matched Sibling; UCBT: Unrelated Cord Blood Transplantation; TBI: Total Body Irradiation; CY: Cyclophosphamide; VP: Etoposide; BU: Busulfan; LPAM: Melphalan; ATG: Anti-Thymocyte Globulin; CSP: Cyclosporine; MTX: Methotrexate; PSL: Prednisolone

Table 1: Profile of patients who developed LONIPC.

history of chronic GVHD before the onset of LONIPC contrary to other patients. The mean onset except for two cases was 161 days (90-345 days), which is comparable to previous reports. Four patients were dead due to LONIPC or its associated complications such as pneumonia. Described case was peculiar in that he had no apparent history of acute and chronic GVHD, and that the onset of LONIPC was extremely late. One possible risk factor is busulfan used in the conditioning regimen. It has been reported that busulfan may be associated with greater long-term lung toxicity than TBI in pediatric patients [3]. In our preliminary data, 18 patients with reduced intensity conditioning regimen during the same period developed no LONIPC.

It has been reported that decline of air flow could be a good hall mark of non-infectious pulmonary complication after SCT [4-6].

However, it is difficult to monitor FEV1/FVC for younger children such as this case. Figure 2 showed the growth chart of this patient after SCT. Retrospectively, retardation of weight gain was found before the onset of LONIPC, although it is difficult to determine whether it was an early sign of pulmonary symptoms or not. We have to be careful to check the development of LONIPC after SCT even in the absence of chronic GVHD especially for infants or younger children because the sign of insidious obstructive pulmonary symptoms is difficult to monitor. It has been recently reported that RIC regimen stabilized long-term pulmonary function in adult patients with allogeneic SCT [7]. To avoid the unexpected LONIPC, introduction of RIC regimen should be considered for younger children, although it has been reported that RIC regimen may increase the risk for GVHD, CMV reactivation and graft rejection [8,9].



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