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Pulmonary Manifestations of the Pre-Engraftment Syndrome after Umbilical Cord Blood Transplantation

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Abstract

Pre-engraftment syndrome (PES) is a condition occurring after umbilical cord blood transplantation (UCBT) characterized by fever and erythematous skin rash prior to neutrophil engraftment. We sought to determine the incidence and characterize the pulmonary manifestations of PES.

A retrospective review of patients who underwent UCBT at the University of Kansas Medical Center over a 5 year period was performed. Data collected included patient baseline characteristics, presence of PES, pulmonary findings, treatments and survival.

Forty-four patients underwent UCBT with 22 of those patients developing PES. Full-intensity myeloablative conditioning regimen was found to be a risk factor for development of PES. Of those 22 patients, 13 had resting hypoxemia. The most common radiographic findings included diffuse ground glass opacities with pleural effusions. Fifteen patients with PES received corticosteroids, of which twelve had improvement in fevers and rash. These patients had a trend towards worse mortality than those not receiving corticosteroids. There was a non-significant trend towards worse survival in patients with PES and hypoxemia compared to those without hypoxemia.

PES is a common complication following cord blood transplantation, with hypoxemia being present in over half of patients with PES. Hypoxemia with PES and treatment with corticosteroids may portend a worse prognosis.

Keywords

Immunocompromised; pre-engraftment syndrome; respiratory failure; umbilical cord blood transplantation

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Introduction

Umbilical cord blood transplantation (UCBT) is regularly used to treat adult patients with hematogenous malignancies in whom there is not an available sibling or matched unrelated donor.[1, 2] Among those patients who receive UCBT, many go on to develop pre-engraftment syndrome (PES).[3] PES is characterized by high-grade fevers of non-infectious etiology and an erythematous skin rash occurring prior to neutrophil engraftment.[4, 5]

PES has been identified as a predictor of acute graft-versus-host-disease (GVHD) in pediatric patients [6] and adult patients.[7] Another study identified patients with PES as being at risk for both acute and chronic GVHD.[8] The use of cyclosporine for GVHD prophylaxis has been established as a risk factor for PES,[9] while the use of methotrexate for acute GVHD prophylaxis has been shown to reduce the incidence of early immune reactions after UCBT.[10]

Specific clinical findings associated with PES vary in published reports. Common symptoms of PES include fever, rash, diarrhea, weight gain, hepatic dysfunction, and renal dysfunction.[4, 7] Pulmonary manifestations of PES are variable. Tachypnea, hypoxemia and pulmonary edema have been reported in 13.3- 69.0% of patients with PES.[5, 6, 9] However, specific radiographic features of PES and how pulmonary dysfunction in PES may affect overall prognosis have yet to be described.

In this study, we reviewed our population of patients who received UCBT to evaluate the pulmonary manifestations of PES. We sought to determine risk factors for PES, define characteristics of pulmonary involvement with PES, and measure responses to current treatment regimens.

Materials and Methods

A retrospective review of all consecutive adult patients who underwent UCBT at University of Kansas Medical Center from March 31, 2008 until November 20, 2012 was performed. All patients were at least 18 years of age and received either single or double UCBT. No patients were excluded from this study which was approved by the institutional human subjects committee, project #HSC 13030.

Forty-four patients met these inclusion criteria. In every transplanted patient there was at least 4/6 human leukocyte antigen (HLA)-matching with the recipient and 4/6 inter-graft matching. All patients underwent either a myeloablative conditioning regimen or a reduced-intensity conditioning regimen prior to UCBT. The conditioning regimens involved an ablative regimen of fludarabine, cyclophosphamide and 1320 cGy of total body irradiation or a reduced intensity regimen of fludarabine, cyclophosphamide and 200 cGy of total body irradiation in all but one patient. That patient received a preparative regimen of cyclophosphamide and anti-thymocyte globulin prior to UCBT as a salvage therapy for graft failure post-matched sibling donor transplant. GVHD prophylaxis consisted of mycophenolate mofetil with either cyclosporine or tacrolimus. Granulocyte colony-stimulating factor was administered intravenously to all patients starting on day +1 and stopped after the absolute neutrophil count was $\geq 2,000$ cells/ μ L for three consecutive days.

Neutrophil engraftment was defined as three consecutive days of absolute neutrophil count ≥ 500 cells/ μ L. Infection prophylaxis consisted of levofloxacin, acyclovir and oral fluconazole given to all patients during the conditioning regimen and in the pre-engraftment period. Ganciclovir was used for cytomegalovirus prophylaxis in cytomegalovirus positive recipients transplanted after 2011.[11]

PES was defined as the presence of both a fever $\geq 38.3^{\circ}\text{C}$ (101°F) and a rash occurring before neutrophil engraftment. All patients had an infectious workup during the febrile episode that included blood cultures, urinalysis, and a chest radiographic study. To qualify as having PES, a patient must not have achieved fever resolution with empiric broad-spectrum anti-microbial therapy and there was no infectious etiology identified by cultures or radiologic studies. The characteristic rash of PES was an unexplained erythematous skin rash resembling acute GVHD; drug-associated rashes were excluded. Treatment directed at PES was at the discretion of the attending transplant physician. Typical treatment of PES was intravenous methylprednisolone at a dose of 1 mg/kg/day for 3 days, which was the regimen used in all patients who were treated with corticosteroids.

Established non-pulmonary manifestations of PES that were evaluated for included weight gain, diarrhea, increase in creatinine, increase in transaminases, and peripheral edema. Weight gain was defined as a 3% increase in body weight from the day of UCBT to the onset of PES symptoms. Increase in creatinine and transaminases were defined as a two-fold increase in these laboratory values from their pre-transplant baseline values. Non-infectious diarrhea was defined as greater than 2 liquid stools per day without evidence of infection by standard diagnostic testing, including analysis for *Clostridium difficile* toxin.

We examined patient medical records for the following specific pulmonary manifestations of PES: subjective dyspnea, presence of rales on physical examination, and hypoxemia. Hypoxemia was defined as a room air oxygen saturation of less than 90% within 24 hours of the fever and characteristic skin rash being present. Because arterial blood gases were not routinely performed at the onset of hypoxemia, this data was not available. Information gathered during computed tomography (CT) of the chest and bronchoalveolar lavage (BAL), when performed within 5 days of the diagnosis of PES, was collected.

Statistical analysis was performed using a statistical software program (GraphPad Prism 6; GraphPad Software Inc., La Jolla, CA). Overall survival analysis was determined using the Kaplan-Meier method. Final follow up was performed on March 21, 2013. All surviving patients were censored on the final day of follow up. Data from continuous variables are presented as mean with ranges in parentheses. Continuous variables were compared using a student's t-test to generate a p-value. Categorical variables were compared using the Fisher's exact test to assess for non-random association among patients with and without PES or hypoxemia. An odds ratio (OR) or hazard ratio (HR) that did not cross 1 or a p-value < 0.05 was used to determine statistical significance.

Results

In total, 44 patients underwent UCBT over the defined time period. The average age was 44.9 years (18-71 years.) There were 25 males and 19 females who underwent UCBT. The most common indication for UCBT was AML, seen in 28 of the 44 patients. All patients but one underwent a conditioning regimen involving myeloablative or reduced intensity fludarabine, cyclophosphamide and total body irradiation (97.7%), and received mycophenolate mofetil and cyclosporine for acute GVHD prophylaxis (97.7%).

Twenty-two of the 44 patients who underwent UCBT subsequently developed PES (50.0 %.) Patients who developed PES after UCBT were compared with those who did not develop PES in Table I. Those patients who had a full intensity myeloablative conditioning regimen had a higher incidence of PES, OR = 5.950 (1.585-22.33.) In addition, patients with PES were more likely to have hypoxemia in the pre-engraftment period than those without PES, 59.1% versus 4.5%, OR= 30.33 (3.432-268.1.) Rates of engraftment, disease relapse, acute GVHD and overall survival did not differ significantly between the two groups.

PES developed on average 12.5 days (7-20) after UCBT. All of the patients with PES had a fever and rash present. Diarrhea, peripheral edema, weight gain and subjective dyspnea were common features in patients with PES. For full features present in patients with PES, see Table II. Eighteen of the 22 patients with PES subsequently engrafted. The average time from UCBT to neutrophil engraftment was 20.6 days in those without PES and 28.6 days in those with PES ($p=0.0006$.) Acute GVHD developed in 8 patients with PES syndrome. Of the patients with PES who survived 1 year following HSCT, none had evidence of chronic GVHD.

Objective hypoxemia developed in 13 patients with PES in the pre-engraftment period. Table III compares patients with PES and hypoxemia to those patients with PES and normal oxygenation. Common findings on chest CT in these hypoxemic patients included bilateral pleural effusions in 8 of 13 subjects (61.5%) and diffuse alveolar ground-glass opacities in 10 of 13 patients (76.9%). A chest CT of a patient with PES and progressive hypoxemia who required mechanical ventilation is shown in Figure 1. Of the 13 hypoxemic patients, 10 had an echocardiogram performed within 5 days of the diagnosis of PES, of which one was found to be abnormal, with a reduced ejection fraction of 30%. The other nine patients who underwent echocardiography had normal findings. None of these patients fulfilled the diagnostic criteria for hepatic veno-occlusive disease.[12]

Four PES patients underwent fiberoptic bronchoscopy with BAL, for which the predominant cell type was monocytic in every patient. Using standard diagnostic testing involving cultures for bacterial, fungal and viral organisms, galactomannan antigen detection, cytomegalovirus polymerase chain reaction and nucleic acid studies to evaluate for community-acquired respiratory viruses, there were no infectious etiologies isolated in those 4 patients. Five patients required mechanical ventilation during the pre-engraftment period; one patient received non-invasive positive-pressure ventilation, and the other four required endotracheal intubation and invasive mechanical ventilation. In those four patients requiring endotracheal intubation, no infectious etiologies or other causes of hypoxemic respiratory

failure were isolated. All of the patients with respiratory failure were treated with corticosteroids, and 2 were successfully liberated from mechanical ventilation. None of the patients who required mechanical ventilation survived to censorship, with an average of 149.8 days (29-491) between UCBT and death.

Fifteen of the 22 patients with PES were treated with intravenous methylprednisolone, of whom 12 had an improvement in their rash and fever. Seven patients did not receive glucocorticoids because of milder symptoms, of which 3 had spontaneous improvement. Nine of the thirteen patients with PES and hypoxemia received corticosteroids, of which 5 had an improvement in their oxygen requirement and resolution of their pulmonary infiltrates. There was a trend towards worse survival that did not reach statistical significance in patients who received corticosteroids, which is displayed on the Kaplan-Meier curves in figure 2, HR = 2.675 (0.9472-7.555.)

Overall survival in groups of patients with and without PES is shown in the Kaplan-Meier curves in figure 3. In addition, survival of patients with PES who developed hypoxemia compared with those without hypoxemia in the pre-engraftment period is displayed in figure 4. There was a non-significant trend towards reduced survival in those patients who developed hypoxemia as a feature of PES, HR = 2.538 (0.909-7.081.) Causes of death for groups of patients with and without PES is shown in table IV, with relapse of underlying disease being the most common cause of death in both groups.

Discussion

PES is a common occurrence following UCBT in adult patients. In our cohort of patients, the incidence of PES was 50%, with an average of 12.5 days separating onset of symptoms of PES from the day of transplantation. Previous studies have identified an incidence ranging from 20-78%, [3, 5, 8, 9] with an average onset of PES 4-22 days after UCBT. [9]

We have described that hypoxemia during the pre-engraftment period commonly complicates this clinical condition, and can predispose these patients to a potentially worse outcome. In patients with PES who underwent fiberoptic bronchoscopy with BAL during the pre-engraftment period, a monocyte-predominant BAL cell differential was seen in every patient. This cell differential is consistent with normal, non-smoking adult patients undergoing BAL, and suggests that the hypoxemia is due to influx of fluid into the alveoli due to increased pulmonary epithelial permeability, rather than infection, [13] which would be associated with an increase in lymphocytic or granulocytic cell lines. Another plausible explanation for the cell differential from BAL fluid could be that these patients were neutropenic at the time of bronchoscopy and accordingly have not recovered their counts to demonstrate an increase in non-monocytic cell lines.

The most common radiographic finding in PES was diffuse ground-glass opacity with bilateral pleural effusion, a finding consistent with pulmonary edema. Pulmonary edema can be either cardiogenic or non-cardiogenic, with cardiogenic pulmonary edema having an increased pulmonary capillary pressure as the source of the influx of protein-poor alveolar fluid. [14] Non-cardiogenic pulmonary edema is characterized by increased pulmonary

epithelial permeability leading to a protein-rich alveolar edema fluid.[15] The probable cause of non-cardiogenic pulmonary edema following UCBT is the capillary leak syndrome, similar to what is seen in the engraftment syndrome following autologous and allogeneic stem cell transplantation.[16] The currently recommended treatment of non-cardiogenic pulmonary edema is supportive care, low tidal volumes in those requiring mechanical ventilation,[17] and a fluid conservative strategy, which may shorten duration of mechanical ventilation when required.[18]

In our cohort of patients with PES, 15 received systemic corticosteroids, 12 of whom had improvement in fevers and rash. Corticosteroids were first used in treatment of the engraftment syndrome following autologous [19-21] and allogeneic hematopoietic stem cell transplantation.[22, 23] Treatment of PES following UCBT with corticosteroids has been successful at resolving both fever and rash in several retrospective studies,[4-7] though it did not influence mortality.[9] Treatment with corticosteroids is not without risk, as Park *et al* demonstrated those patients with PES after UCBT who required longer and higher doses of corticosteroids had an increased incidence of bacterial infection.[6] While we did observe a trend toward higher mortality in patients with PES who received corticosteroids, it did not reach statistical significance. The use of corticosteroids, especially for prolonged periods of time, is potentially a marker for worse PES and not necessarily the cause of increased mortality in these patients. A larger cohort of patients who have undergone UCBT will certainly aid in validating these observations.

The pathogenesis of PES is largely unknown. However, the manifestations of fever, skin rash, and pulmonary infiltrates related to non-cardiogenic pulmonary edema are quite similar to the presentation of engraftment syndrome.[16] Engraftment syndrome following autologous or allogeneic stem cell transplantation is thought to occur secondary to the release of pro-inflammatory cytokines.[16] Given the common manifestations of the two conditions, we speculate that PES might be related to the release of pro-inflammatory cytokines that contribute to fever, rash, and non-cardiogenic pulmonary edema. Graft-versus-graft interactions between units following a double unit UCBT to determine unit dominance has been suggested as a mechanism leading to cytokine release,[24] although we have observed that PES occurs following both single and double unit UCBT. Future studies should focus on this interesting phenomenon, which may help to shed light on unit dominance post UCBT. This graft-versus-graft interaction and the resulting time needed to establish unit dominance might also explain the delay in neutrophil engraftment seen in patients with PES.

Another finding that deserves mention was the significant difference in time to engraftment between patients with PES. Hypoxemic patients were less likely to engraft than those patients without hypoxemia. However, the hypoxemic patients who did engraft did so at a statistically significant earlier time than those with normal oxygenation. The cause of this finding is unclear. There was no significant difference in total nucleated cell dose, HLA matching or use of single versus double cord units between these two groups to explain this result. This difference may be secondary to the relatively small sample size, but should be evaluated in future studies.

In summary, we have reviewed our population of UCBT patients who developed PES. We found that full-intensity myeloablative conditioning regimens were associated with the development of PES. Over 50% of patients with PES developed hypoxemia and had CT chest and BAL consistent with non-cardiogenic pulmonary edema. There were non-significant trends toward increased mortality in patients with PES who developed hypoxemia and in patients treated with corticosteroids.

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Figure 1.

A representative chest CT of a patient with PES and hypoxemia. This chest CT shows prominent bilateral ground glass opacity with peripheral sparing, consistent with pulmonary edema.

Survival of Patients with Pre-Engraftment Syndrome

Figure 2.

Kaplan-Meier curve comparing survival in patients with PES who were treated with corticosteroids compared to those who did not receive corticosteroids. No statistically significant difference was found.

Survival of Patients Following Cord Blood Transplantation

Figure 3.

Kaplan-Meier curve comparing survival of patients following UCBT who developed PES compared to those that did not develop PES. No difference in survival was found between the two groups.

Survival of Patients with Pre-Engraftment Syndrome

Figure 4.

Kaplan-Meier survival curve of patients with PES who developed hypoxemia compared to PES patients without hypoxemia is shown.

Table I
Comparison of Patients with and without Pre-Engraftment Syndrome

		PES (n=22)	No PES (n=22)	Odds Ratio or P-value
Age (years)				
	Mean (Range)	42.7 (18-66)	48.1 (28-71)	p = 0.6443
Gender				
	Male	13	12	1.204 (0.3645-3.975)
	Female	9	10	0.8308 (0.2516-2.744)
Underlying Diagnosis				
	Acute Myelogenous Leukemia	11	17	0.2941 (0.08005-1.081)
	Myelodysplastic Syndrome	4	0	10.95 (0.5524-216.9)
	Acute Lymphoblastic Leukemia	4	1	4.667 (0.4771-45.65)
	Hodgkin's Lymphoma	0	1	0.3185 (0.0129-8.260)
	Non-Hodgkin's Lymphoma	2	0	5.488 (0.2483-121.3)
	Aplastic Anemia	1	0	3.140 (0.1211-81.42)
	Chronic Myelogenous Leukemia	0	1	0.3185 (0.0129-8.260)
	Chronic Lymphocytic Leukemia	0	1	0.3185 (0.0129-8.260)
	Biphenotypic Acute Leukemia	0	1	0.3185 (0.0129-8.260)
Conditioning Regimen				
	Fludarabine/Cyclophosphamide/Total Body Irradiation	22	21	3.140 (0.1211-81.42)
	Cyclophosphamide/Anti-Thymocyte Globulin	0	1	0.3185 (0.0129-8.260)
Conditioning Intensity				
	Myeloablative Regimen	14	5	5.950 (1.585-22.33)
	Reduced Intensity Conditioning Regimen	8	17	0.1681 (0.0447-0.6309)
Cell Source				
	Single Unit Cord Blood Transplant	3	1	3.316 (0.3171-34.67)
	Double Unity Cord Blood Transplant	19	21	0.3016 (0.0284-3.154)
HLA Matching				
	Single 4/6	1	0	3.140 (0.1211-81.42)
	Single 5/6	1	1	1.000 (0.5856-17.08)
	Single 6/6	1	0	3.140 (0.1211-81.42)
	4/6 + 4/6	7	8	0.8167 (0.2342-2.848)
	4/6 + 5/6	5	4	1.324 (0.3035-5.772)
	5/6 + 5/6	5	5	1.000 (0.2440-4.098)
	5/6 + 6/6	1	2	0.4792 (0.0399-5.675)
	6/6 + 6/6	1	2	0.4792 (0.0399-5.675)
Cell Dose				
	Mean Infused Total Nucleated Cell $\times 10^7$ /kg (standard deviation)	3.16	3.34	p = 0.2911

		PES (n=22)	No PES (n=22)	Odds Ratio or P-value
GVHD Prophylaxis				
	Mycophenolate Mofetil and Cyclosporine	21	22	0.3185 (0.0128-8.260)
	Mycophenolate Mofetil and Tacrolimus	1	0	3.140 (0.1211-81.42)
Engraftment				
	Did engraftment occur	18	20	0.4500 (0.0734-2.759)
	Mean day after transplant that engraftment occurred (Standard Deviation)	28.6 Days (16-41)	20.6 Days (13-29)	p = 0.0006
Complications				
	Hypoxemia in Pre-Engraftment Period	13	1	30.33 (3.432-268.1)
	Acute GVHD Present	8	11	0.5714 (0.1711-1.908)
	Disease Relapse	5	9	0.4288 (0.1146-1.575)
Mortality				
	Patient Survival at 30 Days Post Transplant	20	21	
	Patient Survival at 90 Days Post Transplant	12	17	
	Patient Survival at 1 Year Post Transplant	8	10	
	Mean Survival	108 Days	332 days	
	Hazard ratio	1	1.209 (0.5765-2.535)	P=0.2981

Table II
Characteristics of Patients with Pre-Engraftment Syndrome

Feature	Specific Feature	Number	Percentage
Clinical Features			
	Rash	22	100%
	Fevers	22	100%
	Cough	11	50.0%
	Dyspnea	16	72.7%
	Hypoxemia	13	59.1%
	Rales on Physical Examination	13	59.1%
	Peripheral Edema	21	95.5%
	Weight Gain	18	81.8%
	Diarrhea	21	95.5%
	Increased Creatinine	6	27.3%
	Increased Transaminases	10	45.5%
Radiographic Features			
	No Chest CT performed	2	9.1%
	Normal Chest CT	6	27.3%
	Diffuse Ground-Glass Opacities	11	50.0%
	Reticular Infiltrate	1	4.5%
	Tree-In-Bud Opacities	1	4.5%
	Bilateral Lower Lobe Atelectasis	1	4.5%
	Pleural Effusions	9	40.9%
Respiratory Failure			
	Invasive Mechanical Ventilation Required	4	18.2%
	Non-Invasive Mechanical Ventilation Required	1	4.5%
BAL Findings			
	BAL Performed in Pre-Engraftment Period	4	
	Infectious Etiologies Isolated	0	0%
	Monocyte Predominant Cell Differential	4	100%

Table III
Comparison of Patients with Pre-Engraftment Syndrome with and without Hypoxemia

		With Hypoxemia (n=13)	Without Hypoxemia (n=9)	Odds Ratio or p-value
Age				
	Mean (Range)	40.2 years (18-54)	43.9 years (22-66)	p = 0.5293
Gender				
	Male	7 (53.8%)	6 (66.7%)	0.5833 (0.0997-3.404)
	Female	6 (46.2%)	3 (33.3%)	1.714 (0.2938-10.00)
Conditioning Regimen				
	Myeloablative	9 (69.2%)	5 (55.6%)	1.800 (0.3079-10.52)
	Non-Myeloablative	4 (30.8%)	4 (44.4%)	0.5556 (0.0950-3.247)
Clinical Features				
	Fever	13 (100%)	9 (100%)	1.421 (0.0258-78.20)
	Rash	13 (100%)	9 (100%)	1.421 (0.0258-78.20)
	Diarrhea	13 (100%)	8 (88.9%)	4.765 (0.1732-131.1)
	Weight Gain	12 (92.3%)	6 (66.7%)	6.000 (0.5091-70.71)
	Subjective Dyspnea	13 (100%)	3 (33.3%)	50.14 (2.240-1122)
	Rales on Physical Examination	13 (100%)	1 (11.1%)	153.0 (5.562-4209)
	Increased Creatinine	6 (46.2%)	0 (0%)	16.47 (0.7937-341.6)
	Increased Transaminases	6 (46.2%)	4 (44.4%)	1.071 (0.1941-5.915)
	Peripheral Edema	9 (69.2%)	9 (100%)	0.1111 (0.0052-2.364)
Complications				
	Acute GVHD Present	3 (23.1%)	5 (55.6%)	0.2400 (0.0380-1.515)
	Disease Relapse	3 (23.1%)	2 (22.2%)	1.050 (0.1374-8.025)
Engraftment				
	Did Engraftment Occur	9 (69.2%)	9 (100%)	0.1111 (0.0052-2.364)
	Average Day that Engraftment Occurred after UCBT (Standard Deviation)	23.8 Days (16-40)	33.4 days (26-41)	p = 0.0101
Survival				
	Alive at 30 Days Post Transplant	11(84.6%)	9 (100%)	
	Alive at 90 Days Post Transplant	6 (46.2%)	6 (66.7%)	
	Alive at 1 Year Post Transplant	3 (23.1%)	5 (55.6%)	
	Hazard Ratio of Survival	2.538 (0.909-7.081)	1	p = 0.0753

Table IV
Causes of Death

Cause of Death	PES Present (N=15)	PES Absent (N=14)
Primary Graft Failure	2	1
Secondary Graft Failure	1	2
Severe Sepsis	3	1
Respiratory Failure	2	0
Relapsed Primary Disease	5	8
Intractable GVHD	1	1
Persistent Vegetative State	1	0
Subarachnoid Hemorrhage	0	1