A case of engraftment syndrome in the medical intensive care unit

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ABSTRACT

Engraftment syndrome (ES) is an increasingly diagnosed complication after hematopoietic cell transplantation (HCT). Clinical presentation most commonly includes, but is not limited to fever, diarrhea, and skin rash developing at the time of absolute neutrophil count (ANC) recovery. Due to the broad and pleiotropic clinical presentation, ES can be a challenging diagnosis. Furthermore, despite many reports about the presentation of ES, the syndrome is still not completely understood. While most presentations of ES are mild and can either resolve spontaneously or with a brief course of systemic corticosteroids, mortality rates ranging from 8%-18% have been described. We present a case of ES in a critical care setting. A male patient who had an allogeneic HCT and developed fevers, diffuse skin rash, acute kidney injury and hypoxemic respiratory failure after his absolute neutrophilic count started recovering from nadir. He was subsequently transferred to the medical intensive care unit (MICU) for further management, where he was initially managed with mechanical ventilation, vasopressors and antibiotics. An extensive workup that included bronchoscopy with bronchoalveolar lavage was performed and failed to show an infectious etiology. Due to concern for ES, patient was started on steroids and his clinical status dramatically improved. The patient was eventually extubated and transferred back to the floor in stable condition. It is important for internists and critical care physicians in the MICU to be aware of post-HCT complications and be cognizant of the clinical signs of ES to better understand the syndrome and its management.

Key Words: Engraftment syndrome, Hematopoietic cell transplantation, Noninfectious fevers, Acute multiorgan failure

1. INTRODUCTION

Patients who undergo allogeneic hematopoietic cell transplantation (alloHCT) are at risk of developing complications in the post-transplant phase and often will require admission to the medical intensive care unit (MICU) for treatment.[1] Indications for MICU admissions are usually sepsis, cardiovascular collapse, neurological disorders, arrhythmia, gastrointestinal bleeding, and respiratory failure.[1,2] The pulmonary complications consist mainly of infection, bleeding, and acute respiratory distress syndrome. Patients often will require the use of invasive mechanical ventilation in such pulmonary complications.[1–3]

Not uncommonly, a patient will present post-HCT with fever, multiorgan failure and shock. After thorough evaluation and an unremarkable infectious work-up, other diagnoses should be considered. We can then rely on the post-transplant timeline, the absolute neutrophil count trend and clinical presentation to establish the diagnosis of engraftment syndrome (ES). ES is a febrile syndrome that encompasses multiple complications that occur during the early neutrophil recovery phase after HCT.[14,5] Due to its pleiotropic presentation, it can be difficult to characterize and diagnose. Initial pre-
sentation includes a noninfectious fever with various clinical findings, such as skin rash, diarrhea, non-cardiogenic pulmonary edema, weight gain, encephalopathy, renal and hepatic dysfunction. While many cases of ES can resolve spontaneously or with the administration of steroids, some cases can still be fatal, as mortality rate has been reported to be 8%-18%. It is thus important to understand the presentation of ES so that physicians can better approach treatment in such patients. This case highlights the detailed approach that should be taken when managing these patients and helps review the clinical manifestations and therapeutic options for ES in MICU.

2. CASE PRESENTATION

A 20-year-old male patient with history of B-Cell Acute Lymphoblastic Leukemia (ALL) presented for an alloHCT using peripheral blood stem cells as the graft source. The conditioning regimen consisted of myeloablative doses of total body irradiation (TBI) combined with cyclophosphamide (CY). Additionally, palifermin was provided peri-conditioning to decrease risk of severe mucositis. One month before the alloHCT, he completed two cycles of Blinatumomab and achieved complete remission at the time of alloHCT. On day +2 of his transplant course he had an episode of diarrhea which resolved with loperamide; and on day +6 he spiked a fever of 102.7°F. He was pan-cultured with no source of infection found. He continued to have persistent fevers and was empirically started on broad spectrum antibiotics. On day +11, the patient needed to be admitted to the MICU for acute hypoxemic respiratory failure, requiring intubation and mechanical ventilation. The patient was in distributive shock, febrile, tachycardic and tachypneic. Lung exam revealed bilateral crackles and rhonchi. Extremities were warm and vasodilated. His skin showed a diffuse, completely blanchable, light pink, erythematous rash and innumerable 1-5 mm completely blanchable thin papules and macules coalescing into broad patches and plaques.

Table 1. Laboratory trends since alloHCT

| Days since PBSCT | 0 | 1 | 6 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 |
|-----------------|---|---|---|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| WBC (10^9/L)    | 0.3 | 0.2 | <0.1 | 0.7 | 1.2 | 1.9 | 3.9 | 5.8 | 6.4 | 9.2 | 6.3 | 5.3 | 6.7 | 9.3 | 6.9 | 4.8 | 7.7 | 6.4 | 8.7 | 5.3 |
|ANC (10^9/L)     | 0.26 | 0.05 | 0.59 | 0.96 | 1.50 | 3.12 | 4.87 | 4.67 | 5.43 | 3.60 | 3.60 | 5.03 | 7.07 | 5.87 | 3.79 | 6.93 | 5.25 | 7.83 | 4.77 |
|Plts (10^9/L)    | 109 | 92 | 18 | 23 | 60 | 32 | 28 | 36 | 33 | 23 | 14 | 21 | 17 | 19 | 19 | 29 | 17 | 24 | 38 | 45 | 64 |
|Hgb (g/dl)       | 12.6 | 13.4 | 10.8 | 7.7 | 7.9 | 6.8 | 8.0 | 7.4 | 6.8 | 9.3 | 8.9 | 8.0 | 8.4 | 9.0 | 8.8 | 9.2 | 10.1 | 10.2 | 8.9 | 8.0 |
|Cr (mEq/l)       | 0.38 | 0.47 | 0.40 | 0.62 | 0.76 | 1.16 | 1.72 | 1.82 | 2.55 | 2.77 | 2.05 | 1.40 | 1.22 | 1.07 | 1.39 | 1.59 | 1.42 | 1.22 | 0.97 | 0.80 |
|BUN (mEq/l)      | 15 | 10 | 15 | 15 | 48 | 55 | 80 | 98 | 96 | 78 | 72 | 64 | 64 | 73 | 72 | 60 | 46 | 37 |

Note. As shown in Table 1 the patient was transferred to the ICU on post-alloHCT day 11. ANC was already improving. Creatinine was beginning to increase. He was started on equivalent to solumedrol 1 mg/kg/day on post-alloHCT day 13 with improvement of his fevers, acute kidney injury and rash. On post-alloHCT day 16, his respiratory culture was positive for VRE and he was treated with linezolid. He was transferred out of the ICU on post-alloHCT day 23.

On the date of MICU admission, the patient was beginning to have ANC recovery. His ANC was 0.96 which was an increase from a nadir of 0.05 (see Table 1). During his MICU course, he developed worsening kidney function. Creatinine increased up to 2.77 from a baseline creatinine of 0.47. Liver function panel was within normal limits. Chest X-ray showed cardiomegaly, bilateral patchy air space opacities, pulmonary vascular congestion and bilateral pleural effusions (see Figure 1). CT scan of the chest did show bilateral areas of interlobular septal thickening, scattered ground glass opacities and focal areas of bilateral lower lobe consolidation (see Figure 2). The echocardiogram showed right ventricular overload and non-collapsible inferior vena cava, but was otherwise unremarkable.

Figure 1. Chest X-ray on Admission day to MICU (post-alloHCT day 11)
The patient needed deep sedation, paralysis with neuromuscular blocker and vasopressors. Bronchoscopy with bronchoalveolar lavage (BAL) to the lingula showed that each sequential lavage of 60 ml aliquot of sterile saline returned increasingly bloodier. Bronchoalveolar fluid laboratories confirmed increasing red blood cell count with each aliquot (see Table 2). This was consistent with diffuse alveolar hemorrhage. Viral, bacterial and fungal cultures done on the BAL were negative. However, the patient was continued on broad spectrum antibiotics during his MICU admission.

| Sequential aliquots | 1  | 2  | 3  |
|---------------------|----|----|----|
| RBC count (10¹²/L)   | 3,106 | 10,389 | 13,325 |

Note. As shown in Table 2 each sequential aliquot returned samples with increasing amounts of red blood cells, suggestive of diffuse alveolar hemorrhage.

In view of the noninfectious fevers, shock and acute kidney injury, ES was considered as the diagnosis. This was particularly relevant in the setting of his improving ANC. On his third day in the MICU (day +13 post-transplant), the steroids were increased to the equivalent of methylprednisolone 1 mg/kg IV daily, which was then increased to 2 mg/kg due to concern for progression to Idiopathic Pneumonia Syndrome (IPS). His rash resolved a few days after the administration of steroids and he was successfully weaned off vasopressors (day +14 post-transplant). Oxygenation significantly improved after the steroids. Although the MICU admission was later complicated with Vancomycin Resistant Enterococcus Faecium (VRE) pneumonia, this was successfully treated with linezolid. Patient was extubated after eleven days of mechanical ventilation (day +22 post-transplant). Renal function recovered and his fever curve normalized. Patient was then transferred back to bone marrow transplant service in stable condition after twelve days in the MICU (day +23 post-transplant). The patient underwent further work up later on, including colonoscopy with biopsy, which failed to show development of graft-vs-host disease (GVHD).

3. DISCUSSION

ES comprises a range of signs and symptoms occurring proximal to ANC recovery after HCT. The syndrome has been described after autologous, allogeneic and syngeneic transplants. Since there is no uniform definition of ES, the incidence varies broadly based on the diagnostic criteria with a reported range of 7%–59%. Risk factors have similarly also been difficult to elucidate, mainly due to the broad definition of ES, the different drugs and doses used in the conditioning regimens; and the number of cycles of previous chemotherapy given from the time a patient was diagnosed with a hematologic malignancy up to the time of HCT. Some factors have been suggested to cause increased risk, such as post-transplant granulocyte colony stimulation factor (G-CSF) therapy, busulfan-based conditioning regimens, younger age and female gender. More data is needed to better define the risk factors.

There are few reports on the pathophysiology of ES. It is believed that ES is likely mediated by activated leukocytes and proinflammatory cytokines, leading to vascular leak, organ dysfunction and constitutional symptoms, such as fever. However, the lack of typical clinical features of ES following neutrophil recovery suggest that other factors also contribute to this syndrome. Nevertheless, numerous studies in animal and human models suggest that the immune system plays an active role in the development of ES. The inflammatory nature of ES is further supported by the association of elevated levels of C-reactive protein in ES patients and by their clinical response to corticosteroid therapy.
The clinical features of ES have been defined mainly according to Spitzer and Maiolino diagnostic criteria.[4,5] According to Spitzer, the major diagnostic criteria include a non-infectious fever (≥38.3°C), erythematous rash, and noncardiogenic pulmonary edema. Minor criteria include hepatic dysfunction, renal insufficiency, weight gain, and unexplained transient encephalopathy. The requirement to establish the diagnosis of ES is to have the presence of all three major criteria or two major and one or more minor criteria within 96 hours of neutrophil engraftment (see Table 3). According to Maiolino, ES is defined as the development of a noninfectious fever in combination with diarrhea, rash, or pulmonary infiltrates within 24 hours of engraftment (see Table 3). Other reports have defined a broader timeline in which ES symptoms can occur, with observation of clinical signs of ES occurring as early as 5 days before engraftment to 7 days after engraftment.[7]

Table 3. Diagnostic criteria for engraftment syndrome

| Requirements             | Spitzer                                      | Maiolino                           |
|--------------------------|----------------------------------------------|------------------------------------|
| Major Criteria           | Temperature ≥38.3°C with no identifiable infectious source | Non-infectious Fever               |
|                          | Erythematous rash covering > 25% body surface area (not attributable to any medications) |                                     |
|                          | Noncardiogenic pulmonary edema               |                                    |
| Minor Criteria           | Hepatic dysfunction: bilirubin ≥2 mg/dl or transaminase levels ≥2 times normal | Skin rash                          |
|                          | Renal insufficiency: serum Cr ≥2 times baseline | Pulmonary infiltrates              |
|                          | Weight gain ≥2.5% of baseline body weight    | Diarrhea                           |
|                          | Unexplained transient encephalopathy        |                                    |
| Timeline                 | Symptoms within 4 days of engraftment        | Symptoms within 1 day of engraftment |

The first step to approaching patients when there is a concern for ES is to rule out alternative causes, like infection and drug interactions. If ES is still a concern, the approach to management depends on severity of symptoms. ES is usually self-limited and can resolve with supportive therapy.[7] Indications for treatment with corticosteroids include high noninfectious fever and manifestations of vascular leak, especially pulmonary edema. ES is usually responsive to corticosteroid therapy, with improvement or resolution of symptoms in 2-3 days. Methylprednisolone at a recommended dose of 1-1.5 mg/kg/day is usually sufficient, though higher doses may be warranted for respiratory compromise, development of IPS and diffuse alveolar hemorrhage.[4] The optimal duration of glucocorticoid therapy is not known. However, one suggested alternative is to initiate methylprednisolone 1-1.5 mg/kg/day until the symptoms resolve, which typically occurs within 2 to 3 days. Dosing can then be reduced to prednisone 40-50 mg orally daily for 2 to 3 days, followed by prednisone tapered 10 mg every 2 to 3 days if symptoms continue to resolve.[11] Studies have shown that early intervention with corticosteroids can mitigate progression to more severe manifestations of ES. If symptoms are still refractory to corticosteroid therapy, a biopsy at the site of end-organ damage (i.e. skin biopsy for a rash or colon biopsy for diarrhea) could be considered to diagnose ES.[7] In these cases, the administration of other immune suppressants could alleviate symptoms as well.[7] The role for additional immunotherapy should be determined case-by-case and in consultation with the Bone Marrow Transplant service.

In literature there has been some controversy as to whether ES is a true clinical entity. There is a debate that many features are shared between ES and acute graft vs. host disease (GVHD), and that ES could potentially be an early manifestation of GVHD. However, ES is also reported after autologous transplants, seemingly excluding GVHD.[6,7] GVHD is the most common life-threatening complication after allogeneic HCT, as it would affect 30%-50% of the transplanted patients.[12] It occurs when the immunocompetent T-cells in the donated tissue (the graft) recognize the recipient (the host) as foreign.[12] The typical signs of acute GVHD include maculopapular rash, hyperbilirubinemia and diarrhea. The diagnosis is mainly clinical, but very often requires biopsy. The treatment of acute GVHD includes glucocorticoids; and patient with resistance to steroids, unfortunately will have a dismal prognosis with a survival rate of only 5% to 30%.[12] ES has not been observed during bone marrow recovery in non-transplant settings, such as post-chemotherapy, which suggests that ES only occurs in the setting of stem cell transplantation. There are also several reports of an increased risk...
of developing GVHD in ES patients. Chang et al. specifically reported a higher incidence of GVHD in allogeneic HCT patients who were diagnosed with ES.\cite{10} He also noted a longer hospital stay, more severe GVHD and lower overall survival in patients with ES. However, more studies are needed to uniformly define ES and its risk factors before conclusions can be drawn.

4. CONCLUSION
ES is a multifaceted syndrome that remains poorly defined despite numerous reports. These patients are complex and will often require high quality intensive therapy, supportive care and a multidisciplinary approach in the MICU. Although ES is typically observed and treated on the Hematology/Oncology service, it will also be diagnosed and managed on general medicine floors and the MICU as well. It is important for Internal Medicine physicians and Critical Care physicians to be aware of the symptoms of ES, potential complications and approach to management.

CONFLICTS OF INTEREST DISCLOSURE
The authors have declared no conflicts of interest.

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