Respiratory failure and rash following stem cell transplant

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A 52 year-old man suffered a cardiopulmonary arrest in the bone marrow transplant unit. He had sudden onset of severe hypoxemia and hypotension necessitating endotracheal intubation, titration of his pre-existing vasopressor support, and two ampules of sodium bicarbonate. He had return of spontaneous circulation within minutes of his resuscitation, and was transferred to the medical intensive care unit (MICU) for further treatment.

The patient had been admitted to the bone marrow transplant unit ten days prior to his arrest for a matched, unrelated donor nonmyeloablative transplant (MUD/MNAT). He had a history of small cell lymphocytic leukemia diagnosed 5 years prior to this admission. And had undergone several chemotherapy regimens, including CVP (cyclophosphamide, vincristine, prednisolone); fludarabine and cyclophosphamide; CHOP (cyclophosphamide, adriamycin, vincristine, and prednisolone); and ESHAP (etoposide, methylprednisolone, cytarabine, and cisplatin), but none controlled his leukemia.

His hospital course had been complicated by a neutropenic fever five days after the bone marrow transplant (day +5); coagulase negative Staphylococcus Aureus sepsis on day +6, for which he received vancomycin and had his central venous lines replaced; acute renal failure beginning on day +8 necessitating renal replacement therapy on day +9; and progressive hypotension and hypoxic respiratory insufficiency beginning on day +9 that culminated in his arrest on day +10 and subsequent transfer to the MICU.

His other past medical history was rather unremarkable. He is married and lives with his wife. He is a 60 pack-year smoker who quit in 2005. He denied alcohol or drug use.

At the time of his arrest, his medications included esomeprazole, fluconazole, gentamicin, meropenem, a multivitamin, mycophenolate mofetil 1000 mg twice daily, pentamidine inhaled once monthly, vancomycin, and cyclosporine.

Figure 1- Macular rash in left axillary fold

On physical exam on his arrival to the MICU, his vitals were T 38.8, P 107, BP 73/56 (on dopamine and norepinephrine), RR 22, oxygen saturation of 98% on 100% FiO2. He was intubated, sedated, and in no acute distress. His pupils were equal and reactive, and he had some mild scleral icterus. Heart rate was regular and tachycardic, without murmer, gallop or rub; lung sounds were coarse bilaterally. Abdomen was soft and nontender. Skin demonstrated an erythematous, macular eruption over his face, neck, upper torso, and arms (see figure 1).
Laboratory values demonstrated a WBC of 1.0 with an ANC of 450 cells/mL. Hemoglobin was 9.1, platelet count 24,000. Chemistry demonstrated an anion gap of 14 with a serum bicarbonate of 14. Blood urea nitrogen was 54, and the creatinine was 4.7. ALT was 61, AST was 315, and total bilirubin was 3.7. Serum LDH was 3460. ABG prior to intubation was pH 7.19, pCO₂ 49, pO₂ 81 on 100% BiPAP. He had multiple blood and urine cultures from the previous 5 days, all of which were negative. An echocardiogram immediately following the arrest demonstrated an ejection fraction of 45% without wall motion abnormalities. Chest X-ray immediately following intubation is shown in figure 2.

![Portable chest X-ray upon admission to MICU](image)

*What is the diagnosis and treatment?*
Engraftment syndrome is the clinical constellation of signs and symptoms that occurs during neutrophil recovery following significant cytotoxic chemotherapy or stem cell transplantation. It has also been referred to in the literature as “capillary leak syndrome,” “autoaggression syndrome,” and “aseptic shock syndrome.” Historically, it has generally been associated with autologous stem cell transplants. A clinically similar collection of signs and symptoms accompanying neutrophil recovery after allogeneic stem cell transplant has generally been attributed to early graft-versus-host disease (GVHD). However, newer non-myeloablative preparatory regimens for allogeneic stem cell transplants have demonstrated engraftment syndrome presentations without evidence of GVHD on biopsy specimens, which had led some to hypothesize that ES and GVHD may be entities with similar pathophysiologic etiologies.

Consensus diagnostic criteria for ES have not been adopted by any major scientific organizations. Spitzer (2001) proposed diagnostic criteria for ES in an attempt to standardize the diagnosis:

<table>
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<tr>
<th>Diagnostic Criteria For Engraftment Syndrome</th>
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<td>3 major criteria OR 2 major and one minor criteria within 36 hours of engraftment (ANC&gt;100-500)</td>
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**Major Criteria:**
- Fever >38.3°C without identifiable infectious etiology
- Erythrodermatous rash covering >25% BSA, not attributable to medication
- Diffuse pulmonary infiltrates (non-cardiogenic) and hypoxemia

**Minor Criteria:**
- Hepatic dysfunction: Bilirubin >2mg/dL or transaminase levels >2x normal
- Renal insufficiency: serum creatinine >2x baseline
- Weight gain >2.5% of baseline body weight
- Transient, unexplained encephalopathy

ES is generally a phenomenon with short-lived and mild clinical manifestations. In mild cases, supportive care is appropriate, as the syndrome abates as marrow recovery proceeds. However, a small proportion of patients develop severe symptoms including organ failure, with hemodynamic or respiratory collapse necessitating intensive care monitoring and more aggressive care.

The reported incidence of ES varies widely. Among autologous SCT, incidence reports range from 7-59%, depending on the definition of ES. In the setting of NMAT, Gorak et al. found the incidence to be around 10% in this cohort, the median day of onset was +10, and none of the patients required mechanical ventilation. However, the presence of ES increased 6-month mortality from 16% in those without ES to 49% in those who suffered from ES.

The pathophysiology of ES is thought to be similar to that of GVHD, and is truly a perfect storm of circumstances creating an immunologic milieu in which host tissues are attacked. This process is thought to have three distinct contributing factors (see figure 3). First, the preparative regimen leads to widespread endothelial and epithelial injury within the host. This damage releases a host of inflammatory mediators, including IL-1 and TNF-α, which prime dendritic cells and upregulates the expression of MHC complexes in these cells. The second factor takes place after the infusion of donor T-cells. These cells can be activated by the MHC complex on antigen presenting cells in the absence of any antigenic stimulus, which leads to release of IL-2 and IFN-γ; these act to stimulate further T-cell clonal proliferation. The third factor is the combination of the Natural Killer cells that were primed in phase 2 with lipopolysaccharide released from the gut during the preparative phase, leading to release of TNF-α and widespread tissue destruction.

Tissue sampling often does not occur with ES, as most episodes are only mildly symptomatic. When tissue is obtained, most are dermatologic and demonstrate lymphocytic infiltration of the dermis. Many ES patients undergo bronchoscopy with bronchoalveolar lavage (BAL) as part of the workup to rule out infectious causes of their pulmonary infiltrates. Very little is known about the cellular makeup of BAL in ES, and the utility of cytologic BAL specimens in the diagnosis of this syndrome is unknown. However, further research on BAL in ES may provide clues to the immunologic pathophysiology of the disease, and may be useful to
risk stratify those who would benefit from pharmacologic therapy.

Most cases of ES will manifest with only mild symptomatology and need not be treated, as they will abate as engraftment proceeds. However, more serious cases generally respond quickly and dramatically to corticosteroids. In one series, over 90% of patients with ES improved within 24 hours of initiation of steroid therapy.

Our patient underwent bronchoscopy with BAL for microbiologic studies soon after initiation of mechanical ventilation. Steroids were initiated for presumed sepsis-related adrenal insufficiency, and BAL cultures remained sterile. His hypoxemia improved rapidly, and his rash and renal failure resolved quickly. He was successfully extubated on day 17. His subsequent hospital course was complicated by GVHD of the gut and skin, and disseminated CMV. He was ultimately discharged on day 54.

![Figure 3- Immunologic pathophysiology of acute GVHD](image)

**References**

1. Spitzer TR. Engraftment syndrome following hematopoietic stem cell transplantation. Bone Marrow Transplant 2001; 27:893-898
2. Cahill RA, Spitzer TR, Mazumder A. Marrow engraftment and clinical manifestations of capillary leak syndrome. Bone Marrow Transplant 1996; 18:177-184