

Engraftment Syndrome: An Updated Review **Mutahar E and Al-Anazi KA***

Abstract

Engraftment syndrome is a constellation of clinical manifestations that occur at the time of neutrophil recovery following hematopoietic stem cell transplantation. There are several risk factors, but the reports on some of them are rather conflicting. Additionally, not only the clinical manifestations but also the laboratory findings are nonspecific and may overlap with several conditions such as acute graft versus host disease, drug toxicity, radiation-induced damage and infectious disorders. Treatment of symptomatic and severe forms is similar to that of graft versus host disease. Hence, there is a need for: revision of the diagnostic criteria, establishment of scoring system to determine prognosis and to direct therapy as well as the addition new criteria to differentiate it from other similar conditions.

Keywords: Engraftment syndrome; Hematopoietic stem cell transplantation; Graft versus host disease; Umbilical cord blood transplantation; Capillary leak syndrome

Department of Hematology and Hematopoietic Stem Cell Transplantation, Oncology Center, King Fahad Specialist Hospital, P.O. Box: 15215, Dammam 31444, Saudi Arabia

*Corresponding author: Al-Anazi KA

✉ kaa_alanazi@yahoo.com

Department of Hematology and Hematopoietic Stem Cell Transplantation, Oncology Center, King Fahad Specialist Hospital, P.O. Box: 15215, Dammam 31444, Saudi Arabia.

Tel: 966 - 03- 8431111

Received: October 03, 2017; **Accepted:** October 15, 2017; **Published:** October 24, 2017

Citation: Mutahar E, Al-Anazi KA (2017) Engraftment Syndrome: An Updated Review. J Stem Cell Biol Transplant Vol.1 No.3:16

Introduction

Engraftment syndrome (ES) is a clinical condition that is characterized by fever, skin rash, pulmonary edema, weight gain, liver and renal dysfunction in addition to encephalopathy and it occurs at the time of neutrophil recovery after hematopoietic stem cell transplantation (HSCT) [1-8]. ES typically develops within 4 days of granulocyte recovery or 9-16 days following HSCT with a median of 11 days post-HSCT. However, similar syndrome has been reported >1 week before granulocyte recovery after umbilical cord blood transplantation (UCBT) [3,9]. ES was first described by Lee et al. in a retrospective analysis, published in 1995, of 248 patients with cancer undergoing autologous HSCT [1,5]. ES has been described after allogeneic HSCT, but has been more frequently reported following autologous transplantation [1-5,8-11].

Epidemiology and Pathophysiology

The incidence of ES is very variable depending on the criteria used to define ES. In studies using stringent criteria, the incidence ranges between 7% and 10%, while in studies using wider criteria incidences up to 72% have been reported [6,7,9,10-15]. ES has been described as: auto-aggression syndrome, peri-engraftment respiratory distress syndrome (PERDS), aseptic shock syndrome, capillary leak syndrome and autologous graft versus host disease (GVHD) in the setting of autologous HSCT [1,11,14,16].

The pathophysiology of ES is poorly understood [1,11]. Probably, it involves: (1) release of pro-inflammatory cytokines such as interleukin (IL)-2, IL-6, tumor necrosis factor (TNF)- α , interferon- γ , monocyte-colony stimulating factor (CSF) and erythropoietin, (2) release of products of degranulation and oxidative metabolism, and (3) systemic endothelial damage that may ultimately result in multi-organ failure [1,3,10,11]. ES has been described after: autologous HSCT; allogeneic HSCT with myeloablative and non-myeloablative conditioning therapy, UCBT and haploidentical HSCT; and syngeneic HSCT between identical twins [1,3,5,6,9-11,16-24]. ES has been described in several medical conditions including: (10) plasma cell disorders such as multiple myeloma, amyloidosis, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein and skin changes) and plasma cell leukemia; (2) leukemias including: acute myeloid leukemia, acute lymphoblastic leukemia, chronic myeloid leukemia (CML) and chronic lymphocytic leukemia; (3) lymphomas, mainly non-Hodgkin types; (4) solid tumors such as breast cancer; and (5) autoimmune disorders such as multiple sclerosis [1,3,10,11,16,22]. In addition to the forms of HSCT and the types of medical illnesses described above, additional risk factors for the development of ES include: (1) female gender, (2) older age, (3) absence of previous chemotherapy or the use of less aggressive chemotherapeutic agents prior to HSCT, (4) use of busulfan, cyclophosphamide, fludarabine and etoposide, (5)

use of corticosteroids, bortezomib and lenalidomide, (6) use of amphotericin and granulocyte-CSF, (7) use of radiotherapy prior to HSCT, (8) peripheral blood as the source of hematopoietic stem cells, (9) infusion of higher numbers of CD34+ cells or mononuclear cells in the graft, and (10) infusion-related febrile reactions after haploidentical HSCT [1-3,6,7,10-12,14,16,21,22,25,26].

Clinical Manifestations and Complications

The clinical manifestations of ES include: (1) common and characteristic features that include: non-infectious fever; skin rash; PERDS manifested as pulmonary edema, lung infiltrates and hypoxemia; diarrhea; weight gain; renal dysfunction; hepatic dysfunction with jaundice; transient encephalopathy; and capillary leak syndrome manifesting as: weight gain, edema, ascites as well as hypoalbuminemia; and (2) rarely described manifestations which include: severe colitis, pericarditis, acute brachial neuropathy in addition to bilateral marginal keratitis [1-3,8-11,18,24,27-30]. The diagnostic criteria for ES are included in **Table 1** [1-3,10,11].

Diagnostic Investigations

The laboratory findings in ES include: (1) elevated C-reactive protein (CRP) which is encountered in almost all cases, (2) elevated serum creatinine, (3) elevated serum bilirubin and hepatic transaminases, and (4) decreased serum albumin level [1,11,17,24]. Specific features of ES on skin biopsies include: dominance of CD4+ cells and decreased number of CD1a+ cells in the epidermis [31]. Chest radiography may show: interstitial pulmonary edema, pulmonary infiltrates that may be diffuse, and pleural effusions [11,32]. Recently described findings that may serve as biomarkers of ES include: (1) elevated serum procalcitonin level, (2) expression of elafin, a protein secreted in response to IL-1 or TNF- α , in the peripheral blood or elevated blood level of elafin, (3) elevated proinflammatory cytokines such as IL-1 β , IL-6 and IL-12 followed by a surge in anti-inflammatory cytokines including: IL-4 and IL-13, in addition to (4) elevated CRP [1,11,33,34].

Differential Diagnosis

The differential diagnosis of ES includes: (1) acute and hyperacute GVHD in allogeneic HSCT and autologous GVHD in autologous transplantation, (2) drug-induced toxicity, (3) radiation-induced toxicity, (4) sepsis and infectious disorders, (5) pre-engraftment syndrome (PES), and (6) hematopoietic graft rejection [1-3].

PES was first described by Kishi, et al. [35] in 2005, as immune reaction that occurred in 78% of adults receiving reduced intensity conditioning UCBT. The clinical manifestations were: fever, skin rash, diarrhea, jaundice and weight gain of >10% from baseline [20,35]. PES is not usually explained by infection or adverse drug reactions. It also differs from ES and acute GVHD and it occurs before neutrophil engraftment. However, it has remained poorly characterized with unclear prognosis or appropriate therapy [20,35]. Several recent studies on PES have come to the following conclusions: (1) common occurrence after UCBT, (2) development before neutrophil recovery, (3) associations with: cyclosporine in GVHD prophylaxis and total body irradiation in conditioning therapy, (4) enhancement of engraftment without significant morbidity as well as early achievement of complete donor chimerism, and (5) controversial association with development of acute GVHD [20,36-38].

Treatment and Prevention of ES

Treatment of ES depends on the severity of the illness as it may be self-limited and up to one third of cases require no treatment at all [3]. Indications for treatment of ES include: (1) temperature >39°C, and (2) clinically significant manifestations of vascular leak, especially pulmonary edema [3]. The main therapeutic modalities of ES are: (1) steroids in the one of the following formulations: (a) intravenous (IV) methylprednisolone: 1-2 mg/kilogram (kg) body weight per day, (b) oral prednisolone: 0.5-10 mg/kg/day, or (c) dexamethasone palmitate: 2.5 mg/m²/day for 3 days then to taper quickly over 7-8 days, (2) supportive measures such as: antipyretics, oxygen, diuretics and topical therapy for skin eruptions, and (3) additional measures such as: intubation and mechanical ventilation, renal doses of dopamine to improve renal function, and C1 esterase inhibitor concentrates [2,3,9-11].

Table 1 Diagnostic Criteria for Engraftment Syndrome.

	SPITZER	MAIOLINO
Requirements	3 major or 2 major + 1 minor within 4 days of engraftment	major + 1 minor within 1 day of presence of neutrophils
Major Criteria	- Non-infectious fever, temperature $\geq 38.3^{\circ} \text{C}$ - Skin rash involving > 25% of body surface not attributable to medications - Non-cardiogenic pulmonary edema manifested by diffuse pulmonary infiltrates - Hypoxemia	- Non-infectious fever
Minor Criteria	- Weight gain $\geq 2.5\%$ of baseline body weight - Hepatic dysfunction with either bilirubin ≥ 2 mg/dL or transaminase level ≥ 2 times normal - Renal insufficiency with serum creatinine ≥ 2 times baseline - Transient encephalopathy unexplained by other causes.	- Skin rash - Pulmonary infiltrates - Diarrhea commencing 24 hours before or at any time after the first appearance of neutrophils

11,40]. Recombinant human soluble thrombomodulin has been shown to counteract capillary leak associated with ES [41]. Other immunosuppressive agents such as tacrolimus, mycophenolic acid and etanercept have no defined role in the management of ES [2,3]. Steroid therapy may need to be prolonged in case of persistence of clinical manifestations such as fever or skin rash and may be given in higher doses in the presence of complications such as severe respiratory compromise [2,3,9-11]. Several studies have shown that the following prophylactic measures may prevent the evolution of ES under certain circumstances: (1) GVHD prophylaxis using methotrexate in UCBT, (2) use of cyclophosphamide and prednisolone in induction followed by cyclophosphamide mobilization in patients with POEM syndrome, (3) use of donor lymphocyte infusions in relapsed CML after allogeneic HSCT, and (4) steroid prophylaxis significantly decreases the risk of ES following autologous HSCT and is associated with shortened hospitalization without increasing the risk of infection [42-45].

Course and Prognosis

Most cases of ES are mild and resolve spontaneously or with steroid therapy [1,3]. However, ES can occasionally be fatal and deaths are usually related to respiratory dysfunction and multi-organ failure. Therefore, ES is still an important cause of morbidity and mortality in recipients of various forms of HSCT [1,2,6,13,46]. Early detection of ES is essential to reduce the associated morbidity and mortality [17,31,47,48]. Studies have shown a favorable outcome with: (1) early diagnosis and detection, (2) prompt initiation of corticosteroid therapy, (3) reduction in the unnecessary use of antimicrobial agents, and

(4) reduction in the duration of hospitalization of recipients of HSCT [10,15,17,48]. However, few studies have shown the following long-term complications of ES: (1) poor outcome of ES despite early recognition and early institution of corticosteroid therapy, (2) evolution of acute GVHD in recipients of allogeneic HSCT having ES, and (3) ES may play a role in the development of therapy-related myelodysplastic syndrome in patients with Hodgkin disease and non-Hodgkin lymphoma receiving autologous HSCT [4,23,49,50].

Conclusions and Future Directions

In order to improve the outcome of ES, the following are needed: (1) identification of biomarkers that are specific for ES in order to start pre-emptive therapy so as to decrease the morbidity and mortality related to severe forms of ES, and (2) revision of the current diagnostic criteria to increase the sensitivity of its detection.

Unfortunately, there is no consensus over: the diagnostic criteria or even the risk factors for ES, thus leading to wide variation in the reported incidence of ES that ranges between 7% and 72%. Also, the clinical manifestations as well as the laboratory findings are ill defined and can overlap with many other disorders such as acute GVHD. Therefore, there is urgent need not only for having strict diagnostic criteria and severity scores, but also for a possible change in the nomenclature of the syndrome into: autologous GVHD in the setting of autologous transplantation and hyperacute GVHD in allogeneic HSCT as this approach looks more acceptable particularly in severe forms of ES.

References

- 1 Cornell RF, Hari P, Drobyski WR (2015) Engraftment syndrome after autologous stem cell transplantation: an update unifying the definition and management approach. *Biol Blood Marrow Transplant* 21: 2061-2068.
- 2 Spitzer TR (2001) Engraftment syndrome following hematopoietic stem cell transplantation. *Bone Marrow Transplant* 27: 893-898.
- 3 Spitzer TR (2015) Engraftment syndrome: double-edged sword of hematopoietic cell transplants. *Bone Marrow Transplant* 50: 469-475.
- 4 Chang L, Frame D, Braun T, Gatzka E, Hanauer DA, et al. (2014) Engraftment syndrome after allogeneic hematopoietic cell transplantation predicts poor outcomes. *Biol Blood Marrow Transplant* 20: 1407-1417.
- 5 Lee CK, Gingrich RD, Hohl RJ, Ajram KA (1995) Engraftment syndrome in autologous bone marrow and peripheral stem cell transplantation. *Bone Marrow Transplant* 16: 175-182.
- 6 Gorak E, Geller N, Srinivasan R, Espinoza-Delgado I, Donohue T, et al. (2005) Engraftment syndrome after nonmyeloablative allogeneic hematopoietic stem cell transplantation: incidence and effects on survival. *Biol Blood Marrow Transplant* 11: 542-550.
- 7 Schmid I, Stachel D, Pagel P, Albert MH (2008) Incidence, predisposing factors, and outcome of engraftment syndrome in pediatric allogeneic stem cell transplant recipients. *Biol Blood Marrow Transplant* 14: 438-444.
- 8 Al-Anazi KA (2012) Autologous hematopoietic stem cell transplantation for multiple myeloma without cryopreservation. *Bone Marrow Res* 2012: 917361.
- 9 Kaner RJ, Zappetti D (2017) Pulmonary complications of autologous hematopoietic cell transplantation. Up To Date.
- 10 Maiolino A, Biasoli I, Lima J, Portugal AC, Pulcheri W, et al. (2003) Engraftment syndrome following autologous hematopoietic stem cell transplantation: definition of diagnostic criteria. *Bone Marrow Transplant* 31: 393-397.
- 11 Carreras E, Fernandez-Aviles F, Silva L, Guerrero M, Fernandez de Larrea C, et al. (2010) Engraftment syndrome after auto-SCT: analysis of diagnostic criteria and risk factors in a large series from a single center. *Bone Marrow Transplant* 45: 1417-1422.
- 12 Gonzalez-Vicent M, Ramirez M, Sevilla J, Perez A, Fernandez S, et al. (2004) Engraftment syndrome after autologous peripheral blood progenitor cell transplantation in pediatric patients: a prospective evaluation of risk factors and outcome. *Bone Marrow Transplant* 34: 1051-1055.
- 13 Madero L, Vicent MG, Sevilla J, Prudencio M, Rodriguez F, et al. (2002) Engraftment syndrome in children undergoing autologous peripheral blood progenitor cell transplantation. *Bone Marrow Transplant* 30: 355-358.
- 14 Moreb JS, Kubilis PS, Mullins DL, Myers L, Youngblood M, et al. (1997) Increased frequency of autoaggression syndrome associated with autologous stem cell transplantation in breast cancer patients. *Bone Marrow Transplant* 19: 101-106.

- 15 Gerivaz R, Costa F, Schuh J, Monteiro LP, Ferreira G, et al. (2013) Engraftment syndrome (ES) after autologous stem cell transplantation (SCT): analysis of diagnostic criteria and risk factors. *Blood* 122: 5508.
- 16 Khan SA, Gaa B, Pollock BH, Shea B, Reddy V, et al. (2001) Engraftment syndrome in breast cancer patients after stem cell transplantation is associated with poor long-term survival. *Biol Blood Marrow Transplant* 7: 433-438.
- 17 Lopes da Silva R, Costa F, Ferreira G, de Sousa AB (2012) Post-autologous hematopoietic SCT engraftment syndrome: a single center experience. *Bone Marrow Transplant* 47: 456-457.
- 18 Kaner RJ, Zappetti D (2017) Pulmonary complications after allogeneic hematopoietic cell transplantation. *Up To Date*.
- 19 Brownback KR, Simpson SQ, McGuirk JP, Lin TL, Abhyankar S, et al. (2014) Pulmonary manifestations of the pre-engraftment syndrome after umbilical cord blood transplantation. *Ann Hematol* 93: 847-854.
- 20 Patel KJ, Rice RD, Hawke R, Abboud M, Heller G, et al. (2010) Pre-engraftment syndrome after double-unit cord blood transplantation: a distinct syndrome not associated with acute graft-versus-host disease. *Biol Blood Marrow Transplant* 16: 435-440.
- 21 Chen Y, Huang XJ, Liu KY, Chen H, Chen YH, et al. (2015) Infusion-related febrile reaction after haploidentical stem cell transplantation in children is associated with higher rates of engraftment syndrome and acute graft-versus-host disease. *Pediatr Transplant* 19: 918-924.
- 22 Kawano C, Muroi K, Kuribara R, Matsumoto Y, Ohtsuki T, et al. (2000) Engraftment syndrome after autologous peripheral blood stem cell transplantation with high numbers of peripheral blood stem cells followed by granulocyte colony-stimulating factor administration. *Bone Marrow Transplant* 25: 228-229.
- 23 Omer AK, Kim HT, Yalamarti B, McAfee SL, Dey BR, et al. (2014) Engraftment syndrome after allogeneic hematopoietic cell transplantation in adults. *Am J Hematol* 89: 698-705.
- 24 Chen Y, Xu LP, Liu KY, Chen H, Chen YH, et al. (2016) High incidence of engraftment syndrome after haploidentical allogeneic stem cell transplantation. *Eur J Haematol* 96: 517-26.
- 25 Ravoet C, Feremans W, Husson B, Majois F, Kentos A, et al. (1996) Clinical evidence for an engraftment syndrome associated with early and steep neutrophil recovery after autologous blood stem cell transplantation. *Bone Marrow Transplant* 18: 943-947.
- 26 Edenfield WJ, Moores LK, Goodwin G, Lee N (2000) An engraftment syndrome in autologous stem cell transplantation related to mononuclear cell dose. *Bone Marrow Transplant* 25: 405-409.
- 27 Ninkovic S, Cheah CY, Lasocki A, Harrison SJ (2016) Engraftment syndrome manifesting as acute brachial neuropathy following high-dose chemotherapy for management of plasma cell myeloma. *Leuk Lymphoma* 57: 2942-2945.
- 28 Dai E, Couriel D, Kim SK (2007) Bilateral marginal keratitis associated with engraftment syndrome after hematopoietic stem cell transplantation. *Cornea* 26: 756-758.
- 29 Alkhatib AA, Boynton KK, Badheeb AM (2010) Colitis secondary to engraftment syndrome in a patient with autologous peripheral blood stem cell transplant. *Dig Dis Sci* 55:1500-1501.
- 30 Pakakasama S, Wanitkun S, Hongeng S (2004) Pericarditis occurring with engraftment syndrome in a thalassemic patient. *Bone Marrow Transplant* 34: 819-820.
- 31 Jang KT, Song KY, Kim BK (2012) Histological features and immune cell changes in skin lesions of engraftment syndrome of children undergoing hematopoietic stem cell transplantation. *Histol Histopathol* 27: 235-240.
- 32 Ravenel JG, Scalzetti EM, Zamkoff KW (2000) Chest radiographic features of engraftment syndrome. *J Thorac Imaging* 15: 56-60.
- 33 Shah NN, Watson TM, Yates B, Liewehr DJ, Steinberg SM, et al. (2017) Procalcitonin and cytokine profiles in engraftment syndrome in pediatric stem cell transplantation. *Pediatr Blood Cancer* 64.
- 34 Khandelwal P, Mellor-Heineke S, Rehman N, Lane A, Smiley K, et al. (2016) Cytokine Profile of Engraftment Syndrome in Pediatric Hematopoietic Stem Cell Transplant Recipients. *Biol Blood Marrow Transplant* 22: 690-697.
- 35 Kishi Y, Kami M, Miyakoshi S, Kanda Y, Murashige N, et al. Tokyo Stem Cell Transplant Consortium (2005) Early immune reaction after reduced-intensity cord-blood transplantation for adult patients. *Transplantation* 80: 34-40.
- 36 Kanda J, Kaynar L, Kanda Y, Prasad VK, Parikh SH, et al. (2013) Pre-engraftment syndrome after myeloablative dual umbilical cord blood transplantation: risk factors and response to treatment. *Bone Marrow Transplant* 48: 926-931.
- 37 Hong KT, Kang HJ, Kim NH, Kim MS, Lee JW, et al. (2013) Peri-engraftment syndrome in allogeneic hematopoietic SCT. *Bone Marrow Transplant* 48: 523-528.
- 38 Park M, Lee SH, Lee YH, Yoo KH, Sung KW, et al. Korean Cord Blood Transplantation Working Party (2013) Pre-engraftment syndrome after unrelated cord blood transplantation: a predictor of engraftment and acute graft-versus-host disease. *Biol Blood Marrow Transplant* 19: 640-646.
- 39 Wang X, Liu H, Li L, Geng L, Ding K, et al. (2012) Pre-engraftment syndrome after unrelated donor umbilical cord blood transplantation in patients with hematologic malignancies. *Eur J Haematol* 88: 39-45.
- 40 Sakaguchi H, Matsumoto K, Yoshida N, Narita K, Hamada M, et al. (2016) Dexamethasone palmitate for patients with engraftment syndrome is associated with favorable outcome for children with hematological malignancy. *Bone Marrow Transplant* 51: 1540-1542.
- 41 Ikezoe T, Takeuchi A, Taniguchi A, Togitani K, Yokoyama A (2011) Recombinant human soluble thrombomodulin counteracts capillary leakage associated with engraftment syndrome. *Bone Marrow Transplantation* 46: 616-618.
- 42 Hara M, Kojima K, Nawa Y (1999) Rapid recovery of hemopoiesis and alleviation of symptoms similar to peri-engraftment syndrome after donor leukocyte infusion. *Rinsho Ketsueki* 40: 59-62.
- 43 Iguchi A, Terashita Y, Sugiyama M, Ohshima J, Sato TZ, et al. (2016) Graft-versus-host disease (GVHD) prophylaxis by using methotrexate decreases pre-engraftment syndrome and severe acute GVHD, and accelerates engraftment after cord blood transplantation. *Pediatr Transplant* 20: 114-119.
- 44 Jimenez-Zepeda VH, Trudel S, Reece DE, Chen C, Rabea AM, et al. (2011) Cyclophosphamide and prednisone induction followed by cyclophosphamide mobilization effectively decreases the incidence of engraftment syndrome in patients with POEMS syndrome who undergo stem cell transplantation. *Am J Hematol* 86: 873-875.
- 45 Mossad S, Kalaycio M, Sobecks R, Pohlman B, Andresen S, et al. (2005) Steroids prevent engraftment syndrome after autologous hematopoietic stem cell transplantation without increasing the risk of infection. *Bone Marrow Transplant* 35: 375-381.

- 46 Foncillas MA, Diaz MA, Sevilla J, Gonzalez Vicent M, et al (2004) Engraftment syndrome emerges as the main cause of transplant-related mortality in pediatric patients receiving autologous peripheral blood progenitor cell transplantation. *J Pediatr Hematol Oncol* 26: 492-496.
- 47 Gore AA, Sheth V, Ghanekar A, Jain R, Saikia TK (2015) Engraftment syndrome following hematopoietic stem cell transplant: A retrospective review of 70 cases. *J Clin Oncol* 33: 15.
- 48 Capizzi SA, Kumar S, Huneke NE, Gertz MA, Inwards DJ, et al. (2001) Peri-engraftment respiratory distress syndrome during autologous hematopoietic stem cell transplantation. *Bone Marrow Transplant* 27: 1299-1303.
- 49 Keung YK, Beaty MW, Pettenati M, Levitan D, Hurd DD (2010) Possible role of engraftment syndrome and autologous graft-versus-host disease in myelodysplastic syndrome after autologous stem cell transplantations: retrospective analysis and review of the literature. *Clin Lymphoma Myeloma Leuk* 10: 129-133.
- 50 Gale RP, Lazarus HM (2015) Engraftment syndrome, the Emperor's new clothes and the artist formerly known as Prince. *Bone Marrow Transplant* 50: 483-484.