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OBM Transplantation

Case Report

An Unusual Case of Recurrent Capillary Leak Syndrome Following Lung Transplantation

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Academic Editor: Haval Shirwan

OBM Transplantation
2020, volume 4, issue 2
doi:10.21926/obm.transplant.2002113

Received: April 24, 2020
Accepted: June 11, 2020
Published: June 15, 2020

Abstract

Systemic capillary leak syndrome is a disorder characterized by recurrent, life-threatening episodes of acute capillary hyperpermeability resulting in edema and hypovolemic shock. We report a case of systemic capillary leak syndrome in a lung transplant recipient who developed recurrent episodes of volume overload, respiratory failure, and acute kidney injury in association with hypotension and hypoalbuminemia. Initiation of monthly high dose intravenous immunoglobulin prophylaxis effectively abrogated the syndrome.

Keywords

Capillary leak syndrome; lung transplant; intravenous immunoglobulin; inflammation

1. Introduction

Lung transplantation is the definitive treatment for end-stage lung disease, but given the complex nature of the surgery and postoperative management, it can be associated with a variety

of potential complications. Systemic capillary leak syndrome (SCLS) is a condition characterized by the leakage of protein-rich fluid from the vascular space to the interstitium, leading to edema, effusions, hypotension, and sometimes shock. It can be associated with specific conditions and/or triggers, or it may be idiopathic. Isolated, acute episodes of capillary leak syndrome in response to medications have been described in liver or kidney transplant recipients [1, 2], and a single case of fatal idiopathic SCLS in a kidney transplant recipient was described in 1997 [3]. Herein, we present an unusual case of recurring systemic capillary leak syndrome in a patient following lung transplantation, and we describe the challenging diagnostic and treatment dilemmas encountered in the case.

2. Case Report

Written, informed consent was obtained from the patient, and the work was conducted under IRB-approved protocol #2018H0084.

A 60 year-old female former smoker with chronic obstructive pulmonary disease (COPD) underwent bilateral lung transplant. Past medical history was significant for an episode of *Clostridium difficile* colitis 2 years prior to transplant, hyperlipidemia, anxiety, depression and several COPD exacerbations treated with antibiotics and steroids. Pre-transplant testing revealed normal cardiac and renal function, no evidence of pulmonary hypertension, normal esophageal and gastric function, no endocrine abnormalities, and an unremarkable infectious disease evaluation. Bilateral sequential lung transplantation was performed utilizing cardiopulmonary bypass, and the patient was extubated on post-operative day (POD) 2. Basiliximab was used for induction immunosuppression, while maintenance immunosuppression included tacrolimus, mycophenolate mofetil, and prednisone. The post-operative course was notable for a brief episode of hyponatremia that resolved with tolvaptan and new onset acid reflux symptoms. The patient was discharged home from the hospital on POD 12.

On POD 75, the patient was admitted with shortness of breath, abdominal pain, nausea, vomiting, diarrhea, shaking chills and night sweats (Episode 1, Figure 1). Her condition quickly deteriorated to acute hypoxemic respiratory failure requiring non-invasive ventilation with the development of pulmonary edema and pleural effusions. Blood, urine, stool, and respiratory cultures were negative for infection. Transbronchial biopsy was negative for acute cellular rejection (International Society for Heart and Lung Transplantation grade A0B0), and no de novo donor specific antibodies were detected in the serum. Given the constellation of symptoms and negative testing for infection and rejection, aspiration pneumonitis was considered as the most likely etiology. Her condition improved with conservative management, and she was discharged 9 days later. She returned to the hospital on POD 95, POD 157, and POD 177 (Episodes 2-4, Figure 1), each time with dyspnea and acute onset lower extremity edema with rapid weight gain (~2 kg/day) over the preceding 2-3 days. With each subsequent episode, her presenting condition was more severe with acute hypoxemic respiratory failure, hyponatremia, and acute kidney injury (AKI) present at Episode 3 and hypotension, confusion, and acute hypoxemic respiratory failure necessitating mechanical ventilation present on admission for Episode 4. Again, infectious workup was consistently unrevealing. Evaluation of cardiac function via echocardiography showed no change in her normal cardiac function compared to her pre-transplant baseline. Despite this, a sodium-restricted diet was recommended given concern for a dietary contribution to the edema.

Interestingly, Episode 3 occurred one week after a routine surveillance bronchoscopy was positive for Coronavirus 229E despite absence of respiratory symptoms at the time of the procedure. With each admission, diuresis was attempted, but by Episode 4, the edema became refractory to diuresis. Pulse dose steroids were also utilized without significant effect. During Episode 4, serum immunoglobulin G levels were noted to be low (372 mg/dL, normal 600-1714 mg/dL), a common occurrence after solid organ transplantation [4], and intravenous immunoglobulin (IVIG, 1 g/kg) was administered. With conservative management, the patient's condition eventually resolved each time, and she was discharged home.

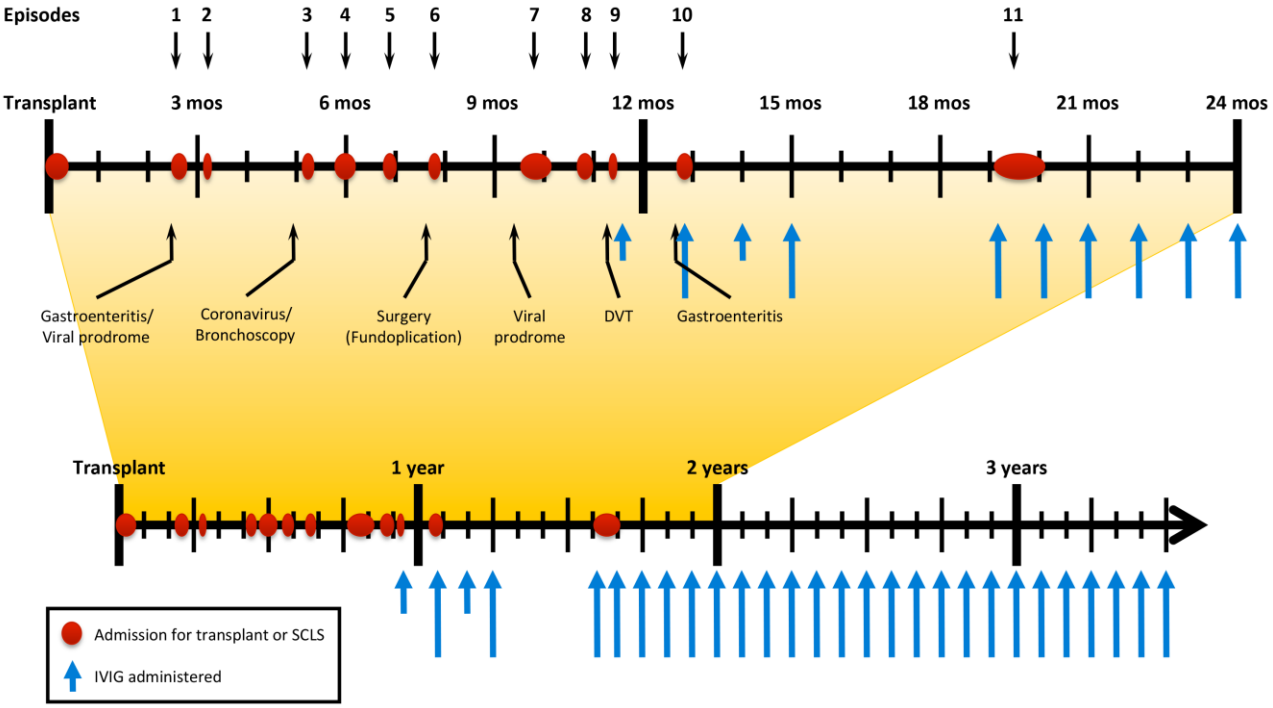

Figure 1 Timeline of recurrent SCLS episodes. Bottom graph represents time from transplant to present day, while top graph highlights SCLS episodes and triggering events in greater detail. Admissions for lung transplant and SCLS episodes are denoted by red ovals (length of oval is proportional to duration of admission). Precipitating factors or events are indicated below the upper timeline. Length of blue arrows indicate moderate dose (1 g/kg, short blue arrows) or high dose (2 g/kg, long blue arrows) IVIG treatments.

Over the next 5 months, the patient presented, on a monthly basis, with recurrent episodes (Episodes 5-9) of acute onset pulmonary and lower extremity pitting edema and weight gain (up to 2.3 kg/day) preceding hypoxemic respiratory failure, hypotension, hypoalbuminemia, and AKI (Figure 2). Facial and supraclavicular edema, but no angioedema, were also noted during Episode 9. A wide differential diagnosis was considered for the etiology of these episodes, including allograft rejection, infection, cardiac, endocrine (adrenal, thyroid), autoimmune (vasculitis), and medication-related. The patient underwent multiple bronchoscopies with biopsy never having more than minimal (A1B0) grade ACR, and no donor specific antibodies were detected in her serum making allograft rejection unlikely.

Repeated testing for viral, bacterial, and fungal pathogens during each episode was consistently negative. Echocardiogram and right heart catheterization were unrevealing. Thyroid hormone levels were normal, and the hypothalamic-pituitary axis was appropriately suppressed due to supraphysiologic doses of prednisone used as part of the patient's transplant immunosuppression. The patient kept a meticulous diary of her compliance with medications and a fluid and sodium-restricted diet, and no potential toxic or allergic exposures in the home environment were identified through extensive questioning. Vascular endothelial growth factor, insulin growth factor 1, ADAMTS13, and C1 esterase inhibitor levels and activity were normal (data not shown). Serology for antinuclear, antineutrophil cytoplasmic, and double-stranded DNA autoantibodies was negative. Tryptase levels were not checked. However, her presentations were not felt to be consistent with anaphylaxis due to the regular and repeated nature of the episodes in the absence of any known or potential allergen, or to systemic mastocytosis given the absence of skin or mucosal findings (no pruritus, hives, or angioedema) and the development of dyspnea only with the onset of pulmonary edema and pleural effusions. She was noted on several admissions to have extremely elevated C-reactive protein (CRP) levels (range 255.1 mg/L to 381.2 mg/L for Admissions 4, 5, 7, 10 and 11), much higher than even the peak CRP level immediately following lung transplant (157.9 mg/L) (Figure 3). In other instances (Episodes 1 and 9), CRP levels were elevated but to much lower levels. Other inflammatory markers were also elevated (ferritin 785 ng/mL [normal range 10-291 ng/mL] and fibrinogen 651 mg/dL [normal range 220-410 mg/dL] during Episode 5, and D-dimer 3.98 mcg/mL and 7.98 mcg/mL [normal range <0.50 mcg/mL] during Episodes 10 and 11, respectively). Erythrocyte sedimentation rate, IL-1, IL-6 and TNFα were not measured. Serum protein electrophoresis was normal on POD 443 (at clinical baseline between Episodes 10 and 11) and showed an isolated increase in the Alpha 1 region during Episode 11, consistent with an acute phase response. With the presence of a highly inflammatory condition in the absence of detectable infection, allograft rejection or heart failure, the patient was diagnosed with recurrent capillary leak syndrome, but the etiology remained unknown. Given reports of successful prophylaxis of the idiopathic form of SCLS with monthly infusions of high-dose IVIG (1-2 g/kg), we initiated this treatment in our patient (Figure 1, blue arrows). Prior to high-dose IVIG initiation, the patient experienced 9 admissions in 9 months for episodes that included combinations of hypoxia, weight gain, AKI, and confusion. Approximately one month after the first dose of high-dose IVIG, the 10th capillary leak episode occurred on POD 386, but there were no further episodes over the next 3 months. Due to the patient's stability, an attempt was made to discontinue monthly IVIG prophylaxis around POD 460, but approximately 4 months later on POD 581, the patient was admitted with her most severe episode of hypoxemic respiratory failure, shock, and AKI requiring renal replacement therapy. Following the patient's recovery from this episode, we resumed monthly high-dose (2 g/kg) IVIG prophylaxis, and there have been no further capillary leak episodes since, a period of 2 years. Currently, the patient continues to do very well, and her allograft function is at an all-time high.

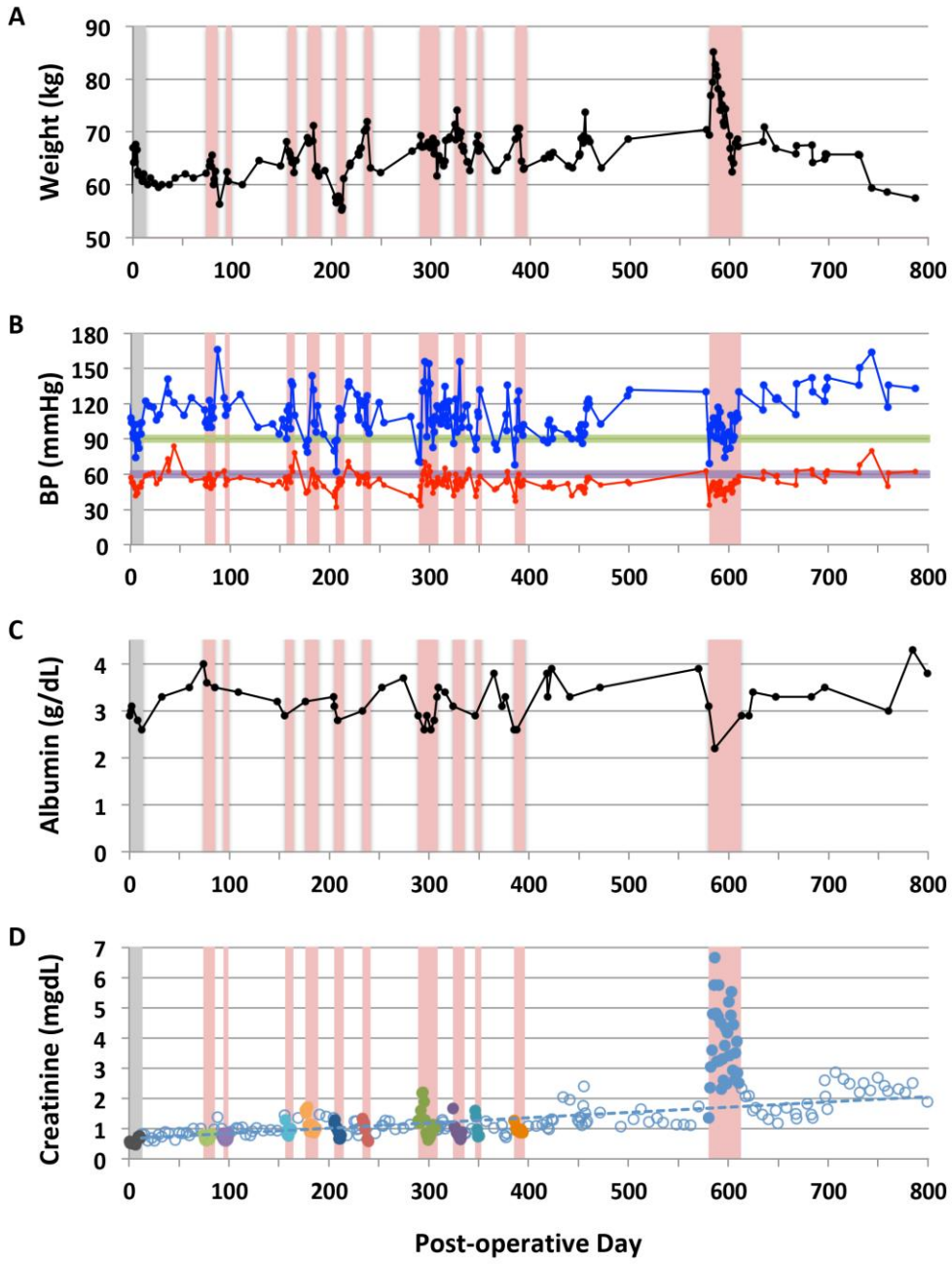

Figure 2 Vital signs and laboratory data. (A) Weight in kilograms plotted from time of transplant through >2 years post-transplant. Grey shaded areas represent lung transplant admission while pink shaded areas represent admissions for SCLS episodes. (B) Lowest daily systolic (blue line) and diastolic (red line) blood pressures. Cut-offs for hypotension are indicated by the green line at 90 mmHg for SBP and the purple line at 60 mmHg for DBP. (C) Trend in serum albumin levels over time. (D) Creatinine levels over the first 2 years post-transplant. Open circles represent outpatient levels, while solid colored circles represent creatinine levels during admissions for lung transplant and SCLS episodes. The blue dotted line is an exponential trendline (R^2 = 0.60) of the outpatient creatinine values provided for visual reference. SBP, systolic blood pressure; DBP, diastolic blood pressure.

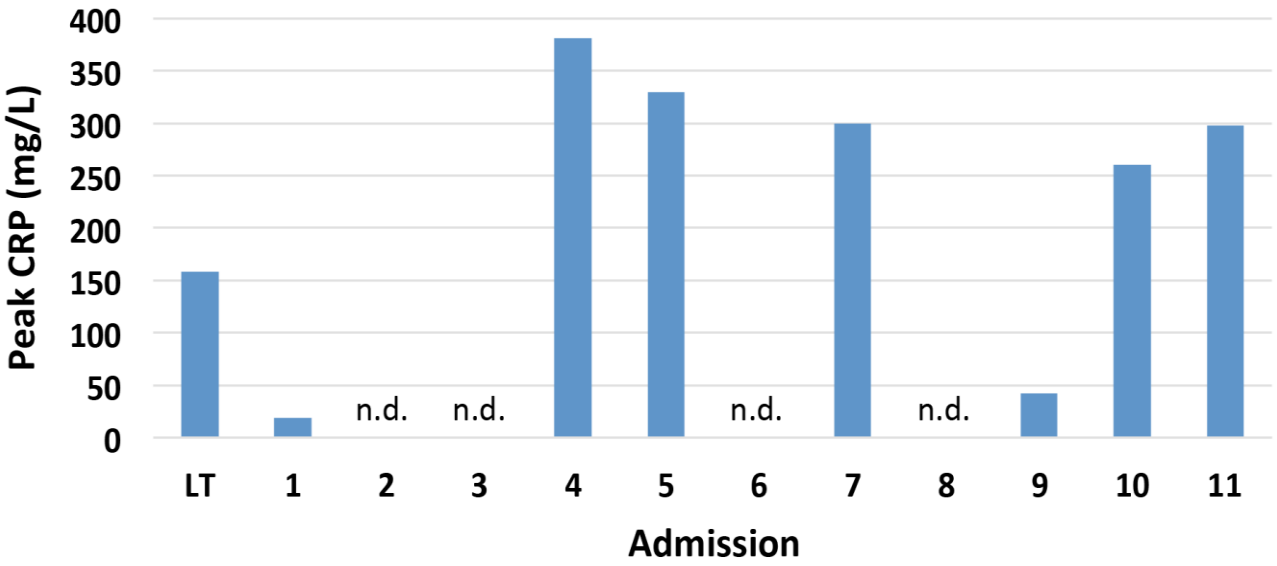

Figure 3 Peak CRP levels following lung transplant and SCLS episodes. When measured, CRP levels were often dramatically elevated compared to the peak CRP level observed following lung transplantation. CRP was not measured during episodes #2, 3, 6, or 8. n.d., no data.

3. Discussion

SCLS is a process encompassing a constellation of symptoms due to leakage of intravascular protein-rich fluid to the interstitium resulting in pitting edema, noncardiogenic pulmonary edema, serous effusions, and hypotension, sometimes severe enough to cause hypovolemic shock [5]. Capillary leak is associated with a variety of clinical entities including sepsis, engraftment syndrome, differentiation syndrome, ovarian hyperstimulation syndrome, viral hemorrhagic fevers, autoimmune diseases, snakebite envenomation, chemotherapeutic and biologic agents, cancer, and surgery [6, 7]. An idiopathic form of SCLS also exists, but is a rare, life-threatening form of capillary leak with less than 300 cases described in the literature to date [5]. While data is lacking for SCLS in general, for idiopathic SCLS, approximately 25% of patients die within 5 years of diagnosis, and due to the rare nature of idiopathic SCLS and overlap with other etiologies, diagnosis is delayed, on average, 7.9 months [5]. Mean age of onset of idiopathic SCLS is 42.6 years with a 5:4 male to female predominance [5]. SCLS can exist in a classic acute form or as a chronic disease process. The classic acute form of SCLS is characterized by recurrent episodes of plasma and protein leakage into the extravascular space, resulting in the 3 H's: hypotension, hemoconcentration, and hypoalbuminemia. Episodes are characterized by a prodromal phase followed by a "leak" phase and then a "post-leak" phase of autodiuresis [8]. To date, no effective treatment other than supportive care (respiratory and cardiovascular support including intravascular fluid resuscitation and vasopressors during the "leak" phase followed by diuresis for edema during the "post-leak" phase) has been identified for acute episodes. However, there is accumulating data on the effectiveness of prophylactic measures for idiopathic SCLS with high-dose IVIG showing the most promise over B2-agonists and methylxanthines [9]. In fact, the

addition of IVIG either alone or in combination with B2-agonists or methylxanthines leads to improved survival at 1, 5, and 10 years [5].

Our patient's case shows many similarities to idiopathic SCLS, but also some notable differences. Consistent with the original descriptions of idiopathic SCLS, our patient's syndrome initially developed following an acute gastrointestinal illness. Subsequent episodes were commonly preceded by inflammation-promoting events such as viral infections, surgery (Toupet fundoplication), venous thrombosis, or gastroenteritis (Figure 1). Not all inflammation-promoting events led to SCLS episodes, particularly after the initiation of IVIG prophylaxis. For example, the patient developed AKI around POD 450 and 700 in the absence of SCLS episodes (Figure 2D and Supplementary Figure 1). In the first instance, AKI occurred in the early post-operative period following an elective surgical procedure, while the second instance was due to dehydration from emesis following an episode of diverticulitis. In both cases, IVIG had been administered monthly for at least 4 months preceding each event. Notably, SCLS episodes were characterized by hypotension and hypoalbuminemia (Figure 2, Panels B and C), but not consistently with hemoconcentration (data not shown), a key factor in the diagnosis of idiopathic SCLS. In lung transplant recipients, anemia is common post-transplant due to acute blood loss from the surgical procedure itself and introduction of transplant medications that impair bone marrow productivity. Therefore, it may be challenging to delineate clearly acute hemoconcentration in this population. Our patient's common presentation of acute weight gain (often 2 kg/day over 2-3 days), hypotension, peripheral edema, and hypoxemic respiratory failure related to noncardiogenic pulmonary edema in the setting of a proinflammatory state (as demonstrated by elevated CRP levels) are consistent with SCLS but do not completely fulfill the criteria for the classic idiopathic form of SCLS. Specifically, in idiopathic SCLS, pulmonary edema is usually a later manifestation following rapid mobilization of peripheral edema, whereas in our patient, pulmonary edema was often noted at presentation. While certain features were common to each SCLS episode, there was variation in other characteristics such as the degree of inflammation as measured by CRP, need for respiratory support, and degree of kidney injury. An extensive investigation into potential triggers for the recurring episodes of SCLS in our patient failed to identify a specific etiology. During acute episodes, a variety of treatment modalities (corticosteroids, antibiotics, and diuresis) failed to rapidly reverse the disease. However, similar to the effects seen in idiopathic SCLS, the introduction of monthly high-dose IVIG prophylaxis has completely prevented further episodes of SCLS in our patient.

4. Conclusions

SCLS is a serious and potentially, life-threatening, condition characterized by leakage of intravascular protein-rich fluid to the interstitium. To our knowledge, ours is the first report of the diagnosis and successful treatment of recurrent SCLS as a rare complication following lung transplantation. The exact etiology of the recurrent SCLS episodes remains unknown, though episodes tended to follow inflammation-inducing events (e.g. infection, surgery) and were associated with dramatic increases in inflammatory markers. The introduction of monthly prophylaxis with high-dose IVIG completely abrogated recurrence of the syndrome, consistent with results seen in idiopathic SCLS.

Acknowledgments

The authors thank Jeffrey Sneddon and Desmond Wong in The Ohio State University Comprehensive Transplant Center for assistance with data collection.

Additional Materials

The following additional materials are uploaded at the end of this paper.

1. Figure S1: Renal function trend from transplant to present day.

Author Contributions

BCK wrote the manuscript. All authors were involved in the clinical care of the patient and contributed to the review and final approval of the manuscript.

Competing Interests

The authors have declared that no competing interests exist.

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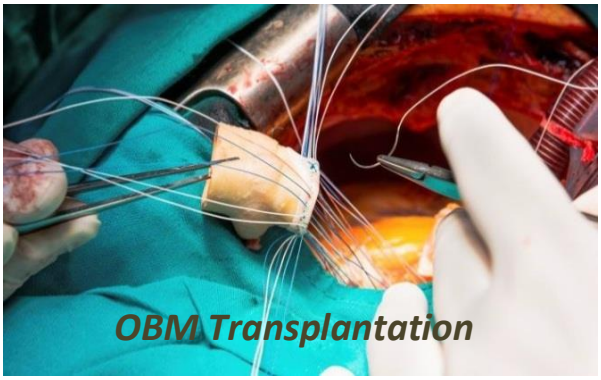

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