Hematological Abnormalities Post Renal Transplantation

Rasha kamal Abouelenein and Ayman F. Refaie
Urology & Nephrology center, Mansoura, Egypt
*Corresponding author: Rasha kamal Abouelenein Urology&Nephrology center, Mansoura, Egypt, Tel: +20502202222 ; E-mail: dr.rasha40@yahoo.com

Keywords: Post -transplant anemia; Post-transplant polycythemia, Transplantation

Introduction

Renal transplantation is considered the surgical procedure used in renal replacement therapy. It has better patient survival. Although it may has some hematological disorders which may be categorized into two groups.

A-Common Disorders

1. Post renal transplant anemia.
2. Post renal transplant lymphoproliferative disorder.
3. Post renal transplant erythrocytosis.
4. Post renal transplant cytopenias (PTC, leukopenia / neutropenia, thrombocytopenia, and pancytopenia).

B-Less Common Disorders

1. Hemophagocytic syndrome.
2. Thrombotic microangiopathy.
3. Therapy related myelodysplasia.

Post renal transplant anemia

It is a well-known complication after renal transplantation; it raises attention more in urological community [1]. It could be classified in to acute (within 6 months post-renal transplant) and chronic (more than 6 months post-renal transplant). Anemia after renal transplantation may persist or reoccur transplantation. It had occurred at least once in 38.3%, and reoccurred in 42% of renal transplant recipients within 5 years [2]. Post renal transplant anemia may occurs due to several factors in renal transplant recipients, including renal allograft dysfunction, drugs [immunosuppressive agents, angiotensin II receptor antagonists, Angiotensin-Converting Enzyme (ACE) inhibitors, and antiviral and
antimicrobial medications], acute rejection, nutritional deficiency, viral infections and blood group ABO incompatibility [3]. Treatment of Post-Transplant Anemia (PTA) is to restore EPO production, to maintain hemoglobin at an adequate level, to enhance kidney graft survival, and to treat underlying cardiovascular disorders [4]. The use of ESAs (even with high doses) in treatment of PTA has been found to slow the progression of post-transplant CKD and improve the quality of life in renal transplant recipients [5].

**Post Renal Transplant Lymphoproliferative Disorder**

Epstein-Barr virus (EBV) infection after renal transplantation is considered the main cause of Post-Transplant Lymphoproliferative Disorder (PTLD) [6]. PTLD occurs in 1 - 5% of renal transplant recipients [7].

**Potential Treatments**

(I) Immunomodulator agent (rituximab).

(II) Antiviral therapy against cytomegalovirus (CMV): acyclovir, valacyclovir, ganciclovir, or foscarnet.

(III) Passive immunization with anti-EBV monoclonal antibodies (anti-B-cell monoclonal antibody, anti-CD21 antibody, or anti-CD24 antibody).

(IV) Interferon Alfa-2b (Intron A) therapy.

(V) T-cell–based therapy (specific cytotoxic T lymphocytes).

(VI) Intravenous gamma globulin (IVIG) therapy (gamimune, gammagard S/D, sandoglobulin).

(VII) Combination chemotherapy: rituximab followed by cyclophosphamide, adriamycin, oncovin, and prednisone.

(VIII) Antineoplastic agents (prednisone, cyclophosphamide, doxorubicin, vincristine, etc.).

(IX) Surgical excision.

(X) Localized radiation therapy [8].

**Post Renal Transplant Erythrocytosis (PRTE)**

It is defined as elevated hemoglobin (Hb) (>17 g/dL) and hematocrit (>51%) that persists for more than 6 months [9]. In renal transplant recipients the incidence rate of Post-Transplant Erythrocytosis (PRTE) varies between 10-20% of renal transplant recipients and usually develops within 2 years after transplantation. Clinically the patient may complains of malaise, headache, dizziness, lethargy, plethora, and thromboembolism. Complications of PRTE may end by death in 1-2% of patients [10]. PRTE usually undergoes spontaneous remission but may occasionally persist for years. Its etiology is not clearly known, multiple mechanisms have been proposed to explain its occurrence, including:

- Rennin–angiotensin system activation [10, 11].
- Increase in endogenous androgens production post transplantation [10, 11].
- Insulin-like Growth Factor1 (IGF-1) has been recognized to be involved [11, 12].

Many underlying conditions had been linked to PRTE including; male, gender, smoking, duration of dialysis, presence of native kidneys, transplant artery stenosis, type and dose of immunosuppressive therapy, the extent of allograft function, acute and chronic graft rejection [10, 13].
A number of therapies are available for the management of PRTE. These include Serial phlebotomy [14, 15], native kidney nephrectomy [16], theophylline [14] and Angiotensin Converting Enzyme Inhibitors (ACEI) [14, 17]. The prevalence of PRTE, however, has seen a steady decline over the years, probably due to the increased prescription of ACEI/ARBs and/or the more intensive use of antiproliferative immunosuppressant [4].

**Post renal Transplant Cytopenias (PTC)**

Cytopenia is defined as marked reduction or cessation in the production of one or more blood cell types. It is caused by immunosuppressive therapy, chemotherapy, and viral infections after transplantation. Cytopenia may occur in the form of anemia (RBCs deficiency), leukopenia or neutropenia (WBCs or leukocytes deficiency), thrombocytopenia (platelets deficiency), and pancytopenia (a deficiency of all three blood cell types—RBC, WBC, and platelet [18].

**Leukopenia or Neutropenia**

Leukopenia commonly occur following organ transplantation. It is defined as total WBC count less than 3000–4000 cells/μL [19]. Neutropenia (abnormally low count of neutrophils) is the most common form of leukopenia, which is defined as neutrophilic count of 1500 or fewer cells/μL [20]. Leukopenia/neutropenia may occur in about 20–63% of kidney recipients. It usually occurs around day 100 after transplantation and may last for 1 to 4 weeks [21]. Many factors are involved in occurrence of leukopenia/neutropenia

- AZA is a known immunosuppressive agent that causes leukopenia/neutropenia in 50% of renal transplant recipients. However, this could be reversed with decrease or discontinuation of the drug [22].
- T-cell depleting agents: Thymoglobulin, Atgam, Alemtuzumab, and Basiliximab all may induce some degree of leukopenia/neutropenia by eliminating targeted lymphocytes [23].
- Mycophenolate Mofetil (MMF) induced leukopenia/neutropenia occur in about 13–35% of renal transplant recipients. This is related to active metabolite, Mycophenolic Acid (MPA).
- The anti-CMV medications: Valganciclovir & Ganciclovir were found to cause leukopenia/neutropenia in 50% of transplant patients in a dose-dependent manner [24].
- Antibiotics such as: Trimethoprim-sulfamethoxazole, Beta-lactam antibiotics, and Piperacillin may also cause leukopenia/neutropenia [25].
- Deficiencies of some essential nutrients, such as folic acid, vitamin B12, zinc, and copper, may also lead to leukopenia/neutropenia [26].
- Viral infections have marked myelosuppression effects in renal transplant recipients that may result in leukopenia/neutropenia as a manifestation, including PVB19, herpes virus-6 (HHV-6), CMV, and influenza [27].

As regard treatment of leukopenia/neutropenia after renal transplantation, the most effective way to improve leukopenia/neutropenia is to discontinue the accused medications such as MMF, valganciclovir, cyclosporin, and Tacrolimus (FK-506) or decrease their doses. Recombinant granulocyte-colony stimulating factors (G-CSF), such as: filgrastim (Neupogen), may be used in treating leukopenia/neutropenia. In addition, stem cell transplants may be useful in treating some types of severe leukopenia/neutropenia, including those caused by the myelosuppressive agents [28].

**Thrombocytopenia**

Thrombocytopenia is defined as that a total platelet count is less than 50,000/μL. It is common during the first year after transplantation especially the firquite prevalent in the
first year after renal transplantation. The first three months the clinical manifestations of thrombocytopenia include bruising, mild to serious bleeding, petechial, fatigue, malaise, and general weakness [29]. It occurs due to bone marrow suppression by immunosuppressant agents, infection, chemotherapy, antiplatelet antibody therapy, acute rejection episodes, microangiopathy, or deficiencies of folate and Vitamin B12 [30]. Causes of thrombocytopenia are similar to those of anemia and leukopenia in renal transplant recipients. The use of sirolimus and/or calcineurin inhibitors may lead to microangiopathy as a cause of thrombocytopenia in renal transplant recipients [31]. Many drugs can cause thrombocytopenia including rabbit antithymocyte globulin, valganciclovir, ganciclovir, linezolid, and heparin [32]. Viral infections, particularly CMV or EBV infection, can cause thrombocytopenia and Hemophagocytic Syndrome (HPS) [33].

The goals of therapy in thrombocytopenia are to stimulate the bone marrow production of platelets, to maintain adequate platelet level, and to treat microangiopathy, this could be achieved by stoppage of the offending drugs [34]. Corticosteroids may be used to increase platelet production. Lithium carbonate or folate may also be used to stimulate the bone marrow production of platelets. Rituximab, daclizumab, and other new antibody preparations may be effective for patients with transplant associated TMA. Thrombopoietin growth factors: Romiplostim and Eltrombopag have been used as second line therapy of immune thrombocytopenia for hematopoietic stem cell transplant patients [35], and may be effective in treating post-transplant thrombocytopenia.

Pancytopenia, the deficiency of all three blood cell types (RBCs, WBCs, and platelets), is characteristic of aplastic anemia, a potentially life-threatening disorder that requires a stem cell transplant. Pancytopenia has widespread effects on the entire body by leading to oxygen shortage as well as problems with immune function [36]. Pathologies involving the WBC and platelet population often exist in the context of pancytopenia, which can probably be a manifestation of systemic infection [37]. In renal transplant recipients, PVB19 infection is a common cause of pancytopenia and leads to various forms of glomerulopathy and allograft dysfunction [38]. In addition, visceral leishmaniasis, a disease caused by protozoan parasites of the genus Leishmania and spread by the bite of certain types of sandflies, can also cause pancytopenia in some immunocompromised renal transplant recipients [39]. Other potential factors involved in the development of pancytopenia include immunosuppressive drugs (azathioprine, MPA, anti-thymocyte globulins, and alemtuzumab), chemotherapy drugs that cause bone marrow suppression, antibiotics (linezolid and chloramphenicol), and radiation therapy [37]. Symptoms of pancytopenia can include bleeding, bruising, fatigue, shortness of breath, and weakness. Treatments for pancytopenia include drugs that suppress the immune system, bone marrow stimulant drugs, blood transfusion, bone marrow transplant, and stem cell replacement therapy [38].

Other Hematological Complications of Renal Transplantation

There are less common hematologic complications post renal transplantation include HPS, Thrombotic Microangiopathy (TMA), and therapy-related Myelodysplasia (t-MDS) and therapy-related acute Myeloid Leukemia (t-AML) [37]. Death may occur in more than 50% of patients with these hematologic complications [40].

Hemo Phagocytic Syndrome (HPS)

HPS, also known as Macrophage Activation Syndrome (MAS) or Hemophagocytic Lymphohistiocytosis (HLH), is characterized by uncontrolled proliferation of hematophagic monocytes/macrophages/ histiocytes that are actively ingesting other blood cells. In most cases, HPS is associated with opportunistic infection following intensive immunosuppression. HPS is seen in association with viral infections [such as CMV, adenovirus, EBV, human herpes virus-8 (HHV-8), , human herpes virus-6 (HHV-6), Parvo virus-19 (PVB19), and polyoma virus, bacterial infections such as tuberculosis, Bartonella henselae, and Escherichia
coli and protozoal infections such as toxoplamosis, leishmaniasis, pneumocystis carini pneumonia, and babebiosis [41, 42].

Pathogenesis of post-transplant HPS is multifactorial including:

(a) The activation of T helper-1 (Th-1) cells and the increased production of cytokines, tumor necrosis factor-alpha (TNF-α) and interferon-gamma (IFN-γ) caused by severe infection.

(b) Abnormalities of CD8 + T lymphocyte and natural killer-cell (NK-cell) cytotoxicity caused by immunosuppression.

These cellular and biochemical alterations may lead to excessive Th-1 lymphocyte and macrophage activation and uncontrolled proliferation under lack of NK cell and T lymphocyte cytotoxicity, thus causing hemophagocytosis [42].

HPS usually occur within two month after renal transplantation, but it may occur years after transplantation in recipients with parasitic infection or neoplasia. Generally, post-transplant HPS is associated with a higher rate (53%) of renal transplant recipients may die due to HPS [43]. Patients with HPS may present with fever, cytopenia of two lines, hypofibrinogenemia, hypertriglyceridemia, hyperferritinemia (>500 μg/L), hemophagocytosis, elevated soluble interleukin-2 receptor (CD25), decreased NK-cell activity, and hepato-splenomegaly [42].

Treatment of HPS aims to recognize and treat the etiological microorganism. Reduction or withdrawal of the accused drugs is usually recommended in order to control infection. Intravenous methylprednisolone may reduce the activation of macrophages and cytokines, although it may worsen the underlying infection [41]. CMV infection could be treated with intravenous ganciclovir. Reduction of immunosuppression and the administration of foscarnet might be used in HH-8 infection. Treatment of BK virus infection includes withdrawal of immunosuppressive therapy, infusion of intravenous IVIg and increasing prednisone [42]. The use of IVIg may also be useful for treating bacterial and protozoan infections. In patients with resistant HPS graft nephrectomy may be a possible therapeutic option for renal transplant recipients [43].

Thrombotic Microangiopathy (TMA)

TMA is a group of disorders characterized by thrombocytopenia, MAHA (intravascular hemolysis and presence of peripheral blood schistocytes), purpura, microvascular occlusion (thrombi and coagulation) neurological symptoms, fever, and renal dysfunction. TMA has two major causes HUS and Thrombotic Thrombocytopenic Purpura (TTP) [44]. TMA can also occur in both renal transplantation and HSCT that are closely associated with calcineurin inhibitors and often cause graft failure [45]. The calcineurin inhibitors (CsA and FK-506) are toxic to microvascular endothelial cells and can induce microvascular constriction and platelet aggregation that may result in TMA in renal transplant recipients. Intravascular thrombi of aggregated platelets lead to thrombocytopenia and various degrees of organ ischemia and anemia. Furthermore, viral infections (CMV, HIV, and PVB19), antibody-mediated acute humoral rejection and severe renal ischemia may also be implicated in TMA [45].

In renal transplant recipients, the majority of TMA cases occur de novo (triggered by immunosuppressive drugs and acute antibody-mediated rejection), sometimes it recur in patients with previous history of HUS [46]. Clinical presentations of de novo TMA include anemia (hemoglobin <10 g/dL), thrombocytopenia, increased lactate dehydrogenase decreased haptoglobin and schistocytes [47]. The first step in the management of post-transplantation TMA is to stop or decrease the dose of Calcineurin inhibitor, then to start plasma therapy (fresh frozen plasma infusion or plasmapheresis) [46]. Some of these patients may also need dialysis therapy [47]. The targeted complement C5 inhibitor therapy (eculizumab for atypical HUS and rituximab for TTP) could be effective in treating TMA [44]. Rituximab (with or without cyclophosphamide) may be efficacious as treatment for TTP [45].
Therapy-Related Myelodysplastic Syndromes (T-MDS) and Acute Myeloid Leukemia (T-AML)

T-MDS (also called myelodysplasia) means ineffective production of all blood cells. It is characterized by blood cytopenias, ineffective hematopoiesis, dyserythropoiesis, dysgranulopoiesis, dysmegakaryopoiesis, and increased myeloblast. T-MDS develops 3-5 years after transplantation [48]. Patients with T-MDS usually have severe anemia, cytopenias and refractory AML.

T-AML, also known as acute myelogenous leukemia or Acute Non-Lymphocytic Leukemia (ANLL), is a disorder of the myeloid line of blood cells, in which rapid growth of abnormal white blood cells occur and accumulate in the bone marrow and thus interfere with the production of normal blood cells. Timing of T-AML is usually 5 years after transplantation. Clinically the patient of T-AML may have fatigue, shortness of breath, petechiae, bone and joint pain, easy bruising and bleeding, and persistent or frequent infections. Untreated T-AML progresses rapidly and the patients may die within weeks or months [49]. Both T-MDS and T-AML are two therapy-related complications that occur in organ transplant recipients maintained on immunosuppressive agents. The two conditions are often associated with heavy post-transplant immunosuppression by azathioprine (a thiopurine prodrug) [50] or by ATG [51].

Genetic variation (deletions or translocations of different chromosomal bands caused by different drugs) may play a role in the development of T-MDS/T-AML [48]. Furthermore, epigenetic changes in DNA structure have been considered as a mechanism of T-MDS/T-AML [52-54]. Other predisposing factors may include (polymorphisms in detoxification and DNA repair enzymes), granulocyte-colony-stimulating factor, topoisomerase II inhibitors, and radiotherapy, may cause chromosome abnormalities (of bone marrow cells. These factors may induce T-MDS/T-AML [55, 56].

Stoppage or replacing azathioprine with a nonthiopurine alternative (such as mycophenolate, sirolimus, or everolimus), was proved to reduce the incidence of post-transplantation T-MDS/T-AML [57], Three DNA methyltransferase inhibitors (5-azacytidine, decitabine, and lenalidomide) can restore normal blood counts and retard the progression of MDS to acute leukemia and thus it was approved for treatment of T-MDS [58]. Supportive care with blood product support (RBC transfusion), iron chelators (deferoxamine and deferasirox), and hematopoietic growth factors (erythropoietin), is the mainstay of therapy for T-MDS/T-AML [59]. Chemotherapy with the hypomethylating agents (5-azacytidine and decitabine) might slow the progression of MDS to AML [60].

Treatment for AML is usually divided into two phases:

- Induction and consolidation therapy, with cytarabine (Ara-C) and anthracylines reduce the number of leukemic cells to an undetectable level and this achieve a complete remission.
- Consolidation therapy, it is the intensive chemotherapy to eliminate any residual disease [61].

After the completion of consolidation therapy, relapse of AML could be prevented by a combination Immunotherapy with Histamine Dihydrochloride (INN) and interleukin 2 [62]. For patients with relapsed T-AML or T-MDS, HSCT can be considered as a potentially curative therapeutic option [63].

References


37. Yango et al., 2002


