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IMMUNOLOGICAL ASPECTS OF GRAFT-VERUS-HOST DISEASE IN PATIENTS WITH ACUTE MYELOID LEUKEMIA

Anny Rhyllary Dos Santos Ribeiro Ramos
Student of the biomedicine course at ``Instituição de Ensino Superior`` (IES) of network ``Ânima Educação``. Article presented as a partial requirement for completion of the Undergraduate course in Biomedicine at: ``Instituição de Ensino Superior`` (IES) of network ``Ânima Educação``. 2023. Advisor: Prof. Luciana Paroneto Medina. Doctorate Degree

Develyn Thais Santos De Paula
Student of the biomedicine course at ``Instituição de Ensino Superior`` (IES) of network ``Ânima Educação``. Article presented as a partial requirement for completion of the Undergraduate course in Biomedicine at: ``Instituição de Ensino Superior`` (IES) of network ``Ânima Educação``. 2023. Advisor: Prof. Luciana Paroneto Medina. Doctorate Degree

Júlia Ribeiro Teodoro
Student of the biomedicine course at ``Instituição de Ensino Superior`` (IES) of network ``Ânima Educação``. Article presented as a partial requirement for completion of the Undergraduate course in Biomedicine at: ``Instituição de Ensino Superior`` (IES) of network ``Ânima Educação``. 2023. Advisor: Prof. Luciana Paroneto Medina. Doctorate Degree

Abstract: Graft Versus Host Disease has as its main focus the patient's immune system, as well as the marrow received, and may arise from complications after transplantation, very common in patients with Leukemia. The present study had the function of carrying out the analysis of the cellular pathway to combat the pathology in question and how the disease acts in the transplanted person's body so that an immunological understanding of the reaction is possible and thus the possibility of alternative options for treatment. most effective treatment of the disease. Data analysis was carried out using phenomenological methods, which seeks to clarify in a broader way through other research already carried out previously, to reach current considerations on a given topic. After analyzing all the research instruments collected, it was possible to see a higher incidence of Acute Myeloid Leukemia in male patients, and most cases of Graft Versus Host Disease in elderly people of the same sex, due to deficiency in the production of T cells. With everything that has been pointed out, this research aims to clarify the contribution to the development of future treatments for Graft Versus Host Disease.
Keywords: Graft Versus Host Disease. Acute Myeloid Leukemia. Immune system. T Cells. Hematological Neoplasms. Bone marrow transplant.

INTRODUCTION

About 45% of bone marrow transplants to treat leukemias result in Graft Versus Host Disease (GVHD). (Guedes M. C. et al, 2021, p. 270). This is particularly relevant for patients with Acute Myeloid Leukemia (AML), who have an average age of 68 years. Bone marrow transplantation is often recommended for the elderly due to the challenges associated with treatment, such as tolerance to intensive interventions and risk of complications (Camelo, 2014, p. 4).

According to the National Cancer Institute (INCA, 2023), it is estimated that more than 11 thousand cases of leukemia will be registered in Brazil between 2023 and 2025. The etiology of leukemia is not yet completely understood, but it involves genetic changes in the progenitor cells of the bone marrow due to several factors, including radiation, drugs, chemical agents and genetic factors (Santos et. al, 2019, p. 279). AML mainly affects elderly men. Treatment is challenging due to the aggressiveness of the disease, and in most cases, induction chemotherapy and stem cell transplantation are the most common treatment methods. Bone Marrow Transplantation (BMT) is indicated after a long chemotherapy treatment without case remission, however it is very common for BMT to result in complications such as GVHD (Camelo, 2014, p. 4).

GVHD is a serious complication of bone marrow transplantation, characterized by the immunological response of the graft by the recipient due to the T cell response. It can manifest itself acutely or chronically, being more common in the elderly due to the weakening of the immune system. GVHD can lead to immunosuppression, putting the patient at risk of severe complications (Mercadante, 2013, p. 8 and 9).

Based on everything that has been presented, this work aims to analyze the cellular pathway to combat the pathology in question and how the disease acts in the transplant recipient's body so that an immunological understanding of the reaction is possible and, thus, the possibilities of alternative options. for more effective treatment of the pathology.

METHODOLOGY

This study consists of a narrative review, for which bibliographical research was carried out through immunology and hematology books, magazines and scientific articles, made available in databases such as Scielo and Pubmed in a qualitative manner between the years 2000 to 2022, in the languages in Portuguese, English and Spanish. For the inclusion criteria, current articles were considered, with solid foundations, such as publications of Scientific Initiations/Masters/Doc/Post-Doc and Experimental Research.

LITERATURE REVIEW

ACUTE MYELOID LEUKEMIA

Leukemias are classified after observing the maturation and type of cells involved. In acute leukemias, there is a high proliferation of clones and a variable interruption of cell maturation, called anaplasia. In Myeloid Leukemia, there is an abnormal proliferation of monoclonal neoplastic cells in the bone marrow, which are malignant cells originating from the same clone and may or may not involve the peripheral blood. In the bone marrow, these genetic changes affect stem cells, which results in the expression of proto-oncogenes and anti-oncogenes, with proto-oncogenes consisting of genes responsible for cell growth, multiplication and differentiation, and anti-oncogenes, which encode proteins capable of to block cell division or induce apoptosis of cells with altered genetic material (Santos et. al, 2019, p. 279 and 280).

Among the subtypes of Leukemia, Aguada Myeloid Leukemia (AML) is present, which is characterized by the uncontrolled growth of myeloid blasts. This subtype has a high rate in older and male patients, but is not limited to this population. Among the triggering factors for leukemia are exposure to radiation, drugs and chemical agents, viruses, genetic factors, immunodeficiency and chronic bone marrow dysfunction (Camelo, 2014, p. 4). An example of how the Bone Marrow changes after being affected by this disease is shown in figure 1.

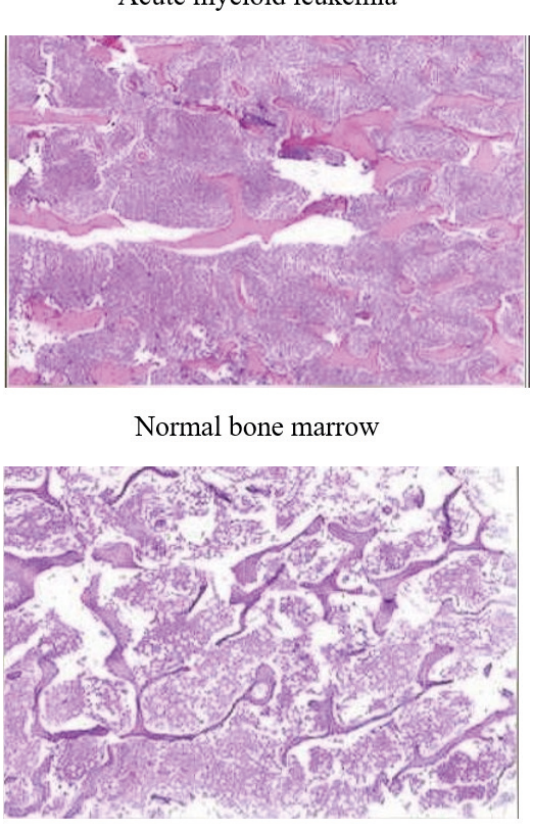

Figure 1: Difference between a slide from a patient with acute myeloid leukemia and a patient with cells within normal limits.

On the left, bone marrow with the presence of Acute Myeloid Leukemia, and on the right, healthy bone marrow. Source: Pathological Anatomy for Undergraduate Parts and Slides from the UNICAMP Repository. Available in: https://anatpat.unicamp.br/aulas2.html

During AML, many congenital regulatory cytogenetic changes occur, such as, for example, the T (15; 17) present in M3, the T (8; 21) and the inversion or deletion of chromosome 16. Within the subdivisions of Leukemia (acute and chronic), the LMA has seven different types, categorized between M0 and M7, as described below (Velloso, 2011, p. 185).

MO - undifferentiated blasts positive for immunological markers of the myeloid series
Predominant granulocytic component M1 = myeloblast without maturation 90% of myeloblasts in which + 3% of blasts peroxidase + rare azurophilic granulation
M2 = myeloblastic with maturation + 50% myeloblasts and promyelocytes • maturation beyond the present PM
M3 = hypergranular promylocytic • abnormal promyelocytes (100% + for peroxidase) • Auer rods
Predominant monocytic component M4 = myelomonicitic + 20% monocytes (20 to 80% + for non-specific esterase) + 20% myeloblasts and promyelocytes
M5 = monoblastic M5a > 80% monoblasts (+ for esterase) M5b < 80% monoblasts less than 20% granulocytes
Predominant erythroid component M6 = erythroleukemia + 50% of erythroid precursor cells (abnormal or not) presence of myeloblasts and promyelocytes (Aauer rod) abnormal megakaryocytes
Predominant thrombocytic component M7 = megakaryocytic + 30% megakaryoblasts, megakaryocytes

Table 1: Classification of Acute Myeloid Leukemias (FAB)

Source: BASIC HEMATOLOGY – PHYSIOPATHOLOGY AND LABORATORY DIAGNOSIS 4th ed., Rio de Janeiro, 2013, p. 154.

BONE MARROW TRANSPLANT AS A TREATMENT FOR ACUTE MYELOID LEUKEMIA

Systemic polychemotherapy is the method currently used to treat Leukemia, which consists of a dose of induction therapy with low doses of Ara-C (anthracyclics/cytarabine) with the aim of eliminating leukemic cells, blasts and consequently reduce their number in the bone marrow, following a consolidation phase, in which it is administered after the patient recovers from induction with the aim of destroying the remaining leukemia cells, for this stage, the doses of Ara-C are higher. It is still valid to comment on the maintenance of remission which consists of the administration of a low dose of chemotherapy, but this is no longer common in protocols described for new treatments (Hamerschlak et. al, 2006, p. 12).

They are often associated with consolidation therapy, the option of Bone Marrow Transplantation (BMT). When the possibility of low remission is noted in a patient with good conditions to undergo this type of procedure, the hypothesis of carrying it out is raised, but only around 40% of patients within the selection criteria have a compatible donor for the procedure. of Allogeneic Transplantation, thus they are referred for autologous transplantation (Tabak, 2006, p.2). Thymic function is compromised after bone marrow transplantation, due to radiation and the use of cytotoxic drugs, which can generate an immunological response (Reis, 2004, p. 212 - 217).

The main objective of bone marrow transplantation is to graft the hematopoietic stem cell to reconstruct the hematopoietic organ, which has been damaged by destruction, malignant infiltration or genetic disorder. There are several ways to perform a BMT, but the best known and most common options are autologous transplantation, which consists of removing one's own hematopoietic stem cells for reimplantation after the administration of high doses of chemotherapy and radiotherapy to complement the treatment, allogeneic, in which, through a donor (related or not) stem cells are removed and transplanted to the patient, and syngeneic, consisting of the donation of the recipient's identical twin. Hematopoietic stem cells can be obtained from bone marrow, peripheral blood or umbilical cord blood (Santos, 2019, p. 287).

After allogeneic bone marrow transplantation is performed, a very common immunological response is the systemic syndrome that we call Graft Versus Host Disease, when the donor's lymphocytes are immunocompetent and generates a pathophysiology that consists of the presence of skin lesions, asthenia and diarrhea (Silva;

Bouzas; Filgueiras, 2003, p. 61 and 62).

GRAFT-VERSUS-HOST DISEASE

The causes of GVHD can be as varied as possible, the best known being the incompatibility between donor and host, however, the source of the stem cell can also be a decisive factor in triggering the disease, as well as high doses of chemotherapy and radio previously. applied (Azevedo, 2010, p. 17 and 18).

According to criteria described by Billingham in 1966, GVHD can develop shortly after transplantation of hematopoietic progenitor cells, when there is the presence of immunologically competent cells in the graft, when the recipient does not show a response to combat the cells present in the transplant, or when the donor does not have tissue antigens present in the host. GVHD is likely to occur in any case involving tissue transfer, and issues such as age group, gender of the donor and recipient, allotransplants, use of immunosuppressive medication, among others, increase the possibility of developing GVHD (Silva; Bouzas ; Filgueiras, 2003, p. 63). In GVHD, immunological aggression occurs to the recipient's organs by lymphocytes that are present in the transplanted graft, thus the pathological and clinical manifestations of the disease begin (Mancilha, 2022, p. 300 and 301).

During hematopoietic progenitor cell transplantation, inflammatory cytokines, including interleukin 1 (IL-1), interleukin 6 (IL-6), and tumor necrosis factor alpha (TNF-α), are released during the conditioning period. These cytokines perform the function of activating T cells, including those of the donor, and stimulate the release of other cytokines, such as IL-2 and IFN-γ, which participate in the immune response of cells such as Natural Killer. This immune response can contribute to tissue damage due to its toxicity. This way, we can consider that restricting the number of disparities in MPC (major histocompatibility complex) alleles between the donor and recipient reduces the probability of GVHD occurring (Vizzoni et. al, 2008, p. 142 and 143).

In addition to the aforementioned cells, some studies show that TH17 cells are capable of inducing GVHD, this is due to a small amount of these cells contributing to the production of pro-inflammatory cytokines and consequently aggravating GVHD in allogeneic recipients (Normanton, 2013, p.173 and 174).

The pathology in question is also associated with some other body response functions, such as the release of pro-inflammatory cytokines after tissue damage is caused by treatment, which will activate immunological reactions, when the donor's lymphocytes recognize host antigens and there is an activation and proliferation of T cells and other immunocompetent cells, and also when the donor's T cells are activated, causing a cytotoxic reaction with the host cells, in this case, the cytokines interact with each other causing an effect known as "storm of cytokines." Cytokines are secreted proteins or glycoproteins, with a role in cellular communication and control of the immune response, as they regulate the magnitude and nature of these responses, influencing the growth and differentiation of lymphocytes, making GVHD a pathophysiology with a deregulated response from a normal immune system. to host tissues. The recipient's HLA (human leukocyte antigen) molecules can function as nominal antigens by presenting the mHag (minor histocompatibility antigens) to T lymphocytes, these antigens can provoke a strong cytotoxic response to CPH (major histocompatibility complex) and a proliferative response to helper T lymphocytes, such as the production of antibodies by B cells (Vizzoni, 2008, p. 144 and 149). In figure 2 we can

observe the pathophysiology of GVHD more clearly as it is divided into three phases.

Research has shown that female donors to male recipients are more susceptible to having GVHD, the minor histocompatibility antigens (mHag), encoded by genes on the Y chromosome can develop GVHD, another possible factor that influences the outcome of the transplant is the presence of the donor's NK cells (Vizzoni, 2008, p. 144). GVHD also has a higher incidence in the elderly, due to an increase in sensitized antigens and an involution of the thymus (Soares, 2007, p. 91 113).

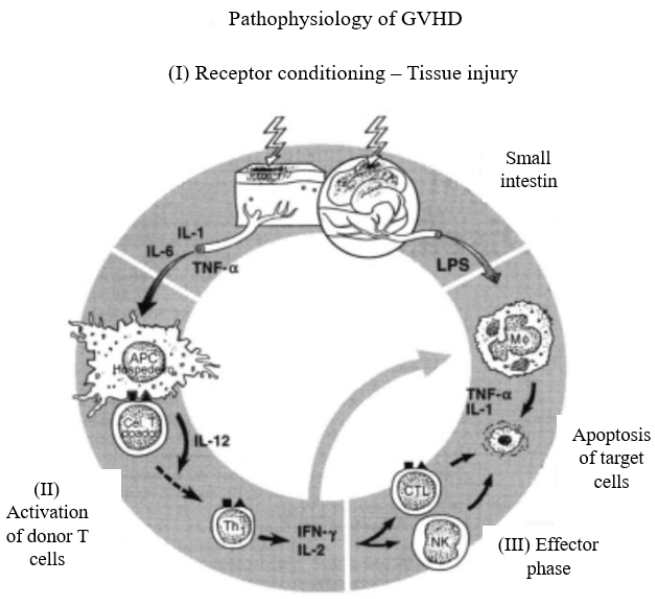

Figure 2 – Summary of the pathophysiology of GVHD divided into three phases.

Pathophysiology of GVHD divided into three phases, in the first it is possible to visualize the effects of the disease and its previous infections, in the second the donor's T cells are activated by antigens and in the third phase the T lymphocytes lyse the recipient's cells and other cytotoxic cells are activated.

Source: Diagnosis and Treatment of Acute Complications of Hematopoietic Progenitor Cell Transplantation, v. 33, no. 3, p. 264, 30 September. 2000. Available at: https://www.revistas.usp.br/rmrp/article/view/7698

Graft Versus Host Disease can be subdivided into two parts according to its clinical analysis, acute (aGVHD) and chronic (cGVHD). In cGVHD, the diagnosis was considered for a long time when its signs occurred approximately 100 days after transplantation, even though the difference between watery and chronic is often indistinguishable, however this has been discussed after surveying recent studies as it was found that patients who received consolidation treatment at lower doses than required for a good prognosis, aGVHD may appear approximately 3 months later, in addition to the possibility that both subtypes occur concomitantly (Jagasia et al. 2014, p. 947). GVHD is considered a multiorgan syndrome (because it resembles autoimmune diseases), known for two forms: limited, where there is localized involvement of the skin and/or liver, and the extensive form, where there is generalized involvement of the skin (Silva; Bouzas; Filgueiras, 2003, p. 63).

CD8+ cytotoxic T lymphocytes concentrate in the host so that they directly cause tissue damage. On the other hand, there is the presence of effector cells such as mast cells, NK cells and macrophages, in addition to other cytokines (TNF-a) that mediate all cytotoxicity. The role of mediators is the induction of MHC molecules to stimulate fibroblasts to produce collagen in target tissues, and a strong contribution to fibrosis in GVHD is the degranulation of mast cells, leading to the formation of various antibodies that is caused by polyclonal activation. of B cells. Briefly and succinctly, cGVHD is nothing more than an epithelium that has been damaged by mononuclear cells, and the formation of fibrosis (Silva; Bouzas; Filgueiras, 2003, p. 63).

AGVHD depends largely on the presence of NK cells in the graft, which in large quantities will have their functionality increased. aGVHD can be characterized

in two different ways, efferent and afferent. The efferent phase is characterized by a high production of cytokines (IL-2, IL-3, IL-4, IFN) by T cells that are activated, with the function of stimulating effector cells that intend to attack the tissues of the graft and host, in addition, NKs act by causing damage to the epithelium by reaching cells that do not present autologous surface antigens. These cells (activated by the cytokines mentioned above) produce several other cytokines with the purpose of stimulating hematopoietic colonies. In the afferent phase, category I and II alloantigens present in the recipient react with the donor's CD4+ and CD8+ T cells, on the surface of the APCs, through chemical mediations between the cells of the immune system, allorelative T cells transform into suppressors influenced by interleukin, causing the "boom" of the immunological response (Silva; Bouzas; Filgueiras, 2003, p. 64).

TREATMENT AND PREVENTION

For greater effectiveness in the treatment of GVHD, it is necessary to break the reaction of the donor's T cells while still acting in the afferent phase. In milder cases, immunosuppressants, antihistamines and treatment with significant doses of corticosteroids are used, in patients with difficult evolution, in more severe cases, medications such as thalidomide, mycophenolate which helps in acute organ rejection, azathioprine as an immunosuppressant and puva photochemotherapy are used as alternatives (Silva; Bouzas; Filgueiras, 2003, p. 63).

As forms of prevention of GVHD, the choice of the most compatible donor through the analysis of major and secondary histocompatibility antigens is taken into consideration, preferably a donor of the same sex, avoiding female donors for male recipients and, if not If possible, female donors must have lower parity, that is, a lower chance of alloimmunization; immunosuppressive treatment with cyclosporine A as the most used, inhibiting the proliferation of T cells, differentiation of cytotoxic lymphocytes and the release of IL-2; Partial or complete depletion of T cells; Reducing the intensity of conditioning, enabling immunological tolerance between donor and host; Cryopreservation of stem cells before their infusion, reducing the disease by using umbilical cord blood (if it has already been collected), instead of marrow; and decreasing the use of high doses of chemotherapy and radiation, as their high dose will increase cytokines (Vizzoni, 2008, p. 144).

There are currently studies in Brazil carried out in Rio Grande do Sul in partnership with MD Anderson Cancer Center Texas in the United States as an alternative treatment for replacing BMT with greater efficacy and safety, using NK cells, in English (Natural Killer), as an injection model (Pedroso, 2017, p.290).

NK cells being used as immunotherapy in the immune system reaching the tumor without causing further damage to the patient's other tissues. Studies show considerable data to lead to remission in some cases of cancer such as Myeloid Leukemia, however it is extremely important that the patient's immune system is silenced and ready to accept new cells (Pedroso, 2017, p.290).

At the end of 2021, through methodological research, selected nursing professionals were interviewed and helped in the production and validation of a booklet for educational purposes. The booklet consists of guidance on the necessary care for patients undergoing transplantation to mitigate the development of GVHD. The material's instructions contain care tips and treatments depending on which organ was affected by GVHD. The booklet was tested and approved by professionals, who, in addition to providing information to the affected population, had their work

disseminated and significantly improved the practice of care for the pathology in question. (Soares, 2022, p. 1734– 1735).

FINAL CONSIDERATIONS

In view of the above, the utmost importance of the chosen topic could be observed. Families in high socioeconomic conditions carry out cryopreservation of embryonic cord cells, enabling possible future treatment if any complications occur with their children, however this method is not accessible to the entire population, which results in secondary treatment methods such as example, allogeneic transplantation. However, all methods have risks and due to serious problems with allogeneic BMT where an immunological response can occur, this response is known as Graft versus Host Disease and is divided into acute or chronic,

The greater the compatibility between donor and recipient, the lower the chance of GVHD occurring, when there is no possibility of a fully compatible donor, as occurs in bone marrow banks, after the transplant, chemotherapy is performed using the post-transplant drug cyclophosphamide or post-transplant thymus globulin, to increase immunosuppression and attempt to prevent GVHD.

Treatment for this pathology depends on a case-by-case basis, and can be considered, from the use of ointments to the injured areas to corticosteroids with higher doses. Its changes are easy to observe due to its injuries to both the skin and other organs (Santos, 2005, p.)

The cGVHD and aGVHD are of great importance for science, through studying the development of this unique pathology, it is possible that we understand its action within the immune system and the capacity for its evolution. This way, through knowledge, study and updating, it is possible to develop more consistent treatment methods so that patients who present this condition can return to a healthy life. That said, the importance of bone marrow donation and updating on the development of GVHD must be highlighted.

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