OASIS DERMATOLOGY GROUP

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Graft Versus Host Disease

Graft-versus-host disease (GVHD) is a significant immunological complication that arises following the transplantation of allogeneic(similar but not identical from a donor) tissue, such as hematopoietic stem cells, liver, or non-irradiated blood products. It occurs when immunocompetent donor-derived T-lymphocytes(functional immune cells from the tissue donor) recognize the recipient's tissue as foreign, leading to a systemic inflammatory response. While GVHD is most commonly associated with allogeneic hematopoietic stem cell transplantation (HSCT), it can also develop after other types of organ transplants that are rich in lymphocytes, including liver transplants and transfusions of non-irradiated blood products. GVHD can cause severe organ damage and significantly impact the patient's recovery and quality of life.

Pathophysiology of GVHD

GVHD is a consequence of an immunologic attack by donor-derived T-lymphocytes against recipient tissues. These donor T-cells recognize host cells as "non-self," a response triggered by discrepancies in human leukocyte antigens (HLAs). HLA molecules play a crucial role in immune regulation by presenting antigenic peptides to T-cells, which then differentiate into effector cells capable of attacking foreign cells.

In the context of HSCT, the donor's T-lymphocytes may mount an immune response against host tissues, especially when there is an HLA mismatch between the donor and recipient. While autologous HSCT (where the patient's own stem cells are transplanted) avoids this issue, allogeneic HSCT (involving donor cells) carries a higher risk for GVHD, even when HLA matching is performed. This heightened risk is attributed to the fact that perfect HLA matching is rare, and minor mismatches can still provoke immune responses.

Classification of GVHD

GVHD is typically classified into two main types based on the time of onset following transplantation: acute and chronic.

- ***Acute GVHD***: Acute GVHD occurs within the first 100 days following transplantation. It is primarily a result of a type IV hypersensitivity reaction, where donor T-cells recognize host tissue antigens as foreign, leading to inflammation and cellular destruction. Without prophylactic treatment, acute GVHD can affect 70-100% of patients undergoing allogeneic HSCT. However, prophylaxis with immunosuppressive agents such as cyclosporine significantly reduces this risk to 9-50%. Acute GVHD primarily targets the skin, gastrointestinal tract, and liver.
- ***Chronic GVHD***: Chronic GVHD develops after 100 days post-transplantation and often involves both T- and B-lymphocyte-mediated responses. Unlike acute GVHD, which is

generally self-limited, chronic GVHD can persist for months or years and lead to long-term complications such as fibrosis, organ dysfunction, and increased mortality.

Clinical Manifestations of GVHD

The clinical features of GVHD vary depending on the organs involved and the timing of onset. The two forms—acute and chronic—manifest differently.

- ***Acute GVHD:***
  - *Skin*: The most common symptom is a pruritic (itchy), maculopapular rash, which can involve the ears, neck, shoulders, palms, and soles. The rash may progress to erythema(redness) and blistering, and in severe cases, it can cause skin necrosis(death).
  - *Gastrointestinal*: Acute GVHD often presents with symptoms of nausea, vomiting, diarrhea, and abdominal pain. Diarrhea may be severe, leading to fluid and electrolyte imbalances.
  - *Liver*: Hepatic involvement is common, with symptoms such as jaundice, hepatomegaly, and elevated liver enzymes. Bilirubin concentration increases due to liver dysfunction, causing the characteristic yellowing of the skin and sclera.
- ***Chronic GVHD:***
  - *Skin*: Chronic GVHD may present with scleroderma-like changes, including skin thickening, fibrosis, and contractures. It can also cause lichenoid eruptions, characterized by itchy, plaque-like lesions.
  - *Ocular and Oral*: Sicca syndrome, involving dry eyes and dry mouth, is a hallmark of chronic GVHD. These symptoms are associated with lacrimal and salivary gland dysfunction.
  - *Pulmonary*: Pulmonary involvement in chronic GVHD can manifest as cough, wheezing, and dyspnea due to bronchiolitis obliterans, a form of chronic lung damage that destroys the bronchioles.
  - *Hepatic and Gastrointestinal:* Similar to acute GVHD, chronic GVHD can cause liver dysfunction, but the onset is more gradual. Chronic GI symptoms can include malabsorption, weight loss, and chronic diarrhea.

Diagnosis of GVHD

Diagnosis of GVHD is based on clinical findings, histopathological examination, and sometimes, biopsy. For acute GVHD, biopsy of affected organs, particularly skin and liver, may show inflammatory infiltrates, apoptosis(programmed cell death) of epithelial cells, and tissue necrosis. In chronic GVHD, biopsy findings can include fibrosis and atrophic changes in the affected organs. Additionally, diagnostic criteria for GVHD have been developed by the National Institutes of Health, which provide a framework for grading the severity and extent of the disease.

Treatment of GVHD

Management of GVHD is aimed at controlling the immune response and minimizing tissue damage. Treatment strategies are determined by the severity of symptoms, the type of GVHD, and the timing post-transplant.

- ***Prophylaxis***: Prophylactic treatment is crucial in preventing GVHD. Immunosuppressive drugs such as cyclosporine, tacrolimus, methotrexate, and corticosteroids are commonly used to reduce the incidence and severity of GVHD. The aim is to prevent donor T-cells from attacking the recipient's tissue. Total body irradiation may also be used in certain cases to suppress immune function further.
- ***Acute GVHD:***
  - *Topical Steroids:* For mild skin involvement (e.g., less than 50% of body surface area), topical corticosteroids are the first-line treatment. These are effective in reducing inflammation and controlling skin rash.
  - *Systemic Steroids*: If the rash involves more than 50% of the body, or if there are signs of liver or GI involvement, systemic corticosteroids are administered. Prednisone is typically the steroid of choice, but other immunosuppressants like methylprednisolone may also be used.
  - *Other Immunosuppressive Agents*: In cases where corticosteroids are insufficient, second-line agents such as antithymocyte globulin (ATG), ruxolitinib, or infliximab may be utilized. These agents target specific immune pathways involved in GVHD pathogenesis.
- ***Chronic GVHD:***
  - *Corticosteroids*: The first-line treatment for chronic GVHD remains systemic corticosteroids, often used in combination with other immunosuppressive agents.
  - *Second-Line Treatments:* For refractory chronic GVHD, additional treatments may include cyclosporine, mycophenolate mofetil, or sirolimus. In some cases, novel therapies such as ibrutinib (a Bruton's tyrosine kinase inhibitor) or ruxolitinib (a Janus kinase inhibitor) are being investigated in clinical trials.
  - *Supportive Care*: Symptomatic management of chronic GVHD includes treatment for dry eyes (e.g., cyclosporine A eye drops), oral mucosal care, and pulmonary support for lung involvement.

Conclusion

Graft-versus-host disease remains a major complication of allogeneic transplantation, particularly hematopoietic stem cell transplantation. The condition results from the immunological attack of donor T-cells on host tissues, leading to significant morbidity. Early diagnosis and appropriate management, including prophylactic immunosuppressive therapy and symptom-specific treatments, are essential to reducing GVHD severity and improving patient outcomes. Advances in targeted therapies and immunosuppressive regimens offer hope for better control of both acute and chronic forms of GVHD.

References

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