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GRAFT VERSUS HOST DISEASE: ORAL CLINICAL ASPECTS, DIAGNOSIS, AND TREATMENT IN DENTAL PRACTICE

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ABSTRACT

Introduction: Hematopoietic Stem Cell Transplantation (HSCT) is a therapeutic modality for hematological diseases, and the use of which can trigger secondary problems, and one of them is the Graft Versus Host Disease (GVHD). **Objective:** To report the pathogenesis, diagnostic, treatment and clinical oral manifestations of GVHD. **Methodology:** This is a narrative literature review, with data collection in the *Pubmed*, was used from December 2019 to February 2020. The crossing was made through the descriptors Decs / Mesh "graft-versus-host disease", "oral graft-versus-host disease", "allogeneic bone marrow transplant" and "oral manifestations". A total of 32 articles were included to this review. **Results:** The determination of the diagnosis through the clinical manifestations of oral GVHD is well established in the literature, however there is a lack of suficient content to support the pathogenesis and treatment options. Further studies are necessary to improve understanding, collaborating for the elaboration of more effective therapeutic strategies. **Final Considerations:** It is emphasized the importance of a systemic analysis of the patient for the correct diagnosis, because the treatment becomes more satisfactory and effective.

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INTRODUCTION

Bone marrow transplantation represents a therapeutic modality that involves hematopoietic stem cell transplantation (HSCT) from an individual's own bone marrow (autologous) or from a donor (allogeneic) according to the level of compatibility of the blood material (Mays, 2013). This therapy, better known as stem cell transplantation, is indicated for several malignant as well as benign hematological diseases (Deeg, 2006). HSCT requires prior conditioning of the host through high dosages of cytotoxic chemotherapy with or without total body radiotherapy. In cases of allogeneic transplantation, the precursor cells are derived from another individual. Hence, numerous side effects such as graft versus host disease (GVHD) and primary or secondary malignancies can arise (Deeg, 2006 and Zadik, 2017).

GVHD is considered one of the main complications after allogeneic transplantation. It can interfere with the success of allogeneic transplantation in a transient or a definitive way. It comprises of an immunological reaction in which the transplanted lymphocytes attack the host tissues, triggering numerous manifestations systemically and in the oral cavity. Such manifestations vary depending on the type of GVHD (acute or chronic). Especially in the oral cavity, alterations including lesions similar to lichen planus, hyperkeratotic plaques, dysfunction of the salivary glands, perioral scleroderma, and changes on the palate are commonly observed in addition to painful symptoms and discomfort. Systemic manifestations may include skin lesions, liver dysfunction, and skin sclerosis (Zadik, 2017). Current therapeutic strategies include the use of immunosuppressants and corticosteroids. The most commonly used drugs include dexamethasone, triamcinolone acetonide, clobetasol,

betamethasone, prednisone, and tacrolimus (Zadik, 2008). Every patient undergoing HSCT needs prior dental treatment including removal of the possible foci of infection in the oral cavity as well as post-transplantation follow-up to considerably lower the incidence of effects such as secondary infections and GVHD (Imanguli, 2008). Thus, the objective of the present review was to discuss the pathogenesis, diagnosis, treatment, and clinical aspects of oral GVHD, as this condition is associated with high rates of morbidity and mortality in patients undergoing HSCT.

MATERIALS AND METHODS

The methodology for the present study consisted narrative literature review based on search for related articles in the PubMed database from December 2019 to February 2020. The search was conducted by crossing of the DeCS/MeSH descriptors in English including "graft-versus-host disease," "oral graft-versus-host disease," "allogeneic bone marrow transplant," and "oral manifestations" through Boolean operators AND and OR. Additionally, the references of the initially selected studies were evaluated to identify additional works with the proposed theme that were not found in the initial research. Selection of the articles was based on the titles that addressed the pathogenesis and classification of GVHD for diagnostic purposes as well as the clinical manifestations in the oral cavity and the general aspects of treatment and clinical results. The abstracts available in the PubMed database were collected. Initially, 233 articles were found through this search platform and 10 articles were found through the references of these studies. After the initial reading, studies that provided an update on GVHD were selected. Since the published data on GVHD is scarce, articles relevant to the theme were selected irrespective of the publication period. Only the articles written in the English language were included. Articles that did not have abstracts in the database were excluded. After this initial analysis, 22 articles from PubMed and 10 articles found through free search (total 32 articles) were included in the present narrative literature review.

Review of Literature

Classification: GVHD can be classified as acute or chronic. According to Glucksberg et al. (1974), time is the determining factor for this classification. Lesions that appear within 100 days after the transplantation are considered acute, whereas lesions that develop after this period are classified as chronic. However, a recent change in this classification suggested disease categorization based on symptoms and specific clinical characteristics that may persist after this period. The acute form presents mainly with maculopapular cutaneous lesions, liver dysfunction, and less gastrointestinal involvement. Acute GVHD can be classified as classic acute or late acute. The classic acute disease refers to the appearance of lesions within 100 days after transplantation, while the late acute GVHD shows features of acute GVHD beyond 100 days (Filipovich, 2005). The chronic form is considered a distinct entity, which can affect practically all organs. It has a variable clinical presentation, which often simulates autoimmune diseases. Manifestations include lesions resembling lichen planus of the skin and the oral cavity, sclerosis of the skin, and damage to the salivary glands (e.g., Sicca Syndrome) among others. Usually, the chronic phase is observed at 3 to 15 months after the transplantation and can be preceded by acute injuries (Filipovich, 2005 and Nicolatou-Galitis, 2001). This condition is mainly responsible for long-term mortality in patients who survived the transplantation (Fraser, 2006). The time of onset depends on the degree of histocompatibility, the amount of T cells received by the donor, and the prophylactic regimen used to avoid GVHD (Deeg, 2006).

Pathogenesis

For the transplantation procedure, it is mandatory for the patient to be preconditioned to reduce the tumor effect and the resistance of the host to the graft. The methods used to deplete the host's immune cells include the use of radiation with a single or fractional dose, cytotoxic chemotherapeutic agents, immunosuppressants, and antibiotics to minimize graft rejection (Mays, 2013). However, conditioning schemes are associated with progressive cell damage with increased epithelial permeability and main involvement of the skin and gastrointestinal tract (Cooke, 2001). Conditioning promotes the donation of new T cells to the host that are fundamental to the success of the transplantation procedure through promotion of adaptive immunity and control of malignancy. However, these immunocompetent cells have a high capacity to trigger GVHD (Imanguli, 2009). Upon reaching the organ, T lymphocytes cause direct epithelial damage through release of cytokines such as interferon (IFN) gamma. This event activates local macrophages, which release additional pro-inflammatory cytokines such as interleukin IL-6, IL-1, and tumor necrosis factor alpha (TNF-alpha).

The pathogenesis of GVHD, especially that of the chronic form, has not been completely elucidated to date due to the difficulty in carrying out long-term prospective studies. Current concepts include the exaggerated permanence of reactive T cells, incomplete tolerance mechanisms, cellular immune response different from that of the Th1 and Th2 cytokines, increasing production of autoantibodies against the host by B cells, and chronic non-specific inflammation, which promotes tissue fibrosis (Ferrara, 2009). In a recent study, it was demonstrated that IFN-1 and IL-15 can play a fundamental role in the pathogenesis of GVHD (Imanguli, 2002). Despite the importance of understanding the origin of GVHD to develop more effective treatment strategies, understanding the pathogenesis of this complex disease remains a target to be reached. Recent studies suggest that triggering of such a disease may be related with Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway, which is a pathway responsible for the first inflammatory response in innate immunity. Inhibition of this pathway impairs the differentiation and activation of antigen presenting cells and negatively regulates the expression of signals to T cells. Activation of the JAK/STAT pathway can also promote chronic evolution of alloreactivity characterized by the long-term persistence of inflammation and fibrosis. Based on the cited information and the preclinical data, the logic of using JAK/STAT inhibitors in the treatment of GVHD is reviewed by (Mannina, 2016).

General characteristics, diagnosis and manifestations in the oral cavity: GVHD is considered a clinicopathological syndrome, which affects about 50 to 80% of the patients undergoing allogeneic HSCT. It has a 5-year survival rate of about 40% in patients who show multisytemic manifestations of this disease (Deeg, 2006 and Imanguli, 2009). It may involve the entire gastrointestinal tract, skin, lung, salivary glands, and lacrimal glands among other organs (Imanguli,

2009). The involvement of an organ can occur in isolation or in association with another organ and the diagnosis requires interpretation of clinical findings and laboratory tests (Deeg, 2006). In the oral cavity, any anatomical site can be affected. However, there is a greater predisposition for involvement of the tongue and the jugal mucosa. Oral lesions are frequent in patients with GVHD and can often represent the first sign of the disease (Treister, 2005; Imanguli, 2006; Noce, 2011). GVHD affects a large number of transplant patients and is associated with great damage to the health of the patients, resulting in increased morbidity and decreased quality of life (Imanguli, 2008 and Gomes, 2014). Innumerable presentations of this condition, especially those of chronic GVHD, can be observed in the oral cavity. Lesions similar to lichen planus, hyperkeratotic plaques, trismus, gingivitis, erythema, sclerosis, and erosive and painful atrophic lesions resembling mucositis are among the most common manifestations. The most unusual manifestations may not determine the diagnosis of the disease. However manifestations such as hyposalivation, xerostomia, mucoceles, and mucosal atrophy can serve as auxiliary tools in the diagnosis (Woo, 1997). It is worth mentioning that this morphological spectrum of oral lesions varies according to the period of disease manifestation (Gomes, 2014).

Oral manifestations of acute GVHD resemble oral mucositis with the presence of erythematous, scaly, and painful lesions. On the other hand, chronic GVHD presents a wide diversity of clinical presentations including ulcers, hyperkeratotic plaques, lesions that resemble lichen planus, trismus, or even dysfunction of the salivary glands (Filipovich, 2005). Involvement of the salivary glands is associated with signs and symptoms of hyposalivation and xerostomia, which often resemble autoimmune diseases such as Sjogren's Syndrome. Hyposalivation occurs due to destructive or atrophic process in the glandular parenchyma (Nagler, 2004). However, xerostomia does not necessarily correlate with hyposalivation. This can be explained by the change in the chemical composition of the saliva and by sensory alteration (Torres, 2002). The consequences of salivary gland involvement may include tissue damage and increased risk of developing cavities in addition to verbal and nutritional limitations and affected tissue repair (Fox, 1985). Moreover, it is believed that inflammation of the minor salivary glands in association with hyposalivation occludes the excretory ducts with consequent development of mucoceles (Filipovich, 2005). Usually, patients undergoing HSCT and patients with oral GVHD are susceptible to various opportunistic fungal, viral, and bacterial infections of the oral cavity. The high incidence of infections is due to hyposalivation and the presence of severe immunosuppression (Meier, 2011). Among the common infections that affect these patients, oral candidiasis stands out. In a previous study, 28,542 patients were evaluated for the assessment of the incidence and the risk factors associated with candida infections during the initial 100 days after HSCT. Among these, 347 patients presented with candidiasis in the initial 100 days.

Candidiasis was present in 1.2% of the cases with peak incidence on the 22nd day after the transplant. Despite the low incidence, a mortality rate of 22% (76/347) was observed in patients in the initial 100 days. Among the principal associated risk factors, concomitant presence of GVHD could be highlighted (Cesaro, 2018). On the other hand, trismus occurs due to the continuous inflammatory process associated with the healing of the oral mucosa. This phenomenon can generate difficulties in hygiene maintenance and ingestion of food, with a consequent increase in the patients' morbidity (Schubert, 2008).

Development of secondary malignancies, especially that of squamous cell carcinoma (SCC) of the oral cavity, is another complication associated with chronic GVHD. The malignant process can occur due to prolonged immunosuppression, toxicity of the conditioning regimen that often involves radiation in addition to chemotherapy, disturbances in the host's immune mechanism, and constant inflammatory irritation (Demarosi, 2005). Patients who survive HSCT are automatically at risk of developing malignant lesions. In the oral cavity, the appearance of such lesions is increasingly common due to patients' exposure to GVHD and due to therapies with multiple immunosuppressive drugs to control the manifestations of GVHD (Gomes, 2014). In a case report by (de Araújo, 2014), secondary manifestation of SCC was observed in the oral cavity after allogeneic HSCT with consequent development of chronic GVHD in a 43-year-old patient. The possible causes for the secondary appearance of SCC may include patients' exposure to GVHD in addition to concomitant immunosuppressive therapeutic treatment consisting of azathioprine, cyclosporine, prednisone, and tacrolimus. Understanding the possible correlation between changes in the oral cavity and immunologically mediated diseases is extremely important, since systemic changes can trigger or contribute to the development of secondary lesions (Imanguli, 2006). In a patient undergoing HSCT, (Hashimoto, 2019) observed multiple whitish lesions on the tongue associated with areas of erosion, a finding consistent with chronic GVHD. During periodic follow-up, rapid evolution of a single exophytic lesion on the back of the tongue was noted. It was diagnosed as SCC after incisional biopsy.

Diagnosis of GVHD according to the National Institute of Health (NIH) criteria: In 2006, National Institute of Health (NIH) recommended criteria to determine the signs and symptoms characteristic of GVHD for accurate diagnosis of oral GVHD. In addition, NIH has also reported distinct signs that do not immediately confirm the presence of the disease. Characteristic signs and symptoms include the presence of hyperkeratotic plaques, lesions that resemble lichen planus, and trismus. The distinct signs include dry mouth, mucoceles, mucosal atrophy, and ulcers. The exclusive presence of distinct signs does not confirm the diagnosis of GVHD. Complementary laboratory, histological, and radiological examinations should be performed to confirm the diagnosis. Additionally, when a malignant lesion in the oral cavity is suspected, biopsy should be performed immediately (Meier, 2011). NIH developed a scale for measuring the severity of GVHD and its different clinical manifestations (Table 1). It is also recommended to apply an 11-point visual analog scale with scores ranging from 0 to 10 for the pain related to the oral cavity, xerostomia, and tolerance to certain foods (Imanguli, 2006).

Treatments of oral manifestations: The primary treatment for oral manifestations consists of prevention and relief of symptoms, prevention of dental problems, maintenance of food intake, and improvement in the patients' quality of life. The exclusive involvement of the oral cavity requires the use of topical agents. However, when GVHD affects other organs concomitantly, it is necessary to use additional systemic

Table 1. Scale for measuring the severity of GVHD (NIH, 2006)

Oral cavitychanges	Absenceofevidence		Weak		Moderate		Severe	
Erythema	Absent	0	Little tomoderateerythema (<25%)	1	Moderatetosevereerythema (≥25%)	2	Erythema Severe (≥25%)	3
Lichenoid lesions	Absent	0	Hyperkeratoticchanges (<25%)	1	Hyperkeratoticchanges (25% to 50%)	2	Hyperkeratoticchanges (> 50%)	3
Ulcers	Absent	0	Absent	0	Ulcers (≤20%)	3	Severeulcers (>20%)	6
Mucoceles*	Absent	0	1-5 mucoceles	1	6-10 mucoceles	2	More than 10 mucoceles	3
							Total score	

agents. Thus, several factors must be considered in the treatment of GVHD, since it is associated with many deleterious effects on the patients (Imanguli, 2008 and Meier, 2011). Patients should be advised regular visits to the dentist and good oral hygiene habits to reduce the risk and the severity of GVHD. Guidance regarding biofilm control should be provided through instructions for meticulous oral hygiene using soft brushes and alcohol-free rinses. Additionally, preventive measures such as use of fluoride and dietary guidance help minimize demineralization of dental tissues (Schubert, 2008). Numerous topical medications can be used to control this condition. Among them, corticosteroids are widely used for local treatment. Non-steroidal immunomodulators are also used to a lesser extent. For pain control, topical anesthetics can be used as complementary therapy (Schubert, 2011). Local therapy has some advantages including a decrease in the systemic effects and a consequent possibility of intensifying the therapeutic effect in a specific area (Schubert, 2008). Although topical corticosteroids do not have specific therapeutic approval for GVHD, they are widely used for the treatment of this condition due to their beneficial effect on other conditions that affect the oral mucosa, particularly lichen planus. Previous reports have mentioned the use of budesonide, dexamethasone, triamcinolone acetonide, fluocinonide, clobetasol propionate, betamethasone, and prednisone. Topical dexamethasone has shown results that corroborate its indication. It is highly effective in oral lesions and has minimal side effects (Imanguli, 208 and Schubert, 2008).

In a randomized double-blind clinical study, two topical corticosteroids (clobetasol 0.05% and dexamethasone 0.1 mg/ml) for the treatment of symptomatic oral GVHD were compared in 32 patients who were divided into two groups (clobetasol and dexamethasone). The medications were administered over a period of Noce *et al*. (2014). consecutive days and the assessment was made using the modified oral mucositis assessment scale, originally proposed by the World Health Organization. Both the drugs showed good efficacy. However, 0.05% clobetasol showed a better performance in the resolution of lesions and symptoms of oral GVHD. It is worth mentioning that the use of topical corticosteroids increases the risk of fungal infections in the oral cavity, which may require concomitant use of a local antifungal agent with low absorption (Meier, 2011). Tacromilus is an immunosuppressive drug widely used for the treatment of systemic GVHD. Due to its satisfactory results, its topical application was started for the oral manifestations of GVHD. Despite its high effectiveness, it is absorbed systemically. Hence, 0.1% tacrolimus must be applied twice a day to avoid undesirable effects (Meier, 2011).

The Food and Drug Administration has issued a warning about the possible carcinogenic potential of tacrolimus in skin lesions. However, there is no evidence of its malignant potential in topical application in the oral cavity (Meier, 2011). In previous studies, it was found that tacromilus combined with other drugs provided more satisfactory results (Rowlings, 1997 and Ramachandran, 2019). Glucksberg et al. reported that tacrolimus combined with methotrexate (MTX) demonstrated evident benefits with reported GVHD (grade II to IV) prevalence rate of 31.9% (Glucksberg, 1974). Patients who received the combination of cyclosporine and MTX had a prevalence of 44.4% (Rowlings, 1997).

Management of salivary gland dysfunction in GVHD aims to maintain adequate quantity of saliva in the oral cavity and to decrease the risk of caries and opportunistic infections in these patients. Several agents can be used to minimize these harmful effects (Imanguli, 2008). Patients should be instructed to maintain constant hydration of the oral cavity through consumption of water or other non-cariogenic and non-erosive fluids. In case of complete absence of salivary flow, salivary substitutes such as artificial saliva should be used. When salivary remnants exist, mechanical or chemical sialagogues can be used to stimulate the production of saliva by the glands. It is also necessary to establish a defined protocol for the use of fluoride compounds such as varnish with 25,000 ppm fluoride content, mouthwashes, and appropriate pastes to reduce the risk of tooth decay. In addition, patients must be monitored through regular visits to the dentist every 3 months (Imanguli, 2008).

In the literature, there are a few reports of treatment of salivary dysfunction with cholinergic drugs. Among the drugs studied, pilocarpine, a parasympathomimetic agent with predominantly muscarinic activity, has greater scientific monitoring compared to cevimeline, which has efficacy and safety similar to pilocarpine (Meier, 2011). Singhal *et al* (1997). investigated the possible benefits related to salivary flow after pilocarpine administration. Pilocarpine was administered orally in 13 patients with moderate (n=6) and severe (n=7) hyposalivation due to chronic GVHD. Ten patients (77% of the total) reported a significant improvement in salivary flow and symptomatic relief with consequent benefits in speech and food consumption. However, pilocarpine should be administered with caution and only under professional guidance, as its indiscriminate use can result in adverse effects such as dizziness, tachycardia, flushing, urinary incontinence, frequent urination, worsening of asthma, and fatigue. Patients with GVHD are exposed to progressive changes similar to sclerosis, which can affect several areas of the body including the oropharynx. Such involvement has a direct impact on patients' quality of life. Hence, ways are sought to repair these changes.

Clinical evidence indicates that the use of photobiomodulators can be beneficial in resolving these conditions, as it is a minimally invasive technique with an analgesic, anti-inflammatory, and photobiomodulatory effect. When combined with the main treatment consisting of multiple drug therapy (mostly corticosteroids), it promotes therapeutic synergism with a consequent decrease in the painful symptoms and increased patient comfort (Epstein, 2018). In addition to the conventional therapies mentioned above, a new line of research suggests that appropriate treatment for GVHD may be directly related to understanding its origin. In a recent study, it was possible to observe the possible relationship between GVHD and JAK/STAT pathway. This finding suggests the potential employability of JAK inhibitors, a new class of drugs with a high anti-inflammatory potential, which have shown effective action in GVHD resistant to corticosteroids. However, further confirmation of their effectiveness in the management of GVHD is needed (Mannina, 2019).

Final Considerations

There are several manifestations of GVHD in the oral cavity. The current literature lacks sufficient data regarding pathogenesis and treatment of this condition and further studies are essential to increase the understanding of GVHD for the scientific community to develop effective treatment strategies based on knowledge about its pathogenesis. It is also important to emphasize the importance of systemic analysis of patients, as analysis of isolated sites may result in a hasty diagnosis, leading to inadequate treatment and consequently, increased morbidity and mortality. Correct diagnosis ensures successful treatment with increased benefits to patients.

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