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Oral chronic graft-versus-host disease: A short review

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Abstract

Allogeneic Hematopoietic Steam Cell Transplantation (allo-HSCT) treat a wide range of malignancies, including: neoplastic and non-neoplastic hematologic disease and immune deficiency states, and autoimmune disease. Chronic Graft-versus-host disease (cGVHD) is a major late complication of allo-HSCT, representing a clinical syndrome characterized by complex allogeneic and autoimmune dysregulation of the immune system, leading cause of non-relapse-related morbility and mortality among long-term transplant survivors. The oral cavity is frequently involved, as the second most common site involved after skin due to HSCT.

The spectrum of clinical manifestation and histopathological characteristics of oral cGVHD are similar to several autoimmune conditions including Sjögren syndrome, oral lichen planus and scleroderma.

Ancillary therapy is used for symptomatic oral mucosal or erythematous or ulcerative disease in GVHD treatment by using routine systemic drugs, several topical treatments as corticosteroids, non-corticosteroids, immunosuppressants, and phototherapy. For affected salivary glands, artificial saliva or saliva stimulators are commonly used to relief the xerostomia symptoms.

Introduction

The first Allogeneic Hematopoietic Stem Cell Transplantation (allo-HSCT) was performed in 1957 to treat end-stage leukemia [1], and it has seen a steady increase in the overall success and applicability to treat a wide range of malignancies, including: neoplastic and non-neoplastic hematologic disease and immune deficiency states, and autoimmune disease [2-5].

Annually, it has increased steadily over the past three decades, worldwide 15.000 out of over 40.000 individuals are performed with cells an allogeneic donor by receiving HSCT [2,3,6]. Graft-versus-host disease (GVHD) is one of the principal complications of allo-HSCT and it is important cause of morbidity and mortality among patients undergoing HSCT, resulting a severe impairment of the quality of life among survivors, and it is likely to occur if the host receives a graft from an unrelated donor, or if the host or donor is older [3,7,8].

In 1966, it was outlined the 3 fundamental requirements for GVHD: the graft must contain immunological competent cells; the host must express tissue antigens that seem foreign to the graft (antigenic mismatch); the host must be incapable of rejecting the donor graft (immune compromise) [3,5]. This disease is mediated by autoreactive T lymphocytes that infiltrate and attack various target organs and tissues, including oral mucosa and salivary glands, leading to salivary hypofunction and oral damage [7,9].

The two forms of GVHD, acute and chronic, are distinct in both onset and clinical features [10]. Traditionally, when it targets the immune system, by definition, if seen before Day +100 it is called as acute GVHD (aGVHD), but if it occurs after day 100 it is defined chronic GVHD, however, according to NIH Consensus criteria it is recommended to classify GVHD based on characteristic symptoms and signs rather than a rigid temporal definition [2,3,5,8,10].

Acute GVHD (aGVHD)

The aGVHD occurs through three related stages: conditioning; activation and expansion of allo-reactive cells; the effector phase. Aggressive myeloablative conditioning is associated with higher risk and increased severity of GVHD, it is accomplished with chemotherapy and/or irradiation to deplete the host immune system, permiting successful engraftment of donor stem cells. The conditioning allows the activation and expansion of newly infused donor T cells, those are vital for transplant success, also providing adaptive immunity to infections and controlling the malignancy. Thus, following the activation stage, graft T cells acquire an effector phenotype, exit secondary lymphoid organs, enter the blood stream and finally migrate to the host target tissues [3].

Clinically aGVHD is characterized by strong inflammatory features and it is diagnosed by presence of diffuse maculopapilar rash, erythroderma, nausea, vomiting, anorexia, profuse diarrhea, ileus or cholestatic hepatitis, and it is considered the major cause of early lethality [3,5,11]. Normally, skin, liver and/or digestive tract are targets of aGVHD, however cGVHD is characterized by selective damage to the skin and mucosa, hair and/or nails, eyes, liver, lungs, gastrointestinal tract and muscle fasciae [7,8].

Chronic GVHD (cGVHD)

Chronic Graft-versus-host disease (cGVHD) is a major late

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complication of allo-HSCT, representing a clinical syndrome characterized by complex allogeneic and autoimmune dysregulation of the immune system, leading cause of non-relapse-related morbility and mortality among long-term transplant survivors [11,12]. It occurs in approximately 30-80% of long-term survivors of HSCT, either adults or children [2,3,11].

Clinically and histologically, cGVHD has similarity to some common autoimmune disorder such as: lichen planus, Sjögren syndrome, scleroderma, systemic lupus erythematosus, dermatomyositis and primary biliary cirrhosis [3]. The diagnostic features for cGVHD include sclerosis, lichen-planus-like lesions, poikiloderma, esophageal webs, fascitis and bronchiolitis obliteran, but also some distinctive features suggest cGVHD as: oral ulcers ADN atrophy, onchodystrophy and sicca syndrome [3,11].

The major risk factor for GVHD development is human leukocyte antigens (HLA) disparity [5]. Other risk factors associated with cGVHD include Peripheral blood stem cell transplantation (PBSCT); increasing CD3 (T cell) dose in the graft; increased donor or recipient age; use of an unrelated donor; different gender donor/recipient combination; total body irradiation (TBI); diagnosis of chronic mielogenous leukemia or myelodysplastic syndrome and preceding history of aGVHD [3].

Both morbidity and mortality associated with cGVHD is caused by cGVHD-associated immunodeficiency and organ dysfunction and also by the immune suppressive medications used to treat this illness [11]. It may persist for several months or years, possibly affecting multiple organ systems including the skin, mouth, liver, eyes, lungs, joints, esophagus, and gastrointestinal and genitourinary tracts [2,11,12]. The skin and oral cavity are most commonly involved organs, and the diagosis is based on physical examination and biopsy findings [11,13].

Oral GVHD

The oral cavity is frequently involved, as the second most common site involved after skin due to HSCT, and oral manifestations occuring in 25 – 90% of all cGVHD patients, often coexisting with cutaneous, hepatic or ocular cGVHD [2,7,9,12-16]. It can be characterized as mucosal, salivary or sclerotic in nature, similary to several autoimmune conditions including Sjögren syndrome, oral lichen planus and scleroderma both clinical and histopathological presentation [12,13].

Radiotherapy and chemotherapeutic agents used for the conditioning regimens of transplantation have directly damaged the mucosal progenitor cells, leading to loss of mucosal integrity, thus evaluation of the periodontal status is needed prior to management with high-dose chemotherapy and/or HSCT and when the treatment will result in myelossupression [17].

In 2006, the NIH Consensus Development Project published criteria of the measurement of therapeutic response in clinical trials of cGVHD, presenting the NIH cGVHD Oral Mucosal Score (NIH OMS) as a clinitian-evaluated measure of oral mucosal manifestations of cGVHD, developed to increase objectivity and quantification in serial

Table 1. Characteristics between those readmitted within 30 days and those who were not readmitted.

	30-day readmission (n=32)	**Not readmitted (n=37)**	
Gender	Male (17) Female (15)	Male (23) Female (14)	P=0.45
Race	Caucasian (24) African American (5) Hispanic (3)	Caucasian (27) African American (8) Hispanic (2)	P=0.70
Average Age	57	58	P=0.86
Etiology of cirrhosis	HCV (14) Alcohol (7) HCV/Etoh (4) NASH (3) AIH (1) Other (3)	HCV (11) Alcohol (11) HCV/Etoh (1) NASH (3) AIH (4) Other (7)	P=0.29
Average MELD on index admission	20.36	19.1	P=0.24
Insurance Type	Medicare (10) Private (17) Medicaid (5)	Medicare (14) Private (16) Medicaid (7)	P=0.71
Decompensations	Ascites/SBP (14) Esophageal varices (16) Hepatic encephalopathy (11) Hepatic hydrothorax (4) Hepatocellular carcinoma (4) Hepatorenal syndrome (1)	Ascites/SBP (21) Esophageal varices (10) Hepatic encephalopathy (15) Hepatic hydrothorax (2) Hepatocellular carcinoma (6) Hepatorenal syndrome (5)	

Table 2. Index MELD scores between those readmitted within 30 days, those not readmitted in 30 days, and those with multiple readmissions within 30 days.

	30 day readmission (n=32)	**Not readmitted (n=37)**	**Multiple readmissions within 30 days (n=6)**
Average index MELD	20.36	19.1	24.3
Median index MELD	20	18	22

Table 3. Post-transplant patients enrolled in care coordination.

	30-day readmission (n=8)	**Not readmitted (n=7)**
Reason for transplant	HCV (4) Etoh/HCV (2) Other (2)	HCV (4) Etoh (2) AIH (1)
Recurrent HCV cirrhosis	5/8	3/7

monitoring of oral cGVHD [3,12].

Oral GVHD clinical features

The spectrum of clinical manifestation of oral cGVHD is variable including white papules, plaques, lichenoid hyperkeratosis, erythema, mucoceles, mucosal atrophy, edema, fibrosis, pseudomembrane, ulcerations, bleeding and xerostomia. Lesions on gingiva can induce a "desquamative gingivitis", presenting epithelial desquamation, erytomatous zones, erosive lesions on the gingival tissue, very similar to that of oral lichen planus and mucous membrane pemphigoid. It can involve any site in the oral cavity, but according to literature, the most commonly sites include buccal, glossal and labial mucosa. [2,5,7,9,11-16,19].

Oral pain, dental caries, taste disorders, dry mouth and other oral problems are frequent complains among most patients undergoing allo-HSCT, resulting discomfort, diminished oral health, taste disturbance, impaired oral cavity function, difficulty in speaking and swallowing, and decreased in food intake and weight loss, thus reducing quality-of-life [2,3,7,9,12,13,15,19]. Additionally, sclerodermatous changes could cause perioral fibrosis restricting opening and interfering with oral function, including hindering alimentation, the maintenance of oral hygiene and the provision of dental care [3,5,11,13,15]. Thus, oral hygiene is particularly difficult and the periodontal status often worsens [19].

Frequently, cGVHD patients with salivary gland involvement report dry mouth and present with signs of mucoid, viscous saliva, reduced or completely absence of moist film over the mucosal surfaces, absent floor of mouth pooling, accumulation of soft debris and erythematous mucosal surfaces. It results in quantitative and qualitative alterations in saliva, certainly including altered concentration of electrolytes, epidermal growth factor and salivary protein [5]. Commonly, it can develop mucoceles and also it can be involved at the increased risk for developing dental caries, and also can be associate to candidiasis development even without using intraoral topical steroids [5,15,16].

Studies assessing the risk of cancer among long-term survivors of HSCT has demonstrated a low but significant risk of secondary neoplasm, including: hematologic malignancies, lymphoproliferative disorder and solid tumor, this last one in patients who have undergone HSCT is two or three times greater than in general population [2,3,13]. All patients with cGVHD should be warned about their increased risk for developing oral squamous cell carcinoma and other malignancies, also undergo annual screening by examination [15,16].

Oral GVHD histopathological features

Generally, the typical histologic findings are subepithelial lymphocytic infiltration with epithelial changes in the oral mucosa and diffuse lymphocytic infiltration in the salivary glands [10].

In oral mucosa shows hydropic degeneration of the basal cells, interspersed areas of hyperparakeratosis and/or atrophy, presence of subepithelial cleft and apoptotic spinal layer cells with pyknotic nuclei. The connective tissue is characterized by variable amounts of perivascular inflammation and lymphocytic infiltration, due to alterations by using immunosuppressive medications, and occasionally it shows separation of the epithelium from the connective tissue [3].

In GVHD salivary gland disease is featured by lymphocytic infiltration of the salivary gland ducts, individual ductal epithelial cell necrosis, destruction of acinar tissues with presence of periductal fibrosis. Possibly, oncocytic ductal metaplasia can be observed in children. When dense fibrosis and acinar destruction is noted, mostly it reflect past disease, on the other hand, the presence of fibroplasia, acinar and periductal inflammation and ductal damage reflect current disease activity [3,20].

Treatment

Usually, ancillary therapy is used for symptomatic oral mucosal or erythematous or ulcerative disease in GVHD treatment by using routine systemic drugs, several topical treatments as corticosteroids (prednisone, dexamethasone, betamethasone), immunosuppressants (ciclosporine, azathioprine, tacrolimus, sirolimus) and phototherapy. The topical treatment might improve clinical response and prevents the patient from side effect of systemically used drugs [3,5,7,8,14-16]. Solutions are used mainly when manifestation are generalized, whereas gels, creams and ointments are used for localized lesions, it is very easy to apply with finger or gauze, preferable gels due to their hydrofilic properties [5,15].

Alternative non-corticosteroid rinse formulations of tacrolimus or cyclosporine maybe also be very effective, depending on patients symptoms [15]. Application of topical calcinerium inhibitors is an alternative to locally applied corticosteroids, because long-term use of topical steroids has been associated with atrophy of the lip vermilliomm, but not on oral mucosa. Frequently it could result in side effect of oral candidiasis and other systemic effects from long- term use of topical potent steroid [15].

All patients should be counseled to avoid acidic, spicy strongly flavored, and rough or crunchy foods and/or drinks due to the sensitivity and discomfort. Usually toothpaste could cause oral burning, so patients should use children's toothpaste instead. When symptomatic oral mucosal GVHD impairs nutrition or communication, viscous lidocaine may provide a topical analgesia and some relief [15,16].

For dry mouth patient can be instructed for frequent water drinking, to use gustatory and mechanical saliva stimulants (sugar free chewing gums and candies), to avoid xerogenic medications and to use oral moisturizing agents and saliva substitutes, and also parasympathetic agents e.g. pilocarpine may help [5,15,16].

Routine dental care, including Professional cleanings, fluoride applications, infections prophylaxis and monitoring for the development of osteonecrosis of the jaw in long-term bisphosphonates users are very important to improve the quality-of-life [15]. Some intraoral phototherapy have been reported to be beneficial in the management of oral mucosal cGVHD, including psoralen-UVA (PUVA); UVB therapy; low level laser therapy; carbon dioxide laser therapy [5,15].

Conclusion

cGVHD is a late complication among patients those undergo allo-HSCT, and it can damage directly to oral mucosa integrity and salivary glands function, interfering their speaking, eating and drinking. Nowadays we have different corticoid or non-corticoid topical treatment, good quality of dental care and phototherapy to treat injured oral mucosa, and or affected salivary glands, artificial saliva or saliva stimulators are commonly used to relief the xerostomia symptoms, those can improve patient's quality-of-life.

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