

## GRAFT VERSUS HOST DISEASE- ORAL PRESENTATION

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### ABSTRACT

#### BACKGROUND

Graft-versus-host disease (GVHD) is described as a potentially life-threatening complication caused by allogeneic haematopoietic cell transplantation. It is an exaggerated manifestation of a normal inflammatory mechanism in which donor lymphocytes encounter foreign antigens in an atmosphere that promote inflammation. 90% of the patients show oral features in case of cGVHD. Oral mucosal lesions and salivary gland dysfunction are the main oral features of chronic GVHD. Trismus or reduction of the mouth opening due to the perioral deposition of collagen is also commonly seen. Purpose of this review is to understand pathophysiology of oral presentations of GVHD.

#### MATERIALS AND METHODS

Review related to GVHD pathophysiology, oral lesions after haematopoietic cell transplant encompassed literature from 1966 through 2015. Review of Medline/PubMed Journals were done.

#### RESULTS

It is difficult to describe the pathophysiology of oral manifestations because there is no well accepted definition.

#### CONCLUSION

Larger well-designed clinical studies are needed to understand the pathobiology of oral cGVHD and determine best treatments for this disease.

#### KEYWORDS

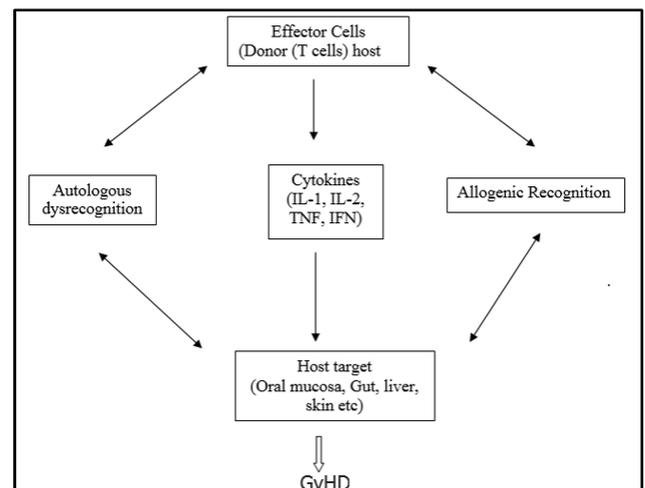
cGVHD, HSCT, Pathophysiology of cGVHD, Oral Mucosa Lesions, Lichen Planus-Like Changes.

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#### BACKGROUND

GVHD is an autoimmune and alloimmune disorder and is a leading cause of morbidity and mortality in HSCT recipients. In GVHD, the donated bone marrow or peripheral blood stem cells view the recipients' body as foreign and the donated cells/bone marrow attack the body. This complex interaction between donor and recipient adaptive immunity can be explained in the following way.

This disorder most likely to occur if graft received from an unrelated donor to host or if either of one is older. It affects multiple organs and tissues and exhibits different clinical features. It is estimated that approximately 40,000 individuals receive allogeneic haematopoietic cell transplantation in which 15,000 people known to be from an allogeneic donor. There are two forms of GVHD-



- Acute graft versus host disease (aGVHD).
- Chronic graft versus host disease (cGVHD).

As an allogeneic transplant recipient, patient might experience either form of GVHD, both forms or neither.

Acute GVHD has common clinical conditions like erythematous lesions, diarrhoea and liver involvement. But, chronic GVHD may affect most major organs, but most commonly all mucosal layers, lacrimal gland, skin and salivary glands. It is noted that majority of the patients

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eventually develop chronic GVHD and requires multidisciplinary approach for management.<sup>1</sup>

Dick W. van Bekkum during nuclear warfare at the end of World War II studied total body irradiation in animal models. After high-dose TBI, mice died from bone marrow aplasia or primary disease. Intravenous administration of allogeneic bone marrow cells delayed mortality. Initially, the delayed deaths were said to be caused by secondary disease and it was later renamed as graft-versus-host disease (GVHD).<sup>2</sup>

According to the National Institutes of Health (NIH), the oral features of cGVHD can be classified as-

1. Diagnostic (lichen planus-like changes, hyperkeratotic plaques and reduction in mouth opening).
2. Distinctive (xerostomia, mucocelles, mucosal atrophy, pseudomembranes and ulcers).
3. Common to both acute graft-versus-host disease and cGVHD (gingivitis, mucositis, erythema and pain).<sup>3</sup>

The acute GVHD is potentially fatal and it typically affects the skin, gastrointestinal tract and liver. The chronic GVHD shows involvement of a number of organs, including the oral cavity. Moreover, the oral cavity maybe the only affected site in chronic GVHD. The clinical manifestations of chronic oral GVHD includes lichenoid lesions, hyperkeratotic plaques and limited mouth opening secondary to sclerosis. The oral manifestations are usually mild, but moderate-to-severe erosive and ulcerated lesions may also be seen.<sup>4</sup> It is important for oral health providers and other medical professionals to understand and discuss the pathogenesis of oral manifestations for better management of the disorder.

## MATERIALS AND METHODS

Research articles related to GVHD pathophysiology, oral lesions after haematopoietic cell transplant encompassed literature from 1966 through 2015. Review of Medline/PubMed Journals were done.

**Pathophysiology-** GVHD is believed to be an exaggerated manifestation of a normal inflammatory mechanism in which donor lymphocytes encounter foreign antigens in an environment that promotes inflammation.

The immunocompetent T lymphocytes of the donor recognises foreign antigens expressed by the recipient cells and it triggers an immune reaction, which is accompanied by intense inflammatory responses that may result in damage to different organs and tissues of the recipient. This condition is referred as graft versus host disease and is the result of the incompatibility between the HLA system antigens of the donor and recipient.<sup>4</sup> Human Leukocyte Antigens (HLA),<sup>2,5,6</sup> which are the necessary proteins are encoded by the Major Histocompatibility Complex (MHC).<sup>7</sup>

There are three sequential phases, which can be used to illustrate the complex cellular interactions and inflammatory cascades and which ultimately evolve to acute GVHD- These are-

- (i) Activation of antigen presenting cells.
- (ii) Donor T-cell activation, proliferation, differentiation and migration; and
- (iii) Target tissue destruction.<sup>5</sup>

Billingham formulated the requirements for the development of GVHD after the work done by Barnes and Loutit- The requirements are-

- i) The graft must contain immunologically competent cells.
- ii) The recipient must express tissue antigens that are not present in the transplant donor.
- iii) The recipient must be incapable of organising an effective response to destroy the transplanted cells.<sup>8</sup>

In many cases, manifestations of cGVHD closely resembles both clinically and histologically with those of common autoimmune disorders including lichen planus, scleroderma, Sjogren's syndrome, systemic lupus erythematosus, dermatomyositis and primary biliary cirrhosis. This lead to the suggestion that cGVHD is the disorder of dysregulated immunity.<sup>9</sup> Definition for cGVHD states any manifestation lasts or occurring beyond day hundred post-transplant as classic cGVHD. Pathogenesis of cGVHD is poorly understood due to multiple factors, like-

- a) Most animal studies concentrate on acute GVHD with early mortality.
- b) Very few proposed animal studies performed doesn't reproduce complexity of human structure.
- c) Since chronic in manifestation, data collection is always difficult.
- d) Multiple organ system may be involved leading to variety of symptoms.
- e) Most studies depend on peripheral smear.

The known risk factors for cGVHD are-

- i) HLA incompatibility between the donor and recipient.
- ii) Advanced age of the donor or recipient- a female donor and male recipient (in cGVHD).
- iii) Childbirth (parity) in female donors (allosensitization).
- iv) Transplantation of mobilised peripheral blood cells (in cGVHD).
- v) Infusion of donor lymphocytes.
- vi) Antecedents of aGVHD.

Risk factor for acute GVHD and chronic GVHD are almost similar. Most acute cases may end as chronic manifestations or patients may present with chronic GVHD without any acute clinical signs. Clinical similarity to autoimmunity in contrast to acute GVHD, cGVHD affects multiple target organs and produces a constellation of clinical manifestations.<sup>10</sup> In many cases, these manifestations closely resemble both clinically and histologically those of common autoimmune disorders including lichen planus, Sjogren's syndrome, scleroderma, systemic lupus erythematosus, dermatomyositis and primary biliary cirrhosis.<sup>10</sup> Unlike classical autoimmune disorders in which tolerance to native antigens is lost and the immune system recognises and mounts a detrimental immune response to

host antigens, donor T cells recognise antigens of the host and perpetuate the disease process in cGVHD.

**GVHD and Oral Manifestations-** cGVHD shows various oral manifestations in 90% of the patients. Moreover, oral manifestations can be the first signs of cGVHD and it can be considered a disease marker.<sup>11</sup> Oral mucosal lesions and salivary gland dysfunction are the main manifestations of oral cGVHD and there can be a reduction in mouth opening due to the perioral deposition of collagen.<sup>4</sup>

Common features of both aGVHD and cGVHD includes gingivitis, mucositis, erythema and pain and oral distinctive features are xerostomia, mucocoeles, mucosal atrophy, pseudomembranes and ulcers. Oral cGVHD may be represented by some clinical changes like a telangiectatic appearance of the mucosa, inflammation and loss of the stippling of the attached gingival. But, these features are not considered in the NIH criteria. Most severe forms of cGVHD may be associated with erosive lesions and are followed by pain and it may interfere in oral hygiene and food ingestion.<sup>9</sup>

The most commonly involved sites are the buccal mucosa and the tongue. The diagnosis of the oral lesions is usually based on clinical features. However, a biopsy of the oral mucosa or minor salivary glands may become needful when oral and systemic clinical features are not sufficient for the diagnosis of cGVHD.<sup>4</sup>

**Histopathological Features-** Oral mucosal changes consist of localised or generalised epithelial changes like lichenoid interface inflammation, exocytosis and apoptosis. Minor salivary glands show intralobular lymphocytic inflammation and exocytosis of lymphocytes into intralobular ducts and acini. Periductal fibrosis is often present. Horn et al has developed a histological grading system for cGVHD of minor salivary glands. The grading was based on the degree of lymphocytic infiltration and destruction of glandular acini. Soares et al found that the most specific histological feature of oral chronic GVHD was minor salivary gland periductal lymphocytic inflammation with exocytosis and it was correlated with extensive chronic GVHD and decreased survival.<sup>11</sup>

**Cellular Biomarkers-** Tregs (regulatory T cells) are the most promising cellular biomarkers for aGVHD. There has been study done on the same marker and it showed that Tregs frequency and aGVHD severity were negatively correlated. CD30 is expressed on some activated memory T cells and it is released as a soluble form. Both have recently been shown as potential markers of aGVHD. Another cell population, which was detected as potential cellular biomarkers of aGVHD is the Invariant Natural Killer T (iNKTs) cells. Other cellular subsets, which are identified as potential markers are dendritic cells, monocytes and gamma-delta T cells, B cells and their modulators, such as B-cell activating factor are possible future biomarkers for cGVHD.<sup>12</sup>

## RESULTS

It is difficult to describe the pathophysiology of oral manifestations because there is no well-accepted definition. This may be due to lack of long-term documentation availability, multidisciplinary approach leading to poor coordination between healthcare providers. Clinically and histologically mimicking, the autoimmune lesions also maybe a factor for lack of documentation of this entity.

## DISCUSSION

GVHD is one of the most important complications in bone marrow transplantation. It may affect any organ systems like skin, GIT, liver and weight loss. In particular, nearly 90% of cGVHD have oral presentations of the disorder. In most cases, oral lesions stand for the leading or even only cGVHD. Chronic GVHD- graft-versus-host disease occurring or lasting beyond day 100 post-transplant has been defined classically as chronic. Although, practical for the epidemiologic purposes, such definition is inadequate for the following reasons-

1. Symptoms and signs typical of cGVHD frequently develop before day 100.
2. Signs classically associated with acute GVHD, e.g. diarrhoea or diffuse erythematous rash, may occur after day 100, particularly in the setting of Donor Lymphocyte Infusion (DLI).

All the oral presentations mimic autoimmune disorders clinically and histologically. Attempt was made in this article to review literature available to distinguish the cGVHD oral manifestations. As, at present, specific standardised clinical protocols are still lacking the multidisciplinary approach must be anyway primarily focused not on the prevention and treatment of soft and hard tissue lesions of the oral cavity as well as on the resumption of normal feeding. Understanding the pathophysiology may help in treating doctor to diagnose the cGVHD and differ the treatment plan from treating as an autoimmune disorder. Locally-applied corticosteroids are the treatment of choice and oral cGVHD is not regarded as a determinant for patient survival.

## CONCLUSION

GVHD can be clinically classified into acute (aGVHD) and chronic (cGVHD). Acute GVHD occurs when it is induced only by the cytotoxic effect of the donor T lymphocytes in host tissues. Chronic GVHD occurs when it is caused by a cytotoxic effect associated with severe immunodeficiency.<sup>13</sup> The oral diagnostic features like lichenoid/hyperkeratotic lesions were more frequently found in patients in the early stage of cGVHD.<sup>14</sup> Long-term immunosuppressive drugs are usually the treatment regimen for GVHD. The criterion standard for primary prophylaxis of acute GVHD is cyclosporine for 6 months and short-course methotrexate in T-cell-replete allogeneic HCT; currently, tacrolimus is often substituted for cyclosporine because of its more potent immunosuppressant capacity and lower risk of nephrotoxicity. For early, mild oral lesions observation or a trial of topical corticosteroids (e.g., triamcinolone 0.1%)

maybe used. For large chronic lesions, immunosuppressive prophylaxis and adding methylprednisolone (commonly starting at 2 mg/kg/day in two divided doses) may help and tapering the dosage in following week. Early immunosuppressive prophylaxis has become a new common in prevention of GVHD.

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