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Graft versus Host Disease: Cases from New Zealand with Oral Manifestations

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Abstract

Background and objectives: In recent decades increasing numbers of haematopoietic stem cell transplants have been undertaken for the treatment of various haematological conditions. Increased use of allogeneic transplants, in particular those utilising peripheral blood stem cell transplants (PBSCT) is likely to result in an increased burden of graft versus host disease (GvHD) associated with transplantation. Survivors are living for longer, and dentists are therefore likely to see more patients presenting with the chronic manifestations of this disease. Oral manifestations of GvHD are not uncommon, and carry a high burden of morbidity. This paper documents cases reported as GvHD in the Oral Pathology Centre (OPC) in the Faculty of Dentistry, the University of Otago in the last two decades.

Methods: A computerised search of the OPC database for the period spanning from 1 January 2000 to 30 June 2019 was undertaken to identify cases diagnosed as GvHD.

Results: Five cases from a total of 31,024 accessions in the time period were identified from the database that were diagnosed as 'possible GvHD' or 'likely GvHD'. These consisted of four males and one female, with an average age (at time of biopsy) of 55 years.

Conclusions: Whilst biopsy of the oral cavity for the diagnosis of oral GvHD is not common, GvHD often presents orally and prompt clinical recognition is important. Immunosuppressive therapy is the mainstay of treatment for GvHD and has clear implications for dental management. Dentists have a duty of care to review these patients regularly to assist in the maintenance of excellent oral health and to check for the development of secondary malignancy in the oral region, due to the increased risk of oral squamous cell carcinoma development.

Introduction

Haematopoietic stem cell transplantation (HSCT) is the preferred treatment modality for a number of haematological conditions, and has been in use since the 1950s. However, significant side effects and risks have been found to be associated with the use of HSCT, in particular the development of graft versus host disease (GvHD) in the context of allogeneic transplants (between a separate donor and host). GvHD has been reported as the second leading cause of transplantation related mortality (TRM), second only to relapse of the primary disease (Anasetti et al. 2012; Mawardi et al. 2019).

GvHD is an immune-mediated disease, where the transplantation of haematopoietic cells from a donor essentially confers a foreign immune system into a new host; with subsequent cellular recognition of the new host environment as foreign. The donor immune system then facilitates initial immunological destruction and damage in response to the foreign antigenic stimulus, the host cells. Billingham was the first to succinctly summarise and articulate these conditions in his seminal Harvey Lecture in 1966, outlining the requirements for development of GvHD as:

1. Immunocompetent cells in the transplanted graft
2. Inability of the host cells to reject the graft (immunocompromise of the host)
3. The ability of the transplanted graft cells to recognise the host as foreign (antigenic mismatch between the donor and the host) (Billingham 1966).

Billingham's postulates have proven self-evident in the field of transplant medicine for the last 50 years.

Initially GvHD was divided into two subsets: acute (aGvHD) and chronic (cGvHD) based, as the names suggest, on the chronology of presentation. aGvHD typically manifested <100 days post transplantation while cGvHD typically manifested >100 days post transplantation. However, in time this was seen to be an oversimplification, as the two entities showed markedly different clinical presentations that did not always follow the prescribed chronology, and at times overlapped in both temporal and clinical presentations. The United States National Institutes of Health (NIH) recognised this and developed guidelines that defined these as discrete clinical syndromes of GvHD, that may have various sub-classifications such as a 'late acute' subset of aGvHD, or an 'overlap' subset of cGvHD (Jagasia et al. 2015). Classic aGvHD predominantly affects the skin, gastrointestinal tract and liver, with a variable degree of other mucosal involvement, such as oral (Ball and Egeler 2008; Jagasia et al. 2015). Comparatively, cGvHD has a vast number of manifestations and is typically characterised by chronic inflammatory and fibrotic changes (Jagasia et al. 2015). Being immunologically mediated, cGvHD often mimics or shares clinical features with other immune-related diseases such as lichen planus, scleroderma or lupus erythematosus (Mawardi et al. 2019). Specific organ and global scoring of severity has been developed to reflect the degree of organ impact and functional impairment; this has been validated to

Table 1. Classification of GvHD

Classification of GvHD	
Acute:	**Chronic:**
Classic acute	Overlap
• Late acute	• Classic chronic
• Persistent	• Progressive
• Recurrent	• Quiescent
• De novo	• De novo

(Jagasia et al. 2015; Mawardi et al. 2019; Kuten-Shorrer et al. 2014)

Table 2. 2014 NIH severity staging system for oral cGvHD

Oral severity staging of cGvHD	
Score	**Symptoms**
0	No symptoms
1	Mild symptoms with disease signs but not limiting oral intake significantly
2	Moderate symptoms with disease signs with partial limitation of oral intake
3	Severe symptoms with disease signs on examination with major limitation of oral intake

(Jagasia et al. 2015)

predict overall survival (OS) and non-relapse mortality (NRM) (Jagasia et al. 2015). (Tables 1 and 2)

More than half of the survivors of HSCT will go on to develop GvHD (Stem Cell Trialists' Collaborative 2005), and the oral mucosa is one of the most common sites affected in cGvHD (Flowers et al. 2002).

There are many risk factors for the development of GvHD, but mismatched human leukocyte antigen (HLA) is considered to be a fundamental risk. The use of HLA-mismatched donors or HLA-matched unrelated donors, the conditioning regimen, and gender mismatch all lead to significantly increased risks of developing aGvHD. Similarly, the risk of developing cGvHD has been shown to be significantly increased in the context of HLA-mismatched donors or HLA-matched unrelated donors, gender mismatch, stem cell source, older donor or recipient age, or a past history of aGvHD (Flowers et al. 2011). Further to this, the increasing use of many of these factors (such as peripheral blood stem cell transplants (PBSCT), older recipients, or alternative donors) has manifested in an increase in both incidence and severity of cGvHD presentations (Arai et al. 2015). Interestingly, increasing use of transplants from first degree relatives with a single HLA haplotype match has shown promise in the context of particular post-transplant regimens to improve tolerance (high dose cyclophosphamide). This regimen has been shown to produce lower rates of GvHD, in addition to its benefits in terms of clinical practicalities in sourcing potential donors for patients (Ciurea 2019).

Complicating the clinical picture however, is that some degree of allogeneic mismatch is inevitable even in HLA-matched transplants, and this plays a key role in the development of graft vs. tumour effect (GvT). This effect is notable as it refers to the process by which the transplanted donor immune cells recognise residual tumour cells and eliminate them. One therapy shown to reduce the incidence of GvHD in recipients is the process of T-cell depletion in the graft (Flowers et al. 2011; Arai et al. 2015). However, this results in a decreased GvT effect, as the cells that mediate the GvT effect also mediate GvHD, and a subsequent increase in relapse-related mortality and graft failure is seen as a result of the T-cell depletion (Kolb 2017). While the principles of GvHD have been understood for decades, deeper understanding of the specific pathophysiology, and subsequent development of directed treatment has proven elusive, highlighting our difficulties in the effective management of this disease. In practice, efforts are still largely directed at symptomatic relief and preventive supportive care, in conjunction with immunosuppressive therapy. (Ferrara et al. 2009; Treister et al. 2012)

A notable finding from the Center for International Blood and Marrow Transplant Research (CIBMTR) was that while NRM for patients with active cGvHD had decreased over time in the one to three year period post-transplant, at five years post-transplant the NRM and OS outcomes were not significantly different (Arai et al. 2015). The authors speculated that (1) in the short-medium term, the GvHD may have had a protective effect against relapse, and additionally with the impact of improved supportive care, outcomes improved in this time period; (2) in the longer term, the adverse effect of prolonged immunological derangement associated with the GvHD was still significant (Arai et al. 2015).

In the New Zealand (NZ) context, the Ministry of Health data shows the total annual number of bone marrow transplants (BMT) more than doubled between 2002-2016. Projections recently released forecasted the annual number of transplants to continue increasing until 2025. Despite this, these services are only available in a limited number of NZ centres (currently Auckland, Waikato, MidCentral, Capital & Coast, and Canterbury) (Ministry of Health 2018). In light of this report, the aim of this paper was to investigate the number of biopsies, and their features, reported as GvHD, received by the Oral Pathology Centre (OPC) in the Faculty of Dentistry, the University of Otago from 1 January 2000 to 30 June 2019, and to bring this condition and its oral implications to the attention of dentists.

Methods

A computerised search of the OPC database in Faculty of Dentistry, University of Otago was performed using the search terms "graft", "graft disease", "host disease", "graft versus host disease", "graft vs host disease", "graft-versus-host", "graft-vs-host", "GvHD", "transplant", and "stem cell" for the period spanning from the 1st of January 2000 to the 30th of June 2019.

All records identified were individually screened on a case by case basis, and evaluated by both the primary author (KM) and a consultant oral pathologist (AMR) to verify a histological diagnosis of "possible GvHD" or "likely GvHD", according to the histological features observed in the context of the clinical information

Table 3A. Oral histopathological features of acute and chronic GvHD

Histopathological features of GvHD	
Acute	**Chronic**
Mucosa • Lichenoid interface lymphocytes with infiltration of mucosa (exocytosis) and variable apoptosis* • Intracellular oedema • Dyskeratosis	Mucosa • Lymphohistiocytic interface mucositis (lichenoid) with epithelial exocytosis • Basal cell hydropic degeneration • Variable keratinocyte apoptosis • Interspersed atrophy and hyperkeratosis
Subepithelial clefting • Ulceration	Subepithelial clefting • Ulceration
Connective tissue • Superficial and perivascular inflammation	Connective tissue • Lymphocytic infiltration • Perivascular inflammation • Variable fibrosis (sclerosis)
	Salivary glands • Periductal lymphocytic infiltrate with infiltration and damaged intralobular ducts, fibroplasia in periductal stroma, mixed lymphocytic and plasmacytic inflammation with destruction of acinar tissue†

* NIH 2014 Pathology Working Group minimum histological criteria for acute/active GvHD
† NIH 2014 Pathology Working Group minimum histological criteria for chronic GvHD

(Imanguli et al. 2008; Carpenter et al. 2015; Jagasia et al. 2015; Shulman et al. 2015; Mawardi et al. 2019)

received (i.e. a history of HSCT). This histological evaluation was undertaken in accordance with the NIH 2014 Pathology Working Group Report guidelines on the histological criteria required for diagnosis of GvHD (see Table 3.1) (Shulman et al. 2015). These guidelines make recommendations for change in the reporting protocol for histological diagnosis of GvHD, in order to facilitate better interobserver reproducibility, through stratification into three diagnostic categories: "Not GvHD, "Possible GvHD" and "Likely GvHD". This is key in the context of a disease entity like GvHD which has a smorgasbord of presentations, and is unable to be diagnosed definitively on the basis of histology alone (Shulman et al. 2015).

Five cases were identified from our database, verified as described, then reviewed specifically in the context of the NIH (2014) guidelines. For cases predating the OPCs adoption of these guidelines, the diagnosis was retrospectively coded to conform to these. Two of the cases consisted of multiple biopsy sites and specimens from the same patient and these were considered an individual case.

Results/case series

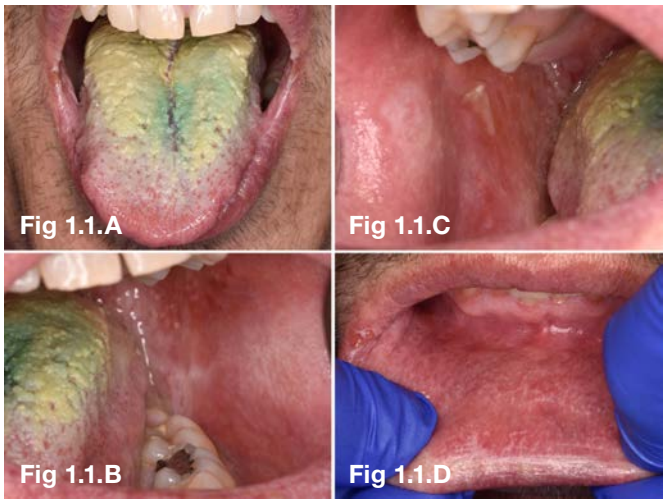
These cases consisted of four males and one female, with an average age (at time of biopsy), of 55 years. All cases underwent standard histopathological processing, paraffin embedding, haematoxylin and eosin (H&E) and periodic acid Schiff (PAS) staining protocols were undertaken.

Case 1: 05/0722

A 49-year-old male presented to the Oral Medicine Clinic at the University of Otago School of Dentistry with a sore mouth and a medical history of chronic lymphocytic leukaemia, allogeneic bone marrow transplant (allo-BMT), and donor lymphocyte infusion. Medications consisted of the antimicrobials, pentamidine and penicillin. Oral examination showed red, atrophic areas on the buccal mucosa with interspersed white patches. Preliminary oral treatment was with itraconazole, but no improvement was observed. Three clinical differential diagnoses were provided: GvHD, oral lichen planus (OLP), and candidosis. An incisional biopsy of the right buccal mucosa was performed, and the specimen fixed in formalin. The histopathological findings were that of a stratified squamous epithelium (SSE) with a thick surface parakeratin layer and no dysplastic change. Basal cell lysis, apoptotic keratinocytes and ingress of lymphocytes into the lower half of the epithelium were observed. The superficial connective tissue showed a scanty infiltrate of mixed chronic inflammatory cells. No evidence of candidal infection was noted.
Diagnosis: Likely GvHD.

Case 2: 07/0497A&B

A 53-year-old female presented to the Oral Surgery Clinic at the University of Otago School of Dentistry, with a burning mouth and a history of a BMT nine years before. She reported prolonged systemic steroid therapy. Oral examination showed bilateral buccal white striae. Two clinical differential diagnoses were provided: GvHD and oral lichen planus. An incisional biopsy of the right buccal mucosa was performed, and two specimens received in the laboratory; one fresh, and the second fixed in formalin. The fresh specimen was processed for direct immunofluorescence (DIF), and the formalin fixed specimen underwent standard histopathological processing. The histopathological findings were that of a parakeratinised, SSE demonstrating a flat epithelial-connective tissue junction, overlying mature connective



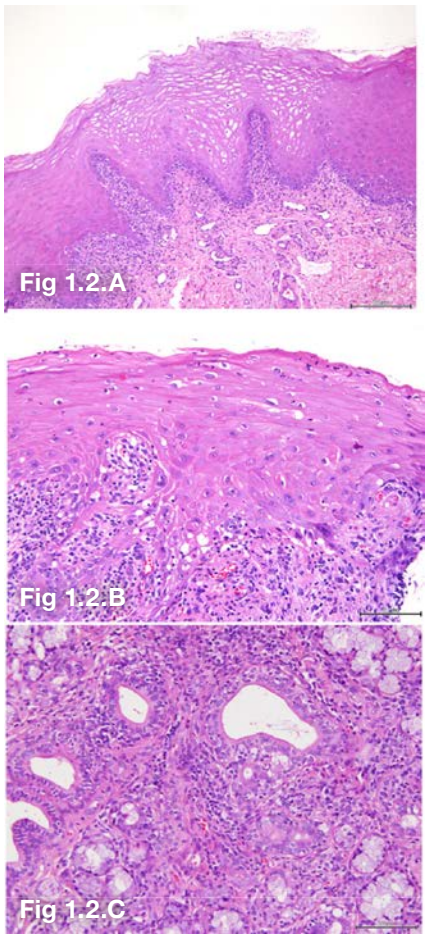


Figure 1.1 Case 4 Clinical Photographs: (A) heavily coated dorsal tongue surface and sloughing in the commissures bilaterally; (B) lichenoid reticular white striae on the left buccal mucosa; (C) lichenoid reticular white striae on the right buccal mucosa, with an area of ulceration and erythema; (D) lichenoid reticular white striae on the mucosal surface of the lower lip.

Figure 1.2 Case 4 Photomicrographs: (A) epithelial acanthosis, intracellular oedema, hyper-parakeratosis, mild interface mucositis with some inflammatory exocytosis; (B) interface mucositis with epithelial exocytosis, basal cell disruption, apoptotic keratinocytes and mucosal atrophy; (C) atrophic minor salivary gland lobules, periductal inflammation and fibrotic replacement.

Clinical images provided by Wellington Hospital Dental Department.

tissue. Epithelial disruption and focal loss of intercellular cohesion was observed, however, apoptotic bodies were not conspicuous. A sparse-moderate mixed chronic inflammatory cell infiltrate was present in the superficial lamina propria. No evidence of candidal infection was noted. DIF for anti-fibrinogen, anti-C3, anti-IgA, anti-IgG and anti-IgM were all negative.
Diagnosis: Likely GvHD.

Case 3: 18/0971

A 72-year-old male was referred to Wellington Hospital Dental Department for biopsy with a history of acute myeloid leukaemia, stem cell transplant two years prior, and a previous diagnosis of GvHD. Oral examination showed formation of flaccid bullae, erythema and generalised ulceration. A number of clinical differential diagnoses were provided including “lichenoid reaction”, Stevens-Johnson syndrome, GvHD and paraneoplastic pemphigus. An incisional biopsy of the right buccal mucosa was performed. The histopathological findings were that of an atrophic parakeratinised SSE, showing extensive surface ulceration, intercellular oedema, disruption and basal cell lysis in focal regions associated with ingressed lymphocytes. Occasional apoptotic bodies were noted, and multiple areas of neutrophilic micro-abscess in the superficial epithelium were also observed. The underlying connective tissue showed an ill-defined superficial infiltrate of mixed chronic inflammatory cells. No evidence of candidal infection was noted.
Diagnosis: Possible GvHD.

Case 4: 19/0131 &19/0132

A 40-year-old male presented to Wellington Hospital Dental Department with a history of chronic myelomonocytic leukaemia. Oral examination showed the presence of mucosal white linear striae and ulceration of the buccal mucosa. The clinical differential diagnosis was GvHD. Two incisional biopsies were performed, one of the lower lip mucosa, and the second of the right buccal mucosa. The histopathological findings in the lip biopsy were that of an acanthotic parakeratised SSE, showing intracellular oedema, basal cell lysis, and scattered apoptotic bodies. A band-like, moderate infiltrate of lymphohistiocytic cells was present in the superficial connective tissue showing ingress into the overlying epithelium. Lobules of mixed minor salivary glands present showed mild chronic inflammation, acinar atrophy and periductal fibrosis. The histopathological findings in the right buccal mucosa biopsy were that of an atrophic, keratinised SSE, with a large area of ulceration and fibrinopurulent membrane formation. The epithelium demonstrated prominent basal cell lysis, scattered apoptotic bodies, and lymphocytic ingress. The underlying connective tissue showed a mild-moderate lymphohistiocytic infiltrate, with scattered neutrophils.
Diagnosis: Likely GvHD. (See Figures 1.1 and 1.2)

Case 5: 19/0643 &19/0644

A 62-year-old male presented to Wellington Hospital Dental Department with a history of mild, extensive, cGvHD (oral and ocular), diagnosed six months before. Oral examination showed fine, faint, white striae. The clinical differential diagnosis was GvHD.

Two incisional biopsies were performed, one of the right buccal mucosa, and the second of the left buccal mucosa. The histopathological findings in the right buccal mucosal biopsy were that of an acanthotic, oedematous parakeratinised SSE, with an area of ulceration and fibrinopurulent membrane formation. The superficial connective tissue showed a very mild inflammatory infiltrate, while the deeper connective tissue showed evidence of scar formation with concurrent inflammation extending to the muscle fibres. No evidence of candidal infection was noted. The findings in the left buccal mucosal biopsy were that of an atrophic SEE, demonstrating basal cell lysis. A prominent eosinophilic coagulum was present in the basement membrane zone, and the connective tissue showed a diffuse, mild chronic inflammatory cell infiltrate. No evidence of candidal infection was noted.

Diagnosis: Likely GvHD. (See Figures 2.1 and 2.2)

Discussion

The Oral Pathology Centre (OPC) service is unique in NZ, being the only referral service fully staffed by specialist oral pathologists, and acting as both a diagnostic laboratory as well as a tertiary referral centre. The OPC processes specimens from dentists, dental specialists and anatomical pathologists from both public and private settings across the country. The OPC does not receive all oral biopsies taken in NZ, with some general pathology services accepting oral biopsies.

It is interesting to consider the relatively low number of cases received that were diagnosed as GvHD (five of 31,024 accessions in the time period examined), particularly with regard to the ever increasing numbers of HSCT occurring. The NZ Ministry of Health published updated projections for HSCT activity in 2018, and projected the rates of transplantation to continue increasing due to factors including treatment of haematological malignancies, increased utilisation in population groups previously ineligible for therapy, and use of alternative donor sources. It is worth noting that the past projections underestimated both the number of transplants, and overall rate of increase; with the total number of transplants, per year, in NZ, more than doubling between 2002-2016 (Ministry of Health 2018).

Worldwide, the substantial increase in the use of nonmyeloablative/reduced-intensity conditioning regimes have enabled previously ineligible patients to undergo transplantation (Majhail et al. 2013). Concurrently, there has been an increased use of peripheral blood stem cell transplants (PBSCT) (Arai et al. 2015) which has been shown to result in faster engraftment, decreased relapse and improved disease free survival when compared to traditional BMT. However, the use of PBSCT has been found to be significantly associated with increased incidence and severity of cGvHD (Stem Cell Trialists'

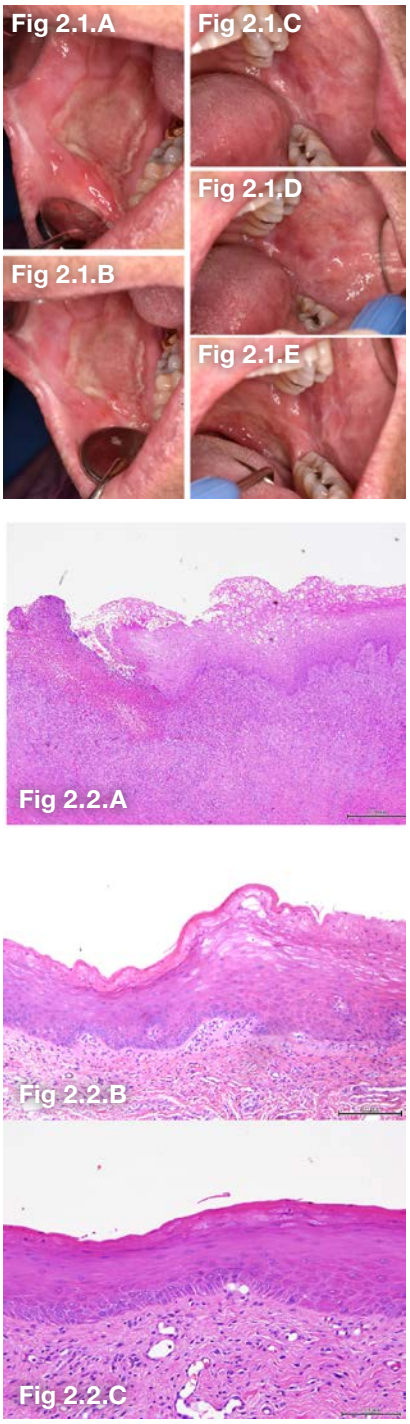


Figure 2.1 Case 5 Clinical Photographs: (A) & (B) extensive ulceration involving the right buccal mucosa; (C) & (D) left buccal mucosa showing marked reticular white striae and alternating areas of erythema; (E) reticular white striae and alternating erythema extending beyond the left buccal mucosa onto the pillars of fauces.

Figure 2.2 Case 5 Photomicrographs: (A) epithelial acanthosis, with marked hyper-parakeratosis and intracellular oedema, with an intense interface mucositis and prominent ulceration; (B) atrophic, hyper-parakeratotic epithelium with intracellular oedema, and a mild scattered lymphocytic infiltrate in the connective tissue; (C) atrophic, hyper-parakeratotic epithelium demonstrating basal cell disruption, and a mild scattered lymphocytic infiltrate in the connective tissue.

Clinical images provided by Wellington Hospital Dental Department.

Collaborative 2005; Flowers et al. 2011; Anasetti et al. 2012; Arai et al. 2015), as well as increased severity (but not incidence) of aGvHD in some reports (Stem Cell Trialists' Collaborative 2005). In recent decades, progress in supportive care has resulted in the increased survival of patients both undergoing HSCT and of those suffering from GvHD (Socié and Ritz 2014; Arai et al. 2015). Data from the United States and the CIBMTR show expected five-fold increases in the number of haematopoietic cell transplant survivors between 2009 and 2030 (Majhail et al. 2013). As such it could be reasonably concluded that with increased numbers of HSCT occurring, increased survival, and in the context of greater use of PBSCT, that there will be an increased incidence of GvHD. CIBMTR data supports this supposition, showing an increased incidence of cGvHD at one year post transplant rising from 28% between 1995-1998, to 37% from 2004-2007 (Arai et al. 2015). The NIH 2014 Pathology Working Group Report found the incidence of reported cGvHD to vary widely, and quoted a range of 35-70% in allogeneic transplant recipients, dependent on factors including the time period specified, the source of the HSCT, type of donor and post-transplant immunosuppression (Shulman et al. 2015).

At the OPC this reported increase in incidence has not translated into increased numbers of biopsies diagnosed as GvHD over the 19 year period reviewed. However, a weakness in our investigation is the complete reliance of the reporting pathologist on the referring clinician to provide the relevant clinical context and medical history for the case. We cannot exclude the possibility of misdiagnosis and under-reporting of GvHD if the referring clinician did not supply the relevant medical history of the patient.

Diagnosis of GvHD, particularly in an oral setting is often made clinically by physicians in the context of the broader clinical picture. The NIH 2014 Diagnosis and Staging Report guidelines consider that if a *diagnostic* clinical feature is present, then biopsy is not required to confirm diagnosis of cGvHD, with the exception that where the presence of persistent ulceration is noted, biopsy may be necessary to both confirm cGvHD and to exclude malignancy (Jagasia et al. 2015). Diagnostic features of oral cGvHD include lichenoid changes with/without erythema or ulceration. Further to this, the guidelines considered a biopsy reported as "likely GvHD" together with one *distinctive* clinical feature of cGvHD (xerostomia, mucocoeles, mucosal atrophy, ulceration, pseudomembrane formation) to be sufficient to confirm positive diagnosis of cGvHD, but that biopsy alone was insufficient to confirm diagnosis (Jagasia et al. 2015). In this context, the relative lack of oral biopsies received appears consistent with current practice. However, the NIH 2014 Pathology Working Group Report stressed the risk of misdiagnosis in the absence of biopsy, but acknowledged that accurately assessing histological signs of activity is difficult in practice (Shulman et al. 2015). We speculate that given the relative ease of access to the oral cavity for biopsy, that if biopsy becomes increasingly important in diagnostic protocols, more biopsies may be received in future.

From a pathological standpoint, diagnosis is inextricably linked to the clinical context with no histopathognomic features specific to GvHD. With no specific biomarkers that can identify active GvHD, it can be particularly difficult to distinguish active cGvHD from cumulative damage (i.e. fibrotic change, or loss of secretory salivary acini) (Paczesny et al. 2015). Also it should be emphasized that it is not feasible or meaningful to attempt to distinguish between categories of GvHD through histology (Shulman et al. 2015).

In a dental context recognition of clinical manifestations of GvHD (Table 3B) is of paramount importance as early diagnosis and prompt management may avoid the development of severe disease for a patient. It is important to remember that GvHD is considered the leading cause of NRM, either directly, or indirectly due to immunosuppression (Kuten-Shorrer et al. 2014; Arai et al. 2015; Mawardi et al. 2019). Immediate referral to the treating physician and an oral medicine specialist for management and regular review is crucial if new disease is suspected.

Dentists will see increasing numbers of patients who either have active GvHD, a history or if it, or are at risk

Table 3B. Typical oral clinical manifestations of acute and chronic GvHD

CLINICAL FEATURES OF GvHD		
	Acute	**Chronic**
Oral mucosal GvHD	• Erythematous or atrophic changes • Ulceration and pseudomembrane formation • Lip crusting	• Lichenoid changes * – White reticular striae and hyperkeratotic plaques • Erythematous or atrophic changes † • Ulceration and pseudomembrane formation† • Superficial mucocoele formation †
Salivary gland GvHD		• Xerostomia/hyposalivation † • Production of mucoid, viscous saliva
Sclerotic GvHD		• Fibrosis • Trismus

* NIH 2014 Diagnosis and Staging Report guidelines, organ specific manifestations of cGvHD: Mouth: diagnostic feature
† NIH 2014 NIH 2014 Diagnosis and Staging Report guidelines, organ specific manifestations of cGvHD: Mouth: distinctive feature

(Imanguli et al. 2008; Treister et al. 2012; Carpenter et al. 2015; Jagasia et al. 2015; Mawardi et al. 2019)

of developing it. It is less likely that acute GvHD will be encountered outside of hospitals, particularly in terms of oral management. However, if it is suspected then it is important to exclude other causes such as chemotherapy or radiotherapy induced mucositis, or infection (new or reactivated) due to immunosuppression (Imanguli et al. 2008). Conversely, oral cGvHD is more likely to present in general dental practice being by nature prolonged, and is reported to occur in upwards of 80% of GvHD sufferers (Flowers et al. 2002). It typically presents with a characteristic lichenoid appearance that may mimic numerous other immune-related conditions, and similar to aGvHD, exclusion of other causes such as drug reaction, infection (new or reactivated), or malignancy (secondary or recurrent) needs to be considered (Treister et al. 2012; Jagasia et al. 2015; Mawardi et al. 2019).

From a clinical perspective GvHD is a heterogenous disease, with a plethora of presentations and sequelae, many of which have oral implications, such as the development of hyposalivation. In all cases the only treatment is prolonged immunosuppressive therapy in addition to symptom specific management (such as the use of sialagogue therapy to reduce xerostomic symptoms), in order to suppress the immunologically mediated destruction, control disease severity, and reduce the risk of NRM (Carpenter et al. 2015). Management of the oral symptoms can be challenging, and is directed at alleviation of symptoms rather than cure. Common symptoms include sensitivity and pain to hard/crunchy, hot, spicy, acidic, salty, and alcohol containing foods and drinks, as well as dysgeusia, and difficulty eating dry foods, swallowing, speaking, chewing, or waking at night with xerostomic symptoms. Decreased food clearance due to hyposalivation, and difficulties maintaining oral hygiene typically lead to an increased risk of caries, and opportunistic candidal infections (Treister et al. 2012).

Immunosuppressive therapy inevitably leads to increased infective risks, but crucially it also plays a role in the mediation of a significantly increased risk of the development of secondary solid malignancy. Numerous studies have demonstrated an increased risk of solid malignancy, particularly squamous cell carcinoma of the skin and oral mucosa, associated with both cGvHD, and a longer duration of immunosuppressive therapy (Curtis et al. 2005; Rizzo et al. 2009; Mawardi et al. 2011). This risk has been further associated with increasing severity of the GvHD, as well as the use of combined immunosuppressive therapy incorporating azathioprine (AZA). However, the individual roles that the severity of the GvHD, duration of immunosuppression, and the use of AZA have is difficult to assess, as patients with durable, refractory, or severe GvHD were almost inevitably on long term, combined immunosuppressive therapy with AZA in the study cohorts investigated (Curtis et al. 2005). Regular screening and review of patients with a history of cGvHD is therefore imperative to detect malignant changes early.

To conclude, general dental practitioners need to be aware of GvHD, its clinical presentations, the implications of both the disease and its treatment, and crucially the increased risk for development of secondary malignancy. Regular review is paramount to detect malignant change, and a high index of clinical suspicion should be maintained when treating these patients.

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