Assessment of Gingival Status and Gingival Overgrowth among Immunosuppressed Patients in Universiti Sains Malaysia Hospital

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Recommended Citation

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Cover Page Footnote

ORIGINAL ARTICLE

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ABSTRACT

Drug-induced gingival overgrowth (DIGO) is defined as an abnormal growth of the gingiva due to adverse effect of some drugs such as immunosuppressant, calcium channel blocker, and anticonvulsant. Immunosuppressive drugs play an important role in controlling organ transplant rejection and were widely used to treat different diseases. **Objective:** Immunosuppressive drugs are used for prevention of transplant rejection and management of autoimmune disease. Drug-induced gingival overgrowth (GO) is abnormal growth of gingiva due to adverse effect of these drugs. This study aimed to assess the gingival status, the prevalence of gingival overgrowth and its associated factors among immunosuppressed patients. **Methods:** A total of 33 patients had participated in this cross-sectional study. Patients' data such as age, race, gender, type of medication, and dosage were retrieved from patients' medical record. Clinical oral examination was performed to assess the periodontal parameters: oral hygiene index, bleeding index and clinical gingival overgrowth index. Data were analysed using SPSS version 24.0. **Results:** The prevalence of gingival overgrowth among immunosuppressed patients is 57.6% at 95% confidence interval (40%,75%). Clinical index of gingival overgrowth shows 45.5% in grade 1 and 15.2% in grade 2. Oral hygiene status is significantly associated with gingival overgrowth based on plaque score (p= 0.01) and bleeding index score (p=0.05). **Conclusion:** The presence of gingival overgrowth among immunosuppressed patients is quite evidenced which could be contributed by poor oral hygiene. Thus, taking care of oral hygiene should be reinforced in such patients to prevent this unwanted effect.

Key words: gingival status, gingival overgrowth, immunosuppressed patients

INTRODUCTION

Drug-induced gingival overgrowth (DIGO) is defined as an abnormal growth of the gingiva due to adverse effect of some drugs such as immunosuppressant, calcium channel blocker, and anticonvulsant. Although these drugs have different mechanism of actions, the adverse effect experienced by patients pertaining to gingival overgrowth is similar.[1] The initial presentation of gingival overgrowth usually begin 1 to 3 months after initiation of the treatment and commonly found at the interdental papillae of the anterior segment on the labial surfaces.[2] It would gradually formed gingival lobulation that may appear inflamed and more fibrotic in nature that confined to the attached gingiva.[1] These appearance would later interfere with aesthetics, mastication, and speech. Disfiguring of gingiva triggered by these medications was not only aesthetically displeasing but also impaired the nutritional status. Non compliance to oral hygiene resulting in increased risk of caries and periodontal disease.[3]

Immunosuppressive drugs play an important role in controlling organ transplant rejection and were widely used to treat different autoimmune diseases such as glomerulonephritis, myasthenia gravis, arthritis, lupus, rheumatoid arthritis, and Crohn disease. Drugs such as cyclosporine, tacrolimus, cyclophosphamide, azathioprine, mycophenolate mofetil, sirolimus,

methotrexate, glucocorticoids, leflunomide were used either alone or in combination for immunosuppressive treatment.[4]

These drugs produce their actions by inhibition of the cytokines production, cytokines action, DNA synthesis or cell activation/ maturation. They are available in various dosage forms and the dose of these drugs depends on various factors. However, the final dose of these drugs is usually decided by the physician.[5] The side effects associated with these drugs are spreading of malignant tumor, decrease the efficacy of immune system to resist infection, hypertension, dyslipidemia, hyperglycemia, peptic ulcers, liver damage, kidney injury, and interaction with other drugs in terms of their metabolisms and actions.[4]

This aims of this preliminary study is to evaluate the gingival overgrowth and enlargement in our local population. The findings of this study would be beneficial in terms of management of patients receiving immunosuppressive therapy. Many patients experienced this unwanted adverse effect secondary to immunosuppressive drugs. Therefore, it is crucial to propose the clinical guideline to hospital administration for better management of such cases.

METHODS

Study design
A total of 33 immunosuppressed patients had participated in this cross-sectional study by using convenience sampling method. This study had been carried out at Haematology-Oncology Ward and Haematology-Oncology Clinic of Hospital Universiti Sains Malaysia (Hospital USM), Kubang Kerian, Kelantan, Malaysia from July 2019 until October 2019. The inclusion criteria includes age more than 18 years old, patients on at least 3 months of immunosuppressive drugs, and presence of minimum of 6 teeth. Pregnant and lactating women, patients who took other drugs and had diseases which affect gingival tissues such as diabetes mellitus and leukaemia were excluded from the study. Ethical approval was obtained from Jawatankuasa Etika dan Penyelidikan Manusia (JEPeM), Hospital USM [Ref: USM/JEPeM/19010027].

Patients who fulfilled the criteria were invited to participate in this study and informed consent was obtained. Information regarding medical history, drug history, and duration of the drugs taken were obtained from medical record. Bedside clinical examination was performed using periodontal probe and mouth mirror. The periodontal parameters such as number of teeth, oral hygiene index, bleeding index, and clinical gingival overgrowth index were recorded. Assessment of all parameters were done by single examiner upon calibration with periodontist.

Oral Hygiene Status
The measurement of the state of oral hygiene by Silness-Löe Plaque Index[6] is based on recording both soft debris and mineralized deposits on the following teeth. Missing teeth are not substituted. Each of the four surfaces of teeth (buccal, lingual, mesial and distal) is given score from 0 to 3. The scores from the four areas of the tooth are added and divided by four in order to give the plaque index for the tooth based on the following scores:

0-Absence of microbial plaque; 1-Thin film of microbial plaque along the free gingival margin; 2-Moderate accumulation with plaque in the sulcus; 3-Large amount of plaque in sulcus or pocket along the free gingival margin.

The plaque score index for each patient was calculated for by total all surfaces presence with plaque over the total number of tooth surfaces examined and is expressed by percentage. Oral hygiene status then is classified as mild (PS <30%), fair (PS 30-<60%) and poor (PS≥60%)

Bleeding index
This index is used for all four surfaces of the teeth and it is recorded based on absence or presence of bleeding.[7] If bleeding is absent, '-' was charted while if the bleeding is present '+' was charted. A minus indicates gingival bleeding index score of 0 and 1, while a plus indicates gingival bleeding score of 2 and 3, based on the following scores:

0-Normal gingiva; Up to 1-Mild inflammation, no bleeding with probing, change in colour, and oedema; Up to 2-Moderate inflammation, bleeding on probing, redness, oedema, and glazing; Up to 3-Severe inflammation, spontaneous bleeding, marked redness, and oedema.

Clinical Index for Drug-induced Gingival Overgrowth
The Clinical Index for Drug-induced Gingival Overgrowth was used to assess the severity of drug-induced gingival overgrowth.[8] The intraoral photographs was recorded as supplementary to the clinical assessment of the overgrowth if present. This index is easy to use and does not require diagnostic casts or graphs. It provides some indication of the severity of the lesions as well as aid in deciding appropriate treatment intervention. The grading is based on the following criteria:
- Grade 0 - No overgrowth, firm adaptation of the attached gingiva to the underlying alveolar bone. No or slight stippling, as well as no or only slightly granular appearance. Knife-edged papilla is present toward the occlusal surface and there is no increase in density or size of the gingiva.
- Grade 1 - Early overgrowth, increase in density

of the gingiva with marked stippling and granular appearance. The tip of papilla is rounded.

- Grade 2 - Moderate overgrowth, manifested by an increase in the size of the papilla and/or rolled margins. The contour of gingival margin is still concave or straight. Gingival enlargement has a buccolingual dimension of up to 2 mm, measured from the tip of the papilla outward. The papilla is somewhat retractable.
- Grade 3 - Marked overgrowth, represented by encroachment of the gingiva onto clinical crown. The contour of the gingival margin is convex rather than concave. Gingival overgrowth has a buccolingual dimension of approximately 3 mm or more, measured from the tip of the papilla outward. The papilla is clearly retractable.
- Grade 4 - Severe overgrowth, characterized by a profound thickening of the gingiva. A large percentage of the clinical crown is covered. As in grade 3, the papilla is retractable. The buccolingual dimension is approximately 3 mm.

Statistical analysis

Data were analyzed using Statistical Package for Social Sciences (SPSS) version 24.0. Descriptive statistics was used for analysis of the demographic data, oral hygiene factors and periodontal parameters. Crosstabulation and Chi-Square test were used to determine the association between gingival overgrowth and demographic data as well as periodontal parameters. The p-value of < 0.05 was considered to be significant.

RESULTS

A total of 33 subjects with the mean age of 40.4 (SD14.3) had participated in this study. Most of the subjects were females (60.6%), from Malay ethnic group (90.1%) and had higher education level, which is from university or college (48.5%). Mean duration of the disease and mean drug dosage taken by the subjects were 3 years (SD3.24) and 21.7mg (SD29.18) respectively (Table 1). The type of immunosuppressive drugs that received by patients include azatiadine, azitromycin, cyclophosphamide, cyclosporine, dexamethasone, methotrexate, nilotinib, and prednisolone. They were treated for diseases such as autoimmune haemolytic anaemia, B-cell ccute lymphoblastic lymphoma, breast carcinoma, Castleman disease, diffuse large B-cell lymphoma, gastrointestinal malignancy, hodgkin lymphoma, multiple myeloma, mantle cell lymphoma, mixed connective tissue disease, primary mediastinal B-cell lymphoma, post-transplant, primary central nervous system lymphoma, rheumatoid arthritis, Sjögren syndrome, and testicular carcinoma.

Oral hygiene factors show most subjects brushed their teeth two times per day (60.6%) and majority of them used fluoridated toothpaste (93.9%) (Table 2). Most of them had their last dental visits less than 6 months

Table 1. Demographic data of the study subjects (n=33)

Variables	Mean (SD)	Frequency, n (%)
Age (years)	40.4 (14.3)	
Gender		
Male		13 (39.4)
Female		20 (60.6)
Ethnicity		
Malay		30 (90.1)
Chinese		2 (6.9)
Indian		0 (0.0)
Others		1 (3.0)
Education levels		
Primary		3 (9.1)
Secondary		14 (42.4)
University / College		16 (48.5)
Duration of disease (years)	3.09 (3.24)	
Dosage of medication (mg/day)	21.7 (29.18)	

*SD: Standard deviation

Table 2. Oral hygiene factors of the study subjects (n=33)

Variables	Frequency (n(%))
Frequency of toothbrushing	
1 times per day or less	7 (21.2)
2 times per day	20 (60.6)
More than 2 times per day	6 (18.2)
Type of toothpaste	
Fluoridated	31 (93.9)
Non-fluoridated	2 (6.1)
Last dental visit	
Less than 6 months	18 (54.5)
6-12 months	11 (33.3)
2-5 years	1 (3.0)
More than 5 years	3 (9.1)
Oral aids	
None	4 (12.1)
Mouth rinse	10 (30.3)
Floss	5 (15.2)
Both	14 (42.4)

Table 3. The periodontal parameters of the study subjects (n=33)

Variables	Frequency (n(%))
Plaque score	
Good (<30%)	7 (21.2)
Fair	23 (69.7)
Poor	3 (9.1)
Bleeding index	
Mild (<30%)	5 (15.2)
Fair	23 (69.7)
Poor	5 (15.2)
Clinical gingival overgrowth index	
Grade 0	14 (42.4)
Grade 1	15 (45.5)
Grade 2	4 (12.1)

(54.5%) and almost half of them used floss and mouth rinse (42.4%) as oral aids (Table 2).

Most subjects had fair oral hygiene (69.7%) and fair bleeding index (69.7%). Out of 33 subjects, 14 (42.4%)

Table 4. Association between demographic data and periodontal parameters with clinical gingival overgrowth (n=33)

Variables	GO present (n=19) Mean (SD)	GO absent (n=14) Mean (SD)	p-value
Age	42.4 (14.8)	37.6 (14.4)	0.48
Gender			0.50
Male	8	5	
Female	11	9	
Ethnicity			0.24
Malay	17	13	
Chinese	2	0	
Others	0	1	
Plaque Score Index			0.01
Good	1	6	
Fair and poor	18	8	
Bleeding Index			0.05
Mild	14	14	
Fair and poor	5	0	

*GO: Gingival overgrowth
*SD: Standard deviation

had clinical gingival overgrowth index score of 0, 15 (45.5%) of them had grade 1 while 4 (12.1%) had grade 2 (Table 3).

The mean age for patients presented with clinical gingival overgrowth is 42.4 (SD14.8). Among patients presented with gingival overgrowth, eleven of them were female and majority were Malays. No significant association between gingival overgrowth and gender (p=0.50), and ethnic (p=0.24). Eighteen subjects presented with gingival overgrowth had fair and poor plaque score and its association with gingival overgrowth was significant (p=0.01). Five subjects had fair and poor bleeding index also presented with clinical gingival overgrowth, and the remainder had mild bleeding index. There is significant association between bleeding index and gingival overgrowth (p=0.05).

DISCUSSION

The prevalence of gingival overgrowth in this study was 57.6%, significantly higher compared to study by Cota et al.[9] which was 34.8%. Out of 33 subjects, 15 (45.5%) had clinical index of gingival overgrowth of grade 1 and 4 (12.1%) had grade 2. Fourteen (42.4%) subjects showed no gingival overgrowth. None of the subjects had significant clinical gingival overgrowth (grade 3), compared to previous study by Cota et al.[9] which was 10 (7.4%) out of 47 subjects. Accurate comparison of the prevalence of gingival overgrowth was difficult to establish due to different population, the differences of indices used, type of systemic condition treated, age of the patients, poorly controlled underlying periodontal condition as well as other factors.[1]

This study shows female has higher prevalence of gingival overgrowth, which is 11 (58%) compared to male, 8 (42%). However, Gopal et al. reported in their study male showed higher prevalence of gingival overgrowth, which was 23 (63.9%) compared to female, 13 (36.1%).[10] In addition, study by Rapone et al. also reported contradictory findings.[11] They found that males were at greater risk from developing gingival overgrowth compared to female following the combination of cyclosporine and nifedipine or amlodipine treatment. There was no significant association between gingival overgrowth and gender in this study (*p*=0.50). Nevertheless, these may be contributed by the type of disease itself as autoimmune disease and cancer were generally more frequent affecting females compared to males.[12] However, the mechanisms that influence female predominance are relatively unknown.[13]

Most subjects were taking care of their oral hygiene, 20 (60.6%) which brushed their teeth twice per day and majority of them 31 (93.9%) were using fluoridated toothpaste. This indicates the increase in awareness of taking care of oral hygiene among our patients. Reali et al. reported only 23% of their patients with good oral hygiene had gingival overgrowth, and grade 1 to 3 were found exclusively in patients who neglected teeth cleaning and had poor oral hygiene.[14] As periodontal health worsens, degree of gingival overgrowth increases.[15] Besides, the present study shows 18 (54.5%) subjects had their last dental visit less than 6 months and 14 of them were using oral hygiene aid such as mouth rinse and floss. Plaque control is the first step in the treatment of drug-induced gingival overgrowth. Correct oral hygiene and professional plaque removal, including tooth surface cleaning and periodic scaling, should be carried out when essential.[1] Improved oral hygiene has been observed by frequent tooth brushing and professional dental cleaning.[16] In their study of 80 transplant patients, professional cleaning was found to be effective in reducing cyclosporine A-induced gingival overgrowth. Considering these facts, all subjects were given oral hygiene instructions and reinforcement and those subjects presented with gingival overgrowth of grade 2 and grade 3, were recommended to be referred to periodontist to re-establish a good baseline status.

The present study shows plaque score was significantly associated with gingival overgrowth (p=0.01). Bacterial plaques exerts a direct toxic effect on the gingival tissue. Dental plaque causes inflammation, which subsequently enhances gingival overgrowth in such patients.[1] Meanwhile Bekit et al. reported that plaque was significantly associated with gingival overgrowth (p<0.05) even when the evaluation of effect of different immunosuppressive agents has been carried out.[17] However, study by Cota et al.[9] showed a contradictory finding by which the plaque score was not significantly influence the gingival overgrowth

(p=0.058). The association of between plaque with gingival overgrowth remains controversial whether plaque was a contributing factor to gingival overgrowth or a consequence of gingival overgrowth. Nevertheless, majority of gingival overgrowth cases were reported in patients with poor oral hygiene maintenance.[18]

Bacterial plaque appeared to be a contributing factor and the severity of gingival overgrowth and was believed to be directly proportional to the degree of plaque buildup and plaque-induced inflammation.[18] Dental plaque causes inflammation and subsequently alters the upregulation of transforming growth factor beta 1 (TGF-beta 1) and release of proinflammatory cytokines causing fibroblastic proliferation and increases the production of collagen and Glycosaminoglycans (GAGs) synthesis, leading to accumulation of connective tissue and collagen due to lack of collagenase and subsequently further causing gingival overgrowth.[1]

In this study, significant association was found between bleeding index and gingival overgrowth (p=0.05). Bleeding causes gingival inflammation and subsequently leads to gingival overgrowth. Previous study by Costa et al. showed similar findings by which there was significant association between bleeding index and gingival overgrowth (p=0.0001).[19] In renal transplant recipient, the bleeding upon stimulation presented as gingival inflammation was confirmed as the variable associated with gingival overgrowth. The potential mechanism for gingival overgrowth was the inflammation which alter the microflora in the gingival sulcus.[9] Plaque scores and gingival inflammation exacerbate the expression of drug-induced gingival overgrowth, irrespective of the initiating drug. The severity of gingival enlargement in patients taking medications correlates well with poor plaque control and is correspond with the degree of plaque-induced inflammation.[1]

CONCLUSION

Gingival overgrowth was prevalent (57.6%) among immunosuppressed patients. Nonetheless, none of the patients had clinical significant of gingival overgrowth. Plaque accumulation secondary to poor oral hygiene is the most possible contributing factor. Thus, taking care of oral hygiene should be reinforced in such patients to minimise the complication.

ACKNOWLEDGMENT

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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