Clin Oral Invest (2012) 16:565–570
DOI 10.1007/s00784-011-0529-8

ORIGINAL ARTICLE

Oral cGVHD screening tests in the diagnosis of systemic chronic graft-versus-host disease

Renata Gonçalves Resende · Jeane de Fátima Correia-Silva · Telma Cristina Arão · João Artur Ricieri Brito · Henrique Bittencourt · Ricardo Santiago Gomez · Mauro Henrique Nogueira Guimarães Abreu

Received: 23 August 2010 / Accepted: 16 February 2011 / Published online: 3 March 2011

Abstract To determine the diagnostic properties of oral manifestations and histological features of graft-versus-host disease (GVHD) screening tests in the diagnosis of systemic chronic graft-versus-host disease (cGVHD). Sixty patients having undergone allogeneic haematopoietic stem cell transplantation were selected. The patients were submitted to a clinical oral examination to assess symptoms and clinical changes in the oral mucosa. Histopathologic analysis of the lower lip oral mucosa (LLOM) and salivary glands (SG) was also performed. Systemic cGVHD was used for a comparison to oral cGVHD. The accuracy of oral cGVHD tests was low for all methods (58.4% and 52.6% for white lesions and white/red lesions, respectively, in the clinical analysis; 50.4% for the presence of oral pain; and 66.8% and 55.1% for LLOM and SG histopathologic tests, respectively). However, the presence of oral pain had good diagnostic properties [specificity: 100.0, 95% confidence interval (CI): 88.0–100.0; positive predictive value (PPV): 100.0, 95% CI: 94.4–100.0; and negative predictive value (NPV): 72.0, 95% CI: 57.3–83.3]. Moreover, SG alterations revealed by the histopathological analysis also exhibited good diagnostic properties (sensitivity: 98.6, 95% CI: 81.5–99.8; PPV: 71.1, 95% CI: 62.1–79.7; NPV: 85.9 95% CI: 32.9–99.4). The clinical severity of oral lesions and histophatological changes in the LLOM did not exhibit adequate diagnostic properties, whereas both oral pain and SG histopathological analysis exhibited adequate properties for the diagnosis of systemic cGVHD. Histological changes in lip oral mucosa and salivary glands together with a clinical manifestation of the disease in the oral mucosa can be useful to determining the systemic cGVHD.

Keywords Haematopoietic stem cell transplantation · Chronic graft-versus-host disease · Oral chronic graft-versus-host disease

R. G. Resende · J. de Fátima Correia-Silva · T. C. Arão · J. A. R. Brito · R. S. Gomez
Department of Oral Surgery and Pathology, School of Dentistry, Universidade Federal de Minas Gerais, Belo Horizonte, Brazil

M. H. N. G. Abreu
Department of Community and Preventive Dentistry, School of Dentistry, Universidade Federal de Minas Gerais, Belo Horizonte, Brazil

H. Bittencourt
Stem Cell Transplant Unit, Hospital das Clínicas, Universidade Federal de Minas Gerais, Belo Horizonte, Brazil

M. H. N. G. Abreu (✉)
Faculdade de Odontologia, Universidade Federal de Minas Gerais, Av. Antonio Carlos, 6627, Belo Horizonte, MG 31270–901, Brazil
e-mail: maurohenriqueabreu@ig.com.br

Introduction

Allogeneic haematopoietic stem cell transplantation (allo-HSCT) is a well-established curative treatment for many haematological malignancies and some non-malignant disorders [1]. Graft-versus-host disease (GVHD) is a major complication of allo-HSCT and responsible for significant morbidity and mortality [2]. GVHD is a multi-systemic disorder with various clinical, pathological and immunological manifestations that occur as a result of complex immunological interactions between the host and transplanted donor cells. GVHD may be either acute or chronic, depending on the time of occurrence and clinical manifestations [3].

Chronic GVHD (cGVHD) affects 25% to 40% of long-term HSCT survivors and most frequently occurs 100 days or more after the transplant [4]. Traditionally, cGVHD is further classified as either limited or extensive, depending on the degree of organ involvement [5]. Limited cGVHD manifests as localised skin involvement, liver dysfunction or both, whereas extensive cGVHD affects multiple organs, such as the skin, liver, eyes, salivary glands, oral mucosa and other target organs [6]. More recently, the Diagnosis and Staging Working Group of the NIH Consensus Development Project on Criteria for Clinical Trials in Chronic GVHD has proposed new criteria for the diagnosis, organ scoring and global assessment of cGVHD severity [6].

Oral manifestations occur in about 80% of patients with extensive cGVHD. The most common findings are erythema, mucosal atrophy, lichenoid changes, mucositis, xerostomia and infections [6]. Pain associated with oral mucosistis may be debilitating and lead to dysphagia [7]. A clinical oral examination and biopsy of the lip salivary glands (SG) have been proposed as valuable screening tests for the diagnosis of cGVHD 3 months following HSCT due to the high incidence of oral mucosa involvement [3, 8]. As the properties of these tests have not been clearly established, the purpose of this study was to determine the diagnostic properties of clinical, oral and histological screening tests for systemic cGVHD.

Patients and methods

Subjects

A total of 60 consecutive allo-HSCT recipients at the university hospital of the Universidade Federal de Minas Gerais who had undergone biopsy of the lip SG and lower lip oral mucosa (LLOM) between April 2006 and October 2008 were included in this study. The recipients were conditioned for allo-HSCT based on the specific protocols of the stem cell transplant unit of the hospital. Cyclosporin was used in combination with either methotrexate or mycophenolate mofetil for GVHD prophylaxis. The clinical data on the patients are displayed in Table 1.

Systemic chronic GVHD grades

Systemic cGVHD was clinically diagnosed (with or without histopathological confirmation) by a physician. All patients were classified as either having the limited or extensive form of the disease, as previously described by Shulman et al. [5]. Systemic cGVHD was used for comparison with oral cGVHD.

Table 1 Clinical and demographic characteristics of patients and donors

Parameters	Total (n=60)
Male gender	43 (71.6%)
Female gender	17 (28.4%)
Primary disease	
Malignant	40 (66.7%)
Chronic myeloid leukaemia	11 (18.3%)
Acute myeloid leukaemia	17 (28.4%)
Acute lymphoid Leukaemia	5 (8.3%)
Non-Hodgkin's lymphoma	4 (6.7%)
Hodgkin's lymphoma	3 (5.0%)
Other malignancies[a]	3 (5.0%)
Bone marrow failure syndrome[b]	17 (28.3%)
Male Donor	35 (58.3%)
Female Donor	25 (41.7%)
Conditioning regimen	
BU/CY	21 (35.0%)
CY +/− ATG or Alemtuzumab	13 (21.7%)
BU + FLUD +/− Alemtuzumab	10 (16.6%)
CY + FLUD +/− Alemzutumab	5 (8.4%)
MEL + FLUD +/− Campath	8 (13.3%)
Others[c]	3 (5%)
Immunosuppression at time of biopsy[d]	12 (20%)
Ethnic group	Mixed Brazilian population
Source of stem	
Bone marrow	32 (53.3%)
Peripheral blood stem cells	28 (46.7%)

BU busulfan, *CY* cyclophosphamide, *FLUD* fludarabine, *MEL* melphalan, *ATG* anti-thymoglobulin

[a] Myelodysplastic syndrome (n=2); multiple myeloma (n=1)

[b] Paroxysmal nocturnal haemaglobinuria (n=2); severe aplastic anaemia (n=14); Fanconi's anaemia (n=1)

[c] BU/MEL (n=1); cytarabine/campath/FLUD (n=1)

[d] Prednisone

Clinical grading of oral chronic graft-versus-host disease

In all patients, a modified model of the Oral Mucosa Rating Scale was employed to quantify the extent and severity of oral mucosal involvement in chronic GVHD. The clinical signs evaluated were erythema ("red lesions"), atrophy and lichenoid lesions ("white/red lesions"), based on the number of anatomic sites (tongue, lips, palate, floor of the mouth and cheeks) affected (0 to 4). The patients were categorised on a scale ranging from 0 to 4 (0: normal; 1: white lesions (1 to 2 sites); 2: white lesions (>2 sites); 3: white/red lesions (1 to 2 sites); 4: white/red lesions (>2 sites) [9].

Oral pain

Oral pain was classified as absent, mild or intense based on visual analog scale (VAS). The determination of this symptom was adapted from Schubert et al. [10].

Histological criteria for oral cGVHD

Histopathological analyses of LLOM and SG were performed on 59 biopsy specimens (for one sample, it was only possible to analyse SG sections). The sections were evaluated blindly. The histological grading of GVHD in the oral mucosa and salivary glands was performed as described elsewhere [11]. Briefly, samples were classified as mild, moderate or severe based on the number of inflammatory cells in the oral mucosa and the acini and ducts of the salivary glands in six microscopic fields (×400). The samples were divided into three groups based on the total number of inflammatory cells: mild, when inflammatory cells numbered from 30 to 140; moderate, when there were between 141 and 250 inflammatory cells; and severe, for samples with more than 250 inflammatory cells. For statistical purposes, all cases with mild, moderate or severe inflammation were grouped as positive for GVHD.

Statistical analysis

Data analysis was performed using the Receiver Operator Characteristic (ROC) and area under the ROC curve (SPSS Inc., version 17.0, Chicago, IL). Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated at each threshold (Epi Info, version 6.0, Seattle, WA, USA). Analyses were performed for the presence or absence of oral cGVHD (histological analyses, clinical severity of lesions and symptoms) and the presence or absence of systemic cGVHD.

Results

Clinical outcome

A total of 39 patients (65%) had systemic cGVHD; 17 patients had the limited form of the disease and 22 had developed the extensive form. Eighteen patients (30%) had oral GVHD. White lesions were seen in 16 patients (26.7%) and white/red lesions were found in two patients (3.3%). Six patients (10%) reported oral symptoms. The histopathological analysis revealed cGVHD in the LLOM and SG in 34 (56.6%) and 42 (70%) patients, respectively (Table 2).

Table 2 Prevalence of systemic and oral chronic GVHD (n=60)

Parameters	Total (n=60) (%)
Systemic	39 (65.0)
Limited	17 (28.3)
Extensive	22 (36.6)
Oral cGVHD	
White/red lesions	16 (26.7)
Red lesions	2 (3.3)
Oral pain	6 (10.0)
LLOM histophatological analyses	34 (56.6)
SG histophatological analyses	42 (70.0)

cGVHD chronic graft-versus-host disease, *LLOM* lower lip oral mucosa, *SG* salivary glands

Accuracy of oral cGVHD tests

Table 3 displays the scores obtained with the oral cGVHD screening tests in comparison with systemic cGVHD. The accuracy of the oral cGVHD tests was low for all samples (52.6% and 58.4% for mixed white/red and white lesions, respectively; 50.4% for symptoms; and 66.8% and 55.1% for LLOM and SG histopathological tests). Oral pain achieved a sensitivity of 10.3% [95% confidence interval (CI): 3.3–25.2%], specificity of 100.0% (95% CI: 88.0–100.0%), PPV of 100.0% (95% CI: 94.4–100.0%) and NPV of 72.0% (95% CI: 57.3–83.3%). The histological analysis of the SG also exhibited good diagnostic properties, with a sensitivity of 98.6% (95% CI: 81.5–99.8%), specificity of 33.3% (95% CI: 15.5–56.9%), PPV of 71.1% (95% CI: 62.1–79.7%) and NPV of 85.9% (95% CI: 32.9–99.4%).

On the other hand, the clinical severity of oral lesions did not exhibit good properties for the assessment of systemic cGVHD due to the low sensitivity and low NPV [sensitivity of white lesions: 35.9% (95% CI: 21.7–52.8%); sensitivity of white/red lesions: 10.5% (95% CI: 1.8–34.5%); NPV of white lesions: 42.5% (95% CI: 30.0–53.8%); and NPV of oral white/red lesions: 39.6% (95% CI: 36.6–47.2%)]. Similar findings were observed in histopathological analysis of the LLOM, which achieved low specificity (63.6%; 95% CI: 40.8–82.0%) and a low NPV (56.3%; 95% CI: 30.4–75.6%).

Discussion

Chronic GVHD is a complex entity and major complication following HSCT [12]. Studies have shown that immunological mechanisms of cGVHD include donor-derived alloreactive T lymphocytes, autoreactive T lymphocytes

Table 3 Sensitivity, specificity, accuracy, positive and negative predictive values for prevalence of oral chronic GVHD in the diagnosis of systemic chronic GVHD

Variable	Sensitivity (95% CI)	Specificity (95% CI)	ROC Area (95% CI)	PPV (95% CI)[a]	NPV (95% CI)[a]
White/red lesions[b]	35.9 (21.7–52.8)	81.0 (57.4–93.7)	0.584 (0.451–0.757)	76.2 (46.4–93.4)	42.5 (30.0–53.8)
Red lesions[c]	10.5 (1.8–34.5)	100.0 (80.8–100.0)	0.526 (0.374–0.679)	100.0 (61.4–100.0)	39.6 (36.6–47.2)
Oral pain	10.3 (3.3–25.2)	100.0 (88.0–100.0)	0.504 (0.352–0.661)	100.0 (94.4–100.0)	72.0 (57.3–83.3)
LLOM histopathological analyses	71.1 (53.9–84.0)	63.6 (40.8–82.0)	0.668 (0.529–0.818)	76.8 (60.7–88.8)	56.3 (34.0–75.6)
SG histopathological analyses	98.6 (81.5–99.8)	33.3 (15.5–56.9)	0.551 (0.342–0.666)	71.1 (62.1–79.7)	85.9 (32.9–99.4)

PPV positive predictive value, *NPV* negative predictive value, *CI* confidence interval, *LLOM* lower lip oral mucosa, *SG* salivary glands, *ROC* Receiver Operator Characteristic

[a] Prevalence of systemic chronic GVHD: 65%

[b] Atrophy and lichenoid lesion

[c] Erythema area

and regulatory T lymphocytes as well as the dysregulation of cytokine expression [13].

The first grading scheme for the severity of systemic cGVHD was proposed in 1980 based on data from 20 subjects classifying the disease as limited when it affects skin and/or liver or as extensive when present skin involvement or localized skin involvement or hepatic dysfunction caused by chronic GVDH in combination with histological changes of the liver that showed chronic aggressive hepatitis, bridging necrosis or cirrhosis, involvement of the eye, histologically proven involvement of minor salivary glands or oral mucosa on labial biopsy, or proven involvements of any other target organ [5]. Although the new staging proposed by the NIH Consensus Development Project on Criteria for Clinical Trials in Chronic GVHD was proposed in 2005, the classification employed in the present study was proposed by Shulman et al. [5], which was used by the Universidade de Minas Gerais Hospital until 2008, when the study was carried out.

The most common sites of cGVHD involvement are the skin, oral cavity, eyes, GI tract and lungs; however, the spectrum of clinical involvement is variable [14]. The early and precise diagnosis of cGVHD is important to determine the optimal treatment at an early stage of the disease. While skin and liver manifestations may be confused with signs of other disorders, the presence of oral cGVHD is a frequent, prominent and useful component of cGVHD diagnosis and staging [14, 15]. Oral involvement has been described as a diagnostic sign of cGVHD and one of the first signs or symptoms of the disease [15]. Moreover, oral mucosa and salivary gland alterations are reported to reflect the status of cGVHD better than other affected organs [16, 17]. However, the accuracy of each oral screening test is unclear in the diagnosis of systemic cGVHD.

In the present study, the clinical data and biopsies of 60 patients having undergone HSCT were evaluated in attempt to determine the diagnostic properties of oral screening tests in the diagnosis of systemic chronic GVHD. The absence and presence of oral alterations were compared with the absence and presence of oral changes in systemic chronic GVHD. The analysis revealed that the general accuracy of all tests was low (66.8% and 55.1% for LLOM and SG histopathological tests and between 50.5% and 58.4% for other oral parameters). However, in the analysis of other diagnostic properties, the clinical appearance of the oral lesion demonstrated high specificity (81.0% and 100.0% for white and white/red lesions, respectively) and PPV (76.6% and 100.0% for white and white/red lesions, respectively). This indicates that the high capacity of these tests to exclude the disease in patients that do not have systemic cGVHD and that the proportion of patients with white and white/red lesions who have systemic cGVHD is also high. Nevertheless, these tests demonstrated low sensitivity and NPV when compared with systemic cGVHD. This benchmark standard can be understood as follows: the ability of the test to identify the disease is low and its tendency to produce false-negative results is high. Recently, according to NIH consensus, only lichenoid changes are diagnostic for cGVHD, while other signs like erythema are considered insufficient alone to diagnose the disease [6].

On the other hand, the presence of symptoms demonstrated high specificity, PPV and NPV (100.0%, 100.0% and 72.0%, respectively) when compared with systemic cGVHD. Specificity indicates that the test is suitable for diagnosing subjects without systemic cGVHD. The PPV shows that the patients with symptoms always had the systemic disease and the NPV of 72.0% reveals that this clinical parameter yields a false negative 28% of the time. However, sensitivity was low, meaning that most patients with cGVHD do not exhibit oral symptoms. Based on these findings, clinical lesion types do not adequately discriminate patients with cGVHD; whereas, oral symptoms seem to be a good test for confirming a diagnosis of systemic

disease and an important clinical criterion for determining cGVHD without performing other invasive procedures.

In the analysis of histopathological parameters for the determination of cGVHD, the histopathological test of the LLOM proved adequate for the detection of systemic cGVHD, considering its good sensitivity and specificity. The findings also reveal that there were a high proportion of patients with positive histopathological findings for cGVHD of the LLOM who also had systemic cGVHD, as demonstrated by the high PPV. However, when the test indicated the absence of the disease in the histopathologic LLOM evaluation, the proportion of patients not affected by systemic cGVHD was low, as demonstrated by the low NPV.

The histopathological analysis of the SG exhibited good diagnostic properties regarding the detection of systemic cGVHD, with high sensitivity, PPV and NPV (98.6%, 71.1% and 85.9%, respectively). The results of the present study demonstrate that the SG test identifies systemic cGVHD in 98.6% of cases, that 71.1% of the patients with cGVHD of the SG had the systemic disease and that this histopathological parameter yields a false negative 14.1% of the time. These findings show that histological analysis is suitable for determining cGVHD, especially SG histopathological examination. This is in agreement with Soares et al. [18], who studied the most relevant histopathologic features for oral cGVHD diagnosis and found that the SG exam is important to establish the diagnosis and determine the grade of cGVHD. Thus, oral biopsy could be a suitable tool for the diagnosis and monitoring of cGVHD, as it is accessible for examination and sampling and has an important relationship with systemic cGVHD.

In a recent paper, Imanguli et al. [15] found that involvement of the salivary glands in cGVHD contributes to morbidity in patients having undergone HSCT and further demonstrated the distinction between salivary and oral mucosal involvement. In another study, the authors attempted to identify the most relevant histological features for the diagnosis of cGVHD and found that the SGs are more frequently affected by cGVHD than LLOM, which is in agreement with other studies [19, 20] and with the results of the present study. However, Horn et al. [21] investigated the clinical relevance of histological findings for the outcome of HSCT and found that histological alterations in the oral cavity do not correlate with the overall HSCT outcome, cutaneous cGVHD or earlier acute GVHD.

Therefore, although the criteria proposed by Shulman et al. [5] allow the diagnosis of systemic cGVHD based on clinical presentation, there are situations in which the alterations are less distinct. In such cases, the examination of the oral cavity and biopsy of both the mucosa and minor salivary glands can provide supportive diagnostic information.

In summary, this is the first study to demonstrate the accuracy of oral tests for determining systemic chronic GVHD. The overall accuracy of these tests is not good. Nevertheless, the data revealed that oral chronic GVHD screening tests have good properties for the diagnosis of systemic cGVHD. Both the presence of oral symptoms and histopathological manifestations in the salivary glands have good properties regarding the diagnosis of systemic cGVHD. Oral screening tests remain an important tool for the diagnosis and grading of cGVHD and should be employed, especially when further diagnostic information is needed, thereby contributing to the accurate and early diagnosis of chronic GVHD. These findings should be explored further in a larger group of patients, using the new staging proposed by the NIH Consensus Development Project on Criteria for Clinical Trials in Chronic GVHD, which may better characterise the extent of chronic GHVD.

Acknowledgements This study was supported in part by grants from the Brazilian fostering agencies Fundação de Amparo à Pesquisa do Estado de Minas Gerais (FAPEMIG) and Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq). RS Gomez is a research fellow of CNPq. The authors thank Daniele Ramalho da Silva for her technical assistance.

Conflicts of interest The authors declare that they have no conflict of interest.

References

1. Markey KA, MacDonald KP, Hill GR (2008) Impact of cytokine gene polymorphisms on graft-vs-host disease. Tissue Antigens 72:507–516
2. Imanguli MM, Alevizos I, Brown S, Pavletic SZ, Atkinson JC (2008) Oral graft-versus-host disease. Oral Dis 14:396–412
3. Nicolatou-Galitis O, Kitra V, Van Vliet-Constantinidou C, Peristeri J, Goussetis E, Petropoulos D, Grafakos S (2001) The oral manifestations of chronic graft-versus-host disease (cGVHD) in paediatric allogeneic bone marrow transplant recipients. J Oral Pathol Med 30:148–153
4. Parkman R (1998) Chronic graft-versus-host disease. Curr Opin Hematol 5:22–5
5. Shulman HM, Sullivan KM, Weidn PL et al (1980) Chronic graft-versus-host syndrome in man. A long-term clinicopathologic study of 20 Seattle patients. Am J Med 69:204–217
6. Filipovich AH, Weisdorf D, Pavletic S et al (2005) National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and staging working group report. Biol Blood Marrow Transplant 11:945–956
7. Curtis JW Jr, Caughman GB (1994) An apparent unusual relationship between rampant caries and the oral mucosal manifestations of chronic graft-versus-host disease. Oral Surg Oral Med Oral Pathol 78:267–272
8. Loughran TP Jr, Sullivan K, Morton T et al (1990) Value of day 100 screening studies for predicting the development of chronic graft-versus-host disease after allogeneic bone marrow transplantation. Blood 76:228–234

9. Busca A, Locatti F, Vai S, Dall'Omo AM et al (2005) Clinical grading of oral chronic graft-versus-host disease in 104 consecutive adult patients. Haematologica 90:569–568
10. Schubert MM, Sullivan KM (1990) Recognition, incidence and management of oral graft-versus-host disease. NCI Monogr 9:135–143
11. Souza LN, Carneiro MA, Azevedo WM, Gomez RS (2004) Vascular endothelial growth factor (VEGF) and chronic graft-versus-host disease (cGVHD) in salivary glands of bone marrow transplant (BMT) recipients. J Oral Pathol Med 33:13–16
12. Sullivan KM, Deeg HJ, Sanders J et al (1986) Hyperacute graft-v-host disease in patients not given immunosuppression after allogeneic marrow transplantation. Blood 67:1172–1175
13. Fall-Dickson JM, Mitchell SA, Marden S et al (2010) Oral symptom intensity, health-related quality of life, and correlative salivary cytokines in adult survivors of hematopoietic stem cell transplantation with oral chronic graft-versus-host disease. Biol Blood Marrow Transplant 16:948–956
14. Schubert MM, Correa ME (2008) Oral graft-versus-host disease. Dent Clin North Am 52:79–109
15. Imanguli MM, Atkinson JC, Mitchell SA, Avila DN, Bishop RJ, Cowen EW, Datiles MB, Hakim FT, Kleiner DE, Krumlauf MC, Pavletic SZ (2010) Salivary gland involvement by chronic graft-versus-host disease: prevalence, clinical significance and recommendations for evaluation. Biol Blood Marrow Transplant 16:1362–1369
16. Nakamura S, Hiroki A, Shinohara M et al (1996) Oral involvement in chronic graft-versus-host disease after allogeneic bone marrow transplantation. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 82:556–563
17. Nakhleh RE, Miller W, Snover DC (1989) Significance of mucosal vs salivary gland changes in lip biopsies in the diagnosis of chronic graft-vs-host disease. Arch Pathol Lab Med 113:932–934
18. Soares AB, Faria PR, Magna LA, Correa ME, de Sousa CA, Almeida OP, Cintra ML (2005) Chronic GVHD in minor salivary glands and oral mucosa: histopathological and immunohistochemical evaluation of 25 patients. Oral Pathol Med 34:368–373
19. Logan RM, Stringer AM, Bowen JM et al (2007) The role of pro-inflammatory cytokines in cancer treatment-induced alimentary tract mucositis: pathobiology, animal models and cytotoxic drugs. Cancer Treat Rev 33:448–460
20. Elad S, Levitt MMYS (2008) Chronic graft-versus-host-disease involving the oral mucosa: clinical presentation and treatment. Refuat Hapeh Vehashinayim 25:19–27, 72
21. Horn TD, Rest EB, Mirenski Y, Corio RL, Zahurak ML, Vogelsang GB (1995) The significance of oral mucosal and salivary gland pathology after allogeneic bone marrow transplantation. Arch Dermatol 131:964–965