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The Histopathological Difference Between Oral Lichen Planus and Oral Lichenoid Mucositis in Immunological Epithelial Barrier

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Abstract:

Objectives: To explore alternations of immunological epithelial barrier in oral lichenoid reaction (OLR) patients and to compare the difference between oral lichen planus (OLP) and oral lichenoid mucositis (OLM).

Methods: The patient-based case control study utilize twelve antibodies to check 74 biopsy specimens by the immunohistochemistry technique (IHC). Participants included 28 cases of oral lichen planus (OLP), 16 cases of contact stomatitis from dental restorative materials (OLM-dental) cases, 14 cases of mucosal reaction to systemic drug administration (OLM-drug), 15 cases of contact stomatitis from topical chemical exposure (OLM-contact) and one traumatic fibroma (TF) case. Twelve antibodies include anti-CD3 (CD3), anti-CD4 (CD4), anti-CD8 (CD8), anti-NKp46 (NKp46), anti-mast cell chymase (MCC), anti-interferon gamma (INFG), anti-cytokine IL-17 beta (IL-17B), anti-cytokine IL-22 (IL-22), anti-cytokine IL-7 receptor (IL-7R), anti-T-bet/Tbx21 (T-bet), anti-ST2 (ST2) and anti-HAND2-Carboxyterminal End (HAND2). "Pattern-based comparison" and Cohen's Kappa test are applied for analysis.

Conclusions: OLM-contact maintains a normal immunological epithelial barrier, while the weakness is detected and arranged in a descending order of OLM-drug, OLM-dental and OLP. OLM-drug is less likely involved in MHC I alteration and/or loss related immune response. The significant difference between OLP and OLM is CD4 distribution pattern in subepithelial region. OLM always shows a patched infiltration, while OLP only displays a band-like infiltration.

Keywords: Oral Lichenoid Reaction, Oral Lichen Planus, Oral Lichenoid Mucositis, Immunological Epithelial Barrier, and Immunohistochemistry Technique

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Introduction

Oral lichenoid reaction (OLR) refers to oral lichen planus (OLP) or oral lichenoid mucositis (OLM). Oral lichenoid mucositis could be one of three conditions, which include lichenoid contact stomatitis from dental restorative materials (OLM-dental), mucosal reaction to systemic drug administration (OLM-drug), and contact stomatitis from topical chemical exposure (OLM-contact). These four types of oral lichenoid reaction share a similar clinical appearance that is white reticular striations on erythematous mucosal base. An incisional biopsy is required to confirm a definitive diagnosis [1]. **Please see figure 1.**

However, it is still a challenge for oral pathologists to differentiate four types of oral lichenoid reactions histopathologically. Oral lichen planus (OLP) shows a band-like lymphohistiocytic infiltration immediately demolishing the basal cell layer of keratinized stratified squamous epithelium. Oral lichenoid mucositis (OLM) displays the similar histopathological

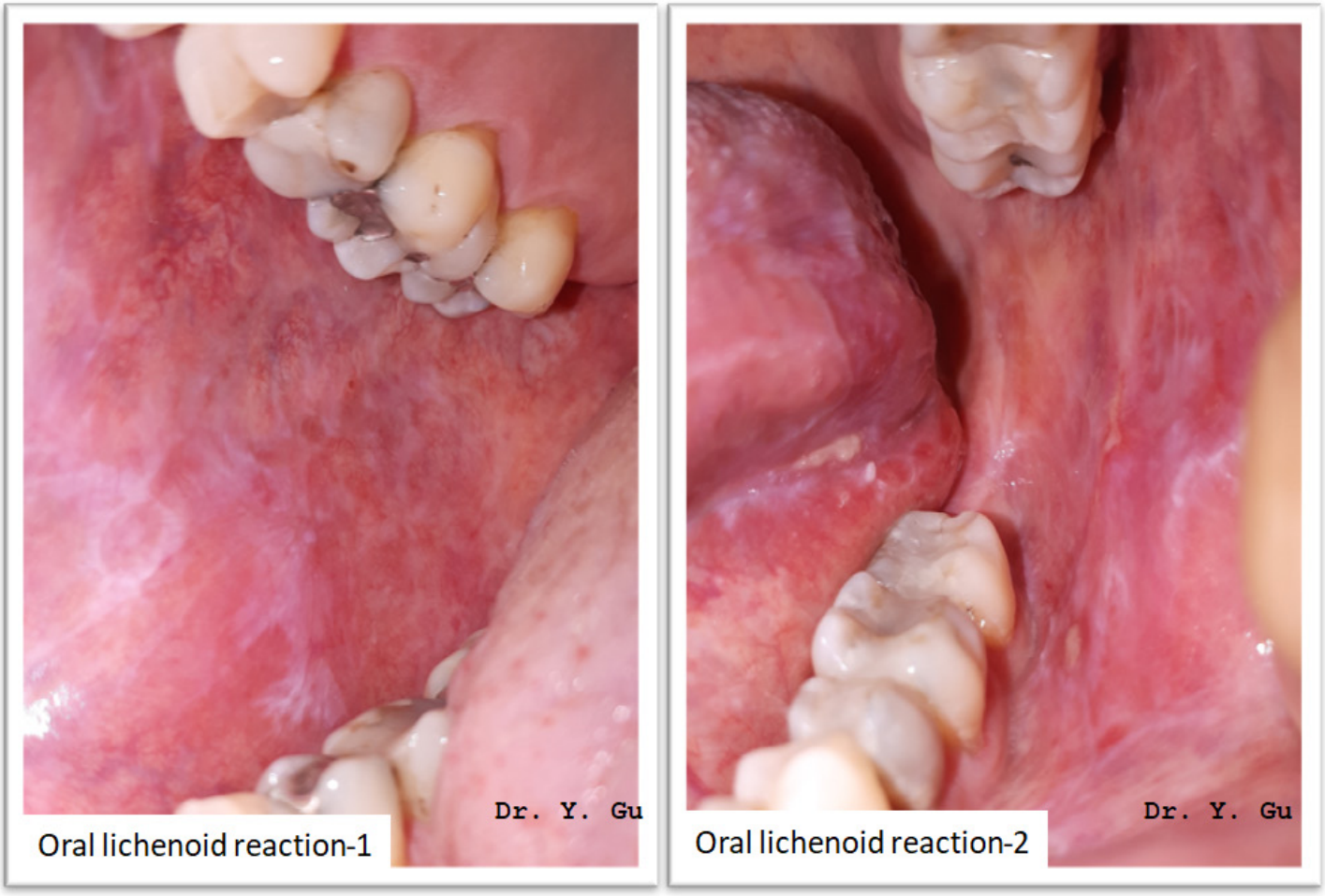

Figure 1. The clinical appearance of oral lichenoid reaction is white reticular striations in the erythematous mucosal base with or without ulcerations

features of OLP, but may have other features as well, which include patched lymphohistocytic infiltration and /or other inflammatory cells, such as plasma cells, eosinophils, and mast cells. Nevertheless, there is no gold standard that can be followed [2]. **Please see figure 2.**

Epithelial cells are liaisons of immunity. They are not only antigen presenting cells, but also are generals that orchestrate immune cells and tissue response [3]. Findings in an individual or several molecular markers of OLP cases can't not draw a big picture for the immunological epithelial barrier. It could be one of reasons that the inflammatory mechanism of OLP and OLM is not clear yet. The purpose of this case-control study by using human tissue specimens is to detect twelve molecular markers for different types of OLRs in the same matrix.

Materials and Methods

The case-control study used twelve antibodies to check biopsy specimens of 28 OLP cases and 45 OLM cases by immunohistochemistry (IHC) technique. OLM cases included 16 OLM-dental, 14 OLM-drug and 15 OLM-contact specimens. In addition, a traumatic fibroma (TF) on buccal mucosa, was arranged in the study as a non-specific inflammation control. Participants aged between 28- and 72-year-old (average 43) and with 82% gender ratio (Female by Male) had OLR on buccal mucosa (64%), gingivae (35 %) or tongue (1%). Twelve antibodies are grouped in four crews. T cell related markers include CD3 (anti- CD3), CD8 (anti-CD8) and CD4 (anti-CD4). Non-specific inflammatory cell markers cover NKp46 (anti-NKp46) and MCC (anti-mast cell chymase). Cytokine markers involve INFG (anti-interferon gamma), IL-17B (anti-cytokine IL-17 beta) and IL-22 (anti-cytokine IL-22). Epithelial barrier markers consist of IL-7R (anti-cytokine IL-7 receptor), T-bet (anti-T-bet/Tbx21), ST2 (anti-ST2), and HAND2 (anti-HAND2-Carboxyterminal End).

We used a double-blind working protocol to manage the entire study. Specimens in four study groups were numbered alphabetically only by a medical laboratory technologist (AK) herself. The result was unveiled after the scoring and before the data analysis. For avoiding bias, we have positive controls, negative controls, a non-specific inflammation control, the crucial inclusion and exclusion standards in each step.

Inclusion, Exclusion and Preparation

The medical laboratory technologist (AK) searched OLP and/or OLM as key words in the system of Oral Biopsy Service (OBS) Laboratory of Faculty of Dentistry, Dalhousie University, Halifax, Canada. Totally 296 cases with intact demographics were found between

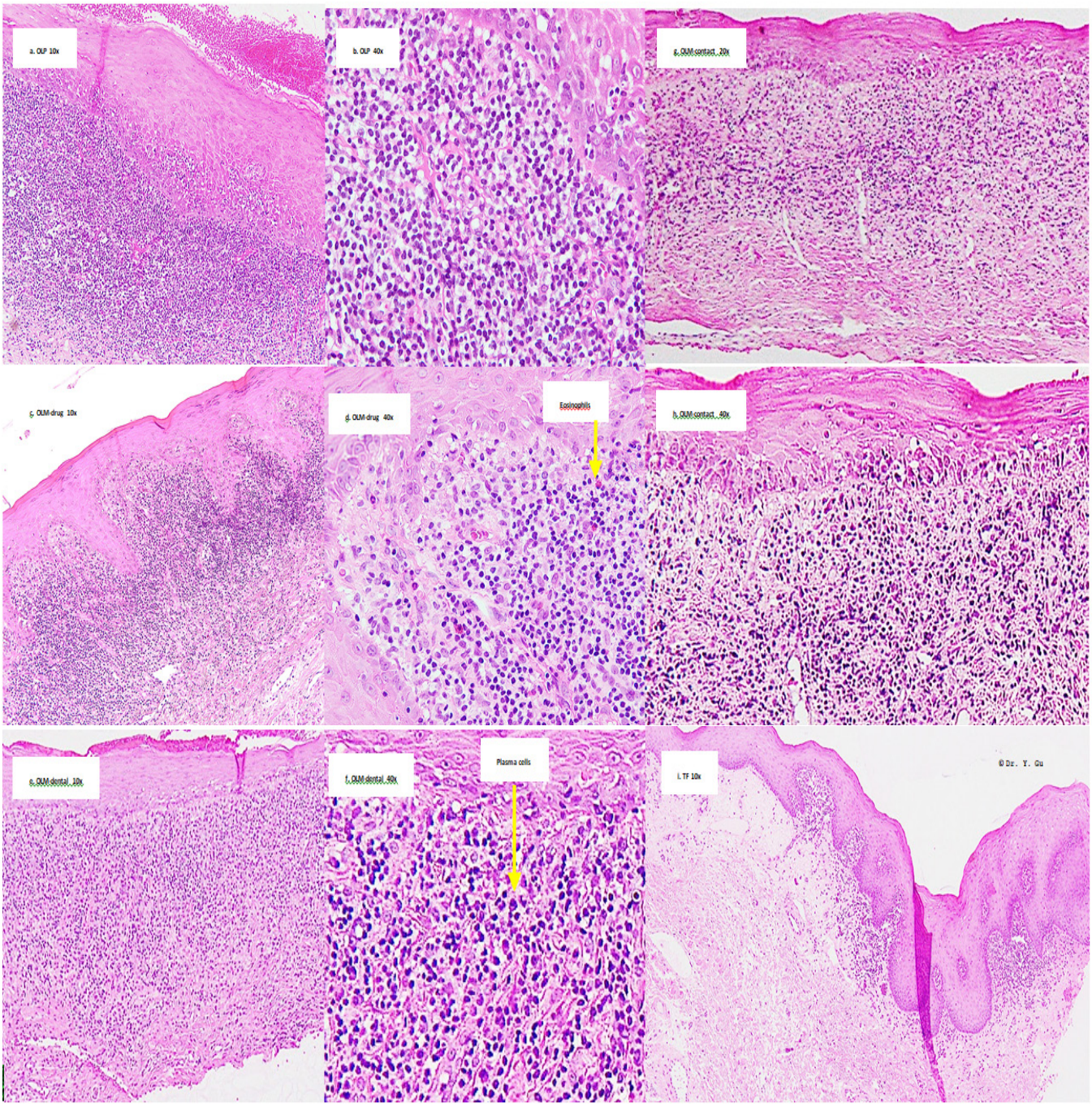

Figure. 2: Histopathological features of oral lichenoid reactions

a./b. OLP (oral lichen planus): Band-like lymphohistiocytic infiltration immediately demolishing the basal cell layer of keratinized stratified squamous epithelium.

c./d. OLM-drug (mucosal reaction to systemic drug administration): The similar feature as OLP, but has scattered eosinophils.

e./f. OLM-dental (contact stomatitis from dental restorative materials): The similar feature as OLP, but has scattered plasma cells.

g./h. OLM-contact (contact stomatitis from topical chemical exposure): The similar feature as OLP, but has patched distribution.

i. TF (traumatic fibroma): Dense fibrous connective tissue mass covered by keratinized stratified squamous epithelium with focally mild chronic inflammation.

January 1st 2011 and May 31, 2017. An oral pathologist (YG) read all H&E slides. Only 87 OLP and OLM specimens plus one traumatic fibroma specimen were selected. Exclusion is ulcerative type of OLR, bullous type of OLR, OLR combined with fungus infection, inappropriate biopsy specimens and inadequate tissue blocks.

The inclusive standard of study groups obeys to relatively specific histopathological features about OLP and OLM described in 4th edition of Neville's oral and maxillofacial pathology [2]. OLP showed band-like lymphohistocytic infiltration immediately demolishing the basal cell layer of keratinized stratified squamous epithelium. OLM-dental showed the similar feature as OLP, but has scattered plasma cells. OLM-drug showed the similar feature as OLP, but has patched distribution. **Please see figure 2.**

The medical laboratory technologist (AK) sectioned specimens (4 um thickness, 3-5 mm length and 2-3 mm wideness) from paraffin tissue blocks, which were stored in the pathology archive of the OBS. She mounted 5 - 8 specimens on one glass slide. Therefore, 88 specimens were arranged in 14 slides. We named it "**Macro-Array Plate**". Totally 252 slides (14 x 18) wereprepared for IHC study. The process was conducted in the OBS laboratory.

A chief medical laboratory technologist (PC) conducted the IHC manual staining procedure (Capillary Gap Technology) in the IHC laboratory of Faculty of Medicine, Dalhousie University, Halifax, Canada. The oral pathologist (YG) read all IHC slides. Eventually 28 OLP and 45 OLM specimens plus one traumatic fibroma specimen were selected. Exclusion is uneven staining, unusual weak or absent staining, background or artifactual staining and inadequate amount of a specimen.

Antibodies and Optimal Dilution

Twelve primary antibodies and the antibody dilution buffer were purchased from Abcam (Toronto, ON, Canada M5W 0E9). Second antibody (mouse IgG) and reagents were bought from Inter Medico (Markham, ON, Canada L3R 6E9). All antibodies are able of reacting to human tissue. We toned the optimal antibiotic dilution in positive control specimens that were recommended by Abcam and published reference. Negative controls were obtained by replacing the primary antibody with mouse IgG. **Please see details in table 1.**

Antibody	T-bet	ST2	IL7R	HAND2	IL17B	IFNG	IL22	MCC	NKp46	CD3	CD8	CD4
Abcam Number	Ab150440	Ab25877	Ab118527	Ab60037	Ab198891	Ab9657	Ab18499	Ab111239	Ab214468	Ab16669	Ab4055	Ab133616
Primary antibody type	Rabbit Mono-clonal	Rabbit Poly-clonal	Rabbit Polyclonal	Rabbit Poly-clonal	Rabbit Polyclonal	Rabbit Polyclonal	Rabbit Poly-clonal	Goat Polyclonal	Rabbit Polyclonal	Rabbit Mono-clonal	Rabbit Poly-clonal	Rabbit Mono-clonal
Positive control	Lymph Node	Placenta	Lymph Node	Mouse Heart	Rat Spleen	Verrucous Carcinoma	Tonsil	Tonsil	Lung Carcinoma	Tonsil	Tonsil	Tonsil
Cellular location of IHC staining	Nucleus	Secreted & Cell Mem-brane	Secreted & Cell Mem-brane	Nucleus	Secreted & cell Mem-brane	Secreted	Secreted	Endo-plasmic Reticulum & Secreted	Cell Mem-brane	Cell Mem-brane	Secreted & Cell Mem-brane	Cell Mem-brane
Optimal titrated dilution	1:125	1:1600	1:100	1:50	1:200	1:500	1:250	1:1000	1:400	1:100	1:200	1:500

Table 1: Twelve antibodies and optimal titrated dilutions

Note: All primary antibodies react to human tissue. Positive controls are recommended by Abcam and published reference. Type of retrieval solution is Decloaker Citrate buffer solution (PH6.0). Second antibody is mouse probe. Detection system is MACH4 polymer and HRP polymer with DAB chromogen, but Dako envision polymer is applied for anti-mast cell chymase. Antibody dilution buffer was purchased in Abcam. T-bet: anti-T-bet/Tbx21; ST2: anti-ST2; IL-7R: anti-cytokine IL-7 receptor; HAND2: anti-HAND2-Carboxyterminal End; IL-17B: anti-cytokine IL-17 beta; INFG: anti-interferon gamma; IL-22: anti-cytokine IL-22; MCC: anti-mast cell chymase; NKp46: anti-NKp46; CD3: anti-CD3; CD8: anti-CD8; CD4: anti-CD4.

Immunohistochemistry Procedure

Antigen retrieval was processed in the Biocare Autoclave by PH 6.0 citrate buffer solution (DeCloaker) immediately after deparaffinization. The enzymatic digestion was conducted by Proteinase K. The procedure of protein block and endogenous enzyme block was achieved by Peroxidizer, Biocare's background Sniper, automation buffers (Triton-X-100 and Tween 20). The primary and secondary antibody were washed by automation buffer (1% BAS and 0.025% Triton X-100) after enough incubation time respectively. The detection system was MACH 4 probe plus HRP-Polymer with DAB (diaminobenzidine) chromogen. The counterstain was Hematoxylin.

Quantification of the Data

IHC slides were analyzed under an optical microscope (Olympus BX51 microscope; Olympus Optical Co., Tokyo, Japan) connected to a digital color camera/Q-Color 5 (Olympus). Images were obtained with 10x, 20x and 40x objectives UPLanFI (resolution: 2.75 mm), at a size of 2560 x 1920 pixels (resolution: 1 mm = 3000 pixels), under standard conditions. Pictures were taken from the whole slide to perform image analysis. The proportion of immune-positive cells is used to account scores if the staining located in the nucleus, on the cellular membrane or within the endoplasmic reticulum. The combinative semiquantitative scoring is applied for the secreted staining. The scoring outcome will be the combination of two types of accounting methods if antibodies have

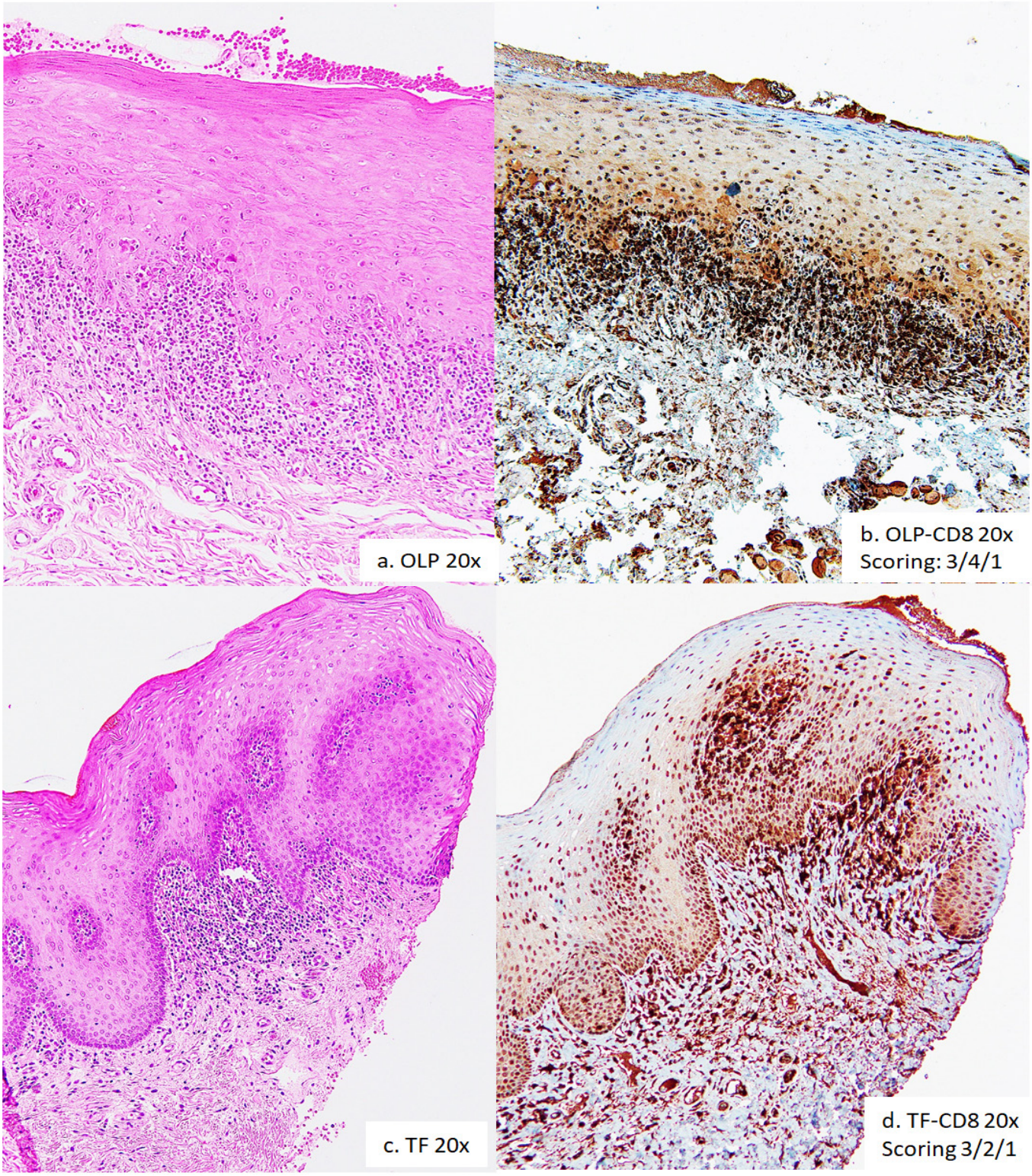

Figure 3. "Sandwich Scoring"

I. Scoring principle: Score 1: < 10% and/or mild stain; Score 2: 10-50% and/or mild-moderate stain; Score 3: 50-90% and/or moderate-strong stain; Score 4: >90% and/or strong stain.

II. Scoring protocol: Epithelial region; Subepithelial region; Submucosal region.

a. OLP (oral lichen planus). b. OLP CD8 IHC scoring: Epithelial region 3; Subepithelial region 4; Submucosal region 1.

c. TF (traumatic fibroma). d. TF CD8 IHC scoring: Epithelial region 3; Subepithelial region 2; Submucosal region 1.

two staining locations. The scoring principle is score 1: < 10% and/or mild stain; score 2: 10-50% and/or mild-moderate stain; score 3: 50-90% and/or moderate-strong stain; score 4: >90% and/or strong stain. The scoring procedure was conducted by two researchers (EL and TB) and an oral pathologist (YG) respectively for 18 times. The scoring protocol is to score the staining outcome to epithelial region, subepithelial region and submucosal region separately. Each case was marked by three scores. We called it **"Sandwich Scoring"**. **Please see figure 3.**

Analysis of the Data

The study size are 28 cases in OLP group, 16 cases in OLM-dental group, 14 cases in OLM-drug group and 15 cases in OLM-contact group. The final outcomes of immunopositive scores in each group was obtained by the mean value of all cases in that group. It is surprised that the standard deviation for the mean value in each group is one and the confidence level is 95%. **Please see details in table 2.** It means specimens in each study group showed the same immunopositive pattern. Therefore, we did the comparison and contrast based on patterns, rather than individual data. We call it **"Pattern-based Comparison"**. The pattern-based comparison has been used in the analysis of histopathological images for research and practice [4]. Our comparison baseline is the non-specific inflammation control. The significant difference between study groups in the epithelial region is calculated by Cohen's Kappa test.

Result

The consistency of the immunopositive staining is different between study groups. Oral lichenoid mucositis (OLM) demonstrated a patched staining distribution. Oral lichen planus (OLP) addressed a band-like staining distribution. Traumatic fibroma showed a nest-like staining distribution. The identified distribution is more prominent in CD3 and CD4 IHC staining. **Please see details in table 2 and figure 6.**

Heart-and neural crest derivatives-expressed protein 2 (HAND2) is encoded by HAND2 gene and is a transcription factor plays an important role in heart, limb and branchial arch development through Sonic Hedgehog (SHH) pathway [www.genecards.org]. A recent research found it reduced expression in breast cancer [5]. There is no significant difference between traumatic fibroma and four study groups in epithelial, subepithelial and submucosal regions. This result provided evidence that all study specimens didn't have a developmental abnormality and a malignant potential. **Please see details in table 2 and figure 4.**

Antibody/pattern	TF	OLP	OLM-dental	OLM-contact	OLM-drug
CD3	1/2/0*	1/4/1	1/3/1	1/3/1	1/3/1
CD4	1/2/0	1/4/1	1/3/1	1/3/1	1/2/1
CD8	3/2/1	3/4/1	3/3/1	3/3/1	1/3/1
NKp46	3/1/0	3/4/2	3/4/2	3/4/2	2/4/2
MCC#	0/0/1	0/0/2	0/1/2	0/0/1	0/1/2
INFG	1/1/0	1/3/1	1/3/1	1/2/1	1/1/1
IL-17B	4/2/0	3/4/1	3/4/1	4/4/1	3/4/2
IL-22	1/2/0	2/4/1	1/4/1	2/4/1	2/4/2
IL-7R	3/2/0	3/4/1	2/4/1	3/4/1	2/4/2
T-bet	4/1/0	3/4/1	3/4/1	4/4/1	3/4/2
ST2	4/2/0	3/4/1	3/4/1	4/4/1	3/4/2
HAND2	4/2/0	4/4/4	4/4/4	4/4/4	4/4/4
Pattern difference in epithelial region	Base line pattern	Weaker in IL-17B, T-bet, ST2; Stronger in IL-22.	Weaker in IL-17B, IL-7R, T-bet, ST2.	Stronger in IL-22.	Weaker in CD8, NKp46, IL-17B, IL-7R, T-bet, ST2; Stronger in IL-22.
Pattern difference in subepithelial region	Base line pattern	Stronger in all items, except MCC.	Stronger in all items.	Stronger in all items, except MCC.	Stronger in all items, except CD4, INFG.
Pattern difference in submucosal region	Base line pattern	Stronger in all items.	Stronger in all items.	Stronger in all items.	Stronger in all items.
Immunopositive distribution	Nest-like	Band-like distribution	Patched distribution	Patched distribution	Patched distribution

Table 2. Mean values of IHC outcome in oral lichenoid reactions

Note 1: *Scoring location: epithelial region/subepithelial region/submucosal region

Note 2: #MCC didn't showed the difference between groups in the immunopositive distribution.

Note 3: CD3: anti- CD3; CD8: anti-CD8; CD4: anti-CD4; NKp46: anti-NKp46; MCC: anti-mast cell chymase; INFG: anti-interferon gamma; IL-17B: anti-cytokine IL-17 beta; IL-22: anti-cytokine IL-22; IL-7R: anti-cytokine IL-7 receptor; T-bet: anti-T-bet/Tbx21; ST2: anti-ST2; HAND2: anti-HAND2-Carboxyterminal End. TF: traumatic fibroma; OLP: oral lichen planus; OLM-dental: lichenoid contact stomatitis from dental restorative materials; OLM-contact: contact stomatitis from topical chemical exposure (OLM-contact); OLM-drug: allergic mucosal reaction to systemic drug administration.

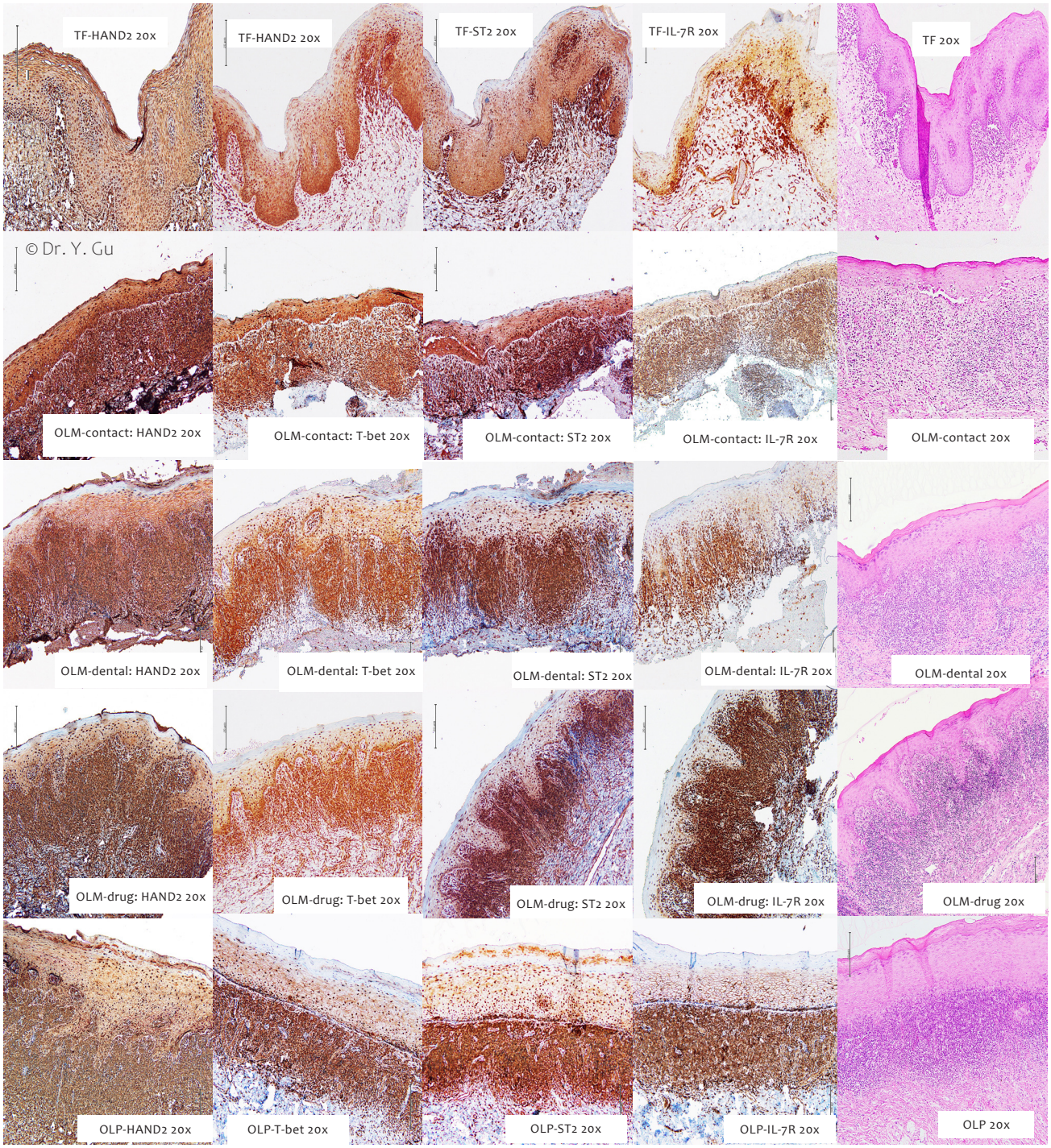

Figure 4. Immunohistochemistry (IHC) outcome of oral lichenoid reactions regarding to antibodies of HAND2, T-bet, ST2 and IL-7R, plus H&E images

Four study groups: oral lichen planus (OLP); mucosal reaction to systemic drug administration (OLM-drug); contact stomatitis from dental restorative materials (OLM-dental); contact stomatitis from topical chemical exposure (OLM-contact). Non-specific inflammation control: traumatic fibroma (TF). Four IHC antibodies: anti-HAND2-Carboxyterminal End (HAND2), anti-T-bet/Tbx21 (T-bet), anti-ST2 (ST2), and anti-cytokine IL-7 receptor (IL-7R).

The significantly stronger expression in subepithelial region and submucosal region of OLP and OLM compared with the expression in the non-specific inflammation control for all testing molecular markers is prominent, except MCC in OLP and OLM-contact, also CD4 and INFG in OLM-drug in the subepithelial region. **Please see details in table 2 and figure 5 and 6.**

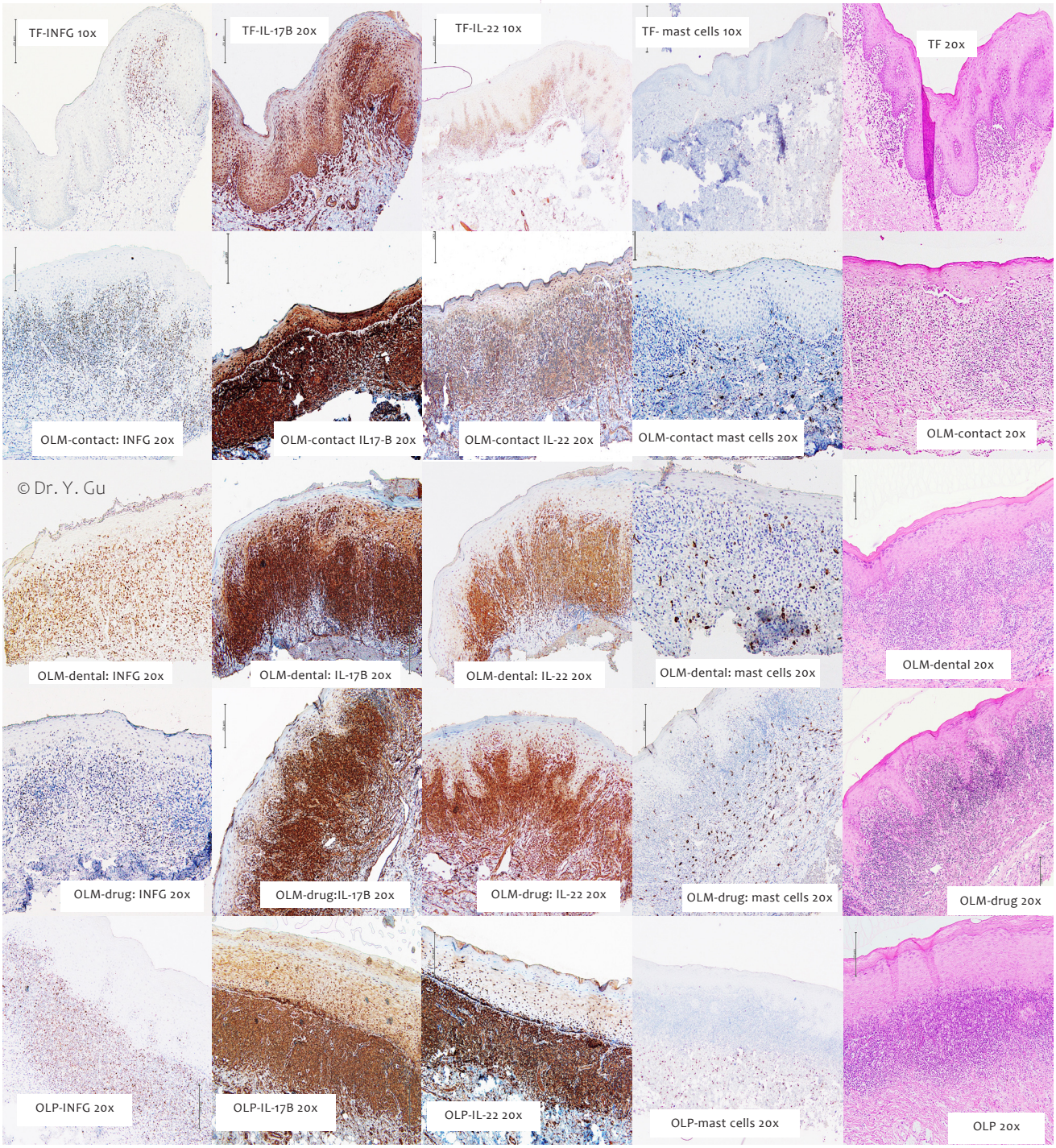

Figure 5. Immunohistochemistry (IHC) outcome of oral lichenoid reactions regarding to antibodies of INFG, IL-17B, IL-22 and MCC, plus H&E images.

Four study groups: oral lichen planus (OLP); mucosal reaction to systemic drug administration (OLM-drug); contact stomatitis from dental restorative materials (OLM-dental); contact stomatitis from topical chemical exposure (OLM-contact). Non-specific inflammation control: traumatic fibroma (TF). Four IHC antibodies: Interferon gamma (INFG), anti-cytokine IL-17B (IL-17B), anti-cytokine IL-22 (IL-22) and anti-mast cell chymase (MCC).

Common molecular signals of T cells are CD3, CD4 and CD8. The same expression level of CD3, CD4 and CD8 in the epithelial region of OLP, OLM and the non-specific inflammation control is identified. However, the significant weaker expression of CD8 (Kappa -0.073, 95% confidence interval from -0.286 to 0.140) in the epithelial region of OLM-drug is remarkable. **Please see details in table 2 and figure 6.**

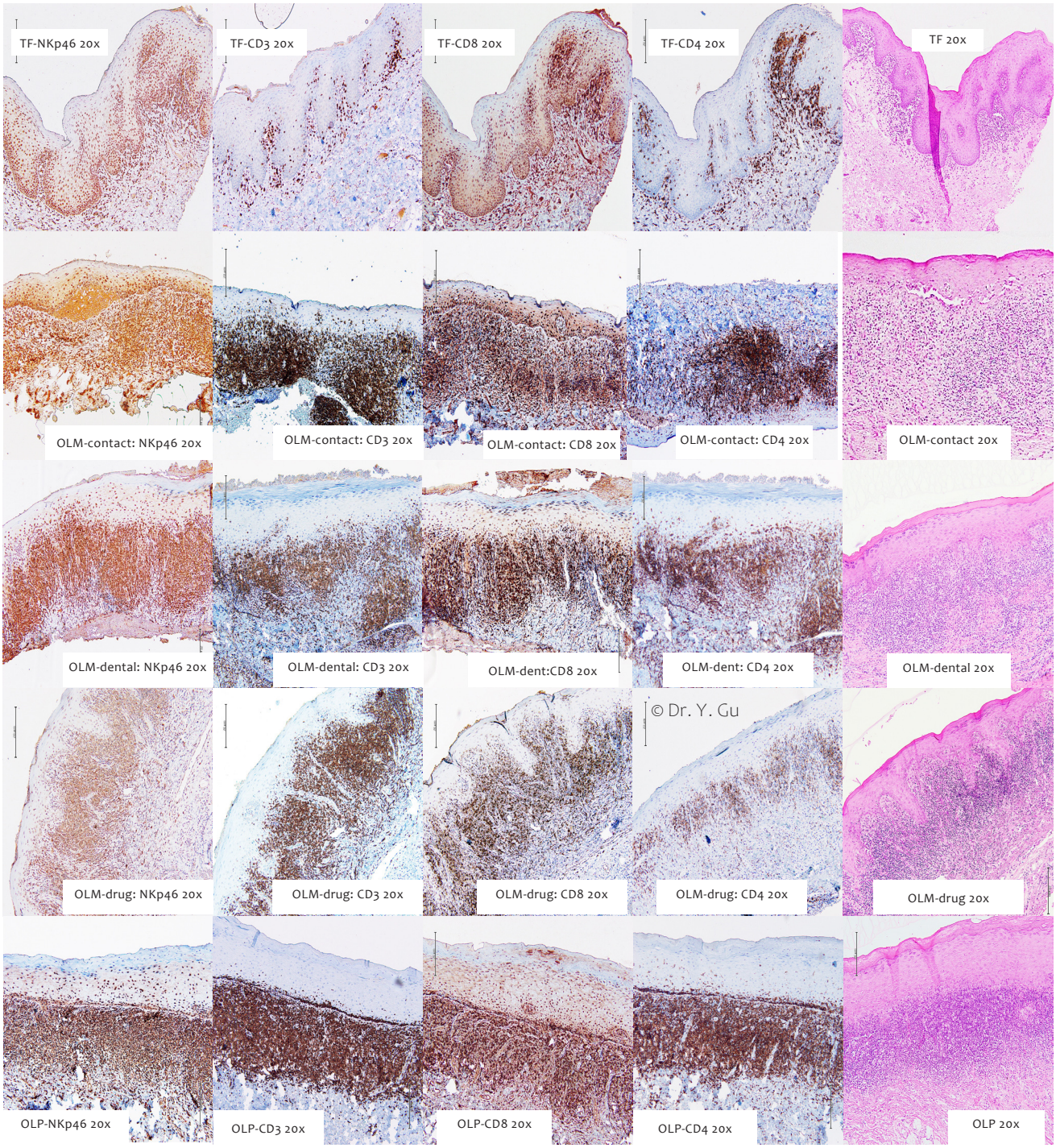

Figure 6. Immunohistochemistry (IHC) outcome of oral lichenoid reactions regarding to antibodies of NKp46, CD3, CD8 and CD4, plus H&E images.

Four study groups: oral lichen planus (OLP); mucosal reaction to systemic drug administration (OLM-drug); contact stomatitis from dental restorative materials (OLM-dental); contact stomatitis from topical chemical exposure (OLM-contact). Non-specific inflammation control: traumatic fibroma (TF). Five IHC antibodies: anti-NKp46 (NKp46), anti-CD3 (CD3), anti-CD8 (CD8), and anti-CD4 (CD4).

NKp46 and MCC are non-specific inflammatory cell markers. The same expression level of NKp46 and MCC in the epithelial region of OLP, OLM and the non-specific inflammation control is special. However, the significant weaker expression of NKp46 (Kappa -0.006, 95% confidence interval from -0.244 to 0.231) in the epithelial region of OLM-drug is found. **Please see details in table 2 and figure 5 and 6.**

Molecular markers of INFG, IL-17B and IL-22 reflex the activity of Th1 and Th17. The same expression level of INFG in the epithelial region of OLP, OLM and the non-specific inflammation control is reasonable. The significant weaker expression of IL-17B in the epithelial region of OLP, OLM-dental and OLM-drug (Kappa 0.078, 95% confidence interval from -0.166 to 0.321) is notable. However, the significant stronger expression of IL-22 in the epithelial region of OLP, OLM-contact and OLM-drug (Kappa -0.040, 95% confidence interval from -0.222 to 0.143) is impressive. **Please see details in table 2 and figure 5.**

Epithelial barrier markers of T-bet, ST2 and IL-7R are related to the normal response of innate lymphoid cells (ILCs). The significant weaker expression of T-bet and ST2 in the epithelial region of OLP, OLM-dental and OLM-drug (Kappa 0.078, 95% confidence interval from -0.166 to 0.321) is important. The significant weaker expression of IL-7R in the epithelial region of OLM-dental and OLM-drug (Kappa -0.008, 95% confidence interval from -0.234 to 0.217) is dominant. **Please see details in table 2 and figure 4.**

Discussion

Oral mucosal epithelial cells provide an intrinsic epithelial barrier for immune response. T-bet is a transcription factor encoded by TBX21 gene involving in developmental process, especially in the Th1 lineage, and controlling the INFG expression [www.genecards.org]. T-bet is considered as a molecular signal of innate lymphoid cell 1 (ILC1). T-bet was found expression on the epithelium of reproductive tract as well [6]. Serum stimulation-2 (ST2) is encoded by IL-1 receptor like 1 (IL1RL1) gene and involved in ILCs differentiation [www.genecards.org]. ST2 is IL-33 receptor expressed on inflammatory cells and epithelial cells and possibly involves in Th2 function [7]. IL-7R is encoded by IL-7R gene and plays a critical role V(D)J recombination during lymphocyte development [www.genecards.org]. IL-7R expresses on lymphocytic precursors, innate lymphoid cell 3 (ILC3) and antigen presenting cells [8]. Epithelial regions of OLM-dental and OLM-drug show significant weaker expression in T-bet, ST2 and IL-7R. In addition, the epithelial region of OLP displays significant weaker expression in T-bet and ST2, but the epithelial region of OLM-contact demonstrates a normal expression. The immunological epithelial barrier was weaker in OLM-drug, OLM-dental and OLP. However, it is normal in OLM-contact group.

Interferon gamma (INFG) is encoded by INFG gene and classified by ontology as cytokine activity [www.genecards.org]. INFG is produced by inflammatory cells and mucosal epithelium. In addition, IFNG promotes the Th1 differentiation first, and then Th1 produces INFG consequently [9]. IL-17B is encoded by IL-17B gene and classified by ontology as cytokine activity [www.genecards.org]. IL-17B stimulates monocytes to produce TNF-alfa and IL-1 beta, while epithelial cells and inflammatory cells produce IL-17B as well [10]. IL-17B has 29% similarity with IL-17A, which produced by Th17. IL-22 is encoded by IL-22 gene and classified by ontology as cytokine activity [www.genecards.org]. Th17 cells and ILC3 mainly produce IL-22, while the IL-22 receptor expresses on epithelial and stromal cells. The receptor-ligand interaction leads to activation of the transcription factor STAT3 in the target cell [11]. Epithelial regions of OLP, OLM-dental and OLM-drug exhibit significant weaker expression in IL-17B, while epithelial regions of OLP, OLM-contact and OLM-drug reveal significant stronger expression in IL-22. Therefore, results prove the immunological epithelial barrier is normal in OLM-contact group again.

CD8, a transmembrane glycoprotein binding to major histocompatibility complex (MHC)I, mainly expresses on cytotoxic T cells. CD4, a membrane glycoprotein binding to major histocompatibility complex (MHC) II, mainly expresses on T helper cells and macrophages. CD3 is a protein complex of T cell co-receptor. The epithelial region of OLM-drug manifests a significant weaker expression in CD8. The subepithelial region of OLM-drug only present with the same expression level of CD4 and INFG as non-specific inflammation control. The conclusion could be OLM-drug is less likely involved in cytolysis type of T-cell mediated hypersensitivity type IV.

NKp46 is encoded by NCR1 gene and related to pathways of major histocompatibility complex (MHC) I presentation and ILCs differentiation [www.genecards.org]. NKp46 mainly expresses on NK cells and NK-T cells [12]. Mast cells are sensitive to stimuli of neuropeptides (CGRP and Substance P), damage associated molecular pattern (DAMP) and pathogen-associated molecular pattern (PAMP). Those stimuli bind G protein-couple receptor (GPCR) or pattern recognition receptor (PRR) [13]. The degranulation of mast cells triggers innate immunity and aggravates adaptive immunity. The epithelial region of OLM-drug shows significant weaker expression of NKp46, while the subepithelial region and submucosal region of OLM-drug display a remarkable strong expression of MCC. The refractory inflammation of OLM-drug is less likely related to MHC I loss situation and is more likely related to mast cell mediated immune response.

Conclusion

1.Contact stomatitis from topical chemical exposure (OLM-contact) maintains a normal immunological epithelial barrier, while the weakness of immunological epithelial barrier exhibits a spectrum arranged in a descending order of OLM-drug, OLM-dental and OLP.

2.Mucosal reaction to systemic drug administration (OLM-drug) is less likely involved in MHC I alteration and/or loss related immune response and is most likely related to mast cell mediated inflammation.

3.The significant histopathological difference between oral lichenoid planus (OLP) and oral lichenoid mucositis (OLM) is CD4 distribution pattern in subepithelial region. OLM always shows a patched infiltration, while OLP only displays a band-like infiltration.

Disclosure of Conflicts of Interest

All authors declare they have no conflict of interest in any financial and personal relationship with other people or organization that could inappropriately influence their work.

Ethical Approval

All procedures performed in this study were in accordance with the principles of the Tri-Council Policy Statement Ethical Conduct for Research Involving Humans. This study was approved by Health Sciences Research Ethics Board of Dalhousie University with REB number 2016-4020.

Disclosure of Source of Funding

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Reference

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