BRIEF REPORT



What Do the Lips Say in Chronic Graft-Versus-Host Disease After Allogeneic Hematopoietic Stem Cell Transplantation? A Case Series

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ABSTRACT

Introduction: Chronic graft-versus-host disease (cGvHD) affects around half of allogeneic hematopoietic stem cell transplantation (alloHSCT) recipients, with frequent involvement of the oral mucosa and lip vermillion, that clinically may resemble other autoimmune and inflammatory conditions. Our objectives were to define the dermoscopic patterns of lip vermilion in patients suffering from cGvHD and to compare the presentation with previously published dermoscopic presentations of other disease entities presenting on the lip vermillion.

Methods: A group of 16 patients diagnosed with cGvHD was assessed clinically and dermoscopically. The dermoscopic descriptions were made according to recent consensus on terminology of non-neoplastic disorders.

Results: Dermoscopy of vermillion frequently revealed dotted vessels that were found in all patients, while linear vessels without bends or branches were seen in 10 of them (62.5%).

Anastazja Szlauer-Stefańska and Grażyna Kamińska-Winciorek contributed equally. Peripheral scale, mainly in white color (13/16, 81.2%) was often present. Most striking features were parallel and perpendicular white lines, found in all patients. Other structures included brown dots and blood spots that were present in 10 patients (62.5%). Four patients (25.0%) had blurred vermillion border and in 8 (50.0%) linear fissures or ulceration were found. Typical Wickham striae were found in 3 (18.8%) patients.

Conclusions: The dermoscopic features observed in cGvHD affecting lip vermillion warrant differentiation with inflammatory (lichen planus), autoimmune (lichen sclerosus, discoid lupus erythematosus), precancerous (actinic keratosis, leukoplakia), and neoplastic diseases (squamous cell carcinoma), among others. Dermoscopy of lip vermillion might be an additional tool to visualize diagnostic mucoscopic features of cGvHD (lichen planuslike, lichen sclerosus-like lesions).

Keywords: Dermoscopy; Mucoscopy; Graftversus-host disease; Lip vermillion; Lichen planus-like; Lichen sclerosus-like

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Key Summary Points

Why carry out this study?

Involvement of oral mucosa is frequent in patients after allogeneic hematopoietic stem cell transplantation; however, no dermoscopic presentations of changes in the lip vermillion were published so far.

The study investigated the dermoscopic patterns found in lip vermillion in patients with chronic graft-versus-host disease (cGvHD).

What was learned from the study?

The dermoscopic features resemble those described in inflammatory, autoimmune, precancerous, and neoplastic diseases.

Dermoscopy of lip vermillion might be an additional tool to visualize diagnostic features of cGvHD, helping to establish the diagnosis without the need for biopsy.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.14501277.

INTRODUCTION

Dermoscopy is a useful tool for rapid diagnosis and monitoring the response to treatment of various skin disorders, and the use of specific dermoscopy algorithms allows one to achieve high interobserver agreement [1, 2]. Inflammatory dermatoses were also the subject of dermoscopic assessment [3, 4], and its use was recently reported in patients with graft-versus host disease (GvHD) after allogeneic hematopoietic stem cell transplantation (alloHSCT) [5–8].

The use of dermoscopy has also spread to the assessment of oral mucosa in so-called mucoscopy [9] and the dermoscopic patterns of labial mucosa according to age and sex [10] were previously described. Assessment of mucous membranes has its technical limitations, and is not always feasible, because existing dermoscopes are not well designed to explore the mucosa [11]. On the other hand, lip vermillion, a unique entity covered by specialized stratified squamous epithelium, a border between the skin and mucosa, is readily accessible by dermoscope, without need for technical modifications.

Oral GvHD occurs in 45–83% patients who develop chronic GvHD (cGvHD) [12], and encompasses a wide spectrum of clinical presentations, paralleling autoimmune and inflammatory conditions [12]. Lip vermilion is one of the locations scored for the presence of erythema, lichenoid changes, erosions, and ulcers in the course of cGvHD [12].

Our study aimed to investigate if the characteristic dermoscopic patterns exist on the lip vermillion in patients with cGvHD and if they resemble previously published inflammatory and autoimmune conditions presenting in this location.

METHODS

Ethical Considerations

The study protocol was approved by the Bioethics Committee of Maria Sklodowska-Curie National Research Institute of Oncology, Gliwice Branch (KB/430 43/18). The study was performed in accordance with the Declaration of Helsinki. Informed consent for publication was obtained from all participants.

Study Design

In this case series study, 16 unselected consecutive patients aged over 18 years old, treated in the Bone Marrow Transplantation and Oncohematology Department in 2019, after alloHSCT with diagnosis of cGvHD according to National Institutes of Health (NIH) criteria [13], underwent clinical and dermoscopic assessment of lip vermillion. All dermoscopic images were captured and saved using a DermLite Cam (3Gen, LLC, Dana Point, California, USA) in polarized light, at tenfold magnification, and assessed independently by two study authorscertified dermoscopists (GK-W, AS-S). To compare the dermoscopic presentation with other diseases presenting on the lip vermillion we have performed the search in PubMed using the search terms dermoscopy OR dermatoscopy AND lip OR vermillion AND autoimmune OR inflammatory OR lichen planus OR lichen sclerosus OR discoid lupus erythematosus OR acitinic cheilitis (Table 2).

Statistics

Specific findings were considered present if both observers agreed. For the description of dermoscopic features, standardized terminology from recent dermoscopic consensus on non-neo-plastic disorders was used [14].

RESULTS

Details of the patients, including transplant and dermoscopic characteristics, are given in Table 1. Dotted vessels were noted in all patients, while linear vessels without bends or branches were seen in 11 of them (68.8%). Vessels were of unspecific (14/16, 87.5%) or clustered (2/16, 12.5%) distribution. Scale, mainly in white color (13/16, 81.2%), was distributed peripherally (10/13, 76.9%) or patchy (3/13, 23.1%). In all dermoscopic images white lines were found; most commonly they were parallel (14/16, 87.5%), sometimes accompanied by perpendicular or angulated lines. Other structures included brown dots (6/16, 37.5%), and blood spots were present in 10 patients (62.5%). Four patients (25.0%) had blurred vermillion border and in 8 (50.0%) linear fissures or ulceration were found. Typical Wickham striae were found in 3 (18.8%) patients.

DISCUSSION

Changes in the lip vermillion found in own observation in patients with chronic GvHD resemble lichen planus, lichen sclerosus, discoid lupus erythematosus, and actinic cheilitis (summary presented in Table 2). There is scarce literature on dermoscopic characteristics of lip vermillion in selected inflammatory or autoimmune dermatoses, mainly in the form of case reports or case series, that we discuss below.

Lichen Planus

Lichen planus on the lip has a specific sign-Wickham striae-which is considered to be a marker of active disease [15]. Various patterns of those shiny whitish structures were described, including reticular, linear, and circular [15]. Its pathogenesis is equivocal-it is explained by the increase in granular cell layer in the epidermis by some authors and to the focal increase in the epidermal activity by others [15]. Wickham striae are usually seen on violaceous background, often accompanied by scaling, with dotted and linear peripheral vessels [15]. In our cohort, similar structures were seen in three patients suffering from lichen planus-like chronic GvHD (one of them is shown in Fig. 1a, b).

Lichen Sclerosus

The white, linear, dense homogenous area in long-standing lesions of lichen sclerosus in dermoscopy was suggested to correlate with the fibrosis affecting the upper dermis seen in histology [16]. In our patients, linear, white homogenous areas in biopsy-proven lichen sclerosus-like cGvHD were found (Fig. 1c, d). Dermoscopy of some patients demonstrated parallel and perpendicular white lines (Figs. 1e, f, 2g, h).

Discoid Lupus Erythematosus

In a study concerning mucosal and labial discoid lupus erythematosus the most common

Table 1 Patients' characteristics								
Patient number, gender, age (years)	1, M, 52	2, M, 21	3, F, 28	4, F, 35	5, M, 34	6, F, 31	7, F, 47	8, F, 45
Primary disease	CLL	ALL	HL	HL	AML	HL	PMF	PMBCL
Type of transplantation conditioning	RD-PBSCT, Flu + TBI	RD-PBSCT, Ctx + TBI	URD-PBSCT, BeEAM	RD- PBSCT, BeEAM	URD- PBSCT, Bu + Ctx	RD-PBSCT, Be + Mel	RD-PBSCT, Flu + TBI	RD- PBSCT, Be + Mel
cGvHD NIH overall grading and organ involvement staging	Severe (mouth 3, lungs 2)	Severe (skin 1, mouth 3, eyes 1, GI tract 1)	Severe (skin 2, mouth 1, joints 2, eyes 1, lungs 2)	Moderate (mouth 1, liver 2)	Severe (skin 3, GI tract, liver 2)	Moderate (skin 1, eyes 1, mouth 1, liver 1)	Severe (skin 1, mouth 3, GI tract 1, genital tract 1)	Severe (eyes 2, mouth 1, lungs 2)
Scale (color)								
White	1	I	1	1	1	1	1	I
Yellow	I	I	I	I	I	1	I	I
Scale (distribution)								
Peripheral	I	I	1	1	I	1	1	I
Patchy	1	I	I	I	1	I	I	I
Other structures (color)								
White	1	1	1	1	1	1	1	1
Brown	1	I	I	1	1	1	I	I
Gray	I	I	I	I	1	I	I	I
Other structures (morphology)								
1. Diffuse, 2. focal	2	2	1	1	2	1	2	1

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1. Dots, 2. globules	I	2	I	1	1, 2	1, 2	I	I
Lines (1. parallel, 2. reticular, 3. angulated, 4. perpendicular, 5. unspecifically arranged)	-	1	1	1, 4	3, 4	1	1, 3, 4	Т
Vessels (morphology)								
Dotted	1	1	1	1	1	1	1	1
Linear (1. without bends or branches, 2. with branches, 3. curved)	1, 3	Π	1	Т	Т	1	ñ	Т
Vessels (distribution)								
 Reticular, 2. clustered, 3. unspecific 	ω	6	£	\mathfrak{C}	\mathfrak{C}	5	5	\mathfrak{C}
Other								
Color of the background (1. red, 2. violaceous, 3. pinkish)	ω	1	3	\mathfrak{C}	б	\mathfrak{S}	С	1
Other structures (1. blood spots, 2. blurred vermillion border, 3. Wickham striae, 4. linear erosions, 5. ulceration)	7	4, 5 5	1, 4	1, 3	4	-	1, 3	4, 5

Table 1 continued								
Patient number, gender, age (years)	9, F, 29	10, F, 4 8	11, F, <i>6</i> 7	12, M, 32	13, F, 55	14, F, 27	15, F, <i>4</i> 7	16, M, 46
Primary disease	MM	MM	AML	MDS/MPN	ALL	HL	AML	ALL
Type of transplantation conditioning	URD- PBSCT, Be + TMI	RD-PBSCT, Be + TMI	haplo-PBSCT, Ctx + Flu + TBI	RD-PBSCT, Flu + Mel	URD- PBSCT, Ctx + TBI	URD- PBSCT, Be + Mel	URD- PBSCT, Ctx + Bu	RD-PBSCT, Ctx + TBI
cGvHD NIH overall grading and organ involvement staging	Severe (skin 1, eye 2, lungs 3)	Mild (skin 1, mouth 1)	Severe (skin 3, GI tract 1, lungs 2)	Severe (mouth 3, skin 3, eyes 2, GI tract 3, lungs 3)	Moderate (skin 2, mouth 1, eyes 1)	Moderate (skin 1, mouth 1, eyes 1, GI tract, 1, joints 1)	Moderate (skin 1, mouth 2, eyes 2, joints 2)	Severe (skin 3, mouth 2 gut 1, eyes 1)
Scale (color)								
White	1	1	1	1	1	I	1	1
Yellow	1	I	1	I	I	I	I	I
Scale (distribution)								
Peripheral	1	1	1	1	1	I	1	I
Patchy	I	I	I	I	I	I	I	1
Other structures (color)								
White	1	1	1	1	1	1	1	1
Brown	I	I	1	1	I	1	I	1
Gray	I	I	I	I	I	I	I	
Other structures (morphology)								
1. Diffuse, 2. focal	1	1	1	1	1	1	1	1
1. Dots, 2. globules	I	I	1	1	I	1	1	2

Table 1 continued								
Lines (1. parallel, 2. reticular, 3. angulated, 4. perpendicular, 5. unspecifically arranged)	1, 4	1, 3	1, 3	1, 3, 4	1, 4	\sim	1, 4	1
Vessels (morphology)								
Dotted	1	1	1	1	1	1	1	1
Linear (1. without bends or branches, 2. with branches, 3. curved)		1	г	Т	I	I	I	-
Vessels (distribution)								
 Reticular, 2. clustered, 3. unspecific 	\mathfrak{c}	ŝ	ŝ	б	n	n	ŝ	1
Other								
Color of the background (1. red. 2. violaceous, 3. pinkish)	ŝ	7	<i>ლ</i>	ŝ	Э	ω	7	1
Other structures (1. blood spots, 2. blurred vermillion border, 3. Wickham striae, 4. linear erosions, 5. ulceration)	2, 4	1, 3, 4	7	1	4	1 ,2	1, 4, 5	-
<i>ALL</i> acute lymphoblastic leu <i>cGvHD</i> chronic graft-versus-l peripheral blood stem cell tra myeloproliferative neoplasm,	ıkemia, <i>AM</i> 10st disease, 11splantatio 11 <i>MM</i> mult	<i>L</i> acute myeloid <i>CLL</i> chronic lyr n from haploider iple myeloma, <i>1</i>	l leukemia, <i>Be</i> bendar nphocytic leukemia, <i>C</i> ntical donor, <i>HL</i> Hod <i>VIH</i> National Institu	mustine, <i>BeEAM</i> <i>Ix</i> cyclophosphar gkin lymphoma, ntes of Health,	bendamustine, nide, F female, <i>I</i> <i>M</i> male, <i>Mel</i> m <i>PMBCL</i> primar	etoposide, cytara 7/u fludarabine, C elphalan, <i>MDS/I</i> ry mediastinal B	lbine, melphalan 31 gastrointestinz MPN myelodyspl 3 cell lymphoma	<i>Bu</i> busulphan, ll, <i>haplo-PBSCT</i> astic syndrome/ <i>PMF</i> primary

myelofibrosis, RD-PBSCT allogeneic peripheral blood stem cell transplantation from related donor, TBI total body irradiation, TMI total marrow irradiation,

URD-PBSCT allogeneic peripheral blood stem cell transplantation from unrelated donor

	Literature	Patients with cGvHD
Lichen planus	Wickham striae, usually on violaceous background, often accompanied by scaling, with dotted and linear peripheral vessels [13]	Structures resembling Wickham striae were seen in three patients suffering from lichen planus-like chronic GvHD (one of them is shown on Fig. 1a, b)
Lichen sclerosus	White, linear, dense homogenous areas that correlate with the fibrosis affecting the upper dermis seen in histology [14]	Linear, white homogenous areas (Fig. 1c, d). Parallel and perpendicular white lines (Fig. 1e, f)
Discoid lupus erythematosus	Late lesions—telangiectasia and white structureless areas, brown pigment spots, blood spots, and erosions [15]	Brown dots, linear erosions, and blood spots were also frequently reported in our study (Fig. 1g, h)
Actinic cheilitis	Pale, flaking or scaly lips, areas of erythema, chronic ulcerations and erosions, white plaques, blurring of the lip vermillion border, and vermillion atrophy [16]	Scaling, white structures, blurred vermillion border, linear erosions, and ulceration (Fig. 2a–d)
Other features	Multiple yellow white spots resembling Fordyce spo lesions (histopathology revealed sclerotic-type cG	ots (Fig. 2e, f). Accompanied by exophytic mucosal vHD with GvHD-associated angiomatosis)
	Brown dots and parallel and perpendicular lines, ac	companying white lines (Fig. 2g, h)

Table 2 Comparison of dermoscopic features of lip vermillion in selected entities and our cohort

cGvHD chronic graft-versus-host disease

dermoscopic signs, present in over half of the patients, were follicular keratotic plugs and scales [17]. In early lesions they were accompanied by perifollicular white halos and in late lesions by telangiectasia and white structureless areas, with additional features present on the lip—brown pigment spots, blood spots, and erosions. Brown dots, linear erosions, and blood spots were also frequently reported in our study (Fig. 1g, h).

Actinic Cheilitis

Oncological vigilance is of extreme importance in patients after alloHSCT, and oral GvHD is a known risk factor of lip squamous cell carcinoma (SCC). SCC can be preceded by actinic cheilitis that may present in many forms, including pale, flaking, or scaly lips, areas of erythema, chronic ulcerations and erosions, white plaques, blurring of the lip vermillion border, and vermillion atrophy [18]. In our patients the following features were often found: scaling, white structures, blurred vermillion border, linear erosions, and ulceration (Fig. 2a–d).

Others

Dermoscopy of Fordyce spots, which may arise in healthy individuals, showed yellow lobules surrounded by nonarborizing vessels [19]. In one of our patients suffering from cGvHD, multiple yellow white spots occurred after transplantation, resembling Fordyce spots (Fig. 2e, f). These were accompanied by exophytic mucosal lesions. In this case histopathology revealed sclerotic-type GvHD with GvHD-associated angiomatosis.

Oral Involvement in cGvHD

Despite the progress in alloHSCT procedures, the prevalence of cGvHD continues to grow [20], and it remains one of the main causes of



Fig. 1 Clinical (a, c, e, g) and dermoscopic (polarized light, tenfold magnification) (b, d, f, h) presentations of lip vermillion in patients with chronic graft-versus-host disease (cGvHD). a (Patient 4). In the clinical picture focal hyperpigmentation and depigmentation areas and shiny whitish linear scarring-like structures were noted. **b** (Patient 4). Dermoscopy showed white peripheral scale, multiple diffuse brown dots, white parallel and perpendicular shiny lines. Dotted and linear vessels, blood spots, and Wickham striae are also visible. c (Patient 1). In clinical examination of atrophic lips focal hyperpigmented areas were seen. d (Patient 1). Dermoscopy revealed patchy white scale, parallel brown and white lines, dotted, linear without bends, and linear curved vessels of unspecific distribution, blurred vermillion border. e (Patient 12). Clinical presentation of dried, flaking lips with multiple brown hyperpigmented areas. f (Patient 12). Dermoscopy showed white peripheral scale, white and brown parallel, angulated, and perpendicular lines, brown dots, dotted and linear vessels. g (Patient 6). In the clinical picture dry lip vermillion, hyperpigmentation, and whitish areas were noted. h (Patient 6). Dermoscopy revealed white and yellow peripheral scale, diffuse brown and white parallel lines, brown dots, white globules, dotted vessels of unspecific distribution, and blood spots



Fig. 2 Clinical (a, c, e, g) and dermoscopic (polarized light, tenfold magnification) (b, d, f, h) presentations of lip vermillion in patients with cGvHD. a (Patient 13). In the clinical picture chapped lips were seen. b (Patient 13). Dermoscopy showed white peripheral scale, white diffuse parallel and perpendicular lines, dotted vessel of unspecific distribution, and multiple linear almost parallel erosions. c (Patient 8). Clinical presentation involved chapped lips and central linear ulceration. d (Patient 8). Dermoscopy showed short, white, diffuse parallel lines between numerous dotted and linear vessels, linear erosions, and ulceration. e (Patient 2). In the clinical picture whitish, cobblestone-like areas covering all surfaces of the upper lip, ulceration, and several linear erosions were observed. f (Patient 2). Dermoscopy revealed focal white globules as a predominant feature, dotted and linear vessels, linear erosions, and ulceration. g (Patient 5). In the clinical picture multiple, hyperpigmented foci were seen. h (Patient 5). Dermoscopy revealed white patchy scale, brown and gray dots, white globules, and white and brown perpendicular and angulated lines with dotted and linear vessels. Linear erosions are also visible

long-term mortality and morbidity for patients surviving for longer than 2 years after alloHSCT [21]. Oral cGvHD is clinically diagnosed by history, context, and clinical examination [12]. According to NIH criteria, lichen planus-like changes belong to diagnostic clinical signs for cGvHD, while erythematous and ulcerative changes are distinctive signs [13]. Oral lesions frequently accompany involvement of other organs and treatment is based on systemic therapy with local topical treatment including high-potency glucocorticosteroids and calcineurin inhibitors [12]. The differential diagnosis of oral changes in the late phase after alloHSCT includes cGvHD but also infectious and other immunological reactions such as Stevens-Johnson syndrome. Clinical history and exclusion of infection are of foremost importance. Histopathology may be not conclusive, as diffuse T cell infiltration was reported in the labial minor salivary glands and in the buccal mucosa in oral cGvHD, with other features including thickening of the epithelium, interface submucosal lymphocytic infiltrate, epithelial atrophy, and basal cell apoptosis and degeneration [12]. Such diffuse T cell infiltration has also been reported in autoimmune or chronic inflammatory diseases that clinically resemble cGvHD [12].

CONCLUSIONS

On the basis of the dermoscopic presentation, we found the following types of lip vermillion morphology in patients suffering from chronic GvHD: (1) lichen planus-like (with Wickham striae); (2) lichen sclerosus-like with predominance of linear, white homogenous areas; (3) resembling discoid lupus erythematosus with blood spots, brown dots, and erosions; (4) resembling actinic cheilitis with fissures and/or ulceration.

This case series presents the first insight into the dermoscopic features of lip vermillion in patients with cGvHD. The limitations of the observation include the small number of cases and lack of control group. Further prospective studies with dermoscopic pictures assessed by researchers blinded to diagnosis are needed to establish the diagnostic accuracy of dermoscopy of lip lesions in cGvHD.

All in all, while the clinical picture may be non-alarming, dermoscopy of the lip vermilion may show more, pointing to the diagnosis of cGvHD. Oral cavity involvement may be highly predictive of the presence of systemic cGvHD [12]; and if the diagnostic signs are present, histopathological examination is not needed to confirm the diagnosis of cGvHD [13]. Dermoscopy of lip vermillion might be an additional diagnostic tool that reveals those diagnostic features (lichen planus-like, lichen sclerosus-like lesions), sometimes subtle and not visible in naked eye examination, thus contributing important information to clinical assessment.

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Disclosures. Anastazja Szlauer-Stefańska and Grażyna Kamińska-Winciorek have nothing to disclose.

Compliance with Ethics Guidelines. The study protocol was approved by the Bioethics Committee of Maria Sklodowska-Curie National Research Institute of Oncology, Gliwice Branch (KB/430 43/18). The study was performed in accordance with the Declaration of Helsinki. The patients in this manuscript have given

written informed consent to publication of their case details.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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