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ORIGINAL ARTICLE

Cheilitis glandularis: clinico-histopathological diagnostic criteria

S Reiter[1], M Vered[2], N Yarom[2,3], C Goldsmith[1], M Gorsky[2]

[1]*Department of Oral Rehabilitation, The Maurice and Gabriela Goldschleger School of Dental Medicine, Tel Aviv University, Tel Aviv;* [2]*Department of Oral Pathology and Oral Medicine, The Maurice and Gabriela Goldschleger School of Dental Medicine, Tel Aviv University, Tel Aviv, Israel;* [3]*Oral Medicine Clinic, Department of Oral and Maxillofacial Surgery, Sheba Medical Center, Tel-Hashomer, Israel*

OBJECTIVES: To present a combination of clinical and histopathological criteria for diagnosing cheilitis glandularis (CG), and to evaluate the association between CG and squamous cell carcinoma (SCC).

MATERIALS AND METHODS: The medical literature in English was searched from 1950 to 2010 and selected demographic data, and clinical and histopathological features of CG were retrieved and analysed.

RESULTS: A total of 77 cases have been published and four new cases were added to the collective data. The clinical criteria applied included the coexistence of multiple lesions and mucoid/purulent discharge, while the histopathological criteria included two or more of the following findings: sialectasia, chronic inflammation, mucous/oncocytic metaplasia and mucin in ducts. Only 47 (58.0%) cases involving patients with a mean age of 48.5 ± 20.3 years and a male-to-female ratio of 2.9:1 fulfilled the criteria. The lower lip alone was most commonly affected (70.2%). CG was associated with SCC in only three cases (3.5%) for which there was a clear aetiological factor for the malignancy.

CONCLUSIONS: The proposed diagnostic criteria can assist in delineating true CG from a variety of lesions with a comparable clinical/histopathological presentation. CG in association with premalignant/malignant epithelial changes of the lower lip may represent secondary, reactive changes of the salivary glands.

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Keywords: cheilitis glandularis; diagnostic criteria; squamous cell carcinoma

Correspondence: Dr Shoshana Reiter, Department of Oral Rehabilitation, The Maurice and Gabriela Goldschleger, School of Dental Medicine, Tel Aviv University, Tel Aviv 69978, Israel. Tel: +972 3 6409305, Fax: 972 3 6409250, E-mail: shosh5@bezeqint.net
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Introduction

Cheilitis glandularis (CG) is a rare chronic inflammatory disease affecting the minor salivary glands. Its clinical signs include macrocheilia caused by swelling of the minor salivary glands, and mucous and/or purulent discharge through an enlarged ductal orifice. The most commonly affected site is the lower lip (Nico *et al*, 2010). Other intra-oral sites less commonly reported include the lower and upper lips simultaneously (Lourenço *et al*, 2007), both lips and the buccal mucosa (Lederman, 1994), the upper lip only (Matsumoto *et al*, 1989) and the hard palate (Williams and Williams, 1989). The term "stomatitis glandularis" is generally used when any mucosal site other than that of the lips is involved, (Williams and Williams, 1989).

Clinically, CG may resemble many other conditions. The differential diagnosis of CG includes multiple mucocele, chronic sialadenitis of the minor salivary glands, sialolithiasis of minor salivary gland, factitious cheilitis, actinic cheilitis, cheilitis granulomatosa, angio-oedema, and benign and malignant minor salivary gland tumours (e.g. cystadenoma, cystadenocarcinoma and mucoepidermoid carcinoma). It is quite possible that early reports have actually described lesions that were very similar and therefore they have been misdiagnosed as CG. The histopathological features of CG are non-specific and they include ectasia of the salivary ducts, accumulation of mucus in the lumen of the ducts, fibrosis of the gland, chronic sialadenitis, oncocytic metaplasia and mucous metaplasia (Musa *et al*, 2005). The non-specific histopathology of CG and the wide variety of possible clinical differential diagnoses highlight the diagnostic challenge posed by this lesion and the need for clear clinico-histopathological correlation for establishing the correct diagnosis.

Cheilitis glandularis has assumed to play a causative role in the development of an overlying epithelial malignancy. This belief was based on two publications from the mid-20th century, which reported overlying epithelial malignancies in 18–36% of the CG cases

(Touraine, 1950; Michalowski, 1962). However, afterwards, researchers assumed that the co-occurrence of CG and malignancy may be incidental (Rada *et al*, 1985), or that it may result from an additional exposure of the lower lip to different possible triggers of oral carcinomas such as the sun and toxic chemicals (Stuller *et al*, 1982; Stoopler *et al*, 2003; Nico *et al*, 2010). Musa *et al* (2005) concluded that further studies are needed to establish any possible association between CG and oral mucosal cancer. Indeed, the lack of clinical and histopathological diagnostic criteria for CG, in combination with the non-specific histopathological findings, and clinical resemblance to other disease entities might serve to explain the opposing views in these publications. As such, we aimed to recommend clinical and histopathological diagnostic criteria for CG based on a profound analysis of all the cases reported in the English literature between 1950 and 2010 together with additional four new cases from our clinic. The possibility of an association between CG and malignancy is also discussed.

Materials and methods

A PubMed search of the English literature from 1950 until 2010 has been conducted using the key words ''cheilitis glandularis'', ''apostematosa'', ''stomatitis glandularis'' and ''CG''. Four new cases from the files of the Oral Medicine Clinic at the School of Dental Medicine, Tel Aviv University, and the Chaim Sheba Tel Aviv University affiliated Medical Center were added. The data were analysed to establish CG diagnostic criteria based on clinical and histopathological findings to differentiate it from a wide variety of lesions with comparable morphological and histological characteristics.

Results

A total of 77 cases have been published and four new cases were added to the collective data. The most common clinical feature when reviewing these 81 cases of CG was the involvement of more than one anatomical site (90.1%). The presence of either mucoid or purulent discharge from the orifice of these lesions was the second most common finding (86.4%) (Figure 1). A histopathological description was available for 68 cases. No biopsy had been taken in six cases, and the biopsy results were not provided for additional seven cases. The complete range of non-specific findings within the salivary glands, consisting of the ectasia of the ducts and accumulation of mucus in the lumens, chronic inflammation and fibrosis, oncocytic metaplasia and mucous metaplasia was reported for only two lesions (Table 1, cases 28, 44). Although all the above-cited histopathological findings were given for an additional 20 cases, the type of metaplasia was not specified (Nico *et al*, 2010). Overall, the most common histopathological findings among those 68 cases were chronic inflammation (n = 54, 79.4%), followed by ductal ectasia (n = 51, 76.1%), mucous/oncocytic metaplasia (n = 34, 50.0%), mucin in the dilated ducts (n = 15, 22.1%) and fibrosis within the gland (n = 15, 22.1%).

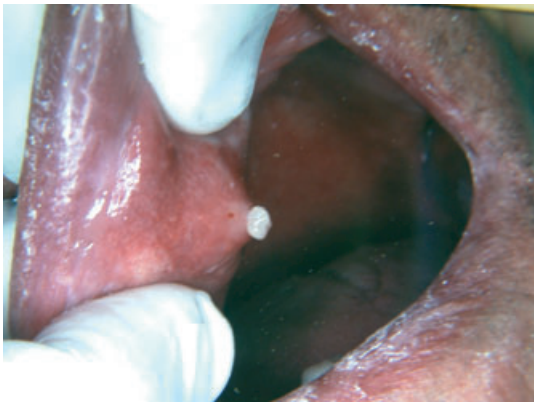

Figure 1 Thick mucus expressed from enlarged opening of affected minor salivary gland

Figures 2–4 display the various histopathological findings in the diagnosed CG lesions.

The combinations of clinico-histopathological diagnostic criteria proposed for the diagnosis of CG are presented in Table 2. Based on those criteria, establishment of a diagnosis of CG requires the identification of the two clinical criteria together with at least two out of four histopathological criteria. A review of all 81 collected cases believed as being of CG showed that only slightly over one-half of them (47 cases, 58.0%) met both the clinical and histopathological criteria as presented in Table 2. The relevant characteristics of these 47 cases are presented in Table 1. An analysis of these 47 cases revealed that the mean age of the patients was 48.5 ± 20.3 years (range 5–86), and that 35 (74.5%) were males and 12 (25.5%) were females (M:F ratio of 2.9:1). The CG predominantly involved the lower lip alone (n = 33, 70.2%), followed by involvement of both lips (n = 8, 17.0%) and the upper lip alone (n = 2, 4.3%). Involvement of multiple mucosal sites, including the buccal mucosa, was present in four cases (8.5%). No other intraoral mucosal sites such as the soft palate, floor of the mouth and ventral area of the tongue were cited.

Discussion

The lack of established correlations between clinical and histopathological findings may explain the variability of theories reported over the years regarding the aetiology of CG. Various conditions such as syphilis (von Volkman, 1870), hereditary hyperplasia of the minor salivary glands (Sutton, 1914), emotional disturbances (Woodburne and Philpott, 1950), chronic exposure to sun and wind (Oliver and Pickett, 1980; Swerlick and Cooper, 1984), chemical exposure (Everett and Holder, 1955), genetic abnormalities (Weir and Johnson, 1971), poor oral hygiene (Yacobi and Brown, 1989) and smoking (Everett and Holder, 1955) were implicated over the years as possible aetiological factors. Rada *et al* (1985) reviewed the relevant literature, in which 27 cases were included, and reported that the histopathological findings demonstrated widening of the ducts of the minor salivary glands in seven of 19 (37%) lesions, therefore concluding that CG is a disease of ductal

Table 1 A summary of 47 clinical cases, reported in the English literature (1950–2010), fulfilling the proposed diagnostic criteria of cheilitis glandularis

					Clinical features			*Histopathological findings*				
Case #	*Author*	*Age, years*	*Gender*	*Location*	*Multiple lesions*	*Discharge from lesion*	*Ductal ectasia*	*Chronic inflammation*	*Oncocytic metaplasia*	*Mucous metaplasia*	*Mucin in ducts*	*Salivary gland fibrosis*
1	Nico *et al*, 2010	26	M	LL	+	+	+	+	UT	UT	–	–
2		55	F	LL	+	+	+	+	UT	UT	–	–
3		33	M	LL	+	+	+	+	UT	UT	–	–
4		22	M	LL + UL	+	+	+	+	UT	UT	–	–
5		44	F	LL	+	+	+	+	UT	UT	–	–
6		20	M	LL + UL	+	+	+	+	UT	UT	–	–
7		63	M	LL	+	+	+	+	UT	UT	–	–
8		57	F	LL	+	+	+	+	UT	UT	–	–
9		42	F	LL	+	+	+	+	UT	UT	–	–
10		64	M	LL	+	+	+	+	UT	UT	–	–
11		56	M	LL	+	+	+	+	UT	UT	–	–
12		61	F	LL + UL	+	+	+	+	UT	UT	–	–
13		47	M	LL	+	+	+	+	UT	UT	–	–
14		65	M	LL + UL	+	+	+	+	UT	UT	–	–
15		69	M	LL	+	+	+	+	UT	UT	–	–
16		60	M	LL	+	+	+	+	UT	UT	–	–
17		72	M	LL	+	+	+	+	UT	UT	–	–
18		86	M	LL + UL	+	+	+	+	UT	UT	–	–
19		64	M	LL	+	+	+	+	UT	UT	–	–
20		52	M	LL	+	+	+	+	UT	UT	–	–
21	Andrade	12	M	LL	–	–	+	+	–	–	–	–
22	*et al*, 2009	23	M	LL	–	–	+	+	–	–	–	–
23	Stanton *et al*, 2008	62	F	LL	+	+	+	+	+	–	+	+
24	Lourenço	34	M	LL + UL	+	+	+	+	UT	UT	–	–
25	*et al*, 2007	51	M	LL	+	+	+	+	UT	UT	–	–
26	Erkek *et al*, 2007	39	M	LL	+	+	+	+	–	–	–	–
27	Musa *et al*, 2005	64	F	LL + UL	+	+	+	+	+	–	–	+
28	Stoopler *et al*, 2003	60	F	LL	+	+	+	+	+	+	+	+
29	Cannell *et al*, 1997	59	M	LL + UL + BM	+	+	+	+	+	–	+	+
30	Lederman, 1994	43	F	LL + UL + BM	+	+	+	+	–	–	–	+
31	Cataldo and Santis, 1993	32	M	LL	+	+	+	+	–	–	+	–
32	Yacobi and Brown, 1989	11	M	LL + UL	+	+	+	+	–	–	–	–
33	Matsumoto *et al*, 1989	63	M	UL	+	+	+	+	+	+	+	–
34	Winchester *et al*, 1986	56	M	UL	+	+	+	+	+	+	+	+
35	Rada *et al*, 1985	64	M	LL	+	+	+	–	–	+	–	–
36	Joshi and Dayal, 1984	45	F	LL	+	+	+	+	–	–	–	–
37	Stuller *et al*, 1982	40	M	LL	+	+	+	+	–	–	+	+
38	Epinette and Hurwitz, 1973	59	M	LL	+	+	+	+	–	–	+	–
39	Weir and	34	M	LL	+	+	+	+	–	–	+	+
40	Johnson,	11	F	LL	+	+	+	+	–	–	+	+
41	1971	5	M	LL	+	+	+	+	–	–	–	–
42	Doku *et al*, 1965	10	M	LL	+	+	+	+	–	–	–	–
43	Everett and Holder, 1955	41	M	LL	+	+	+	+	–	–	–	–
44	Case 1[a]	73	M	LL + UL + BM	+	+	+	+	+	+	+	+
45	Case 2[a]	77	M	LL	+	+	+	+	+	–	+	+
46	Case 3[a]	71	F	LL	+	+	+	+	+	–	+	+
47	Case 4[a]	62	F	LL + M	+	+	+	+	+	–	+	+

+, present; –, absent; UT, unknown type of metaplasia; LL, lower lip; UL, upper lip; BM, buccal mucosa.
[a]Current study.

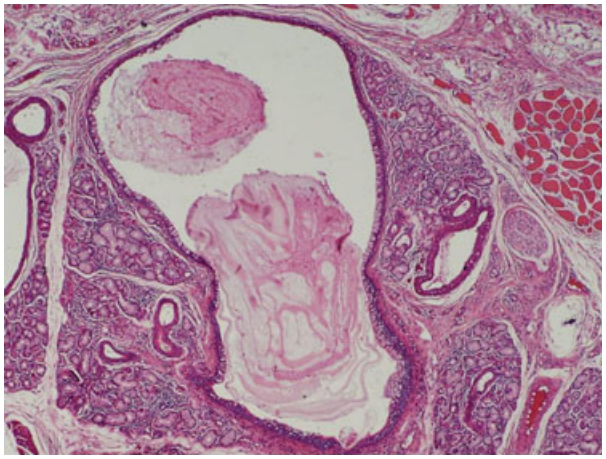

Figure 2 Ectasia of the salivary ducts and accumulation of mucus in the lumen of the ducts (original magnification ×40)

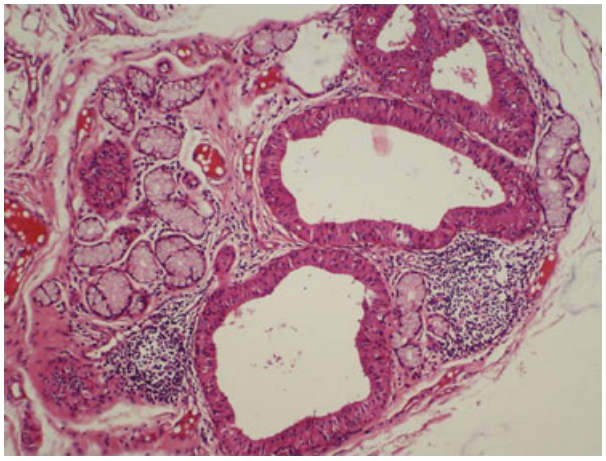

Figure 3 Chronic inflammation, fibrosis and oncocytic metaplasia of the ducts and some of the acini (arrow) (original magnification ×100)

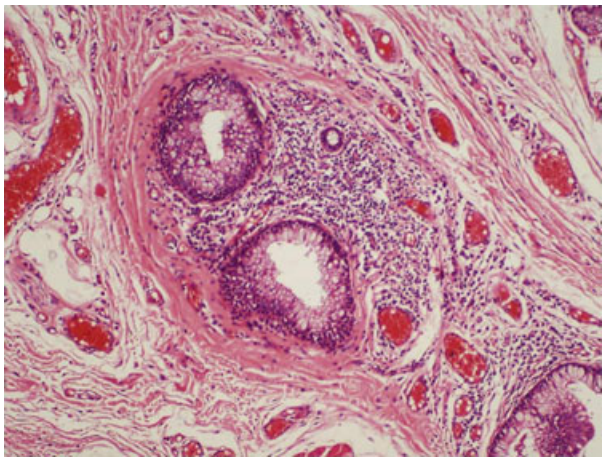

Figure 4 Mucous metaplasia of the minor salivary gland ducts (original magnification ×100)

ectasia. More recently, Lourenço *et al* (2007) and Nico *et al* (2010) suggest that CG originates in the epithelium rather than in the salivary gland, and that ultraviolet radiation may cause epithelial changes leading to alteration of the minor salivary gland duct orifices, with consequent salivary retention and inflammation leading to the clinical presentation of CG.

Table 2 Proposed clinical and histopathological diagnostic criteria for cheilitis glandularis

Clinical diagnostic criteria[a]	*Histopathological diagnostic criteria*[b]
Multiple lesions: involvement of more than one minor salivary gland	Sialectasia
Mucoid and/or purulent discharge (suppuration) from the apertures of the involved minor salivary glands	Chronic inflammation
	Mucous/oncocytic metaplasia (ducts and/or acini)
	Mucin in ducts

[a]Both mandatory.
[b]≥2 criteria must be present.

While the present study showed an average patient age of 49.8 years at the time of diagnosis, CG was actually diagnosed in all decades of life, and slightly more commonly seen in patients in their fifth to seventh decades of life. Noteworthy, seven of the reported patients were in their first to third decades of life (Table 1). Therefore, it is not unreasonable to consider that multiple aetiologies may be associated with the clinical presentation of CG.

The most commonly affected site of the CG lesion was the lower lip (95.7%). Involvement of the upper lip is, however, more common than previously thought (30.4%). A link to sun-induced epithelial changes should be considered when only the lower lip is involved, especially when actinic cheilitis is also present. On the other hand, when other intraoral sites are involved, for instance the upper lip and buccal mucosa, irritants such as smoking should be ruled out.

We placed special emphasis on searching for an association between CG and squamous cell carcinoma (SCC). Michalowski (1962) reported six cases of co-occurrence of CG and SCC. However, no one of them met either the clinical or the histopathological proposed criteria for establishing the diagnosis of CG (Table 2). Interestingly, the lesions in those six cases occurred in males aged 44–64 years, all farmers by profession with a history of prolonged sun exposure and all six lesions affected their lower lips. Indeed, Rada *et al* (1985) suggested that the co-occurrence of malignancy and CG may be incidental. Others have reported co-occurrence of CG and mucosal malignancy: one interesting case of CG and carcinoma of the lip was recently described in a 51-year-old albino male (Lourenço *et al*, 2007) (Table 1, case 25). The biopsy in that case showed actinic cheilitis with mild dysplasia associated with intense solar elastosis and superficially invasive SCC in several sections. The mucous glands were hypertrophic. Dilated and metaplastic excretory ducts were present together with mild chronic sialadenitis and congested blood vessels. Another case of concomitant CG and carcinoma of the lower lip was reported by Carrington (2006). However, the diagnosis of CG was based only on clinical findings and there was no histological confirmation. A case of CG in an HIV-

positive patient (Butt *et al*, 2007) did not meet the clinical criteria of multiple lesions, and histopathology showed periductal inflammation only, consistent with non-specific sialadenitis. The biopsy of CG in the lower lip of a 23-year-old male (Andrade *et al*, 2009) showed chronic inflammation and dilated ducts as well as the presence of many atypical epithelial cells and some mitoses. This lesion also failed to meet the current clinical diagnostic criteria for CG (i.e. the mandatory presence of multiple lesions and discharge from the minor salivary gland orifices). Nico *et al* (2010) evaluated 22 patients diagnosed with CG and reported two cases of superficially invasive carcinoma on the lower lip of two albino patients (one of them had already been reported by Lourenço *et al*, 2007) (Table 1, cases 5 and 25) and one case of carcinoma *in situ* on the lower lip (Table 1, case 15). These three cases did meet the diagnostic criteria suggested for the diagnosis of CG. In addition, all three cases had solar elastosis and two of them involved albinos. Thus, as suggested by Nico *et al* (2010), in the setting of predisposing aetiological factors for development of SCC of the oral epithelium (i.e. albino patients, long-time sun exposure), CG may represent secondary, reactive changes within the adjacent salivary glands rather than being a frank aetiological factor for the development of epithelial malignancy. The enlarged lip may in turn become more susceptible to actinic damage.

In conclusion, recommendations for clinico-histopathological diagnostic criteria for the diagnosis of CG are proposed. These criteria enabled us to identify cases of actual CG with greater precision, based on clear-cut characteristics. However, the assumption that CG may represent a clinical entity with multiple aetiologies including genetic disorders, actinic exposure and chemical irritants cannot be ruled out. The location of the lesions and age of the patient may assist in exploring the variously associated conditions. Rather than considering CG as a premalignant condition, the co-occurrence of lower lip CG lesions and actinic damage should alert for increased susceptibility to develop SCC of the lower lip. Further studies are needed for the validation of the current diagnostic criteria, exploration of different aetiologies for CG and for a conclusive establishment of an association between CG and malignancy.

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