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"Plasma cell gingivitis" encompasses multiple entities: a retrospective series of 37 cases

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Background: Plasma cell gingivitis is defined as gingival inflammation comprised of plasma cell infiltrates. This diagnostic criterion is non-specific and underlying mechanisms remain unknown. *Objectives*: We performed a multidisciplinary clinico-pathological review of cases previously identified as "gingivitis with plasma cell infiltrates", with assessment of putative contributing factors and critical appraisal of the final diagnosis. *Materials & Methods*: Cases previously identified as "gingivitis with plasma cell infiltrates" between 2000 and 2020 were included from archives from the GEMUB group, a French multidisciplinary network of physicians with expertise on oral mucosa. *Results*: Among the 37 included cases, multidisciplinary clinico-pathological review allowed differential diagnosis in seven cases (oral lichen planus n=4, plasma cell granuloma n=1, plasmacytoma n=1, and mucous membrane pemphigoid n=1). The remaining cases were classified as "reactive plasma cell gingivitis" (induced by drugs, trauma/irritation or periodontal disease) (n=18) or "idiopathic plasma cell gingivitis" when no contributing factors were identified (n=12). Clinico-pathological characteristics did not differ significantly between "reactive" and "idiopathic" cases, preventing us from identifying specific features of "idiopathic" plasma cell gingivitis. *Conclusion*: "Plasma cell gingivitis" is a polymorphous, non-specific entity with various aetiologies, of which the diagnosis requires multidisciplinary anatomo-clinical correlation for exclusion of secondary causes of plasma cell infiltration. Although our study was limited by its retrospective design, most cases of "plasma cell gingivitis" appeared to be associated with an underlying cause. We propose a diagnostic algorithm to properly investigate such cases.

Key words: gingivitis, plasma cell, plasma cell gingivitis, plasma cell mucositis

Plasma cell gingivitis (PCG) is defined as a gingival inflammation predominantly comprised of plasma cells, however, its diagnostic criteria, contributing factors and aetiological mechanisms remain poorly characterized. Most reports consist of single cases or small case series [1-3] except from a recent retrospective series of 45 PCG cases which constituted the first clinico-pathological study of this entity [4]. PCG appears to affect patients of any age [4] and displays polymorphous clinical features including erythema, oedema, hyperplasia, bleeding and ulceration [5], rarely associated with bone lysis [6, 7]. By definition, PCG harbours plasma cells in the chorion [5, 8] which are frequently mixed with other inflammatory infiltrates [4]. Given the non-specific diagnostic criteria of PCG, its nosological classification remains unclear. Initially, three types of PCG were described, as allergic, neoplastic and idiopathic PCG [8, 9]. Local triggering agents, either by irritation or hypersensitivity [10] have typically been reported in case reports (colocasia leaves [11], kat [12], spices [13], chewing gum [3] or toothpastes [10, 14, 15]) but are currently not reported in most PCG cases [4]. On the other hand, the link between PCG and dental plaque remains debated, as PCG has recently been classified as a non-plaque-induced gingivitis [16] whereas oral hygiene has been shown to significantly improve the disease [17]. Some PCG cases were found to be associated with plasma

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cell cheilitis [13. 18] leading to the concept of *orificial plasmacytosis* (*plasma cell mucositis*) which can affect the entire aerodigestive tract [5]. Given the scarcity and heterogeneity of reported data on PCG, as well as the absence of known contributing factors, the aim of our study was to describe clinical and histological features of cases identified as "plasma cell gingivitis", their putative causative factors and outcome. Given the non-specific diagnostic criteria of "plasma cell gingivitis", we performed a systematic multidisciplinary review of included cases for critical appraisal of final diagnosis.

Materials and methods

Study design, location and settings

This retrospective observational study was carried out among physicians from the GEMUB group, a multidisciplinary French network of practitioners with expertise in oral mucosal diseases [19]. Physicians retrieved cases of "plasma cell gingivitis" with no other specific diagnosis based on their clinical and pathological archived files, between 1st January 2000 to 31st December 2020. To this end, a working group (JCF, FP, PQ, JR, MS, AL) established a list of ADICAP codes to retrieve cases classified as "plasma cell gingivitis". The French ADICAP coding system is an accurate mnemonic alphanumeric thesaurus, currently used in France to classify histological subtypes [20]. The ADICAP codes used for this study included "plasma cell granuloma", "plasma cell inflammation", "plasma cell hyperplasia", "lymphocyte- and plasma cell-predominant inflammation" combined with "gingivitis", "oral system", "gum", and "oral cavity". Additional cases were retrieved by clinicians according to their medical archives. Eligible patients were sent an information datasheet requesting their non-opposition for use of their anonymized data and histological specimens. The study was approved by the French data protection authority (CNIL F20210325150131).

Inclusion and exclusion criteria

Cases were included if clinical and histological reports encompassed the standard definition of "plasma cell gingivitis" (*id est*, "gingivitis with plasma cell infiltration") not related to a specific disease and if histological material was available for analysis. Exclusion criteria were lesions identified as plasma cell granuloma according to the clinical and histological reports (an isolated exophytic nodule arising from gingiva with plasma cell infiltrates), extra-gingival lesions or non-specified site of biopsy, and patients who were opposed to the analysis of their data.

Clinical data

Data collected from files were related to: age; gender; alcohol or tobacco use; medications used at the time of diagnosis; clinical features of gingivitis (type and site); clinical images for review if available; presence of a local traumatic mechanical factor; presence of dental, bone and periodontal damage; cutaneous patch tests if performed; therapeutic strategies undertaken for the gingivitis; duration of follow-up; disease course including either chronic course (>three months duration), intermittent flare-ups or recovery.

Histological data

All haematoxylin and eosin-stained (H&E) histology slides were reviewed by two pathologists (FP, TK) who were blind to clinical data, with a standardized description of the epithelium (hyperplasia, erosion, ulceration, spongiosis, parakeratosis, exocytosis), chorion infiltrate (type, density and location of inflammatory infiltrates), Russel bodies (eosinophilic spherical or globular cytoplasmic inclusions which represent immunoglobin inclusion), and atypical cells. Perls staining for haemosiderin detection, Periodic Acid Schiff (PAS) staining and kappa/lambda immunohistochemistry were performed in all cases.

Expert agreement on diagnosis

Clinical and histological data, as well as follow-up data, were reviewed collegially by a multidisciplinary group composed of three oral surgeons (JCF, JR, AL), one dermatologist (MS) and one pathologist (FP) for definitive classification of included cases using the three following categories: "reactive plasma cell gingivitis" if underlying putative factors contributing to gingivitis (irritation, trauma, infection, drugs) were identified, "idiopathic plasma cell gingivitis" if no underlying factors were identified, and other specific diagnosis.

Statistics

Quantitative data are given as median, first and third quartiles (Q1-Q3) and/or ranges, and qualitative data in numbers and percentages. Qualitative data were compared using Fisher's exact test and quantitative data using non-parametric Mann-Whitney tests. Statistical analyses were performed using XL-stat software (Addinsoft France) and p values were set at 0.05.

Results

Clinical characteristics

Among the 45 cases retrieved from eight investigational sites (11 physicians) from the GEMUB group, 37 cases of "plasma cell gingivitis" were included (*figure 1*). Clinical characteristics are shown in *table 1*. Median age was 48 years (range: 9-86) and patients were predominantly female (70%). Gingivitis predominated on the maxilla (n=13, 43%) or on the maxilla and mandible (n=14, 47%). Lesions were raised (n=25, 86%), either focal (n=16, 50%) or multiple (n=16, 50%), involving marginal and attached gingiva (n=16, 47%) and were predominantly erythematous (n=32, 86%) whereas erosion/ulceration (n=6, 16%) or keratosis (n=3, 8%) were rare. No blisters were reported. A contributing factor of gingivitis was reported in 19 cases (51%), including

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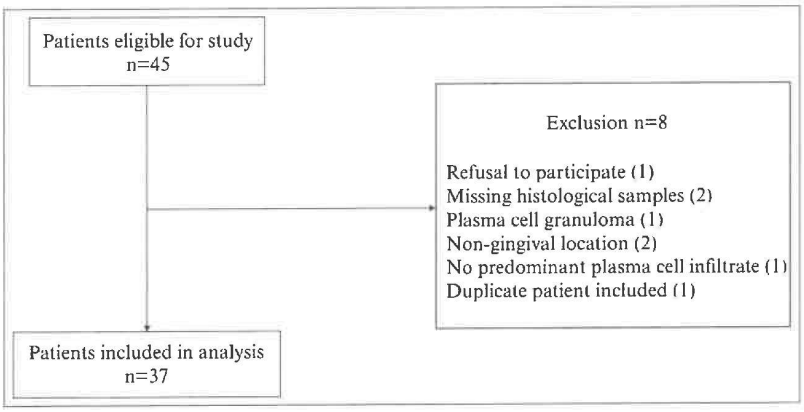

Figure 1. Flow chart.

tobacco and alcohol intoxication (n=4), local traumatic factor (dental prosthesis or braces) (n=8), underlying dental, and periodontal and/or bone damage (n=10). Calcium channel blocker intake, which is an aetiological factor of gingival enlargement, was reported in five cases (13%). Cutaneous patch tests had not been performed in the absence of anamnestic evidence of contact hypersensitivity.

Histological characteristics

Histological characteristics are shown in *table 2*. According to inclusion criteria, all samples showed a sub-epithelial infiltration of plasma cells. The epithelium mostly showed hyperplasia (n=18, 54%) or spongiosis (n=10, 30%) whereas erosion/ulceration was rare (n=6, 18%). Exocytosis was present in 75% of cases (n=25), composed of lymphocytes in 36% (n=12) and/or polynuclear neutrophils (PNN) in 57% (n=19) of cases. The infiltrate was mostly located in the papillary chorion (n=28, 85%) and was predominantly mixed with other immune cells (31 cases, 84%) including lymphocytes in 30 cases (97%). Case 26 showed monoclonal kappa production, however, other cases did not show any light chain predominance. Case 21 showed lichenoid features with inflammatory infiltration in the superficial chorion and vacuolar degeneration of keratinocytes in the basal layer. Haemosiderin deposits (evidenced by Perls staining) were very rare and no dysplasia was observed. Direct immunofluorescence (DIF) was performed in 11 cases (30%) and was subsequently positive in one additional biopsy performed a few months later in one patient (Case 21), displaying linear deposits of IgG and C3 along the basal membrane.

Clinico-pathological multidisciplinary classification of cases

After clinical and histological review of the 37 cases, seven were related to a specific diagnosis (*figure 2*). Diagnosis of OLP was retained in four cases, based on review of clinical images with evidence of lace-like lesions (n=1) (Case 6), on anamnestic data (presence of vulvovaginal lichen planus, n=2) (Cases 17 and 36), and on subsequent biopsies showing OLP (n=1) (Case 34). The other diagnoses were: plasma cell granuloma (based on an exophytic nodular morphology evidenced by clinical and histological review [Case 5]), mucous membrane pemphigoid (MMP) (based on positive DIF on one subsequent biopsy performed a few months later [Case 21]), and monoclonal plasma-cell plasmacytoma (based on monoclonal kappa production on IHC [Case 26]).
Among the 30 remaining cases, 18 gingivitis were classified as "reactive" to an underlying suspected factor: five were drug-related (Cases 1, 7, 10, 28 and 37) and 13 were linked to a local factor (trauma/periodontal disease) (Cases 8, 9, 11, 15, 22-5, 27, 29, 30, 31 and 35) (*figure 3*). Given the absence of underlying contributing factors, 12 cases of gingivitis were classified as "idiopathic" (Cases 2-4, 12-14, 16, 18, 19, 20, 32 and 33) (*figure 4, 5*).

Characteristic features of "reactive" versus "idiopathic" PCG

Clinical characteristics did not differ significantly between groups (*table 3*). Of note, patients with "idiopathic PCG" more frequently had extra-gingival extension (25% vs 0%, affecting the palate or vestibule), although this was not significant. Similarly, histology did not reveal discriminant patterns between groups. Parakeratotic epithelium was only observed in reactive cases (35% vs 0%), although this was not significant. The inflammatory infiltrates were located in the deep chorion only in reactive cases (27% vs 0%) whereas exclusive papillary location was only found in idiopathic cases (27% vs 0%) (p=0.037) (*table 3*).

Treatment and outcome

Follow-up data were available for 21 patients (11 idiopathic cases and 10 reactive cases) (median follow-up:12.0 months, Q1-Q3: 5.5-36.0). Of note, the patient with *a posteriori* diagnosis of gingival plasmocytoma (Case 26) was lost to follow-up with no further investigation available. Overall, 13 patients had a chronic disease course

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Table 1. Patient characteristics and clinical description of gingivitis.

N°	Sex	Age	Smoking	Alcohol *	Drugs inducing gingival enlargement	Local trigger**	Location	Unifocal / Multifocal	Marginal/ Attached	Flat / Raised	Clinical aspect
1	M	83	No	No	Amlodipine	Yes	Max, Mand	M	A	R	Verrucous, Bleeding
2	M	52	No	NA	No	No	NA	U	A,Ma	NA	Erythema
3	F	86	No	No	No	No	NA	M	A	NA	Erythema, E/U
4	F	60	No	No	No	No	NA	U	A	R	Erythema
5	F	24	NA	NA	NA	NA	Max	U	A	R	NA
6	F	63	No	NA	No	Yes	Max, Mand	M	A	F	Erythema, E/U, Bleeding
7	M	61	Yes	No	Amlodipine	No	Max, Mand	U	A,Ma	R	Erythema
8	M	59	Yes	NA	No	Yes	Mand	U	A,Ma	NA	Erythema
9	M	66	No	No	No	No	Max	U	A	R	NA
10	M	83	No	No	Amlodipine	Yes	Max	U	A,Ma	R	Erythema, Keratosis, E/U, Bleeding
11	F	56	No	No	No	No	Max	U	Ma	R	Erythema
12	F	78	No	No	No	No	Max	U	A,Ma	R	Erythema
13	F	32	No	No	No	No	Max	M	A,Ma	R	Erythema
14	F	69	No	No	No	No	Max	U	A,Ma	R	Erythema
15	F	25	No	No	No	Yes	Max	U	A,Ma	F	Erythema
16	F	40	No	No	No	No	Max, Mand	M	A,Ma	R	Erythema
17	F	60	No	Yes	No	Yes	Max	U	A,Ma	F	Erythema, Keratosis
18	F	52	No	No	No	No	Max	U	Ma	R	Erythema
19	M	45	No	No	No	No	Max, Mand	NA	A,Ma	R	Erythema, Bleeding
20	F	43	No	No	No	No	Max, Mand	M	A,Ma	R	Erythema
21	M	69	No	No	No	Yes	Max, Mand	M	A,Ma	R	Erythema, Bleeding
22	F	9	No	No	No	Yes	Max	U	A,Ma	R	Erythema, Bleeding
23	F	16	No	No	No	Yes	Max	U	A	R	Erythema, Bleeding
24	F	36	No	No	No	No	NA	U	A	R	Erythema
25	F	74	No	No	No	Yes	NA	NA	NA	R	Erythema
26	M	46	No	NA	No	No	Mand	NA	A,Ma	NA	Erythema, E/U
27	F	39	No	NA	No	No	Max, Mand	NA	NA	NA	Erythema
28	F	49	No	No	Nicardipine	Yes	Max, Mand	M	A	R	Erythema
29	F	20	No	No	No	Yes	Max	M	A	R	Erythema
30	H	29	No	No	No	No	Mand	U	Ma	R	Erythema
31	H	17	No	No	No	Yes	Max, Mand	M	A,Ma	R	Erythema

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N°	Sex	Age	Smoking	Alcohol *	Drugs inducing gingival enlargement	Local trigger**	Location	Unifocal / Multifocal	Marginal/ Attached	Flat / Raised	Clinical aspect
32	F	16	No	No	No	No	Max, Mand	M	A,Ma	R	Erythema
33	F	27	No	No	No	No	Max, Mand	M	A,Ma	R	Erythema
34	H	77	No	No	No	Yes	Max, Mand	M	A	NA	Keratosis
35	F	27	No	No	No	Yes	Max, Mand	M	A	NA	Erythema, E/U
36	F	44	No	Yes	No	Yes	NA	NA	Ma	NA	Erythema, E/U
37	F	45	No	No	Verapamil	No	NA	M	Ma	R	Erythema

A: attached gingiva; E/U: erosion/ ulceration; Ma: marginal gingiva; Max: maxilla; Mand: mandible; M: multifocal; NA : not available; U: unifocal; F: flat; R: raised.
**Daily alcohol consumption > two drinks for a woman and > three for a man.*
***Local trauma (prothesis), local dental, periodontal and/or bone damage.*

Table 2. Histopathological characteristics.

N°	Epithelium	Exocytosis	Congestive Papillary Chorion	Type of immune cell infiltration	Quantification of plasma cell infiltrate	Location of infiltration	Plasma cell secretion (kappa, lambda)	Deep Peri capillary infiltration	Russel body	DIF	PAS	Perls
1	PARA	PN	Yes	Pure PL	++	Deep	Mixed	Yes	Yes	-	-	-
2	Normal	No	No	Mixed (PL+Ly)	+	Pap + Deep	Mixed	Yes	Yes	NA	-	-
3	Normal	PN	No	Mixed (PL +PN)	++	Pap	Mixed	No	Yes	-/+	-	-
4	NA	NA	No	Mixed (PL+ Ly+PN)	++	Pap + Deep	Mixed	Yes	Yes	NA	-	-
5	H	No	No	Mixed (PL+Ly)	++	Pap + Deep	Mixed	Yes	No	-	-	-
6	NA	NA	No	Mixed (PL+Ly)	++	Pap + Deep	Mixed	Yes	Yes	-	-	-
7	H	Ly	No	Mixed (PL+Ly)	+	Pap + Deep	Mixed	Yes	Yes	NA	-	-
8	H	PN	Yes	Mixed (PL+ Ly+PN)	++	Pap + Deep	Mixed	Yes	Yes	NA	-	-
9	PARA	No	No	Pure PL	++	Pap + Deep	Mixed	NA	Yes	NA	-	-
10	ERO	Ly	No	Mixed (PL+Ly)	+++	Pap + Deep	Mixed	No	Yes	-	-	-
11	H	PN	No	Pure PL	++	Pap + Deep	Mixed	Yes	Yes	NA	+	-
12	SPO	Ly	Yes	Mixed (PL+Ly)	++	Pap	Mixed	No	Yes	-	-	-
13	H, SPO	PN	No	Mixed (PL+ Ly+PN)	+	NA	Mixed	NA	Yes	-	-	+

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N°	Epithelium	Exocytosis	Congestive Papillary Chorion	Type of immune cell infiltration	Quantification of plasma cell infiltrate	Location of infiltration	Plasma cell secretion (kappa, lambda)	Deep Peri capillary infiltration	Russel body	DIF	PAS	Perls
14	ERO, SPO	PN	Yes	Mixed (PL+ Ly+PN)	+++	Pap + Deep	Mixed	Yes	No	-	-	-
15	H, SPO	Ly	No	Mixed (PL+Ly)	+	NA	Mixed	NA	No	NA	-	-
16	SPO	Ly PN	No	Mixed (PL+Ly)	+++	Pap + Deep	Mixed	No	No	NA	-	-
17	NA	NA	No	Mixed (PL+Ly)	++	Pap	Mixed	No	Yes	-	-	-
18	Normal	Ly	No	Mixed (PL+Ly)	+++	Pap + Deep	Mixed	No	Yes	NA	-	-
19	H	Ly PN	No	Pure PL	++	Pap	Mixed	Yes	Yes	NA	-	-
20	H, SPO	Ly PN	Yes	Mixed (PL+Ly)	+++	Pap + Deep	Mixed	Yes	No	NA	-	-
21	PARA	PN	No	Pure PL	+++	Deep	Mixed	No	Yes	+	-	-
22	SPO	No	Yes	Mixed (PL+Ly)	+	NA	Mixed	NA	No	NA	-	-
23	Normal	Ly PN	No	Mixed (PL+ Ly+PN)	++	NA	Mixed	NA	No	NA	-	-
24	H, SPO	Ly	No	Mixed (PL+Ly)	++	Pap + Deep	Mixed	NA	No	NA	-	-
25	H, PARA	No	No	Mixed (PL+Ly)	+	Deep	Mixed	Yes	No	NA	-	-
26	H, ERO	PN	No	Pure PL	+++	Pap + Deep	Kappa	No	Yes	NA	+	-
27	SPO	No	No	Mixed (PL+Ly)	++	Pap + Deep	Mixed	Yes	Yes	NA	-	-
28	H, PARA	PN	No	Mixed (PL+Ly)	++	Pap + Deep	Mixed	Yes	Yes	NA	-	-
29	H, ERO	PN	No	Mixed (PL+Ly)	++	Pap + Deep	Mixed	Yes	Yes	NA	-	-
30	Normal	No	No	Mixed (PL+Ly)	+	Pap + Deep	Mixed	Yes	No	NA	-	-
31	H, ERO, PARA	PN	No	Mixed (PL+Ly+PN)	++	Deep	Mixed	Yes	No	NA	-	-
32	H	PN	No	Mixed (PL+Ly+PN)	++	Pap + Deep	Mixed	Yes	No	NA	-	-
33	H	Ly PN	No	Mixed (PL+Ly)	++	Pap + Deep	Mixed	NA	No	-	-	-
34	Normal	PN	No	Mixed (PL+Ly+PN)	++	Pap + Deep	Mixed	Yes	No	NA	-	-
35	H, PARA	Ly PN	No	Mixed (PL+Ly)	++	Pap + Deep	Mixed	No	Yes	NA	-	-
36	H, ERO, SPO	No	Yes	Mixed (PL+Ly+PN)	++	Pap + Deep	Mixed	Yes	Yes	NA	-	-
37	NA	NA	No	Mixed (PL+Ly)	++	Deep	Mixed	Yes	Yes	NA	-	-

H: hyperplastic; SPO: spongiosis; ERO: erosion, PARA: parakeratosis, PAS : Periodic Acid Schiff; PL: plasma cells, PN: polynuclear cells, Ly: lymphocytes, NA: not available, Pap: papillary, DIF : direct immunofluorescence.

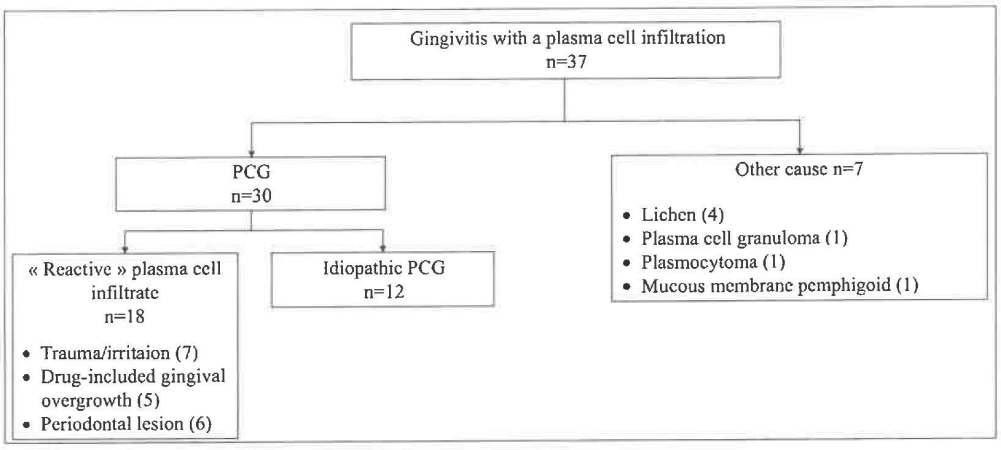

Figure 2. Final classification of cases of "gingivitis with plasma cell infiltrates" after multidisciplinary clinico-pathological review.

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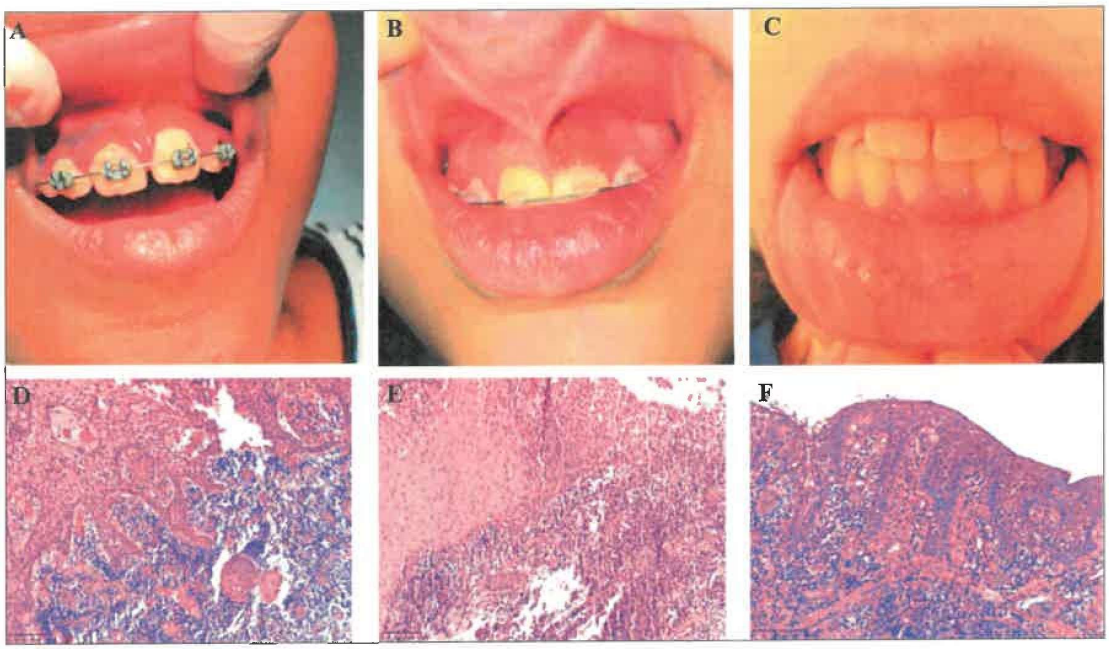

Figure 3. Representative cases of "reactive" plasma cell gingivitis. **A**) Case 22: a nine-year-old male with a lesion in the attached gum of the maxilla, which is focal, raised, erythematous and bleeding. **B**) Case 23: a 16-year-old female with a lesion in the attached gum of the maxilla, which is focal, raised, erythematous and bleeding. **C**) Case 24: a 36-year-old female with a lesion in the attached gum of the mandible, which is focal, raised and erythematous. **D-F**) H&E-stained (x20) histological samples of Case 22 (**D**) Case 23 and (**E**) Case 24 (**F**) showing a dense sub-epithelial infiltrate of plasma cells.

(seven idiopathic cases and six reactive cases). Patients with chronic "reactive" gingivitis had a history of calcium channel inhibitor intake (including after drug withdrawal) (Cases 1, 7 and 10) or dental braces (Cases 22 and 23). Oral hygiene and/or dental care was effective in 3/7 "idiopathic" cases and 2/5 "reactive" cases. Topical corticosteroids (clobetasol propionate cream or dipropionate betamethasone ointment, with a duration of 1-6 months) provided at least transitory efficacy in 4/6 "idiopathic" cases and 0/2 reactive cases. Topical tacrolimus, applied for two months in one patient with idiopathic PCG (Case 14), was not effective. Systemic drugs (dapsone for three months and doxycycline for three months), assessed in one patient with idiopathic PCG (Case 3), were not effective.

Discussion

In this retrospective review, we collected 37 cases identified as "gingivitis with plasma cell infiltrates" among

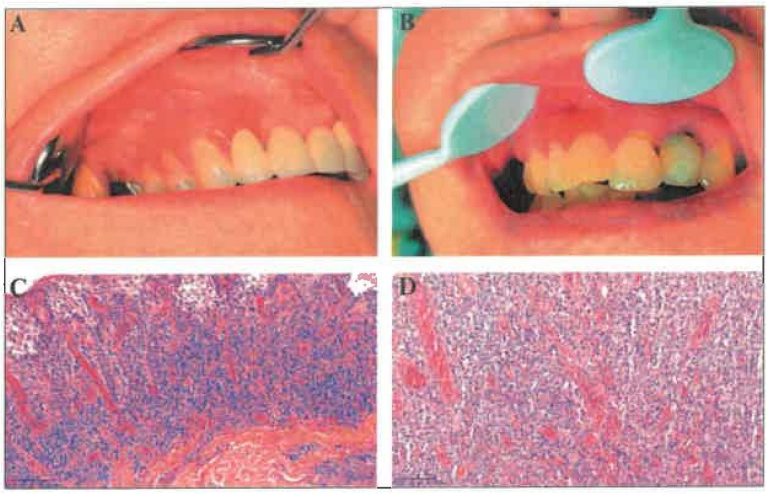

Figure 4. Representative cases of focal "idiopathic plasma cell gingivitis". **A)** Case 12: a 78-year-old female with a lesion in the marginal and attached gum of the maxilla, which is focal, raised and erythematous. **B)** Case 14: a 69-year-old female with a lesion in the marginal and attached gum of the maxilla, which is raised and erythematous and associated with an ulcerated lesion of the vestibule as a "kissing lesion". **C, D)** H&E-stained (x20) histological samples from Case 12 (**C**) and Case 14 (**D**) showing a dense sub-epithelial infiltrate of plasma cells.

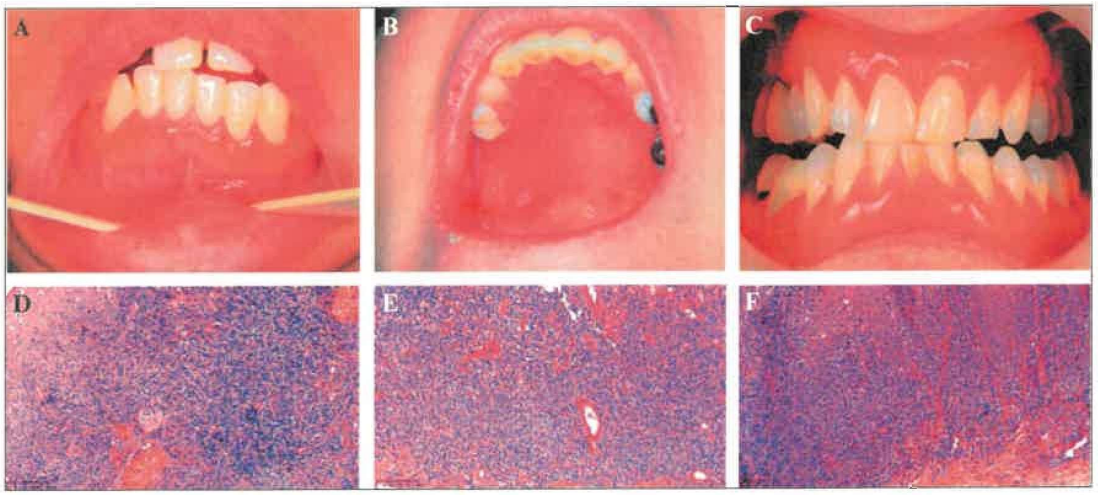

Figure 5. Representative cases of diffuse "idiopathic plasma cell gingivitis". **A)** Case 16: a 40-year-old female with a lesion in the marginal and attached gum affecting the maxilla and mandible, which is raised and erythematous. **B)** Case 18: a 52-year-old female with a lesion in the marginal gum of the maxilla extending onto the palate, which is focal, raised and erythematous. **C)** Case 19: a 45-year-old male with a lesion in the marginal and attached gum affecting the maxilla and the mandible, which is raised and erythematous and associated with bleeding. **C-F)** H&E-stained (s20) histological samples from Case 16 (**D**) Case 18 (**E**) and Case 19 (**F**) showing a dense sub-epithelial infiltrate of plasma cells.

eight French investigational sites over a 20-year period. A multidisciplinary clinico-pathological review led to a specific aetiology in seven cases whereas 18 were classified as "reactive" (due to the presence of a possible contributing irritative/traumatic factor, infectious process or drug intake) and 12 as "idiopathic" in the absence of such underlying factor(s). Overall, this case series highlights the diversity of conditions encompassed by the concept of "plasma cell gingivitis", which, in our opinion, is in line with the heterogeneity of previously reported cases [1-4]. Indeed, the clinical appearance in our patients was polymorphous with no specific feature. Anecdotally, we observed that idiopathic PCG was more likely to be associated with extra-gingival inflammation (palate, vestibular mucosa) and we observed one case of "kissing lesion" on the vestibular mucosa in contact with the gingival lesion (Case 14) (figure 4B), resembling "kissing" lesions typical of Zoon's plasma cell balanitis [21]. Of note, erosions/ulcers were seldom reported in our cases and

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Table 3. Clinical and histological characteristics between reactive and idiopathic PCG.

			Idiopathic PCG (n=12)	Reactive PCG (n=18)	p value **
Clinical Characteristics*		Female sex (n, %)	10 (83.3)	11 (61.1)	0.25
		Age, years (median, range)	48.5 (16.0-86.0)	42.5 (9.0-83.0)	0.50
		Gingival location			
		Attached gingival (n, %)	2 (17)	8 (50)	
		Marginal gingiva (n, %)	1 (8)	3 (19)	0.09
		Attached and marginal gingiva (n, %)	9 (75)	5 (31)	
		Extra-gingival extension (n, %)	3 (25)	0 (0)	0.05
		Oral location			
		Maxillary and mandibular (n, %)	5 (56)	6 (40)	
		Maxillary (n, %)	4 (44)	7 (47)	0.08
		Mandibular (n, %)	0 (0)	2 (13)	
		Focal (n, %)	5 (45)	9 (56)	0.70
		Raised (n, %)	9 (90)	14 (93)	1.00
		Erythema (n, %)	12 (100)	15 (83)	0.25
		Keratosis (n, %)	0 (0)	1 (6)	1.00
		Verrucous (n, %)	0 (0)	1 (6)	1.00
		Erosion/ulceration (n, %)	1 (8)	2 (11)	1.00
		Bleeding (n, %)	1 (8)	4 (22)	0.62
Histological Characteristics*	Epithelium	Hyperplasia (n, %)	5 (45)	10 (59)	0.70
		Spongiosis (n, %)	5 (45)	45 (30)	0.44
		Parakeratosis (n, %)	0 (0)	6 (35)	0.05
		Erosion (n, %)	1 (9)	3 (18)	1.00
		Exocytosis (n, %)	10 (90)	12 (71)	0.35
		Exocytosis of Ly (n, %)	2 (20)	4 (33)	
		Exocytosis of PN (n, %)	4 (40)	6 (50)	0.64
		Exocytosis of Ly and PN (n, %)	4 (40)	2 (17)	
	Chorion	Congestive papillary chorion (n,%)	3 (25)	3 (17)	0.66
		Pure plasma cell infiltration (n, %)	1 (8)	3 (17)	0.63
		Type of mixed infiltrates (n, %)			
		Plasma cell and Ly infiltrates	6 (55)	12 (80)	
		Plasma cell and PN infiltrates	1 (9)	0 (0)	0.26
		Plasma cell, Ly and PN infiltrates	4 (36)	3 (20)	
		Quantification of infiltration (n, %)			
		+	2 (17)	5 (28)	
		++	7 (58)	12 (67)	0.41
		+++	3 (25)	1 (5)	
		Location of infiltrates (n, %)			
		Papillary only	3 (27)	0 (0)	
		Deep only	0 (0)	4 (27)	0.037
		Papillary and deep	8 (73)	11 (73)	
		Deep peri-capillary infiltration (n, %)	6 (60)	11 (84)	0.34

Ly: lymphocytes. PN: polynuclear cells.
**Proportions were assessed among cases with available data.*
***Qualitative data were compared using Fisher's exact test and quantitative data with non-parametric Mann-Whitney*

we did not observe blisters or epithelial detachment on histological samples. By contrast, most patients of a monocentric series collected over a 20-year period in Naples, Italy [4] had "pure bullous PCG" (25 out of 45 PCG cases), a feature which had not been previously reported. This striking finding raises the question of differential diagnosis with other known causes of "desquamative gingivitis" [22]. Although no circulating auto-antibodies had been detected in the Italian series, four of these patients had a positive DIF, consistent with auto-immune blistering disease. Indeed, circulating auto-antibodies are usually not detectable in MMP located on oral mucosa [23] and the definitive diagnosis of MMP may require multiple and repeated biopsies for DIF analysis, as nearly a third of cases may be overlooked if relying on one single DIF analysis [24]. In our series, a patient with an initial diagnosis of PCG was reclassified as MMP after a DIF was performed during subsequent follow-up (Case 21) and another clinically suspicious case was finally classified as idiopathic PCG after two biopsies for DIF ruled out MMP (Case 3). In the absence of DIF available in 70%

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of cases of this series, it is therefore possible that some patients still classified as PCG may actually represent under-diagnosed cases of MMP. Similarly, differential diagnosis with OLP may be challenging as biopsies of erosive OLP were reported to harbour plasma cells in 80% of cases [25]. Such plasma cell infiltrates remain consistent with the diagnosis of OELP as long as characteristic lichenoid features, such as vacuolar degeneration of basal layer cells, are detected. In our series, four cases (6, 17, 34 and 36) were reclassified as OLP based on clinical and histological review, whereas the initial diagnosis of "PCG" was based on a biopsy where the epidermis was not representative; a typical pitfall in such erosive forms of OLP. Similarly, the series by Leuci et al. reported five patients with either clinical or histological "lichenoid" lesions, which may be classified as OLP. Overall, this highlights the challenge of the definitive diagnosis of PCG, and accordingly, the case review by a multidisciplinary group (dermatologist, oral surgeon and pathologist) assigned differential diagnoses in nearly one of five patients in our series. Interestingly, a systematic clinico-pathological correlation of cases of "plasma cell balanitis" led to a specific diagnosis in a similar proportion of cases [26], in line with the non-specific feature of mucosal infiltration by plasma cells.

Although the aetiology of PCG remains unclear, a triggering factor had been reported in earlier case reports involving either mechanical trauma [27] or localized hypersensitivity reaction [2, 11, 13, 14, 28, 29]. Although there was no anamnestic evidence of contact hypersensitivity according to clinical files of patients from our series, none of them had systematic cutaneous patch testing, preventing us from establishing a definite conclusion regarding the role of contact hypersensitivity in their gingivitis. On the other hand, we found at least one putative contributing factor (irritation, trauma, infection, drugs) in 18 out of 30 cases. Whether tobacco may trigger or worsen PCG remains unknown as no information on smoking habits is available in previous reports [4, 5], however, the contrast between the rarity of PCG and the large prevalence of tobacco use worldwide makes its role unlikely as a sole factor. Periodontal lesions were reported in two cases: a case of plaque-induced gingivitis with inflammatory border on the marginal gingiva (Case 27) and a case of local periodontitis with inflamed free gingiva associated with oedema of the papillae and alveolar bone loss (Case 11). Of note, the two paediatric cases from our series had a dental appliance (Cases 22 and 23), both displaying a chronic disease course despite oral hygiene (with poor compliance) and topical corticosteroids. The role of traumatic triggers, including presence of braces, had not been assessed in the previous series of 11 paediatric cases of PCG [17]. Finally, calcium channel inhibitor intake was reported in five of our patients. Calcium channel inhibitors are well known by oral practitioners to induce gingival overgrowth which is typically characterized by abundant hyperplastic connective tissue and epithelium with excess amorphous extracellular matrix. Cases of "amlodipine-induced plasma cell gingivitis" have previously been described [30], which likely represent drug-induced gingival overgrowth or plaque-induced gingivitis associated with gingival overgrowth. This highlights the need for exhaustive drug listing and withdrawal of potential culprit drugs when managing patients with features of PCG. Overall, 60% of our cases were finally classified as "reactive" PCG (drugs, irritation, trauma, infection). In line with this, plasma cell genital mucositis, such as Zoon's vulvitis or balanitis, have been associated with numerous underlying factors including trauma, maceration, chronic infection and hormonal changes, whereas circumcision is the definitive curative treatment of Zoon's balanoposthitis, arguing for a chronic irritative mechanism [31, 32]. Similar to our findings, the clinico-pathological analysis of 45 cases of "plasma cell balanitis" revealed that plasma cells actually predominate in infiltrates in only half of cases, mostly mixed with lymphocytes and neutrophils. Overall, such findings and the results from our study do not support a primary causative role for plasma cells in the pathogenesis of these diseases – these infiltrates rather represent a marker of non-specific, long-lasting, reactive mucosal inflammation [26].

Although therapeutic management and follow-up data of our patients were sparse, oral hygiene measures were effective in nearly half of cases. The effectiveness of oral hygiene in our series - which mostly consisted of a single session of surfacing/scaling - was rather low compared to more stringent protocols with several treatment sessions [17]. In another series, oral hygiene coupled with the use of topical corticoids was effective in 44% of cases [4]. In our series, topical corticosteroids were effective in most idiopathic cases, but none of the reactive cases. Regarding second-line therapies, efficacy of topical ciclosporin [27], topical tacrolimus [33] or immunemodulatory medications [4] have previously been reported, but we did not observe efficacy of tacrolimus, dapsone or doxycycline in refractory patients in our series.

The limitations of this study are due to its retrospective nature, with no standardized investigation (no systematic DIF examination or patch testing) or standardized treatment. In addition, in this retrospective review of cases, we identified potential triggers, but we could not definitively conclude on their causal role as an exclusion test was not systematically performed. It is, however, plausible that a significant proportion of gingivitis with plasma cell infiltrates can be either given a specific diagnosis after thorough investigation and repeated biopsies or be reactive to a local factor. Overall, the prevalence of "idiopathic" PCG was rare in this cohort, and more importantly, such cases did not display any discriminant clinical or histological characteristic that would allow a definite diagnosis of this condition. As previously suggested for plasma cell mucositis of the genitals, we may even speculate that PCG is not a true disease but seems to be a non-specific response to a triggering factor. As such, a diagnosis of "idiopathic PCG" should be retained only after systematic exclusion of various aetiologies of gingivitis with plasma cell infiltrates, as illustrated in the decisional algorithm proposed by the working group (*figure 6*). ■

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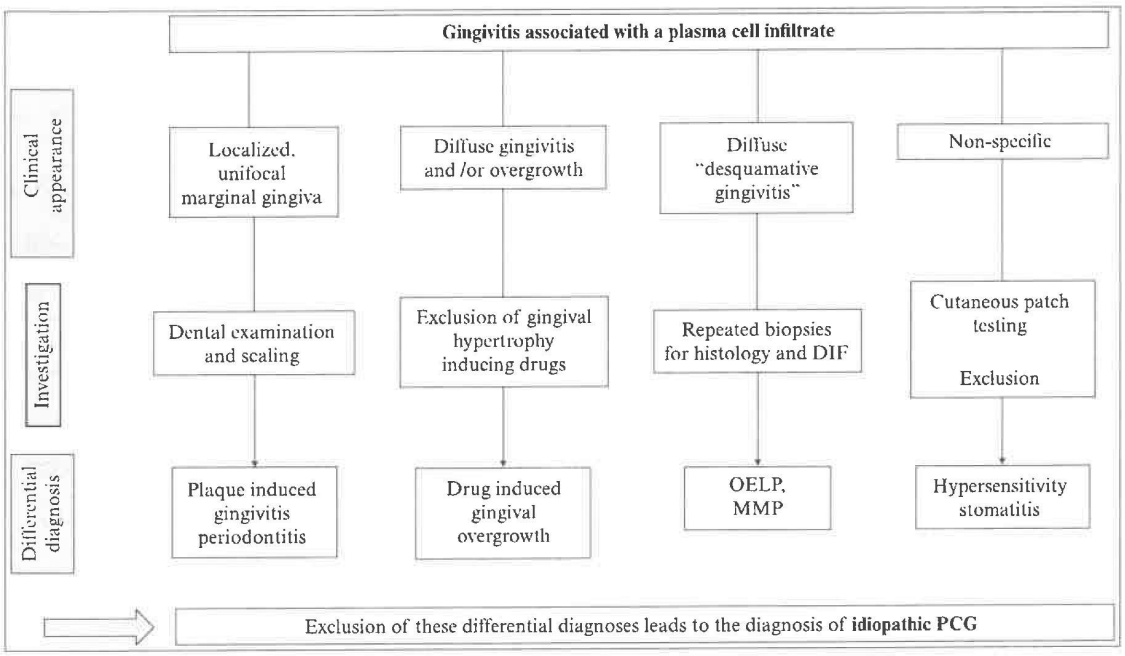

Figure 6. Diagnostic algorithm of cases of gingivitis with plasma cell infiltrates. OELP, Oral Erosive Lichen Planus; MMP, mucous membrane pemphigoides; DIF, direct immunofluorescence.

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Conflicts of interest: none.

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