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Review Article

Ligneous Gingivitis a Systematic Review

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Abstract

Objective: Ligneous gingivitis (LG) is an uncommon disease caused by plasminogen deficiency with fibrin deposition, which affects principally the conjunctiva of the eyes. A systemic review of reported cases and case series was undertaken to evaluate this disease.

Methods: Searches of detailed databases were performed. The variables were demographics, treatment, follow-up, location, histopathological findings, symptoms and plasminogen test results.

Results: 49 cases were identified; LG was most frequently seen in white females (68.4%). The average age was 20.0 years, for males 17.1 years and for females was 20.9 years. The main symptom was pain with (40.8%), followed by painless presentation with (20.4%). The most common sign was bleeding (32.3%). Clinically, both upper and lower gingiva where most commonly evident in 49% of the cases, followed by the lower gingiva only with (18.4%). The mean size was 2.7cm. The presence of concurrent ligneous conjunctivitis was (69.4%). The average for plasminogen activity test was 24.7 mg/mL. The recurrence was 59.2% and the mean follow-up was 18.9 months.

Conclusion: The diagnosis was difficult to establish, there is not standard treatment, and recurrence is common. For the oral clinician this disease needs to be addressed in the differential diagnosis of gingival oral lesions.

Keywords: Plasminogen deficiency; Fibrinolysis; Gingival hyperplasia; Ligneous gingivitis; Ligneous periodontitis.

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Introduction

Ligneous gingivitis (LG), a rare disorder which is characterized by generalized gingival enlargement [1], with possible periodontal tissue destruction [2], that may cause loss of teeth [3] and occurs as a part of a systemic disorder that involves mainly the eye (ligneous conjunctivitis) [4], which has been the most common clinical manifestation of the condition in 80% of cases [5]. Extraocular signs of this disease, include involvement of mucosal surfaces including the middle ear, nasopharynx, vocal cords, gingiva, larynx, tracheobronchial tree, kidneys, and the female genital tract [6]. Lesions are often inflammatory and painful and can compromise organ function, resulting in cases life-threatening conditions such as renal and respiratory failure (e.g., tracheobronchial lesions) in certain cases [7]. LG occurs due to plasminogen deficiency (hypoplasminogenemia), which compromises fibrin clearance during minor trauma or infection, promoting thrombosis and delayed tissue repair, leading to pseudomembranous mucosal lesions [8,9].

There are 2 types of hypoplasminogenemia:

- Type I deficiency: It is the deficiency of normal plasminogen (hypoplasminogenemia) quantitatively, and
- Type II deficiency: It is a deficiency of normal abnormal plasminogen (dysplasminogenemia) levels qualitatively [10].

LG is almost exclusively present in patients with type 1 hypoplasminogenemia [9,10]. The most common genetic defect found in patients with type I plasminogen deficiency is the K19E mutation, in 34% of the cases, located on chromosome 6q26-27 [5]. The "ligneous" word used may replace normal mucosa that refers to a wood-like consistency of a substance [11]. It is more prevalent in the European or Turkish population [12], mainly due to a high rate of marriage between relatives in the past [13]. However, various cases have been reported worldwide [14-17]. LG commonly develop in younger individuals; nevertheless adult-onset symptoms have been reported in some patients [3]. Histology shows eosinophilic amyloid like material deposits in the sub-epithelial connective tissue [1,18]; positive for fibrin accumulation, between inflammatory cells and fibroblasts [19]. Concerning treatment, little success has been reported, combinations of topical heparin, topical corticosteroids, chlorhexidine rinses, oral hygiene care, surgery and systemic tetracycline have been attempted with no significant improvement [20]. This is the first systematic review which summarizes studies published in English describing LG in the oral area, with emphasis on radiographic features, demographic data, gender, clinical, race, and plasminogen blood test, histopathology, treatment, and follow-up.

Materials and methods

A systematic review of the literature of LG was performed. The protocol was registered in the National Institute for Health Research PROSPERO, International Prospective Register of Systematic Reviews (registration number CRD-310053). IRB approval was not necessary because only a literature search was done, and non-human subject research was conducted.

Search strategy

A PubMed/Scopus/Science-direct search was performed using the search term 'oral ligneous gingivitis", and "oral ligneous

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periodontitis". A systematic review was carried out according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses). Also, manual search was made. The results included human subjects, only for oral presentation, other anatomic sites with oral presentation, the English was used as language only, and publications were analyzed. The analyses were carried from publications of 14 different countries, most of them from Europe.

Selection criteria

Data was collected from the studies with individuals suffering from LG. Exclusion Criteria included: cadaveric studies, animal studies, not English language, letters to the editor, not including oral lesion, and studies deemed non-diagnostic by the authors. Two investigators (A.P.L. and L.M.) independently performed the search review to determine that all appropriate articles were included in the analysis. Any disagreements were resolved through discussion with all authors.

Data extraction

The variables were for demographics, follow-up, treatment, sample size, study type, year, author, symptoms, histopathology, and plasminogen test results. Data analysis was performed using Microsoft Excel 2018 (Microsoft corp., Redmond, Washington, USA).

Data analysis

The analysis was performed using the Statistical Package for the Social Sciences (SPSS) software, version 20.0 ©Copyright IBM (SPSS Inc., Chicago, IL, USA).

Results

Searches identified a total 59 papers, and after final analysis according to the inclusion criteria 27 papers were acceptable (Figure 1).

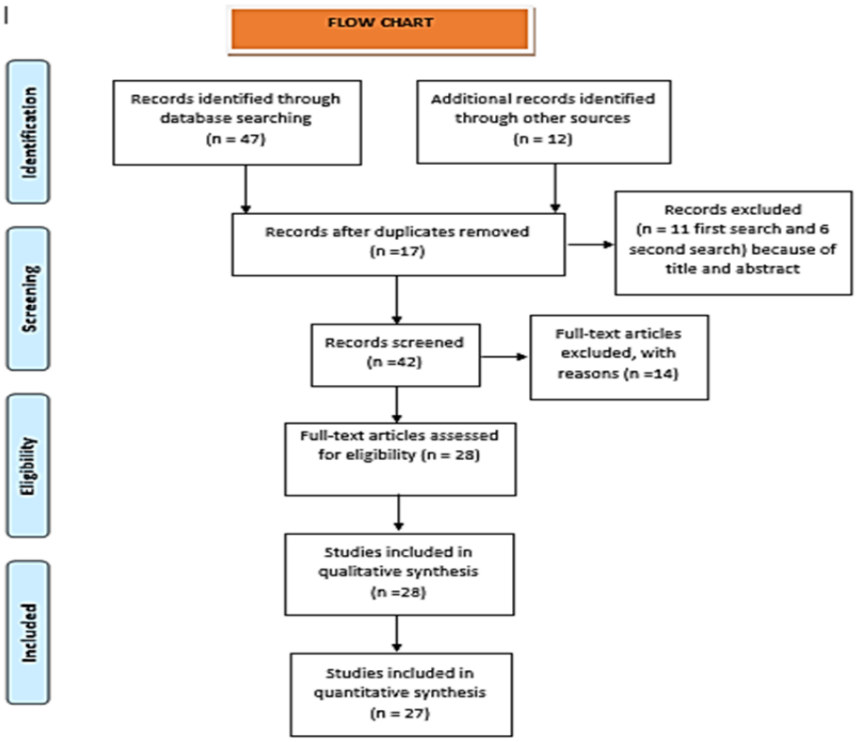

Figure 1: Flow chart.

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There were 21 case reports [10,14-21,23,24,26,27,30-33,38-41], and six were case series [1,2,8,9,34,35]. Variables included sex, age, lesion localization, clinical presentation, symptoms, diagnosis, other organs affected outside the mouth, treatment, plasminogen test results, histopathology, follow-up, and country of the study. A descriptive analysis was carried out to record the data and variables. Many papers did not report data for all the variables. The strength of evidence of the included articles was assessed with an aggregate level of evidence 3b oxford analyze. (Table 1) Concerning the missing data, for each of the variables studied with the Listwise deletion method, when some cases had missing values of a particular variable; only cases with all or almost all variables in the analyses where used.

Year	Author	Study Type	Cases(n)	Level of evidence	Country
2011	Cha S[18]	Case report	1	3a	USA
2020	MacPherson M[10]	Case report	1	3a	Canada
2019	Malthiery E[40]	Case report	1	4	France
2019	Sartori MT[30]	Case report	1	3b	Italy
2017	Ertas U[31]	Case report	1	4	Turkey
2006	Naudi KB[38]	Case report	1	4	England
2001	Scully C[2]	Case series	6	3b	England
1991	Diamond JP[26]	Case report	1	4	England
2007	Toker H[19]	Case report	1	4	Turkey
2007	Kurtulus I[20]	Case report	1	3a	Turkey
2006	Pierro VS[17]	Case report	1	3a	Brazil
2003	Suresh L[39]	Case report	1	3a	USA
1999	Günhan O[9]	Case series	3	3a	Turkey
1997	Gokbuget AY[1]	Case series	5	3b	Turkey
2009	Fine G[16]	Case report	1	3a	USA
2004	Baykul T[27]	Case report	1	4	Turkey
2009	Chi AC[14]	Case report	1	3b	Turkey
2015	Neering SH[21]	Case report	1	4	Germany
1973*	Frimodt-Moller J[41]	Case report	1	4	Denmark
2007	Scully C[32]	Case report	1	4	England
2009	El-Darouti M[15]	Case report	1	4	Egypt
2014	Galeotti A[24]	Case report	1	4	Italy
2020	Sadasivan A[23]	Case report	1	3a	India
2011	Kurtulus I[33]	Case report	1	3b	Turkey
1987*	Hidayat AA[35]	Case series	1*	3b	USA
2018	Shapiro AD[34]	Case series	3	3a	Norway
2018	Kızılocak H[8]	Case series	9	3a	Turkey

Table 1: Oxford analyses for case reports, case series studies, with country of origin.

Demographics

Sex: For the 49 patients, 77.6% (n=38) were females and 22.4% (n=11) were males (Table 2).

Age: The average was 20 years, ranging from 1 year to 66 years. The mean age for males was 17.1 years and for females was 20.9 years (Table 2).

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Race: Data from 34 patients were calculated, out of all white was the most common race with 63.3% (n=31), where 68.4% (n=26), were females, followed by black patients with 6.1% (n=3), in 30.6% (n=15) of the cases, the race was not reported (Table 2).

Family descent: Data was available for 39 cases, of whom 53.1% (n=26) were Turkish descendants, and 52.6% (n=20) of those were females. Italian descendants made up 8.2% (n=4). Family descents was not available in 20.4% (n=10) (Table 2).

	FEMALE 77.6%(N=38)	**MALE 22.4%(N=11)**	**TOTAL SAMPLE SIZE 100% (N=49)**	
AGE (YEARS)	**Mean ± SD (Min/Max)** 20.9 ± 16.1 (1/66)	**Mean ± SD (Min/Max)** 17.1 ± 10.4 (3/33)	**Mean ± SD (Min/Max)** 20 ± 14.9 (1/66)	**[CI95%]** [15.8 – 24.2]
RACE	**FEMALE 100% (n=38)**	**MALE 100% (n=11)**	**100% (n=49)**	
WHITE	68.4% (n=26)	45.5% (n=5)	63.3% (n=31)	[49.8 – 76.8]
BLACK	2.6% (n=1)	18.2% (n=2)	6.1% (n=3)	[-0.6 – 12.8]
NO REPORT	28.9% (n=11)	36.4% (n=4)	30.6% (n=15)	-
FAMILY DESCENDENT				
TURKISH	52.6% (n=20)	54.5% (n=6)	53.1% (n=26)	[39.1 – 67.1]
ITALIAN	7.9% (n=3)	9.1% (n=1)	8.2% (n=4)	[0.5 – 15.9]
USA	7.9% (n=3)	0%	6.1% (n=3)	[-0.6 – 12.8]
ENGLAND	7.9% (n=3)	0%	6.1% (n=3)	[-0.6 – 12.8]
SPAIN	0%	9.1% (n=1)	2% (n=1)	[-1.9 – 5.9]
EGYPT	2.6% (n=1)	0%	2% (n=1)	[-1.9 – 5.9]
INDIA	0%	9.1% (n=1)	2% (n=1)	[-1.9 – 5.9]
NO REPORT	21.1% (n=8)	18.2% (n=2)	20.4% (n=10)	-
SYMPTOMS				
PAIN - SORENESS	42.1% (n=16)	36.4% (n=4)	40.8% (n=20)	[27 – 54.6]
PAINLESS LESION	23.7% (n=9)	9.1% (n=1)	20.4% (n=10)	[9.1 – 31.7]
NO REPORT	34.2% (n=13)	54.5% (n=6)	38.8% (n=19)	-
SIGN				
BLEEDING	36.8% (n=14)	18.2% (n=2)	32.7% (n=16)	[19.6 – 45.8]
ERITHEMATOUS	21.1% (n=8)	9.1% (n=1)	18.4% (n=9)	[7.6 – 29.2]
ULCER	19.6% (n=7)	18.2% (n=2)	18.4% (n=9)	[-0.6 – 12.8]
NO REPORT	22.5% (n=9)	54.5% (n=6)	30.5% (n=15)	-
LOCATION				
UPPER AND LOWER GUMS	50% (n=19)	45.5% (n=5)	49% (n=24)	[35 – 63]
UPPER GUMS	5.3% (n=2)	0%	4.1% (n=2)	[-1.5 – 9.7]
LOWER GUMS	21.1% (n=8)	9.1% (n=1)	18.4% (n=9)	[7.6 – 29.2]
NO REPORT	23.7% (n=9)	45.5% (n=5)	28.6% (n=14)	-
DESCRIPTION OF THE LESION				
GINGIVAL MASSES WITH ULCER	31.6% (n=12)	27.3% (n=3)	30.6% (n=15)	[17.7 – 43.5]
GINGIVAL GRANULATION TISSUE	7.9% (n=3)	27.3% (n=3)	12.2% (n=6)	[3 – 21.4]
GINGIVAL IRREGULAR OVERGROWTH	44.7% (n=17)	27.3% (n=3)	40.8% (n=20)	[27 – 54.6]
NO REPORT	15.8% (n=6)	18.2% (n=2)	16.3% (n=8)	-
TOOTH MOVILITY				
YES	18.4% (n=7)	27.3% (n=3)	20.4% (n=10)	[9.1 – 31.7]
NO	7.9% (n=3)	0%	6.1% (n=3)	[-0.6 – 12.8]
NO REPORT	73.3% (n=28)	72.7% (n=8)	73.5% (n=36)	-

Table 2: Demographic of LG, race, family descendants, symptoms, tooth mobility.

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Symptoms: Symptoms in 30 cases were reported. Pain was the most common symptom with 40.8% (n=20) cases, females reported pain in 42.1% (n=16) cases, and males in 36.4% (n=4) cases, in 38.8% (n=19) cases, symptoms was not reported (Table 2).

Sign: The information was available for 34 cases. Bleeding was the most common presentation with 32.7% (n=16) cases, for males in 18.2% (n=2) cases and females 36.8% (n=14) of the cases and an erythematous presentation and ulcer were the second most common sign with 18.4% (9) cases, for females 21.1% (n=8) cases, and males with 9.1% (n=1) cases. Erythematous presentation, and ulcer with 19.6% (n=7) cases for females and 18.2% (n=2) for males. There were 30.5% (n=15) not reported cases (Table 2).

Oral presentation: Data was available for 83.6% (n=41) cases, where "gingival irregular overgrowth" was the most common description in 40.8% (n=20) of cases. Females made up 44.7% (n=17) and males 27.3% (n=3) of cases, followed by "gingival ulcer mass" with 30.6% (n=15) of the cases, with females accounting for 31.6% (n=12) cases, and males 27.3% (n=3) cases. There were 16.3% (n=8) cases, that did not report a description of the oral lesion (Table 2).

Size of the lesion: 31 cases mentioned it with a mean size of 2.7cm; 2.6cm for females reported in 26 cases and 3.4cm in 5 male patients (Table 2).

Location: 35 cases reported this information. Involvement of both upper and lower gingiva was common presentation with 49% (n=24) cases, in females occurring in 50% (n=19) cases, and in males with 45.5% (n=5) cases. The lower gingiva only was the second most common oral area of involvement, affecting females in 21.1% (n=8) cases, and males with 9.1% (n=1) of cases. Interestingly an upper gingiva only presentation occurred only in females with 5.3% (n=2) cases. There were 28.6% (n=14) cases, not mentioned this variable (Table 2).

Tooth mobility: Data was available for 13 cases, where 20.4% (n=10) of cases were positive for tooth mobility. In females 18.4% (n=7) reported tooth mobility, and males 27.3% (n=3) of cases. On the other hand, 6.1% (n=3) of cases were reportedly negative for tooth mobility. For this variable there were 73.5% (n=36) cases that did not provide data (Table 2).

Radiographic bone loss: Mentioned in 28.6% (n=14) of cases, for females 26.3% (n=10) cases, and for males 36.4% (n=4) cases. No bone loss was reported in 14.3% (n=7) of cases. There were 57.1% (28) without this data (Table 2).

Evolution time before diagnosis: Mentioned in 35 cases, with an average duration of 32.5 months; the average for females was 29.2 months and for males 43.7 months (Table 3).

Ligneous conjunctivitis: Data was positive for 69.4% (n=34) of the cases showed ligneous conjunctivitis in conjunction with oral lesions. In 71.1% (n=27) of the cases, a predominance for females was present and 63.6% (n=7) were males. 30.6% (n=15), were negative for ligneous conjunctivitis with oral presentation (Table 3).

Other compromised tissue: Data were available for 36.7% (n=18) of the cases. Respiratory tract was involved in 10.5% (n=4) cases, in female followed by vagina and vocal cords with 3 reported cases for each. For males, the ear was involved with 18.2% (n=2). There were 63.3% (n=31) cases

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that did not report data for this variable (Table 3).

Histology: The information was available for 57.2% (n=28) of cases, where sub-epithelial fibrin deposition was described in 23.7% (n=9) cases (only in females). Epithelial disorganization with amyloid like deposition, and acute and chronic inflammation were both the second most common description with 18.4% (n=7) each.

There were 42.9% (n=21) cases, where the histopathology was not mentioned (Table 3).

PRESUMPTIVE DIAGNOSIS	FEMALE	MALE	TOTAL	CI
DESQUAMATIVE GINGIVITIS	7.9% (n=3)	-	6.1% (n=3)	[-0.6 – 12.8]
WEGENER (GRANULOMATOSIS WITH POLYANGIITIS)	2.6% (n=1)	-	2.0% (n=1)	[-1.9 – 5.9]
PERIODONTITIS	2.6% (n=1)	-	2.0% (n=1)	[-1.9 – 5.9]
GRANULOMA	5.3% (n=2)	-	4.1% (n=2)	[-1.5 – 9.7]
NO REPORT	81.6% (n=31)	100% (n=11)	85.7% (n=42)	-
EYE CONJUNTIVAL COMPROMISE				
YES	71.1% (n=27)	63.6% (n=7)	69.4% (n=34)	[56.5 – 82.3]
NO	28.9% (n=11)	36.4% (n=4)	30.6% (n=15)	[17.7 – 43.5]
OTHER COMPROMISED TISSUE				
VAGINA	7.9% (n=3)	NA	6.1% (n=3)	[-0.6 – 12.8]
SKIN	5.3% (n=2)	9.1% (n=1)	6.1% (n=3)	[-0.6 – 12.8]
RESPIRATORY	10.5% (n=4)	0%	8.2% (n=4)	[0.5 – 15.9]
ANAL	2.6% (n=1)	0%	2.0% (n=1)	[-1.9 – 5.9]
VOCAL CORDS	7.9% (n=3)	NA	6.1% (n=3)	[-0.6 – 12.8]
EARS	5.3% (n=2)	18.2% (n=2)	8.2% (n=4)	[0.5 – 15.9]
NO REPORT	60.5% (n=23)	72.7% (n=8)	63.3% (n=31)	-
SPECIAL STAINING				
MARTIUS SCARLET BLUE (MSB)	5.3% (n=2)	9.1% (n=1)	6.1% (n=3)	[-0.6 – 12.8]
FRASER-LENDRUM	2.6% (n=1)	9.1% (n=1)	4.1% (n=2)	[-1.5 – 9.7]
FIBRIN AND MSB	23.8% (n=9)	18.2% (n=2)	22.4% (n=11)	[9.1 – 31.7]
PAS POSITIVE	2.6% (n=1)	9.1% (n=1)	4.1% (n=2)	[-1.5 – 9.7]
NO REPORT	65.8% (n=25)	54.5% (n=6)	63.3% (n=31)	-
IMNUNOFLUORESCENCE				
IGA IGM IGG NEGATIVE	2.6% (n=1)	0%	2.0% (n=1)	[-1.9 – 5.9]
FIBRINOGEN	5.3% (n=2)	18.2% (n=2)	8.2% (n=4)	[0.5 – 15.9]
I_GA I_GM I_GG POSITIVE	2.6% (n=1)	0%	2.0% (n=1)	[-1.9 – 5.9]
NO REPORT	89.5% (n=34)	81,8% (n=9)	87,8% (n=43)	-
HISTOLOGY				
EPITHELIAL DISORGANIZATION + AMYLOID LIKE	18.4% (n=7)	18.2% (n=2)	18.4% (n=9)	[7.6 – 29.2]
ACUTE AND CHRONIC INFLAMATION	18.4% (n=7)	27.3% (n=3)	20,4% (n=10)	[9.1 – 31.7]
SUB-EPITHELIAL FIBRIN DEPOSITION	23.7% (n=9)	0%	18,4% (n=9)	[7.6 – 29.2]
NO REPORT	39.5 % (n=15)	54.5 % (n=6)	42,9 % (n=21)	-
TREATMENT				
CORTICOID	5.3% (n=2)	0%	4.1% (n=2)	[-1.5 – 9.7]
FROZEN PLASMA	21.1% (n=8)	45.5% (n=5)	26.5% (n=13)	[14.1 – 38.9]
TOOTH EXTRACTION	10.5% (n=4)	9.1% (n=1)	10.2% (n=5)	[1.7 – 18.7]

Table 3: Information regarding presumptive diagnosis, histopathological findings, special stains, treatment, and evolution.

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Special staining: Data was available for 36.7% (n=18) of cases. Fibrin and Martius scarlet, blue (MSB) were the most commonly used in 22.4% (n=11) cases, followed by MSB with 6.1% (n=3) cases. In 63.3% (n=31) of the cases, special stains were not utilized (Table 3).

Plasminogen test: Plasminogen type 1 was mentioned in 51% (n=25) of cases, females comprised 44.7% (n=17), and males 72.7% (n=8). The average for plasminogen activity test was 24.7mg/mL with a range of 5 to 54mg/mL (Table 4).

PLASMINOGEN				
	FEMALE	**MALE**	**Total Sample size**	
	Mean ± SD (n)	Mean ± SD (n)	Mean ± SD (min/max) (n)	[CI95%]
Plasminogen activity	28.1 ± 21.5 (n=20)	16,3 ± 12.4 (n=8)	24.7 ± 19.9 (5/90) (n=28)	[17.3 –32.1]
Plasminogen Type 1	44.7% (n=17)	72.7% (n=8)	51% (n=25)	[37 – 65]
No report	55.3% (n=21)	27.3% (n=3)	49% (n=24)	-

Table 4: Plasminogen test results.

Treatment: The information was found for 73.5% (n=36) of cases, whit frozen plasma used in 26.5% (n=13) cases, followed by prophylaxis and Chlorhexidine with 14.3% (n=7) of cases. There were 26.5% (n=13) cases that did not report treatment (Table 3).

Follow-up: In 29 cases, follow-up was available with an average of 18.9 months, with a range of 2 to 60 months. The mean follow-up for males 7.75 months and females was 22.2 months (Table 3).

Recurrence: The information was found for 29 patients, where 59.2% (n=29) of cases, were positive for recurrence, and 36.7% (n=18) cases, not reporting this variable (Table 3).

Discussion

Ligneous gingivitis is a permanent and difficult disease to diagnose, that affects the quality of life in children and young adults principally. This study synthesizes the clinical, histological findings, plasminogen blood test results, available treatment and follow-up for patients with LG for the first time in the literature. This study found a total of 49 patients, of whom 77.6% (n=38) were females and 22.4% (n=11) were males, similar with the review by Sivolella et al, (77%) with 27 females [3], expressing a female male relation of 2:1. The mean age of patients was 20 years, different from the reports by MacPherson et al, which described 12.5 years as an average age [10], Neering et al with 14.5 years [21], and 16.5 years in a study by Kurtulus et al [22]. The most affected group was between 1 to 26 years with 36 cases, followed by 31 to 66 years with 13 cases. There was an interesting gap between 27 to 30 years where no cases were found in the literature.

Concerning race there was a predominance of white patients with 63.3% (n=31) cases, principally from Turkish descendants in 53.1% (n=26) of cases, although in that country there a lot of races, the literature mentioned there were white, however, it is important to mention that in 30.6% (n=15) cases, race was not reported. For this reason, publication bias could increase "white" race for the patients reported and may not reflect true incidence of oral LG,

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due to black cases were only 6.1% (n=3), because LG cases demonstrated a worldwide distribution, which in our study were from 14 countries [10-17,20,23,24]. Regarding symptoms, pain was the most common with 40.8% (n=20) cases, similar to the result by Klammt J et al, in a series of 23 cases with low PLG activity [7], followed by a painless lesion in 20.4% (n=10) of cases. These are different results compared with Gunhan O et al [9], Gokbuget AY et al [1], Kurtulus I et al [22], and Scully C et al [2], where more of the cases were reflected as painless. These differences could be because of the few cases reported by them and because some cases manifest at infancy where pain is difficult to assess. Also, symptoms generally decrease with age, with occasional spontaneous clinical and symptomatology improvement [25]. This could also be more detailed if the data set was more complete, since symptoms were not reported in 38.3% (n=19) of the cases. It is important to mention a study by Diamond JP et al, who found 1 case of acquired disease associated with the administration of an anti-fibrinolytic agent, tranexamic acid, for the treatment of menorrhagia [26].

Concerning the clinical presentation of 33 cases reported in the gingiva, describing the oral lesions for LG "gingival irregular yellow-white overgrowth" was the most common description with 40.8% (n=20) cases [1,8,9,15-17,21,23,27,39,41], followed by "gingival ulcer mass", [1,2,10,18,19,24,26,31,34,38] with 30.6% (n=15) cases. The description of gingival enlargements covered by yellow white pseudomembranes was more prevalent for gingival overgrowth, than for gingival ulcer mass. Regarding tooth mobility and radiographic bone loss, these two variables were almost equal, because tooth mobility was positive for 10 cases, and for radiographic bone loss there were 14 cases. It is possible in 4 radiographic cases at the time of the study tooth mobility was just beginning but not detected. These variables in the studies of LG must be further investigated for their relevance. The extent of bone loss and periodontal disease may be so severe that it can cause tooth loss if left untreated [9,27].

Ligneous conjunctivitis (LC) at the time of oral LG was positive in 69.4% (n=34) cases, close to results reported by Sivolella S et al. with 60% (21) cases [3]. Regarding LG without LC was in found 30.6% (n=15) cases. In consideration of ligneous disease in other organs or tissues, this study found a respiratory tract compromised in 10.5% (n=4) cases in females, different to Sivolella et al; with (14%), the ears 8.2% (n=4) cases, almost similar with Sivolella (9%), and vagina 7.9% (n=3) cases, different from Sivolella with (14%) [3].

Histopathologically, sub-epithelial fibrin deposition was the most common histological description with 23.7% cases [15,16,19,21,26,31,32,35,40], interestingly only described in females, followed by epithelial disorganization and amyloid like material, and acute and chronic inflammation [9,10,14,20,23,31] seen in both sexes with 18.4% (n=7) of cases; this is an important fact to mention, according to Günhan Ö et al in 2012, there are histological early and late changes of ligneous disease, where PMN exudation, immunoreactivity to fibrinogen, keratin positivity and amorphous accumulation, occurs at early stage principally, and sub-epithelial amorphous accumulation occurs at late stage with chronic inflammation cells [13] (Figure 2). This is key to allow accuracy in the diagnosis, where the differentiation

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between amyloid and other proteins like fibrin, with a similar histologic appearance [29], could be excluded with a Congo red positively for amyloid and using special stains such as Fibrin and MSB to confirm fibrin deposition, which in this study was found in 22.4% of the cases [1,9,10,38]. Also, because the late stage could promote bone resorption. Regarding immunofluorescence only 8.2% (n=4) cases (Table 3) were positive for fibrinogen [9,17,39]. This is in concordance with Scully C et al, who found immunoglobulin and possibly other serum proteins, suggesting vascular exudation, clotting, and a deficient removal for deficient fibrinolysis [2]. In this regard more than 65% were diagnosed only with hematoxilin eosin staining. As an important detail 42.9% (n=21) of cases did not report the histological findings.

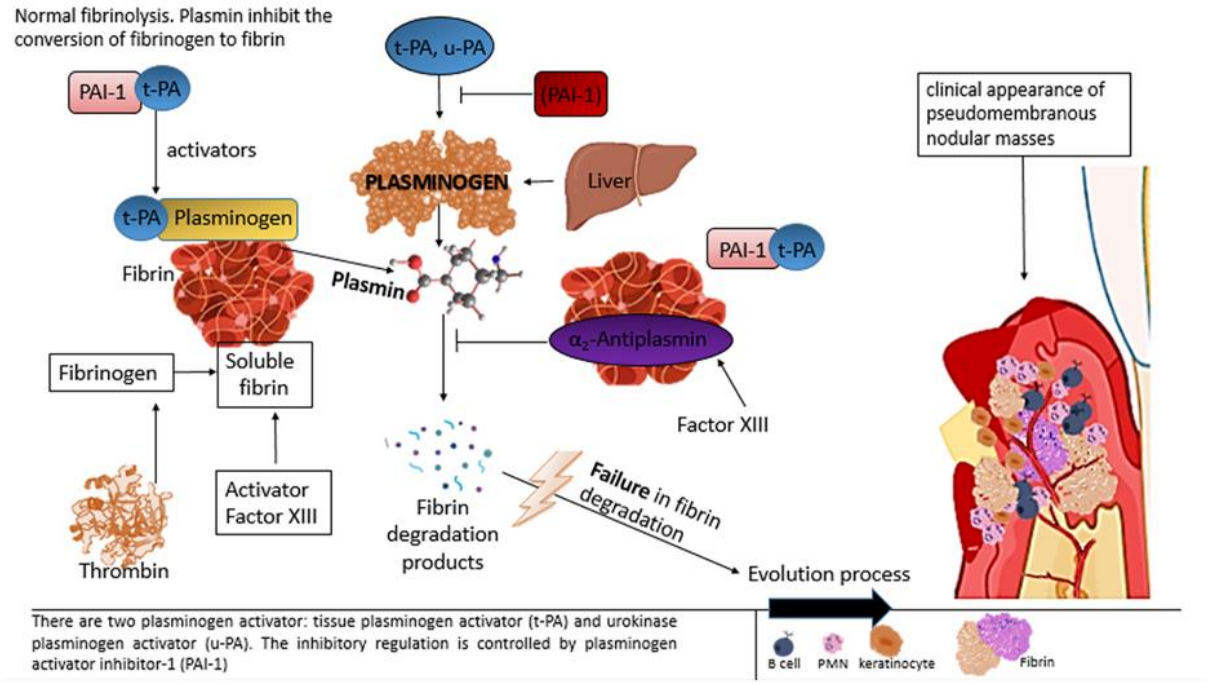

Figure 2: Fibrin deposits of all body fluids are cleared by the fibrinolytic system. In the crevicular fluid plasminogen activators convert plasminogen into plasmin, eliminating fibrinogen deposits. The absence of plasmin activity results in the formation of fibrin-rich membranous material, which is typically observed in patients with LG, promoting pseudomembranous white-red lesions.

In relation to plasminogen test, this study found the confirmation of type 1 plasminogen deficiency in 51% of the cases. According to the literature this is limited in patients with hypoplasminogenemia (type I plasminogen deficiency) [8,10,16-19,21,23,28,30,32-34]; defined as normal activity of plasminogen but the antigen level is below normal [35]. Historically the first report of PLG deficiency in a patient with LG and LC was 1997 by Schuster et al [28]. And before that the plasminogen deficiency (type 1) was evident investigating the etiology of occlusive hydrocephalus, LC and shunt obstruction in a 26-month-old girl in 1994 [36]. Our study found an average for plasminogen activity test of 24.7mg/mL in 28 cases, with a range of 5 to 54mg/mL, and the plasminogen antigen was mentioned in five reports [10,16,18,20,33] with an average of 1.9mg/mL that did not allow for statistics analysis. An interesting finding was that the severity of the clinical symptoms seems to correlate with the degree of PLG deficiency

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[2,25,30,37]. On the other hand, Naudi KB et al, reported a case of LG in the absence of PLG deficiency [38]. However according to Tefs K et al, LG is seen in approximately one-third of patients with homozygous plasminogen deficiency [5].

Ligneous disease has an autosomal recessive pattern, caused by homozygous or compound- heterozygous type I PLG deficiency, and a genetic inheritance has been demonstrated [12,15,16,28,39]. However, the studies were almost noncontributory for this information to be analyzed. For differential diagnosis, this study found only 7 studies describing other possible presumptive diagnoses. These included necrotizing ulcerative periodontal disease, desquamative gingivitis [18,20,40], hormonal hyperplasia [39]. Systemic causes linked to medication and hematologic malignancies like leukemia producing gingival enlargement must also be considered in the differential diagnosis [1]. Other possibilities include oral granulomatosis with polynangiitis (wegener's) [14]; or a pyogenic granuloma [35]. Also, in adult patients' metastatic disease might be considered [1,42].

Treatment of LG is exceedingly difficult. Many of the recommendations on management have come from ophthalmologists [3]. This study found that frozen plasma was the most used therapy in 26.5% (n=13) cases [8,30,34], principally done in case series, followed by prophylaxis and clorhexidine use in 14.3% (n=7) of cases [10,21,23,24,39], which is not considered treatment but a control measure. Surgical and periodontal procedures proved to produce no satisfactory permanent cure in all reported cases [4,9,20,39,43], except in some cases, when total tooth extraction was performed [17,27,31,33,41]. To the best of our knowledge, no generally accepted therapy is effective on LG patients. For that reason, avoiding dental plaque formation with good oral hygiene is mandatory in these patients. Neering et al, suggests where patients with PLG-deficiency Type I may benefit from nonsurgical periodontal therapy in combination with adjunctive antibiotic therapy and a strict supportive periodontal therapy regime every three months [21]. This is linked with the follow-up of 18.9 months found in our study, and the recurrence that was found in 59.2%, which could increase if the follow up is extended.

The main limitation of this review stems from the grounded reliance on case reports and small case series. Consequently, some of the variables were missing for numerous patients. Unpublished data were not identified even though we tried to reach most of the authors. For this reason, it was difficult to totally exclude the effect of confounding factors, and heterogeneity in the selected studies. Prospective studies are needed to confirm these findings. Interpretation of ethnic prevalence from systematic review is subject to publication bias, so comparison might be compromised. Thus, large-scale cross-sectional studies are needed to confirm these findings.

Recommendations

Further analysis of matrix metalloproteinase dysfunctions may be important in understanding the pathogenesis of oral ligneous mucosal disorder.

Conclusion

Congenital plasminogen deficiency is a rare autosomal recessive disorder that leads to the development of wood-like pseudomembranes on oral mucosal

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membranes called ligneous gingivitis, caused by the same process as ligneous conjunctivitis. Although there is an alteration in the fibrinolysis process, there is no tendency to thrombosis development.

However, this disease remains a clinical challenge for the health care professional due to the uncommon occurrence of cases. Research is necessary for the development of an effective treatment that can prevent or reverse the destructive course of LG. Increased awareness of this disease process by dentists is necessary so more patients may be diagnosed, and further studies completed.

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Conflicts of interest

All authors declare that they have no conflict of interest.

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