REVIEW

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Ligneous Periodontitis Associated with Plasminogen Deficiency: A Review of the Literature with Two Additional Cases

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Abstract

BACKGROUND/AIMS: Ligneous lesions are rare diseases characterized by fibrin deposition due to plasminogen deficiency and they may affect the mucosal areas as conjunctivae and gingiva. The course of this disease is progressive and typically results in early tooth loss. In this study, we aimed to evaluate the demographic, clinical, and histopathological features and treatment approaches for ligneous periodontitis lesions in the literature with additional cases of our own.

MATERIALS AND METHODS: Two patients, siblings, were referred to our clinic with nodular and fragile gingival overgrowth on both jaws. Brown-yellow gingival growths which were prone to bleeding and covered the teeth were observed. While one of the siblings received pharmaceutical treatment, the other received surgical treatment. A literature search was performed to congregate articles using the PubMed database based on the following terms: [(ligneous periodontitis) OR (ligneous)] OR [(ligneous periodontal disease)] AND [English (Language)]. Lesions which were not located on the gingiva were the exclusion criterion.

RESULTS: The literature review revealed 72 cases of ligneous gingival lesions during the years 1973-2020. All lesions found were classified in tables according to their characteristics, treatment approaches, recurrence rates, and follow-up periods. Ligneous lesions are rare diseases characterized by fibrin deposition due to plasminogen deficiency and they may affect the mucosal areas.

CONCLUSION: It has been reported that there is still no consensus on treatment for these lesions. More studies are needed in the future in order to provide effective periodontal treatment for cases of ligneous periodontitis.

Keywords: Ligneous periodontitis, ligneous gingivitis, plasminogen deficiency, treatment

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INTRODUCTION

Plasminogen is a proenzyme which is converted into active plasmin by plasminogen activators on the fibrin surface. Plasminogen plays an important role in many events, such as cell migration, angiogenesis, and fibrinolysis. It passes into the bloodstream in proenzyme form after being synthesized in the liver and turns into plasmin, the active enzyme format. During the healing of a wound surface, it activates the "tissue plasminogen activator" and thus leads to the destruction of the fibrin.[1] Mucosal areas acquire a coarse appearance due to the accumulation of fibrin in the absence of complete or partial plasminogen. For this reason, the term "ligneous", which means "woody" in Latin, is used.[2] The term "ligneous periodontitis" was first defined by Günhan et al.[3] as a periodontal disease characterized by membranous gingival overgrowth and severe bone loss due to the accumulation of amyloid-like material.

Plasminogen deficiency, which can be congenital or acquired, is characterized by the development of fibrin-rich pseudo-membranes on mucosal surfaces such as the mouth, eyes, nasopharynx, trachea, and genital mucosa as a result of impaired fibrin organization and delayed wound healing.[4]

Ligneous mucosal diseases are very rare (0.3-0.4%) autosomal recessive conditions characterized by fibrin deposition in the tissue due to plasminogen deficiency.[5] Generally, children are affected, but this disease can occur at any age.[6] Ligneous mucosal diseases may show involvement in several tissues. However, gingival and conjunctival involvements are often observed in childhood.[7]

Among these rare involvements, gingival tissue is a remarkable early sign which is characterized by asymptomatic gingival enlargement and severe periodontal tissue damage.[8] Local factors, such as poor oral hygiene, infections, irritations, and surgical procedures are predisposing factors in the formation of ligneous periodontal lesions.[9] The course of this disease is progressive and typically results in early tooth loss. In the hypoplasminogenemic condition, the rare periodontal disease, characterized by ulcerated gingival tissue and rapid tooth loss is defined as "destructive membranous periodontal disease" or "ligneous periodontitis".[10]

In this case report, we share the cases of two siblings with ligneous periodontitis and their long-term therapeutic results in order to (1) bring attention to and foster greater familiarity with the clinical and histopathologic features of this condition among dentists, which is essential for its timely diagnosis and management, and (2) review the literature for features and treatment options about this rare disease.

MATERIALS AND METHODS

Cases

The patients (18- and 21-year-old females) were referred to our clinic with nodular, fragile, and painless gingival overgrowth at the maxilla and mandible. Prior to their dental examination, they were also referred to the department of ophthalmology for various eyelid lesions and they were diagnosed with ligneous conjunctivitis. The conjunctival lesions were detected at 6 months in the younger sibling, and at 10 years in the older sibling.

Their medical examinations revealed hydrocephalus and respiratory distress for the younger sibling and vision loss in the left eye and bilateral hearing loss (30%) for the older sibling.

Both siblings were very similar in a clinical perspective in respect to the appearance and the extension of their ligneous lesions. The brown-yellow gingival overgrowths were prone to bleeding and covered the teeth (Figure 1). Radiographic examination showed severe bone destruction and floating teeth in both siblings (Figure 2). Since the older sibling could not get approval for general anesthesia due to hydrocephalus, she was treated using only pharmaceutical methods.[11] This treatment included 2% corticosteroid eye drops applied every 2 hours for 4 weeks for ligneous conjunctivitis and chlorhexidine mouthwash combined with systemic doxycycline for ligneous periodontitis. The younger sibling was operated on under general anesthesia with the support of the replacement of plasminogen. All overgrowth gingival tissue was

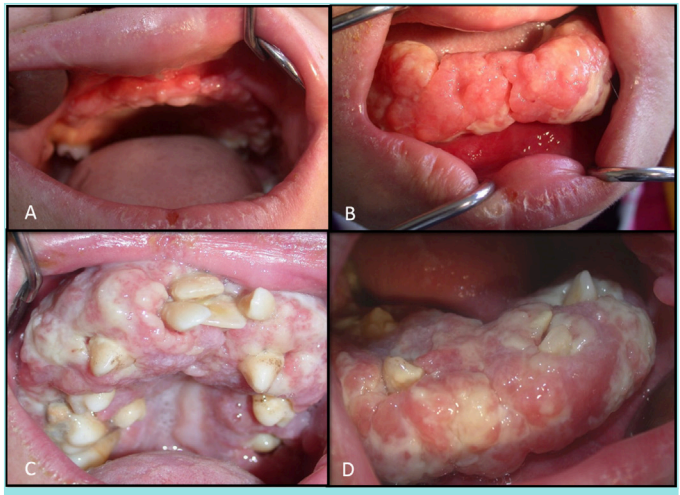

Figure 1. (A) Intraoral view of the older sibling's maxilla. (B) Intraoral view of the older sibling's mandible, (C) Intraoral view of the younger sibling's maxilla, (D) Intraoral view of the younger sibling's mandible.

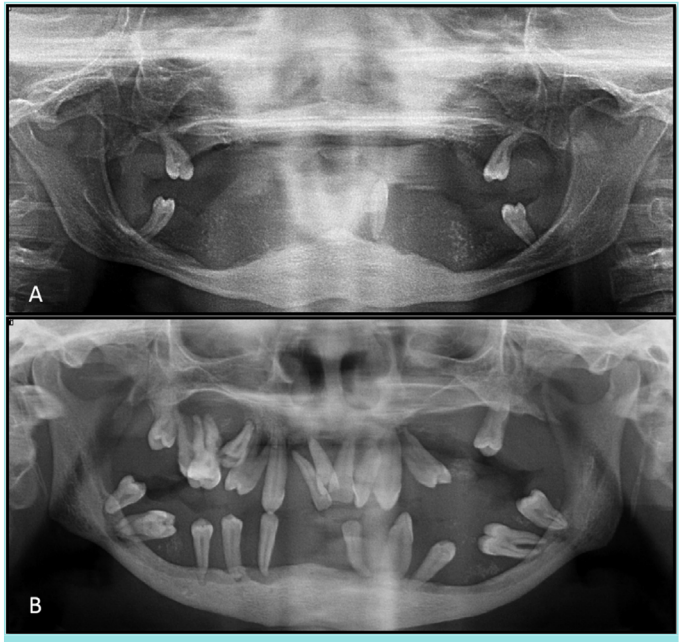

Figure 2. (A) The orthopantomograph of the older sibling. (B) The orthopantomograph of the younger sibling.

removed along with the teeth. After clinical healing was established, a total prosthesis was fabricated in order to restore/regain/maintain oral function and esthetics (Figure 3). Recurrence was observed at a 1-year follow-up. One of the siblings was treated with a combination of surgical and pharmaceutical treatment, and the other was given only pharmaceutical treatment because general anesthesia was contraindicated, yet recurrence was found in both.

The histological findings of our cases revealed acanthotic squamous epithelium showing hyperplasia on the surfaces, accumulation homogeneous eosinophilic fibrinous material deposition and inflammatory reactions around the underlying epithelium. These histological findings revealed ligneous periodontitis.

Literature Review

A literature search was performed to gather articles published in English using the PubMed database. The literature review was based on the following terms and words: (ligneous periodontitis) OR (ligneous periodontal disease) OR (ligneous gingivitis) OR (ligneous) AND [English (Language)]. We evaluated the features of ligneous lesions, including age, age at onset, gender, nationality, presence of consanguineous marriage, medical condition, oral findings, histopathological findings, affected organs other than the mouth, treatment, recurrence, and follow-up (Table 1, 2). Lesions which were not located in the gingiva were excluded.

RESULTS

Our PubMed search identified 31 articles and 72 cases with ligneous gingival lesions dating from 1973 to 2020. The demographic features of all reported cases are given in Table 1 and the characteristic features of all reported cases are given in Table 2. The treatment approaches with different success rates are listed in Table 3. In the literature, different treatment results were reported with varying success and recurrence rates. The recurrence and follow-up results are very important and these are summarized in Table 4.

DISCUSSION

Since ligneous periodontitis is a rare disease, it is usually presented as case reports in the literature. There are also reviews which focus on the genetic sequences and plasminogen levels of ligneous diseases.[4,12] Biopsy is the gold standard in the diagnosis of ligneous diseases. Fibrin deposition is diagnosed by hematoxylin, eosin staining, and a negative response to Congo Red. The patient is investigated systemically for plasminogen deficiency and ligneous disease is diagnosed after a biopsy.[9] Since there is no comprehensive review of the clinical features and treatment of cases, a literature review was needed regarding the clinical evaluations of this disease.

Figure 3. 1-year of post-operative follow-up of the younger sibling. (A) Clinical appearance, (B) Recurrence in the maxilla, (C) Intraoral image of the mandible.

Features of Population

As stated before, this condition may be congenital or acquired. The patients in the literature are reported with a wide age range (1 to 66 years old).

Plasminogen deficiency is an autosomal recessive disease caused by homozygous or compound heterozygous mutations of the plasminogen gene (PLG).[12] Plasminogen deficiency is a rare condition with autosomal recessive inheritance OMIM (Online Mendelian Inheritance in Man): 217090 and its incidence increases with the consanguineous marriage of parents. There are few articles focusing on this condition.[1,10,12-17] Our review is the first comprehensive review in which consanguineous marriage was questioned. Unfortunately, there was no data regarding consanguineous marriage in 44 out 74 cases. Furthermore, among 30 cases reporting on the presence of consanguineous marriage, only 19 cases were positive (1.7:1).

The Turkish population constitutes the majority of cases involving ligneous lesions in the literature.[1-3,10,13,16,18-22] In our review, focusing on gingival involvement, a total of 74 cases were included, and nearly half of them (30/74) were reported as being of Turkish origin (40.5%). It is estimated that the reason why many cases are seen in the Turkish population is due to the prevalence of consanguineous marriages, especially in rural areas.

In a genetic disorder with an autosomal recessive inheritance pattern, a female-to-male ratio of 1:1 is expected. However, according to the literature, the female/male ratio in ligneous lesions ranges from 1.4:1 to 2:1.[23] In a 2012 review in which only oral ligneous lesions were evaluated, the female/male ratio was reported to be 3.4:1 (77%).[24] Similarly, the female (n=55)/male (n=19) ratio was 2.89:1 (74.3%) in our review.

Clinical Features of Lesions

The characteristic clinical features of ligneous gingival lesions are solid, painless, nodular, fragile erythematous, hyperplastic, white-yellow fibrinous pseudomembrane-covered gingival enlargements involving the marginal and attached gingiva, generalized severe periodontal tissue destruction, and ulceration with generalized gross plaque accumulation.[3,10,12,25,26]

The intraoral clinical examination of our cases had characteristic clinical features as described above. The extension of the gingival overgrowth along with the severe periodontal tissue and alveolar bone destruction both in the maxilla and mandible had the tendency to bleed. A floating teeth appearance within the overgrowth tissue was observed.

Histological Features of Lesions

Early studies in the literature suggested that this disease was caused by a substance which accumulated in the eyes. This amyloid-like eosinophilic material was found to be fibrin. Subepithelial and perivascular fibrin deposition became the characteristic finding of this disease in later studies.[24]

Characteristic histological features in ligneous lesions are areas of ulceration and hyperkeratosis, acanthosis, granulation tissue formation, an amorphous, fibrin-rich, amyloid-like substance deposition due to insufficient fibrin degradation, subepithelial, and perivascular mixed inflammatory cell infiltrate as neutrophils, lymphocytes, and plasma cells.[12,13,19,27]

Other Involvements

Ligneous lesions can occur in all organs covered by mucous membranes. Initial studies of ligneous mucosal diseases focused on ligneous conjunctivitis, where the disease is more serious and disruptive. Severe hypoplasminogenemia often presents with ligneous conjunctivitis. The most frequently affected organs in the literature were reported as conjunctiva (81%) and gingiva (30%), respectively.[12,23,24] In more than 12% of the patients, hydrocephalus was also present.[28]

In parallel with the literature, the most frequently affected organs in our review were conjunctiva (60.8%), genital tract (17.5%), respiratory tract (14.8%), ear (10.8%), skin (4%), hydrocephalus (4%), vocal cords (2.7%), and peritoneum (1.3%).

Treatment Approaches

There is no clear-cut treatment regimen for the management of ligneous lesions.[4] Various pharmacuetical, surgical, or combined treatment approaches have been tried for these lesions, and most have been found to be successful. The clinician may prefer a more precise and effective treatment method by surgically removing the lesion, as in one of our cases, or consider a pharmaceutical approach in early lesions. In the surgical method, although the patient has postoperative pain, recurrence is expected to occur later as the lesion is eliminated.[1,12,19,29] The total number of cases which provided information about treatment was 55 out of all 74 cases. Surgical methods were preferred in 36.3% (n=20) of the reported cases with a 29.4% (n=5) success rate (no recurrence), whereas pharmaceutical methods were preferred in 43.6% (n=24) of the cases with a 64.2% (n=9) success rate; there are also combined (surgical + pharmaceutical) method reports found in 20% (n=11) of all cases with a 83.3% (n=5) success rate (Table 3).

Systemic or topical corticosteroids, systemic warfarin, low-dose doxycycline, chlorhexidine rinsing, cyclosporine A, PLG eye drops, PLG oral preparations, fresh frozen plasma eye drops, oral contraceptives, topical heparin, topical plasminogen, and azathioprine are some agents of these treatments.[3,4,14,17,19,26,27] The most popular agents preferred were antibiotics (doxycycline or tetracycline) with chlorhexidine rinsing.[3,12,19,21,27,30] However, it must be emphasized that evaluation of success is generally dependent on the initial response to any kind of treatment, including surgery.

Glu-plasminogen,[31] a new treatment method at the approval stage, achieved clinical efficacy and improved disease management by increasing patients' plasminogen levels. Glu-plasminogen is defined as the naturally circulating form of the plasminogen molecule. Plasmin is activated much more efficiently when bound to cells than in solution. This plasmin binds to plasminogen receptors and produces plasminogen. Thus, Glu-plasminogen therapy promises to increase patients' plasminogen levels. This promising treatment, whose effect on ligneous periodontitis lesions and its recurrence rate are not yet known, requires more studies and clinical trials.[32]

Table 1. Review of all reported cases of gingival ligneous lesions

No	Authors	Publication year	Age	Age at onset	Gender	Patient's origin	Consanguineous marriage	Medical condition	Oral findings
1	Frimodt-Moller[33]	1973	4	14 months	F	ND	ND	Diffuse, hard thickening and redness of the eyelid	Recurrent mandibular mucosa swelling
2	Hidayat and Riddle[34]	1987	7	ND	F	ND	ND	ND	Membranous gingival swelling
3	Nüssgens and Roggenkämper[18]	1993	12	10	F	Turkish	ND	ND	Gingival hyperplasia
4	Günhan et al.[13]	1994	20	15	M	Turkish	Yes	Healthy	Diffuse and yellowish-pink gingival enlargement
5			20	ND	F	Italian	ND	No relevant past medical history and no other dermatologic disorder	Diffuse with pinkish, waxy, painless gingival overgrowth with no tendency to bleed
6			18	ND	M	Turkish	ND	No relevant past medical history, the family history was negative	Pinkish and pale, waxy, nodular gingival enlargement with no tendency to bleed
7	Gokbuget et al.[19]	1997	24	6 months for conjunctivitis	F	Turkish	ND	Mild hypochromasia	Generalized gingival swelling, ulcerated and friable
8			15	ND	M	Turkish	ND	ND	Generalized ulcerated gingival swelling and pain
9			10	ND	F	Turkish	ND	ND	Gross gingival swelling with ulcerated surface
10			4	ND	F	Turkish	ND	Iron deficiency anaemia due to poor dietary iron intake	Ulcerated gingival swelling around deciduous molars
11			10	ND	F	Turkish	ND	ND	Generalized gingival swelling
12	Schuster et al.[2]	1999	16	14	F	Turkish	ND	ND	Gingival hyperplasia

Table 1. continued

No	Authors	Publication year	Age	Age at onset	Gender	Patient's origin	Consanguineous marriage	Medical condition	Oral findings
13	Günhan et al.[3]	1999	19	17	M	Turkish	ND	ND	Painless, nodular, fragile gingival enlargements, covered by white-yellow membranes
14			18	16	F	Turkish	ND	ND	
15			14	1 year for ligneous conjunctivitis	F	Turkish	ND	ND	Nodular, membranous, pale yellow to pink, fleshy gingival overgrowth
16	Scully et al.[35]	2001	35	10	F	United States	ND	ND	Ulcerated gingival swelling
17			8	5	F	United Kingdom	ND	ND	
18			31	12	M	Spain	ND	ND	
19			19	13	F	Turkish	ND	ND	
20			11	9	F	Turkish	ND	ND	
21			13	6	F	United States	ND	ND	
22	Watts et al.[14]	2002	5	2 years for ligneous conjunctivitis	F	Caucasian	No	ND	Gingival hyperplasia
23			18 months	1 month for ligneous conjunctivitis	M	Libyan	No	ND	Severe form of the disease with gingival involvement
24	Suresh et al.[8]	2003	59	53	F	ND	ND	Hypertension, miral valve prolapse, allergy to meperidine hydrocloride	Recurrent gingival hyperplasia with ulceration
25	Pantanowitz et al.[15]	2004	46	ND	F	Italian	No	Enlarged ovaries with multiple ovarian cysts	Gingival hyperplasia and multiple friable, white plaques; significant bone loss and loss of teeth
26	Baykul and Bozkurt[21]	2004	32	ND	F	Turkish	ND	Nodules, vaginal discharge, menstrual disorder and chronic conjunctivitis with acute attacks	Gingival membranous enlargement and periodontal tissue destruction
27	Silva et al.[30]	2006	9	8	M	ND	ND	ND	Painless nodular gingival enlargement with ulceration covered by yellowish pseudomembrane
28	Pierro et al.[26]	2006	12	ND	M	Italian	ND	Low functional plasminogen level, hyperextensibility, hypermobility of the limb joints, atrophic scars on knees, spontaneous ecchymoses, diagnosed as Ehlers-Danlos syndrome type VIII	Generalized gross plaque accumulation and a painless, massive, nodular fragile gingival enlargement with white-yellowish membranes, with a tendency to bleed
29	Tefs et al.[1]	2006	ND	10 years	F	U.S.	No	ND	ND
30		2006	ND	Childhood	F	Turkish	Yes	ND	ND
31		2006	ND	3 months	F	Turkish	Yes	ND	ND
32		2006	ND	Childhood	M	Turkish	Yes	ND	ND
33		2006	ND	Adolescence	M	Turkish	No	ND	ND
34		2006	ND	18 years	F	Turkish	Yes	ND	ND
35		2006	ND	24 years	F	Turkish	No	ND	ND
36		2006	ND	3 months	F	Brazil	ND	ND	ND
37		2006	ND	6 months	F	US	ND	ND	ND
38		2006	ND	Early childhood	F	US	No	ND	ND
39		2006	ND	Early childhood	F	US	No	ND	ND
40		2006	ND	3 days	M	Turkish	Yes	ND	ND
41		2006	ND	ND	M	Brazil	ND	ND	ND
42		2006	ND	20 days	F	Turkish	Yes	ND	ND
43		2006	ND	2 months	F	Turkish	Yes	ND	ND

Table 1. continued

No	Authors	Publication year	Age	Age at onset	Gender	Patient's origin	Consanguineous marriage	Medical condition	Oral findings
44	Naudi et al.[36]	2006	46	Several years before	F	ND	ND	Systemically healthy, no known allergies, non-smoker	A granular, ulcerated, erythematous area on the alveolar ridge in the lower left molar region, 36-37 numbered teeth had been extracted several years previously
45	Karaer et al.[16]	2007	21	1 month for ligneous conjunctivitis	F	Turkish	Yes	Polipoidal growth on the vaginal wall and chronic conjunctivitis and had a malodorous vaginal discharge + dyspareunia	Gingival hyperplasia and ulceration
46	Kurtulus et al.[10]	2007	18	9	F	Turkish	No	Medical history was clear	Painless, massive, membranous, nodular and fragile gingival enlargement with bone loss
47	Baltacioğlu et al.[29]	2007	13	ND	F	ND	ND	Bilateral vesicoureteral reflux, phenytoin usage and suffered from delayed puberty and some hearing loss	Painless fragile nodular gingival enlargement covered with a yellow-white membrane
48		2007	15	10	F	ND	ND	90% visual loss in the right eye and 50% in the left eye owing to a condition	
49	Chi et al.[25]	2009	33	26	F	ND	ND	Chronic rhinosinusitis	Gingival inflammation due to poor oral hygiene, ulceration, whitish yellow pseudomembrane
50	El-Darouti et al.[9]	2009	12	9	F	ND	ND	No medical history of disease	Painless gingival swelling, massive alveolar bone loss, lips swelling
51	Fine et al.[27]	2009	52	13	F	ND	ND	History of infertility, and was diagnosed with ligneous cervicitis	Multiple, tender firm ulcerated nodular growths, gingival pain, loss of several teeth.
52	Cha et al.[37]	2011	66	ND	F	ND	ND	Hypertension, peripheral neuropathy, mild arthritis and glaucoma in her left eye	Ulcerated interdental papilla between the right first and second lower molars with significant gingival enlargement and inflammation, exhibited loss of stippling and an uneven hypertrophic surface right above the right upper central incisor with bleeding on palpation
53	Neering et al.[22]	2015	17	9	F	Turkish	ND	Type I PLG deficiency, severe pneumonia and hematocolpos	Generalized increased pocket, tooth mobility, gingival hyperplasia
54	Kızılocak et al.[17]	2017	11	6 months	F	ND	Yes	Cervicovaginitis, hydrocephaly	Ligneous gingivitis, tooth loss
55			12	2 months	F	ND	Yes	Hydrocephaly, mental retardation, deafness, cervicovaginitis	Ligneous gingivitis
56			3	10 days	F	ND	Yes	ND	Ligneous gingivitis
57			3	3	M	ND	No	Deafness, hydrocephaly	Ligneous gingivitis
58			7	2	M	ND	No	ND	Ligneous gingivitis
59			8	3	F	ND	Yes	Severe pulmonary disease	Ligneous gingivitis
60			4	3	M	ND	Yes	ND	Ligneous gingivitis, tooth loss
61			1	4 months	F	ND	Yes	ND	Ligneous gingivitis
62			7 months	10 days	F	ND	Yes	ND	Ligneous gingivitis
63			24	4	M	ND	Yes	ND	Ligneous gingivitis
64	Ertas et al.[38]	2017	6	4	F	ND	ND	White membrane surrounding in the lower and upper eyelids mucosa	Nodular symptomatic gingival hypertrophy and ulceration around the molar site

Table 1. continued

No	Authors	Publication year	Age	Age at onset	Gender	Patient's origin	Consanguineous marriage	Medical condition	Oral findings
65	Shapiro et al.[31]	2018	24	ND	F	ND	ND	ND	Gingival lesions
66			37	ND	F	ND	ND	ND	Gingival lesions
67			33	ND	M	ND	ND	ND	Gingival lesions
68			42	ND	F	ND	ND	ND	Gingival lesions
69	Sartori et al.[4]	2019	43	Childhood	F	ND	ND	Ligneous conjunctivitis, pseudomembranes on vocal cords, ligneous pseudomembranes on uterine cervix	Ligneous mucositis, multiple nodular gingival lesions
70	Malthiery et al.[39]	2019	35	25	F	Turkish	ND	Cervical lymphadenopathy in the right side, bilateral early stage of ligneous conjunctivitis with no pseudomembranes	Gingival granulomatous masses and whitish neck proliferations
No	**Authors**	**Publication year**	**Age**	**Age at onset**	**Gender**	**Patient's origin**	**Consanguineous marriage**	**Medical condition**	**Oral findings**
71	Sadasivan et al.[12]	2020	26	15	M	ND	Yes	Ulticystic hydrocephalus which was drained by ventriculoperitoneal shunt, profuse granulomatous growth in conjunctiva in both eyes, plasminogen activity <5%	Solid, nodular, fragile erythematous and hyperplastic gingival enlargements involving the marginal and attached gingiva and severe periodontitis, white-yellow fibrinous pseudomembranes
72	MacPherson et al.[40]	2020	14	ND	M	ND	ND	Systemically healthy, no history of any medical conditions	Multiple, exophytic, ulcerated masses of soft tissue resembling granulation tissue of the posterior mandibular aspects of the gingiva
73	Kayhan et al.	2001	18	3 months	F	Turkish	Yes	Low functional plasminogen level, hydrocephalus	Generalized nodular, fragile, painless, gingival overgrowth covered by brown-yellow pseudomembranes with severe periodontal tissue destruction on both the maxilla and mandible with a tendency to bleed
74		2001	21	ND	F	Turkish	Yes	Low functional plasminogen level, visual loss in the left eye and bilateral hear loss (30%)	

Recurrence Rates According to the Treatment Approaches

The total number of patients for whom information about recurrence was available was 37. The reported recurrence rate was 50%, and there was no information about recurrence in 37 of them. Recurrence was observed in 48.6% (n=18) of all 37 cases. No information was reported about recurrence in 3 out of 20 cases who were treated surgically, while recurrence was observed in 70.5% (n=12) of the remaining 17 patients, and recurrence was not observed in 29.4% (n=5) of them. No information about recurrence was reported in 10 out of 24 patients who were treated with pharmaceuticals, recurrence was observed in 35.7% (n=5) of 14 patients, and recurrence was not observed in 64.2% (n=9) of them. There is a gap regarding recurrence among 5 out of 11 patients who were treated with the combined method, and recurrence was observed in 16.6% (n=1) out of 6 (Table 3). The rate of recurrence seems to be higher in those cases treated only surgically when the follow-up period is not considered.

Follow-up Periods According to the Treatment Approaches

The follow-up periods were classified into three groups in order to estimate the long-term success of treatment modalities given in the literature. The categories were determined as: up to one-year, 1-3 years, and more than 3 years. Considering the follow-up periods according to treatment approaches, no information was reported about the follow-up periods in 11 out of 20 cases who were treated with surgery, and follow-up rates were 22.2% (n=2) for up to one year, 66.6% (n=6) for 1-3 years, and 11.1% (n=1) for more than 3 years in 9 cases. The recurrence rate in surgically treated patients with follow-up information was 66.6% (n=6).

No information was provided in 21 out of 24 cases who were treated pharmaceutically, and follow-up data was only given for 33.3% of 3 cases (n=1) up to 1 year, and 66.6% of them (n=2) for more than 3 years. The recurrence rate of pharmaceutically treated (antibiotics) cases with follow-up information was 100% (n=3).

The follow-up period was not reported for 7 out of all 11 patients who were treated with the combined method. There was no case followed up to 1-year, the follow-up rate in 1-3 years was 75% (n=3), and more than 3 years was 25% (n=1) out of the 4 patients. No recurrence was reported among those patients with follow-up information for the combined method, and the success rate was 100% (n=3) (Table 4).

Table 2. Features of all reported cases of gingival ligneous lesions

No	Authors	Histopathological findings	Affected organs	Treatment	Recurrence	Follow-up
1	Frimodt-Moller[33]	ND	Conjunctivae	Surgical excision, extraction and antibiotic therapy	Disease disappeared after dental extraction	3 years
2	Hidayat and Riddle[34]	Subepithelial, eosinophilic, amorphous material; hyperpermeable blood vessels	Conjunctiva, vocal cords, larynx, trachea, vagina, cervix	Multiple surgical excisions	ND	ND
3	Nüssgens and Roggenkämper[18]	ND	Conjunctivae; occlusive hydrocephalus	Excision of gingival lesions	ND	ND
4	Günhan et al.[13]	Areas of ulceration, granulation tissue, subepithelial inflammatory infiltration and amorphous nodular deposits of a homogeneous, eosinophilic substance beneath the gingival squamous epithelium.	ND	Unsuccessful periodontal treatment, lost all teeth	No recurrence was found in two years follow-up	2 years
5			ND	ND	ND	ND
6			Conjunctivae	ND	ND	ND
7	Gokbuget et al.[19]	Hyperplastic epithelium; focal areas of ulceration. Moderate chronic inflammatory cell infiltrates and deposits of hyalinized eosinophilic fibrin in the connective tissue.	Conjunctivae	A detailed professional oral hygiene care + long-term systemic tetracycline + chlorhexidine + gingivectomy	ND	ND
8					ND	ND
9			ND		ND	ND
10			ND		ND	ND
11			Conjunctivae		ND	ND
12	Schuster et al.[2]	ND	Conjunctivae; occlusive hydrocephalus	ND	ND	ND
13	Günhan et al.[3]	Subepithelial, homogeneous, eosiniphilic, sometimes mineralized, amyloid-like material.	Conjunctivae; ear; kidney	Subgingival curettage, gingivectomy, chlorhexidine rinsing, antibiotics	Rapid regrowth after excision	1 year
14			Conjunctivae; delayed puberty			1 year
15			Conjunctivae	Gingivectomy	Recurrence 3 months after excision	3 months
16	Scully et al.[35]	Ulcerated surface epithelium and subepithelial eosiniphilic infiltrates containing fibrin	Larynx; genital tract; eye	ND	ND	5 years
17			ND	ND	ND	5 years
18			ND	ND	ND	5 years
19			ND	ND	ND	5 years
20			ND	ND	ND	5 years
21			ND	ND	ND	5 years
22	Watts et al.[14]	Focally atrophic thickened epithelium with subepithelial focal necrosis, fibrinous eosinophilic exudates, amorphous eosinophilic debris, and acute and chronic inflammatory cells fibrin and fibrovascular tissue infiltrated with lymphocytes, plasma cells, neutrophils, and eosinophils.	Conjunctivae; respiratory tract	ND	ND	ND
23			Conjunctivae; occlusive hydrocephalus	Corticosteroid drops and surgical debridement + cyclosporin A	No recurrence	1 year
24	Suresh et al.[8]	Surface ulceration; large subepithelial deposits of eosinophilic material	ND	Surgical excision	Recurrence of asymptomatic lesions several times.	ND
25	Pantanowitz et al.[15]	Reactive squamous epithelium with subepithelial eosiniphilic fibrin deposition, acanthosis and focal inflammation	Genital tract; infertility; middle ear	ND	ND	ND
26	Baykul and Bozkurt[21]	ND	Conjunctivae; genital tract	Subgingival curettage, gingivectomy, chlorhexidine rinsing and antibiotics in the past. Extraction of all mobile teeth	Conservative treatments were unsuccessful; regression after teeth extraction	3 years
27	Silva et al.[30]	Hyperplastic epithelium, large subepithelial eosinophilic deposits of fibrin-like material	Eye; conjunctivae; skin; polydactylia	Gingivectomy followed by chlorhexidine and dexamethasone elixir; topical and systemic heparin; topical and systemic corticosteroids	No efficacy of chlorhexidine and heparin protocols. Complete remission after corticosteroid therapy	3 years

Table 2. continued

No	Authors	Histopathological findings	Affected organs	Treatment	Recurrence	Follow-up
28	Pierro et al.[26]	Areas of ulceration, granulation tissue, subepithelial inflammatory infiltration, amorphous nodular deposits of a homogeneous, eosinophilic substance beneath the gingival squamous epithelium	Conjunctivae	Topical plasminogen, together with periodontal therapy	ND	ND
29	Tefs et al.[1]	ND	Gingiva; larynx; vagina	Surgical removals every 6 to 12 weeks; heparin shots after surgeries; warfarin, sodium daily; Fluticasone propionate and salmeterol twice daily	Fluticasone propionate and salmeterol successful almost 3 years since any surgery on vocal cords, voice improved.	ND
30		ND	Gingiva	ND	ND	ND
31		ND	Conjunctiva; gingiva; colloid millium	ND	ND	ND
32		ND	Gingiva, eyelid lesions	ND	ND	ND
33		ND	Gingiva	ND	ND	ND
34		ND	Gingiva	Gingivectomy	Without any success; lost all of her teeth	ND
35		ND	Conjunctiva; gingiva	Gingivectomy	Without any success; lost all of her teeth	ND
36		ND	Conjunctiva; gingiva	ND	ND	ND
37		ND	Gingiva; ears	Warfarine sodium heparin mouthwash - no longer using	ND	ND
38		ND	Gingiva	Oral steroids	ND	ND
39		ND	Gingiva	Oral steroids	ND	ND
40		ND	Conjunctiva; gingiva	Topical cyclosporin; chemotrypsin; eye drop with antibiotic	ND	ND
41		ND	Gingiva; Ehlers-Danlos syndrome	ND	ND	ND
42		ND	Conjunctiva; gingiva	Excision of the membranes in the eyes many times + gingivectomy of the mouth lesions	Recurrences occurred	ND
43		ND	Conjunctiva; gingiva	Excision of the membranes in the eyes many times + gingivectomy of the mouth lesions	Recurrences occurred	ND
44	Naudi et al.[36]	Lightly keratinized epithelium, which was atrophic in parts and acanthotic in others, non-specific chronic ulceration area, a scattered chronic inflammatory cell infiltrated within the areas of hyalinization of upper lamina propria	Gingiva	Incisional biopsy	The lesion remained unchanged	3 months
45	Karaer et al.[16]	Massive deposition of amorphous eosinophilic material	Conjunctivae; genital tract	Ethinil estradiol and gestoden combination	ND	ND
46	Kurtulus et al.[10]	Subepithelial homogeneous eosinophilic deposits, inflammatory infiltration	ND	SRP, gingivectomy, chlorhexidine, topical heparin and corticosteroids	Recurrence	ND
47	Baltacioğlu et al.[29]	Intense acute inflammation, subepithelial fibrin accumulation	Conjunctivae; ear	Gingivectomy every 3 months	Recurrence	ND
48			Conjunctivae	Cyclosporine for ligneous conjunctivitis; gingivectomy every 2 months, dental extractions	Partial regrowth even after dental extraction	ND
49	Chi et al.[25]	Subepithelial and perivascular deposits of eosinophilic material, ulceration, chronic inflammation	Genital tract, peritoneum, paranasal sinuses	ND	ND	ND
50	El-Darouti et al.[9]	Epithelial hyperplasia, subepithelial and perivascular fibrin deposition	Conjunctivae	ND	ND	ND
51	Fine et al.[27]	Hyperkeratosis, epithelial eosinophilic deposition, focal inflammation, acanthosis	Genital tract	Surgical excision, chlorhexidine mouth rinses, low-dose doxycycline and warfarin daily	No recurrence, no increased tooth mobility	3.5 years

Table 2. continued

No	Authors	Histopathological findings	Affected organs	Treatment	Recurrence	Follow-up
52	Cha et al.[37]	Inflamed multiple fragments of fibrous tissue surfaced in orthokeratinized-stratified squamous epithelium, which exhibited significant thickening of the spinous cell layer, the majority of fibrous connective tissue by the deposition of an amorphous, amyloid-like material	Gingiva	Improvement of oral hygiene, scaling, root planing, gingival curettage and dexamethasone elixir rinse two to three times daily	Partial improvement of soreness, inflammation, and discontinuation of gingival bleeding within 1 year	1 year
53	Neering et al.[22]	A reactive squamous epithelial hyperplasia with localized fibrin precipitation and massive ulcerations	Conjunctivitae, middle ear, respiratory tract, vagina	Periodontal treatment, full mouth disinfection, antibiotics	Supra- and subgingival debridement in every three months	3.5 years
54	Kızılocak et al.[17]	ND	Conjunctivitae, vagina	Eye surgery, FFP IV, cyclosporin	ND	ND
55		ND	Conjunctivitae, vagina, ear	Eye surgery, FFP IV, cyclosporin, FFP eye drops	No response	ND
56		ND	Conjunctivitae	Eye surgery 3 times, FFP IV, cyclosporin, betadin, dexamethason	Clinical benefits	ND
57		ND	Conjunctivitae, ear	FFP eye drops	No response	ND
58		ND	Gingiva	Mouth hygiene theraphy	Clinical benefits	ND
59		ND	Conjunctivitae, respiratory tract	FFP IV + bronchial FFP	Response to FFP	ND
60		ND	Gingiva	Mouth hygiene theraphy	ND	ND
61		ND	Conjunctivitae, gingiva	Eye surgery 8 times, FFP IV, cyclosporin, FFP eye drops	Response to FFP	ND
62		ND	Conjunctivitae, gingiva	Eye surgery 6 times, FFP IV, cyclosporin, FFP eye drops	Response to FFP	ND
63		ND	Conjunctivitae, gingiva	Eye surgery 5 times, FFP IV, cyclosporin, FFP eye drops	ND	ND
64	Ertas et al.[38]	Hyperplastic changes in the epithelium, extensive intraepithelial neutrophilic infiltration and eosinophilic fibrinoid accumulation between the basal membranes	Conjunctivitae, gingiva	Extraction of the tooth, gingivectomy	ND	ND
65	Shapiro et al.[31]	ND	Gingiva, bronchus	Plasminogen replacement therapy	Resolution	ND
66		ND	Conjunctivitae, gingiva, bronchus, nares		Resolution	ND
67		ND	Conjunctivitae, gingiva, skin, palmar and plantar wounds		Improvement	ND
68		ND	Conjunctivitae, gingiva, tumors, palmar warts		Improvement	ND
69	Sartori et al.[4]	Granulation tissue formation due to insufficient fibrin degradation, resulting in the formation of an amorphous, fibrin-rich, amyloid-like substance accumulated in the lamina propria	Conjunctivitae, vocal cords, uterine cervix	Tooth extraction+ a second-stage surgery using diode laser without raising a flap	Nodular gingival lesions due to plasminogen deficiency and the progression of marginal gingivitis to periodontal irreversible lesions	1 year
70	Malthiery et al.[39]	Deposition of amorphous eosinophilic Congo red negative material	Conjunctivitae, gingiva	Rivaroxaban treatment	ND	ND
71	Sadasivan et al.[12]	Parakeratinised stratified squamous surface epithelium with anastomosing rete ridges in association with a fibrovascular connective tissue. The connective tissue showed subepithelial deposits of homogenous eosinophilic material that resembled amyloid. The deeper parts of the connective tissue showed a diffuse mixed inflammatory cell infiltrate comprised predominantly of neutrophils, lymphocytes, and plasma cells.	Conjunctivitae, progressive blindness of the left eye	Supra and subgingival debridement + Oral hygiene instructions + CHX + Surgical excision	Recurrence of the lesion was seen after 3 months	ND

Table 2. continued

No	Authors	Histopathological findings	Affected organs	Treatment	Recurrence	Follow-up
72	MacPherson et al.[40]	Prominent spongiosis and acanthosis of the surface epithelium, granulation tissue, surface erosion, and pools of eosinophilic material located subepithelially	ND	Chlorhexidine mouthwash	Generally stable and fluctuation in the severity of the lesions	Every 6 months
73	Kayhan et al.	The patient was inoperable due to severe hydrocephalus	Conjunctivae, respirotary tract	Medical treatment	Recurrence reported	10 years
74		Acanthotic squamous epithelium showing hyperplasia in the surfaces, accumulation homogeneous eosinophilic fibrinous material deposition and inflammatory reactions around the underlying epithelium	Conjunctivae, ears	Gingivectomy	Recurrence at 1-year follow-up	10 years

Table 3. Distribution of patients according to treatment approaches and presence of recurrence

Treatment approach	(n)	Recurrence (+)	Recurrence (-)	ND
ND (E/A)	19 (10/9)	-	-	-
Surgical (E/A)	20 (8/12)	12 (3/9)	5 (3/2)	3 (2/1)
Medical (E/A)	24 (8/16)	5 (1/4)	9 (6/3)	10 (1/9)
Combined (surgical + medical) (E/A)	11 (5/6)	1 (0/1)	5 (4/1)	5 (1/4)

ND: no data, E: early lesions, A: advanced lesions.

Table 4. Distribution of patients according to treatment and follow-up periods

Follow-up period	Recurrence	Surgical treatment	Medical treatment	Combined treatment	ND
Up to 1 year	1	2	1	-	-
1-3 years	3	6	-	3	-
>3 years	2	1	2	1	6
ND	11	11	21	7	13
Total	17	20	24	11	19

ND: no data.

As stated in the literature, the follow-up period for most cases is between 1-3 years, and in many cases, the follow-up period was not reported. Since the recurrence rate is high regardless of the treatment, the follow-up of these cases is one of the most important stages of the treatment process.

Recurrence rates for advanced lesions were higher than early lesions in all treatment approaches. The advance of the lesion may be a factor which increases the recurrence rate. Clinicians may prefer the pharmaceutical method for early-stage ligneous periodontitis and the combined method which includes both pharmaceutical and surgical treatment for advanced ligneous periodontitis.

Based on the literature and the cases followed, the plasminogen values of individuals should be followed, especially if there is consanguineous marriage in their history. Patients should be followed up by an ophthalmologist and dentist regularly, and treatment should be started as soon as any eye or gingival lesion occurs. If oral ligneous lesions occur, the clinician should keep the patient's oral hygiene at a maximum level in order to keep the patient's teeth functioning longer and slow bone loss, and also clean any lesions as much as possible at each appointment in order to create cleanable surfaces for the patient.

The primary goal of clinicians in treating oral ligneous lesions is to keep teeth in the mouth or to improve the patient's quality of life with a prosthesis which can facilitate the chewing function.

As a treatment approach in oral ligneous lesions, pharmaceutical methods can be used in early lesions and surgical methods in advanced cases. However, it can be said that there is no consensus on the treatment of oral ligneous lesions with a low recurrence rate based on the cases in which different treatments and recurrence rates have been reported in the literature. The possibility of recurrence should be considered for all treatment options.

CONCLUSION

Ligneous lesions are rare diseases characterized by fibrin deposition due to plasminogen deficiency and may affect the mucosal areas. Regular follow-up and maximum oral hygiene are essential for the maintenance of these lesions. The main purpose of this study was to inform clinicians about the features and treatment options for these lesions, although this was not fully achieved due to a lack of long-term follow-up and recurrence reports in the literature. Future studies on ligneous periodontitis lesions which investigate the host response with long-term clinical follow-up can be performed.

MAIN POINTS

- Ligneous lesions are rare and hard-to-manage lesions with high recurrence rates. Therefore, we aimed to present our two cases with a literature review including the features and treatment options of ligneous gingival lesions in this study.
- Ligneous lesions are autosomal recessive conditions characterized by impaired fibrin organization due to plasminogen deficiency. These lesions affect organs covered by mucous membranes such as the conjunctiva, gingiva and genital tract.

• Although there is no consensus about the treatment of ligneous lesions, both pharmceutical and surgical approaches may regress them, however, their recurrence rate is very high.

• Ligneous gingival lesions affect the quality of life and clinicians may not have a good command of their management. Although there is no definitive treatment, the pharmaceutical approach may be preferred in early lesions and radical surgery may be preferred in advanced cases. Regardless of the treatment approach, regular follow-up and maintenance of oral hygiene are essential.

ETHICS

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: K.B.K., B.B., Design: K.B.K., R.B.K.Ü., Supervision: K.B.K., T.Ç., Materials: K.B.K., B.B., T.Ç., Data Collection and/or Processing: K.B.K., B.B., T.Ç., Analysis and/or Interpretation: R.B.K.Ü., Literature Search: R.B.K.Ü., Writing: K.B.K., R.B.K.Ü., Critical Review: T.Ç.

DISCLOSURES

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