Clinical Manifestations Due to Severe Plasminogen Deficiency: A Case Report

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ABSTRACT

Plasminogen deficiency is a rare, destructive, and badly defined disorder. Recurrent and progressive gingival nodular hyperplasia with ulceration would appear to be an unreported complication caused by this deficiency. In some of the reported cases, gingival hyperplasia occurred in association with an eye disease called ligneous conjunctivitis. Including this case report, only 11 patients with proven functional plasminogen and oral lesions have been reported in the literature in English. The purpose of this paper was to present the case of a child patient with recurrent clinical manifestations caused by severe plasminogen deficiency who responded positively to corticosteroid treatment. (J Dent Child 2006;73:179-182)

KEYWORDS: PLASMINOGEN DEFICIENCY, GINGIVAL LESIONS, LIGNEOUS CONJUNCTIVITIS

Plasminogen deficiency (PD) is a rare and unusual condition that may cause severe clinical manifestations such as eyelid lesions, diagnosed as ligneous conjunctivitis[1,2]—a rare eye disease that clinically appears as an acute or chronic recurrent pseudomembranous conjunctivitis.[2]

Recent studies have also stated that gingival enlargement with ulceration due to fibrin accumulation appears to be an unreported complication caused by plasminogen deficiency. This oral lesion is clinically characterized by recurrent gingival enlargement and progressive periodontal tissue destruction that leads to rapid tooth loss.[3]

The etiopathogenesis of these lesions is not clear, but it has been suggested that the deposition of fibrin in the connective tissue of patients with low functional plasminogen levels plays a central role in this rare condition's pathogenesis.[2-5] Blood contains an enzymatic system known as the fibrinolytic system, one of the main functions of which is the dissolution of fibrin clots in blood vessels.[6] The fibrinolytic system is made up of a proenzyme, plasminogen, which can be converted into the active enzyme plasmin.[6] The latter is the main fibrinolytic enzyme involved in the lysis of clots and clearance of extravasated fibrin.[6] Minor trauma, infection, and hypersensitivity have all been proposed as possible predisposing factors in the leakage of fibrin from the vessels. In addition, the impaired fibrinolysis secondary to plasminogen deficiency is responsible for the accumulation of fibrin in the injured mucosal tissue.[2,4,5] This deposition of fibrin into the connective tissue may be responsible for the associated inflammation and delayed tissue repair.[4,5,7]

In a healthy person with normal levels of functional plasminogen (reference range=80%-120%), body-fluid fibrinolytic activity clears fibrin deposits. If plasminogen is deficient, however, this mechanism may fail, causing fibrin deposition.[6] It has been suggested that plasminogen deficiency may be associated with the risk of thrombosis.[6,8] Scully et al,[3] however, reported that there is usually no tendency toward thrombosis, which would suggest the existence of an alternative intravascular fibrinolytic mechanism.[3]

The purpose of this article is to present a new case of a child patient with severe plasminogen deficiency as well as different clinical manifestations, including recurrent and generalized gingival hyperplasia with ulceration and ligneous conjunctivitis. The therapy applied is also discussed.

CASE REPORT

DIAGNOSTIC APPROACH

In May 2003, a 9-year-old male was referred to Centro Goiano de Doenças da Boca at the Dental School of Federal University of Goias, Goiânia, Brazil. The patient was suffering from a painless nodular gingival enlargement involving

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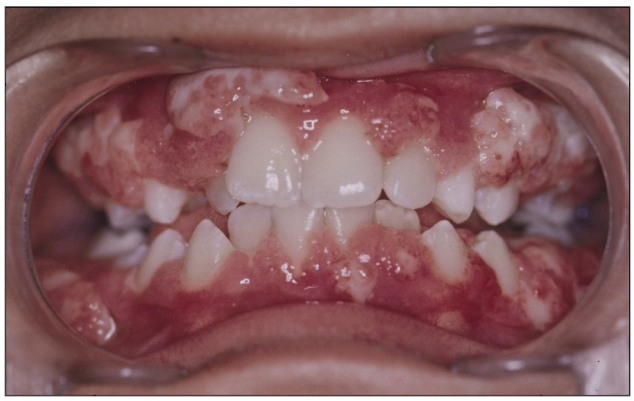

Figure 1. Generalized gingival hyperplasia with nodular enlargement covered by yellowish pseudomembranes.

both maxilla and mandible, which had developed 1 year previously. In this dental clinic, a multidisciplinary team made up of a stomatologist, oral pathologist, oral surgeon, periodontist, and pediatric dentist examined the patient and participated in the follow-up at all stages of diagnosis.

On intraoral examination, a generalized nodular gingival enlargement with ulceration covered with a yellowish pseudomembrane was observed (Figure 1). The clinical examination also revealed yellowish nodular pseudomembranous lesions in the upper eyelid (Figure 2) and a corneal opacity on the right eye with blindness probably due to trauma. The patient was then referred to an ophthalmologist, and clinical evidence of ligneous conjunctivitis and a cataract were found. The presence of polydactyly in both hands and several scars on his skin were also detected. The patient did not show any other mucosal involvement. There was no family history of similar diseases, and his medical history—which included drug use—was not significant.

HISTOPATHOLOGIC AND LABORATORY INVESTIGATION

The oral surgeon performed an intraoral incision biopsy, and the specimen was sent to the oral pathologist for microscopic analysis. The hematoxylin- and eosin-stained sections showed hyperplastic epithelium with surface ulceration. The subjacent connective tissue exhibited large deposits of eosinophilic material similar to amyloid or fibrin with a chronic inflammatory infiltrate surrounding these deposits (Figure 3).

Histochemical staining for amyloidosis using Congo red showed that these eosinophilic deposits did not have the classical features of amyloid, such as green birefringence under polarized light. Histochemical staining for glycogen using periodic acid schiff (PAS) also proved negative. Amyloidosis is Congo red positive, while lipid proteinosis and infantile systemic hyalinosis are PAS positive. Considering that the present case stained negatively for both Congo red and PAS, these differential diagnoses were ruled out. Consequently, microscopic diagnosis of hyperplasic chronic gingivitis with subepithelial deposits of fibrin-like material was confirmed.

A recommendation was made to the Pediatric Hematology/Oncology Service at the Araujo Jorge Cancer Hospital, Goiânia, Brazil, to evaluate the child's plasminogen activity (chromogenic method). The patient had a functional plasminogen level of 3% (reference range=80%-120%). Based on this finding, a diagnosis of clinical manifestations due to severe plasminogen deficiency was made. Moreover, a karyotypic analysis was performed, which revealed no chromosome abnormality.

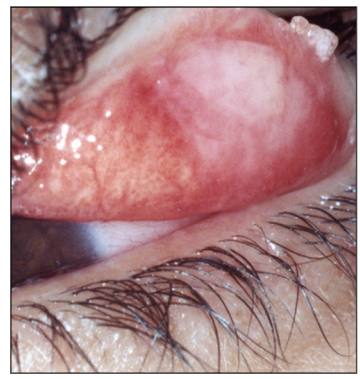

Figure 2. Yellowish nodular pseudomembranous lesions in the palpebral conjunctivae on the right.

TREATMENT

The hospital undertook the treatment of the patient and was accompanied by the hospital pediatric dentist.

Several treatment protocols were tried until a viable and successful clinical treatment was arrived at. The first protocol consisted of a gingivectomy followed by chlorhexidine

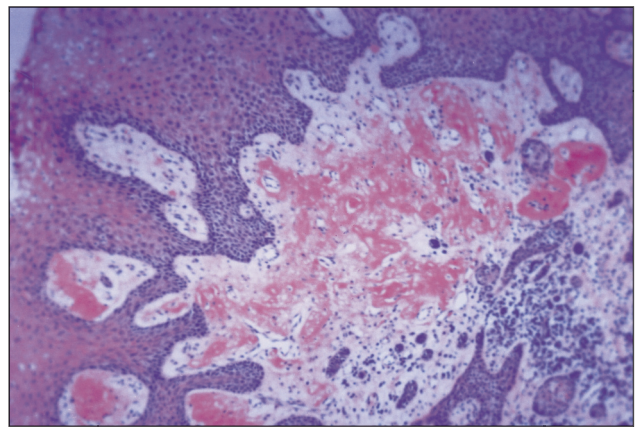

Figure 3. Photomicrograph showing downward proliferation of gingival epithelium with eosinophilic deposits in the subepithelial fibrous connective tissue (hematoxylin and eosin; original magnification X50).

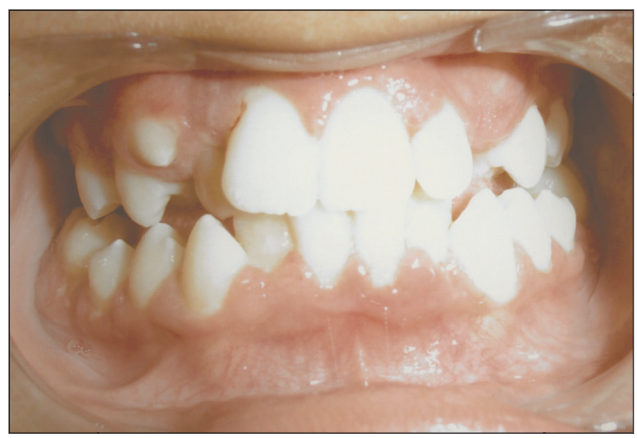

Figure 4. Complete remission of gingival lesions.

Table 1. Review of Reported Cases With Oral Manifestations Due to Plasminogen Deficiency

Reference	Age at onset (ys)/gender	Ulcerated gingival swelling	Other oral involvement	Other lesions (detectable)	Ligneous conjunctivitis	Therapies	Plasminogen functional activity (% normal)*
Scully et al[3] (case 1)	10/F	+†	-‡	Laryngeal, vaginal and ocular	+	NR§	27
Scully et al[3] (case 2)	5/F	+	-	-	-	NR	30
Scully et al[3] (case 3)	12/M	+	-	-	-	NR	27
Scully et al[3] (case 4)	13/F	+	-	-	-	NR	66
Scully et al[3] (case 5)	9/F	+	-	-	-	NR	16
Scully et al[3] (case 6)	6/F	+	-	-	-	NR	45
Scully et al[3] (case 7)	24/F	+	-	Ocular	+	NR	30
Scully et al[3] (case 8)	4/F	+	-	-	-	NR	50
Suresh al[5] (case 9)	59/F	+	-	-	-	No pharmacological intervention	54
Pantanowitz et al[4] (case 10)	46/F	+	Jaw with alveolar bone loss and teeth lost	Female genital tract and middle ear	-	NR	12
Silva et al (present case)	9/M	+	-	Ocular, skin and polidactilia	+	Systemic/local corticosteroid	3

Plaminogen reference range: 80%–120%
†+=present.
‡–=absent.
§NR=not reported.

(0.2%) and dexamethasone elixir (0.5 mg) rinsing and oral hygiene. Rapid regrowth of the gingival tissue occurred within 30 days.

The second protocol involved a gingivectomy followed by topical heparin (5,000 IU) and the use of systemic heparin (nadroparin calcium [2,800 IU]) per day for 45 consecutive days. It was observed that the gingival regrowth occurred slowly, and at the end of this phase the clinical features of the oral lesions were the same as present at the pretreatment phase.

The third protocol involved the use of systemic and topical corticosteroid without gingivectomy. This therapy consisted of the application of methylprednisolone pulses (25 mg/kg/day/IV) for 3 consecutive days every 30 days, followed by the use of oral prednisone (2 mg/kg/day). This third treatment modality, even without the gingivectomy, led to a complete remission of the oral and eye lesions. Since the third modality was successful, a fourth protocol—similar to the third but with a reduced dosage of corticosteroid—was tried to keep the gingival features normal. This fourth protocol consisted of the application of one pulse of methylprednisolone (25mg/kg/day/IV) every 20 days followed by the use of oral prednisone (5 mg/day). Along with this, the patient also used chlorhexidine (0.2%) and dexamethasone elixir (0.5 mg) rinsing. With the spacing out of the methylprednisolone pulse and/or a reduction of the oral corticotherapy, a regrowth of the gingival tissue was observed. To date, the patient is stable—having used the fourth treatment modality over a 3-year-period of follow-up evaluation—with no evidence of recurrence (Figure 4).

DISCUSSION

Plasminogen deficiency is a rare condition occurring in approximately 0.3% to 0.4% of the general population.[1] At present, the most common clinical manifestation reported, caused by severe type I plasminogen deficiency, is ligneous conjunctivitis.[1,2] It is characterized by the development of firm, fibrin-rich, woolly-like pseudomembranous lesions mainly on the palpebral conjunctivae.[2] Only in 2 previously reported cases did the oral manifestations coexist with ligneous conjunctivitis.[3] The eye-oral lesions may also be associated with pseudomembranous lesions of other mucous membranes in the nasopharynx, trachea, and female genital tract[3,4] (Table 1).

According to reports in the literature, oral manifestations due to plasminogen deficiency seem to affect young female patients, who have been diagnosed between the ages of 4 and 59[3-5] (Table 1). All previously reported cases with oral manifestation had a functional plasminogen assay range of 12% to 66%[3-5] (Table 1). It is worthy of note that this study's patient showed the lowest functional plasminogen activity (3%) reported in the English-language literature.

Recently, Suresh et al[5] have suggested that meticulous

oral hygiene should be indicated for mild to moderate gingival hyperplasia associated with plasminogen deficiency. For severe lesions, surgical excision followed by strict oral hygiene should be undertaken. The authors agree with Suresh et al,[5] who believe that inflammation plays a central role in the pathogenesis of these oral lesions. Along with both a gingivectomy and adequate oral hygiene, however, the authors would also suggest that topical and systemic corticosteroid may prove valuable in treating this condition as it reduces inflammation and thereby promotes healing. Other new approaches to treatment must be considered, since the use of systemic corticosteroid over a long period might have a variety of side effects. Schott et al[7] have reported complete remission of ligneous conjuctivitis in a male infant after replacement therapy with lysplasminogen (purified plasminogen concentrate). Despite its proven efficiency in treating eye lesions, this plasminogen concentrate is expensive and not widely available and has not yet been evaluated in patients with oral manifestations.

For this reason, the authors believe that this case could contribute to the profession's knowledge and understanding of clinical manifestations of plasminogen deficiency and help towards an early diagnosis and therapeutic management of these recurrent, progressive, and destructive clinical lesions.

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