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HOT TOPIC

Hypoplasminogenaemia, gingival swelling and ulceration

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This article reviews the evolution of the history related to an unusual type of generalized gingival swelling we first described in a single adult British patient; then recognized by us and others in small cohorts in Turkey; later found in several countries worldwide. We finally recognized it to represent the oral manifestations of plasminogen deficiency (hypoplasminogenaemia).
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Introduction

Generalized gingival swelling may be of genetic origin or acquired, but many cases are a consequence of exposure to drugs (phenytoin, ciclosporin and calcium channel blockers) or other agents (Table 1). A few cases are part of an obvious genetic syndrome – usually with systemic manifestations: even familial gingival fibromatosis is associated at the very least with hirsutism (Bozzo *et al*, 1994), and is sometimes part of a more phenotypically obvious syndrome such as Zimmermann-Laband syndrome (Bakaeen and Scully, 1991). Some cases of gingival swelling are associated with gingival deposits such as amyloid (Table 1).

Gingival and other lesions in a patient treated with tranexamic acid

This story began in 1991, when we encountered a single adult female British patient who presented with unusual generalized chronic gingival swelling associated with ascites and a pronounced form of conjunctivitis with significant circumorbital swelling described by the ophthalmologists as 'ligneous (woody) conjunctivitis'. Ligneous conjunctivitis is a rare form of chronic conjunctivitis, characterized by firm fibrin-rich, pseudomembraneous lesions on the tarsal conjunctivae mainly. Patients may also develop pseudomembranes on the mucosae of the nasopharynx, pharynx, tracheobronchial tree and the female genital tract; in a few cases, there has been congenital obstructive hydrocephalus (Cohen, 1990; Marcus *et al*, 1990; Scurry *et al*, 1993; Chowdhury *et al*, 2000; Ozcelik *et al*, 2001; Hyden *et al*, 2002; Chai and Coates, 2003; Ciftci *et al*, 2003; Pantanowitz *et al*, 2004).

The patient had Epstein's syndrome (congenital nephropathy, deafness with associated thrombocytopenia) and she was on treatment with tranexamic acid. Her gingival swelling was unusual in that it consisted of diffuse multinodular firm swelling of the entire gingivae with multiple, mainly marginal ulcers – often in the long axis of a tooth – and obvious pseudomembranes or exudates, but little gingival haemorrhage (Figure 1). The aetiology of the conjunctivitis was unclear and, though gingival lesions were mentioned in the ophthalmic literature on ligneous conjunctivitis, no good illustrations were found.

Gingival biopsy in this patient revealed only extensive fibrin deposits. We elected to stop the treatment with tranexamic acid and, as her lesions appeared then to ameliorate, we reported the case as a probable reaction to this drug (Diamond *et al*, 1991). In retrospect we should have considered the role of the antifibrinolytic activity of the drug in the aetiopathogenesis of the condition. Indeed, other cases of Epstein's syndrome reported by us, but not on drug therapy, had had no such gingival or conjunctival lesions (Richards *et al*, 1991).

Amyloidaceous gingival hyperplasia

About 5 years later, we encountered a small group of children in Turkey with gingival swellings which had a striking resemblance to those in the first case (Figure 2). Clinically they most closely resembled amyloid disease, but gingival biopsy demonstrated no amyloid deposits – only fibrin deposits (Figure 3) as in the first case. These and several other similar cases, seen mainly in Turkish patients, were thus described as 'amyloidaceous

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Table 1 Systemic causes of gingival swelling

Generalized	*Localized*
Congenital	*Congenital*
Amyloidosis (primary)	Cowden's syndrome
Aspartyl glycosaminuria	Epiloia (tuberous sclerosis)
Fucosidosis	Fabry's syndrome (angiokeratoma corporis diffusum universale)
Hereditary gingival fibromatosis and related syndromes	Granular cell tumour
Hyalinosis (infantile)	Sturge-Weber syndrome
Leprechaunism (Donohue's syndrome)	
Mucopolysaccharidoses	
Pfeiffer's syndrome	
Others	
Acquired	*Acquired*
Haematological	Inflammatory
Aplastic anaemia	Infections
Leukaemias	Herpes simplex virus
Vitamin C deficiency	Papillomaviruses
Deposits	Non-infective
Amyloidosis (secondary)	Fibroepithelial epulis
Lipoid proteinosis	Giant cell epulis
Ligneous conjunctivitis	Granulomatous conditions
Drugs	Crohn's disease
Calcium channel blockers	Orofacial granulomatosis
Ciclosporin	Sarcoidosis
Phenytoin	Pregnancy epulis
	Pyogenic granuloma
	Malignant neoplasms
	Carcinomas
	Kaposi's sarcoma
	Lymphomas
	Langerhans cell tumours
	Multiple myeloma
	Plasmacytomas
	Wegener's granulomatosis

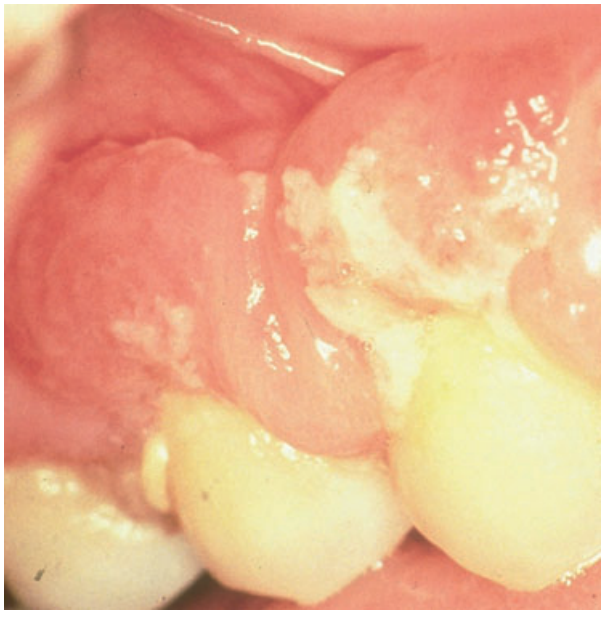

Figure 1 British patient reported as a reaction to tranexamic acid (from Diamond *et al*, 1991)

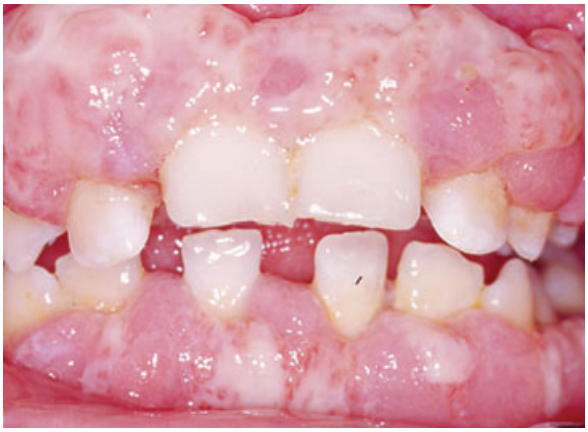

Figure 2 Gingival lesions

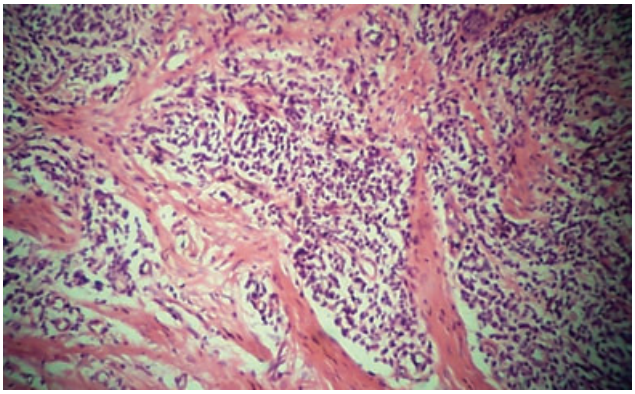

Figure 3 Histology showing fibrin deposits and mononuclear cell infiltrate H&E × 100

ulcerated gingival hyperplasia' or, when periodontal destruction was present, as 'destructive membranous periodontal disease (ligneous periodontitis)' (Frimodt-Moller, 1973; Gunhan *et al*, 1994, 1999; Baykara *et al*, 1995; Gokbuget *et al*, 1997). Only a small minority of these patients had demonstrable conjunctival lesions.

Amyloidaceous gingival hyperplasia is a manifestation of hypoplasminogenaemia

Shortly after this time, ligneous conjunctivitis was reported for the first time to be associated with inherited type I plasminogen deficiency (Mingers *et al*, 1995) and in the German literature. Subsequently, plasminogen gene mutations were demonstrated and an autosomal-recessive inheritance of this disorder confirmed and published in the English literature (Schuster *et al*, 1997, 1999a,b), and these results confirmed (Tefs *et al*, 2006).

We therefore examined several patients with this type of gingival swelling from Turkey and elsewhere, in a collaborative study including Europe and USA, and confirmed hypoplasminogenaemia in most (Scully *et al*, 2001) (Table 1).

Thus a case report of a rare patient with gingival swelling, presumably in a patient who developed severe

lesions because of fibrin deposits caused by the fibrinolytic defect produced by tranexamic acid, had sensitized us to what proved to be a most interesting and more widespread genetic condition affecting several patients. This had involved collaboration with colleagues in several countries and several dental (oral medicine; oral pathology; periodontology; paediatric dentistry) and other (dental, ophthalmology, paediatrics, haematology) disciplines.

Plasminogen and deficiencies

Plasminogen is an enzyme, synthesized in the liver, which circulates in the blood plasma and, on binding to fibrin, converts into plasmin – the active fibrinolysin. The protease plasmin plays an important role in haemostasis through controlled dissolution of the fibrin blood clot that arises from activation of the blood coagulation cascade (Figure 4).

Hypoplasminogenaemia is complete deficiency of plasminogen (type I plasminogen deficiency), and is characterized by undetectable plasminogen antigen (tPA and uPA; normal range 6–25 mg dl^{-1}) and activity (normal range 80–120%) and leads to the accumulation of fibrin in areas where there is activation of fibrinogen. It is associated with ligneous conjunctivitis (Mingers *et al*, 1995) but, surprisingly, widespread vascular thrombosis has not been reported – indicating the existence of alternative mechanisms for clot lysis and fibrin clearance (Plow, 1982; Heiden *et al*, 1996; Scully *et al*, 2001).

The most common clinical manifestations of hypoplasminogenaemia are ligneous conjunctivitis (80%) and ligneous gingivitis (34%), followed by involvement of the respiratory tract (16%), the ears (14%), ligneous vaginitis (8%), and gastrointestinal tract involvement (2%) (Tefs *et al*, 2006). The gingivae appear swollen, painless, nodular and ulcerated and covered with a yellowish-pink pseudomembrane with no special tendency to bleed (Gunhan *et al*, 1994). There may be extensive bone loss adjacent to the gingival lesions (Pantanowitz *et al*, 2004). The condition may remit and recur (Frimodt-Moller, 1973).

Dysplasminogenaemia (type II plasminogen deficiency) is characterized by normal or only slightly reduced plasminogen antigen level. Patients with dysplasminogenaemia rarely if ever develop ligneous conjunctivitis or lesions at other mucosal sites (Schuster and Seregard, 2003).

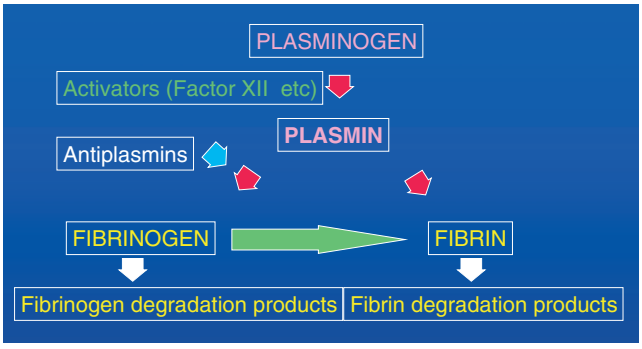

Figure 4 Normal fibrinolysis showing the role of plasmin in inhibiting the conversion of fibrinogen to fibrin

Management of patients with hypoplasminogenaemia

Treatment approaches have, until recently, been generally unsuccessful or achieved only partial resolution. Early efforts to control the conjunctivitis using topically applied fibrinolytics such as plasminogen concentrate (Ramsby *et al*, 2000; Martinovic and Ells, 2001; Watts *et al*, 2002; Heidemann *et al*, 2003), fresh frozen plasma (Tabbara, 2004) or heparin with corticosteroids were of minimal help (De Cock *et al*, 1995), but topical ciclosporin in combination with corticosteroids was of some value (Rubin *et al*, 1991; Tefs *et al*, 2004). Replacement therapy using lys-plasminogen, however, has been successful (Schott *et al*, 1998; Kraft *et al*, 2000).

With respect to the gingival lesions there is thus far reported no reliably effective therapy. Use of scaling and root planing, chlorhexidine and antibiotics has been largely unsuccessful at resolving the condition but may help control ulceration. Gingivectomy has often been employed to remove the gingival swelling but has typically been followed by rapid regrowth of the swelling (Gunhan *et al*, 1994, 1999; Gokbuget *et al*, 1997; Scully *et al*, 2001). Clearly, local measures alone cannot address the fundamental defect. The hypoplasminogenaemia must be addressed.

Plasminogen replacement is the logical treatment, particularly if there are extra-oral lesions in addition, but plasminogen preparations have a short half-life, are costly and may have adverse effects on intravenous administration (Kraft *et al*, 2000). Plasminogen concentrate prepared in the form of a mouth rinse may offer some help. Oral contraceptives have increased plasminogen functional activity in cases with low, but not absent, plasminogen levels and have led to partial clinical improvement (Teresa Sartori *et al*, 2003; Tefs *et al*, 2004).

Conclusions

The story emphasizes the importance of looking beyond the dental literature; of interdisciplinary and global collaboration; of scrutinizing the scientific literature both in the English language and non-English; and of logical thinking when faced with a clinical dilemma.

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