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Periodontal treatment in two siblings with Papillon-Lefèvre syndrome: 12-year follow-up and review of the literature

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Aim: The aim of this report was to present the periodontal treatment and maintenance over a period of 12 years in two siblings with Papillon-Lefèvre syndrome (PLS), aged 17 and 15 years respectively.
Study design: Initial treatment included oral hygiene instructions, a 0.12% chlorhexidine digluconate mouthrinse and scaling and root planing with simultaneous administration of oral 250 mg tetracycline twice daily for 2 weeks. For the first 4 years, patients were enrolled in a 1-month recall maintenance programme. Due to re-establishment of inflammation, during the next 8 years combined mechanical and antimicrobial periodontal therapy was administered. Clinical and radiographic evaluation was performed in 1993, 1996, 2000 and 2004.
Results: In the first period, periodontal disease activity was controlled. In the second period, periodontal breakdown advanced rapidly, especially in the younger sibling. Tooth loss was inevitable, and both patients became edentulous at the age of 29 and 27 respectively.
Conclusions: The role of oral hygiene in PLS may determine the rate of disease advance on an individual basis. As evidenced in the present cases, the adoption of a strict maintenance schedule and a high level of oral hygiene efficacy is a prerequisite for prolonging the life of the dentition.

■ Introduction

Papillon-Lefèvre syndrome (PLS)[1], is a rare, inheritable form of hyperkeratosis palmoplantaris combined with premature destruction of the periodontium.

PLS is believed to be an inherited disease that is autosomal recessive, with a prevalence of 1 to 4 per million[2]. The main clinical symptoms of PLS are diffuse palmoplantar hyperkeratosis and an early-onset form of generalised, rapidly progressive periodontitis, leading to premature loss of both primary and permanent teeth[2-4]. The cause of the disease is still unknown, but a number of factors have been implicated, including a combination of ecto- and mesodermal malformations[5], possible defects of gingival epithelium[2,6,7], cementum[8,9] and periodontal ligament[9,10]. The subgingival microflora associated with the syndrome is characterised by the predominance of Gram-negative anaerobic pathogens such as *Porphyromonas gingivalis*, *Aggregatibacter actinomycetemcomitans* (previously *Actinobacillus actinomycetemcomitans*), *Capnocytophaga* and *Spirochaetes*[9,11-15]. Furthermore, the findings of elevated antibody titres to *A. actinomycetemcomitans* in PLS patients provide further evidence for the involvement of this bacterial species in the pathogenesis of

PLS periodontitis[16,17]. PLS has been associated with a compromised host response, particularly with defects in immune-mediated mechanisms such as: impaired chemotactic, phagocytic and bactericidal functions of the neutrophilic granulocytes[4,13,16,18], decreased lymphocyte response to pathogens[3,18,19], impaired cytotoxicity of natural killer (NK) cells[20], depression of helper-to-suppressor T cells ratio[21], deficient monocytic function[4,17], degenerative changes of plasma cells[22] and elevation of serum immunoglobulin[23,24].

Recent evidence suggests that genetic mutation of the cathepsin C gene (CTSC) is an aetiological factor in PLS[25-29]. Such mutations may result in a loss of function of the cathepsin C enzyme and a subsequent inactivity of neutrophil serine proteases, leading to dysregulation of the inflammatory response of polymorphonuclear leucocytes (PMNs), thereby rendering the periodontal tissues more susceptible to destruction[30-33].

Periodontal treatment of PLS patients on a long-term basis has so far proved to be ineffective in preventing tooth loss, regardless of the different approaches used[4,34-37].

The aim of this report was to present the clinical, radiographic and laboratory findings in two siblings with PLS, as well as their periodontal treatment and maintenance over a period of 12 years.

■ Case description and results

In 1992, a 17-year-old male (case A, born in 1975) and his 15-year-old brother (case B, born in 1977) were referred for periodontal treatment, having been diagnosed with PLS. Neither parent, nor their younger sister was affected. The parents reported that pregnancy, labour and delivery had been normal for all three children.

■ Case A

■ Skin findings

Dermatological examination revealed the presence of hyperkeratotic lesions of the palms (Fig 1) and soles. The lesions were diffuse and mild. The patient was reported to have developed normally until the first 6 months of age, at which time skin lesions started to appear. He received keratolytic and anti-inflammatory ointments and creams for topical use, without any significant improvement. Medical examination did not reveal any other disorders and there was no history of any other serious illness.

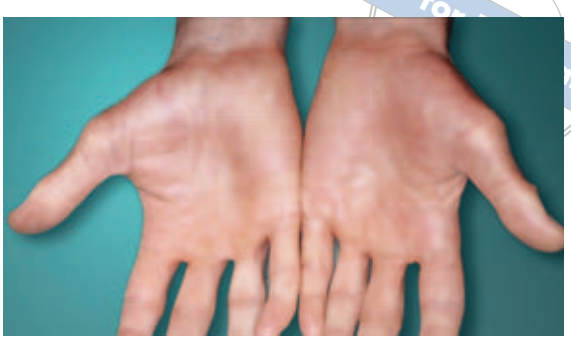

Fig 1 Case A: hyperkeratosis of the palms at initial presentation (1992).

■ Oral findings

On oral examination, the patient's dentition consisted of 22 permanent teeth. Seven teeth had already been exfoliated, whereas three wisdom teeth were impacted, as shown radiographically (Fig 2). The patient presented with a temporary resin-bonded fixed partial denture in the maxillary anterior region (Fig 3), and a removable acrylic partial denture in the mandibular anterior region (Fig 4). All teeth demonstrated pathological mobility, with the right maxillary second premolar being the most severe (grade 3). The gingival tissues were, in general, markedly inflamed, oedematous, and displayed dark red granulomatous proliferations at locus (Fig 3). There was heavy plaque accumulation on all teeth, with calculus deposits present at the lingual aspect of the removable denture and the adjacent canines (Fig 4). The majority of sites bled on probing, and suppurative discharge was noted in some sites. The oral mucosa was normal in both colour and consistency.

A comprehensive periodontal examination was performed and clinical records were obtained during initial examination, prior to any periodontal treatment (Table 1). Plaque index (PI)[38], gingival index (GI)[39], probing depths (PD) and clinical attachment level (CAL) measurements, were assessed at 6 sites per tooth (mesiobuccal, midbuccal, distobuccal, distolingual, midlingual, mesiolingual), by a single calibrated

examiner using a straight graded periodontal probe and rounded to the nearest millimetre. The cemento-enamel junction (CEJ) was used as a reference for the CAL measurements. Assessment of the horizontal attachment levels at each furcation location was made with the use of a colour-coded, calibrated Nabers probe (PCP-15, Hu-Friedy, Chicago), marked at 3 mm intervals (PQ2N, Hu-Friedy)[40]. PD were between 4 and 10 mm, and CAL measurements ranged between 3 and 8 mm (Table 1). Bleeding in response to probing (BOP) to the bottom of the pocket was recorded approximately 20 s after probing[41].

Clinical examination was coupled with radiographic evaluation, according to which there was a generalised pattern of horizontal and vertical alveolar bone loss of approximately 50% (Fig 2). The crown/root ratio in most teeth averaged 1:1, although in some teeth it was poor (2:1 to 3:1). There was evidence of furcation involvements in association with the maxillary and mandibular left molars. The unerupted teeth were in normal stages of development.

Laboratory investigation

Laboratory investigation performed upon presentation included haematological tests (Table 2), as well as alkaline phosphatase, albumin, calcium, phosphate, glucose, iron, cholesterol, triglycerides, urine and immunoglobulin C3 and C4 analysis. All the tests were within normal limits.

Case B

Skin findings

Dermatological examination revealed the presence of moderate, diffuse hyperkeratotic lesions of the palms and soles. Medical examination did not reveal any other disorders, and there was no history of other serious illness.

Oral findings

On oral examination, the patient's dentition consisted of 14 permanent teeth (Figs 5 and 6). Fourteen teeth had already been exfoliated, whereas all four wisdom teeth were impacted, as shown radio-

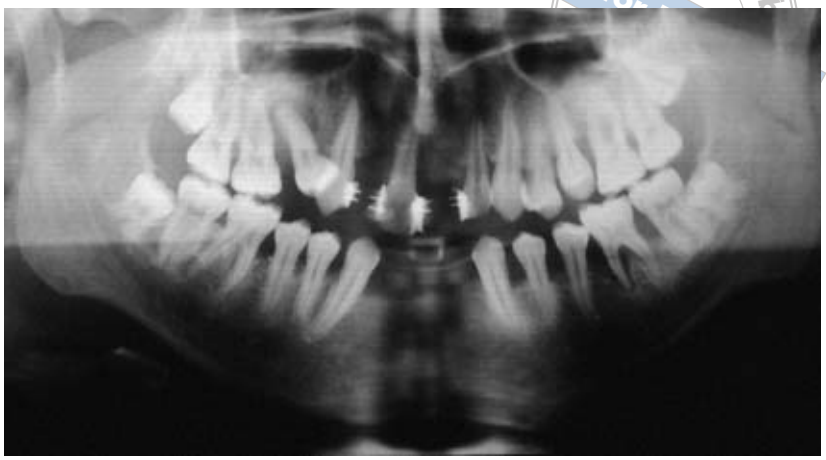

Fig 2 Case A: panoramic radiograph at initial presentation (1992), showing a generalised horizontal and vertical alveolar bone loss of approximately 50%. Three wisdom teeth (28, 38 and 48) are impacted.

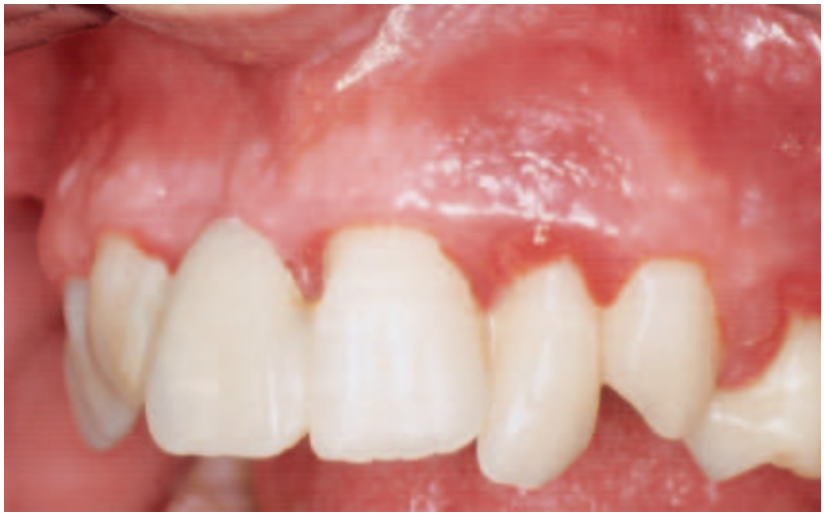

Fig 3 Case A: clinical photograph of the maxillary arch (1992). The gingival tissues around the temporary resin-bonded fixed partial denture exhibit marked inflammation, oedema, and dark red granulomatous proliferations at locus.

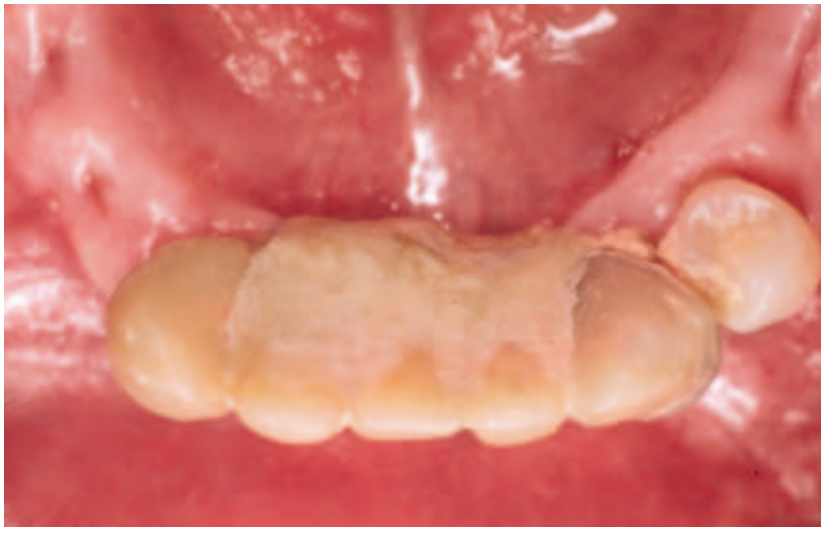

Fig 4 Case A: clinical photograph of the mandibular arch (1992), showing heavy plaque accumulations and calculus deposits at the lingual aspect of the removable denture and the adjacent canines.

Table 1 Mean values of clinical measurements (1992–2004).

	1992		1993		1996		2000		2004	
	A	B	A	B	A	B	A	B	A	B
No of teeth	22	14	21	14	21	16	20	14	8	5
PI (%)	78	83	20	24	21	22	57	63	76	80
GI (%)	61	71	17	20	16	20	44	56	70	78
BOP (%)	73	80	19	21	20	20	47	54	75	84
PD (mm)	4–6	5–7	3–4	3–4	4–5	4–5	5–8	7–9	7–11	9–12
CAL (mm)	3–5	3–6	2–4	2–4	2–4	2–5	4–7	5–9	7–10	8–12

Table 2 Haematological findings upon presentation (1992).

	Case A	Case B	Normal range
White blood cell count (x109/l)	9.5	8.2	4.8–10.8
Red blood cell count (x1012/l)	4.4	4.6	3.8–5.4
Haemogobin (g/dl)	13.2	14.0	10.0–16.0
Haematocrit (%)	40.7	39.7	33.0–42.0
Platelets (x109/l)	361	352	130–400
Neutrophils (%)	56	60	54–62
Monocytes (x109/l)	2.1	2.6	1.7–9.3
Eosinophils (x109/l)	0.9	1.0	0.7–1.2
Lymphocytes (%)	31	29	20.5–51.1

graphically (Fig 7). Two removable partial dentures had been placed by the patient's clinician in the anterior regions of the maxilla and mandible respectively, to replace the missing teeth (Fig 8). All teeth exhibited pathological mobility, with the second premolars being the most severe (grade 3). The patient reported difficulty in chewing and pain in the maxillary right premolar region (tooth 15). For this reason, and in view of its poor prognosis, the tooth was extracted during the clinical examination, and before the radiographic examination. The gingival tissues were severely inflamed, reddened and oedematous, accompanied by dark red granulomatous proliferations at locus (Figs 5 and 6). Deposits of supragingival plaque and calculus were evident on the cervical portion of some teeth, as well as on the surfaces of both partial dentures (Fig 8).

Periodontal recordings of clinical parameters, such as PI, GI, PD, CAL and BOP, were obtained from the younger brother (case A, Table 1). PD were between 5 and 11 mm, and CAL measurements ranged between 3 and 9 mm. Radiographic examination revealed severe bone loss (approximately 70%) around all permanent teeth (Fig 7). In some teeth, bone resorption extended almost to the apical third of the roots, with their crown/root ratio averaging 3:1. However, no furcation involvement in any of the existing molars was detected.

Laboratory investigation

Laboratory tests performed upon presentation for case B were found to be normal (Table 2).

Periodontal treatment and follow-up (1992–2004)

Immediately after clinical and radiographic examination, the patients were subjected to periodontal treatment, which included: personalised detailed oral hygiene instructions, scaling and root planing of all standing teeth with the use of hand instruments and ultrasonic devices, chlorhexidine digluconate mouthrinse (0.12%) twice daily for 3 weeks and simultaneous systemic use of antibiotics (tetracycline: 250 mg, twice/day) for 2 weeks.

Five weeks after completion of the initial treatment, the patients returned for re-evaluation. In both cases, the gingival tissues appeared significantly improved, with no apparent clinical signs of inflammation. On average, PD measured less than 4 mm, with the exception of the mesial sites (5 to 7 mm) of teeth 26 and 36 in case A, and the mesial and distal sites (6 to 8 mm) of teeth 25, 35 and 45 in case B. Their oral hygiene varied between moderate and good, with PI scores of 20% and 24% respectively (Table 1). At that time, the plaque-retentive temporary resin-bonded fixed partial denture and the maxillary right central incisor (tooth 11) in case A were removed, and were replaced by a removable partial denture.

Both patients were placed on a strict maintenance protocol, with monthly recall appointments. At the maintenance visits, the oral hygiene level was evaluated and the PI was recorded. Supragingival scaling and root planing was performed when needed, and oral hygiene was reinforced. In addition, the tooth surfaces were polished with the use of rubber cup and sodium fluoride paste. The programme was maintained for approximately 4 years (1992 to 1996), and proved to be efficacious in controlling inflammation and halting disease progression. The periodontal status in both cases remained more or less stable, as evidenced by the clinical recordings (Table 1) and the radiographic evaluation (Figs 9 and 10). By 1996, most of the patients' third molars had erupted, except from teeth 38 and 48 in case A, which were still impacted.

In the following years, the patients' compliance with maintenance gradually deteriorated, as they were unable to follow the monthly recall appointments. As the intervals between successive appointments increased over time, episodes of disease recurrence and re-establishment of inflammation became more frequent. Clinically, disease exacerbations were characterised by marked swelling and granulomatous proliferations of the gingivae, loss of periodontal attachment, and occasional formation of periodontal abscesses. Periodontal treatment was symptomatic, aimed primarily at resolving inflammation and dealing with the acute symptoms of the disease, i.e. periodontal abscesses. The treatment regimen was the same as before, including mechanical treatment (scaling and root planing) under local anaesthesia, in con-

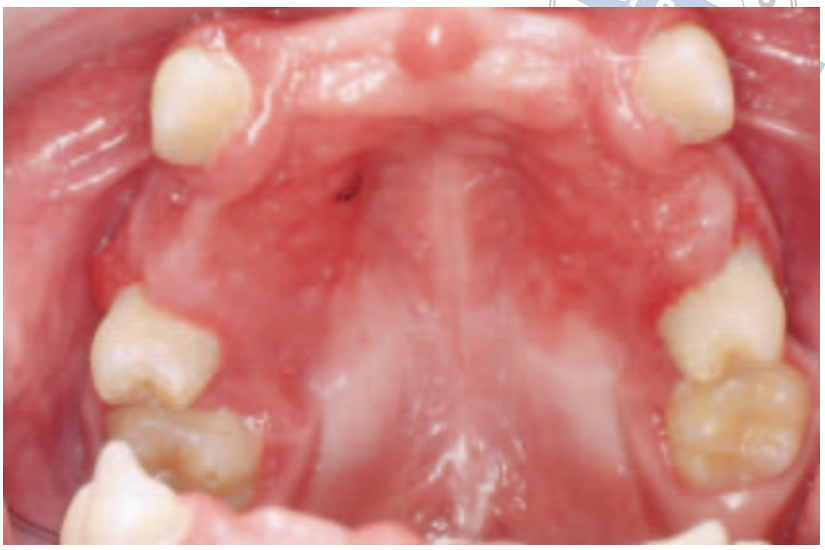

Fig 5 Case B: clinical photograph of the maxillary arch (1992). The gingival tissues appear severely inflamed and oedematous, accompanied by dark red granulomatous proliferations at locus.

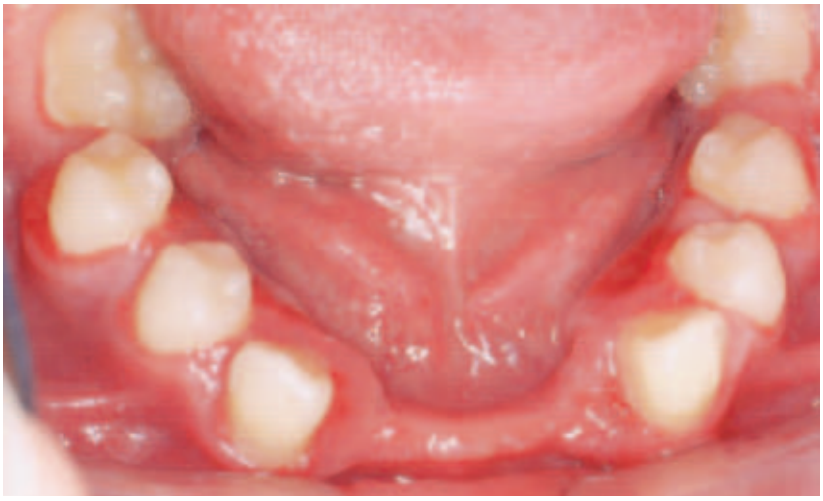

Fig 6 Case B: clinical photographs of the mandibular arch (1992). The gingival tissues appear severely inflamed and oedematous, accompanied by dark red granulomatous proliferations at locus.

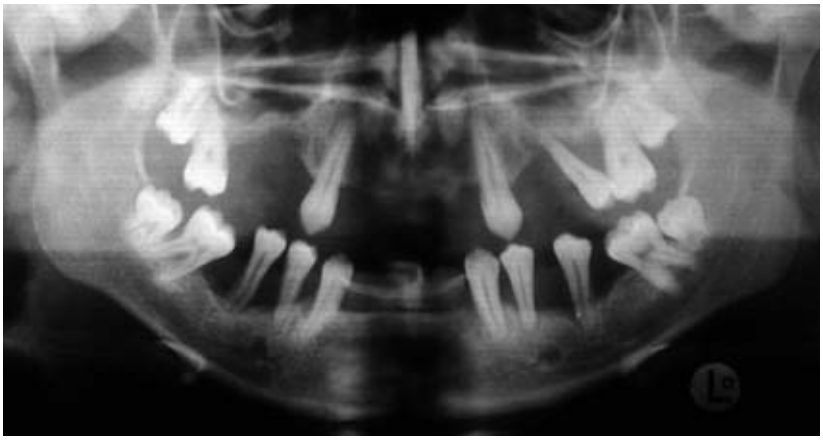

Fig 7 Case B: panoramic radiograph at initial presentation (1992), showing the existence of four impacted wisdom teeth and a generalised horizontal and vertical alveolar bone loss of approximately 70%.

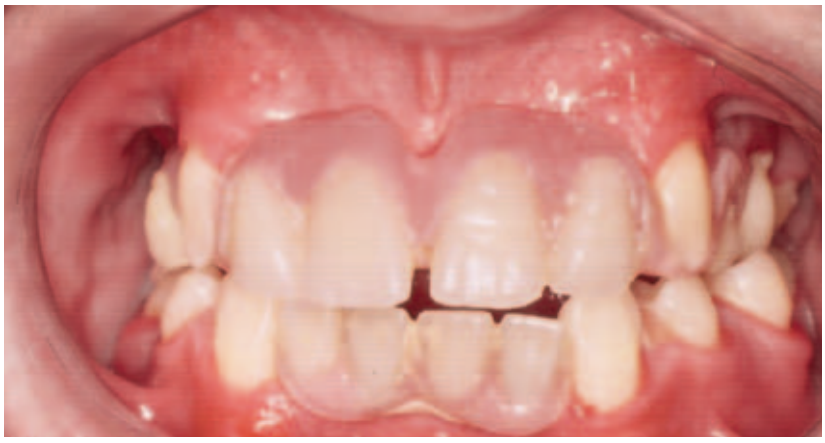

Fig 8 Case B: clinical photograph at initial presentation (1992), with the maxillary and the mandibular removable partial dentures in place. Dental plaque and calculus deposits are evident on the denture surfaces.

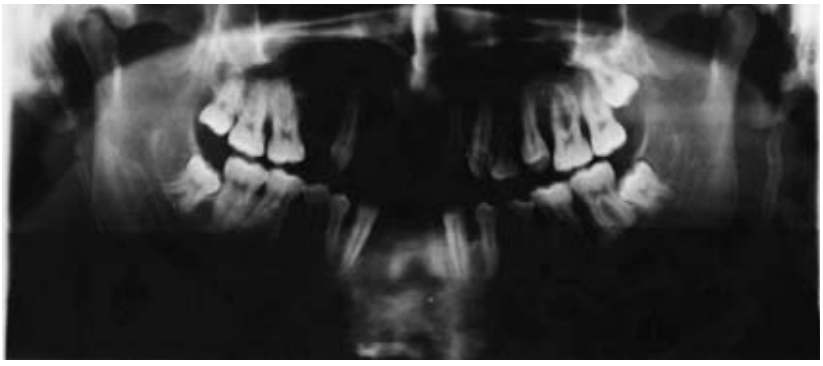

Fig 9 Case A: panoramic radiograph of the situation in 1996. Wisdom teeth 38 and 48 remain impacted.

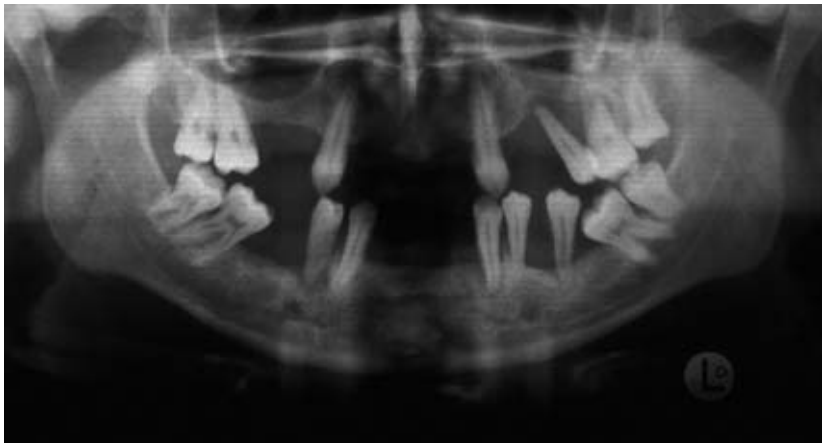

Fig 10 Case B: panoramic radiograph of the situation in 1996.

junction with systemic administration of tetracycline (250 mg, twice/day) for 2 weeks and 0.12% chlorhexidine mouthrinse twice daily for 3 weeks.

In 1998, the maxillary left lateral incisor (tooth 22) in case A had become extremely mobile, and was extracted. At the same time, the removable partial denture in the maxillary anterior region was replaced by a fixed partial denture, which extended from the maxillary right premolar region (tooth 14) to the maxillary left canine (tooth 23). The two canines (teeth 13 and 23) were used as abutments. Occlusion was adjusted to optimal level and to maximum balance, and oral hygiene care for the abutment teeth was reinforced.

By the year 2000, despite the patients' low motivation, most of their teeth had been maintained. In case A, one tooth (tooth 36) had been lost, whereas the mandibular right wisdom tooth (tooth 48) had erupted (Fig 11); in case B, two teeth (teeth 25 and 44) had been lost (Fig 12). In general, according to the evaluation of the periodontal recordings, between 1996 and 2000, deterioration of the periodontal status was greater in case B than in case A (Table 1).

In case A, there was an average increase in probing depths by 2 to 3 mm, and in loss of attachment by 2 to 3 mm (Table 1). PI, GI and BOP scores were also higher (Table 1). Tooth mobility ranged from grade 1 to grade 2. Furcation involvement was noted in most of the molars (Fig 11), ranging from class I (tooth 46), to class II (teeth 17, 27 and 37) and, to class III (tooth 26). As evidenced radiographically (Fig 11), there was a generalised pattern of additional bone loss between 1996 and 2000.

In case B, periodontal recordings showed an average increase of 3 to 5 mm in PD, and of 4 to 5 mm in attachment loss, with PI, GI, and BOP scores also higher (Table 1). All the remaining teeth exhibited increased pathological mobility, ranging from grade 2 to grade 3. Furcation involvement was present in most of the molars, ranging from class I (tooth 17), to class II (teeth 18 and 37) and to class III (teeth 27, 47 and 48). Despite the severity of the periodontal destruction and the mobility of the teeth, the patient did not agree to the authors' recommendation for extraction of the three teeth with the worst prognosis (teeth 33, 34 and 35). Instead, the patient preferred to maintain his compromised natural dentition for as long as possible, fearing that edentulism might have a psychological impact on him.

In the years between 2000 and 2004, maintenance was limited to one or two visits per year, with the patients' compliance towards oral hygiene reduced to

very low levels. Inevitably, repeated episodes of disease activity and multiple periodontal abscesses led to further periodontal destruction, and finally to loss of teeth. By 2004, it was clear that in both patients, masticatory function had been restricted substantially. Only 8 teeth in case A, and 5 teeth in case B were present, exhibiting extreme mobility and little, if any, periodontal support. Periodontal recordings were in accordance with the overall poor periodontal status (Table 1). In view of the resulting situation, there was no choice but to proceed with extractions of all the remaining teeth, and the patients became edentulous at the age of 29 and 27 respectively.

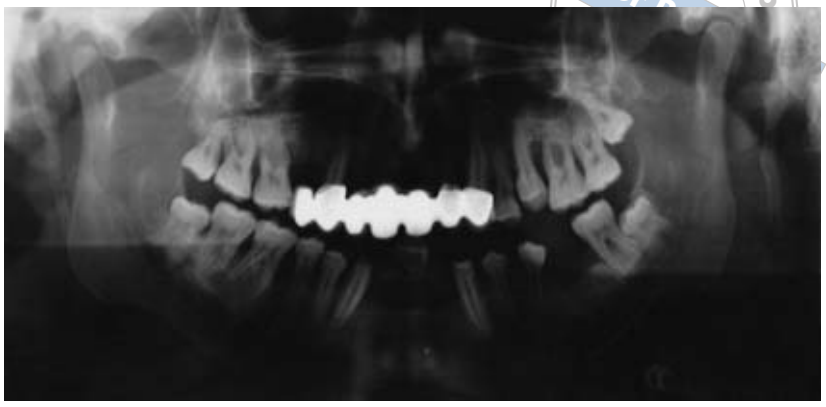

Fig 11 Case A: panoramic radiograph of the situation in 2000, showing furcation involvement in most of the molars, and a generalised pattern of advanced bone loss.

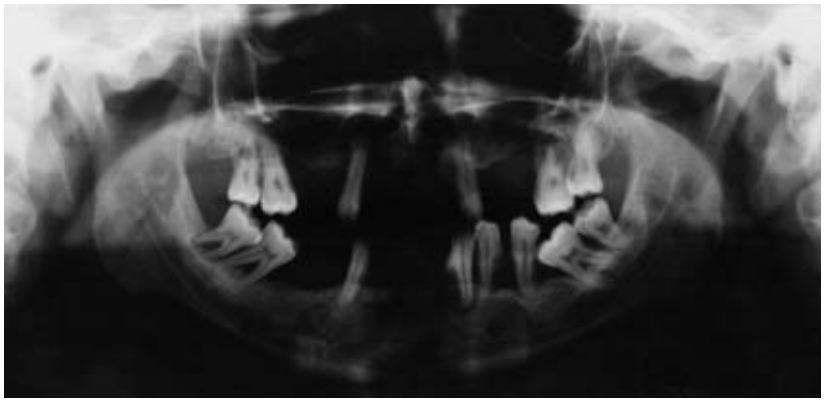

Fig 12 Case B: panoramic radiograph of the situation in 2000, showing furcation involvement in most of the molars, and a generalised pattern of advanced bone loss.

Discussion

Periodontal treatment outcome in patients with PLS still remains unpredictable, despite the diversity of the methods used, including mechanical therapy alone or in conjunction with systemic antibiotics[34,42] and periodontal surgery[43], the use of oral retinoids[16,44], and the extraction of all primary teeth in the hope that elimination of the infection in childhood may prove beneficial for the later erupting permanent teeth[4,35,37,45-47].

Mechanical periodontal therapy with the use of simultaneous antibiotics has been established as the approach most commonly used by clinicians in PLS cases, to eradicate periodontal pathogens such as *A. actinomycetemcomitans*, which has been strongly associated with PLS periodontitis[4,41,43,47]. The antibiotic regimens of choice include a combined amoxicillin and metronidazole scheme[31,43,45-47] and tetracycline administration for long-term and/or short-term use[4,48]. When the present study started in 1992, we decided to proceed with an extensive treatment method including both mechanical and antimicrobial means of plaque-induced inflammation control. Although antimicrobial testing was not performed in the present patients, selection of tetracycline as an adjunctive systemic antibiotic was stimulated by the encouraging results of Preus and Gjermo[4]. During the active phase of the initial treatment, in both cases, tetracycline was administered for a limited period of 2 weeks, in relatively low dosages of 500 mg per day. The effectiveness of the initial treatment phase depends largely on the successful elimination of inflammation, in conjunction with suppression of periodontal pathogens[41]. As evidenced in the present study, the chosen primary, combined approach resulted in significant improvement in all clinical parameters, according to the results of the evaluation of the periodontal status 5 weeks later. At the same time, the patients' oral hygiene standards were raised to a satisfactory level, and iatrogenic factors such as plaque-retentive areas were removed to facilitate oral hygiene.

Despite the absence of a definitive indication that oral hygiene level is the crucial factor for treatment outcome in PLS patients[48], it was our belief that, if a strict maintenance protocol with monthly sessions of supportive care was enforced, with emphasis on professional oral hygiene, maintenance of the periodontal status at an acceptable level may be achieved. Thereby, it was hoped that future episodes of disease activity and further periodontal destruction might be prevented. Based on the assumption that with increasing age, the symptoms associated with PLS decrease[37], it is clear that by prolonging the life of the

dentition well into adulthood in PLS patients, its prognosis may be significantly improved.

In both patients, the outcome of treatment during the first 4-year follow-up period was successful, in accordance with the results from previous studies[4,34,35,41,47,48]. It may be assumed that in some PLS cases, a favourable response to simple supportive care during long-term maintenance is possible, providing that strict oral hygiene measures are enforced. In both the patients, it became evident that their gradual withdrawal from the strict maintenance protocol coincided with recurrence of the disease, leading to re-establishment of inflammation and further periodontal breakdown. The fact that the frequency and the severity of the disease episodes increased over time, as a result of the patients' inability to comply, strengthens the view that strict plaque control and preventive measures through maintenance should be the issues of primary care in PLS cases, regardless of the severity of periodontitis and the type of periodontal therapy.

With the continuing periodontal destruction and the inevitable gradual loss of teeth in PLS patients, it is essential to maintain stability of the remaining teeth at the maximum possible level. Therefore, the decision to provide a fixed prosthesis for patient A was justified by the fact that the abutment teeth used were stable, with no clinical signs of inflammation, and had maintained most of their connective tissue attachment intact since 1992. Furthermore, with the new prosthesis, the practice of oral hygiene in the region became more efficacious.

According to some authors[37], the theory that the timing of the disease burst is different between individual patients may explain why different studies report different clinical outcomes. Furthermore, over the years, a number of possible causative factors have been implicated in the pathogenesis of PLS periodontitis, including anatomical defects, impaired host response, microbiological factors and, most recently, genetic defects. The role of genetic factors with the ability to affect the host response and/or the structural defences of the periodontium, thus rendering the tissues more susceptible to destruction, emerges as the most likely primary aetiological factor that may initiate and enhance the pathogenetic mechanisms in this type of aggressive periodontitis. Therefore, it may be assumed that a combination of different predisposing factors, possibly of genetic origin, in conjunction with certain external modifying agents, such as oral hygiene level or provision of dental care, may determine the onset of the disease and its rate of progress, as well as the degree of the patient's response to therapy, on an individual basis.

Under the limitations of the present case report, the following conclusions can be drawn. Despite the increasing wealth of information, the pathophysiology of PLS remains unclear. However, the presence of certain genetic defects exerting a direct, and/or an indirect pathogenic potential may shed light on the multi-factorial process in PLS periodontitis. The influence of other factors, such as oral hygiene, on this model may possibly determine the rate of disease advance on an individual basis. On the other hand, the early diagnosis and provision of periodontal treatment, followed by the adoption of a strict maintenance programme, seem to be the primary issues in prolonging the longevity of a patient's dentition.

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