Oral diagnosis of Behcet disease in an eleven-year old girl and the non-surgical treatment of her gingival overgrowth caused by Cyclosporine

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A case of an eleven-year old girl with Behcet disease is presented. Non-surgical treatment of gingival overgrowth caused by the use of Cyclosporine was successfully treated. This case emphasizes the need for cooperation between the medical and dental professionals and the responsibility of dental professionals to lead the diagnosis of systemic diseases like Behcet.
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INTRODUCTION

Behcet disease is a multi-system autoimmune disorder of unknown etiology,[1] its onset is typically in young adults,[2,3] but it may also affect children and adolescents.[2-7] It has a worldwide distribution, but is more prevalent in Japan, the Middle East and some Mediterranean countries.[2,8-10]

The multi-system expression of Behcet disease predominantly includes: the oral mucosa, skin and eyes, however, it may also involve the urogenital, gastrointestinal, respiratory and central nervous systems, muscles and large vessels, leading in some cases to life threatening pathologic conditions.[1-17]

The expression of Behcet disease varies significantly in each individual, therefore, its diagnosis may be unclear.[2] Moreover, treatment is complicated by the necessity to tailor it based on the particular symptoms of each individual.[2] Corticosteroids, Interferon-alpha, Oxybutynin, Thalidomide and Cyclosporine are among the numerous medicaments, utilized for treatment.[3,4,10,18-20]

Behcet disease is of particular interest to the dental profession since: 1) It involves the oral mucosa with recurrent and painful episodes of ulcerations,[1-3,9,10,13] that may impede regular oral hygiene facilitating the establishment and worsening of gingivitis.[1] 2) Cyclosporine, which is utilized for the treatment of Behcet disease may cause gingival overgrowth.[20,21]3) The oral manifestations Behcet may be the leading clue to diagnosis.[7]

This is a report of a case of "N", an young female child, who was referred to a pediatric dentistry clinic for the treatment of severe gingival overgrowth and inflammation. These conditions were related to plaque accumulation and the use of Cyclosporine for the treatment of uveitis (uvea: the vascular tunic of the eye consisting of the choroid, ciliary body and the iris[22]). The report is characterized by the recognition of signs that eventually led to the diagnosis of Behcet Disease, and by the success of the non-surgical treatment of the severe gingival overgrowth and inflammation.

CASE REPORT

General history

"N", an 11-year-old girl, was the second of 6 children from an Arab middle socioeconomic class Jerusalem family, who had no record of familial or hereditary diseases. "N" had no history of any uncommon disease until one year before, when she was diagnosed as having uveitis with and unknown etiology. Since the diagnosis, she was hospitalized twice for the treatment of acute eye inflammation and increased internal eye pressure. The selection and combination of the medicaments with the purpose to save her eyesight were frequently

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changed based on her eyes situation and the appearance of undesired side effects.

The last treatment protocol included Cyclosporin (initiated 3 months previously), Prednisone, Kolhazin and eye ointments: Xalatan, Iopidine, Tiloptic, Voltaren and Sterodex. In addition, two days before the visit to our clinic, "N"s physician prescribed her Amoxicillin and clavulanic acid (Augmentin) for the treatment of severe gingival inflammation and referred her to our clinic.

Dental history

"N" received dental treatment only once several years previously. This procedure involved a traumatic extraction of a primary tooth under physical restraint by several adults. Since then, "N" avoided any further dental examination or treatment. During the last few months, "N" has been experiencing increasing discomfort and pain, while eating and brushing, from the gingiva. She reported an increased mobility of the teeth, and gingival bleeding after brushing. Therefore, "N" refrained from tooth brushing facilitating further deterioration of her gingival disease. Lately, the pain and gingival bleeding became severe and spontaneous, and severe halitosis evident.

Initial examination

"N" was extremely reluctant to enter the dental clinic. Only after repeated efforts, in which non-pharmacological behavior management techniques were applied, did she agree to enter the clinic and undergo clinical and radiographic examinations.

Extra oral findings

"N" was found to be a physically well developed child. Her face appeared swollen, she had eye asymmetry (the left eye being more closed than the right one) and slightly higher than normal hairiness above the upper lip and forehead. The submandibular lymph nodes were palpable, but not tender, facial muscles and mouth movements were normal. Severe halitosis was evident.

Intra oral findings (Figures 1 and 2)

Extensive dental plaque accumulation, supra and subgingival calculus, severe gingival overgrowth and intense generalized gingivitis affecting the marginal and attached gingiva were prominent. The oral mucosa was within normal limits. The clinical dental findings included:

Pit and fissure caries in both maxillary second primary molars, and all first permanent molars.

Mesial caries in the maxillary right second primary molar. Buccal caries was found in both maxillary primary cuspids.

Increased tooth mobility of the maxillary primary cuspids, maxillary second primary molars and the maxillary left first primary molar. Any attempt to check the degree of mobility of the primary molars induced significant pain and a negative behavior response.

Erupting maxillary right first premolar, both mandibular first premolars and mandibular right second premolar.

Missing mandibular left second primary molar with corresponding premolar still unerupted, distal drift of the mandibular left first premolar and mesial drift of the mandibular left first permanent molar.

Angle Class I malocclusion, with anterior cross-bite of the permanent left lateral incisors.

Radiographic findings

Panoramic, anterior periapical and bite-wing radiographic examination indicated a normal oral development. The primary teeth with an increased mobility were close to normal exfoliation. No clinical or radiographic signs of childhood periodontitis were evident.

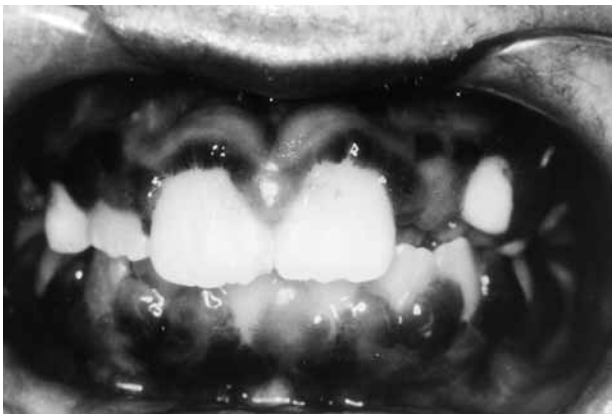

Figure 1. Initial anterior clinical picture in which severe gingival generalized overgrowth and inflammation, cross-bite of the permanent left lateral incisors and buccal caries in the maxillary primary cuspids are evident.

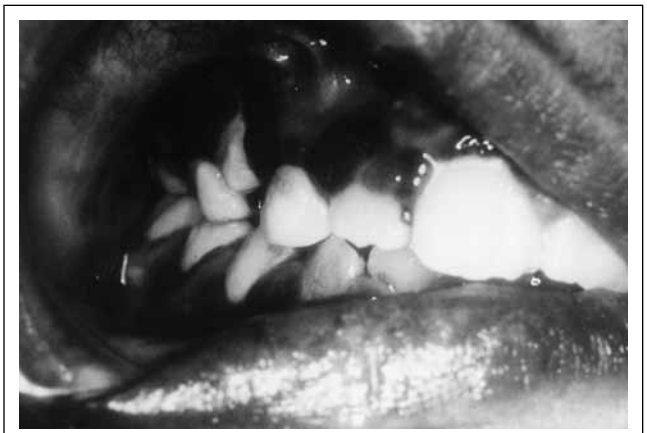

Figure 2. Initial lateral right clinical picture in which severe gingival overgrowth and inflammation are evident.

TREATMENT PLAN

In order to establish a comprehensive treatment plan, a periodontic and orthodontic consultations were done. The periodontist recommended initial periodontal preparation (oral hygiene instructions, prophylaxis and scaling) and subsequent gingival surgery. The orthodontist indicated that the treatment of malocclusion should only be considered after achieving oral hygiene and gingival health. Therefore, the initial treatment plan included:

Attain rapport to facilitate compliance for oral health care and attendance to dental appointments.

Gradual reduction of dental fear by non-pharmacological behavior management techniques.

Comprehensive oral treatment, which included:

Introductory dental prophylaxis and home oral care instructions.

Scaling.

Chlorhexidine rinses.

Pit and fissure sealants.

Restoration of the carious permanent teeth.

Extraction of the primary molars.

Repeated meticulous oral hygiene reinforcement.

Gingival surgery.

Institution of a follow up schedule.

Initial treatment

In order to attain rapport, gradually reduce the fear to dental treatment and to initiate oral hygiene, a dental prophylaxis with a rotary brush mounted in a slow speed hand piece was performed, tooth-brushing techniques were demonstrated, and the significance of home oral self-care was explained.

Based on a previous report, which describes a significant reduction of severe gingival inflammation after systemic antibiotic treatment in children with childhood periodontitis,[23] and after consulting with the physician, the antibiotic treatment was changed to Amoxycillin® (1200 mg., t. i. d.). and Metronidazole® (420 mg., t.i.d.) for 7 days. The possibility to substitute Cyclosporin with Tacrolimus that has less undesired influence on the gingival tissues than Cyclosporine,[19,24-26] was discussed with "N"s physician, however, based on the case history and the main goal to prevent blindness, he recommended continuing with Cyclosporin.

A few days after reinitiating tooth brushing and the new antibiotic therapy, a significant gradual decrease in gingival pain and inflammation, concomitant to a reduction in the severity of halitosis, began to take place.

During the next month, at weekly intervals, extraction of the primary molars, amalgam restorations, pit and fissure sealants, scaling, prophylaxis and chlorhexidine rinses inside the gingival pockets were performed by quadrants.

The non-pharmacological behavior management techniques were successful for the extractions of the primary molars and caries removal with a high-speed turbine. However, the use of a low-speed hand piece induced significant behavior management problems that eventually led to the use of nitrous oxide sedation, which solved the behavior management difficulties.

Oral hygiene was constantly reinforced, compliance was excellent and a steady decrease in gingival overgrowth and inflammation with a concomitant reduction in halitosis, took place. Therefore, the periodontist recommended to continue with periodical professional prophylaxis and oral hygiene reinforcements, and reconsider the need for gingival surgery after eruption of all the permanent teeth. Follow up appointments every 3 months, with the purpose to reinforce adequate oral hygiene and perform frequent oral examinations were scheduled. At every second appointment, a radiographic examination was performed.

Follow up

First recall. Three months after initial treatment.

"N' was still under treatment with Cyclosporine, no gingival overgrowth, no halitosis, no caries, moderate gingivitis adjacent to an erupting maxillary left second premolar and the tooth in cross-bite were evident. On the other hand, "N" complained of several sore areas beside the lower anterior incisors, clinical examination revealed the presence of aphtous ulcers. Despite that an history of recurrent oral lesions was denied, the emergence of aphtous ulcers in a child with uveitis, led to consider the possibility of Behcet disease.[1,3,7,10,13] Additional possibilities included that the lesions were related to the reduced immune activity caused by medication, avitaminosis or other systemic diseases.[27] "N" was referred to her physician for systemic evaluation that disclosed the presence of antigen HLA B51, confirming the presence of Behcet disease.

Second recall. Six months after initial treatment.

"N" was still under the treatment with Cyclosporine. Mild gingival overgrowth was evident at the site of a recently exfoliated maxillary left primary cuspid, mild gingivitis adjacent to an exfoliating maxillary right primary cuspid (Figure 3), no caries and no halitosis were evident. At this point, it was clear that the need for gingival surgery was avoided. The orthodontist still recommended postponing the orthodontic treatment, due to the possibility that orthodontic appliances would facilitate plaque accumulation and regression of the gingival inflammation and overgrowth.

Third and fourth recalls – 9 months and one year after initial treatment.

"N" was still under the treatment with Cyclosporine. All permanent teeth with exception of the 3rd permanent molars were erupted. Mild gingivitis adjacent to the maxillary left lateral incisor that was is cross-bite, mild gingival overgrowth adjacent to the erupting max-

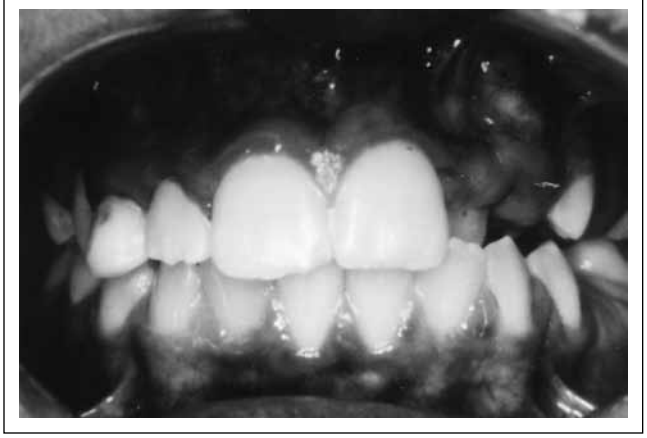

Figure 3. Clinical oral picture 6 months after the first appointment. A significant reduction in gingival overgrowth and inflammation is evident. Mild gingival inflammation is evident at the maxillary right primary cuspid that is about to be exfoliated in the lower incisor area. Mild gingival overgrowth is evident at the area of the recently exfoliated maxillary left primary cuspid.

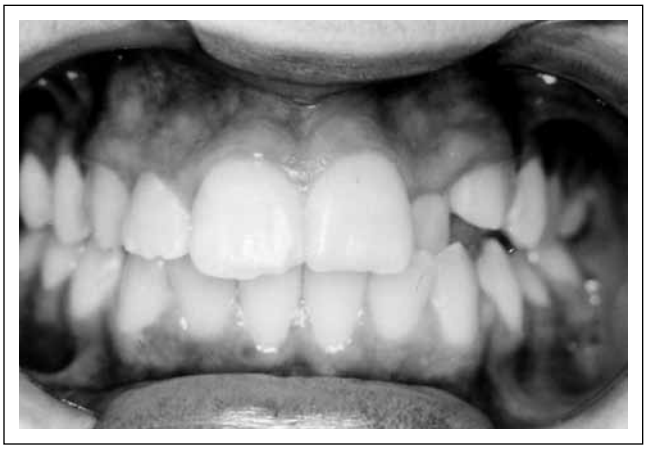

Figure 4. Clinical oral picture one year after the initial treatment, the child has a permanent dentition with minimal gingival overgrowth limited to the erupting maxillary left permanent cuspid. No gingival inflammation is evident.

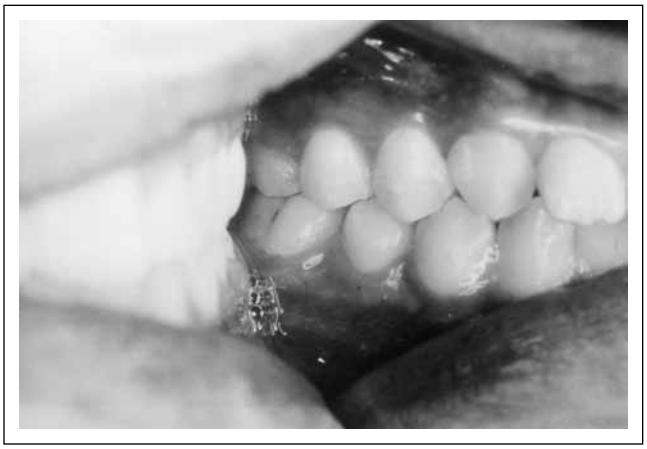

Figure 5. Clinical oral picture of the posterior right area (inverted mirror view) one year after the initial treatment, no gingival inflammation or overgrowth are evident.

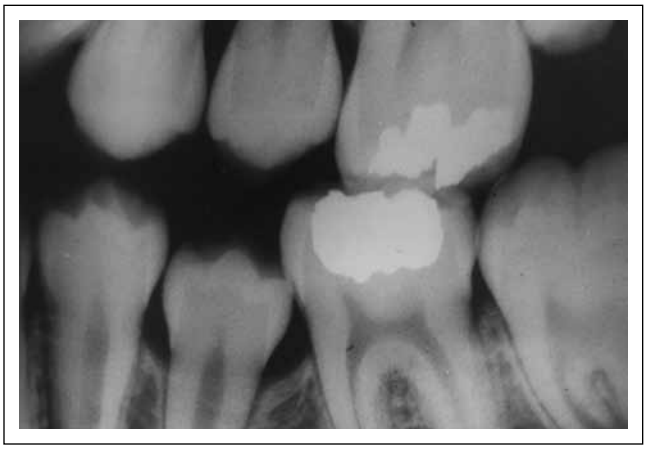

Figure 6. Left bite-wing radiograph one year after initial treatment. Neither caries nor periodontal diseases are evident. Space loss prevents the adequate eruption of the mandibular left second premolar.

illary right permanent cuspid, no periodontitis, a caries free dentition (Figures 4 to 6) and no halitosis were evident. The adequate eruption of the mandibular left second premolar was obstructed by the space loss.

During the whole follow up period, "N", her father and the dental staff were very pleased with the treatment out-come, which implied a significant increase in "N"s quality of life. Most notable was the behavioral change, from the initial refusal to enter the clinic and to brush her teeth, to willingness to visit the dental clinic and excellent oral health care.

Long term follow up and prognosis.

While the oral treatment out-come was most encouraging, the prognosis for "N"s eyesight and systemic condition appears adverse. She will require continuous and intense systemic and local treatments to increase the possibility to save her eyesight. Therefore, "N" will also require frequent visits to the dental clinic for reinforcement of adequate oral hygiene, and examinations with the purpose to prevent or early treat oral diseases. In the future, the relative significance and the possibility of orthodontic treatment will also be evaluated.

DISCUSSION

Autoimmune diseases are believed to have the potential to affect patients at any age and organs of any organ system.[5] Behcet disease has been reported to involve:[1-17]

- bladder dysfunction that includes genital aphtous ulcers, epidemytis, urethritis, neurogenic bladder and recurrent cystitis,

- colitis with aphtoid or punched out ulcerations,
- episodic arthritis,
- hemostasis changes such as low thrombomodulin and high von Willebrand factor and high tissue plasminogen activator, hepatic artery aneurysm, segmentation pancreatitis, nervous system disturbances and sequel, intracardiac thrombus formation, pulmonary artery thrombosis, localized myositis, oral aphtous ulcers,
- skin symptoms, which include erythema nosodum, pseudofolliculitis, papulopustular lesions, acneiforms nodules and a positive pathergy test.
- uveitis that may lead to blindness.

The manifestation of these signs and symptoms vary significantly in every patient complicating the diagnosis of Behcet disease, especially if the typical ulcers are not obvious at presentation,[2] even though that they are present in most cases.[10] Moreover, despite that Behcet's onset usually takes place in young adults[3] the clinician should consider that it may also appear in children.[4,6,7]

In the present case, the appearance of apthous ulcers in a child with severe eye disease,[7] led the treating dentist to the suspicion Behcet disease, which was subsequently verified by the disclosure of antigen HLA B51. This fact emphasizes once more the close relation between systemic and oral diseases,[27] the role of the dentist in diagnosing systemic diseases by the manifestation in the oral tissues, and the importance of cooperation between the physician and dentist. In addition, the dentist should consider that systemic diseases like Behcet may have a genetic background with a strong genetic aggregation,[6,28] therefore, family members should also be examined for the possible presence of the disease. In the present family however, "N" was the only member with the disease.

Drug-influenced gingival enlargement may be caused by anticonvulsants such as phenytoin, immunosuppresors such as Cyclosporine and calcium channel blockers such as Nifepedine, Verapamil, Diltiazen and sodium Valproate.[21] Not every patient receiving these medicaments develops gingival overgrowth, and the overgrowth varies among those who develop it.

It has been indicated that appearance and variability of the enlargement is related to genetic predisposition, age, oral hygiene and a minimal period from the initiation of medication of at least three months.[21] In the present case however, an earlier than three months onset of gingival enlargement was suggested by the presence of already severe gingival overgrowth and inflammation three months after initiation of the Cyclosporine treatment.

The leading theory on the reason Cyclosporine affects the gingival tissues is that the principal metabolite of Cyclosporine, hydroxycyclosporine (M-17), in conjunction with the parent compound stimulates fibroblast proliferation. In addition, this increase in cell number, coupled with a reduction in the breakdown of gingival connective tissues has been postulated to be the cause of excessive extracellular matrix accumulation.[21] A relatively new immuno suppressant, Tacrolymus (FK-506), has been recently proven to have a lesser gingival enlargement effect than Cyclosporine.[19,24-26] However, based on the previous beneficial effect of Cyclosporine in the present case, the physician preferred not to risk the eyesight by changing to another medicament. An increased use of Tacrolymus instead of Cyclosporine may be expected in the future, as evidence of the advantages of the use of Tacrolymus as compared to Cyclosporine, without a significant change in the immuno suppressive effect, accumulates in the literature.

In the present case, the initial clinical picture of severe gingival overgrowth and inflammation strongly suggested the need for gingival surgery. However, a non-surgical approach, which included meticulous oral hygiene instructions, prophylaxis, scaling, extraction of the mobile primary molars, Clorhexidine rinses, antibiotic therapy and excellent compliance resulted in a significant reduction in gingival inflammation and overgrowth, eliminating the need for gingival surgery.

While plaque control and Clorhexidine rinses are accepted treatments for gingivitis,[29] antibiotic therapy is not. Our decision to prescribe antibiotic treatment in the present case, was based on two issues: 1) the presence of severe inflammation; 2) a previous report in which antibiotics given to cases with childhood periodontitis, resulted in a most significant and rapid reduction in severe gingival inflammation.[23] In the present case, the initial reduction in gingival inflammation may be attributed to the first professional prophylaxis and motivation for home oral health care, the antibiotic therapy and the restoration of oral hygiene. The following gradual and steady reduction in gingival inflammation and overgrowth was the result of the repeated professional prophylaxis, scaling, chlorhexidine rinses, extraction of the primary mobile aching teeth, continuous motivation for home oral health care and excellent patient compliance.

In children like "N", who have severe systemic diseases, the importance of oral diseases may be considered of no great concern. However, one should not underestimate the possible deleterious effect of oral pain and discomfort on the quality of life in every patient, and more than ever in those who already have more than enough grief from severe systemic diseases and the treatment. Furthermore, elimination of severe halitosis is essential for the prevention of evasion by family and friends.

CONCLUSION

The present case report:

Indicates the distinctive significant influence of oral health in the quality of life of patients with systemic diseases.

Emphasizes the possibility, and responsibility, of the dental professionals to lead the diagnosis of systemic diseases, such as Behcet, by the oral manifestations.

Provides evidence of the success of non-surgical treatment of gingival overgrowth caused by cyclosporine.

Emphasizes the relevance of cooperation between the medical and dental professionals for the treatment of patients who have diseases that affect the systemic and oral tissues.

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