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Oral manifestations associated with leukocyte adhesion deficiency: a five-year case study

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Abstract

A five-year case study of a child with leukocyte adhesion deficiency is presented. The report describes the generalized progressive periodontitis and intraoral infections associated with both the primary and permanent dentition. The associated therapeutic challenges and largely unsuccessful treatment regimens utilized in the attempts to arrest the periodontal disease are described.

Introduction

Many previously unknown disease mechanisms now are being described by molecular biology. A recently defined immunological disease, leukocyte adhesion deficiency (LAD), occurs when three surface glycoproteins are absent or defective on leukocytes (PMN), leaving affected patients susceptible to bacterial infections (Crowley et al. 1980; Arnaout et al. 1982; Dana et al. 1984). Although the defect is rare, studies of patients with the disease help to determine the function of the leukocyte surface glycoproteins in healthy individuals (Fig 1).

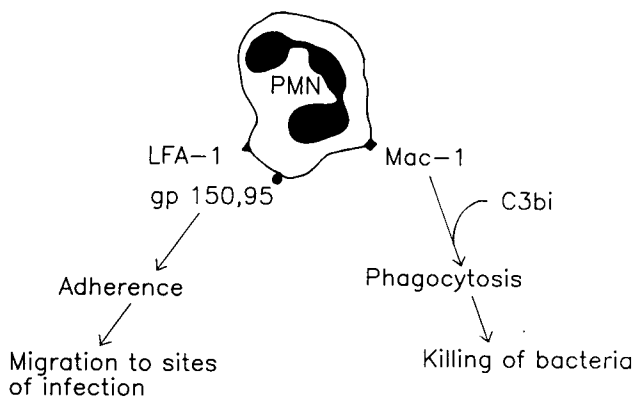

Fig 1. Represented are two neutrophil (PMN) functions and receptors (Mac-1, gp 150,95, and LFA-1) that mediate these pathways. PMNs from patients with LAD lack all three receptors, leaving them susceptible to bacterial infections.

The complete surface glycoproteins in normal leukocytes contain at least three important binding sites necessary for normal leukocyte adherence. These are Mac-1 (also referred to as Mo1) (complement receptor type 3 or CR3) (Buescher et al. 1985), lymphocyte function-associated antigen-1 (LFA-1) (Arnaout et al. 1984) and gp 150,95 (Arnaout et al. 1982). Mac-1 binds an important complement fragment, C3bi, which also is attached to an antigen-antibody complex. The binding of C3bi is thought to promote phagocytosis and eventual destruction of foreign antigens, such as a bacterium. Without the receptor for C3bi, neutrophils ingest very low levels of bacteria. The lack of the adherence receptors LFA-1 and gp 150,95 results in poor attachment of leukocytes to endothelial cells and low neutrophil accumulation at infection sites (Anderson and Springer 1987).

This disease is the result of one defect. Each of the surface glycoproteins lacking LAD normally is composed of a different α subunit joined to a common β subunit (Springer et al. 1984). Individuals with LAD lack only the ability to make the β subunit, but the α portion is not expressed when the β subunit is absent. The degree of immunosuppression varies, as patients with trace levels of the subunit have less severe disease than patients who produce no measurable β subunit (Anderson and Springer 1987).

Delayed separation of the umbilical cord with consequential septicemia may be the earliest clinical manifestation of LAD (Crowley et al. 1980). Recurrent infections of soft tissues, mucous membranes, and intestinal tracts often are caused by staphylococci, gram negative bacteria, or other pyogenic organisms (Anderson and Springer 1987). Common infections observed in these patients include multiple skin abscesses, recurrent otitis media, and pnuemonitis. While bacterial infections develop frequently, viral infections are not a persistent clinical problem in these patients. One of the most striking laboratory findings of these patients is a persistent elevation of the granulocyte count ranging from

15,000 cells/mm^3 to 161,000 cells/mm^3. In spite of the high peripheral blood granulocyte numbers, biopsies of infected areas are nearly void of neutrophils. Consequently, abscesses occur without pus formation.

Inheritance of the disease follows an autosomal recessive pattern that has been mapped to chromosome 21 (Anderson and Springer 1987). Several reported homozygous patients had consanguineous parents who were heterozygous for the defective chromosome. While homozygous patients have severe disease, heterozygous patients are reported to be clinically healthy despite abnormalities in certain leukocyte function assays.

The most dramatic oral finding associated with LAD is severe periodontal disease. One reported patient had all primary teeth extracted by age three years because of periodontitis (Waldrop et al. 1987). The same patient lost several permanent teeth by age 12 years as a result of 50–90% alveolar bone loss. All homozygous patients in this study exhibited generalized rampant periodontal disease involving both the primary and permanent dentitions. Attempts to control the periodontal disease were not successful. Gingival biopsies obtained when teeth were extracted demonstrated only a mononuclear infiltrate in the tissue. Additional reported oral findings in patients with LAD include stomatitis, ulcerations of mucous membranes, and facial cellulitis (Anderson and Springer 1987).

This case report focuses on a child with LAD who has been followed regularly at the National Institute of Dental Research (NIDR) Clinic for the past five years. The associated periodontal disease and eruption pattern is well documented longitudinally. The difficulties in managing such a patient also are presented and discussed.

Case Report

Medical History

A black female, 3 years, 11 months old, product of first cousin parents, was referred to the National Institute of Allergy and Infectious Diseases, National Institutes of Health (NIH); she had a history of mild respiratory distress, pityriasis rosea, fever, and leukocytosis of unknown origin shortly after birth. Throughout the first year following birth, the patient continued to experience poor healing following minor surgery, recurrent cutaneous infections, and abscess formation without purulence that nevertheless required incision and drainage. It was observed that superficial injuries to the skin resulted in severe inflammation. A white blood count (WBC) of 10-20,000/ml was present throughout this period.

Admitting laboratory studies showed the following: hemoglobin — 10.7; hematocrit — 29.8%; reticulocyte count — 0.6%; MCV — 75; and platelet count — 531,000. The WBC was 19,900 with 33 segs, 50 lymphocytes, 11 monocytes, 2 eosinophils, and 2 basophils. Screening tests for thalassemia and sickle cell anemia were negative. The sedimentation rate was 27. Glucose was reported as 57, potassium 4.8, and a serum lactic dehydrogenase 269. Immunoglobulin levels were IgG 1180, IgA 487, and IgM 215. After extensive testing of the patient's leukocytes, it was confirmed by fluorescent cell analysis and rosetting that the white blood cells lacked the C3bi receptor. Additional information and the results of extensive laboratory studies of this patient have been published previously (Buescher et al. 1985). The mother was found to have a C3bi defect as well, but she denied any illnesses except for hay fever. The father's medical history was remarkable only for post-traumatic seizures. The child was placed prophylactically on trimethoprim and sulfamethoxazole (Septra) antibacterial combination, and ferrous sulfate for anemia therapy.

Over the next 5-1/2 years the child required numerous hospital admissions for pneumonia, periorbital sinusitis, and recurrent diarrhea. She was treated with various antibiotic combinations during these episodes. However, since November 1984 the patient has been maintained on prophylactic oral trimethoprim 40 mg, and sulfamethoxazole 200 mg (Bactrim™, Roche Laboratories, Div. of Hoffmann-La Roche, Inc., Nutley, NJ 07110) twice daily with some success in preventing recurrent infections.

Dental History

The patient first was referred at the age of 3 years, 11 months to the NIDR Clinic for evaluation. An oral examination, including panoramic radiograph, was accomplished. The primary dentition was complete, but there was generalized gingival recession, abnormal tooth mobility, gingivitis, and loss of gingival attachment and supporting alveolar bone.

The sedated patient was given a thorough oral prophylaxis with deep scaling. It was recommended that the child's teeth be brushed twice daily by a parent with a sodium bicarbonate paste, and that 0.4% stannous fluoride gel be applied after the evening oral hygiene.

Seven months later the child returned to the dental clinic for reevaluation. Her oral hygiene had improved, but the generalized gingivitis still was prominent with increasing loss of alveolar bone around all primary teeth (Fig 2). The importance of home care was reinforced along with the recommendation that the sodium bicarbonate dentifrice/fluoride gel regimen be continued. Four months later the child presented with a left facial swelling of three days duration, apparently associated with the mandibular teeth. Panoramic and periapical radiographs of the first and second primary left mandibular molars revealed the presence of a periodontal

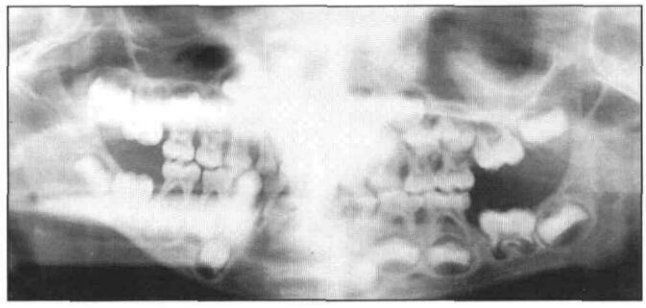

Fig 2. Patient at age 4 years, 6 months. Generalized bone loss is evident around all posterior primary teeth.

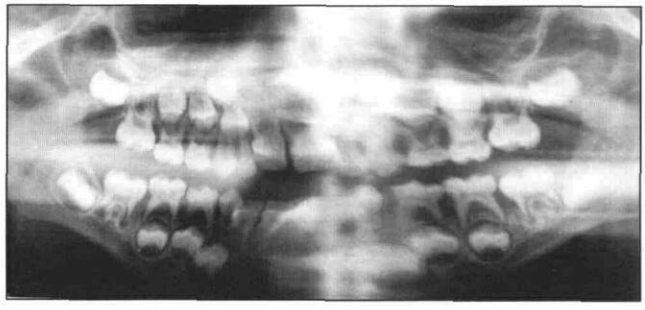

Fig 3. Patient at age 5 years, 4 months. There is progressive loss of tooth-supporting bone.

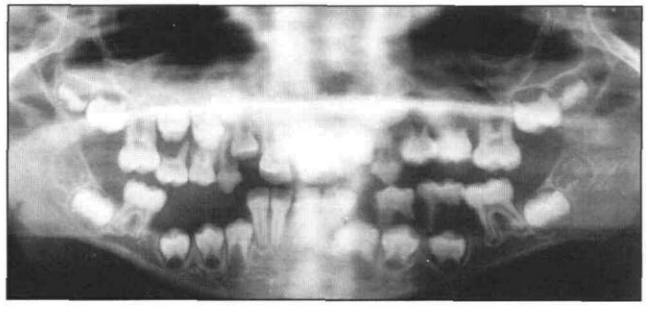

Fig 4. Patient at age 6 years, 8 months. The premature exfoliation of primary molars and initial loss of alveolar bone around permanent molars is evident.

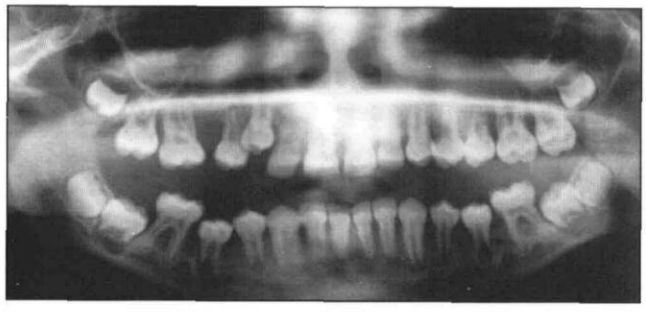

Fig 5. Patient at age 9 years, 0 months. Note early eruption of premolars and generalized stunted root formation of the permanent teeth. The periodontal disease continues to progress.

abscess associated with both teeth. The area was irrigated with hydrogen peroxide/water, and oral potassium penicillin therapy was initiated with resolution of the swelling in eight days along with increased firmness of the teeth.

The patient had exfoliated the two mandibular central incisors spontaneously at age 4 years, 6 months. Ten months later the child returned to the dental clinic for routine examination. The previously observed chronic gingivitis and generalized loss of alveolar bone was noted to have continued, although she remained asymptomatic (Fig 3). A month later the patient presented with a complaint of pain in the right maxilla. Considerable plaque was present on the teeth, and a fetid odor emanated from the oral cavity. A periodontal abscess was noted in the general area of the right maxillary primary canine extending to the second molar, with no associated facial swelling. The teeth were cleaned gently with scalers and polished with prophylaxis paste to remove the adhering bacterial plaque. Home care was again emphasized to the child and mother. Oral potassium penicillin antibiotic therapy was initiated with good results. Chronic progressive periodontitis was evident at the child's regular oral examination at age 6 years, 8 months (Fig 4).

The patient was admitted to the hospital at age 8 years, 7 months with a periorbital sinusitis. She was referred to the dental clinic following subluxation of the right primary second maxillary molar while surgically attempting to enter the sinus to establish drainage. The tooth was extremely mobile and required extraction under local anesthesia.

The patient was asymptomatic when she returned five months later for her next regular dental examination and oral prophylaxis. The left side of the face was slightly swollen with associated submandibular lymphadenopathy. Intraoral examination did not reveal any findings that had not been recorded previously (Fig 5). The daily use of 1.2% chlorhexidine mouth rinse was added to the home care regimen in an attempt to arrest the severe chronic gingivitis.

However, eight months later the child again returned to the hospital in no apparent discomfort but with a grossly swollen left cheek progressing inferiorly toward the submandibular area. A hard, nontender, 1 1/2–3 cm indurated mass was palpable along the lateral border of the left mandible. A panoramic radiograph revealed rapid and continuous loss of alveolar bone from around all permanent teeth but no specific pathology to explain the swollen left cheek (Fig 6, next page). Oral temperature was 38°C, the WBC count was 36,700, hemoglobin 7.3, hematocrit 23.3, mean corpuscular volume (MCV) 67, mean corpuscular concentration

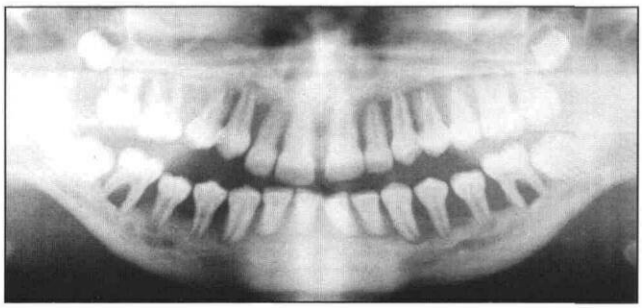

Fig 6. Patient at age 9 years, 8 months. There is virtually total loss of supporting alveolar bone from around the permanent teeth.

(MCH) 21, mean corpuscular hemoglobin concentration (MCHC) 31.4, and platelet count was 952,000. The decision was made to admit the patient to the hospital to initiate intravenous antibiotic therapy and schedule an intraoral incision and drainage the following day.

Preoperative intravenous vancomycin initially was infused but had to be discontinued, since the patient developed urticaria which required diphenhydramine hydrochloride to supress. It was not determined whether this was an allergic reaction to vancomycin or the result of too rapid infusion of the antibiotic. Nevertheless, the antimicrobial agent was changed to penicillin.

The sedated patient was brought to the dental clinic, and, under local anesthesia, an intraoral incision was made into the endurated mass along the left mandible. Although no purulent exudate was detected, specimens were taken for both aerobic and anaerobic culture and sensitivity determination. In addition, specimens were taken from periodontal pockets associated with the right permanent mandibular first and left maxillary first molars. *Proteus mirabilis, Pseudomonas aeruginosa,* and alpha hemolytic streptococcus subsequently were reported in addition to other normal aerobic intraoral microflora. *Anaerobes Bacteroides melaninogenicus* and *Peptostreptococcus micros* also were present in small quantities. Although branching elements were seen on a gram-stained smear, no actinomycetes were isolated.

The patient was prescribed nafcillin and penicillin, and was discharged from the hospital at the request of the child and mother. The parent reported improvement during subsequent follow-up telephone inquiries.

Discussion

Leukocyte adhesion deficiency (LAD) is a rare disorder characterized by recurrent infections. Although there have been case reports describing associated generalized severe periodontal disease (Bowen et al. 1982; Waldrop et al. 1987), a longitudinal description of the intraoral sequela of the disorder has not been published previously. The patient's inability to effectively respond to recurrent infections apparently is related to the severe functional defect in phagocytic chemotaxis, aggregation, and adherence. However, there are strong suggestions that additional antigenic and functional deficiencies also are present. (Buescher et al. 1985; Waldrop et al. 1987).

The clinical and radiographic appearance of our patient resembled generalized juvenile periodontitis (Hormand and Frandsen 1979) or prepubertal periodontitis (Page et al. 1983). However, comparison of patients with LAD to patients with generalized juvenile periodontitis is difficult. LAD involves neutrophils, lymphocytes, and monocytes, while generalized juvenile periodontitis has been associated primarily with only neutrophil defects (Van Dyke et al. 1985).

Actinobacillus actinomycetemcomitans previously has been associated with juvenile periodontitis (Slots et al. 1980). However, there was no evidence of the gram negative rod, *A. actinomycetemcomitans* by anaerobic culture from the periodontal abscess or other selected periodontal pockets in our patient. Specific serum IgG antibody levels against the organism were not obtained. It is much more probable that the periodontal disease resulted from an inability to fight off numerous invasive and/or opportunistic organisms, rather than being the consequence of one particular pathogen. Aggressive periodontal disease also has been described in children with a broad range of systemic disorders such as the neutropenias (Cohen and Morris 1961; Baehni et al. 1983) and Papillon-Lefèvre syndrome (Gorlin et al. 1964).

An aggressive oral hygiene and professionally delivered regimen of care failed to arrest the chronic gingivitis, rapid loss of gingival attachment, destruction of the supporting periodontal tissues and supporting alveolar bone. Although antibiotics appeared to suppress acute orally related infections successfully, the use of a sodium bicarbonate dentifrice, brush-on 0.4% stannous fluoride gel, and a 1.2% chlorhexidine mouthrinse also were apparently ineffective. Unfortunately, it was impossible to determine the degree of parental and patient compliance with home care recommendations.

The importance of maintaining the dentition and preserving the vertical dimension for as long as possible in the child's developing orofacial complex was one of our primary concerns in the initial philosophy of treatment. However, we also were unaware of the difficulty we would encounter in attempting to arrest the incessant periodontal destruction. In retrospect, it could be argued that reducing the risk for future infections was the most important consideration, and our resistance to extracting the severely involved teeth put the child at greater peril.

Conclusion

Patients with LAD effectively demonstrate that maintenance of the periodontium depends on an intact defense system. These patients most likely will be encountered with increasing frequency due to improved antibiotic and support therapy. A few patients have been treated successfully with bone marrow transplants (Anderson and Springer 1987), and others may be candidates for gene therapy. However, they will continue to present unusual and difficult challenges for clinical dental management.

At the time of writing, Dr. Roberts was Chief, Patient Care and Clinical Studies Section, Clinical Investigations and Patient Care Branch, and Deputy Clinical Director at the National Institute of Dental Research (NIDR). Currently, Dr. Roberts is Graduate Program Director for Pediatric Dentistry at the University of North Carolina at Chapel Hill. Dr. Atkinson is Senior Staff Fellow, Clinical Investigations and Patient Care Branch, at NIDR. Reprint requests should be sent to: Dr. Michael W. Roberts, Dept. of Pediatric Dentistry, School of Dentistry CB#7450, University of North Carolina, Chapel Hill, NC 27599-7450.

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