CASE REPORT

Dental implants in a patient with suspected leucocyte adhesion deficiency

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SUMMARY

Aggressive periodontitis and premature tooth loss in leucocyte adhesion deficiency (LAD) have adverse functional and psychological consequences on affected individuals. Dental implant rehabilitation might become necessary to overcome the functional and psychological adverse effects of LAD periodontitis, especially in patients with milder forms who are expected to have a relatively normal life expectancy. Outcome of dental implants in patients with LAD has not been previously reported; we describe the dental rehabilitation of a 24-year-old man with clinical features of LAD using endosseous dental implants.

BACKGROUND

Defects in the expression or function of leucocyte adhesion molecules cause leucocyte adhesion deficiency (LAD), an inherited immunodeficiency disorder characterised by the inability of neutrophils to adhere to the vascular endothelium, extravasate from the circulation and migrate to sites of infection or inflammation.¹

Severe periodontitis with premature loss of primary and permanent teeth is a major component of LAD. The association between LAD and severe generalised periodontitis was first reported in 1987 by Waldrop *et al*² and Page *et al*,³ and the molecular mechanisms underlying LAD associated periodontitis were only recently elucidated by Hajishengallis and Moutsopoulos.⁴⁻⁷ Only few studies have described the periodontal manifestations and management of patients with LAD-associated periodontitis.⁸⁻¹⁴ Interestingly, all of these studies were case reports of children and young adolescents, probably because most patients with LAD die during early years due to complications of infections. Patients with mild LAD however might survive through adulthood when periodontal treatment and rehabilitation become necessary to overcome the adverse psychological and functional consequences of LAD-associated periodontitis. Placement of dental implants in patients with LAD has not been described previously. In this report, we describe the dental implant rehabilitation and the follow-up of a 24-year-old man with clinical features of LAD, and discuss the potential role that dental implants can play in the management of this rare condition.

CASE PRESENTATION

A 24-year-old man presented with generalised tooth mobility and recurrent oral infections. The parents, who were paternal cousins, reported early

loss of the primary dentition and normal eruption of permanent teeth. His medical history was significant for recurrent crusting and scaling lesions of the skin (figure 1), multiple urinary tract infections and delayed separation of the umbilical cord. The family history was unremarkable, and the parents were unaware of similar presentation among their relatives.

Intraoral examination revealed marked halitosis, severe periodontal disease, generalised grade III mobility and spacing of teeth, bleeding on probing, and gingival swelling and erythema. Mucosal surfaces appeared normal with no detectable lesions. Head and neck examination was within normal limits, and there were no enlarged or palpable lymph nodes.

INVESTIGATIONS

Panoramic radiograph showed generalised alveolar bone loss, and the teeth appeared to be floating (figure 2). A complete blood count (CBC) revealed an increase in white cell count (WBC) (18.5×10^9 cell/L) and normal values for haemoglobin (13.9 g/dL), red blood cells (RBC) (5.1×10^{12} cell/L) and platelets (290×10^9 cell/L). Interestingly, review of the patient's medical records revealed that his WBC was persistently elevated (the lowest recorded value was 13.7×10^9 cell/L) (table 1). Culture samples obtained from periodontal crevicular fluid showed *Pseudomonas aeruginosa*, *Viridans streptococci* and *Candida albicans*.

DIFFERENTIAL DIAGNOSIS

Several diseases can cause aggressive periodontitis and early onset tooth loss, including Haim-Munk syndrome, Ehlers-Danlos syndrome, Kostman syndrome, Felty's syndrome, Herman-Sky-Pudlak syndrome, hyperimmunoglobulin-E syndrome, lazy leucocyte syndrome, Down's syndrome, Kindler syndrome, Papillon-Lefevre syndrome and Chediak-Higashi syndrome.

TREATMENT

Comprehensive periodontal examination concluded that the teeth had a hopeless prognosis, and a decision to extract all remaining teeth was made. Teeth were extracted under local anaesthesia in a single appointment. Extraction sites were thoroughly irrigated with normal saline, and the patient was given a 1-week course of antibiotics (amoxicillin and clavulanic acid 625 mg P.O. three times daily). An immediate denture was also inserted at the time

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Figure 1 Scarring of the skin at sites of cutaneous infections.

of extraction. Healing was uneventful, and the patient showed good tolerance to the immediate denture. Four months later, the patient underwent bilateral maxillary sinus lift (lateral window) together with onlay bone augmentation of the maxillary alveolar ridge using autogenous bone harvested from the iliac crest. Four dental implants (XiVES-Germany) were also placed in the anterior mandibular area at the same operation. All four implants showed good primary stability. The patient was given 1 gm amoxicillin intravenously before the surgery and continued on a 1-week course of antibiotics (amoxicillin and clavulanic acid 625 mg P.O three times daily). The patient recovered well and healing went uneventful. Following a healing period of 3 months, at stage 2, the bone graft healed well, but two of the mandibular implants failed to osseointegrate. The failed implants were removed under local anaesthesia, and the implant site was allowed to heal. One month later, two new implants (XiVES-Germany) with the same length but with larger diameter were placed at the same site to replace the failed mandibular implants, and six implants were placed in the maxilla (XiVES-Germany). The patient was again given a 1-week course of antibiotics (amoxicillin and clavulanic acid 625 mg P.O three times daily), and the healing went uneventful. Five months later, all implants were

Figure 2 Panoramic X-ray of the patient's dentition at the time of initial presentation showing generalised alveolar bone loss. The teeth appeared floating.

Table 1 Findings of laboratory investigations

Investigation	Value	Reference range
Haemoglobin (g/dL)	13.9	12–16
WBC count (cell/L)	18.5×10^9	$4-10 \times 10^9$
Neutrophils (%)	58	40%–75%
Lymphocytes (%)	33	20%–40%
Eosinophils (%)	2	1%–7%
Monocytes (%)	3	1%–9%
RBC count (cell/L)	5.1×10^{12}	$4-6 \times 10^{12}$
Platelets (cell/L)	290×10^9	$150-400 \times 10^9$
MCV (fL)	83	80–100
MCHC (g/dL)	35	32–38
ESR (mm/h)	48	0–22
Hbs-Ag	–ve	–ve
HIV	–ve	–ve
HCV	–ve	–ve

The severe and generalised periodontitis together with a history of recurrent skin infections and a persistently elevated WBC suggested that the patient might have LAD. To confirm the diagnosis, neutrophils and lymphocytes were examined using flow cytometry. A panel of antibodies directed at neutrophil membrane surface antigens associated with CD11 and CD18 revealed a decreased expression of CD18 (82.6% of normal) and normal expression of CD11. Results of NBT reduction test were within normal range (unstimulated neutrophils were 50% positive for NBT, while stimulated neutrophils were 85% positive) indicating a normal function of neutrophil oxidative burst. Therefore, a diagnosis of mild LAD was made.

Hbs-Ag, hepatitis B virus surface antigen; HCV, hepatitis C virus; LAD, leucocyte adhesion deficiency; MCHC, mean corpuscular haemoglobin concentration; MCV, mean corpuscular volume; NBT, nitro-blue tetrazolium; RBC, red blood cell; WBC, white cell count.

successfully osseointegrated, and the patient was referred to the department of prosthodontics where an upper and lower hybrid prostheses were constructed.

The patient was given thorough oral hygiene instructions and was placed on a 3-month periodontal prophylaxis programme.

OUTCOME AND FOLLOW-UP

At 4-year follow-up, the implant prostheses were functional with no mobility, infection, purulent discharge, bleeding on probing or a significant peri-implant bone loss (figure 3).

DISCUSSION

Leucocytes in patients with LAD display decreased ability to adhere to endothelial cells and to migrate to sites of infection or inflammation.¹ Patients with LAD therefore suffer from recurrent bacterial infections together with impaired pus formation and delayed wound healing.¹⁵ The severity of clinical

Figure 3 Panoramic X-ray of the patient at 4 years after dental implant placement and construction of hybrid prostheses. The implants were functional with no signs of infection or significant peri-implant bone loss.

manifestations correlates with the amount of CD18 expression. An expression level of <1% results in a severe phenotype with >75% of affected patients die during infancy. A residual expression of 1%–10% results in a moderate disease. A subgroup of patients with a milder form of LAD, in which there is a residual expression of >10%, survive well beyond infancy and may not be diagnosed until adulthood.^{8 9} The residual expression of CD18 in our patient was 82.6%, a value that explains the relatively mild manifestations and the delay in seeking treatment.

The diagnosis of LAD is primarily made on the basis of clinical features, WBC and flow cytometry analysis of CD18 and CD11.¹⁶ Our patient demonstrated typical clinical features of LAD, including recurrent infections, delayed separation of umbilical cord and early onset periodontitis. Furthermore, laboratory findings (high WBC count and reduced expression of CD18) were typical of LAD. A recent study by Levy-Mendelovich et al demonstrated that the sole reliance on CD18 measurement for diagnosis of LAD1 entails several inherent pitfalls because patients display various levels of CD18 expression on the cell surface, varying from absent to normal levels of functionally defective CD18. In addition, some mutations infer a wide range of CD18 levels from low to within normal limits in different patients with the same mutation. More so there may be varying levels of CD18 in repeated testing from the same patient.¹⁶ Genetic testing for mutations in CD18 therefore might be necessary to confirm the diagnosis of LAD and to reveal the underlying genetic events, but unfortunately this was unavailable in our case.

The aetiology of LAD-associated periodontitis is not exactly known. However, recent molecular studies by Hajishengallis and colleagues have shown that LAD periodontitis does not represent a raging infection but rather is caused by dysregulated overexpression of interleukin (IL)-23 and downstream cytokines including IL-17 and granulocyte colony stimulating factor (G-CSF).^{7 8} This may explain the clinical finding that LAD periodontitis is recalcitrant to antibiotic treatment and/or mechanical removal of the tooth-associated biofilm.

Aggressive periodontitis and premature tooth loss in LAD have adverse functional and psychological consequences on affected individuals. Unfortunately, there are very limited data regarding periodontal treatment of patients with LAD. Most authors however agree that early treatment of periodontal disease with frequent prophylaxis and broad spectrum antibiotics is necessary to prevent local (dental) and systemic infections.^{8–14} Disappointingly, the current treatment of LAD periodontitis is largely unsuccessful, and teeth are ultimately lost. Neutralisation of IL-17 or IL-23 might be a promising therapeutic target for LAD-1-associated periodontitis. Interestingly, preliminary clinical studies have shown that treatment with biologics targeting IL-17 or IL-23 receptor is safe and promising for the treatment of inflammatory diseases such as rheumatoid arthritis and psoriasis.^{17 18} Importantly, a recent report by Moutsopoulos et al demonstrated successful treatment of oral inflammatory lesions in a patient with LAD-1 using ustekinumab, an antibody that of blocks the activity interleukin-23 and interleukin-12 and thereby inhibiting IL-23-dependent production of IL-17.¹⁹ Modulation of oral inflammatory response using targeted therapies might help to improve the success of dental implants in patients with LAD.

Dental implant rehabilitation might become necessary to overcome the functional and psychological adverse effects of LAD periodontitis, especially in patients with milder forms who are expected to have a relatively normal life expectancy. Interestingly, placement of dental implants in patients with LAD has not

been described previously. Therefore, we were initially reluctant to place dental implants for our patient. However, given the mild nature of his LAD and the need to restore dental function and aesthetics, we were encouraged to place endosseous dental implants. The patient tolerated the procedures of bone grafting, sinus lifting and implant placement very well without complications, except the failed two implants. Antibiotic prophylaxis was given for all surgical procedures to prevent the occurrence of local or systemic infections associated with his immune defect. The results of osseointegration were generally encouraging. Two out of eight implants had initially failed to osseointegrate. Whether this failure is related to LAD or not is not known, nevertheless the two new implants replacing the failed ones osseointegrated successfully. In addition, the response of oral mucosal tissues to endosseous dental implants in the present case was favourable, and the peri-implant bone loss at a 4-year follow-up was comparable to normal individuals.

Patient's perspective

- I have always had issues with my teeth. My parents told me that I lost my primary teeth early, and they had to feed me soft food. In school, boys used to laugh on me because I do not have good teeth, and in high school and university, I used to avoid close contact with friends and colleagues because of my bad breath and dental appearance. Teeth cleaning, antibiotics and mouthwashes prescribed by my dentists did not help me a lot.
- When doctors told me that dental implant might help, I was very excited. But, when they informed me that they recommend extraction of all teeth, I got a bit concerned; particularly after they explained to me that there is little known about body immune response to dental implants in patients with LAD. However, I have been reassured that my immune defect is mild, and might not significantly influence the success of dental implant treatment. The other option was to construct a removable complete denture, which was a bit disappointing for me. Therefore, I decided to go for the dental implant treatment plan, and I went through all surgical and prosthetic phases of the treatment with patience and hope.
- When my prosthetic teeth were ready, I was so excited; and the new teeth looked nice. Having good teeth improved my self-confidence, and allowed me to improve my social interaction with colleagues at work. In fact, I got engaged to one of my colleagues and we are planning to get married.

Learning points

- Aggressive periodontitis and early onset tooth loss is a major clinical feature of leucocyte adhesion deficiency (LAD).
- Tooth loss in LAD might negatively influence the quality of life in affected patients.
- Oral rehabilitation using osseointegrated dental implants might help to overcome the functional and psychological adverse effects of LAD periodontitis.
- Assessment of the severity of immune defect in patients with LAD is essential when considering dental implants.
- Antibiotic prophylaxis and frequent oral hygiene visits are needed to prevent infections and maintain healthy peri-implant tissues.

Contributors AAK: treated the patient. FS: was involved in case diagnosis. ZAT: was involved in patient management. YH: designed the study, reviewed the

literature and wrote the manuscript. All authors: read and approved the final manuscript.

Competing interests None declared.

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