

PERIODONTITIS AS A MANIFESTATION OF LARGE GRANULAR LYMPHOCYTE (LGL) LEUKEMIA: A CASE REPORT

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ABSTRACT

The aim of the present paper is to report a case with Large Granular Lymphocyte (LGL) leukemia with severe periodontal destruction. To the best of our knowledge this is the first report of a LGL presented with severe periodontitis. A 20-year-old female presented with neutropenia, hepatosplenomegaly and was taking Mehtorexate 15 mg/day. Intraoral examination revealed aphthous ulcerations at labial and buccal mucosa and an inflamed, red, fragile marginal gingiva with bleeding upon probing. There were multiple deep pockets with furcation involvements. Initial treatment included extraction of hopeless teeth, scaling and root planning and oral hygiene motivation. However, the patient refused dental treatment and did not show up at recall visits. Hematologists are recommended to have consultations with their patients' dentists especially when they face with quantitative or qualitative problems associated with neutrophils.

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BÜYÜK GRANÜLLÜ LENFOSİTİK LÖSEMİNİN BİR BULGUSU OLARAK PERİODONTİTİS: VAKA RAPORU

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ÖZ

Bu vaka raporunda şiddetli periodontal yıkımları olan büyük granüllü lenfositik lösemi (LGL) hastası sunulmaktadır. Litertür taramasına göre bu vaka raporu şiddetli periodontitise sahip LGL hastasının bildirildiği ilk yayındır. 20 yaşındaki kadın hastada nötropeni ve hepatosplenomegali bulunmaktadır ve de hasta 15 mg/gün Metotreksat kullanmaktadır. Ağız içi muayene sonucunda dudak ve yanak mukozalarında aftöz ülserler ve de sondlamada kanayan iltihaplı, kırmızı, fragil marjinal dişetleri tespit edilmiştir. Hastada furkasyon tutulumlarının da olduğu çoklu derin periodontal cepler bulunmaktadır. Başlangıç tedavisi olarak oral hijyen motivasyonu, diştaşı temizliği ve kök düzeltmesi ile umutsuz dişlerin çekimi gerçekleştirilmiştir. Ancak hasta diş tedavilerini onaylamayarak idame randevularına gelmemiştir. Hematologlara hastalarında kalitatif veya kantitatif nötrofil problemleri olduğu durumlarda mutlaka dişhekim konsültasyonu gerçekleştirmeleri önerilmektedir.

Sorumlu Yazar

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INTRODUCTION

Several hematologic and genetic disorders have been associated with the development of periodontitis in affected individuals and classified as "Periodontitis as a Manifestation of Systemic Diseases"^{1,2} at the 1999 International Workshop for the Classification of the Periodontal Diseases.³

The major effect of such disorders is through alterations in host defense mechanisms, which have been clearly described for disorders such as neutropenia, leukocyte adhesion deficiencies and leukemia.⁴ Other non-defense cells such as the red blood cells have crucial roles in maintaining nutrient supply and gas exchange to the periodontium. For efficient hemostasis platelets are needed.¹

Leukemia is a serious malignant disease caused by the proliferation of the white blood cell-forming tissues resulting in a marked increase in circulating immature or abnormal white blood cells. In both acute monocytic and chronic lymphocytic leukemia direct leukemic infiltration into the gingival tissues can be seen. Leukemia can result in enlarged gingiva due to infiltration of these tissues by leukocytes in approximately 10% of cases.^{5,6} Secondary effects from the depression of marrow or lymphoid tissue include hemorrhage, neutropenic ulceration and an increased susceptibility to microbial infections. Clinical periodontal features include anemic pallor of the gingiva, bleeding due to platelet deficiency and reduced resistance to infection due to decreased immune and inflammatory cell numbers. Direct drug toxicity by chemotherapeutic agents may also cause several distinct gingival changes, including erosion and ulceration.⁵⁻⁷

Large granular lymphocyte (LGL) leukemia was first described in 1985 as a clonal disorder involving tissue invasion of marrow, spleen, and liver.⁸ Clinical presentation is dominated by recurrent infections associated with neutropenia, anemia, splenomegaly, and autoimmune diseases, particularly rheumatoid arthritis (RA).⁹⁻¹¹ In 1989, the French-American-British classification identified LGL leukemia as a distinct entity among chronic T-lymphoid leukemias.¹² In 1993, the distinction was made between CD3⁺ T-cell and CD3⁻ NK-cell lineage subtypes of LGL leukemia.⁹ The real classification in 1994 recommended that LGL leukemia be a distinct clinical entity among peripheral T-cell and NK-cell neoplasms and adopted the suggestion of distinguishing the 2 subtypes of T-cell and NK-cell LGL leukemia.¹³ The World Health Organization classification, published in 1999, included T- or NK-cell granular lymphocytic leukemia in the subgroup of mature

peripheral T-cell neoplasms.¹⁴ Furthermore, in 2008, a new provisional entity of chronic lymphoproliferative disorder of NK cells (also known as chronic NK-cell lymphocytosis) was created by World Health Organization to distinguish it from the much more aggressive form of NK-cell leukemia.¹⁵ The frequency of T and NK LGL leukemia is not accurately determined and ranges from 2% to 5% of the chronic lymphoproliferative diseases in North America and up to 5% to 6% in Asia. To the best of our knowledge, this is the first report of a LGL presented with severe periodontitis.

CASE REPORT

Medical Evaluation

A 20-year-old female presented with neutropenia. Her medical history revealed neutropenia ongoing for approximately two years. In December 2010, a bone marrow biopsy was performed which was normocellular and showing an increase in megacaryocytes. Flow cytometry of the bone marrow revealed CD2, CD3, CD4 (25%), CD5, CD7, CD8 (34%), CD38, CD45, HLA-DR positivity. An abdominal ultrasound revealed mild hepatosplenomegaly (vertical length of liver 165 mm, spleen 135 mm). Complete blood count was as follows; Hb: 12.7 gr/dL (12.00-18.00), WBC: $1.7 \times 10^3/\mu\text{L}$ (3.60-10.00), PLT: $355 \times 10^3/\mu\text{L}$ (150.00-450.00). Hepatitis, viral tests, and autoimmune antibodies were all negative. Sedimentation rate and rheumatoid factor were in normal limits. A mild hypergammaglobulinemia (IgG: 2120 mg/dL; range: 694-1618) was detected. In peripheral blood smear 4% neutrophil, 56% lymphocyte, 10% large granular lymphocyte, 28% monocyte and 2% eosinophil was reported. A repeat bone marrow biopsy showed an increase in CD3 positive cells, erythroid hyperplasia, and relative increase of lymphoid cells. Tartrate-resistant acid phosphatase staining was positive in a fine granular manner. Cytogenetic was 46, XX in 20 metaphases. T-cell gene rearrangement was found to be clonal. Flow cytometry of repeat bone marrow was as follows: CD2, CD3, CD4, CD5, CD7, CD8, CD20, CD22, CD45, HLA-DR (+); CD16, CD56, CD57 (-). In conclusion, all these findings led us to a diagnosis of large-granular lymphocyte leukemia (LGL). Methotrexate 15 mg/day once a week peroral was initiated.

Dental Evaluation

The patient was referred from Department of Hematology at Hacettepe University to the Department of Periodontics at the same institution during the spring of 2010. The chief complaint by the patient was her mobile teeth and inability to chew. The patient claimed that she had lost her primary

dentition because of the loosening of her teeth.

The patient's medical history revealed that she had been diagnosed for LGL few months ago and was under the control of her physician since then. The patient was taking Mehtorexate 15 mg/day, and that she had no known allergies. There was no family history of any medical problems and she had low social and economic status. The patient reported that she had periodic childhood illnesses i.e. colds and ear infections. Intraoral examination revealed aphthous ulcerations at labial and buccal mucosa; (Figure 1) however, hard and soft palates and oropharynx were not affected. The patient displayed poor oral hygiene. Periodontal examination revealed inflamed, red, fragile marginal gingiva and bleeding on probing along with multiple pockets >3 mm most of them being at the posterior site were noticed. Gingival recession was present at all posterior segments. Furcation area was exposed at maxillary and mandibular first molars with class IV involvement (Figures 2, 3). Deepest pockets were of 9 mm, and were located around the maxillary and mandibular premolar-molar sites. Grade 3 mobility for the first and the second molars and grade 2 mobility for the second premolars sites were observed. Panoramic radiograph revealed that there occurred advanced bone loss around these teeth (Figure 4). After clinical and radiographic examination it was noted that the periodontal destruction particularly affected the primary dentition and posterior sites of permanent dentition. Because of the horizontal bone loss noted at incisor sites in both maxilla and mandible, diagnosis of aggressive periodontitis was eliminated.

The patient received 2 gr. Amoxicillin one hour before the dental therapy according to the recommendation of her physician. Initial treatment included extraction of the severely affected first and second molars and second premolars (except lower left second premolar), oral hygiene



Figure 1. Frontal intraoral view of the patient



Figure 2. Intraoral view left side



Figure 3. Intraoral view right side

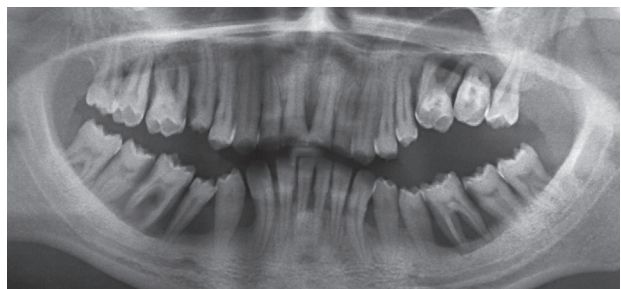


Figure 4. Panoramic radiograph.

instruction was given to the patient, scaling and root planning was performed and an antimicrobial mouth rinse was prescribed twice a day. Monthly recall/maintenance visits were recommended. However, the patient refused dental treatment and did not show up at recall visits.

DISCUSSION

LGL leukemia, classified in the indolent non-Hodgkin lymphomas, is a clonal disease, arising most frequently (85%) from a T cell lineage or, less commonly (15%), from a natural killer (NK) cell lineage.^{9,16} The cause of this rare disorder is not known. Noteworthy, these leukemic cells show all the characteristics of antigen-activated T cells,¹⁷ suggesting that an initial step in LGL expansion is an antigen-driven mechanism.

The persistence and proliferation of LGLs could be due to the stimulatory effect of various cytokines including interleukin (IL)-12 and IL-15, or to genetic polymorphisms in genes involved in the regulation of immune and inflammatory responses.¹⁸⁻²¹ IL-15 stimulates LGL, mediating this activity via IL-2 receptor. IL-15 and platelet-derived growth factor are the two key mediators controlling the interactions among the survival pathways.^{22,23}

The median age of onset of T-cell LGL leukemia is 60 years. Only 10% of patients are younger than 40 years of age.²⁴ Symptoms, when present, are usually related to neutropenia, and include fever with recurrent bacterial infections in 20-40% of patients.²⁵ Infections typically involve oropharyngeal, skin and perirectal areas. Fever, fatigue, night sweats, or weight loss are observed in 20-30% of cases.^{25,26} Nonclonal LGL expansions have been reported in the following clinical situations: Viral infections (eg, EBV, HBV, HCV, HIV, CMV), connective tissue disease, idiopathic thrombocytopenic purpura, non-Hodgkin lymphoma, various skin disorders, and the hemophagocytic syndrome.^{9,27-29} The myelodysplastic syndrome and solid tumors are sometimes associated with reactive T-cell LGL expansion.²⁸

The immune and inflammatory systems are crucial to our survival. Back-up systems are often present, which means that many functional defects are not fatal, but do result in predisposition to various diseases, such as chronic periodontitis. Systemic diseases affecting the host response as primary immunodeficiencies or secondary defects caused by the lack of nutrients or changes in the local tissues are very often accompanied by severe forms of periodontitis. Thus, blood and systemic disorders of the blood and blood-forming organs may have a profound effect on the periodontium.³⁰ However, inflammatory cell disorders may also have a detrimental effect on the integrity of the periodontium. In addition, specific diseases of the periodontium, i.e. today the early-onset forms of periodontitis, are increasingly linked with leukocyte function abnormalities.³¹ The clinical manifestation of many of these

disorders appears at an early age and may be confused with aggressive forms of periodontitis with rapid attachment loss and the potential for early tooth loss.

Although our patient was diagnosed with LGL, her case was unusual as she did not experience recurrent infection although she presented with neutropenia; there were no anti-neutrophil antibodies detected. Periodontal disease was the only medical abnormality that was clinically present. It may be speculated that other signs/symptoms of the neutropenia were subclinical, or the periodontal disease was the first sign of her condition. Persistence and proliferation of LGLs could be due to the stimulatory effect of various immune and inflammatory responses¹⁸⁻²¹ which could mean that the patient may exhibit overreactive host response. This condition and low white blood cell count could explain the severe alveolar bone loss. Local treatment in combination with systemic antibiotics may in milder forms improve the situation, but in many cases the success is questionable and premature loss of teeth occurs.

Even though the patient underestimated her condition, it is important that preventive measures be taken to avoid future periodontal problems. This case also proves that low socioeconomic status has important effects on the awareness of the importance of periodontal treatment and establishment of communication. The patient was unwilling to the dental therapy, did not care about losing her teeth and did not return to our calls. Hematologists are recommended to consult their patients to a dentist especially when they have conditions that may cause quantitative or qualitative problems linked with neutrophils.

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