Oral Manifestations of T-Cell Large Granular Lymphocytic Leukemia: a Case Report

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ABSTRACT

Background: T-cell large granular lymphocytic (T-LGL) leukemia is a rare, chronic, often indolent lymphoproliferative disorder of mature T cells (CD3+). Severe neutropenia and other cytopenias are common features in patients with T-LGL leukemia and may cause infections, thus representing a major cause of morbidity in this disease. Immunosuppressive therapy with low-dose regimes of methotrexate, cyclophosphamide, corticosteroids or cyclosporine A is the treatment of choice. Amongst the variety of T-LGL leukemia complications, oral manifestations such as ulcers have been rarely reported. The purpose of this paper is to report a case of T-cell large granular lymphocyte leukemia with oral manifestations and to discuss their pathogenesis and management.
Methods: In the present case, a 65 year old female with a two-month history of diagnosed T-LGL leukemia presented with oral lesions, including ulcerations on the ventral tongue and soft palate as well as swollen, erythematous and ulcerated gingiva. The patient was under treatment with methotrexate, granulocyte colony-stimulating factor (G-CSF) and erythropoietin.
Results: Considering patients' medical history and clinical appearance of the lesions, a clinical diagnosis of a neutropenic ulcer of the tongue was established. The oral lesions resolved after treatment with antibiotics, topical steroids and antiseptics combined with improvement of the hematological condition. The pertinent literature related to T-LGL leukemia ethiopathology, diagnostics and treatment was discussed.
Conclusions: Although rare, T-cell large granular lymphocytic leukemia should be included in the list of lymphoproliferative disorders, which may present with oral manifestations as a result of the disease and its treatment complications.

Keywords: T-cell large granular lymphocytic leukemia; neutropenia; oral ulcer; acute necrotizing ulcerative gingivitis; methotrexate.

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INTRODUCTION

Large granular lymphocytes (LGLs) constitute a morphologically distinct subset of lymphocytes comprising 10 - 15% of normal peripheral blood mononuclear cells (0.2 - 0.4 x 10^9/l) [1,2]. Cytologically, LGLs are medium to large cells characterized by an eccentric nucleus and an abundant, slightly basophilic cytoplasm containing azurophilic granules [1].

Clonal disorders of LGLs represent a spectrum of distinct lymphoproliferative diseases originating either from mature T cells (CD3+) or less frequently natural killer (NK) cells (CD3-) [1-6]. LGL leukemias comprise 2 - 5% of all T-cell/NK-cell malignancies with only 400 cases reported in the literature [1,2]. T-cell large granular lymphocytic (T-LGL) leukemia is the most common subtype, representing 85% of all diagnosed LGLs leukemias in Western countries [1,2]. The diagnosis of T-LGL leukemia is based on the demonstration of persistent (> 6 months) peripheral blood lymhocytosis with the characteristics of T-LGLs (usually between 2 - 20 x 10^9/l) [1-3,6]. Bone marrow involvement is variable, often presenting as interstitial and sinusoidal infiltration with T-LGLs [1-3,6]. The demonstration of clonality is usually based on Southern blotting and PCR assays demonstrating T-cell receptor (TCR) gene rearrangements [1,6-9].

T-LGL leukemia is diagnosed in older individuals (mean age 60 years) with equal sex distribution [1,2]. It is usually an indolent disorder with a median survival time longer than 10 years (as opposed to the frequently aggressive NK-cell LGL leukemia), although T-LGL leukemias aggressive variants with poor prognosis or transformation to a peripheral large T-cell lymphoma may occasionally occur [1,6,10]. T-LGL leukemia is characterized by a wide spectrum of clinical manifestations affecting approximately two thirds of the patients during the course of the disease [1-3]. Amongst them, recurrent infections, splenomegaly, B symptoms (weight loss, night sweat, and fever) and autoimmune disorders, such as rheumatoid arthritis, are the most common [1-3,11]. Oral manifestations of the disease have been rarely reported [12,13].

The purpose of this paper is to report a case of T-cell large granular lymphocytic leukemia with oral manifestations and to discuss their pathogenesis and management.

CASE REPORT

A 65 year old female of British descent was referred to the Department of Oral Pathology and Medicine by her dentist, complaining for a very painful ulcer on the ventral surface of the tongue present for four days. Her gingiva was also tender for about one week.

The patient had received a diagnosis of T-cell large granular lymphocyte (T-LGL) leukemia 2 months earlier. At the time of presentation, she had an abnormal hematologic profile consisting of a decreased absolute neutrophil count of 0.23 x 10^3/mcl (normal 1.5 - 7.00) and marginally elevated lymphocyte (4.87 x 10^3/mcl, normal 1.5 - 4.00) and monocyte (1.29 x 10^3/mcl, normal 0.2 - 1.00) counts. She also had mild anemia with a red blood cell (RBC) count of 3.40 x 10^6/mcl (normal 3.8 - 5.4), haemoglobin (HGB) 11 g/dl (normal 12 - 16) and hematocrit (HCT) 33% (normal 37 - 47). Additionally, she had thrombocytopenia as the platelet count (PLT) was 60 x 10^3/mcl (normal 130 - 400).

The patient, since the diagnosis of T-LGL leukemia was established, had been under treatment with methotrexate (2.5 mg qid, twice a week), an antimetabolite with well-established chemotherapeutic properties. Moreover she was receiving a regimen of recombinant human erythropoietin (Neorecormon epoetin beta, 30000 U, F. Hoffmann-La Roche Ltd., Basel, Switzerland), which is used in the treatment of various types of anemia by stimulating the production of RBCs in the bone marrow and spleen. Furthermore, every other day she was receiving Granulocyte colony-stimulating factor (G-CSF, Granulokine, Amgen/Roche), a growth factor normally produced by a number of different tissues to stimulate the bone marrow to produce granulocytes and stem cells, thus stimulating the survival, proliferation, differentiation, and function of precursor and mature neutrophils.

Intraoral examination revealed a 2.0 x 1.5 cm ulcer on the right ventral tongue, covered by a yellow pseudomembrane with irregular and slightly firm margins. The mucosa surrounding the ulcer was faintly erythematous (Figure 1). Further, the gingiva were erythematous and swollen, while the tips of several interdental papillae were punched-out with eroded tips (Figure 2).

The differential diagnosis of the ulcerative lesion of the tongue mainly included a neutropenic ulcer with additional possibilities being methotrexate-induced ulcer or leukemic infiltration. Concerning the gingival lesions, the primary diagnostic consideration was acute necrotizing ulcerative gingivitis (ANUG) with a differential diagnosis of gingival leukemic infiltrate. Based on the most likely clinical diagnoses and considering the current hematologic status of the patient (including thrombocytopenia), it was decided to avoid a biopsy at the present time.

The patient was prescribed Amoxicillin (1 gr twice daily), Metronidazole (500 mg three times daily), chlorhexidine 0.2% mouthwash and an oral mucosal

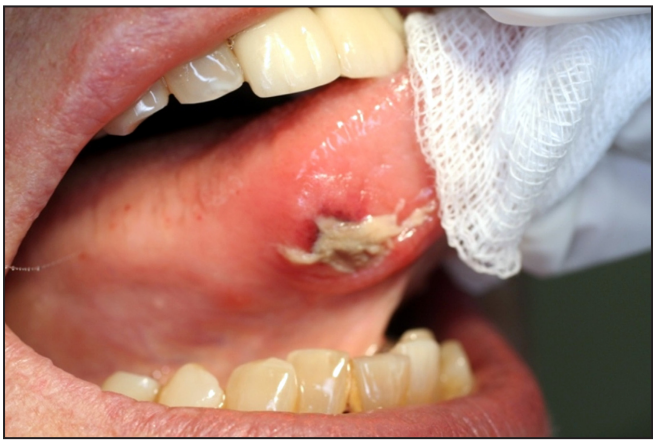

Figure 1. Painful ulcer on the right ventral tongue with irregular margins, covered by a yellow pseudomembrane.

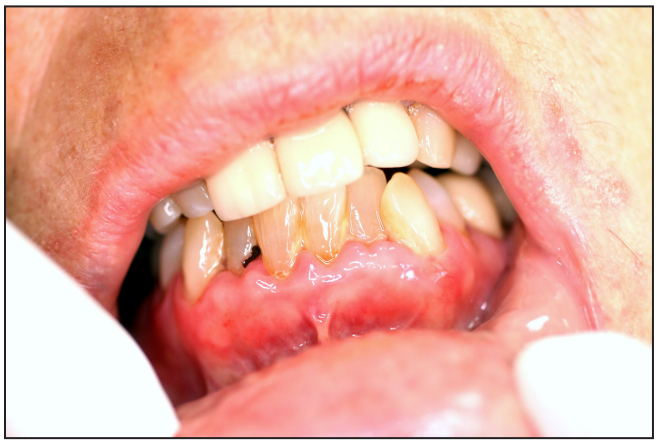

Figure 2. The anterior mandibular gingiva appear erythematous and swollen demonstrating punched-out interdental papillae with eroded tips.

barrier to be applied on the tongue ulcer. Her attending haematologist was consulted and no modifications in her anti-leukemia regimen were instituted at this point. She was asked to return to the clinic in three days, when the intraoral examination demonstrated improved clinical features of the lesions, although the symptoms persisted. She was given instructions to continue the prescribed regimen and was re-examined after four days: the clinical condition of the gingiva was significantly improved and the tongue ulcer showed signs of healing with reduced size (1.0 x 0.5 cm). However, the patient was complaining of continuing pain and dysphagia. In addition, a new ulcer on the soft palate surrounded by red halo was noticed (Figure 3), attributed to the same causes as the tongue ulcer. The regimen was modified with the addition of a topical steroid (fluocinonide 0.05% gel) to be applied 4 times daily on the ulcerative lesions of the tongue and soft palate. Upon further consultation with the attending hematologist, the methotrexate administration was discontinued; current blood examination revealed return of the neutrophils back to normal limits (2.09 x 10^3/mcl). The patient returned to clinic a week later (two weeks after her first admission) with clearly improved condition. The oral and soft palatal ulcers had significantly improved (Figure 4) and the gingival appearance was almost normal (Figure 5).

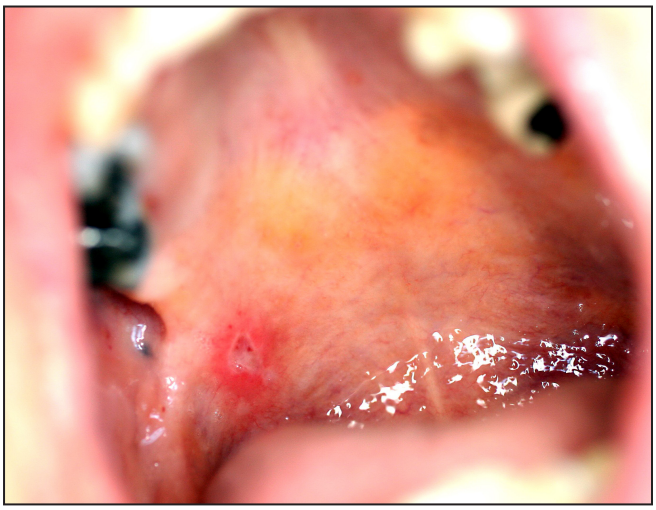

Figure 3. Small ulcer surrounded by erythematous halo on the right soft palate.

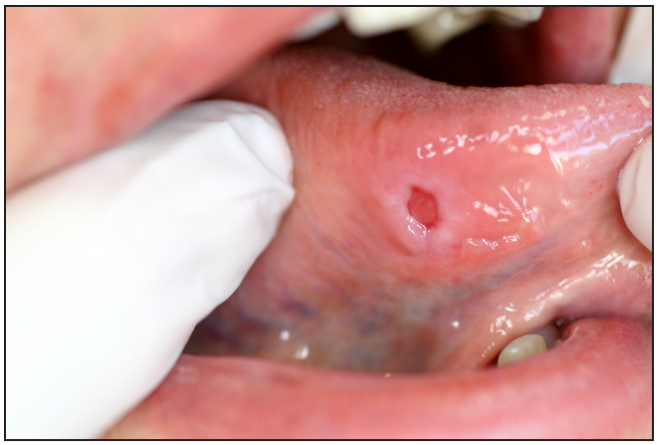

Figure 4. Follow-up examination showing partial healing of the tongue ulcer.

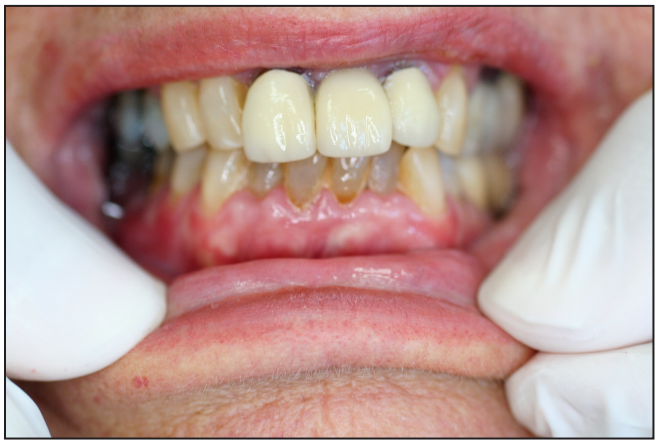

Figure 5. Follow-up examination showing almost complete resolution of the gingival lesions.

DISCUSSION

T-LGL leukemia is the most common subtype of LGL leukemias mainly affecting elderly people; about one third of the patients are asymptomatic at the time of diagnosis [1-4].

The early symptoms of the disease are related to the severe neutropenia observed in 85% of the patients, which results in susceptibility to fever and recurrent bacterial infections manifesting in 20 - 40% of the patients [1,7,14]. The organs usually affected include skin, oropharynx, anus and lungs [1-2]. The pathogenesis of neutropenia in the context of T-LGL leukemia is unclear. Neutropenia does not seem to be a consequence of bone marrow infiltration by LGLs nor caused by direct immunosuppression. It is suggested that neutropenia and other cytopenias are the result of an induced apoptosis participating in T-LGL leukemia pathogenesis [7,14]. Fatigue and B-symptoms (fever, night sweats, weight loss) occur in 20 - 30% of patients [1-2,11]. During the course of their disease patients may develop splenomegaly (20 - 50%) and hepatomegaly (20%). Various autoimmune disorders are often associated with T-LGL leukemia, the most common one being rheumatoid arthritis observed in about 25% of patients [1-3,5].

Oral manifestations constitute a significant part of the clinical spectrum of various types of leukemias [15,16]. Common clinical presentations include diffuse or localized gingival swellings due to leukemic infiltration, gingival or mucosal petechial bleeding due to thrombocytopenia, as well as ulcers and susceptibility to infections due to neutropenia [15,16]. In addition, the treatment of leukemias, e.g. cytotoxic chemotherapy, may cause oral side effects such as mucositis, a condition characterized by inflammation, atrophy and ulcerations of the oral mucosa; its pathogenesis is attributed to direct toxicity of the medications used as well as to chemotherapy-induced myelosuppression [15-17].

Oral manifestations of T-LGL leukemia have been only rarely reported. Copete et al. [12] presented a case of 74 year old man with T-LGL leukemia, who had recurrent oral ulcerations on the labial mucosa for over a year. The presence of the ulcers was correlated to severe neutropenia and possibly attributed to infectious agents. The patient was treated with systemic corticosteroids and the ulcers healed as the neutrophil numbers returned to normal [12]. In the study of Pandolfi et al. [13], oral mucosal ulcers were reported in 4.6% (7/151) of patients with lymphoproliferative disorders of granular lymphocytes [3,13].

In our case, the patient was a 65 year old female with diagnosed T-LGL leukemia, who presented with oral ulcers as well as gingival lesions consistent with acute necrotizing ulcerative gingivitis (ANUG). Based on the clinical features and the resolution of the lesions following the improvement of neutropenia and appropriate treatment, the oral ulcers and the gingival lesions were mainly attributed to T-LGL-induced neutropenia.

Whether the oral ulcers developing as a result of neutropenia are caused by a specific infective etiology is unclear. Topical or systemic steroids are used in such cases in order to reduce the inflammatory reaction and promote healing; in addition, topical antiseptics and antibiotics are occasionally administered to prevent and/or treat bacterial infections. In general, oral ulcers respond well to treatment and clear up as the neutrophil counts return to normal limits [12,18].

ANUG is a condition with a characteristic clinical appearance attributed to specific bacterial species, such as spirochetes and fusiform bacteria [15,16]. The majority of ANUG cases, usually affect patients with suppressed immunity due to various causes, which may include a hematological malignancy and respond well to local measures and antibiotic treatment along with resolution of the predisposing factors [15,16].

Treatment of T-LGL leukemia and the reversal of neutropenia may also contribute to the improvement and/or resolution of the clinical, including oral, manifestations of the disease. Several therapeutic agents have been used with variable success including cytotoxic or immunosuppressive medications, such as cyclosporine, cyclophosphamide, methotrexate and corticosteroids [14,18-20]. Colony stimulating factors have been also employed mainly targeting the neutropenia [14,18]. The use of methotrexate resulting in a complete remission in 50% of cases is considered to be the best therapeutic approach [14,19,20]. However, methotrexate is related to well recognize adverse effects that may complicate patient's clinical condition. Amongst them, oral ulcerations and sore mouth are quite common, are dose dependent and may appear at any time during the course of methotrexate treatment [21,22]. Therefore, oral ulcers developing in T-LGL leukemia patients receiving methotrexate, including our patient, may also be related to methotrexate regimen and may be benefited by temporary methotrexate discontinuation.

CONCLUSIONS

In conclusion, although very rare, T-cell large granular lymphocytic leukemia should be included in the list of lymphoproliferative disorders, which may cause oral

manifestations as a result of complications associated with the disease and/or its treatment.

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The authors report no conflicts of interest related to this case report.

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