Atenção às Mucosas! – Aftose Oral Recorrente como apresentação de Leucemia Linfocítica de Grandes Células Granulares

Heads up for the mucous membranes! – Recurrent oral aphthosis as first sign of large granular cell lymphocyte leukemia

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Resumo

As desordens clonais de linfócitos grandes granulares (LGG) representam um espectro de doenças linfoproliferativas que se originam quer de células T (CD3+) quer de células natural killer (NK) (CD3-) maduras. A leucemia de LGG representa 2 a 5% de todas as neoplasias de células T ou NK, apresentando a maioria dos doentes um curso indolente. A clínica é, sobretudo, uma de infecções recorrentes associada a neutropenia, anemia, esplenomegalia e doenças auto-imunes, em particular a artrite reumatóide. Apesar disso, estão descritos na literatura casos de aftose oral recorrente como primeira manifestação desta entidade, muito embora, esta apresentação se associe maioritariamente à neutropenia crónica apresentada por estes doentes. Os autores pretendem descrever o caso de um doente com LLGG em que o aparecimento de úlceras foi a apresentação clínica inicial associada a hipogamaglobulinemia.

Palabras clave: Aftas, Hipogamaglobulinemia, Leucemia

Abstract

Clonal disorders of large granular lymphocytes (LGLs) represent a spectrum of distinct lymphoproliferative disorders originating either from mature T cells (CD3+) or natural killer (NK) cells (CD3-). LGL leukemia comprises 2 to 5% of all T-cell/NK-cell malignancies and manifests itself mostly as an indolent disease. Clinical presentation is dominated by recurrent infections associated with neutropenia, anemia, splenomegaly, and autoimmune diseases, particularly rheumatoid arthritis. Recurrent oral aphthosis has also been described in the literature as the first manifestation of this entity, although this presentation is mostly associated with chronic neutropenia presented by these patients. The purpose of this article is to report a case of LGLL in which the development of ulcers were the initial clinical presentation, associated with hypogammaglobulinemia.

Keywords: Aphtae, Hypogammaglobulinemia, Leukemia

Introduction

Large granular lymphocyte leukemia (LGLL) was first described in 1985 and classified as a clonal disorder involving the bone marrow, spleen and liver[1]. The clinical presentation is dominated by recurrent infections associated with neutropenia, anemia, splenomegaly and autoimmune diseases, particularly rheumatoid arthritis[2,3]. In 1999 the classification published by the World Health Organization (WHO) included granular T-cell or NK lymphocytic leukemias in the subgroup of mature T-cell neoplasms[4]. This was later revised in 2008, and the division in chronic lymphoproliferative disorders of NK cells was proposed, in order to distinguish the more aggressive subtype of NK cell leukemia[5]. It is estimated that the frequency of LGLL of T and NK cells is around 2 to 5% in North America and up to 5 to 6% in Asia[2], affecting all age groups, with a mean age at diagnosis of 55 years, and no gender distribution difference[6].

Large granular lymphocytes (LGL) are identified by their typical morphology and phenotype. In addition to being above normal size (15 to 18 µm), they also exhibit an abundant cytoplasm containing typical basophilic granules and a kidney-shaped or round nucleus. The normal amount of LGL in the peripheral blood is 0.25 x 10^9/ L and in the initial series published over 20 years ago, more than 80% of the patients had associated lymphocytosis[7]. For years, a LGG count above 2x10^9/ L was considered mandatory for establishing the diagnosis, but currently, advances in flow cytometry and immunohistochemistry now have diagnostic precision with significantly lower counts of clonal populations (0, 4 - 2X10^9 / L)[8,9].

Clinical case

The authors present a 65-year-old male smoker with a history of controlled hypertension undergoing angiotensin-converting enzyme (ACE) inhibitors. He was referred to the outpatient clinic with a history of recurrent oral aphthosis starting 8 years before, whilst having periods of weeks to months without oral mucosa lesions and no scarring. During this time, he had been visiting his Primary Care physician and Stomatologist, who both documented the aphthous lesions. Routine blood tests were unremarkable. The patient denied any other symptoms namely genital ulcers, asthenia, weight loss, arthralgia or gastrointestinal symptoms.

At the time of the patient's first assessment at the outpatient clinic, blood tests showed a haemoglobin value of 16.9 g/dL (normal 13-17), with a mean corpuscular volume 86.2 fL (83-101). The white blood cell count was 9.23 x 10^3/µl (4.00-11.00) with a differential lymphocyte count of 2.00 x 10^3/µl (1.5-4.00), monocytes of 0.8 x 10^3 /µL (0.20-0.80) and neutrophils 6.16 x 10^3/µL (2.00-7.50). The patient had no record of neutropenia during a 6 month follow-up period, however, episodic mild lymphopenia was documented. He also had counts of 0.4% of immature granulocytes and at least two more episodes of oral aphthae, one of which also seen by the attending doctor at the clinic. The immunological study did not show high titers of antinuclear antibodies, however, hypogammaglobulinemia (IgA, IgG and IgM) was noted, on a patient without past

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history of recurrent infections. He had no abnormal iron or vitamin levels. Lymphocyte immunophenotyping showed increased granular lymphocytes / cytotoxic T cells (99% of gamma/delta T lymphocytes) with abnormal phenotypical characteristics. Flow cytometry showed that these cells were positive for CD3 and CD8 and were negative for most other T and B cell markers. Active solid malign neoplasm was ruled out through free Prostate Specific Antigen (PSA) assay, upper and lower endoscopic study, and computerized axial tomography to the thorax, abdomen, and pelvis. The imaging study of the abdomen showed an enlarged homogeneous spleen, which in this case was compatible with the diagnosis of LGLL.

Although most oral ulcer cases are associated with chronic neutropenia in these patients, the patient in question had no evidence of cytopenias other than the mild lymphopenia discussed above, at admission or during the next 6 months of follow-up. For this reason and after Hematology input had been given, no additional testing was performed, and no treatment aimed at the underlying disease was deemed necessary, keeping the patient on symptomatic control of oral ulcers with colchicine.

This case illustrates the complex nature of the evaluation of patients with recurrent oral ulcers.

Discussion

LGLL is a rare disorder characterized by the monoclonal proliferation of a T cell population having either NK activity or cellular suppressor activity, such as the CD3+ subtype. Its aetiology is not completely understood, but dysregulated apoptosis has been implicated as one of the major mechanisms in the disease pathogenesis[8]. Etiological hypotheses of recurrent oral aphthosis as vitamin deficiencies, autoimmune diseases and neoplasms should be considered, keeping in mind that oral ulcers are reported in 4.6% of LGLL patients and may be the initial form of manifestation[10].

It is known today that the LGLL T cell subtype is considered an indolent, chronic disease. In light of these findings, recommendations for initiating treatment include severe neutropenia (or moderate with associated recurrent infections), symptomatic anemia, and autoimmune conditions requiring targeted therapy, none of which have been reported in our patient.

There is no standard treatment for LGLL patients, but most published case reports recommend immunosuppressive treatment as the cornerstone of therapy, including agents such as metrotrexate, cyclosphosphamide and cyclosporine[12].

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