Case Report

Oral Hairy Leukoplakia in a Patient with Systemic Primary Amyloidosis: A Case Report
Jeane de Fátima Correia-Silva, Renata Gonçalves Resende, Fernanda Maia Lodi, Brendan Conn, Ricardo Alves Mesquita, Ricardo Santiago Gomez

Abstract

Oral hairy leukoplakia is characterized by an asymptomatic white plaque on the lateral borders of the tongue. It is associated with immunodeficiency, principally to Human Immunodeficiency virus infection, but it has also been reported in patients with other immunosuppressed states. A 48-year-old man with primary amyloidosis was referred to evaluate a white plaque on the tongue. Based on the patient’s clinical presentation, medical history, and localization of the oral lesion, differential clinical diagnosis included amyloidosis, oral hairy leukoplakia, idiopathic leukoplakia, hyperplastic chronic candidiasis, and uremic stomatitis. The diagnosis of oral hairy leukoplakia was confirmed by histopathological analysis and in situ hybridization showing Epstein-Barr virus. This is an unusual clinical presentation of oral hairy leukoplakia.

Keywords: Amyloidosis; Autologous; EBV; Oral Hairy Leukoplakia; Stem Cell; Transplantation.

Introduction

Amyloidosis is a disease entity defined by the presence of extracellular accumulation at systemic or organ-specific level of insoluble low molecular weight protein fibrils manifesting a beta pleated sheet configuration and a characteristic staining pattern.1 Amyloidosis of the oral cavity is rare.2 Oral hairy leukoplakia (OHL) is characterized by an asymptomatic white plaque on the lateral borders of the tongue. This plaque has a flat, corrugated, or hairy surface that cannot be removed through scraping. OHL is associated with immunodeficiency, principally to Human Immunodeficiency virus (HIV) infection, but it has also been reported in patients with other immune suppressed states.3 Prevalence of OHL in HIV infected Brazilian adults is reported to be 28.8%.4 The etiology is associated with reactivation of (Epstein-Barr virus) EBV infection and the lesions occur primarily on the lateral borders of the tongue. Other rare locations are ventral or dorsal portion of the tongue, labial mucosa, floor of the mouth, and soft palate.5 The purpose of this paper is to present an unusual case of OHL in a patient with systemic primary amyloidosis and discusses on differential diagnoses.

Case Report

A 48-year-old man was referred by the Stem Cell Transplantation Unit of the Hospital das Clínicas, Universidade Federal de Minas Gerais, Belo Horizonte, Brazil to the Oral Medicine Clinic of the School of Dentistry to evaluate a tongue lesion. The patient had noticed the appearance of the lesion three months earlier. Further, he noted that brushing did not remove the lesion and that it was growing. His previous medical history revealed muscle weakness of the lower limbs, which involved unsteadiness when walking and climbing stairs, in October 2010. In February 2011, the patient developed edema of the lower limbs. Extensive clinical research conducted in collaboration with the different medical services led to suspect amyloidosis. Histological analyses showed renal amyloidosis with deposition of lambda light chains. The patient used prednisone 60 mg/day for 13 days, and two doses of methotrexate (50 mg each time) in May 2011. There was, however, no clinical improvement in the systemic condition. In June 2011, the patient received dexamethasone (40 mg/day, for 4 days) and cyclophosphamide (500 mg/week). The patient was a nonsmoker with no history of recreational drug use or risk factors for HIV. Intra-oral inspection revealed the presence of multiple asymptomatic white plaques with regular borders and irregular surface located in the tongue with extension to the ventral and dorsal surfaces. The plaques were not removable when scraped (Fig 1).

Blood tests showed that levels of uric acid and electrolytes were normal; however, the
patients presented a low platelet count (Table 1). The patient was tested for Hepatitis C virus (HCV), Hepatitis B virus (HBV), Human T lymphotropic virus type I (HTLV I), Human T lymphotropic virus type II (HTLV II), Herpes Simplex virus type I (HSV I), Herpes Simplex virus type II (HSV II), EBV, and HIV. Results showed that the patient was EBV seropositive (IgG).

Exfoliative cytological examination of the lesion was carried out, and Candida (sp) was identified. Oral candidiasis was treated with topical nystatin for 15 days. Despite antifungal therapy, the lesion did not present clinical improvement; thus, an incisional biopsy was performed from the dorsal tongue. Histopathological analysis revealed mucosa exhibiting hyperkeratosis and acanthosis (Fig. 2A). Ballooning degeneration was observed in the upper layer of the epithelium; in addition, we observed a vacuolated cytoplasm with small, round, deeply basophilic nuclei surrounded by a clear narrow halo. The reaction for EBV detection was carried out using an EBER probe for EBV and the corresponding anti-fluorescein antibody for localization (Novocastra Laboratories, United Kingdom) following the manufacturer’s instructions. The in situ hybridization for EBV showed strong staining of keratinocytes (Figs. 2B and 2C). Thus, a diagnosis of OHL was made.

The patient underwent autologous hematopoietic stem cell transplantation in February 2012 after receiving prophylactic acyclovir (800 mg/day) before the transplantation. Treatment with the immunosuppressant drug was suspended 30 days after the transplantation, and the patient showed signs of early OHL remission. The patient was disease free 6 months after the transplantation (Fig. 3).

Discussion
Based on the patient’s clinical presentation, medical history, and localization of the oral lesion, differential clinical diagnosis included amyloidosis, OHL, idiopathic leukoplakia, hyperplastic chronic candidiasis, and uremic stomatitis.

Figure 1: Multiple asymptomatic adherent white plaques with regular borders and irregular surface located on the ventral surface of the tongue.

Figure 2: A) Histopathological analysis showed tongue mucosa exhibiting hyperkeratosis, acanthosis, and ballooning degeneration in the upper layer of the epithelium (hematoxylin-eosin, 50× original magnification); B) In situ hybridization for EBV (EBER) showing strong staining of keratinocytes (in situ hybridization, 50× original magnification); C) In situ hybridization for EBV (EBER) (in situ hybridization, 400× original magnification).

Figure 3: Clinical presentation of the tongue showing complete regression of the lesion 6 months after autologous hematopoietic stem cell transplantation.
Amyloidosis of the tongue is generally secondary to systemic disease and is characterized by extracellular deposition of amyloid fibrils derived from the circulating acute-phase reactant serum amyloid A protein. In the tongue, amyloidosis can result in macroglossia, tongue protrusion, and dysphagia. Raised white plaque or yellow nodules can occur, and these are predominately along the lateral border. The histopathological features found in the biopsy ruled out this diagnosis.

Another less probable diagnostic hypothesis was idiopathic leukoplakia. This is a common white lesion of the oral cavity, which carries a recognized risk of malignant transformation. Leukoplakia is generally associated with tobacco habits and mainly affects the buccal mucosa and tongue sites; however, idiopathic leukoplakia can be found where no etiology is apparent. The current patient was a non-smoker. In the current case, chronic hyperplastic candidiasis was also considered because of the clinical appearance of the oral lesion and systemic immunosuppression. The principal etiologic agent of this disease is the oral fungal pathogen Candida albicans. This pathogen manifests as white, well-demarcated, palpable, raised lesions that vary from small translucent whitish areas to large opaque plaques that cannot be scraped off. The lesions are symptomless and regress after appropriate antifungal therapy. The histopathological findings do not support this diagnosis.

Renal disease is a frequent manifestation of systemic amyloidosis and a leading cause of morbidity. Progressive loss of kidney function could lead to the development of chronic renal insufficiency, and this can result in uremia. Uremic stomatitis is a common intraoral clinical finding in cases of end-stage renal disease. It is characterized by the presence of plaques and crusts distributed on the buccal mucosa or on the dorsal or ventral surface of the tongue, gingiva, lips, and floor of the mouth. The patient in the present study presented with renal amyloidosis due to deposition of lambda light chains; however, the biochemical profile did not show renal failure. Therefore, we ruled out a diagnosis of uremic stomatitis.

A definitive diagnosis of OHL is established when the presence of EBV is demonstrated via histological analysis. Other nonspecific histopathological findings could include filiform hyperkeratosis and acanthosis with a vacuolar alteration of epithelial cells. In the present case, the patient was submitted to biopsy, and this revealed papillomatosis, hyperkeratosis, acanthosis, and ballooning degeneration in the stratum spinosum. The vacuolar alteration of prickle cells is an important characteristic of this condition. EBV can be detected by immunohistochemistry, in situ hybridization, and PCR. However, in situ hybridization is the most accurate and is considered as the gold standard technique in OHL diagnosis. OHL is a disease of the oral mucosa and is associated with EBV infection. The precise pathophysiological mechanism by which EBV infection causes OHL appears complex and is unknown. EBV is lymphocytotropic as well as epitheliotropic and can be transmitted through the saliva. Several factors, including repeated direct infection of the tongue’s superficial epithelial cells by EBV originating from saliva, productive EBV replication, EBV genetic evolution, and expression of specific EBV “latent” genes, converge to result in the development of OHL.

Table 1: Hematological and biochemical profile of the patient

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>White blood cells</td>
<td>10.100/mm³</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>7.676/mm³</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>1.818/mm³</td>
</tr>
<tr>
<td>Mononuclear</td>
<td>505/mm³</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>13.1 g/dL</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>38.9%</td>
</tr>
<tr>
<td>Platelets</td>
<td>111,000/mm³</td>
</tr>
<tr>
<td>Uric acid</td>
<td>5.3 mg/dL (normal = 3.4–7 mg/dL)</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>57 U/L (normal = 40–129 U/L)</td>
</tr>
<tr>
<td>Potassium</td>
<td>4.15 mEq/L (normal = 3.5–5.1 mEq/L)</td>
</tr>
<tr>
<td>Phosphor</td>
<td>3.6 mg/dL</td>
</tr>
<tr>
<td>Ca (Calcium)</td>
<td>9.2 mg/dL</td>
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</table>
OHL was first described more than 20 years ago in individuals with HIV infection. However, OHL findings can also be associated with other conditions involving immunosuppression such as organ or bone marrow transplantation, chemotherapy, hematological malignancies, and the use of systemic steroids.

Immunosuppressive drugs may also enable clonal expansion of EBV-infected B cells. In the present report, the patient underwent therapy with prednisone, methotrexate, dexamethasone, and cyclophosphamide which may explain the appearance of the lesion. These drugs have been associated with side effects on the immune system by decreasing the immunological response to various diseases and conditions.

OHL is frequently asymptomatic, and it does not require treatment in such instances. Conversely, extensive OHL that involves taste perturbation could require treatment. This therapy could be oral or topical and includes the use of drugs that inhibit EBV replication. Acyclovir and valacyclovir have caused OHL regression in many patients.

Topical treatment is commonly recommended because it has a low cost, is easy to use, has few side effects and is effective for a long period of time. In the present study, the patient received prophylactic acyclovir before autologous stem cell transplantation. The use of the prophylactic acyclovir and the suspension of immunosuppressant drug use after the transplant were probably responsible for OHL remission.

Conclusion
This is an unusual clinical presentation of OHL in individuals without HIV infection and systemic primary amyloidosis. Others conditions involving immune-suppression such as chemotherapy and the use of systemic steroids may decreasing the immunological response and enable clonal expansion of EBV-infected that has been associated with OHL.

Acknowledgement
We would like to thank National Council for Scientific and Technological Development (CNPq) for their financial help.

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Source of Support: Nil, Conflict of Interest: None Declared.