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CASE REPORT

Lymphomatoid Granulomatosis Presenting with Gingival Involvement in an Immune Competent Elderly Male

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Abstract Lymphomatoid granulomatosis (LYG) represents a B cell lymphoproliferative disorder that appears to be driven by infection of the lesional cells by Epstein–Barr virus (EBV). Although not a common condition, the overwhelming majority of cases affect the lungs and mediastinal lymph nodes. Oral mucosal involvement has been documented in only one other report. We describe an 82-year-old man who developed a chronic oral ulcer following extraction of a mandibular molar tooth. Biopsy of the ulcer identified large atypical mononuclear cells that had a B cell immunophenotype and were associated with the walls of several arterioles in the sample. In situ probes for EBV-encoded small RNA showed prominent labeling of these large cells, suggesting the possibility of LYG. Imaging studies identified mediastinal and hilar lymphadenopathy on CT imaging, while PET scans showed hypermetabolic activity in the lymph nodes as well as the left mandible. Based on these findings, a diagnosis of LYG was made and the patient was treated with rituximab, an anti-CD20 monoclonal antibody, combined with a chemotherapeutic regimen consisting of etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin. After three cycles of therapy, the oral ulcer resolved significantly, as well as the areas of hypermetabolic nodal activity. Remission continued for 3 years, however the patient eventually developed non-small cell carcinoma of the lung and expired as a result of that tumor.

Keywords Lymphomatoid granulomatosis · Epstein–Barr virus · Lymphoproliferative · Oral · R-EPOCH

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Introduction

Infection with Epstein–Barr virus (EBV) is very common in the human population. While systemic infection with this virus causes infectious mononucleosis, EBV-related conditions that specifically affect the oral mucosa, such as hairy leukoplakia and the recently described EBV-positive mucocutaneous ulcer [1], have been documented. Over the past few decades, several neoplasms have been associated with this virus, including African Burkitt lymphoma, nasopharyngeal carcinoma, Hodgkin's lymphoma, gastric carcinoma [2], post-transplant B cell lymphoproliferative disease [3], and extra-nodal NK/T cell lymphoma [4].

Lymphomatoid granulomatosis (LYG) is a rare condition that primarily affects the lungs and mediastinal lymph nodes, typically in an adult male population [5]. While the reactive versus neoplastic nature of this process has been

debated for decades, in recent years modern molecular and immunohistochemical techniques have shown that LYG appears to represent an EBV-driven proliferation of B-lymphocytes, essentially resulting in a process that behaves in a manner similar to lymphoma. In this report, we describe a patient who presented with an ulcerated mandibular mass that histopathologically showed an angiodestructive lymphoid infiltrate. Although the initial examination of the sections suggested a T cell lymphoma, additional studies confirmed that the features were most consistent with LYG. This is the second documented case of LYG involving the oral cavity, to our knowledge.

Report of Case

An 82-year-old man presented with an 18 month history of progressive jaw pain. His left mandibular molar was identified as the likely cause and was extracted by his dentist. The socket failed to heal properly and a follow-up examination by an oral and maxillofacial surgeon revealed an ulcerated growth arising from the extraction site of the left posterior mandible (Fig. 1). The patient had no remarkable past medical history and was not taking any medications. There was no history of tobacco use or alcohol consumption, nor was there any family history of malignancy. On review of systems, he noted a 20 pound weight loss over the past year and progressive fatigue over the past several months. He denied night sweats, fevers, or problems related to other specific anatomic sites. Physical exam revealed an apparently healthy, elderly man without any significant findings with the exception of the mandibular lesion, which was biopsied and submitted for pathologic workup.

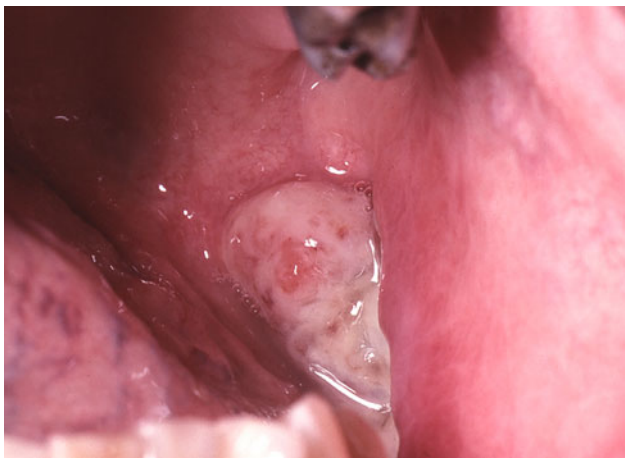

Fig. 1 Clinical photograph showing an ulcerated lesion involving the left posterior mandibular ridge at initial presentation

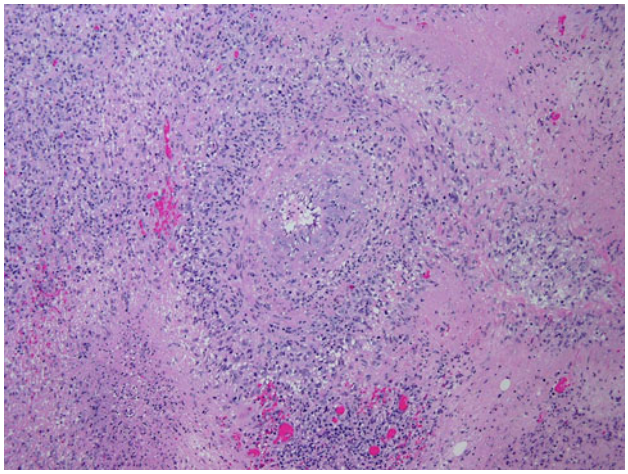

Fig. 2 Low-power photomicrograph showing angiocentric inflammatory cell infiltrate involving an arteriole (original magnification—×5)

Histopathologic examination of hematoxylin and eosin-stained sections revealed ulcerated granulation tissue and subjacent fibrous connective tissue that was infiltrated by a polymorphous population of inflammatory cells. The cellular infiltrate exhibited an angiocentric pattern, producing disruption and infiltration of the walls of several arterioles (Fig. 2). The majority of the angiocentric cellular infiltrate was comprised of relatively small, unremarkable lymphoid cells (Fig. 2). Scattered cells with large, vesicular nuclei and minimal cytoplasm were a component of the infiltrate (Fig. 3). Immunohistochemical studies using antibodies directed against CD-2, CD-3, CD-4, and CD-5 showed immunoreactivity of the smaller lymphoid population, consistent with a T-lymphocyte immunophenotype (Figs. 4, 5). Large, atypical mononuclear cells had positive labeling with antibodies directed against CD20 (Fig. 6),

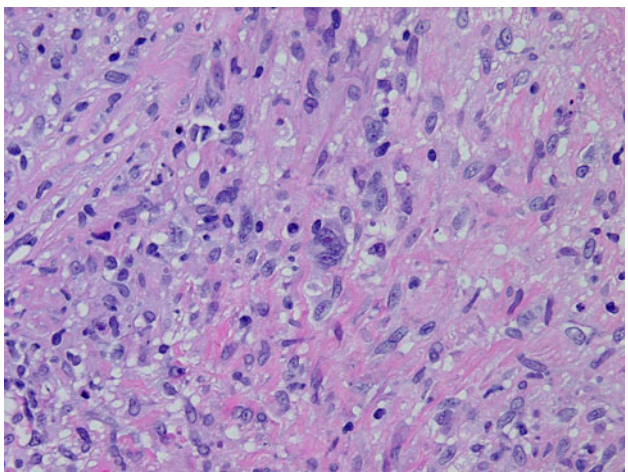

Fig. 3 High-power photomicrograph showing that the majority of the inflammatory cells are relatively small lymphocytes, although large cells with pale-staining, pleomorphic nuclei are a component of the infiltrate (original magnification—×20)

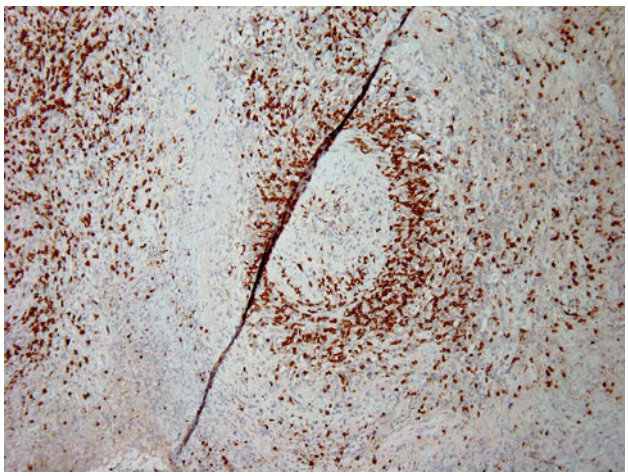

Fig. 4 Immunohistochemical reaction using antibodies directed against CD3 show prominent labeling of many of the small angiocentric lymphoid cells at low power (original magnification—×5)

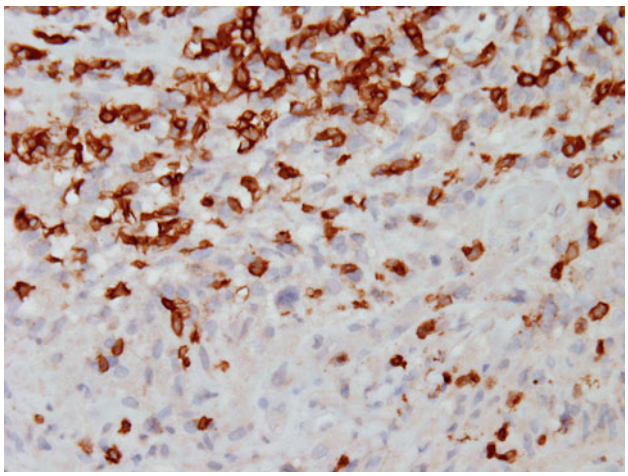

Fig. 5 High-power photomicrograph of the CD3-labeled section confirms that the smaller cells mark with this antibody (original magnification—×20)

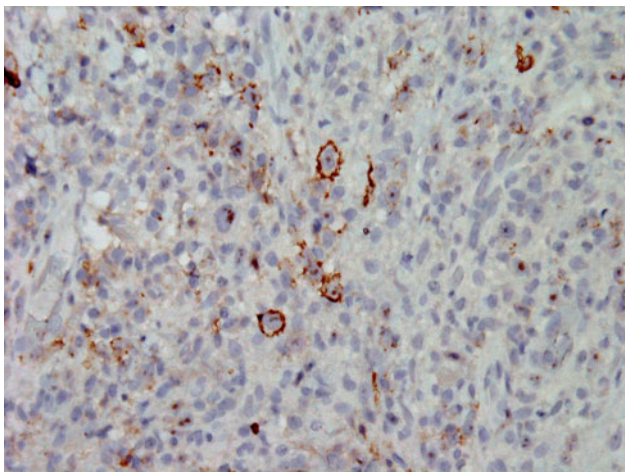

Fig. 6 High-power photomicrograph showing that the large cells with pale-staining pleomorphic nuclei are labeled with antibodies directed against CD20 (original magnification—×20)

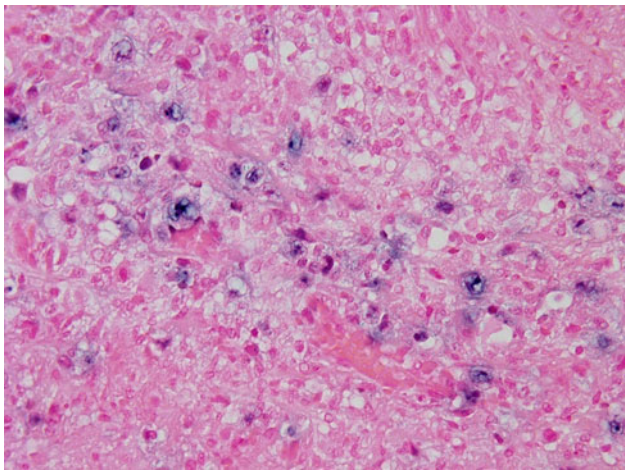

Fig. 7 High-power photomicrograph of in situ hybridization study showing that the large CD20-positive cells also express EBER (original magnification—×20)

CD30, CD45, and CD79a (negative for CD15 and CD56), consistent with a B cell immunophenotype. Antibodies directed against Ki-67 showed these cells undergoing proliferation (not shown), with an estimated proliferation index of approximately 60–80 %. In situ hybridization studies for EBV (EBER probe) showed the presence of EBV to be restricted to the large atypical B cells (Fig. 7). Tissue submitted for clonality studies utilizing polymerase chain reaction to amplify genomic TCRβ and IgH V-D-J regions showed results consistent with a polyclonal population of T-lymphocytes and a monoclonal population of B-lymphocytes (not shown). These microscopic, immunopathologic, and molecular findings were most consistent with a diagnosis of lymphomatoid granulomatosis (LYG). Given the relatively sparse population of the atypical B-lymphocytes and lack of significant necrosis, the lesion was considered to be a grade II process.

The patient was evaluated by medical oncology and underwent staging studies with CT scans that demonstrated hilar and mediastinal lymphadenopathy (not shown). A positron emission tomography (PET) scan revealed an elevated standardized uptake value (SUV) of 9.4 in the left mandibular body (Fig. 8, top left). Paratracheal, subcarinal and suprahilar lymph nodes also showed hypermetabolic activity with SUV ranging from 3.2 to 6.0 (Fig. 8, middle and bottom left). Bone marrow examination was normocellular with trilineage hematopoieisis, without any evidence of an atypical lymphoid infiltrate and normal cytogenetics. The patient's EBV viral DNA copy number in the peripheral

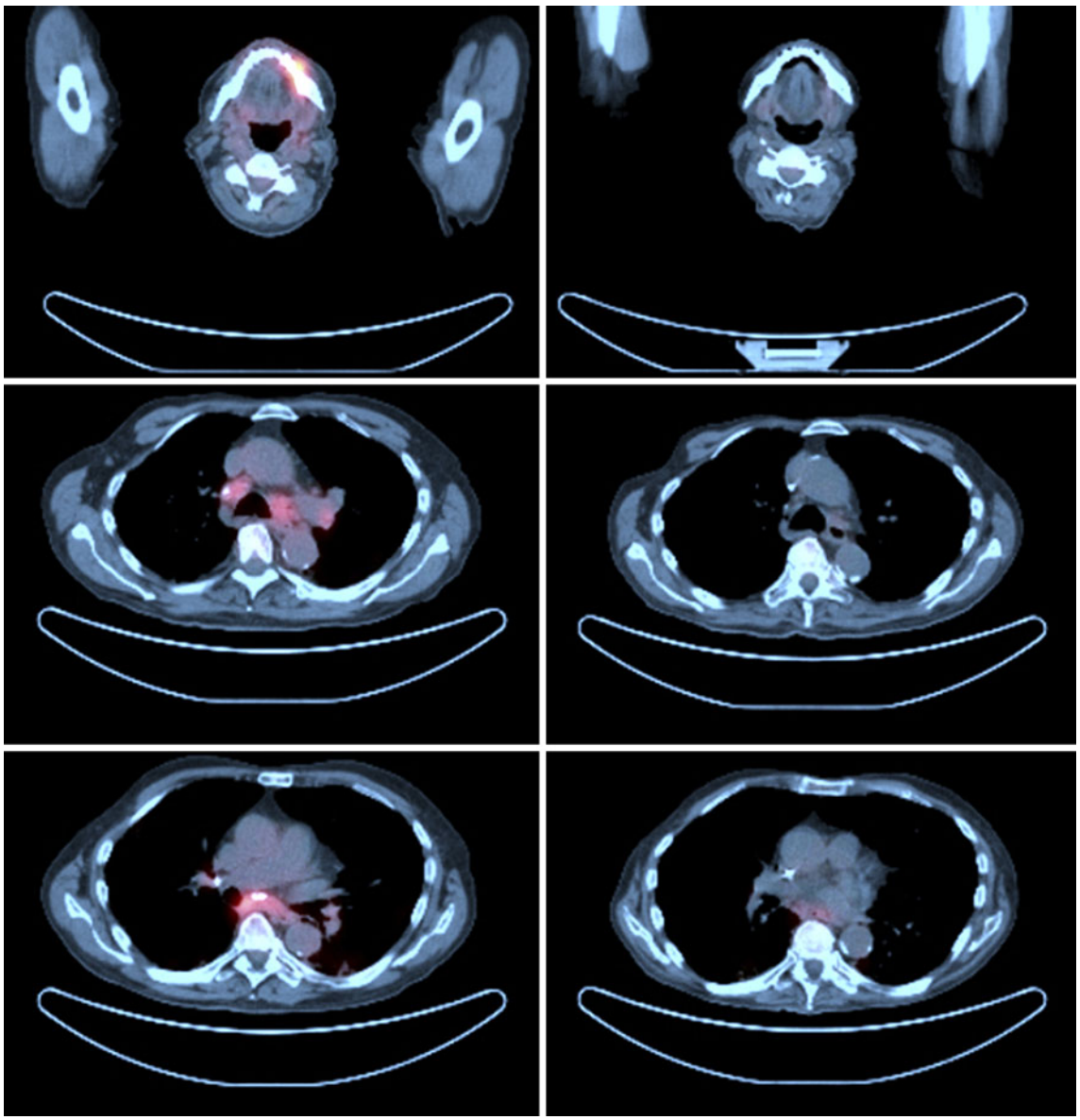

Fig. 8 PET scans showing areas of LYG activity prior to treatment (*left*), and after R-EPOCH therapy (*right*) (*top figure*—mandible; *bottom figures*—thoracic)

blood was negative. Peripheral blood immunophenotyping was normal and serum immune fixation failed to demonstrate any evidence of a monoclonal protein.

After reviewing the pathologic findings and staging studies, and considering the clinical presentation with thoracic lymphadenopathy, the patient was treated with rituximab, an anti-CD20 monoclonal antibody, combined with a chemotherapeutic regimen consisting of etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin (R-EPOCH; Rituximab 375 mg/m^2 on day 1, etoposide 50 mg/m^2/day × 5 days, vincristine 0.4 mg/m^2/day × 5 days, doxorubicin 10 mg/m^2/day × 5 days, cyclophosphamide 750 mg/m^2 on day 5, and prednisone 100 mg × 5 days). Three cycles of therapy resulted in significant resolution of the mandibular mass (Fig. 9). There was also significant radiological improvement with complete resolution of hypermetabolic activity of all involved regions and normalization of hilar and mediastinal lymphadenopathy (Fig. 8, right). The patient went on to receive 3 additional cycles of R-EPOCH and remained in remission for 3 years after completion of his therapy. He eventually expired after developing non-small cell carcinoma of the lung.

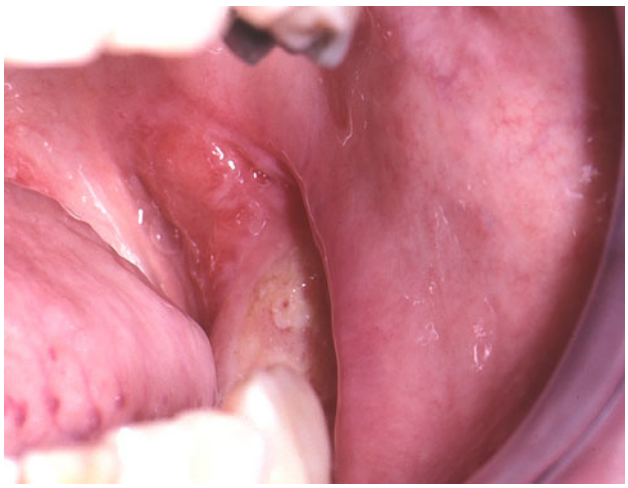

Fig. 9 Clinical image showing significant regression of the original mandibular lesion following R-EPOCH therapy

Discussion

Lymphomatoid granulomatosis is a rare angiocentric, angiodestructive EBV-associated B cell lymphoproliferative syndrome. LYG occurs more frequently in men than in women [6, 7] and is most commonly diagnosed in the third to the fifth decade of life. In a case series of 152 patients, cough was the most common presenting symptom followed by fever, rash, malaise, weight loss, dyspnea, neurological problems and chest pain [7]. Patients most often present with pulmonary involvement, however, this disorder can affect other extranodal sites including skin, central nervous system, kidneys, gastrointestinal tract or the upper respiratory tract. The presentation of our patient with mandibular and lymph node disease without any pulmonary involvement was atypical, particularly considering that this occurred in an apparently immune competent individual. While LYG involving the oral cavity and gingival tissues has been described in patients with HIV/AIDS [8], only one other report has, to our knowledge, documented LYG involving the oral cavity in an immune competent individual [9]. In that case, the patient had a known history of LYG for the preceding 2 years however. Patients with underlying immune deficiency are at increased risk for LYG and most patients thought to be immune competent are often found with underlying immune defects after more a comprehensive workup [10]. Aside from this patient's age, no clinical or laboratory workup was consistent with underlying immune deficiency. Interestingly, EBV-positive mucocutaneous ulcers that often affect the oral mucosa also arise in the setting of immune suppression or in older individuals with presumed immune senescence [1]. These lesions do not appear to have the same aggressive neoplastic potential that is associated with LYG however.

Lymphomatoid granulomatosis is classified under B-cell proliferations of uncertain malignant potential by the World Heath Organization [11], and it is acknowledged that this process has a spectrum of biologic behavior. The histopathologic features consist of a polymorphous inflammatory infiltrate with a predominance of lymphoid cells admixed with plasma cells, histiocytes, and atypical immunoblasts that represent the neoplastic cellular component. The presence of a lymphocytic vasculitis is prominent in LYG and may compromise the vessel wall leading to areas of infarct-like tissue necrosis. The majority of the lymphocytic infiltrate is comprised of mature CD3/CD4 (and less prominent CD3/CD8) positive T cells which are thought to be reactive to neighboring EBV+ immunoblasts. The neoplastic component consists of less numerous, atypical EBV+ B cells that resemble immunoblasts or in some cases, pleomorphic multinucleated cells similar to Reed-Sternberg cells of Hodgkin's lymphoma. Immunohistochemical features of the atypical EBV+ B cells are CD20 positive, occasionally CD30 positive and CD15 negative [12]. In situ studies for EBV-encoded RNA (EBER) within atypical cells are almost universally positive. EBV infection in angiocentric immunoproliferative disorders such as LYG is usually restricted to the expression of two viral genes, EBNA1, and latent membrane protein-1, and negative for all other latent and lytic gene products, consistent with a latency II profile similar to that seen in Hodgkin's disease [13]. Because of similarities between LYG and other EBV-associated lymphoproliferative disorders, careful pathologic review is of critical importance to rule out Hodgkin's lymphoma or other angiocentric disorders like extranodal NK/T cell lymphomas.

Histopathologic grading has been shown to be a useful tool in the management of LYG, and it is clear that the increased frequency of atypical EBV+ immunoblasts in a given specimen is associated with a worse prognosis. Grade I lesions show sparse atypical EBV+ cells, generally fewer than 5 per high-power field, and minimal necrosis. Such features are usually indicative of a good prognosis. Grade II lesions exhibit a moderate population of atypical EBV+ cells, ranging from 5 to 20 per high power field, and more necrosis is evident compared to the grade I lesions. Grade III disease is characterized by numerous (greater than 50 per high power field) atypical EBV+ cells and prominent necrosis, and this process is associated with a poor prognosis. A significant number of patients with grade II disease eventually present with transformation to grade III LYG that behaves essentially as an aggressive diffuse large B cell lymphoma [11].

Currently there is no standard of care for management of LYG due to the lack of treatment data and rarity of this disease. Therapy has ranged from observation to treatment with corticosteroids, alone or in combination with

cyclophosphamide [7], or multi-agent chemotherapy [14, 15]. Regardless of the treatment, complete response rates are not commonly achieved and few long-term remissions are reported [7]. The mortality rate has been reported to be between 53 and 63 %, and with all pathologic grades considered, an overall median survival of only 14 months has been described [7]. Experimental treatment approaches have included interferon-α [16] and rituximab [17, 18]. Interferon-α has been reported to induce complete remissions, presumably due to its antiviral, antiproliferative and/or immunomodulatory effects [16] and rituximab has demonstrated success in treating a limited number of cases of this disease [17, 18]. For asymptomatic patients with grade I disease, observation appears to be reasonable since 25 % of these patients undergo spontaneous regression. Patients who present with adverse symptoms or with grade II or III disease should be considered for treatment with combination chemotherapy regimens. The expression of CD20 on the neoplastic cells, the well-documented efficacy of rituximab and EPOCH regimen in other CD20-positive lymphomas, [19, 20] together with the unusual presentation in the oral cavity and the aggressive clinical behavior (grade II disease with thoracic adenopathy), prompted us to treat this patient with 6 cycles of R-EPOCH. The treatment was well tolerated without major toxicity and led to a significant response after three cycles of R-EPOCH that was sustained more than 13 months after the completion of 6 cycles of therapy.

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