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Lymphomatoid Granulomatosis With Involvement of the Hard Palate: A Case Report

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Lymphomatoid granulomatosis (LYG) is a rare angiocentric-destructive process with Epstein-Barr virus (EBV) positive B-cells and reactive T-cells. LYG is graded with grades I–II showing rare to moderate numbers of Epstein-Barr Virus (EBV) positive B-cells (usually polyclonal or oligoclonal), and grade III showing numerous large EBV positive B-cells (usually monoclonal), likely reflecting the progressive transformation of infected B-cells (1,2). Clinically, LYG nearly always presents in the lung but commonly involves the skin, kidney, and central nervous system (3,4), with lymph nodes rarely being enlarged. Herein, we report an unusual case of an active erosive lesion of the hard palate in a 32-year-old female patient with a history of LYG involving the lungs.

CASE REPORT

A 32-year-old Caucasian female with a 2-year history of LYG involving the lungs developed an erosive lesion of the hard palate. The patient complained of a sloughing white-patch on the roof of her mouth and dysphonia that began ten days earlier, and a 3- to 4- week history of nasal congestion and headaches that only cleared after taking pseudoephedrine for two weeks. On physical examination, the patient was a well-nourished woman with an intermittent dry cough that was in no apparent acute distress. Furthermore, no facial asymmetry was noted and she denied having any oral pain, facial pain, headaches, or visual changes. Intraoral examination revealed a lesion measuring 2 × 3 cm on the right palatal shelf with necrotic and malodorous tissue on the periphery (Fig 1). In view of the patient's history, computed tomography (CT) and magnetic resonance (MR) imaging scans (Figure 2), and biopsy of the lesion were performed with suspected LYG involvement. CT and MRI of the head were carried

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out, with image data showing destruction of the right palatal shelf. Furthermore, a communication between the right nostril and the buccal cavity were appreciated on CT and MR.

Histopathologic examination demonstrated an angiodestructive polymorphous lymphoid infiltrate with extensive necrosis (Fig. 3A). Numerous CD3 positive T cells were observed with only rare CD56 positive NK cells. There were scattered large atypical CD20 positive B-cells, the majority of which were positive for EBV by in situ hybridization using EBER probe (Fig. 3B). The density of the EBV-positive cells varied in the viable tissue; most areas showed <20 cells per high-power field (HPF) but in some the count was >20 cells per HPF. According to the current grading system (2), the biopsy was reported as LYG predominantly grade II with focal areas of grade III. Filamentous bacteria, morphologically consistent with Actinomyces, were also noted. The patient began treatment on a National Cancer Institute (NCI) protocol for LYG consisting of prednisone, vincristine, doxorubicin, etoposide, cyclophosphamide, and rituxamib (DA-EPOCH-R) chemotherapy followed by interferon-alpha therapy. The patient developed rapid pulmonary failure of unknown etiology and died 6 months later.

DISCUSSION

LYG was originally described by Liebow et al. in 1972 as an angiocentric and angiodestructive lymphoreticular proliferative and granulomatous disease with a predilection for the lungs (5). Since 1972 Liebow and other have described more than 80 cases of LYG; however, to our knowledge there have been no previous reports of this entity affecting the oral cavity.

LYG shares some histological similarities with extranodal NK/T-cell lymphoma, with which it was sometimes confused. The terms angiocentric immunoproliferative lesion (AIL) and polymorphic reticulosis were both used for nasal NK/T-cell lymphoma and some cases of LYG. Furthermore, it was believed that these were part of the same nosologic entity (6,7). Nasal NK/T-cell lymphoma frequently involves the upper respiratory tract and midline facial structures, sites that today are recognized as infrequently involved by LYG (8,9). Interestingly, both LYG and nasal NK/T-cell lymphoma are associated with EBV, which accounts in both diseases for many of the pathological manifestations, including vascular damage and necrosis (10). However, a main distinguishing factor of these two pathologic entities is that in LYG EBV is found in B-lymphocytes, while in NK/T-cell lymphomas, EBV infects NK-cells (11). In this case, there was rare expression of CD56 positive NK cells and as noted, EBER expression was restricted to B-cells.

LYG has an increased male predilection with a median presentation in the 5th decade of life (4). Evidence suggests that the pathobiology of LYG is related to a dysregulation of EBV immune surveillance with progressive proliferation of EBV positive B-cells. Although the incidence of LYG is increased in patients with known immunodeficiency, most patients do not have an antecedent history. However, evidence of immune compromise manifested by anergy and loss of CD8 T-cells is present in most patients. Histological grading is important for the management of these patients and reflects progressive histological transformation to an EBV positive B-cell lymphoma. As such, it has important implications for treatment. Grading is primarily related to the proportion of EBV positive B-cells present in the tissue. Whereas in grade I lesions the number of large transformed B-cells in the tissue is low to absent, grade III LYG shows numerous markedly atypical EBV-positive cells and extensive necrosis. Grade III LYG can be further subdivided into IIIA, in which the EBV+ B-cells are frequent but intermixed with reactive T-cell cells and IIIB, in which the EBV+ B-cells sheet out with the appearance of diffuse large B-cell lymphoma. Although the prognosis of LYG has been historically poor, significant advances in treatment have been made. In an initial study by Wilson et al, alpha-interferon was shown to keep 3 patients alive and disease free at 36, 43,

and 60 months. However, 1 patient achieved a partial response for 16 months but discontinued therapy and died with lymphoma (12). In a study at the NCI, patients with grades I and II LYG are treated with alpha-interferon and those with grade III received DA-EPOCH-R chemotherapy. Preliminary results in 27 patients with grade I and II LYG revealed a continuous complete remission of 56% at a median follow-up of 4 years. Furthermore, among 15 patients with grade III disease treated with DA-EPOCH with or without rituximab, 40% achieved complete remission. At a median follow-up of 46 months for the entire study, the overall survival and progression-free survival are 69% and 82%, respectively (13).

Today, LYG remains an infrequently recognized entity that currently can only be reliably diagnosed by tissue examination with clinical correlation. Currently, LYG is considered an EBV-lymphoproliferative disorder associated with dysregulated EBV immune surveillance. Patients with early grade disease appear highly sensitive to immune stimulation with interferon whereas patients with grade III disease require chemotherapy.

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Figure 1.
Clinical photography of the patient at first examination reveals the erosive lesion

Figure 2.

A. Computed tomography (CT) scan showing destruction of the right hard palate (coronal view). B. Magnetic resonance imaging (MR) shows a similar finding as CT.

Figure 3. Histological appearance of LYG. Polymorphous lymphoid cells infiltrate the hard palate submucosa. Note some minor salivary gland acini on the left upper. Angiodestruction is noted

on the right lower field (H&E, 20X). B. EBV-positive large atypical cells. Some areas showing high density of EBV-positive cells corresponded to grade III LYG (In situ hybridization of EBER, 20X)