Unusual gingival presentation of post-transplantation lymphoproliferative disorder: A case report and review of the literature

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Post-transplantation lymphoproliferative disorder is a well-documented complication of solid organ or bone marrow transplantation. Histologically, it is characterized by an abnormal proliferation of lymphocytes, which can range from benign B-cell hyperplasia to malignant lymphoma. Non-Hodgkin's lymphoma (NHL) is associated with several risk factors, such as congenital or acquired immunodeficiency states, autoimmune disorders, and infectious agents (eg, Epstein-Barr virus). Primary sites of presentation in the head and neck are Waldeyer's ring, paranasal sinuses, salivary glands, the oral cavity, and the larynx. Clinical appearance of gingival NHL varies but is usually found to be an asymptomatic gingival enlargement or mass resembling a pyogenic granuloma. We present a patient with a gingival ulceration that was subsequently diagnosed as Epstein-Barr virus malignant lymphoma resulting from the immunosuppression needed to prevent graft-versus-host disease after bone marrow transplantation. **(Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2000;90:436-41)**

Non-Hodgkin's lymphoma (NHL) is the sixth most common cause of cancer-related deaths in the United States after prostate, breast, lung, colorectal, and bladder cancers.[1] NHLs result from the malignant proliferation of lymphoid cells at specific stages of differentiation. Post-transplantation lymphoproliferative disorders (PTLDs) are disorders of lymphocyte proliferation that appear in patients who are on long-term immunosuppressive therapy and who have acquired immunodeficiency states. At the time of diagnosis, the presenting lymphadenopathy has to be distinguished from an infectious process. Up to 40% of symptomatic masses can be found in an extranodal location. The most common extranodal sites are the stomach, intestine, bone, central nervous system, eye, and skin. We report here a case of NHL with presentation in the mandibular gingiva.

CASE REPORT

The patient is a 44-year-old white man with a history of chronic myelogenous leukemia (CML), diagnosed in April of 1992. He was first seen in the dental service at Memorial Sloan-Kettering Cancer Center in November of 1992 for preallogeneic bone marrow transplantation (BMT) dental evaluation. At that time, he had his mandibular right third molar extracted. The patient underwent T-cell depleted allogeneic BMT from a human leukocyte antigen-identical sister in November of 1992. He relapsed in September of 1993 and was treated with donor T-cell immunotherapy with resulting salvage remission. This was complicated by severe chronic graft-versus-host disease (cGVHD), which is a multisystem immunologic consequence of grafting immunocompetent cells from one person to an immunodeficient host.[2] Clinical findings included mucosal and skin lesions. The diagnosis of GVHD was made after a biopsy in June of 1994, which was performed when the patient appeared with a chief complaint of soreness and discomfort in the mandibular gingiva and bilateral cheek mucosa. Oral mucosal lesions were described as plaquelike discolorations in his right and left cheek mucosa. The gingiva was severely erythematous and inflamed, but without discrete ulceration. Clinical hyposalivation was observed. Cutaneous lesions were represented by skin rashes and hyperpigmentation. Chronic bronchitis also developed in the setting of pulmonary involvement by chronic GVHD. The

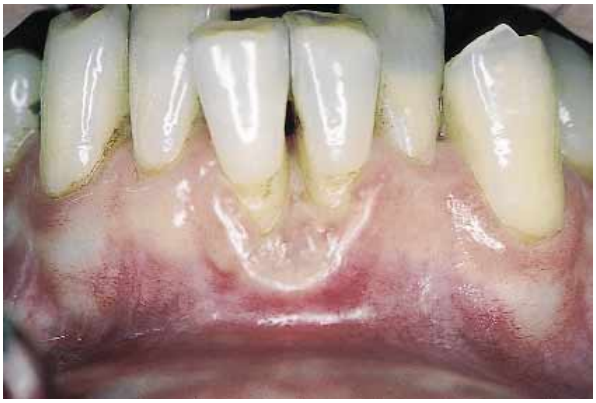

Fig 1. Initial presentation of the lesion: crater-like defect of interproximal gingiva No. 24 to 25, epithelialized but with irregular surface and margins.

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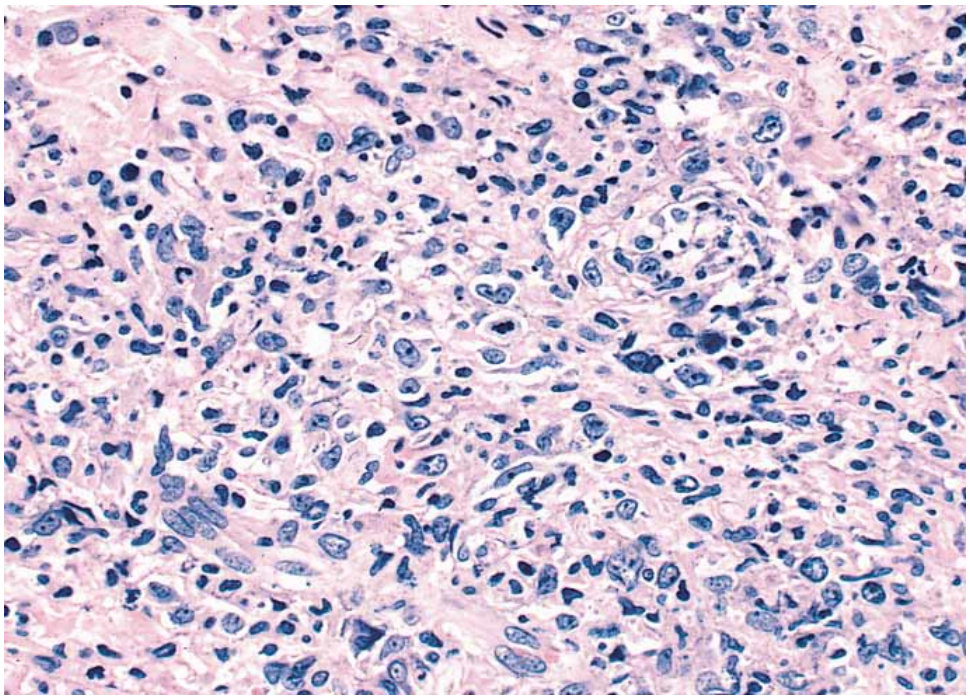

Fig 2. Hematoxylin-eosin staining demonstrating pleomorphic malignant lymphocytes, large cells, and giant tumor cells typical of LPDs (original magnification ×400).

upper GI tract was free of disease. He had been followed in the dental service on a regular basis since his BMT. He returned every 6 months for his recall appointments, but elective treatment was deferred when oral lesions associated with GVHD would exacerbate. The patient is now taking multiple medications, including immunosuppressive agents (cyclophosphamide, 50 mg twice a day by mouth and mycophenolic acid, 1 gm twice a day by mouth), several antibiotics after splenectomy to prevent infections and medications for asthma.

The patient was seen in the dental service with a chief complaint of dental sensitivity in his "lower front teeth" on July 13, 1999. Examination at that time showed mandibular central incisors with less than 1 mm of attached gingiva, with labial frenum pull, exposing 4 mm of the root surfaces. The lesion was described as a crater-like defect of the interproximal gingiva at his mandibular right and left first incisors, epithelialized but with irregular surface and margins (Fig 1). The patient reported that "a piece of gum came off while I was eating," without any bleeding, but he did experience some pain. At that time, it was thought that the frenum pull may contribute to the rapid progression of recession. The remaining dentition was in good condition, with good oral hygiene. The patient had minimal accumulations of plaque and calculus. Differential diagnosis included necrotizing gingivitis, traumatic lesion, chemical burn, and necrotic ulcers of systemic diseases such as leukemia, sickle cell anemia, uremia, and uncontrolled diabetes. He was seen for follow-up 7 and 14 days after his initial visit, at which time he complained of increased pain in the area. The lesion had extended apically and appeared to involve a greater depth of tissue. A culture swab, incisional biopsy, and frenectomy were performed. Seven days later, the culture was reported as positive for *Candida albicans*. The patient was prescribed Nystatin ointment 100,000 units/g for topical use 4 times daily. The surgical site healed slowly, but within normal limits. The initial pathologic diagnosis was reported as suspicious of a lymphoproliferative, or lymphomatous lesion (Fig 2). A second biopsy specimen for molecular studies was requested and obtained 1 week later. The diagnosis was confirmed to be positive for CD20, CD3, CD5, and UCHL-1 markers and was reported as Epstein Barr virus (EBV)-associated lymphoma, diffuse large-cell type. Cyclophosphamide was discontinued and the dose of mycophenolic acid was reduced by half. Six-week follow-up showed that the lesion continued to heal slowly (Fig 3). The patient was started on a course of anti-CD20 monoclonal antibodies (Rituximab 650 mg administered weekly) for a total of 4 weeks.

At the 7-week follow-up, the gingival lesion appeared to have responded to the new treatment. Soft tissues had healed, but root exposure remained (Fig 4). His mandibular left and right first incisors exhibited Class I mobility, with approximately 75% bone loss appearing on periapical radiograph. Further dental treatment is being deferred pending medical treatment. The patient is currently undergoing radiation therapy for newly diagnosed squamous cell carcinoma of the larynx.

DISCUSSION

Clinical presentation

Extranodal NHLs have been reported in the head and neck area, but occurrence in the oral cavity is rare. One

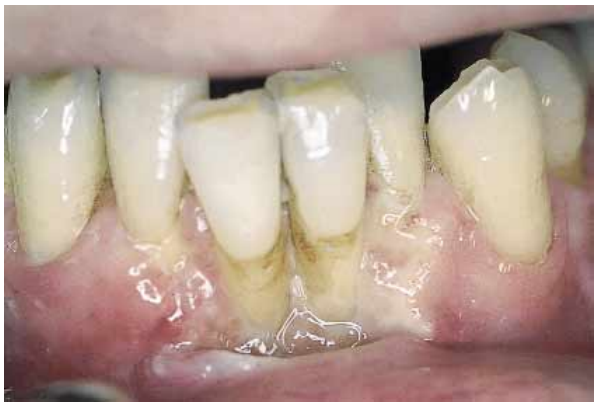

Fig 3. Six-week follow-up when diagnosis was confirmed: EBV lymphoma, diffuse large cell type.

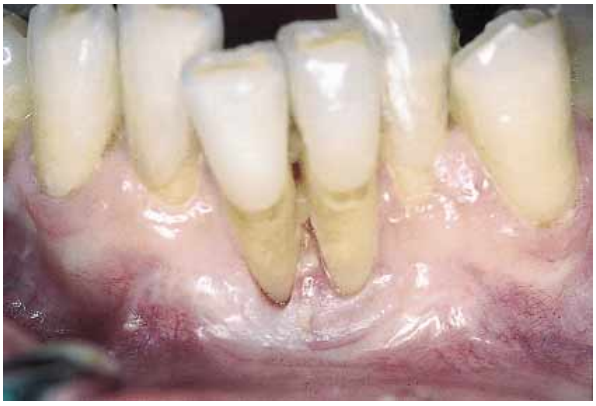

Fig 4. Follow-up status after 4 treatments of Rituximab: good clinical response to treatment.

of the largest reviews with 740 patients shows that 66% of head and neck lymphomas involve Waldeyer's ring.[3] The nasal cavity and sinuses represent 15% of the cases, the salivary glands represent 8%, and the oral cavity represents 5%. Malignant lymphomas in the mandible occur most frequently as bony tumors, with predominance in men. This may be explained by the fact that lymphomatous tissue is normally found in the bone marrow, not in the gingiva.

Only isolated cases of gingival lymphomas have been reported in the literature. Gould and Alpert[4] reported the case of a 30-year-old white woman whose chief complaint was a painless swelling involving the maxillary labial attached gingiva. The diagnosis after biopsy was non-Hodgkin's lymphoma. Park[5] reported the case of a 52-year-old woman diagnosed with NHL of the right anterior gingiva and antrum. The clinical appearance of gingival malignant lymphoma varies: nodular and plaquelike, ulcerating or papillary, and exophytic. The most common presenting symptom is an intraoral swelling or mass. Pain, paresthesia, and ulceration may also be noted. Fukuda et al[6] reviewed 20 cases of malignant lymphoma of the oral cavity, 17 of which originated in the soft tissues and 3 of which involved the jaw bone. Our patient falls into the common description of symptoms (pain, discomfort) reported by other authors, but interestingly, the oral presentation of the disease is not a swelling or mass as expected, but rather an ulcerated, crater-like gingival defect.

Diagnosis

An important factor in establishing a differential diagnosis is a thorough history and an oral and dental examination. The diagnosis of dental abscess or periodontal infection has to be ruled out in the setting of a swelling of the gingiva. A panoramic or periapical radiograph can be helpful in detecting bone lesions, although magnetic resonance imaging (MRI) is far more useful to evaluate the size, characteristics, and extent of tumor, bony involvement, and associated lymph node enlargement. Yasumoto et al[7] studied 5 patients with malignant lymphoma of the gingiva by MRI. Panoramic radiographs available in 3 of the 5 patients showed no bone destruction or lytic areas in 2 of the 3 patients. A computed tomography scan is indicated when there is suspicion of extension to adjacent structures, such as the paranasal sinuses. A complete blood analysis can demonstrate elevated values of alkaline phosphatase and lactate dehydrogenase if lesions are disseminated.[6] Diagnosis is ultimately made on histologic examination.

Several classification systems have been described over the years to categorize NHL.[1] The Rappaport classification separates NHLs by pattern (nodular or diffuse) and degree of differentiation (poorly or well-differentiated), based on the resemblance between their neoplastic cells and normal lymphocytes.[8] The Luke-Collins[9] and the Kiel classifications attempt to correlate lymphoid neoplasms to normal counterparts in the immune system. In the Working Formulation, lymphoma subtypes are divided into prognostic groups: low, intermediate, and high grade.[10] The updated classification is the Revised European-American Classification of Lymphoid Neoplasms (REAL). Three major categories are delineated in this classification: B-cell neoplasms, T-cell neoplasms, and Hodgkin's disease. Our patient's lesion is described as diffuse large B-cell lymphoma, as found in the REAL classification.

The staging system used for non-Hodgkin's lymphoma is the Ann Arbor staging system (Table I), which was initially developed for Hodgkin's disease. This system is based on the number of sites of involvement, the presence of disease above or below the diaphragm, the existence of systemic symptoms, and the presence of extranodal disease, but does not include tumor size in its description.[1] Our patient's clinical stage is stage I.

Table I. Ann Arbor Staging System

Stage	*Description*
Stage I	Involvement of a single lymph node region (I) or a single extralymphatic organ or site (IE)
Stage II	Involvement of two or more lymph node regions on the same side of the diaphragm (II) or localized involvement of an extralymphatic organ or site (IIE)
Stage III	Involvement of lymph node regions on both sides of the diaphragm (III) or localized involvement of an extralymphatic organ or site (IIIE) or spleen (IIIS) or both (IIISE)
Stage IV	Diffuse or disseminated involvement of one or more extralymphatic organs with or without associated lymph node involvement.

Identification of the presence or absence of symptoms should be noted with each stage designation.
A, Asymptomatic; *B*, fever, sweats, weight loss > 10% of body weight.

Post-transplantation lymphoproliferative disorders in patients who have immunosuppression

The acquired immunodeficiency state seen after solid organ or bone marrow transplantation may predispose a patient to PTLD.[11-13] The excessive immunosuppression, which predisposes a patient to graft-versus-host disease, is considered a risk factor.[14] The long-term complication of immunosuppression is histologically characterized by an abnormal lymphoid cell proliferation and may range from polymorphic proliferation of B lymphocytes to monoclonal high-grade malignant lymphoma. Broudy and Sabath's[15] case report on PTLD appearing in the gingiva shows a postcardiac transplantation lymphoproliferative disorder in a 62-year-old man, which appeared as gingival hypertrophy. Lattyak et al[16] conducted a 5-year retrospective study of 61 children with liver transplants at The University of California, San Francisco. PTLD developed in 8 patients (13.1%); it developed in the head and neck in 5. Four had bilateral tonsillar enlargement, and 1 had a soft tissue epiglottic mass. The Waldeyer's ring is the most frequently involved site in the head and neck. Other common anatomic sites include the gastrointestinal tract, central nervous system, chest, and abdomen. Dorr et al[17] reported a first case of a B-cell lymphoproliferative disorder (LPD) in a patient with aplastic anemia treated with immune suppressants. The patient was first seen with a right tonsillar fossa obliterating the pyriform sinus on computed tomography scan. The LPD resulted from the immunosuppression induced by cyclosporine A in a nontransplant setting. Treatment of PTLD consists of reducing the dose of immunosuppressive drugs by 50%, combined with an antiviral medication, such as ganciclovir or acyclovir.

EBV and lymphomas in patients who have immunosuppression

The role of EBV and its implication in the development of lymphomas have been studied extensively.[18-20] EBV is a human herpesvirus linked to endemic Burkitt's lymphoma, post-transplantation lymphoproliferative disease, and non-Hodgkin's lymphoma associated with AIDS. Hauke et al[20] reported 2 cases of EBV-associated lymphoproliferative disorder after autologous bone marrow transplantation. It is believed that PTLD may be the result of primary or reactivated EBV infection in a host with impaired immunity.[16] Liebowitz[21] studied the role of the latent membrane protein 1 (LMP1), produced by EBV-infected B lymphocytes, in the in vitro transformation and proliferation of B cells. He found no evidence that LMP1 contributes to the malignant phenotype of LPD. The role of EBV in the development and maintenance of these diseases is controversial, partly because LMP1 is not expressed in all types of EBV-associated neoplasms. LMP1 is typically found in post-transplantation lymphoproliferative disease, AIDS-related non-Hodgkin's lymphoma, and Hodgkin's disease, but not in Burkitt's lymphoma.

Treatment and prognosis

Treatment modalities depend on histologic examination, primary site of involvement, and staging. The Stanford University experience,[3] combined with other authors' findings, suggests that for patients with stage I or II disease, radiotherapy alone can be used if the lesion is of low or intermediate differentiation. The typical total dose is 4000 to 5000 centigrays (cGy) for involved sites. Patients are treated 4 to 5 times weekly with a daily dose of 180 to 200 cGy. For advanced disease, a combination of chemotherapy and radiotherapy is used. These include single-agent chemotherapy with chlorambucil, or combinations of agents such as cyclophosphamide, 6-mercatopurine, vincristine, and prednisone. Other regimens include cyclophosphamide, hydroxydaunomycin, Oncovin, and prednisone (CHOP), mechlorethamine, Oncovin, procarbazine, and prednisone (MOPP) and methotrexate, bleomycin, Adriamycin, cyclophosphamide, Oncovin, and dexamethasone (M-BACOD).

Prognosis is influenced by age, histologic type, location of disease, and stage. Elderly patients seem to have a poorer prognosis. They may achieve clinical remission similar to that of younger patients, but they have more relapses. Several studies show that primary diffuse oral lymphomas have a more unfavorable outcome than nodular

lymphomas.[8,9] Fukuda et al[6] reported 20 patients with oral soft tissue NHLs who had a poorer prognosis than those with NHL in the jaw bone. Disease staging is also an important prognostic factor. Fortunately, patients tend to be first seen with early disease. In Eisenbud's series,[8] 18 of 31 patients presented with stage I or II disease. Disease control is more successful, and survival rate improves with early diagnosis.

Treatment of non-Hodgkin's lymphoma with monoclonal antibodies

Significant advances have been made in the past 5 years in the treatment of lymphoma with antibody-based therapies.[22-24] NHLs are accessible through the blood stream, and binding of an antibody to its antigen target on malignant cells is accomplished soon after the drug is administered. The ideal cell-surface antigen should be present in high density on the surface of all the tumor cells and should not be expressed on normal cells. Antigens range from truly tumor specific (anti-idiotype) to lineage-specific or more broadly expressed antigens. Antigens such as CD19 and CD20 have been isolated in normal and malignant B lymphocytes, whereas CD5 is a lineage-specific marker for T-cell lymphoma. The CD20 antigen is probably the most widely studied for antibody-based therapies. It is expressed on the cell surface of most of the B-cell NHLs, but not on plasma cells, B-cell precursors, and other stem cells. By targeting the CD20 antibody, a more specific therapy is available for treatment of B-cell NHLs, which account for the majority of all NHLs (90%). Types of monoclonal antibodies include murine, rat, and humanized (unconjugated and conjugated). The antitumor effects of the unconjugated monoclonal antibodies are achieved by 2 mechanisms.[24] One mechanism depends on complement activation or antibody-dependent cell-mediated cytotoxicity. The second depends on a direct effect to cause tumor cell death or growth inhibition. Murine antibodies have been shown to induce a human anti-mouse antibody response. Rituximab (Rituxan), an unconjugated humanized antibody against CD20, is the first monoclonal antibody approved by the FDA (1997) for treatment of cancers. This drug acts efficiently by mediating cell killing by using complement and antibody-dependent cell-mediated cytotoxicity. Some B-cell lines have their growth directly inhibited by the antibody. Side effects can include fever, chills, skin rash, occasional bronchospasm, and mild hypotension. Rituximab can also be used in conjunction with chemotherapy, such as CHOP. Conjugated antibodies refer to the use of monoclonal antibodies with attached chemotherapeutic molecules, biologic toxins, or isotopes. The conjugated complex is used to increase the anti-tumor effect and must be cleaved within the cell to express its action. Current research is directed toward the use of radiolabeled antibody therapy for lymphomas, because they are relatively radiosensitive tumors. Commonly used radioisotopes are iodine-131 and yttrium-90. Further research is needed to increase knowledge in this subject.

CONCLUSION

We reported the case of a 44-year-old man with history of CML who underwent an allogeneic, T-cell depleted BMT complicated by severe chronic graft-versus-host disease, in whom EBV lymphoma subsequently developed, resulting from the immunosuppression needed for the GVHD. The clinical appearance of an extranodal, intraoral, gingival ulceration was unusual. The patient was treated with humanized anti-CD20 monoclonal antibodies (Rituximab) for a total of 4 weeks. At the same time, the dose of immunosuppressive drugs was reduced to lower the risk of other PTLD lesions. The pain subsided with treatment, and the lesion responded well. Clinical appearance on 8-week follow-up is unremarkable.

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