Sporadic Burkitt Lymphoma Mimicking Osteomyelitis of the Mandible Revealing Clinically Unsuspected HIV Infection

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Abstract. *Adult sporadic Burkitt lymphoma is a rare and highly aggressive malignancy, accounting for approximately 1-2% of adult lymphomas in Western countries, and exclusively intra-oral localization is very uncommon. We describe a rare case of a moderately painful sporadic Burkitt lymphoma localized in the posterior third of the left mandibular bone, initially misdiagnosed as osteomyelitis-like lesion, in a patient Epstein-Barr virus infection-negative with unknown human immunodeficiency virus (HIV) positivity and acquired immunodeficiency syndrome. A 52-year-old man was referred to our Department complaining of persistent moderate pain localized in the left mandibular arch. According to clinical and radiological features, a diagnosis of post-extraction osteomyelitis was made and a surgical revision, including soft and hard tissue biopsy, was performed. Histopathology revealed the presence of a diffuse proliferation of lymphoid cells, exhibiting the typical 'starry-sky' appearance that was consistent with the diagnosis of B-type non-Hodgkin lymphoma. Unexpectedly, HIV seropositivity was also found, but the patient was unaware of this, and the history did not reveal any particular risk factor for HIV infection. Positron-emission tomography showed a highly ^{18}F-fluorodeoxyglucose-avid mass in the left maxillofacial region and extensive disease in bone marrow and mediastinum. Thus, the patient was referred to our onco-hematological team for final assessment and care. In conclusion, sporadic Burkitt lymphoma is an aggressive malignancy, which rarely affects adults with initial intra-oral manifestations. In the presence of abnormal gingival or alveolar lesions, a non-odontogenic disease should be suspected and the appropriate diagnostic test should be performed.*

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Burkitt lymphoma (BL) is a rare and aggressive form of non-Hodgkin lymphoma (NHL), originating from monoclonal proliferation of B-lymphocytes, described and studied for the first time by Denis Parsons Burkitt among African children in the 1950s (1, 2). Endemic BL predominantly affects the jaws and occasionally the gastrointestinal tract, central nervous system, ovaries, or other sites (3-6). B-Cell type NHL and Kaposi sarcoma are the most common malignancies worldwide occurring in patients with human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) (7). Abdominal masses are the most common presentations in patients with sporadic BL, especially in children (5). Exclusively intra-oral localization of sporadic BL is a rare and different clinical manifestation of the disease, such as pain with inability to chew food, infraorbital swelling, or painless growth on tooth regions, have been reported (8-10).

We describe a rare case of a moderately painful sporadic BL localized in the posterior third of the left mandibular bone, misdiagnosed as osteomyelitis-like lesion, in an adult negative for Epstein-Barr virus (EBV) infection with unknown HIV infection.

Case Report

A 52-year-old man was referred to our Department complaining of persistent moderate pain localized in the left mandibular arch. His past medical history was negative for any type of trauma but revealed recent episodes of left inferior alveolar nerve paresthesia, which had begun two weeks earlier. No fever or weight loss were reported. Extraoral examination revealed a swelling with no cervical lymphadenopathy, and external palpation accentuated the pain. At intra-oral examination, tooth 37 was painful to percussion.

The panoramic radiography showed the results of a previous endodontic treatment and a periapical radiolucent area at the level of the dental element. In agreement with the patient, the tooth was extracted. After an initial relief of the symptoms, fever and local paresthesia appeared progressively. One month after extraction, the poor intra-oral wound healing suggested the need for examination by computed tomographic (CT) scan (Figure 1A and B).

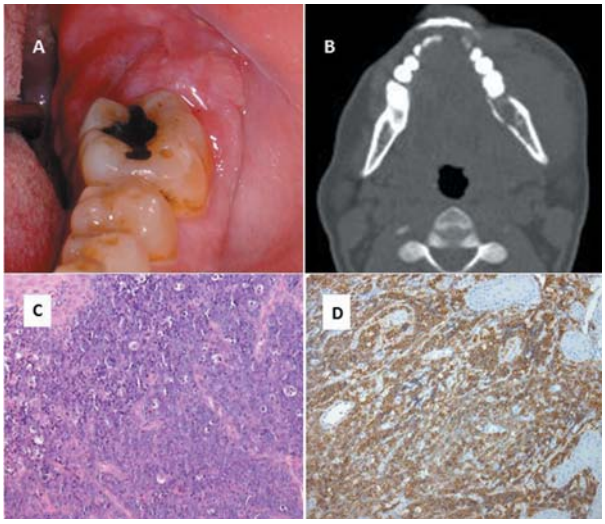

Figure 1. *A: Intra-oral examination revealing a mucosal lesion one month after the extraction of tooth 37. B: Axial view of the tomographic examination showing the irregular radiolucent aspect of the spongiosa and a cribrous aspect of the lingual cortical plate in area 37. C: Diffuse proliferation of medium-sized lymphoid cells and scattered macrophages with 'starry-sky' pattern. Hematoxylin and eosin stain (original magnification 400x). D: On immunohistochemical staining, cells were positive for CD20 (original magnification 200×).*

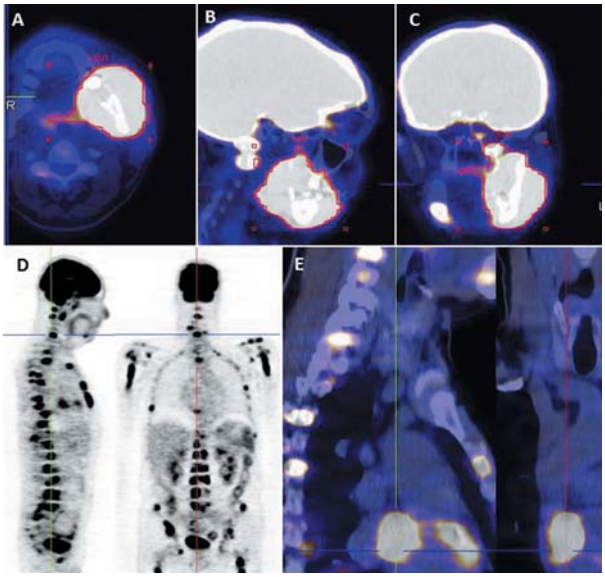

Figure 2. *Positron-emission tomography with ^{18}F-fluorodeoxyglucose (FDG)/computed tomography showing a highly FDG-avid mass in the left maxillofacial region (A-C) and extensive disease in bone marrow and mediastinum (D-E). At the level of the mass, the average standardized uptake value was 8.27 and the average of Hounsfield units was 142.25.*

According to clinical and radiological features, a diagnosis of suspected post-extraction osteomyelitis was made and a surgical revision, including soft and hard tissue biopsy, was performed. However, histopathology of the biopsy revealed the presence of a diffuse proliferation of lymphoid cells, exhibiting the typical 'starry-sky' appearance that was consistent with the diagnosis of sporadic BL (Figure 1C). EBV-encoded messenger RNA and fluorescence in situ hybridization (EBER) was negative and thus the presence of an EBV infection was excluded. The immunohistochemistry showed a strong positivity for the classical B-cell markers, such as CD19, CD20 (Figure 1 d) and CD79a and a moderate positivity for CD10 and B-cell lymphoma (Bcl) 6 protein (Bcl6). Staining for CD5, CD23 and Bcl2 was negative. The high mitotic activity was confirmed by nearly 100% of the cells staining positive for MIB-1.

Unexpectedly, HIV seropositivity was also found, but the patient was unaware of this and the history did not reveal any particular risk factor for HIV infection. He was than referred to the Oncology/Hematology Team for final assessment and care. Two weeks after biopsy, the patient underwent positron-emission tomography with ^{18}F-fluorodeoxyglucose (FDG-PET)/CT study, which showed a highly FDG-avid mass in the left maxillofacial region (Figure 2 A-C) and extensive disease in bone marrow and mediastinum (Figure 2 D-E). As reported in previous studies, the maximum standardized uptake value (SUV), which represents the ratio of the tumoral ^{18}F-FDG concentration to the average tracer concentration in the whole body, was used as FDG uptake measurement (11). The average SUV was 8.27 and the average of Hounsfield units on CT scan was 142.25.

Discussion

Burkitt lymphoma and diffuse large B-cell lymphoma (DLBCL) are the two most common types of NHL observed in patients with HIV/AIDS (9). According to the World Health Organization (WHO) classification, three clinical variants of BL are described: (i) endemic, (ii) sporadic, and (iii) associated with immunodeficiency, usually seen in patients with HIV/AIDS (12). Possible causes of BL are EBV infection and dysregulation of c-myelocytomatosis (*MYC*) oncogene, due to a chromosomal traslocation (13, 14). EBV was the first virus directly associated with the onset of human cancer, although infection alone is not sufficient to cause BL (15). However, there is evidence that EBV promotes B-cell hyperplasia, which represents a fundamental component of lymphomagenesis in BL, leading to ectopic MYC expression and subsequent proliferation of neoplastic cells (16). Sporadic BL is EBV-correlated in a minority of cases and represents the most common type of NHL among children (17).

The estimated incidence of sporadic BL and other forms of NHL in the USA is 22 and 586 per 100,000, respectively (18). Adult sporadic BL is a rare and highly aggressive malignancy, accounting for approximately 1-2% of adult lymphomas in the USA and Europe (19). The majority of sporadic BL affects

extranodal sites, especially in the abdomen and the pelvis, while extra-abdominal manifestations, such as maxillofacial bone involvement and head and neck involvement are uncommon (8, 20). The clinical features of intra-oral sporadic BL can be displaced or mobile teeth, the presence of a growth in the maxillary molar region, intermittent pain, or locoregional lymphoadenopathy (8, 10, 21, 22). Other types of NHL causing intra-oral manifestations, such as plasmoblastic lymphoma, are infrequent, as are other cases of sporadic BL in a patient who was unaware that he was HIV-positive (23, 24). The use of FDG-PET and PET/CT in staging and predicting outcome of patients with NHL, including sporadic BL and DLBCL, is well established and should be suggested for all patients (25, 26).

Conclusion

Sporadic Burkitt lymphoma is an aggressive malignancy, which rarely affects adults with initial intra-oral manifestations. In the presence of abnormal gingival or alveolar lesions, a non-odontogenic disease should be suspected and the appropriate diagnostic test should be performed (27).

References

1 Burkitt D: A sarcoma involving the jaws of African children. Br J Surg *46*: 218-223, 1958.

2 Burkitt D: Determining the climatic limitations of children's cancer common in Africa. Br Med J *2*: 1019-1023, 1962.

3 Kesik V, Safali M, Citak EC, Kismet E and Koseoglu V: Primary gastric Burkitt lymphoma: A rare cause of intraabdominal mass in childhood. Pediatr Surg Int *26*: 927-929, 2010.

4 Citak EC, Sari I, Demirci M, Karakus C and Sahin Y: Primary hepatic Burkitt lymphoma in a child and review of literature. J Pediatr Hematol Oncol *33*: 368-371, 2011.

5 Camilo GB, Machado DC, de Oliveira CE, da Silva Lacerda L, de Oliveira RV, de França Silva M and Lopes AJ: Burkitt lymphoma with initial clinical presentation due to infiltration of the central nervous system and eye orbits. Am J Case Rep *15*: 404-410, 2014.

6 Miyazaki N1, Kobayashi Y, Nishigaya Y, Momomura M, Matsumoto H and Iwashita M: Burkitt lymphoma of the ovary: A case report and literature review. J Obstet Gynaecol Res *39*: 1363-1366, 2013.

7 Epstein JB, Cabay RJ and Glick M: Oral malignancies in HIV disease: Changes in disease presentation, increased understanding of molecular pathogenesis, and current management. Oral Surg Oral Med Oral Pathol Oral Radiol Endod *100*: 571-578, 2005.

8 Jan A, Vora K and Sándor GK: Sporadic Burkitt's lymphoma of the jaws: The essentials of prompt life-saving referral and management. J Can Dent Assoc *71*: 165-168, 2005.

9 Ojha J, Gupta A and Aziz N: Intra-oral diffuse large B-cell lymphoma with Burkitt-like morphology in an HIV-positive patient. A diagnostic dilemma. J Oral Maxillofac Surg *68*: 2632-2638, 2010.

10 Ajila V, Gopakumar R, Hegde S and Babu SG: Intra-oral Burkitt's lymphoma in an HIV positive patient. Indian J Sex Transm Dis *33*: 118-120, 2012.

11 Carrillo-Cruz E, Marín-Oyaga VA, Solé Rodríguez M, Borrego-Dorado I, de la Cruz Vicente F, Quiroga Cantero E, Manzanares Pérez M, Capote FJ, Ramírez Sánchez MJ, Espigado Tocino I, Pérez-Vega H, Vázquez-Albertino R and Pérez-Simón JA: Role of ^{18}F-FDG-PET/CT in the management of Burkitt lymphoma. Eur J Haematol *93*: 469-475, 2015.

12 Jaffe ES: The 2008 WHO classification of lymphomas: implications for clinical practice and translational research. Hematology Am Soc Hematol Educ Program 1: 523-531, 2009.

13 Khanna R, Burrows SR and Moss DJ: Immune regulation in Epstein-Barr virus associated diseases. Microbiol Rev *59*: 387-405, 1995.

14 Chuang SS, Ye H, Du MQ, Lu CL, Dogan A, Hsieh PP, Huang WT and Jung YC: Histopathology and immunohistochemistry in distinguishing Burkitt lymphoma from diffuse large B-cell lymphoma with very high proliferation index and with or without a starry-sky pattern: a comparative study with EBER and FISH. Am J Clin Pathol *128*: 558-564, 2007.

15 Pattle SB and Farrell PJ: The role of Epstein-Barr virus in cancer. Expert Opin Biol Ther *6*: 1193-1205, 2006.

16 Magrath I: Epidemiology: Clues to the pathogenesis of Burkitt lymphoma. Br J Haematol *156*: 744-756, 2012.

17 Brady G, MacArthur GJ and Farrell PJ: Epstein-Barr virus and Burkitt lymphoma. Postgrad Med J *84*: 372-377, 2008.

18 Guech-Ongey M, Simard EP, Anderson WF, Engels EA, Bhatia K, Devesa SS and Mbulaiteye SM: AIDS-related Burkitt lymphoma in the United States: What do age and CD4 lymphocyte patterns tell us about etiology and/or biology? Blood *116*: 5600-5604, 2010.

19 Blum KA, Lozanski G and Byrd JC: Adult Burkitt leukemia and lymphoma. Blood *104*: 3009-3020, 2004.

20 Ardekian L, Peleg M, Samet N, Givol N and Taicher S: Burkitt's lymphoma mimicking an acute dentoalveolar abscess. J Endod *22*: 697-698, 1996.

21 Comfort AO: Burkitt's lymphoma of the jaws: Role of dental practitioner in management. Pac Health Dialog *11*: 89-93, 2004.

22 Pinisetti S, Nalabolu GR, Uvr C and Tadi DP: HIV-associated intra-oral Burkitt's lymphoma: A case report. J Clin Diagn Res *7*: 3088-3089, 2013.

23 Yasuhara R, Irié T, Shiozawa E, Yamochi T, Tanaka J, Kohno Y, Fujikura M, Kimura Y, Hanazawa T, Seki K, Sano T, Shirota T, Kushima M, Takimoto M and Mishima K: Plasmablastic lymphoma of the maxillary sinus with intra-oral manifestation caused by direct alveolar bone infiltration in an HIV-negative patient. Pathol Int *64*: 588-590, 2014.

24 Komatsu N, Kawase-Koga Y, Mori Y, Kamikubo Y, Kurokawa M and Takato T: HIV-associated Burkitt lymphoma in a Japanese patient with early submandibular swelling. BMC Res Notes *6*: 557, 2013.

25 Coughlan M and Elstrom R: The use of FDG-PET in diffuse large B cell lymphoma (DLBCL): predicting outcome following first line therapy. Cancer Imaging *14*: 34, 2014.

26 El-Galaly TC and Hutchings M: Imaging of non-Hodgkin lymphomas: Diagnosis and response-adapted strategies. Cancer Treat Res *165*: 125-146, 2015.

27 Chi AC, Neville BW, Krayer JW and Gonsalves WC: Oral manifestations of systemic disease. Am Fam Physician *82*: 1381-1388, 2010.

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