Pergamon

Oral Oncol, Eur J Cancer, Vol. 30B, No. 1, pp. 61–64, 1994
Copyright © 1994 Elsevier Science Ltd
Printed in Great Britain. All rights reserved
0964–1955/94 $6.00 + 0.00

Case Reports

Unusual Clinical Aspects of Oral Non-Hodgkin Lymphomas in Patients with HIV Infection

Sara Piluso, Simonetta Di Lollo, Gianna Baroni, Francesco Leoncini, Domenico Gaglioti, Annamaria Saccardi and Giuseppe Ficarra

Patients with HIV infection are at greater risk of developing malignancies. We report two HIV-seropositive patients with primary oral manifestation of a B-cell non-Hodgkin lymphoma (NHL). Localisations of tumours were the palate, with an unusual bifocal origin, and the tongue which is rarely the primary site of NHL. Ulcerations and extensive tissue necrosis were observed. Histologically both cases were high grade malignant lymphomas, immunoblastic. Epstein–Barr virus DNA was detected with *in situ* hybridisation in 1 patient.
Oral Oncol, Eur J Cancer, Vol. 30B, No. 1, pp. 61–64, 1994.

INTRODUCTION

THE OCCURRENCE of non-Hodgkin lymphoma (NHL) has been reported with increased frequency in patients with HIV infection [1–15]. Previous studies have shown a similarity between HIV-related lymphomas and lymphomas occurring in patients with genetic or drug-induced immune deficiencies [1, 2, 4, 8, 10, 16, 17]. The great majority of HIV-related NHL are of B-cell origin and are classified, according to the Non-Hodgkin Lymphoma Pathologic Classification (Working Formulation) [18], as high and intermediate grade [8, 9, 11, 12, 19]. HIV-associated NHL are clinically very aggressive and generally occur in extranodal sites involving the central nervous system, gastrointestinal tract, bone marrow, kidney, liver and oral cavity [1, 6, 8, 9, 11, 12, 20]. A short survival time in such patients with NHL is reported and opportunistic infections are the most frequent causes of death [8, 11, 12, 17].

The purpose of the present paper is to present 2 patients with AIDS-associated oral NHL characterised by extensive necrosis and, in one case, bifocality.

CASE REPORT

Patient 1

A 26-year-old HIV-seropositive man was first seen in April 1990 at the Division of Infectious Diseases of the Hospital of Prato for a localized abscess on the left tonsil which appeared to be resistant to antibiotic therapy. His medical history included development of rectal adenoma and severe weight loss. The CD4-T-lymphocyte count and T-lymphocyte helper–suppressor ratio were 21 cells/mm^3 and 0.4, respectively. The patient was classified as Group IV D of the Center for Disease Control (CDC) case definition of HIV infection.

Intraoral examination revealed a painful, ulcerated lesion, 1 cm in diameter in the area of the left tonsil, with a necrotic surface and hyperaemic margin. Cultural examination showed the presence of *Candida krusei*, *C. albicans* and *Streptococcus viridans*. Tests for *Mycobacterium tuberculosis* were negative. An incisional biopsy resulted in a provisional diagnosis of severe ulcerative–necrotic tonsillitis.

Five months later the patient was referred to the Institute of Stomatology because of pain, dysphagia nad trismus. Cervical lymphadenopathy was absent. At oral examination, a diffuse necrotic area of soft palate accompanied by an exophytic mass that involved the posterior third of the tongue, posterior pillar and oropharynx were noted (Fig. 1). An incisional biopsy specimen was taken. The tissue was fixed in 10% formalin solution and stained with haematoxylin–eosin, giemsa and periodic acid-Schiff.

Microscopic examination revealed a lymphoid proliferation, consisting of large cells with uniformly round nuclei with one or more nucleoli (Figs 2 and 3). The lymphoid cells infiltrated smooth muscle and vessels. Necrotic areas were visible. The histological diagnosis was high grade malignant, immunoblastic non-Hodgkin lymphoma, according to the Working Formulation [18].

Paraffin-embedded tissues were stained for immunohistochemical studies with the use of CAM5,2 (Becton Dickinson),

Correspondence to S. Piluso, Institute of Odontology and Stomatology, Viale Morgagni 85, 50134 Florence, Italy; D. Gaglioti, A. Saccardi and G. Ficarra are at the Institute of Odontology and Stomatology, University of Florence and USL 10/D, Florence, Italy; S. Di Lollo and G. Baroni are at the Institute of Pathology, University of Florence, Florence, Italy; and F. Leoncini is at the Division of Infectious Diseases, USL 9, Prato, Italy.
Received 24 Feb. 1993; provisionally accepted 25 Feb. 1993; revised manuscript received 22 Mar. 1993.

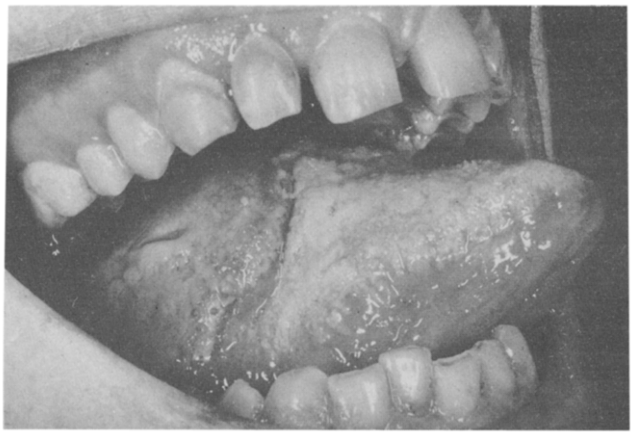

Fig. 1. Patient no. 1. Non-Hodgkin's lymphoma presenting as an ulcerated mass on the posterior tongue.

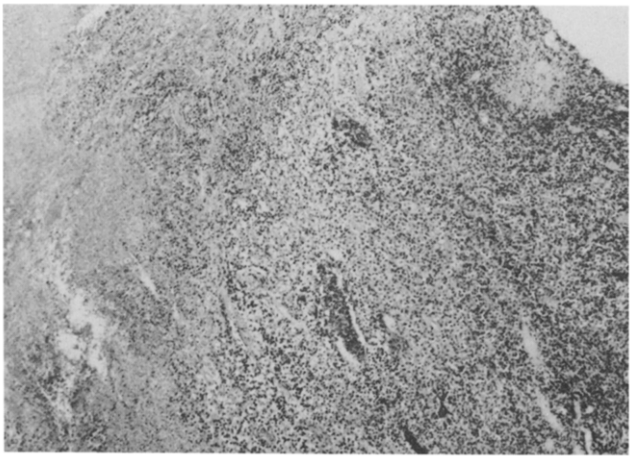

Fig. 2. Patient no. 1. Immunoblastic non-Hodgkin lymphoma: note the tissue necrosis on the left side (Haematoxylin–eosin stain, original magnification ×4).

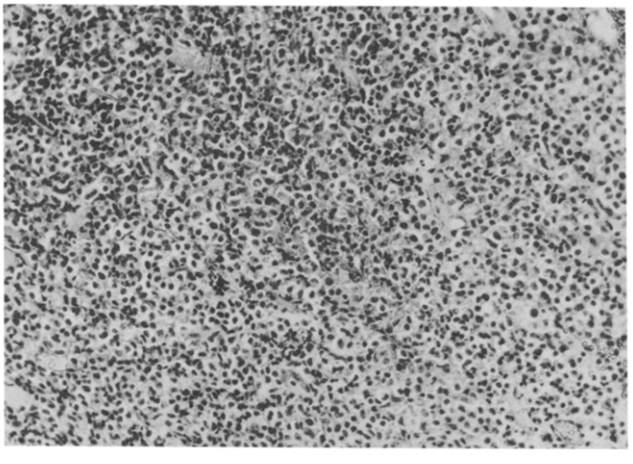

Fig. 3. Patient no. 1. Immunoblastic non-Hodgkin lymphoma. The cellular proliferation is composed of large cells with uniformly round nuclei and pale cytoplasm (Haematoxylin–eosin, original magnification ×10).

CD45 (DAKO), CD20 (DAKO), CD45RO (DAKO) monoclonal antibodies. Results demonstrated a B-cell origin of the tumour. Because of the extensive necrosis, the tissue was not suitable for further *in situ* hybridisation studies.

Computer tomographic (CT) scans showed a mass on the posterior tongue and right site of oropharynx. The patient rapidly deteriorated and died in October 1990 due to massive gastrointestinal haemorrhage before antineoplastic therapy could be instituted.

Patient 2

A 37-year-old homosexual man was referred to our Institute for the first time in 1990 and treated for HIV-associated necrotising periodontitis. Diagnosis of HIV infection had been made in 1985 and he was placed on zidovudine in April 1990.

In January 1992, the patient suddenly developed oral pain. Intraoral examination revealed the presence of generalised periodontitis and two ulcerative-necrotising lesions localised on the hard palate in the area of the right premolars and central incisors (Fig. 4). The upper right second premolar was mobile. A diagnosis of HIV associated necrotising periodontitis was made and the patient was treated with scaling, root planing and curettage of necrotic tissue. In addition, antibiotic therapy with metronidazole was instituted. However, the lesions did not respond to therapy but progressed. Bacteriological and virological examinations to detect fungi, herpes simples virus type 1 and 2, varicella-zoster virus and cytomegalovirus were negative.

At that time the CD4 lymphocyte level was 11 cells/mm^3 with a T helper–suppressor ratio of 0.03. The patient was classified as CDC Group IV C2. An incisional biopsy of the palatal lesion was undertaken. The histological examination showed an infiltration composed of large lymphoid cells (immunoblasts) with uniformly round to oval vescicular nuclei and one or more prominent nucleoli. Intense tissue necrosis was present (Fig. 5). The histological diagnosis was non-Hodgkin lymphoma classified according to the Working Formulation [18] as high grade malignant immunoblastic. Immunohistochemical studies performed on the paraffin-embedded tissue section were consistent with a tumour of B-cell origin. *In situ* DNA hybridisation for EBV infection was performed on the biopsy specimen. Sections were deparaffinised and digested with proteinase K for 15 min at 37°C. Slides were rinsed with buffer and air-dried, one drop of DNA

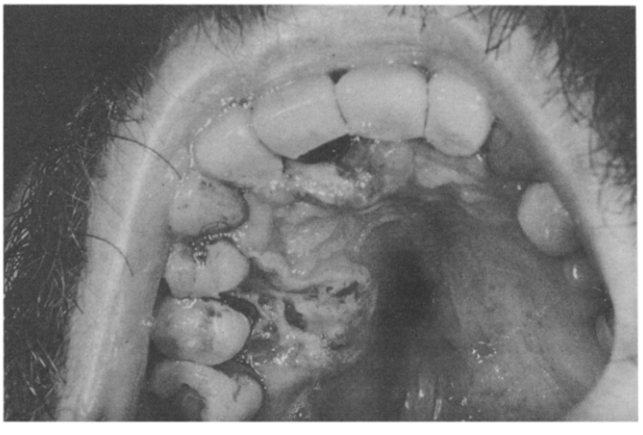

Fig. 4. Patient no. 2. Non-hodgkin lymphoma presenting as a bifocal ulceration of palatal mucosa.

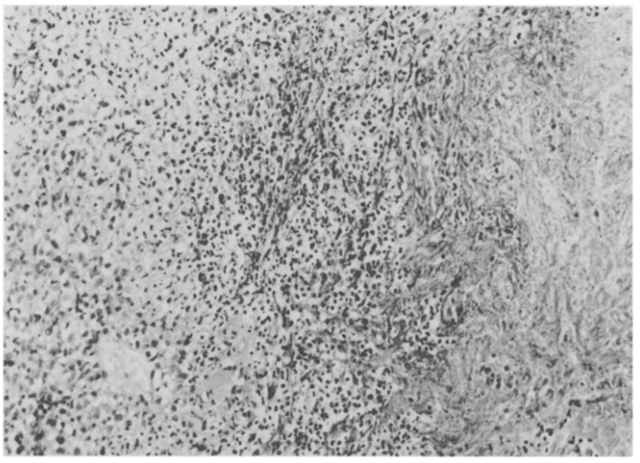

Fig. 5. Patient no. 2. Immunoblastic non-Hodgkin lymphoma. Note the proliferation of cells containing large round nuclei and the tissue necrosis on the right side (Haematoxylin–eosin, original magnification ×4).

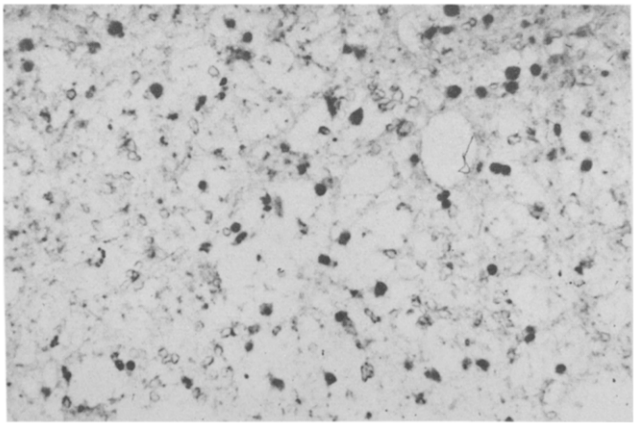

Fig. 6. Patient no 2. Presence of Epstein–Barr virus DNA by *in situ* hybridisation. Positivity is revealed by clear black stain over the nuclei of tumour cells (original magnification ×40).

probe reagent was added (PathoGene DNA Probe Assay, Enzo Diagnostics, New York), coverslips were placed over the slides and then placed on a heating plate for 5 min. Slides were kept at room temperature for 20 min, the coverslip was removed by washing in phosphate buffered saline for 1 min, and one drop of post-hybridisation reagent was added for 10 min at room temperature. Following washing with buffer, one drop of detection reagent was applied for 20 min at room temperature, the slide was washed with buffer, and chromogen (3-amino-9-ethylcarbazole; DAKO) was applied for 5 min. Sections were washed, counterstained with fast green, rewashed, and mounted. Both negative and positive control slides were performed, the positive control consisting of tissue from EBV positive hairy leukoplakia. Positivity to EBV DNA of the nuclei of tumour cells was detected (Fig. 6). A staging procedure for malignant lymphoma was performed. A CT scan of the face showed involvement of the maxillary bone. A chest and pelvic CT scan and bone marrow aspiration gave no evidence of systemic involvement. The patient was treated with radiation therapy and a complete remission of oral lesions was obtained.

At the date of last follow-up (June 1993) the patient was alive. An additional staging work-up has revealed a new malignant lymphoma of the intestine.

DISCUSSION

Patients with HIV infection have an increased risk of developing malignancies [9, 19, 21]. Predisposition to lymphoma seems to be correlated with the impairment of negative feedback control of lymphoproliferation, in particularly linked to suppressor T-cell function [22]. It has been also speculated that EBV may play a role in the development of lymphoma in patients with immunosuppression [10, 16, 23–25]. Lymphomas in AIDS patients are probably produced by expansion of B-cell clones transformed by EBV [22–25]. However, the exact role of EBV is not yet clear because the virus is not always detected and other mechanisms resulting in cells stimulation may be implicated [10, 24, 26]. We found EBV DNA sequences with *in situ* hybridisation in the second patient, whereas in the first patient the tissue was not suitable to perform the test because of the intense necrosis.

The role of zidovudine therapy in the development of NHL has been also debated. Zidovudine is not considered to directly increase the risk of NHL but may prolong survival in the setting of immunosuppression. It has been reported that the incidence of NHL may be higher particularly in patients with less than 50 CD4 cells/mm^3 who have survived for prolonged periods [27, 28].

Oral manifestations of B-cell lymphomas are relatively rare [29]. Intraoral lymphomas in HIV infected subjects have been reported on the maxillary and mandibular alveolar ridge [1, 2, 4–6, 8], palate [5, 6, 8, 15, 26], vestibular mucosa and retromolar pad area [1, 26]. The tongue is an unusual site of presentation [8]. Lesions have frequently been described as exophytic, pedunculated and enlarging masses [1, 2, 4–6]. In our patients the initial lesions were ulcerations characterised by extensive tissue necrosis. This type of presentation may mimic inflammatory lesions and delay final diagnosis and treatment. In the literature are reported cases in which NHL lesions occur in the site of previous inflammation such as periodontal disease or pericoronitis [3, 4, 26, 30]. Another unusual feature is the bifocal origin of the tumour that we observed in patient 2.

Ulcerated lesions of the oral mucosa in subjects with HIV infection may be caused by a large variety of aetiological agents such as viruses, bacteria, fungi, radiotherapy and chemotherapy [31, 32]. It is important to stress that when ulcerative lesions of the oral cavity appear in these patients, NHL must be included in the differential diagnosis.

Our histological findings are in agreement with previous cases of NHL reported, characterised by poorly differentiated histological aspects and highly aggressive behaviour [1, 2, 4–6, 8, 10, 12, 15, 17].

In summary, NHL in patients infected with HIV are characterised by frequent extranodal involvement and clinical aggressiveness. The presentation of NHL on the tongue is an unusual feature. Other atypical clinical aspects that we observed are the bifocality of the palatal lesion and extensive necrosis.

1. Langford A, Dienemann D, Schurman D, *et al.* Oral manifestation of AIDS-associated non-Hodgkin's lymphomas. *J Oral Maxillofac Surg* 1991, **20**, 136–141.
2. Colmenero C, Gamallo G, Pintado V, Patron M, Sierra I,

Valencia E. AIDS-related lymphoma of the oral cavity. *J Oral Maxillofac Surg* 1991, **20**, 2–6.
3. Vallejo, GH, Garcia MD, Lopez A, Mendieta C, Moskow BS. Unusual periodontal findings in an AIDS patient with Burkitt's lymphoma. *J Periodontol* 1989, **60**, 723–727.
4. Rubin MM, Gatta CA, Cozzi GM. Non-Hodgkin's lymphoma of the buccal gingiva as the initial manifestation of AIDS. *J Oral Maxillofac Surg* 1989, **47**, 1311–1313.
5. Kaugars GE, Burns JC. Non-Hogkin's lymphoma of the oral cavity associated with AIDS. *Oral Surg* 1989, **67**, 433–436.
6. Leess FR, Kessler DJ, Mickel RA. Non-Hodgkin's lymphoma of the head and neck in patients with AIDS. *Arch Otolaryngol Head Neck Surg* 1987, **113**, 1104–1106.
7. Sheibani K, Ben-Ezra J, Swartz WG, *et al.* Monocytoid B-cell lymphoma in a patient with Human Immunodeficiency Virus infection. *Arch Pathol Lab Med* 1990, **114**, 1264–1267.
8. Raphael M, Gentilhomme O, Tulliez M, Byron PA, Diebold J. Histopathologic features of high-grade non-Hodgkin's lymphomas in acquired immunodeficiency syndrome. *Arch Pathol Lab Med* 1991, **115**, 15–20.
9. Levine AM. Therapeutic approaches to neoplasms in AIDS. *Rev Infect Dis* 1990, **12**, 938–943.
10. Hamilton-Dutoit SJ, Pallesen F, Franzmann MB, *et al.* AIDS-related lymphoma. Histopathology, immunophenotype, and association with Epstein–Barr virus as demonstrated by *in situ* nucleic acid hybridization. *Am J Pathol* 1991, **138**, 149–163.
11. Loureiro C, Gill PS, Meyer PR, Rhodes R, Rarick MU, Levine AM. Autopsy findings in AIDS-related lymphoma. *Cancer* 1988, **62**, 735–739.
12. Guarner J, del Rio C, Carr D, Hendrix LE, Eley JW, Unger ER. Non-Hodgkin's lymphomas in patients with Human Immunodeficiency Virus infection. *Cancer* 1991, **68**, 2460–2465.
13. Rabkin CS, Hilgartner MW, Hedberg KW, *et al.* Incidence of lymphomas and other cancer in HIV-infected and HIV-uninfected patients with hemophilia. *JAMA* 1992, **267**, 1090–1094.
14. Aricò M, Caselli D, D'Argenio P, *et al.* Malignancies in children with Human Immunodeficiency Virus type 1 infection. *Cancer* 1991, **68**, 2473–2477.
15. Carbone A, Tirelli U, Vaccher E, *et al.* A clinicopathologic study of lymphoid neoplasias associated with human immunodeficiency virus infection in Italy. *Cancer* 1991, **68**, 842–852.
16. Thomas JA, Crawford DH. Epstein–Barr Virus associated B-cell lymphomas in AIDS and after organ transplantation. *Lancet* 1989, **13**, 1075–1076.
17. Levine AM, Sullivan-Halley J, Pike MC, *et al.* Human immunodeficiency virus-related lymphoma. Prognostic factors predictive of survival. *Cancer* 1991, **11**, 2466–2472.
18. The Non-Hodgkin's Lymphoma Pathologic Classification Project. National Cancer Institute sponsored study of classifications of non-Hodgkin's lymphomas. Summary and description of a Working Formulation for clinical usage. *Cancer* 1982, **49**, 2112–2135.
19. Epstein JB, Silverman S Jr. Head and neck malignancies associated with HIV infection. *Oral Surg* 1992, **73**, 193–200.
20. Ioachim HL, Dorsett B, Cronin W, Maya M, Wahl S. Acquired immunodeficiency syndrome-associated lymphomas: clinical, pathologic, immunologic and viral characteristics of 111 cases. *Hum Pathol* 1991, **22**, 659–673.
21. Epstein JB, Scully C. Neoplastic disease in head and neck of patients with AIDS. *J Oral Maxillofac Surg* 1992, **21**, 219–226.
22. Shiramizu B, McGrath MS. Molecular pathogenesis of AIDS-associated non-Hodgkin's lymphoma. *Hematol Oncol Clin North Am* 1991, **2**, 323–330.
23. Pellicci PG, Knowles DM, Arlin ZA, *et al.* Multiple monoclonal B-cell expansions and c-*myc* oncogene rearrangements in acquired immune deficiency syndrome-related lymphoproliferative disorders. Implications for lymphomagenesis. *J Exp Med* 1986, **164**, 2049–2060.
24. Green TL, Eversole LR. Oral lymphomas in HIV-infected patients: association with Epstein–Barr virus DNA *Oral Surg* 1989, **67**, 437–442.
25. Knowles DM, Inghirami G, Ubriaco A, Dalla-Favera R. Molecular genetic analysis of three AIDS-associated neoplasms of uncertain lineage demonstrates their B-cell derivation and the possible pathogenetic role of Epstein–Barr virus. *Blood* 1989, **3**, 792–799.
26. Dodd CL, Greenspan D, Schiodt M, *et al.* Unusual oral presentation of non-Hodgkin's lymphoma in association of HIV infection. *Oral Surg* 1992, **73**, 603–608.
27. Moore RD, Kessler H, Richman DD, Flexner C, Chaisson RE. Non-Hodgkin's lymphoma in patients with advanced HIV infection treated with zidovudine. *JAMA* 1991, **265**, 2208–2211.
28. Centers for Disease Control. Opportunistic non-Hodgkin's lymphomas among severely immunocompromised HIV-infected patients surviving for prolonged period on antiretroviral therapy. *MMWR* 1991, **40**, 597–600.
29. Freeman C, Berg JW, Cutler SJ. Occurrence and prognosis of extranodal lymphomas. *Cancer* 1972, **29**, 252–260.
30. Groot RH, van Merkesteyn JPR, Bras J. Oral manifestation of non-Hodgkin's lymphomas in HIV infected patients. *Int J Oral Maxillofac Surg* 1990, **19**, 194–196.
31. Ficarra G, Piluso S. Lesioni ulcerative della mucosa orale nei pazienti con infezione da HIV. *G Ital AIDS* 1991, **4**, 211–218.
32. Ficarra G. Oral lesions of iatrogenic and undefined etiology and neurologic disorders associated with HIV infection. *Oral Surg* 1992, **73**, 201–211.

Acknowledgements—The work is in part supported by a fellowship from the Istituto Superiore di Sanità (Dr Sara Piluso), Rome, Italy.