REVIEW ARTICLE

Second malignancies in Hodgkin's disease: A review of the literature and report of a case with a secondary Lennert's lymphoma

Ernst JG Norval, Erich J Raubenheimer[1]

Department of Diagnostics, University of the Western Cape, Tygerberg, [1]Department of Pathology, School of Oral Health Sciences, University of Limpopo, Limpopo, South Africa

Address for correspondence:
Prof. Erich J Raubenheimer,
Department of Pathology, School of Oral Health Sciences, University of Limpopo,
0204 South Africa.
E-mail: Erich.Raubenheimer@ul.ac.za

Received: 15-01-2013
Accepted: 16-06-2014

ABSTRACT

A small percentage of patients treated for Hodgkin's disease are at risk of developing a second malignancy. The appearance of secondary malignancies such as leukemia, carcinoma or non-Hodgkin's lymphomas may be attributed to the mutagenic effects of chemotherapy and/or radiotherapy. Most secondary non-Hodgkin's lymphomas are of the B-cell type, but isolated cases were reportedly of a T-cell lineage. A review of the literature pertaining to the development of secondary peripheral T-cell lymphomas is presented along with the description of an additional case. The latter developed in the tonsil and was diagnosed as a Lennert's lymphoma (lymphoepithelioid T cell lymphoma) on histological and immunological grounds. This report also reviews the development of a of peripheral T-cell lymphoma described in patients following chemotherapy and/or radiotherapy for Hodgkin's disease

Key words: Hodgkin's disease, Lennert's lymphoma, peripheral T-cell lymphoma, second malignancies in Hodgkin's disease, secondary non-Hodgkin's lymphoma

INTRODUCTION

Approximately 75% of patients with Hodgkin's disease (HD), regardless of the stage, may achieve long-term survival on modern treatment regimes,[1] but they are at an increased risk of developing a histologically unrelated second primary malignancy as a treatment complication.[2-8] Three types of second primary malignancy are recognized: Solid tumors, leukemia's and non-Hodgkins lymphoma (NHL), of which solid tumors of visceral organs constitute up to three quarters of all cases of second primary malignancy.[3,9-31] The development of second primary malignancies is related to the extent of the initial treatment, whether chemotherapy (CT), radiotherapy (RT) or a combination of chemo- and radiotherapy (CCRT) was employed, gender and age when treatment was initiated.[11,32,33] The increased risk to develop second primary malignancies is attributable to the mutagenic- and immune-suppressive effects of CT or RT, [4,17,34-37] and the risk seems to be higher among those treated by both modalities.[17,18,31,38-43] Treatment with extended-field radiation, rather than involved field radiation or fractionalized radiation was also found to increase the risk for a second primary malignancy.[13,44-47] It was proposed that the increased susceptibility for second primary malignancies are multi-factorial and due in part to persistent immune abnormalities seen in HD, coupled with the carcinogenic effects of RT, CT or CCRT.[6,11,35-38,41,48-50]

A survey of the literature revealed that 19 confirmed cases of peripheral T-cell lymphomas other than mycosis fungoides had developed after treatment of HD.[6,8,19,51,52] In 10 cases, clinical data was supplied, there were six males and four females-the ages varied between 14 and 65 years and they occurred in the pharynx (one case),[40] axillary nodes (two cases),[8,53] inguinal node (three cases),[3,53] lungs (one case),[54] abdominal nodes (two cases)[19] and mediastinal lymph nodes.[54] The interval between diagnosis of HD and appearance of a peripheral T-cell lymphoma varied between the reported cases from eight months to 25 years. Six patients were treated with CCRT, three with CT and one with RT alone. The paper by Oliva *et al*.,[52] was the only case of a secondary Lennert's lymphoma reported in the literature. Amini *et al*.,[54] recorded seven cases of T-cell NHL's that coexisted with HD at the time of diagnosis and Rueffer *et al*.,[55] also mentioned seven cases of T-cell NHL after HD among their study series, but without

Access this article online

Quick Response Code:

Website: www.jomfp.in

DOI: 10.4103/0973-029X.141332

supplying clinical data. The T-cell character of all these cases was immunologically confirmed either by E-rosetting, surface marker analysis or gene re-arrangement studies. Three of the four peripheral T-cell lymphomas reported by Bennet *et al*.,[56] that developed after treatment of nodular lymphocyte predominant Hodgkin's disease (NLPHD) can be excluded, as the latter category is regarded as a B-cell NHL-variant, containing lymphocytic and histiocytic (L and H) cells ("popcorn cells") that stain with pan-B markers.[57] Those T-cell lymphomas that developed after treatment of NLPHD reported by Rysenga *et al*.,[58] and by Arevalo *et al*.,[59] were also excluded on the same grounds.

CASE REPORT

A 74-year-old woman with a negative history of tobacco use was admitted to a teaching hospital with a palpable inguinal mass, which was biopsied. She had been treated by radiotherapy and alkylating agents for an Ann Arbor Stage I Hodgkin's disease nine years previously at another hospital. The original pathology slides were not available for review, but histological examination of the inguinal node biopsy revealed the presence of a mixed cellularity HD. The patient then received fractionalized extended field radiotherapy for a total of 24 rays over a 4-week period. A cervical mass then appeared 15 months after treatment. This mass was biopsied and diagnosed as Hodgkin's lymphoma mixed cellularity. A staging laparotomy was performed, which revealed evidence of liver and para-aortic lymph node involvement. A bone marrow trephine biopsy was found to be free of tumor. The malignancy was asymptomatic and involved more than one groups of lymph nodes on both sides of the diaphragm, with infiltrates into surrounding non-lymphoid tissues (or Stage III AE Hodgkin's disease). She received four cycles of MOPP-regime (mechlorethamine, ovocin/vincristine, procarbazine-prednisone) chemotherapy. The patient was re-admitted seven months later with a rapidly enlarging mass in the right tonsil, for which a tonsillectomy was performed. Clinical examination also revealed the presence of a diffuse swelling in the soft palate. The patient received two cycles of salvage ChlPP (chlorambucil, vinblastine, procarbazine, prednisone) chemotherapy, but died five months after re-admission. No autopsy was carried out. Sections were cut from the tonsillectomy tissue blocks and immunohistologically stained according to the avidin-biotin-peroxidase-complex method. The monoclonal antibodies were obtained from Dakopatts, Denmark and included CD45 (LCA), CD20 (L26), UCHL-1, CD3, CD15 (Leu-M1), CD30 (Ber-H2), CD68 (KP-1), S100, KER, EMA and monoclonal antibodies against the immunoglobulins G, -M, -A and kappa and lambda light chains.

Microscopic examination of the inguinal lymph node showed effacement of the normal architecture by a diffuse growth consisting of Reed-Sternberg cells and atypical mononuclear cells in a background of eosinophils, plasma cells, histiocytes and non-atypical T-lymphocytes [Figure 1]. The tumor cells stained with Leu-M1 and Ber-H2, but failed to react with any lymphoid markers used. The microscopic and immunologic features were considered typical of a Hodgkin's lymphoma, mixed cellularity type.

The tonsillar biopsy revealed a diffuse growth of small and medium-sized lymphocytes with atypical irregular nuclei. A small number of large lymphocytes with prominent nucleoli were noted and occasional large cells were binucleated. No Reed-Sternberg cells were present and mitoses averaged two per 200X magnification. Small clusters of epithelioid histiocytes with vesicular oval or retiform nuclei were scattered among the tumor cells [Figure 2]. The cytoplasm of the histiocytes was abundant, oxyphylic and many contained a pale rounded central vesicular area [Figure 3]. These cells reacted strongly with the monoclonal antibody KP-1, indicative of their macrophage lineage [Figure 4]. Multi-nucleated Langhans-like giant cells as well as scattered eosinophils were also observed. In areas, aggregates of plasma cells dominated and expressed polytypic immunoglobulins. The tumor cells stained with anti-CD45, UCHL-1, anti-CD3, [Figure 5] but not with any of the other monoclonal antibodies used. This tumor was diagnosed as a peripheral T-cell NHL (lympho-epithelioid variant or Lennert's lymphoma).

DISCUSSION

The case reported here represents an additional peripheral T-cell lymphoma that developed as a second primary malignancy after CCRT treatment for HD. The histological and immunological features of this tumor corresponded with that of a lymphoma described by Lennert and Mestdagh.[60] They proposed the term "lymphoepithelioid cell lymphoma", also known as Lennert's lymphoma and this tumor is classified as a specific variant of a T-cell NHL.[61] It is a rare malignancy and diagnosis is based on the presence of clusters of epithelioid histiocytes, Langhans-type giant cells, rare inflammatory cells, atypical small cells and no evidence of increased vascularization.[58,61-63] Cytogenic- and gene re-arrangement

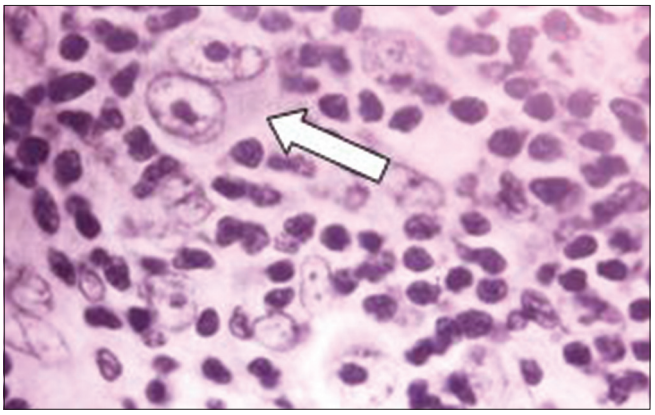

Figure 1: Mixed cellularity Hodgkin's lymphoma, arrow pointing to Reed-Sternberg owl-eye cell (H&E, ×200)

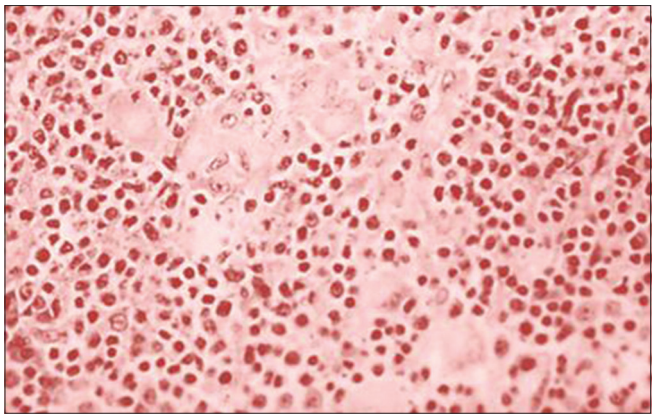

Figure 2: Lymphoepithelioid lymphoma, showing pale epithelioid cell clusters in a background of small atypical cells (H&E, ×200)

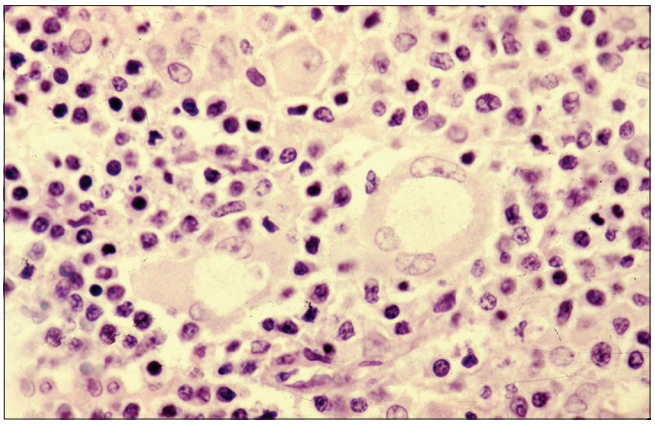

Figure 3: Multinucleated epithelioid histiocytes with large intracytoplasmic vesicles (H&E stain, ×200)

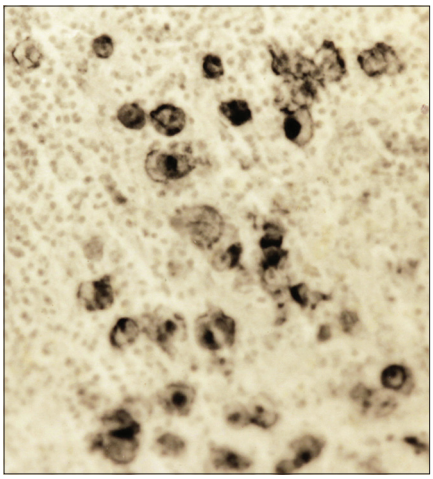

Figure 4: KP-1 positivity highlighting the presence of epithelioid histiocytes (IHC stain, ×100)

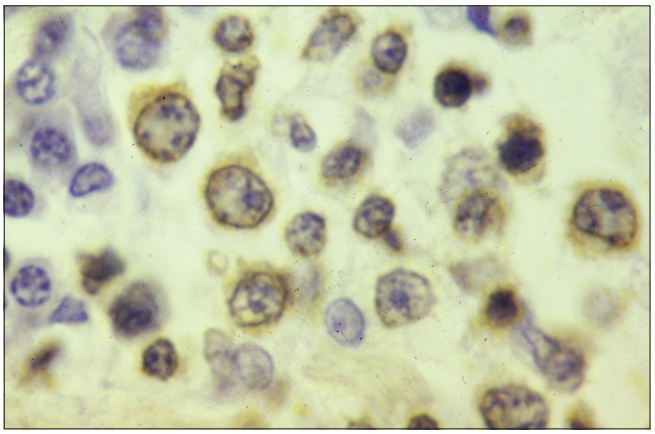

Figure 5: Anti-CD3 staining highlighting the presence of atypical small and medium-sized T-cells (IHC, ×400)

studies of these atypical cells by various authors provided evidence that this tumor is a malignant proliferation of CD-4+ helper/inducer T-cells,[63] or CD8+ cytotoxic T-cells.[59,63,64] Suchi *et al*.,[61] defined the essential diagnostic criteria for this tumor and proposed an updated classification system for peripheral T-cell lymphomas, in which Lennert's lymphoma was placed into the low-grade category. Lennert's Lymphoma have been described as a primary tumor in patents ranging from 23 to 81 years[52,65] and cases were recorded in the nasopharynx, submandibular lymph nodes, Waldeyer's ring, tonsils and pharynx.[60,66,67] This tumor was found to be associated with splenomegaly or hepatomegaly and symptoms in many cases.[66]

The histologic features of Lennert's lymphoma should be differentiated form toxoplasmosis and histiocyte-rich mixed cellularity HD on the grounds of immunologic and cellular findings.[67] A Giemsa-stain of the embedded palatine tissue was done, but revealed no Toxoplasma organisms. The tumor presented here was differentiated from a Hodgkin's lymphoma with a high content of epithelioid cells on the grounds of an absence of diagnostic CD-10- and Ber-H2 staining Reed-Sternberg cells and the presence of a spectrum of atypical T-cells. Almost all the atypical cells in the present case from the tonsil reacted with leucocyte common antigen (LCA) and with the pan-T-cell markers UCHL-1 and anti-CD3. No staining with Leu-M1, Ber-H2, EMA and the pan-B cell marker L26 was observed, confirming the T-cell lineage of this tumor. It was differentiated from the closely related angio-immunoblastic lymphoma by the absence of abundant high endothelial venules with hyalinized vessel walls and less appreciable morphological atypia.[66-68] The presence of polytypic plasma cells in this tumor, differentiated it from a lymphoplasmacytoid lymphoma. The latter may have similar morphology, but the plasmacytoid cells herein express monotypic immunoglobulin.

The relation between a secondary peripheral T-cell NHL and primary HD is obscure as cases of T-cell NHL co-existing with a HL was also reported.[69] Loewenthal *et al*.,[8] suggested that the T-cells involved in the immune response against a HD may be "switched-on", only to be at risk of neoplastic transformation. The possibility of transformation from a Hodgkin's lymphoma expressing T-cell receptor gene re-arrangements to a peripheral T-cell NHL was raised by Nakamura.[70] Although, a substantial

number of NHL's developing after treatment of HD have been mentioned in risk-analysis studies,[30,38,71-74] the number of reported T-cell non-Hodgkin's lymphomas are few, most of the cases reported in the literature developed in peripheral lymph nodes. Subsequent survival after diagnosis of a secondary NHL is said to be less favorable than that of patients with a primary lymphoma.[75] T-cell NHL's are more aggressive than B-cell NHL's,[65] having a poor prognosis[52] and a median survival of 15.6 months.[67] This is reflected in the case described here, as the patient passed away 5 months after diagnosis of the second malignancy.

The more relapses, the more advanced staging at initial diagnosis and additional therapy experienced by a survivor of HD, the higher the risk of developing a second tumor.[75] The increased risk for a second neoplasm in a survivor of HD underscores the importance of continued monitoring of such patients. Those presenting with an apparent relapse should not be accepted as such, but intensive examination and biopsy are mandatory to exclude the possibility of an emerging second tumor. Careful histological evaluation and immuno-profiling are necessary in differentiating a NHL as a second primary malignancy from a recurring Hodgkin's lymphoma. The benefit derived from treatment of HD outweighs the risk for a second primary malignancy and limiting the extent of the RT field, or employing non-alkylating agents coupled with and life-long monitoring and early detection strategies should be implemented to identify a second primary malignancy.

REFERENCES

1. Glicksman AS, Pajak TF, Gotlieb A, Nisson N, Stutzman L, Cooper MR. Second malignant neoplasms in patients successfully treated for Hodgkin's disease: A cancer and Leukemia Group B study. Cancer Treat Rev 1982;66:1035-44.
2. Arseneau JC, Canellos GP, Johnson R, DeVita VT Jr. Risk of new cancers in patients with Hodgkin's disease. Cancer 1977;40 (4 Suppl):1912-6.
3. Kletsky AJ, Bertino JB, Farber LR, Prosnitz LR, Kapp DS, Fischer D, *et al.* Second neoplasms in patients with Hodgkin's disease following combined modality therapy. The Yale experience. J Clin Oncol 1986;4:311-7.
4. Zarato-Osorno A, Medeiros LJ, Longo DL, Jaffe ES. Non-Hodgkin's lymphoma arising in patients successfully treated for Hodgkin's disease. A clinical, histologic, and immunophenotypic study of 14 cases. Am J Surg Pathol 1992;16:885-95.
5. Grossniklaus HE, Farhi DC, Jacobson BR, Abbuhl MF. Malignant lymphoma of the conjunctiva following Hodgkin's disease. Br J Opthalmol 1988;73:212-5.
6. Li FP, Gimbrere K, Ritz J, Saito H, Longtine JA. Lymphoma with clonal T-cell receptor gene rearrangement in a 25-year survivor of Hodgkin's disease. Cancer 1987;60:2213-8.
7. Kim HD, Bedetti CD, Boggs DR. The development of non-Hodgkin's lymphoma following therapy for Hodgkin's disease. Cancer 1980;46:2596-602.
8. Loewenthal MR, Harlow RW, Med AE, Tuck D, Challis DR. T-cell non-Hodgkin's lymphoma after radiotherapy and chemotherapy for Hodgkin's disease. Cancer 1981;48:1586-9.
9. Ng AK, Bernardo P, Weller E, Backstrand K, Silber B, Marcus KC, *et al.* Second malignancy after Hodgkin's disease with radiation therapy with or without chemotherapy: Long-term risk and risk factors. Blood 2002;100:1989-96.
10. Lokich JJ. Secondary uncommon solid neoplasms in cured Hodgkin's disease and follow-up of the original B-DOPA chemotherapy patient group. Am J Clin Oncol 1990;13:247-50.
11. Mauch PM, Kalish LA, Marcus KC, Coleman NC, Shulman LN, Krill E, *et al*. Second malignancies after treatment for laparotomy stage 1A-111B Hodgkin's disease: Long-term analysis of risk factors and outcome. Blood 1996;87:3625-32.
12. Meattini I, Livi L, Saieva C, Marrazzo L, Rampini A, Iermano C, *et al.* Breast cancer following Hodgkin's Disease: The Experience of the University of Florence. Breast J 2010;16:290-6.
13. Chronowski GM, Wilder RB, Levy LB, Atkinson EN, Ha CS, Hagemeister FB, *et al*. Second malignancies after chemotherapy and radiotherapy for Hodgkins' disease. Am J Clin Oncol 2004;27:73-80.
14. Behringer K, Josting A, Schiller P, Eich HT, Bredenfeld H, Diehl V, *et al*., German Hodgkin Lymphoma Study Group. Solid tumors in patients treated for Hodgkin's disease: A report from the German Hodgkin's Lymphoma Study Group. Ann Oncol 2004;15:1079-85.
15. Bhatia S, Yasui Y, Robinson LL, Birch JM, Bogue MK, Diller L, *et al*., Late Effects Study Group. High risk of subsequent neoplasms continues with extended follow-up of childhood Hodgkin's disease: Report from the Late Effects Study Group. High risk of subsequent neoplasms continues with extended follow-up of childhood Hodgkin's disease: Report from the Late Effects Study Group. J Clin Oncol 2003;21:4386-94.
16. Boivin JF, Hucthinson GB, Zauber AG, Bernstein L, Davis FG, Michel RP, *et al.* Incidence of second cancers in patients treated for Hodgkin's disease. J Natl Cancer Inst 1995;87:732-41.
17. Arseneau JC, Sponzo RW, Levin DL, Schnipper LE, Bonner H, Young RC, *et al.* Non-lymphomatous malignant tumours complicating Hodgkin's disease. Possible association with intensive therapy. N Engl J Med 1972;287:1119-22.
18. Baccarani M, Bosi A, Papa G. Second malignancy in patients treated for Hodgkin's disease. Cancer 1980;46:1173-40.
19. Armitage JO, Dick FR, Goeken JA, Foucar MK, Gingrich RD. Second lymphoid malignant neoplasms occurring in patients treated for Hodgkin's disease. Arch Int Med 1983;143:445-50.
20. Tester WJ, Kinsella TJ, Walker B, Makuch RW, Kelley PA, Glatstein E, *et al.* Second malignant neoplasms complicating Hodgkin's disease: The National Cancer Institute experience. J Clin Oncol 1984;2:762-9.
21. Valagussa P, Santoro A, Fossati-Bellani F, Banfi A, Bonadonna G. Second acute leukemia and other malignancies following treatment for Hodgkin's disease. J Clin Oncol 1986;4:830-7.
22. Tucker MA, Misfeldt D, Coleman CN, Clarke WH Jr, Rosenberg SA. Cutaneous malignant melanoma after Hodgkin's disease. Ann Int Med 1985;102:37-41.
23. Brody R, Schottenfeld D, Reid A. Multiple primary cancer risk after therapy for Hodgkin's disease. Cancer 1977;40 (4 Suppl):1917-26.
24. Berg JW. The incidence of multiple primary cancers. I. Development of further cancers in patients with lymphomas, leukemias, and myeloma. J Natl Cancer Inst 1967;38:741-52.

25. Razis DV, Diamond HD, Craver LF. Hodgkin's disease associated with other malignant tumors and certain non-neoplastic diseases. Am J Med Sci 1959;238:327-35.
26. Canellos GP, Arseneau JC, DeVita VT, Whang-Peng J, Johnson RE. Second malignancies complicating Hodgkin's disease in remission. Lancet 1975;1:947-9.
27. Coltman CA Jr, Dixon DO. Second malignancies complicating Hodgkin's disease: A South-West Oncology Group 10-year followup. Cancer Treat Rep 1982;66:1023-33.
28. Valagussa P, Santoro A, Kenda R, Fossati-Bellani F, Franchi F, Banfi A, *et al*. Second malignancies in Hodgkin's disease: A complication of certain forms of treatment. Br Med J 1980;280:216-9.
29. Green DM, Hyland A, Barcos MP, Reynolds JA, Lee RJ, Hall BC, *et al*. Second malignant neoplasms after treatment for Hodgkin's disease in childhood or adolescence. J Clin Oncol 2000;18:1492-9.
30. Swerdlow AJ, Barber JA, Hudson GV, Cunningham D, Gupta RK, Hancock BW, *et al*. Risk of second malignancy after Hodgkin's disease in a collaborative British cohort: The relation to age at treatment. J Clin Oncol 2000;18:498-509.
31. Dores GM, Metayer C, Curtis RE, Lynch CF, Clarke EA, Glimelius B, *et al.* Second malignant neoplasms among long-term survivors of Hodgkin's disease: A population-based evaluation over 25 years. J Clin Oncol 2002;20:3484-94.
32. Griesser GH, Hansmann ML. Soft tissue sarcoma as second malignant lesion after therapy for Hodgkin's disease. Report of two cases and review of the literature. J Cancer Res Clin Oncol 1985;110:238-43.
33. Goodman KA, Riedel E, Serrano V, Gulati S, Moskowitz H, Yahalom J. Long-term effects of high-dose chemotherapy and radiation for relapsed and refractory Hodgkin's lymphoma. J Clin Oncol 2008;26:5240-7.
34. Donaldson SS, Hancock SL. Second cancers after Hodgkin's disease in childhood. N Engl J Med 1996;334:792-4.
35. List AF, Greer JP, Cousar JB, Stein RS, Flexner JM, Sinangil F, *et al.* Non-Hodgkin's lymphoma after treatment of Hodgkin's lymphoma: Association with Epstein-Barr virus. Ann Int Med 1986;105:668-73.
36. Kaldor JM, Day NE, Clark A. Leukemia following Hodgkin's disease. N Engl J Med 1988;318:76-81.
37. Levy R, Kaplan HS. Impaired lymphocyte function in untreated Hodgkin's disease. N Engl J Med 1974;290:181-6.
38. Krikorian JG, Burke JS, Rosenberg SA, Kaplan HS. Occurrence of non-Hodgkin's lymphoma after therapy for Hodgkin's disease. N Engl J Med 1979;300:452-8.
39. Tucker MA, Coleman CN, Cox RS, Varghese A, Rosenberg SA. Risk of second cancers after treatment for Hodgkin's disease. N Engl J Med 1988;318:76-81.
40. Chan WC, Griem ML, Grozea PN, Freel RJ, Variakojis D. Mycosis fungoides and Hodgkin's disease occurring in the same patient: Report of three cases. Cancer 1979;44:1408-13.
41. Dick FR, Maca RD, Hankensow R. Hodgkin's disease terminating in a T-cell immunoblastic leukemia. Cancer 1978;42:1325-9.
42. Jacquillat C, Krayat D, Desprez-Curely JP. Non-Hodgkin's lymphoma occurring after Hodgkin's disease. Semin Diagn Pathol 1992;9:297-303.
43. Mandelli F, Martelli M, Cimino G, Alimena G, Anselmo AP, De Cuia MR, *et al*. A case of Burkitt's lymphoma -L3 ALL t (8; 14) translocation developed 10 years after Hodgkin's disease. Scand J Hematol 1985;34:97-100.
44. Ng AK, Mauch P. The impact of treatment on the risk of second malignancy after Hodgkin's disease. Ann Oncol 2006;17:1727-9.
45. Franklin J, Pluetschow A, Paus M, Specht L, Anselmo AP. Aviles A, *et al*. Second malignancy risk associated with treatment of Hodgkin's lymphoma: Meta-analysis of the randomised trials. Ann Oncol 2006;17:1749-60.
46. Travis LB, Rabkin CS, Brown LM, Allan JM, Alter BP, Ambrosone CB, *et al*. Cancer survivorship- genetic susceptibility and second primary cancers: Research strategies and recommendations. J Natl Cancer Inst 2006;98:15-25.
47. Cutuli B, Kanoun S, Tunon De Lara C, Baron M, Livi L, Levy C, *et al*. Breast cancer occured after Hodgkin's disease: Clinico-pathological features and outcome: Analysis of 214 cases. Crit Rev Oncol Hematol 2012;81:29-37.
48. Crump M, Hodgson D. Secondary breast cancer in Hodgkin's lymphoma survivors. J Clin Oncol 2009;27:4229-31.
49. DeVita VT Jr. The consequence of the chemotherapy of Hodgkin's disease: The 10th David A. Karnofsky Memorial Lecture. Cancer 1981;47:1-13.
50. Fisher RI, DeVita VT Jr, Bostick F, Vanhaelen C, Howser DM, Hubbard SM, *et al.* Persistent immunologic abnormalities in long term survivors of advanced Hodgkin's disease. Ann Int Med 1980;92:595-9.
51. Polychronopoulou S, Panagiotou JP, Papadakis T, Mavrou A, Anagnostou D, Haidas S. Secondary malignancies in a child with Hodgkin's disease: T-cell lymphoma and myelodysplastic syndrome evolving into acute nonlymphoblastic leukaemia. Med Pediatr Oncol 1996;26:359-66.
52. Oliva H, Rivas C, Vicente J, Aguilera B, Rivas F, Obeso G, *et al*. Lennert's lymphoma with giant multivesicular lysosomal bodies optically visible. Ultrastruct Pathol 1992;16:283-90.
53. Gowitt GT, Chan WC, Brynes RK, Heffner LT. T-cell lymphoma following Hodgkin's disease. Cancer 1985;56:1191-6.
54. Amini RM, Enblad G, Sundstrom C, Glimelius B. Patients suffering from both Hodgkin's disease and non-Hodgkin's lymphoma, a clinico-pathological and immmuno-histochemical population-based study of 32 patients. Int J Cancer 1998;71: 510-6.
55. Rueffer U, Josting A, Franklin J, May M, Sieber M, Breuer K, *et al*. German Hodgkin's Lymphoma Study Group. Non-Hodgkin's lymphoma after primary Hodgkin's disease in the German Hodgkin's Lymphoma Study Group: Incidence, treatment, and prognosis. J Clin Oncol 2001;19:2026-32.
56. Bennet MH, MacLennan KA, Vaughan Hudson G, Vaughan Hudson B. Non-Hodgkin's lymphoma arising in patients treated for Hodgkin's disease in the BNLI: A 20 year experience. British National Lymphoma Investigation. Ann Oncol 1991;2 Suppl 2:83-92.
57. Zhao FX. Nodular lymphocyte-predominant Hodgkin lymphoma or T-cell/histiocyte rich large B-cell lymphoma: The problem in "grey zone" lymphomas. Int J Clin Exp Pathol 2008;1:300-5.
58. Rysenga E, Linden MD, Carey JH, Ross CW, Schnitzer B, Sawdyk M, *et al.* Peripheral T-cell non-Hodgkin's lymphoma following treatment of nodular lymphocyte predominance Hodgkin's disease. Arch Pathol Lab Med 1995;119:88-91.
59. Arevalo A, Caponetti GC, Hu Q, Greiner TC, Weisenburger DD. Cytotoxic peripheral T-cell lymphoma arising in a patient with nodular lymphocytic predominant Hodgkin lymphoma: A case report. J Haematop 2010;3:23-8.
60. Lennert K, Mestdagh J. Hodgkin's disease with constantly high content of epithelioid cells. Virchows Arch A Pathol Pathol Anat 1968;344:1-20.

61. Suchi T, Lennert K, Tu LY, Kikuchi M, Sato E, Stansfeld AG, *et al*. Histopathology and immunohistochemistry of peripheral T-cell lymphoma: A proposal for their classification. J Clin Pathol 1987;40:995-1015.
62. Lennert K, Mohri N, Stein H, Kaiserling E. The histopathology of malignant lymphoma. Br J Haematol 1975;31:193-203.
63. Summers TA Jr, Rush W, Aguilera N, Lupton G. Cutaneous involvement in the lymphoepithelioid variant of peripheral T-cell lymphoma, unspecified (Lennert lymphoma). Report of a case and review of the literature. J Cutan Pathol 2009;36 Suppl 1:25-30.
64. Geissinger E, Odenwald T, Lee S, Bonzheim I, Roth S, Reimer P, *et al*. Nodal peripheral T-cell lymphomas and, in particular, their lymphoepitelioid (Lennert's) variant are often derived from CD8+cytotoxic cells. Virchows Arch 2004;445:334-43.
65. Feller AC, Griesser GH, Mak TW, Lennert K. Lymphoepitelioid lymphoma (Lennert's lymphoma) is a monoclonal proliferation of helper/inducer T cells. Blood 1986;68:663-7.
66. Kim H, Jacobs C, Warnke RA, Dorfman RF. Malignant lymphoma with a high content of epithelioid histiocytes: A distinct clinicopathologic entity and a form of so-called "Lennert's lymphoma". Cancer 1978;41:620-35.
67. Burke JS, Butler JJ. Malignant lymphoma with a high content of epithelioidhistiocytes (Lennert's lymphoma). Am J Clin Pathol 1976;66:1-9.
68. Krishnan B, Morgan GJ. Non-Hodgkin lymphoma secondary to cancer chemotherapy. Cancer Epidemiol Biomarkers Prev 2007;16:377-80.
69. Norbut AM, Foulis PR, Bellot PA. Lymphoeptelioid cellular lymphoma (Lennert's Lymphoma) in association with malignant lymphoma, histiocytic type. Am J Clin Pathol 1980;73:597-602.
70. Nakamura S, Takagi N, Kojima M, Mootori T, Kitoh K, Osada H, *et al*. Clinicopathologic study of large cell anaplastic lymphoma (Ki-1 positive lymphoma) among the Japanese. Cancer 1991;68:118-29.
71. Swerdlow AJ, Douglas AJ, Hudson GV, Hudson BV, Bennet MH, MacLennan KA. Risk of second primary cancer after Hodgkin's disease by type of treatment: Analysis of 2846 patients in the British National Lymphoma Investigation. Br Med J 1992;304:1137-43.
72. Henry-Amar M. Second cancer after the treatment for Hodgkin's disease: A report from the International Database on Hodgkin's Disease. Ann Oncol 1992;3 Suppl 4:117-28.
73. Aisenberg AC. Problems in Hodgkin's disease management. Blood 1999;93:761-79.
74. Scully RE, Galdabini JJ, McNeely BU. Case records of the Massachusetts General Hospital. N Engl J Med 1980;302:389-95.
75. Amin R, Anthony P. Non-Hodgkin's lymphoma following successful treatment of Hodgkin's disease. Clin Radiol 1986;37:483-6.

How to cite this article: Norval EJ, Raubenheimer EJ. Second malignancies in Hodgkin's disease: A review of the literature and report of a case with a secondary Lennert's lymphoma. J Oral Maxillofac Pathol 2014;18:90-5.

Source of Support: Nil. **Conflict of Interest:** None declared.