AFRICAN JOURNAL OF MEDICINE and medical sciences

VOLUME 32, NO 1 MARCH 2003

EDITOR
B. O. OSOTIMEHIN

ASSISTANT EDITOR
A. O. UWAIFO

ISSN 1116—4077

Afr. J. Med. med. Sci (2003) 32, 59-63

Primary extranodal non-hodgkin's lymphoma of the upper aerodigestive tract - a descriptive analysis of the pattern seen in the University College Hospital, Ibadan

PA Onakoya[+], OA Adeyi[*], OGB Nwaorgu[+], KO Ojemakinde[*] and JO Thomas[*]
Department of Otorhinolaryngology[+], and Department of Pathology[*], UCH, Ibadan, Nigeria

Summary

This retrospective review highlights primary extranodal non-Hodgkin's lymphoma (NHL), of the upper aerodigestive tract as seen in Ibadan over a ten-year period. There was a male preponderance (m:f ratio of 2:1), with a mean age of 42.5 years and a bimodal age presentation at the fourth and fifth decades. The Waldeyer's ring was the commonest affected site while the tonsil is the highest involved subsite. Sixty-eight percent of the patients had regional lymphadenopathy and thirty eight percent also 'B' symptom at presentation. The peculiar presentations of this NHL are the short duration (10 months) of symptoms, mainly intermediate/high grade diffuse large cell lymphoma especially in the Waldeyer's ring and sinonasal region with absence of low-grade small cell lymphoma. The majority of patients (64.3%) presented with Stage IV disease, which shows that the disease has an aggressive course with high mortality and generally poor outcome with 53.6% of the patients dead within one-year onset of symptoms. The overall mean survival period was 14 months. Comparison of the median survival of the patients that died when matched with the site, Ann Arbor staging, histological grade/subtype and treatment modality yielded no significant differences. These further confirm the aggressive nature of the disease in our environment.

Keywords: *Extranodal non-Hodgkin's lymphoma, upper aerodigestive tract*

Résumé

Une rèvue retrospective a Ibadan durant une pèriode de 10 ans montre un cas de lymphome extra-nodale primaire de non-Hodgkin sur la voie digestive supèrieure. Il y avait une prèponderance de males (m:f, 2:1) avec une moyenne de 42.5 ans. Une rèpresentation bimodale du quatrième au cinquième annèes, le cercle de Waldeyer ètait le cotè commun , plus affectè alorsque la pallaite est la sous couche la plus exposèe. Soixante huit pour cent des patients avait le lymphadènopathie règionale et 38% avait des symptomes B2 a la presentation .Les signes pèculaires de ce NHL sont des symptomes de courte durèe (10 mois),inclu principalement la diffusion faible et rapide des large cellules lympome espècialement dans le cercle de Waldeyer et le règion sino-anale avec la maladie a l'ètape IV. Ceci montre que la maladie a une suite aggrèssive avec une grande mortalitè et gèneralement de 55.6% de dècès par an et de faible revenu. La pèriode moyenne gènerale de suivi ètait de 14 mois comparaison de la pèriode mèdiane de suivi et mort, et la localitè, sous-type histopathologique et la modalitè de traitement produisait des diffèrences non-significative. Ces rèsultants confirment la nature aggrèssive de cette maladie dans cette ennvironement.

Introduction

The frequency and distribution of primary extranodal lymphoma are of considerable interest globally, especially with the increasing recognition of AIDS-related lymphomas. Recent report of an eighteen-year review (1980 – 1998) from this region indicated a rising frequency of extranodal lymphomas with a striking three-fold increase in the frequency of nasopharyngeal lymphoma during the last eight years (1991 – 1998) of the study [1].

Mucosa associated lymphoid tissue (MALT) associated extranodal lymphoma commonly affects the head and neck region, with the frequency ranging from 10% - 5% especially in the nose and throat[2-4]. The Waldeyer's ring, the nasal and paranasal sinuses are commonly affected [5-7].

The clinical presentations of these tumours are variable and difficult to distinguish from other destructive neoplastic and non-neoplastic conditions, like fungal infection [8]. This differentiation is very important in an environment where fungal disease may abound [9]. In addition to the primary site affected, the histological subtype and staging are known to influence the choice of treatment and the prognosis of these tumours [5].

In spite of the high frequency of non-Hodgkin's lymphomas (NHL) in Ibadan, and the rising trend of extranodal lymphomas (ENHL) [1], there is paucity of information on primary upper aerodigestive tract lymphomas in this environment. In view of this and the poor recognitions of these cases, this retrospective review

Correspondence: Dr PA Onakoya, Department of Otorhinolaryngology, University College Hospital, Ibadan, Nigeria
E-mail: paonak@yahoo.com

was carried out to highlight the clinical features, natural history and response to available therapy of primary extranodal NHL of the upper aerodigestive tract seen in Ibadan over a ten-year period.

Materials and methods

All cases of non-Hodgkin's lymphomas with extranodal manifestations registered in the Ibadan Cancer Registry, UCH, from 1989 to 1998 were reviewed retrospectively. Cases with upper aerodigestive tract involvement at presentation were selected and studied, while cases with generalized lymphadenopathy with or without involvement of extranodal sites were excluded.

The clinical records of these patients were retrieved and reviewed for age, sex, site of primary tumour, presenting features, treatment options and the eventual outcome. The clinical staging was done retrospectively using the Ann Arbor staging [10].

The histological sections of the cases were retrieved and reevaluated/reclassified according to the Working Formulation[11]. Due to non-availability of appropriate facilities in our hospital at the time of this review, immunohistochemistry and cyogenetics were not done on these patients.

Clinical response was classified into good, partial or no response using the following criteria:

a. Good response to therapy was considered to be clinical improvement in terms of total disappearance of symptoms and/or the primary tumour mass and the general well-being of the patient
b. Partial response was considered as absence of symptoms but persistence of the primary tumour mass with slight clinical improvement in general well-being while
c. No response as persistence if both the symptoms and the primary tumour mass with rapid deterioration of general well-being of the patient.

The findings were then analysed using Generalised Wilcoxon (Breslow), especially for Kaplan-Meier survival method in the Epi-2000 multivariant system and the results presented in tabular and graphical forms.

Results

A total of 450 cases of NHL of various regions of the body were recorded in the Ibadan Cancer Registry, UCH, Ibadan, from 1989 to 1998. Only thirty-five of these with primary ENHL of the aerodigestive tract were included in the study after applying the exclusion criteria, out of which 28 patients' clinical data were available for analysis.

Age, sex and site distribution

Of the twenty-eight patients with primary ENHL of the aerodigestive tract, nineteen (68%) were male and nine (32%) were female, giving a male to female ratio of 2.1.

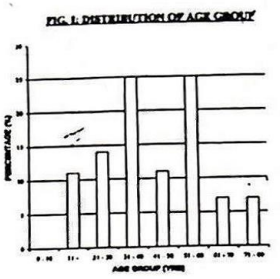

Fig. 1: Distribution of age group.

The age range was 12 years to 75 years, with a mean age of 42.5 ± 17.9 years. There was a bimodal high frequency of occurrence between age groups 31–40 and 51–60 years (Fig. 1). Seventeen patients (60.7%) had their tumour in the Waldeyer's ring while eight patients (28.6%) and three patients (10.7%) had primary involvement of the sinonasal and nasal regions, respectively.

Table 1: Major clinical features according to site and origin.

Clinical Features	Nose	Sinonasal	Naso-pharynx	Oro-pharynx
Symptoms				
Nasal obstruction	3	8	7	-
Epistaxis	2	7	3	-
Difficulty in breathing	2	2	3	-
Cheek swelling	-	6	-	-
Diplopia ± loss or reduced vision	-	4	1	-
Otalgia/Tinnitus/reduced hearing	-	1	2	3
Dysphagia	-	-	2	3
Trismus	-	-	2	6
Lump in the throat	-	-	-	9
Sore throat	-	-	-	6
Weight loss	-	2	2	6
Signs				
Nasal mass	3	6	1	-
Widening of nasal bridge	1	-	-	-
Septal perforation	2	-	-	-
Palatal ulceration/fistula	-	5	-	1
Palatal bulge	-	4	-	-
Proptosis ± blindness	-	1		-
Nasopharyngeal fullness/mass	-	-	7	-
Tonsillar mass ± ulceration	-	-	-	8
Cervical lymphadenopathy	-	4	7	8
CNS involvement	-	3	2	3

Clinical features

The presenting features in twenty-seven patients (96.4%) were directly but not exclusively referable to the site of the lesion, while the diagnosis of ENHL was incidental in the last patient. Physical examination however revealed features of advanced disease such as CNS involvement, weight loss and proptosis in eight patients (28.6%) with sinonasal, nasopharyngeal and oropharyngeal lesion at presentation as shown in (Table 1). Nineteen patients (68%) had palpable regional nodes draining the sites of lesion. The mean duration of symptoms at presentation was 10 ± 9.4 months (range 2 – 36 months), showing that patients generally presented late.

A total of 18 patients (64.3%) presented with stage IV disease, all of whom had primary involvement of the sinonasal and the Waldeyer's ring (Table 2). The three patients with nasal involvement all presented with Stage I disease, without nodal or regional spread.

Table 2: Staging according to site.

STAGE	Nasal	Sinonasal	Waldeyer's Ring		Total
			Nasopharynx	Oropharynx	
	n = 3 (%)	n = 8 (%)	n = 7 (%)	n = 10 (%)	n = 28 (%)
I	3 (100)	-	-	-	3 (10.8)
II	-	-	1 (14.2)	1 (10)	2 (7.1)
III	-	-	3 (42.9)	2 (20)	5 (17.8)
IV	-	8 (100)	3 (42.9)	7 (70)	18 (64.3)

Histological classification/grade

All the tumours were of either intermediate or high grade lymphoma types in 61% and 39% of patients, respectively, with no diagnosis of low-grade lymphoma. The commonest histological subtype was the diffuse large cell lymphoma constituting 61% of the tumours; while the remaining 39% was diffuse mixed small and large cell subtype.

Treatment and outcome

The informed choice of treatment was influenced by the age, clinical features/staging, histological type and the general status of these patients. Radiotherapy was given to nine patients (32%), chemotherapy to two patients (7%) and combined radiation and chemotherapy to thirteen patients (47%). Four patients (14%) did not receive any treatment either because they absconded or died of the disease before treatment commenced. All the patients who received radiotherapy and ten of the thirteen patients given combined therapy had either Stage III or IV diseases. The two patients who received chemotherapy alone had Stage IV disease.

The outcome of treatment is difficult to assess in this retrospective review, since subsequent follow-up after the initial treatment was lacking in most early records. However, out of the twenty-four patients that received treatment as documented, eleven (45.8%) had good clinical response and nine (37.5%), partial response while four (16.7%) had no response.

In all, fifteen patients (53.6%) died of Stage IV disease within one year of presentation of symptoms. The mean survival period was 14.0 ± 10.8 months (range 3 – 32 months). Among these fifteen patients, twelve received treatment and their average survival period was 16 months while the remaining three patients without treatment had an average survival period of 7 months. Comparison of the median survival of the patients that died when matched with the site, Ann Arbor staging, histological grade/subtype and treatment modality yielded no significant differences, that is, p = 0.675, 0.325, 0.130, 0.153 and 0.191, respectively (Table 3).

Table 3: Statistical summary of the survival according to different parameters using the generalised wilcoxon.

Parameters	Statistics	Degree of Freedom	P value
Ann Arbor classification	0.9704	1	0.32451
Site	1.5328	3	0.67472
Grade	2.2911	1	0.13012
Subtype	2.0423	1	0.15298
Treatment	4.7453	3	0.19144

The majority of those who died had the progression of the disease with further evidence of distant spread to the vertebral bodies, chest, abdominal organs and central nervous system especially in those that had the initial partial response to treatment. Three patients with oropharyngeal NHL had initial complete response with no evidence of recurrence at the primary site, but later developed dissemination to distant organs 4–6 months after the completion of the initial treatment.

Nine patients (37.5%) were lost to follow-up after the initial two or three visits, thereby making it difficult to

identify those with relapse of the disease. However, three patients (12.5%) are presently on treatment.

Discussion

A rising frequency of nasopharyngeal lymphoma has been reported in recent years from Ibadan and this disease poses some diagnostic problem in view of its variable manifestations and late presentation in this environment[1]. This study reviews the clinicopathological profile of this aerodigestive extranodal NHL as seen in Ibadan.

It was observed in this series that these tumours have a male preponderance (M:F ratio of 2:1); with a mean age at presentation of 42.5 years. This is slightly lower than 55 – 66 years quoted in other studies done in America and Japan [5, 7,12]. A bimodal age presentation was also noted, this may however be a misrepresentation because of the small number of patients.

The Waldeyer's ring was confirmed as the commonest affected site, while the tonsil was the highest subsite involved as comparable with other studies [2, 5-7,13,14]. The disease is known to remain localised for a very long period before clinical evidence of regional spread [15, 16]. In our study, 68% of the patients presented with regional lymphadenopathy that is similar to reports by Hanna and co-workers[14]. Also, patients presented very late despite the early symptomatology of the disease.

It is interesting to note that the diagnosis of lymphoma can often be suggested on fine needle aspiration cytology or excision biopsies of the regional enlarged nodes. It is therefore important to screen all patients with cervical nodal enlargement positive for lymphoma for primary sinonasal or naso-/oropharyngeal lymphomas. However, this will require the interdisciplinary cooperation of all those involved in the management of this disease in order to enhance the early detection of the primary site in the head and neck region.

Many of the cases presented with local or regional symptoms and were observed to be associated with 'B' symptoms in 38% of cases[17]. These 'B' symptoms (such as significant fever, night sweats or unexplained weight loss exceeding 10% of normal body weight) in patients are associated with an aggressive disease and is known to occur in 40 – 50% of patients at presentation[18]. The peculiar presentation of this disease observed in our study included the short duration (10 months), with progressive painless and multiple neck swellings, which usually prompt patients to seek medical attention for cosmetic reasons. The common symptoms are usually nasal obstruction, nasal mass, epistaxis and difficulty in breathing and/or cheek swelling. However, there is often a unilateral tonsillar enlargement, which may ulcerate and cause dysphagia, lump in the throat, sore throat and trismus in patients with oropharyngeal lymphoma. These symptoms could mimic any non-neoplastic or neoplastic diseases.

The high-grade diffuse large cell tumours were the commonest histological type observed especially in the Waldeyer's ring and the sinonasal site while the low-grade small cell lymphoma was not observed. Although T-cell tumours are considered common in the sinonasal and nasopharyngeal regions, unfortunately, because of limited facilities, the immunotyping of these tumours could not be done[19,20,21]. However, previous report from Ibadan has documented that B-cell tumours are commoner [7].

There is no general consensus as to the best treatment option for aerodigestive lymphomas. The age, symptoms, clinical staging, histological type and general status of the patient influence the choice of treatment. The majority of the patients (47%) had combined therapy for all the clinical stages, while radiotherapy alone was offered to 32% of those with advanced stage. However, because of the small number of cases and the common late presentation of our cases, the efficacy of the different treatment options cannot be adequately assessed.

The disease outcome is very poor in our environment with 53.6% dead within one year of the onset of symptoms and the average survival period 14 months. Generally, early stage disease has better prognosis, unfortunately our patients present with advanced disease and 'B' symptoms. It is uncertain whether this poor prognosis is related to the late presentation or the natural history of the disease, which will require further evaluation in our environment. This Poor prognosis in terms of the survival could not have been influenced by the treatment modalities available to the entire patients that died because the clinical staging and histological grade/subtype that were not significantly different were features of an advanced disease.

Though the increasing frequency of sinonasal lymphomas has recently been associated with HIV infection, the HIV status of our patients is unknown in the early part of this review while those done between 1994 and 1998 were negative. However, the association in this environment is yet to be determined but it is a subject for further study. In conclusion, this review highlights the clinicopathological profile of upper aerodigestive tract extranodal lymphomas in Ibadan.

Acknowledgements

We acknowledge the part played by Miss Bidemi Badru in the analysis of the data especially the survival analysis.

References

1. Thomas JO, Ogunsanwo BO and Ogunbiyi AO. Highlights of Extranodal Lymphomas in Ibadan. Centr. Afr. Med. Journ., 1999; 45: 173 – 175.

2. Freeman C, Berg JW and Cutler SJ. Occurrence and prognosis of Extranodal Lymphoma. Cancer, 1972; 29: 252 – 260.
3. Rudder RA, Ross ME and Dehellis RA. Primary Extranodal Lymphoma. Cancer, 1978; 42: 406 – 416
4. Kong JS, Fuller LM, Butler JJ, Barton JH, Robbins KT, Velasquez WM, and Sullivan JA. Stages I and II non – Hodgkin's Lymphoma of Waldeyer's Ring and the neck. Am Journ Clin. Oncol, 1984; 7: 629 – 639.
5. Conley SF Staszk C, Clamon GH and Maves MD. Non-Hodgkin's Lymphoma of the head and neck: The University of Iowa experience. Laryngoscope, 1987; 97: 291 – 300.
6. Stenson KM, Wolf GT, and Urba S. Extranodal non-Hodgkin's Lymphoma of the head and neck: presentation in facial bones. Am. Journ. Of Otolaryngol. 1996; 17: 276 – 280.
7. Shima N, Kobashi Y, Tsutsui K, Ogawa K, Maetani S, Nakashima Y, Ichijima K and Yamabe H. Extranodal non-Hodgkin's lymphoma of the head and neck. A clinicopathologic study in the Kyoto-Nara area of Japan. Cancer, 1990; 66: 1190 – 1197.
8. Larson DL, Robbins KT and Butler JJ. Lymphoma of the Head and Neck: A diagnostic dilemma. Am. Journ. Surg., 1984; 144: 433 – 437.
9. Lasisi OA, Nwaorgu OGB and Akang EEU. Sinus Mycosis – A cause of persistent chronic sinusitis. Nig J Surg, 1997; 4: 77 – 80.
10. Carbone PP, Kaplan HS, Musshorf K, Smithers DW, and Tubicana M. Report of the committee on Hodgkin's Disease Staging Classification. Cancer Res., 1971; 31: 860 – 861.
11. The Non-Hodgkin's Lymphoma Pathologic Classification Project. National Cancer Institute sponsored study of classification of Non-Hodgkin's Lymphoma. Cancer, 1982; 49: 2112 – 2135.
12. Wallace C, Ramsay AD and Quiney RE. Non-Hodgkin's Extranodal Lymphoma, a clinico-pathological study of 24 cases involving head and neck sites JLO, 1988; 102: 914 – 922.
13. Neilly IJ, Dawson AA, Russell D and Laing MR. Non-Hodgkin's Lymphoma of the head neck: experience in the Grampian area. JLO, 1990; 104: 972 – 975.
14. Hanna E, Wariamaker J, Adelstein D, Tubbs R, and Lavertu P. Extranodal Lymphomas of the head and neck: A 20-year experience. Arch. Otolaryngol Head and Neck Surg., 1997; 123: 1318 – 1323.
15. Issacson P and Wright D. Extranodal Malignant Lymphoma arising from mucosa associated lymphoid tissues. Cancer, 1985; 53: 2515 – 2524.
16. Banfi A, Bonnadonna G, Ricci SB, Milani F, Molinavi R, Monfardini S and Zucahi R. Malignant Lymphoma of Waldeyer's Ring. Natural History and Survival after Radiotherapy. Bri. Med. Journ, 1972; 3: 140 – 143.
17. Fierstein JT and Thawley SE. Lymphoma of the head and neck. Laryngoscope, 1978; 88: 582 – 593.
18. Skarin AT and Dorfman DM. Non-Hodgkin's Lymphomas: Current Classification and Management. Ca Cancer J. Clin, 1997; 47: 351 – 372.
19. Chan JKC, Ng CS, Lau WH, and Lo STH. Most nasal/nasopharyngeal Lymphomas are peripheral T-cell neoplasm. Am. Journ. Surg. Pathol, 1987; 11: 418 – 429.
20. Armitage JO, Greer JP, Lavine AM, Weizenburger DD, Formenti SG, Bast M, Conley S, Pierson J, and Cousar JB. Peripheral T-cell Lymphoma. Cancer, 1989; 63: 158 – 163.
21. Robbins KT, Fuller LM, Vlasak M, Osbourne B, Jing BS, Velasquez WS and Sullivan JA. Primary Lymphoma of the nasal cavity and paranasal sinuses. Cancer, 1985; 56: 814 – 819.