Clinical Medicine Insights: Ear, Nose and Throat

ORIGINAL RESEARCH

Nasopharyngeal Cancer in Sudan: Epidemiology, Clinical and Histological Characteristics

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Abstract

Objectives: To study the epidemiology, clinical features, staging, etiology and pathology of nasopharyngeal cancer in Sudan.

Study design: This is a retrospective study.

Setting: Ear, Nose and Throat Department Khartoum Teaching Hospital, Khartoum City, Sudan.

Subjects and methods: Patients suspected to have nasopharyngeal cancer were assessed during the period March 2004 to May 2010. Data from confirmed cases was obtained; it included clinical and epidemiological information.

Results: Three hundred and eighty five cases were studied. Bimodal age distribution of the disease was noted with two peaks, one at 15–19 years and one at 50–54 years. The male to female ratio was 2.6:1 and a distinct geographical distribution of the disease was noted, with clustering of cases in the towns of Dilling, Kadogli and the surrounding rural area of the Nuba Mountains. These areas in the Western States were reported to be of high background radiation due to naturally produced radioactive uranium. The Nuba tribe headed the list among other tribes, demonstrating a clear ethnic predilection.

Sixty-eight cases presented at stage IV. There was a predominance of Type II (15.58%) and Type III (65.97%). Patients were treated by neoadjuvant chemoradiotherapy.

Conclusions: NPC is an important form of cancer in Sudan. Some tribes are significantly more affected than others. Patients present with advanced disease. Environmental and genetic factors need further studies. Screening at risk populations that aim at early diagnosis and management of patients is recommended.

Keywords: nasopharyngeal cancer, Sudan, epidemiology, clinical staging, pathology, etiology

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Introduction

Clinically speaking, nasopharyngeal cancer (NPC) is one of the most deceptive cancers[1] and it has a complex interaction between genetic, environmental, dietary and viral factors in its etiology.[2,3] This makes it one of the most challenging diseases to clinicians and researchers.

Genetic susceptibility is proposed as a risk factor for the development of nasopharyngeal cancer. Certain haplotypes of human leukocyte antigens (HLA) are associated with NPC; these include: HLA-A2, HLA-B46 and HLA-B58.[4,5]

Nasopharyngeal cancer has a distinct racial distribution in countries with multiracial populations; this has been reported in high risk countries like China,[6] and intermediate risk countries like Malaysia[6,7] and Sudan.[8] Even the low risk countries like North America and Britain are not exempt from this distinct ethnic predilection.[9] The racial distribution and the fact that certain haplotypes are associated with this malignancy support genetic susceptibility to this cancer.

The link between NPC and Epstein-Barr virus (EBV) is well established, as the sera of patients with this malignancy were found to contain precipitating antibodies against the virus;[10] the virus genome was also detected in biopsy material from most NPC patients.[11]

Environmental factors also play a role in the etiology of this disease, which is evident from the remarkable geographical distribution seen even in countries inhabited by a single ethnic group such as China.[12]

NPC forms around 6% of all cancer cases in the Sudan Cancer Registry (SCR) records, and 7% at the Radiation Isotope Center—Khartoum (RICK). Although Sudan is categorized as an intermediate risk country, there have been only two reports since 1983.[8,13]

This paper describes the epidemiology, clinical manifestations and tribal distribution of NPC in Sudan. It shows that the disease is more common in certain tribes in the country and that patients report in advanced stages of the disease.

Objectives

To study the epidemiology, clinical features, staging, possible etiology and pathology of nasopharyngeal cancer (NPC) in Sudan.

Materials and Methods

Cases of biopsy-proven NPC, who attended the Ear, Nose and Throat (ENT) Department of the Khartoum Teaching Hospital between March 2004 and May 2010, were investigated.

The ENT department of Khartoum Hospital is the national center for ENT diseases. Data collected on all patients included: age, gender, self-reported ethnic group, residence, nutritional habits, smoking and alcohol use as well as clinical data, pathology results and staging according to the AJCC/UICC 2002 system.[14]

Patients were assessed clinically; where nasopharyngoscopy was performed, nasopharyngeal specimens were taken for histological examination. Evaluation of locoregional extension was assessed by MRI and/or CT scan. Patients with histologically proven NPC, who signed an informed consent form, were included in the study; patients with incomplete clinical data

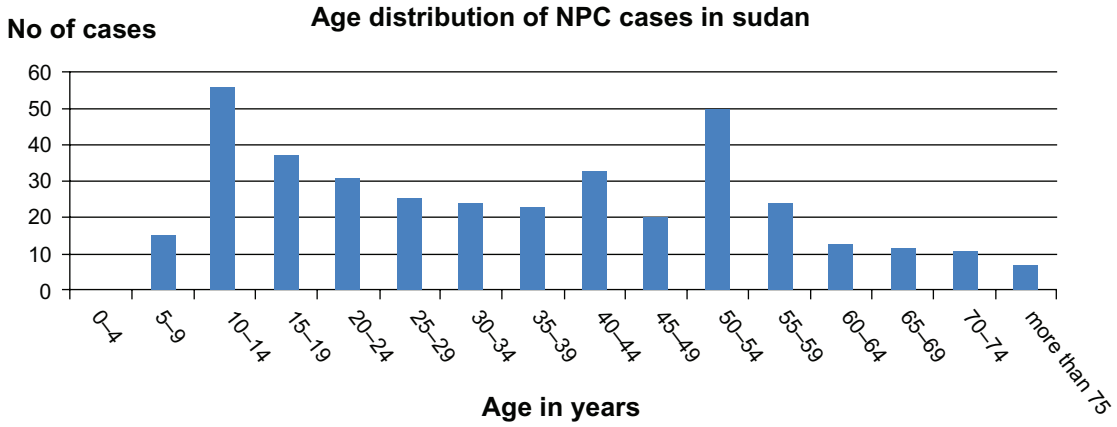

Figure 1. Age distribution in years of studied patients. A bimodal pattern is observed, with an early peak at the 15–19 years and a later peak at 50–54 years.

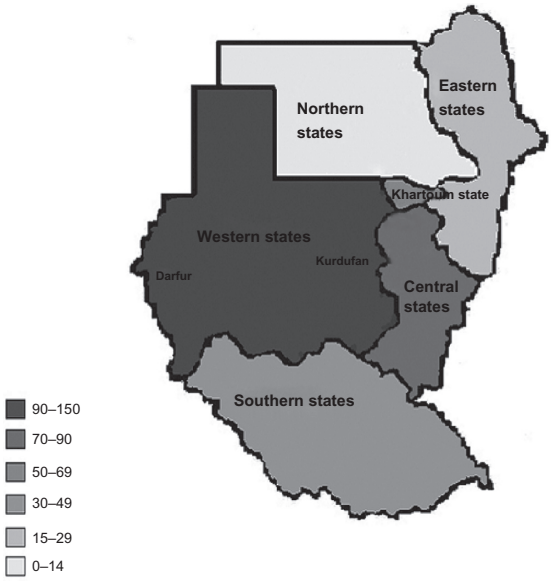

Figure 2. Distribution of NPC patients in different states of Sudan. Patients were evenly distributed according to population density except for the Western States, where a higher number than expected is reported. (*P*-value = 0.00004836).

were not included. Patients that were diagnosed with nasopharyngeal lymphoma were excluded.

Confirmed cases of NPC were sent to RICK for management.

Data was analyzed using SPSS version 15. Statistical significance was determined by the two-tailed *P*-value using Fisher's test.

This research was approved and ethically cleared by the Ethical Committee Board of the Institute of Endemic Diseases, University of Khartoum in March 2005.

Results

The total number of NPC patients was 385. The age distribution showed two peaks: one at 15–19 years and the other at 50–54 years, as shown in Figure 1. The male-to-female ratio was 2.6:1.

The geographical location of patients according to their origin is shown in Figure 2. Western states showed the highest percentage, accounting for 36.62% of all cases; 75% of these were from Kurdufan state and 25% were from Darfur state. On the other hand, the distribution of cases from other states is equivalent to or less than expected according to population density, as shown in Table 1.

Detailed distribution of patients in the western part of the country showed clustering of patients in the Kadugli and Dilling areas of the Nuba Mountains, as shown in Figure 3.

The Nuba tribe accounted for 17.1% of cases, a significantly higher percentage than expected (see Table 2), followed by the Denka tribe (12.98%) and the Galien tribe (9%). Both the Gawama'h and Messairy tribes accounted for 3.9%; other tribes showed nearly even distribution.

The mean age of Nuba patients was 39 years and that of non-Nuba patients was 41 years. The *P*-value was less than 0.0001, stating no significant statistical difference.

Smoking and alcohol consumption were found to be well correlated with NPC when data from this series were compared to a similar number of non-NPC patients attending the ENT hospital at the time of the study. On the other hand, lifestyle factors such as nutrition and cooking habits showed no correlation with NPC in our series.

Symptoms and signs at presentation, in order of frequency, were audiological in 89% of patients, followed by cervical lymphadenopathy in 78% and

Table 1. Geographical distribution of NPC patients in Sudan, compared to geographical distribution of the general population. *P*-value is calculated using Fisher's exact test.

Region	Expected percentage	Observed percentage	Population of the region (N)	Expected cases (N)	Observed cases in the study (N)	*P*-value (two-tailed)
West	23.07%	36.62%	9,000,000	88	141	<0.0001
East	10.24%	5.71%	4,000,000	39	22	0.032
North	1.53%	3.11%	600	0	12	0.0004
South	20.50%	12.46%	8,000,000	77	48	0.0061
Khartoum	15.38%	17.40%	6,000,000	57	67	0.03776
Central Provinces (apart from Khartoum)	23.22%	22.07%	12,000,000	89	85	0.7961
Total	100	100	39,600,000		385	

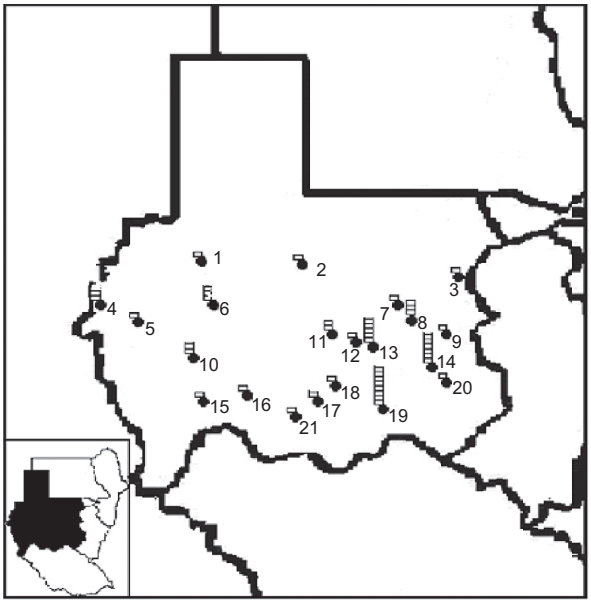

Figure 3. The distribution of patients in western Sudan according to their origin; mean residence is 27 years. The total number of patients distributed in western states is 141, which accounts for 36.62% of all patients.
Notes: Each square represents three cases.
1. Kutum, 2. Hamrrat Esheikh, 3. Um Sayala, 4. Geneina, 5. Zalinje, 6. Fashir, 7. Bara, 8. El Obeid, 9. Um Ruwaba, 10. Nyala, 11. En Nahud, 12. Abu Zabad, 13. Dilling, 14. Nuba Mountains, 15. Buram, 16. De'en 17. Babanusa, 18. El Fula, 19. Kadugli, 20. Abu Gubeiha, 21. El Muglad.

nasal symptoms in 69.7%. Cranial nerve involvement was present in a considerable number of patients, as it occurred in 39.3% of patients. Some effects of cranial nerve involvement are illustrated in Figures 4, 5 and 6.

Patients were classified at presentation according to the AJCC/UICC 2002 system[14] as shown in Table 3. Nearly 68% of cases were classified as stage IV disease.

In all cases, biopsies were taken from the nasopharynx under local anesthesia; it was conclusive in 97.4% of cases. The remaining 2.6% were re-biopsied under general anesthesia to reach a firm diagnosis.

The World Health Organization (WHO) histological classification of nasopharyngeal specimens is shown in Table 4. Types II and III, and mixed II and III accounted for 96.87%, whereas Type I was identified in only 1.18%.

Patients were followed up during treatment and three monthly thereafter. The initial response to treatment was excellent with regard to local control; details of outcome in terms of disease-free survival rates and residual disease are to be reported elsewhere.

Discussion

Sudan is a country with more than 15 main ethnic groups.[15] There is a clear tribal pattern of the disease in our study, where 17.1% of patients belong to the Nuba tribe, which is statistically significant. Nuba people are distributed in all states of Sudan; less than half of them, according to local reports, inhabit the Nuba mountains area. This is similar to the tribal pattern of NPC in a study conducted by Hidayatalla et al in 1983;[8] however, the remaining tribal distribution of Hidayatalla et al's study is different from that of ours. We observed that the Denka tribe, the biggest southern tribe, was second to Nuba in the prevalence of NPC.

The age distribution of our studied patients showed two peaks, in a manner resembling that of intermediate risk countries and different from that observed in endemic areas.[16] One peak was observed in the 15–19 year age group and the other peak was in the 50–54 year age group. The early peak and distinct tribal distribution reflect a genetic susceptibility, which necessitates further detailed investigations such as HLA typing to identify high risk populations.

Geological studies showed that radiation exposure rates around the Nuba Mountains are among

Table 2. Tribal distribution of studied patients (only the three commonest tribes are listed). The percentage of a specific tribe's distribution in relation to the general population is obtained from local reports. *P*-value is calculated using Fisher's exact test.

Tribe	Percentage in general sudanese population	Percentage in the study	Actual No.	Expected No.	*P*-value (two-tailed)
Nuba	6%	17.10%	66	23.1	<0.0001
Dinka	8%	12.98%	50	30.8	0.078
Gaaliin	6.25%	9%	34	24.06	0.2188

Figure 4. Multiple cervical lymphadenopathy, showing levels 2, 3, 4 and 5; note skin tethering.

the highest in the world in regard to background radiation. Radiation exposure in the Nuba Mountains is mainly due to uranium, a byproduct of usable rock phosphate fertilizers.[17,18] On one hand, the use of ground rock phosphate as fertilizers by local farmers would lead to direct external radiation exposure by handling and storage; on the other hand, inhalation of rock phosphate dust may increase internal exposure considerably. This could explain the clustering of patients around the Nuba Mountains area.

Figure 5. Complete ophthalmoplegia of the right eye in a patient presenting with ipsilateral nasopharyngeal mass but no palpable cervical lymph nodes.

Figure 6. Cranial nerve involvement raises the stage to T4. Note the deviation of the tongue, which signifies hypoglossal nerve involvement.

Recent studies showed that certain crops showed an increased accumulation of some metals that are contained in the soil, including radioactive substances.[19] Drinking water in the Nuba Mountains area, which is also used for irrigation of crops, could be contaminated with radioactive uranium and crops could accumulate radioactive metals. Studies are needed to verify this and its impact on health.

Histological classification of the samples resembles that of endemic areas, with a predominance of Types III and II. According to previous studies, these types are associated with high rates of EBV detection.[20]

Table 3. Stage classification of the study population, according to the AJCC/UICC system.[14]

Stage classification	No. of cases	Percentage
Stage I	11	2.85
Stage IIa	17	4.4
Stage IIb	29	7.53
Stage III	60	15.58
Stage IVa	96	24.93
Stage IVb	166	43.11
Stage IVc	6	0.015
Total	385	100

Table 4. Histopathology of nasopharyngeal tissue biopsy, according to the WHO classification.

Histology Type	N	Percentage
Type I	7	1.81
Type II	60	15.58
Type III	254	65.97
Mixed type II & III	56	14.54
Mixed type I & III	3	0.78
Salivary gland origin	2	0.51
Others	3	0.78
Total	385	100

The use of endoscopy has enabled accurate visualization of the nasopharynx and precise biopsy, as it is capable of diagnosing 97.4% of patients. Biopsy under local anesthesia is cost-effective in terms of hospital admission and it avoids the hazards of general anesthesia.

Unfortunately, about 68% of the cases were diagnosed at stage IV, which is a significantly high percentage of late presentation. Is it possible that this is due to difficulty in accessing the health care system and/or lack of patient knowledge about worrisome symptoms that might signal NPC.

Since prognosis is well correlated to the stage of presentation, conducting screening programs for at-risk populations could help in earlier diagnosis and probably a better prognosis.

Conclusions

Nasopharyngeal cancer in Sudan has a distinct tribal and geographic pattern. The age distribution of NPC has two peaks, an early peak and a late one. The tribal tendency of the disease and an early peak support a genetic predisposition; HLA typing is required in future studies. The second peak, histology and geographic distribution support the role of environmental factors.

Setting up screening programs for early diagnosis and management of NPC in high risk populations such as the Nuba tribe are advocated. Further studies are strongly needed to identify environmental factors that are involved in the etiology of NPC in Sudan, including radiation levels in drinking water and crops at Nuba mountains area.

Acknowledgements

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Disclosure

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material. Written consent was obtained from the patient or relative for publication of this study.

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