Original Article

Epstein-Barr Virus (EBV) Expression in Nasopharyngeal Carcinoma in Kano

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Abstract

Background: Nasopharyngeal carcinoma (NPC) is one of the most common types of head and neck cancers and has a distinct geographic distribution. However, the prevalence of Epstein-Barr virus (EBV) involvement in its development has been rarely studied in Nigeria. This study aims to evaluate the immunohistochemical expression of EBV in NPC cases. **Methods**: This was a retrospective study covering five years (2015 to 2019) and included all NPC cases diagnosed at the Department of Histopathology, Aminu Kano Teaching Hospital, Kano (AKTH). The collected data included patient demographic details, clinical information, histological diagnosis, and EBV Immunohistochemistry positivity. **Results:** NPC cases showed a bimodal age distribution, with a mean age of 40 years. The majority of patients were male, giving a male-to-female ratio of about 3:1. EBV positivity was observed in nearly half of the cases, more frequent in males than females. Keratinising squamous carcinoma was the most common subtype among EBV-positive tumours. **Conclusion**: This study highlights the distinct immunohistochemical profile of NPC within this population, emphasising the role of IHC as a vital, accessible tool for characterisation. Our findings underscore the necessity of integrating molecular EBV subtyping into routine diagnostics to refine risk stratification and personalise therapeutic strategies for NPC patients in this region.

Keywords: Nasopharyngeal carcinoma (NPC), Epstein-Barr virus (EBV), Immunohistochemistry, Nigeria.

Introduction

Nasopharyngeal carcinoma (NPC) is a malignancy of the nasopharyngeal respiratory epithelium characterised by unique geographical and racial variations.[1] In 2022, the International Agency for Research on Cancer reported 120,416 new cases globally (0.6% of all cancer diagnoses), with 73,476 deaths and a notable male predominance.[2] While incidence remains extremely rare in Western populations (<1 per 100,000), NPC is highly endemic in Southeast Asia and Southern China, where lifetime risk can reach 1 in 40.[3,4]

In the African context, nasopharyngeal carcinoma (NPC) is the most prevalent head and neck malignancy. The highest age-adjusted incidence rates are observed in North Africa, particularly in Tunisia and Algeria. In West Africa, Nigeria reports a significant burden, with NPC accounting for up to 39% of all head and neck cancers. [5,6]

Within Nigeria, regional data from Southwest Nigeria further highlight this burden, where NPC constitutes approximately 16.8% of head and neck malignancies. [7,8] Although NPC is most commonly

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diagnosed between the fourth and sixth decades of life, a secondary peak in incidence is observed among adolescents aged 11–18 years. [1,9]

The aetiology of Nasopharyngeal Carcinoma (NPC) is predominantly linked to chronic Epstein-Barr virus (EBV) infection, a critical biomarker for early detection and risk stratification.[10] Although most cases are EBV-associated, EBV-negative NPC highlights additional causative factors, including HIV, HPV, and environmental carcinogens such as cigarette smoke and formaldehyde.[10, 11] Genetic susceptibility, particularly high-risk HLA haplotypes (e.g., HLA-B46) and polymorphisms in immune-regulatory genes, further modulates this oncogenic process and predisposes risk. [10, 11]

Clinically, EBV drives aggressive tumour behaviour through latent proteins like Latent Membrane Protein 1 (LMP1) (expressed in most tumours). [10,12] promoting immune evasion, local invasion, and metastasis. Overexpression of EGFR and cell cycle dysregulation further contribute to poor prognosis. These etiological factors thus inform targeted screening, prognostic monitoring, and therapies. [13]

These etiological insights, which EBV is the primary driver, combined with genetic and environmental co-factors, have directly informed current clinical strategies for EBV-associated malignancies such as nasopharyngeal carcinoma. Population-based EBV screening in endemic areas, prognostic monitoring via circulating EBV markers, and personalised treatment approaches, including emerging targeted therapies and immunotherapies, serve as a powerful prognostic tool for risk stratification and treatment response assessment. [14]

Although NPC is one of the most common Head and Neck malignancies with a distinct geographical distribution, the frequency of EBV involvement in its pathogenesis has been scarcely studied in Nigeria, particularly in Northern Nigeria, where documented cases are rare, and EBV data are extremely limited compared to southern regions. Therefore, there is a pressing need to evaluate the immunohistochemical expression of EBV in NPC cases to fill the data gap, contribute to national epidemiology, inform potential screening or diagnostic strategies and enhance global insights into EBV-NPC association in non-endemic African settings.

Materials and Methods

This was a 5-year retrospective study of all cases of nasopharyngeal carcinomas diagnosed at the Department of Histopathology at Aminu Kano Teaching Hospital (AKTH) from January 2015 to December 2019. The minimum sample size was estimated using Cochran's formula, based on a 5-year prevalence of 4.4 per 100,000 reported in earlier studies, yielding a minimum required sample of 65 cases.

Inclusion Criteria

These records included requisition forms, histopathology reports, tissue blocks, and haematoxylin and eosin (H&E)-stained slides. The data retrieved included patient biodata, clinical information, histological diagnosis, and EBV Immunohistochemistry positivity.

Exclusion Criteria

Exclusion criteria included records with inadequate clinical information, missing archival slides and tissue blocks, and damaged tissue blocks.

Histopathological Diagnosis

The histopathologic diagnoses were made from old slides and classified according to the 2005 WHO classification of nasopharyngeal carcinomas. [5] In cases where slides were missing, faded, or broken, new sections were cut from archived formalin-fixed paraffin-embedded (FFPE) tissue blocks and stained with haematoxylin and eosin (H&E).

Immunohistochemistry Procedure

The DB-Biotech immunohistochemistry staining protocol was used to assess latent membrane protein-1 (LMP-1) expression in tumour cells. Abcam Anti-EBV Latent Membrane Protein 1 antibody (ab78113) was utilised, while the Abcam Expose Mouse and Rabbit Specific HRP/DAB 27 (ab80436) detection kit was employed to visualise the signals from the cells.

Sections were cut at 3 microns from tissue blocks and placed on 2 negatively charged APES-coated slides. These sections were then deparaffinized in xylene and rehydrated in decreasing concentrations

of alcohol. The 2 slides for each case were then processed for immunohistochemistry staining using anti-Epstein-Barr virus latent membrane protein-1(LMP-1) antibody. Heat-induced antigen retrieval was performed in 10 mM citrate buffer using a pressure cooker for 30 minutes. Endogenous peroxidase activity was blocked by treating the sections with hydrogen peroxide for 10 minutes before incubating with the primary antibodies for 45 minutes. After primary antibody binding, the signal was amplified using a horseradish peroxidase (HRP)-conjugated secondary antibody polymer and visualised with 3,3'-diaminobenzidine (DAB) chromogen. The sections were then counterstained with hematoxylin, dehydrated, and mounted with coverslips. All steps were performed at room temperature. Negative controls using skin tissue for LMP1 and positive controls using Hodgkin lymphoma Reed-Sternberg cells for LMP1 were included alongside the test samples to validate the staining.

Immunohistochemistry Interpretation

The slides were examined independently by 2 different pathologists under a light microscope, and the staining intensity was graded as follows:

Brown granular cytoplasmic and membrane staining was interpreted as positive for EBV LMP-1, while nuclear and para-nuclear brown dot staining was interpreted as a false positive.

Similar to the scoring pattern adopted by Li J et al. [15], LMP-1 was scored as:

0 <5% stained - Negative

15 – 25% - Weak

226 – 50% - Moderate

3>50% - Strong

0 was interpreted as Negative while 1, 2 and 3 were interpreted as Positive. [15]

Data Analysis

The data obtained were analysed using SPSS version 23, and the results were presented in the form of photomicrographs, figures, and tables. Quantitative data were summarised and shown as means/medians, ranges, and frequency distribution tables, while qualitative data were summarised and presented using frequencies and percentages. Statistical comparisons between groups were done using the Chi-square test as appropriate. The histopathological data included the distribution of histological subtypes by age and sex, as well as the relationships between age, sex, and histological subtype. These data were then correlated with the immunohistochemical expression of LMP1. Statistical significance was set at a 95% confidence interval, with a p-value of ≤0.05.

Ethical Consideration

Ethical approval was obtained from the Ethics and Scientific Committee of Aminu Kano Teaching Hospital, Kano, with approval number: NHREC/28/01/2020/AKTH/EC/2857.

Results

A total of 83 NPC cases were diagnosed during the five-year study period (2015 to 2019). Five (6%) cases were excluded for not meeting the inclusion criteria due to missing tissue blocks or exhausted tissues. Therefore, only 78 cases were analysed.

The age of the patients ranges from 12 to 81 years, with a mean of 40.8±13.5 years and a median of 35 years. The most common age group was 31 to 40 years (30.2%), while the least common was 10 to 19 years (7.7%). Nasopharyngeal carcinoma was more frequent in patients under 50 years (70%) than in older patients (30%).

Males constituted 60 (77%) of the 78 cases, and females made up the remaining 18 (23%), resulting in a male-to-female ratio of 3.3:1. The mean age for males was 41.9 ± 13.5 years, while for females it was 36.3 ± 13.5 years. The peak age among males was in the 31–40-year age group, whereas for females it was in the 21–30-year age group. Among males, NPC cases also showed a bimodal age distribution, with a higher peak in the 3rd decade and a lower peak in the 5th decade [Figure 1].

***Histologic Subtypes*:** Undifferentiated nasopharyngeal carcinoma was the most frequent histologic type, accounting for 38(49%) cases. This was followed by 27(35 %) cases of keratinising squamous cell carcinomas and 13(16 %) cases of non-keratinising squamous cell carcinomas [Table 1].

EBV (LMP-1) Expression: Thirty-five (45%) of the 78 NPC cases were EBV-positive, while the remaining 43 tumours (55%) were EBV-negative.

Among males, 31 (51.7%) of 60 cases were EBV-positive, whereas only 4 (22.2%) of the 18 female cases were EBV-positive. Among EBV-positive cases, keratinising squamous carcinoma showed the highest frequency of positivity, with 16 (46%) of 35 positive cases. [Table 1].

Age Group and EBV(LMP-1) expression: EBV (LMP-1) positivity was observed in 35(45%) of the 78 cases of NPC. Peak EBV positivity was found in the age group of 31-40 years, then declining progressively with increasing age. There was no statistically significant difference in the pattern of EBV expression with age (p= 0.03) [Table 1].

Morphologic subtype and EBV (LMP-1) Expression: Of the 27 keratinising squamous cell carcinomas, 59% were EBV+ and 41% were EBV-. Of the 13 non-keratinising squamous cell carcinomas, 53.8% were EBV+ and 46.2% were EBV-. Of the 38 undifferentiated carcinomas, 68.4% were EBV- and 31.6% were EBV+ [Figures 2-4].

Overall, EBV+/ phenotype was more frequent among the KSCC phenotypes and was least frequent among the NKSCC. These differences in phenotypic expression were found to be statistically significant (p = 0.015) [Table 1].

Table 1: Sex distribution and EBV positivity by histologic subtypes of nasopharyngeal carcinoma (NPC)

Histologic Subtype	Male	Female	Total (M:F Ratio)	EBV+	EBV-
KSCC	20	7	27 (2.8:1)	16	11
NKSCC	12	1	13 (12:1)	7	6
UDC	31	7	38 (4.4:1)	12	26
Total	63	15	**78 (4.2:1)**	35	43

Chi-square for sex distribution by subtype: 1.9095, p=0.38.

p-value for EBV pattern by subtype: 0.03.

Key: KSCC = keratinising squamous cell carcinoma; NKSCC = non-keratinising squamous cell carcinoma; UDC = undifferentiated carcinoma.

Discussion

A total of 78 cases of NPC were analysed in the five-year study period (2015 to 2019) in Aminu Kano Teaching Hospital.

Age and Sex: The age range was 12 to 81 years, with a mean of 40.8 ±13.5 years and a median of 35 years. A similar age pattern was observed in other regions of Nigeria and parts of Africa, including Ibadan, Sokoto, Jos, Maiduguri, and Nairobi in Kenya. In these studies, the ages range from 11 to 85 years, while the mean age range was 40 to 42. [16-18, 19, 20]

Our study revealed a significant male dominance in nasopharyngeal carcinoma (M: F ratio = 3.3:1), exceeding reported ratios from Northern Nigeria (2.1:1) while closely matching data from Southern Nigeria (3.5:1). This gender difference suggests possible regional variations in risk factors or genetic susceptibility across Nigeria. [16-18, 20, 21] Males showed a peak incidence of NPC a decade earlier than females, indicating sex-specific risk patterns. We observed a bimodal age distribution with peaks in the third and fifth decades, consistent with findings from Ibadan, Lagos, Ghana, and Ethiopia, reinforcing the pattern's consistency across various African populations.

Histologic Subtypes: Our study found undifferentiated carcinoma as the most common histologic subtype (49%), followed by keratinising and non-keratinising squamous cell carcinomas. This distribution matches findings from Ilorin, Nigeria, reported by Alabi *et al.* [26] (71%) and Sidler et al. [27] *in* Switzerland (70%). However, other global studies indicate non-keratinising carcinoma as the most prevalent (>90%) [16-18,22-27], reflecting classification differences: the undifferentiated subtype (formerly WHO type III, ~80%) now falls under non-keratinising carcinoma, while the differentiated subtype (formerly WHO type II) accounts for a smaller proportion.

EBV (LMP-1) Positivity; Our study showed an almost equal distribution of EBV (LMP-1)

positivity in NPC cases, with 45% EBV-positive and 55% EBV-negative tumours. This predominance of EBV-negative cases aligns with patterns in several non-endemic or low-incidence populations, including Israel by Kuten *et al*. [28], Morocco by Tabyaoui *et al*. [29], Spain by Vera-Sempere et al. [30], and Zaria (Nigeria) by Yates *et al.* [21]. Although our study did not evaluate clinical outcomes, existing evidence strongly links this phenotype to poor prognosis and lower survival rates. [31-33] These findings suggest potentially unfavourable outcomes for patients in our study group, though definitive conclusions require prospective outcome studies in this region.

Keratinising Squamous Cell Carcinoma (KSCC) showed the strongest association with EBV in this study, accounting for 46% of all EBV-positive cases. This finding agrees with reports by Omoseebi *et al*. [33], in Lagos, Yates et al. [21], in Zaria, and Vera-Sempere *et al.* [30], among Spanish patients, potentially reflecting a higher keratinising subtype frequency in African non-endemic contexts.

Morphologic Subtype and EBV Phenotypes: In the index study, it was found that the EBV-negative phenotype was the most common, accounting for 45% of the 78 cases. This is significantly higher than the 4% reported by Shibosawa et al. [32] for the same phenotypic subtype. Although the index study did not assess patient outcomes, many studies have shown an association between this phenotype, poor prognosis, and lower survival rates. [30,31] This may indicate an unfavourable prognosis for patients with this phenotype in our study area. However, this can only be confirmed through outcome-based studies conducted in the study area.

The second most common EBV+ phenotypic subtype in our study was found in 28% of the 78 cases and showed a preference for non-keratinising squamous cell carcinoma (NKSCC). This rate is significantly lower than the 80% reported by Shimizu et al. and Shibosawa *et al*. [28,32] Although previous studies, including those by Jiang *et al*. [15]and Makitie *et al*. [33], have reported that EBV positivity may be associated with improved overall survival (OS) and disease-free survival (DFS), our dataset did not allow for evaluation of these prognostic implications. Further studies incorporating survival outcomes are warranted to clarify the significant EBV status.

Conclusion

Our study highlights the notable presence of EBV-positive non-keratinising squamous cell carcinoma within our cohort, adding to the understanding of EBV's role in nasopharyngeal carcinoma biology. While our findings suggest potential prognostic relevance, definitive clinical implications cannot be drawn without outcome-based validation. Future research should focus on molecular subtyping and prospective survival studies to clarify the prognostic impact of EBV status and guide biomarker-driven treatment strategies.

Limitations of the Study

This study has several limitations inherent to its hospital-based design, which may restrict the generalizability of findings due to potential selection bias from differential healthcare access and community representation. Molecular subtypes of EBV were not performed in this index due to limited funds. The retrospective nature of the study further introduced constraints, as unavailable request forms, archival samples (blocks/slides), and duplicate reports limited comprehensive analysis for some cases. We acknowledge that interpretation of EBV immunohistochemistry (IHC) may be subject to observer bias, which could influence staining assessment. Our study did not evaluate inter-laboratory reproducibility of EBV IHC staining, an important consideration for standardisation and broader applicability of findings. Future studies incorporating multi-centre validation and standardised scoring approaches are warranted.

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