Primary Lymphoma of Nasal Cavity and Paranasal Sinuses

Negar Azarpira, MD,1* Mohammad J. Ashraf, MD,1 Ahmad Monabati, MD,1 Alireza Makarempour, MD,1 Bijan Khademi, MD,2 Afsoon Hakimzadeh, MSC,1 Elham Abedi, MSC,1 Behnaz Valibeigi, MSC1

ABSTRACT

Background: There are several reports of lymphomas arising in the nasal cavity, either T cell/NK cell or B cell type. We studied several cases of lymphoma involving the nasal cavity or paranasal sinuses.

Method: In our case series, pathology records of patients from 2003 through 2011 revealed 13 cases. The association between Epstein-Barr virus (EBV) and lymphoma was studied by immunohistochemistry and PCR methods.

Results: The cohort included 9 males and 4 females, aged 16 to 78 years. Histology revealed diffuse large B-cell lymphoma (DLBL) in 7 of the patients, sinonasal extramedullary plasmacytoma, one with follicular lymphoma, one peripheral T-cell lymphoma, one extranodal NK/T-cell lymphoma, and one Burkitt lymphoma. The latent membrane protein (LMP) of EBV was not expressed, and the PCR results were negative, in all patients.

Conclusion: In this study, primary lymphomas arising in the nasal cavity were mostly of B cell origin.

Keywords: nose, paranasal sinuses, lymphoma, Epstein Barr virus

Nasal lymphoma with natural killer (NK) or T-cell phenotype is more common in Far East Asian countries (Japan, Korea, Taiwan, and China) and also in Mexico and South America. On the other hand, nasal lymphoma with B-cell phenotype are typically more common in Western populations.2,4,5,6 The most common presentations are epistaxis, nasal obstruction, and nasal swelling. Less commonly, proptosis or hard palate perforation are observed.5,6

Associations between Epstein Barr virus (EBV) and malignancies such as Burkitt lymphoma, Hodgkin’s lymphoma, and non-Hodgkin’s lymphoma (NHL) of either B or T immunophenotypes, have been reported. The association between nasal NK/T-cell lymphoma with EBV has been demonstrated.7–10

The aim of this study was to investigate the clinical characteristics, stage and histological type of sinonasal NHL.

Materials and Methods

A review of medical records from 2003 through 2011 revealed 13 cases with NHL of nasal cavity and paranasal sinuses. Physical examination, with nasal endoscopy,
showed masses in the nasal cavities and/or paranasal sinuses. In one patient, swelling of the soft palate was also identified. Tissue biopsies were performed under general anesthesia.

The tissue specimens were fixed in 10% buffer formalin solution, embedded in paraffin, and 5 μm were stained with haematoxylin-eosin. Immunohistochemical staining was performed on formalin-fixed, paraffin-embedded tissue sections using the following primary antigens: CD3, CD10, CD20, CD56, CD45RO, CD 79a, TdT and CD43, BCL2, BCL6, CD23, CD7, CD5, CD38+, MUM1+, Ki67 (MIB1), κ-light chain, λ-light chain (Dako, Denmark). The Envision method (Dako, Denmark) was used for antibody staining. Specimens were evaluated according to the World Health Organization (WHO) classification system.11,12,13 Staging was done with computed tomography (CT) scans of the chest and abdomen and bone marrow biopsies. Immunohistochemistry (IHC) and polymerase chain reaction (PCR) were used for detection of EBV in tissue. Latent membrane protein (LMP-1; Dako, Denmark) was used as the primary antibody for detection of EBV. DNA was extracted using a commercial extraction kit (DNP, Cinagene, Tehran, Iran). The β-actin was used as internal control.

A forward primer, 5’ CCA GAC AGC AGC CAA TTG TC 3’, and a reverse primer, 5’ GGT AGA AGA CCC CCT CTT AC 3’ (MOLBIOL company, Berlin) were used for amplification of 129 bp of LMP-1 gene. The region was amplified with a Maste recycler (Eppendorff, Germany), (35 cycles of 94 °C for 60 seconds, 60 °C for 60 seconds, and 72 °C for 1 minute), in a 25 μL reaction solution containing 0.5 μg genomic DNA, 1× PCR buffer, 0.3 mM MgCl2, 0.3 mM dNTPs, 2 U Taq DNA polymerase (Cinagene, Iran), and 0.3 μmol of each primer.

**Determination of the Sensitivity and Specificity of PCR**

LCL-PI 133, an EBV transformed human lymphoblastoid cell line (NCBI Code: C344) was used as positive control. To assess the sensitivity of the PCR assay, template DNA was extracted from 10-fold serial dilutions of this control that had been seeded into plasma samples negative for EBV-DNA. Conventional gel electrophoresis was used to analyze the PCR amplification products from these templates. The specificity of PCR was determined using DNA extracted from a herpes virus group HCMV and HeLa cell line.

The microscopic findings of sinonasal lymphoma found in our archives are described according to Revised European-American Lymphoma; REAL/WHO 2001/ WHO 2008 classification.12,13

**Diffuse Large B Cell Lymphoma (DLBL)**

There is diffuse involvement of nodal architecture, either complete or partial. Mitosis is widespread with occasional necrosis. Cytologically, the individual tumor cells have large vesicular nuclei with prominent nucleoli, and a deeply amphophilic cytoplasm with a distinct nuclear Hof. Some of the cells were binucleated, and a few Reed-Sternberg cells were present. Immunohistochemically, DLBL was positive for B-lineage markers (CD20). There was a high proliferation index in Ki-67 staining.

**Peripheral (Post Thymic) T Cell Lymphoma (PTCL)**

There is effacement of the cellular architecture including a lymphohistiocytic infiltrate, often accompanied by plasma cells and eosinophils. In addition to this polymorphic cell population, proliferation of small vessels with prominent endothelial cells was also seen.

The tumor cells were immunoreactive for CD3, CD45RO, CD5, CD7, CD4, and CD56-. Most cases of PTCL express a CD4+/CD8- helper phenotype. Approximately 20% of the tumor cells express a CD4-/CD8+ cytotoxic/suppressor phenotype; rare cases express both markers, whether negative or positive phenotypes. At the molecular level, PTCL exhibits clonal rearrangements of the γ T-cell receptor genes.

**Burkitt Lymphoma**

Diffuse lymphoid involvement with medium sized, round to oval tumor cells and multiple prominent basophilic nucleoli and coarse chromatin characterize this disease. The starry sky appearance is seen. Burkitt lymphomas are of B-cell lineage and express CD20. These tumors are negative for TdT, a helpful marker for differentiating from lymphoblastic lymphoma.

**Follicular Lymphoma**

The most distinctive feature of follicular lymphoma is a nodular growth pattern. The cytologic composition of nodules is characterized by a mixture of small and large lymphoid cells. The small cells have scant cytoplasm, irregularly cleaved nuclei with prominent indentations and involutions. Tumor cells are larger than normal lymphocytes. The large cells are 2 to 3 times the size of mature lymphocytes, with a rim of cytoplasm and a vesicular nuclei, with prominent nucleoli adjacent to the nuclear membrane. The cells are immunoreactive for B-cell markers (CD19, CD20, and CD79a). There are
variable numbers of non-neoplastic T cells, macrophages and follicular dendritic cells, corresponding to the cellular composition of a normal germinal center. BCL2 and BCL6 proteins are typically present.

Extranodal NK/T-cell Lymphoma, Nasal Type
These cells comprise a broad cytologic spectrum, ranging from small or medium sized to large transformed cells. Angioinvasion by tumor cells within the area of necrosis is typical. These tumor cells are immunoreactive for CD56 and negative for CD3. Although investigators have noted T-cell receptor rearrangements in some cases, no clonal rearrangement of the T-cell receptor gene was detected in our patients.

Plasma Cell Neoplasms (Plasma Cell Myeloma/Plasmacytoma)
These neoplasias are characterized by monomorphic infiltration of mixed mature plasma cells with eccentric nuclei, a clear paranuclear area, and coarse chromatin mixed with immature plasma cells. The immature plasma cells exhibited binucleation and large nucleoli. The cells were immunoreactive for \( \lambda \) and \( \kappa \) light chains as well as CD38 and MUM1.

Results
The mean age of the patients was 40 years (range, 16-75 years) and the male to female ratio was approximately 2:1 (Table 1). The major symptoms were epistaxis (6 patients) and nasal obstruction (7 patients). Histological examination revealed DLBL (7/13), follicular lymphoma (1/3), peripheral (post thymic) T-cell lymphoma (1/3), extranodal NK/T-cell lymphoma, nasal type (1/3), and Burkitt lymphoma (1/3) (Table 1). The B cell phenotype was detected in 11 patients (85%), and the remaining (2 patients; 15%) had NK-T cell phenotype. In PTCL, T cell type, molecular analysis of T-cell receptor (TCR) gene rearrangements was performed using polymerase chain reaction-based TCR-\( \gamma \) gene, with positive results. TCR gene rearrangements were not found in extranodal

---

Table 1. Clinical Features of Patients with Sinonasal Lymphoma

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age</th>
<th>Tumor Type</th>
<th>Stage</th>
<th>Extra Nasal Involvement</th>
<th>Initial Therapy</th>
<th>Length of Follow-up</th>
<th>Outcome</th>
<th>IHC Markers</th>
</tr>
</thead>
<tbody>
<tr>
<td>F</td>
<td>64</td>
<td>Diffuse large B cell lymphoma</td>
<td>III</td>
<td>None</td>
<td>CT. RT</td>
<td>20 months</td>
<td>Dead</td>
<td>CD20+, CD79 a+, CD30+, CD3+, CD43+, KI67 90% (High)</td>
</tr>
<tr>
<td>M</td>
<td>56</td>
<td>Diffuse large B cell lymphoma</td>
<td>I</td>
<td>Yes</td>
<td>CT. RT</td>
<td>10 months</td>
<td>Alive without disease</td>
<td>CD20+, CD79 a+, CD3+, CD43+, KI67 70% (High)</td>
</tr>
<tr>
<td>F</td>
<td>78</td>
<td>Diffuse large B cell lymphoma</td>
<td>I</td>
<td>Yes</td>
<td>CT. RT</td>
<td>12 months</td>
<td>Alive without disease</td>
<td>CD20+, CD30+, CD43+, KI67 90% (High)</td>
</tr>
<tr>
<td>F</td>
<td>64</td>
<td>Diffuse large B cell lymphoma</td>
<td>III</td>
<td>None</td>
<td>CT. RT</td>
<td>20 months</td>
<td>Dead</td>
<td>CD20+, CD79 a+, CD3+, CD43+, KI67 90% (High)</td>
</tr>
<tr>
<td>M</td>
<td>64</td>
<td>Diffuse large B cell lymphoma</td>
<td>I</td>
<td>None</td>
<td>CT. RT</td>
<td>8 months</td>
<td>Alive without disease</td>
<td>CD20+, CD79 a+, CD23+, CD43+, CD10+, KI67 90% (High)</td>
</tr>
<tr>
<td>M</td>
<td>23</td>
<td>Diffuse large B cell lymphoma</td>
<td>I</td>
<td>None</td>
<td>CT. RT</td>
<td>24 months</td>
<td>Alive with disease</td>
<td>CD20+, CD79 a+, CD23+, CD43+, CD10+, KI67 90% (High)</td>
</tr>
<tr>
<td>M</td>
<td>16</td>
<td>Diffuse large B cell lymphoma</td>
<td>I</td>
<td>None</td>
<td>CT. RT</td>
<td>24 months</td>
<td>Alive without disease</td>
<td>CD20+, CD79 a+, CD3+, CD10+, KI67 90% (High)</td>
</tr>
<tr>
<td>M</td>
<td>50</td>
<td>Follicular lymphoma, high grade</td>
<td>II</td>
<td>Yes</td>
<td>CT. RT</td>
<td>10 months</td>
<td>Alive with disease</td>
<td>CD20+, CD79 a+, BCL2+, BCL6+, CD23+, CD43+, KI67 70% (High)</td>
</tr>
<tr>
<td>M</td>
<td>75</td>
<td>Peripheral (post thymic) T-cell lymphoma</td>
<td>II</td>
<td>None</td>
<td>CT. RT</td>
<td>12 months</td>
<td>Dead</td>
<td>CD3+, CD45RO+, CD5-, CD7-, CD56+, CD4+, CD20+, KI67 70-80% (High)</td>
</tr>
<tr>
<td>M</td>
<td>23</td>
<td>Extramedullary NK/T-cell lymphoma, nasal type</td>
<td>II</td>
<td>None</td>
<td>CT. RT</td>
<td>26 months</td>
<td>Dead</td>
<td>CD56+, CD3+, CD20+, KI67 70% (High)</td>
</tr>
<tr>
<td>M</td>
<td>16</td>
<td>Burkitt lymphoma, B-cell a</td>
<td>III</td>
<td>None</td>
<td>CT. RT</td>
<td>8 months</td>
<td>Dead</td>
<td>CD19+, CD20+, CD10+, TdT+, KI67 85-90% (High)</td>
</tr>
<tr>
<td>M</td>
<td>16</td>
<td>Sinonasal Extramedullary plasmacytoma</td>
<td>I</td>
<td>None</td>
<td>RT</td>
<td>16 months</td>
<td>Alive without disease</td>
<td>( \kappa )-light chain*, CD38+, MUM1*, ( \lambda )-light chain, KI67 30%</td>
</tr>
<tr>
<td>M</td>
<td>42</td>
<td>Sinonasal Extramedullary plasmacytoma</td>
<td>I</td>
<td>None</td>
<td>RT</td>
<td>8 months</td>
<td>Alive without disease</td>
<td>( \kappa )-light chain*, CD38+, MUM1*, ( \lambda )-light chain, KI67 20%</td>
</tr>
</tbody>
</table>

CT: Chemotherapy, RT: Radiotherapy
NK/T-cell lymphoma. The LMP protein was not expressed in any of the cases (Figure 1).

The patients in this study were treated with radiotherapy and chemotherapy. The radiation doses ranged from 45 to 55 Gy, with most patients receiving 50 Gy. Patients with plasmacytoma were treated with local 50 Gy radiation. The chemotherapy regimen used was CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone). The follow-up period ranged from 6 to 26 months; 5 patients died from the disease, 6 patients survived free of disease, and 2 survived with the disease.

**Figure 1**

PCR for EBV and internal control.

Lanes 1–3: The patient samples are negative for EBV.
Lanes 4: 50–base pair (bp) DNA ladder.
Lane 5: 129-bp product of EBV positive control.
Lanes 6–9: A 317-bp product of β-actin, as an internal control.

**Discussion**

The majority of NHLs of the head and neck occur in extranodal sites, such as the paranasal sinuses, nasal cavity, oral cavity, salivary glands, and laryngopharynx. NHLs of the sinonasal tract are uncommon malignancies representing 3% to 5% of all malignancies. Early diagnosis of primary lymphoma in this region is challenging.

However, lymphomas must be included in the differential diagnosis of unilateral lesions of the nasal cavity and paranasal sinuses. Early diagnosis and staging are necessary for effective treatment. With the combined chemotherapy and local radiation, patients with lymphoma of the nasal cavity and paranasal sinuses have a better prognosis.

Geographic factors play a role in the frequency and histological subtype of NHL. Maxillary sinus tumors are more common than nasal cavity tumors in Western populations. In Asian people, the nasal cavity is a more common site of malignancy.

Our study showed a predominance of male NHL patients over female patients, a finding that is consistent with many previous studies in the literature. Primary nasal lymphomas in Asian patients are mostly of natural killer (NK) or T-cell lineage, whereas B-cell subtypes are more common in Western populations, South America and the Far East.

In a report from Poland by Zagolski et al., NHL was the most common head and neck malignancy occurring in children, and DLBL was the most common subtype. Chalastras et al. from Greece reported that the most frequent histological type was B-cell lymphoma. According to Hatta et al., the most common histological type of this disease in Japan is angiocentric lymphoma (35.9%), followed by B-cell lymphoma (22.6%), peripheral T-cell lymphoma types (15.1%), and other lymphomas.
Kim et al. reported that extranodal nasal-type natural killer (NK)/T-cell lymphoma (NKTL) was rare, but it is well known in Asian populations. Suzuki et al. reported that of 33 cases of nasal lymphoma they examined in Japan, 28 cases were of the NK/T-cell phenotype and the remaining were of the B-cell phenotype. Li et al. reported that of 48 cases of sino-nasal lymphoma in China, only one case was a B-cell lymphoma. The results of Kitamura et al. also confirmed that primary lymphomas arising in the nasal cavity were mostly of NKT-cells derivation among Japanese people. DLBL is the most common nasal lymphoma in our study. The majority of our cases have B-cell phenotype (11/13), with the T-cell phenotype having been detected in one patient. This finding is similar for most areas outside of Mexico, South America, and the Far East.

The etiological role of EBV in the development of nasal NK/T-cell lymphoma (NNKTL) was first suggested by Harabuchi et al. in 1990. It is now possible to detect the presence of EBV DNA in serum, and as a serum tumor marker, measured by real-time PCR, to confirm a diagnosis of NNKTL. EBV DNA is also very useful in monitoring the clinical course of the patients. Studies have indicated that EBV DNA levels decrease during treatment, and increase upon relapse.

In our study, neither LMP protein nor the EBV genome was detected in tumor cells. Previous reports emphasized that the protein was expressed in only 50% of the patients, because of highly methylated LMP coding sequences. Therefore, methylation could explain why we did not detect genomic EBV DNA. Additionally, it is difficult to obtain high quality amplifiable DNA from paraffin-embedded tissues. Tumor heterogeneity may also have contributed to our results.

Overall, in situ hybridization (ISH) of the EBV-encoded small nuclear early region RNA (EBER) is the most sensitive, specific, and reliable test for EBV detection. Early-stage nasal lymphoma has a significantly better prognosis than later stage tumors. The findings of the current study are consistent with previous data, indicating a favorable prognosis in stage I patients.

References


---

Why let manual document control be your weak link? Automate now with MediaLab's Document Control system. It’s easy to implement and use. And, it helps you comply with CAP, Joint Commission, and ISO document control requirements. Best of all, it works seamlessly with MediaLab’s Compliance and CE solution. Schedule your free demonstration today.

**MediaLab, Inc.**

www.medialabinc.net