Primary sinonasal lymphoma in immunocompetent patients: A 10 years retrospective clinicopathological study

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Abstract

Introduction: Sinonasal tumors occur in the nasal cavity or paranasal sinuses (PNS). These tumors are rare and lymphomas are even rarer. Lymphoma of the nose and PNS may mimic benign processes and may manifest either in an isolated fashion or in conjunction with systemic diseases. B-cell lymphomas, a more favorable diagnosis, account for the majority of cases, whereas T-cell and extranodal natural killer lymphoma are associated with rapid disease progression and death.

Materials and Methods: All patients with sinonasal lymphomas who were nonreactive for HIV and were operated and treated in our hospital from 2006 to 2016 were included in the study. Histopathological diagnosis and immunohistochemistry using a panel of antibodies (CK, CD99, CD 15, CD30, CD45, Bcl 2, anaplastic lymphoma kinase-1, CD 16, CD 57 and ki-67) were reviewed and recorded.

Results: Out of 153 malignant sinonasal tumors, 18 were diagnosed with lymphoma. Non-Hodgkin's lymphoma constituted 88.8% of cases with the most common subtype being diffuse large B-cell lymphoma (n = 12, 66.6%). Maxillary sinus was the most frequently involved site (62%). The average age of presentation was 52 years with a slight male predominance. Computed tomography and magnetic resonance imaging scans were done in virtually all cases to assess the extent of the tumor as well as bony destruction. Average 5-year survival was 50%. Local recurrence was the most frequent cause of treatment failure.

Conclusion: Malignant lymphomas constituted 11.7% of all malignancies of PNS. The association of diffuse large B-cell tumors with obstructive nasal mass and T-cell tumors with septal perforation, orbital extension and ophthalmological symptoms were more commonly seen.

Keywords: Histology, immunocompetent, immunohistochemistry, nose, paranasal sinuses

INTRODUCTION

The nasal cavity and the paranasal sinuses are considered as a single functional unit affected by common pathological processes. Sinonasal tumors are tumors that occur in the nasal cavity or paranasal sinuses (PNS). These tumors are rare and account for only 3% of tumors in the upper respiratory tract.¹ These are rare in Western populations but relatively common among Asians, Mexicans and South Americans of American Indian descent.² They are twice as common in males than females and are usually seen in...
Sinonasal lymphomas may manifest either in an isolated fashion or in conjunction with systemic disease. B-cell lymphomas, which account for most of these cases, carry a more favorable diagnosis, whereas extranodal natural killer cell lymphoma (ENKL) is associated with rapid disease progression and death. Histologic diagnosis with immunohistochemical confirmation is of utmost importance, and clinicians should remain aware of this entity to differentiate it from other sinonasal malignancies.

Aims and objectives
The study was carried out to study the incidence of sinonasal lymphoma in immunocompetent patients as well as to study the clinical presentation, location, histopathological diagnosis and immunohistochemical profile of sinonasal lymphomas.

MATERIALS AND METHODS
This study was a retrospective medical record-based observational study carried out in the Department of Pathology during September 2006 and September 2016 (10 years) at a tertiary referral center of North India.

Inclusion criteria
All patients with malignant lymphoma of the nose and PNS irrespective of age, diagnosed, operated and treated in our hospital in the study duration.

Risk factors for Hodgkin’s lymphoma include Ebstein–Barr Virus (EBV) infection and positive family history while risk factors for Non-Hodgkin’s lymphoma (NHL) include autoimmune disease, HIV/AIDS, infection with human T lymphotropic virus, immunosuppressant medication and some pesticides. The association of malignant lymphoma in the immune compromised or HIV patients has been discussed earlier, however, there are very few studies published describing the incidence of malignant sinonasal lymphoma in immunocompetent patients and none from the hilly state of Uttarakhand in North India. This study highlights the hospital based prevalence, mode of presentation and histological types of sinonasal lymphomas in a tertiary referral center of North India.

RESULTS
Of a total of 153 malignant tumors of sinonasal tract, 18 were diagnosed with lymphoma thus constituting 11.7% of all sinonasal malignancies. Majority of the cases presented with unilateral nasal obstruction (n = 11) followed by rhinorrhea (n = 10) and epistaxis (n = 9). It was observed that proptosis, diminished vision and nonhealing nasal ulcers were seen more frequently associated with NK/T-cell lymphomas [Table 1]. Nasal endoscopy revealed a smooth polypoidal mass partly occluding the nasal cavity in 40% of cases [Figure 1]. The maxillary sinus was the most frequently involved site (62%) followed by ethmoid sinus [Table 2]. The average age of presentation was 52 years, and the male-to-female ratio was 1:6:1. Histologically, NHL was the most common type (n = 16, 88.8%) while 11.1% of cases were Hodgkin’s disease. The most common subtype was diffuse large B-cell lymphoma (n = 12, 66.6%) followed by anaplastic large cell type (ALCL) (n = 4, 22.2%) [Figure 2]. All the B-cell tumors were positive for CD20 and CD45 along with ALK-1 in ALCL [Table 3 and Figure 3]. Ki-67 as a marker for cell proliferation ranged from 3% to 67%. Extranodal NK/T-cell lymphomas expressed CD3, CD56 and were associated with high Ki-67 values. Angiocentric pattern with vascular invasion was seen in all cases of
NK/T-cell lymphoma. One case was associated with intense eosinophilia. Rosette formation was seen in focally in one case of small cell NHL and differential diagnosis of esthesioneuroblastoma was rendered. One case of anaplastic large-cell lymphoma was histopathologically reported as poorly differentiated carcinoma. However, the immunohistochemical profile was characteristic of NHL in both these cases.

CT and MRI scans were done in virtually all cases to assess the extent of the tumor as well as bony destruction. Tumor was localized to the sinonasal tract at the time of presentation in six cases [Figure 4]. Bone marrow biopsy was done in all 18 cases as part of staging process, however, showed involvement by NHL in only 1 case. Majority of the patients (n = 7, 38.8%) were in stage IIE of Ann-Arbor staging at the time of presentation [Table 4].

Table 1: Clinical presentation of sinonasal lymphoma (n=18)

| Presentation                                | Hodgkins (n=2) | NHL: B-cell type (n=12) | NHL: Extranodal NK/T-cell type (n=4) |
|--------------------------------------------|----------------|------------------------|-------------------------------------|
| Nasal obstruction                          | 1              | 9                      | 1                                   |
| Rhinorrhea                                  | 1              | 8                      | 1                                   |
| Epistaxis                                   | 1              | 7                      | 1                                   |
| Headache                                    | 1              | 1                      | 1                                   |
| Facial swelling                             | 1              | 1                      | 3                                   |
| Nonhealing ulcer                            | 0              | 1                      | 2                                   |
| Septal perforation                          | 0              | 3                      | 3                                   |
| Bone destruction                            | 0              | 1                      | 1                                   |
| Cervical lymphadenopathy                    | 1              | 1                      | 0                                   |
| Proptosis                                   | 0              | 1                      | 2                                   |
| Vision loss                                 | 0              | 3                      | 2                                   |
| B-symptoms (fever, night sweats, 10% weight loss) | 1              | 3                      | 1                                   |

NHL: Non-Hodgkin’s lymphoma, NK: Natural killer

Table 2: Site of involvement (n=18)

| Site of involvement | Hodgkins (n=2) | NHL: B-cell type (n=12) | NHL: Extranodal NK/T-cell type (n=4) |
|---------------------|----------------|------------------------|-------------------------------------|
| Maxillary sinus     | 1              | 6                      | 2                                   |
| Ethmoid sinus       | 1              | 4                      | 2                                   |
| Frontal sinus       | 0              | 2                      | 0                                   |
| Sphenoid            | 0              | 0                      | 0                                   |
| Antronasal          | 1              | 0                      | 0                                   |

NHL: Non-Hodgkin’s lymphoma, NK: Natural killer

DISCUSSION

Malignant tumors of the sinonasal tract are extremely rare, accounting for 0.2% of all invasive cancers and 3% of the head-and-neck cancers. The majority arise in the maxillary sinus, approximately 20% arise in the ethmoid sinuses and the remainder (<1%) originate in the frontal and sphenoid sinuses. Squamous cell carcinoma is the most common histology, and lymphomas are uncommonly encountered. The incidence of sinonasal lymphomas is higher in Asian countries than in the West; these malignancies account for 2.6%–6.7% of all lymphomas in Asia, and they are the second most common extranodal lymphoma, after gastrointestinal lymphoma. In this study, malignant lymphomas constituted 11.7% (18/153) of all malignant sinonasal tumors. This is slightly higher than the incidence reported by Aozasa et al. in Japan.

Malignant lymphomas have a predilection for males, and they tend to occur in younger adults. The average age of presentation was 49 years, and the male-to-female ratio was 1.5:1. This finding is similar to previously published studies by Danesh-Sani et al. where there was male preponderance (male-to-female ratio of 1.6:1), with a median age of 49 ± 12.2 years (range 21–88 years). Another study by Ashraf et al. showed the peak incidence of malignant lymphomas in the 5th to 6th decades.
A large study by Peng et al. found that maxillary and ethmoid sinuses were affected more frequently (n = 8 patients each) than sphenoid and frontal sinuses (n = 5 patients each). This was similar to our study where maxillary sinus was involved in 62% of cases followed by ethmoid sinus. However, another study by Logsdon et al. in Asian patients found nasal cavity as the main site of involvement. Two advanced cases of NHL in our study (1 DLBCL and one follicular) had involvement of ethmoid sinus with orbital plate destruction.

Histologically, the most common type of lymphoma in our study was diffuse large B-cell lymphoma (n = 12, 66.6%) which is similar to the study by Peng et al. who documented the maximum cases of diffuse large B-cell lymphoma (53%), followed by ENKL/T-cell lymphoma, (21%). On the contrary, according to Hatta et al. the most common histological type, in Japan, is angiocentric lymphoma (35.9%), followed by B-cell lymphoma (22.6%), peripheral T-cell lymphoma types (15.1%) and other lymphomas and non-specific types.

The average duration of the presentation was 13 months which is slightly higher as seen in the study by Fasunla and Lasisi in West Africa which was 8.5 months. This delay in our setting can be attributed to the initial nonspecific symptoms of the tumor, local treatment by quacks and sociocultural beliefs. Furthermore, these lesions develop in an anatomic space and expand toward the sinus, nasal cavity or nasopharynx, not usually causing symptoms in the early stages.

Clinical presentations of sinonasal lymphoma vary according to the histological type of tumor. Most of the low-grade lymphomas are associated with sinonasal mass along with obstructive symptoms and/or lymphadenopathy. The high-grade lymphomas (38% of NHL in the sinonasal tract) are more likely to present with aggressive signs and symptoms including nonhealing ulcer, cranial nerve manifestations, facial swelling, epistaxis, pain, bony destruction or proptosis. T-cell lymphomas are associated with nasal septal perforation and/or destruction. Nasal obstruction and rhinorrhea were seen in the majority of our patients while aggressive tumors of ENK/T-cell type presented with nonhealing ulcer, diminution of vision and proptosis. None of the patients with Hodgkin’s lymphoma had lymphadenopathy.

Table 3: Spectrum of sinonasal lymphomas (n=18)

| Type                      | Male | Female | Age range (years) | Mode of diagnosis | Immunohistochemical profile |
|---------------------------|------|--------|-------------------|-------------------|----------------------------|
| Hodgkin’s (n=2)           |      |        |                   |                   | CD15, CD30, CD45           |
| Mixed cellularity         | 1    | 1      | 25-56 (40.5)      | Biopsy            |                            |
| NHL: B-cell type (n=12)   |      |        |                   |                   | CD20                       |
| DLBL                      | 4    | 3      | 33-84 (58.5)      | Biopsy            | CD20, ALK-1                |
| Anaplastic large cell     | 2    | 1      | 58-77 (67.5)      | Partial maxillectomy | CD20               |
| Follicular                | 1    | 3      | 67                | Partial maxillectomy | CD20               |
| Small cell                | 1    | 1      | 16                | Biopsy            | CD20               |
| NHL: Extranodal           | 2    | 2      | 48-77 (62.5)      | Biopsy            | CD16 CD56               |
| NK/T-cell type (n=4)      |      |        |                   | Maxillectomy with orbital exenteration |                  |

NHL: Non-Hodgkin’s lymphoma, NK: Natural killer, ALK: Anaplastic lymphoma kinase, DLBL: Diffuse large B-cell lymphoma

Figure 2: Photomicrograph showing sheets of mostly monomorphic cells having scanty cytoplasm and hyperchromatic nuclei (H&E, x200)

Figure 3: Photomicrograph showing cytoplasmic CD56 positivity in natural killer/T-cell lymphoma (immunohistochemistry, peroxidase-antiperoxidase, x400)
findings were similar to previously reported studies by Chalastras et al.[15]

T-cell lymphomas are aggressive tumors, and histomorphologically, they are characterized by angiotropism or angiocentricity. The tumor cells infiltrate and destroy blood vessel walls and cause variable degrees of geographic necrosis. They express T-cell markers such as CD2, CD45RO and CD 43. They may also express CD 56, but the absence of CD 16 and CD 57 distinguishes them from typical NK cell lymphomas.[16] All T-cell lymphomas in our study were positive for CD 56. Immunophenotyping could not be performed in any of these cases for subclassification.

ExTRANAL dissemination occurs rarely in lymph nodes, skin and testes. At presentation, approximately 50% of patients have associated nodal disease, and only 20% report systemic or B symptoms.[8] B-symptoms were seen in five cases in our study. There is a high incidence (15%) of extranodal relapse outside the gastrointestinal tract in patients with oral-sinonasal lymphoma to larynx, skin, liver, uvula, kidney, breast, lacrimal gland, testis and prostate gland.[17]

Several types of mutation are known to occur in NHLs. In sinonasal lymphoma, the frequency of mutations in p53, K-ras, c-kit, beta-catenin and BAK gene is found with mutation frequency in all genes being higher in B-cell than in NK TCL cases.[18] These findings suggest that gene mutations might be the driving-force for B-cell lymphoma, whereas combined EBV infection and gene mutations contribute to NK TCL development.[19,20]

Contrast-enhanced CT and MRI were done in all our cases to assess the extent of the tumor, bone destruction, staging and also to decide the most suitable site of the biopsy. Treatment involved chemotherapy (CHOP regimen with cyclophosphamide, doxorubicin, vincristine and prednisolone) and Radiotherapy. In this study, the 5 years survival rate for sinonasal lymphomas was 50%, however, Logsdon et al. found a better prognosis in sinonasal lymphomas as compared to the Waldayer’s lymphomas of similar histological grades in Western populations.[12]

The prognosis depends on the type and stage of disease, the number of sites of extranodal spread, invasion of the central nervous system and the patient’s general condition.[20] Patients with lymphomas of high histopathologic grade and recurrent or disseminated disease have the worst prognosis.[21] Two-third of the patients remain in the remission phase after initial therapy. In one-third of the patient’s diseases, relapse and three-fourth of these patients die of the disease.[21]

Correct diagnosis results from tissue biopsy, which should be performed in patients with any unilateral nasal mass. Early diagnosis and staging are essential for effective treatment, and lymphomas should always be included in the differential diagnosis of lesions of the nasal cavity and PNS.

CONCLUSION

Malignant lymphomas constituted 11.7% of all malignancies of PNS with DLBCL type of Non Hodgkins Lymphoma being the commonest subtype. Stage is the most important prognostic factor for sinonasal lymphomas. The findings of the current study are consistent with most of the earlier published studies. [8,13,20,21]

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Conflicts of interest
There are no conflicts of interest.

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