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Original Research Paper

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B-CELL NON-HODGKIN'S LYMPHOMA OF THE SINONASAL TRACT: A REVIEW OF A SINGLE INSTITUTION EXPERIENCE IN NORTH INDIA

Mukesh Sonkaria	MD, Assistant Professor, Department of Radiation Oncology, MBS hospital and Govt. Medical College, Kota, Rajasthan, India.
R. K. Tanwar*	MD, Professor & Head, Department of Radiation Oncology, MBS hospital and Govt. Medical College, Kota, Rajasthan, India. *Corresponding Author
Laxmi Agarwal	MD, Consultant, Department of Pathology, Pushpadi Hospital, Kota, Rajasthan, India.
Bharti Saxena	MS, Professor, Department of Obstetrics & Gynecology, J K Lon hospital and Govt. Medical College, Kota, Rajasthan, India.

ABSTRACT

Objectives: This study aims to review the current literature and to study the etiopathogenesis, clinical profile, diagnosis, treatmentprotocols & outcome of sinonasalB-cell lymphoma.

Materials and Methods: A retrospective study of sinonasal lymphoma from January 1997 to Dec 2019. We hereby share our experience of 7 cases of sinonasalB-cell lymphoma.

Results: A total of 7 cases of thesinonasal B-cell lymphoma (six diffuse large B-cell lymphoma(DLBCL)& one follicular) were identified. The average age of presentation was 45 years (range 2 to 89 years), with a male predominance. All patients had an ECOG score of 1. Paranasal sinus (PNS) and nasal cavity together were most common sites involved in 5 patients. PNS only were involved in 2 patients. Maxillary sinus was the most frequently involved site (100%) with or without PNS followed by nasal cavity (71%). Out of 7 patients, 3 (43%) received chemo-radiotherapy, three patients received chemotherapy alone and one received radiotherapy alone. The mean progression-free survival (PFS) rate was 53 months and mean overall survival (OS) was 57 months. Chemotherapy and radiation therapy resulted in improved survival. In majority of cases recurrence developed locally.

Conclusion: primary sinonasal lymphomas exhibit different clinical profiles, different patterns of failure, and different treatment outcomes due to which they carry poor prognosis, usually worse than lymphomas in other sites in the body. Multidrug chemotherapy (R-CHOP regimen) followed by radiotherapy appears to be the most effective treatment approach.

KEYWORDS : Sinonasal lymphoma, B-cell NHL, chemotherapy, Radiotherapy.

INTRODUCTION

Sinonasaltumors are tumors that occur in the nasal cavity or PNS. Sinonasal lymphoma is an uncommon malignancy.[1] However, primary sinonasal lymphomas are likely to be comprised of a diverse group with a variety of immunophenotypic features. Non-Hodgkin's lymphoma (NHL), specifically DLBCL and natural killer T-cell lymphoma (NKTCL) are the most common variants, often localizing to the maxillary and ethmoid sinuses.[1] About 15% of the totalsinonasal malignancies are NHL.[2] Sinonasal NHLs are relatively common in Asia, comprising up to 7% of all NHLs with a marked preponderance more than 90% demonstrating an extranodal NK/T-cell lymphoma, nasal type (NK/T-cell lymphoma) and the majority of them demonstrate Epstein-Barr virus (EBV) genomes in their tumor cells.[3] In contrast, sinonasal NHLs are uncommon in Western countries, accounting for only about 1.5% of NHLs.[3]

Globally, there exist clear regional and racial variations in the incidence of NHL. Western populations more commonly present with B cell lymphoma (DLBCL), whereas Asian and Latin American populations are more likely to present with NKTCL or T cell which accounts for 10% of all NHL.[1,4] The etiopathogenesis is unknown but it is related to EBV infection, which is often associated with poor prognosis.[4]

Treatment of sinonasal lymphoma has also evolved over the last 3 – 4 decades, like other localised lymphomas, from local treatment with surgery followed by radiotherapy, to anthracycline- based chemotherapy regimens with or without loco-regional radiotherapy.[5,6] Role of surgery is limited to establish the diagnosis only. Because of the rare incidence of sinonasal lymphoma, the relatively small cohorts of patients are reported in the literature who hasreceived heterogeneous treatment modalities even for a same histological entity.

We present here our single centre experience of primary sinonasal B-cell lymphoma with their clinical features, and treatment outcomes.

MATERIAL AND METHODS

A retrospective study was conducted on patients of primary sinonasal tract (nasal cavity and paranasal sinuses) B-cell lymphoma diagnosed between January 1997 and December 2019. A total of 7cases wereidentified and their medical records were analysed. Studyparameters included 1) gender, 2) age at diagnosis, 3) primary site, 4) Ann Arbor lymphoma stage, 5) use of surgery, 6) use of chemotherapy, 7) use of radiation therapy and 8) survival in months.

All patients were treated with 4- 6 treatment courses of R-CHOP chemotherapy (inj. Rituximab 375mg/M inj. Adriamycin 50 mg/M^2, inj. Cyclophosphamide 750mg/M^2, Vincristine 1.4mg/M^2 for day 1 and tab. prednisone 100mg in divided doses for 5 days every 3 weekly), with or without localised radiotherapy. The dose of radiotherapy given was 45–50 Gy with daily fractions of 1.8–2.0 Gy by conventional technique. The field was extended to cover the cervical region for patients with cervical lymph node involvement. Outcome analysis end-points comprised of PFS and overall survival (OS).

RESULTS

A total of 7 cases of thesinonasal B-cell lymphoma (six DLBCL & one follicular) were identified. The average age of presentation was 45 years (range 2 to 89 years), with a male predominance(Table 1 & 2). All patients had an ECOG score of 1. PNS combined with nasal cavity were most common sites involved in 5 patients. PNS only were involved in 2 patients. Maxillary sinus was the most frequently involved site (100%) with or without nasal cavity followed by nasal cavity (71%) and ethmoid sinus. Majority of the cases presented with unilateral nasal obstruction (n = 6) followed by rhinorrhoea (n = 5), facial swelling (n = 5), headache (n = 3)& B symptoms(n = 2).

Bone destruction was seen in one patient. CT scans were done in all cases to assess the extent of the tumor as well as bony destruction. Bone marrow biopsy was done in all 7 cases as part of staging process, however didn't show infiltration in any case. All patients (*100%*) were in stage IIE of Ann-Arbor staging at the time of presentation [Table 1 & 2]. Of 7 patients, 3 (43%) received chemotherapy and radiotherapy ; and three patients received chemotherapy alone, and one patient received radiotherapy alone. One patient is still alive, one was dead and other five patients were lost to follow up. The mean progression-free survival (PFS) was 53 months and mean overall survival (OS) was 57 months. Local recurrence was the most frequent cause of treatment failure. Survival was better in patients who received chemotherapy & radiation therapy both and who were without B symptoms.

DISCUSSION

The nasal cavities and PNS are rarely affected by primary NHL. Variations in the histopathology and site of sinonasal lymphomas exist between different races.However, incidence of malignant lymphomas of the PNS and nasal cavity in Asian countries is greater than in Western countries. Sinonasal NK/T cell lymphomas accounts for 75% of lymphoma in Korea but rarely seen in India.[4] Even though, B-cell lymphomas are much more prevalent in Western countries.[6] It isnoteworthy that it may be prevalent in Indian scenario as seen in our study. Sinonasal lymphoma can occur over a wide range of ages, peaking in the sixth decade, with malepreponderance. [7,8] which is also seen in our study. Peng*et al*. found that maxillary and ethmoid sinuses were affected more frequently than sphenoid and frontal sinuses.[9] However, another study by Logsdon *et al*. in Asian patients found nasal cavity as the main site of involvement.[10] DLBCL of the sinonasal tract classically has a predilection for the maxillary sinus as well as for the nasal cavity.[10,11] This is represented in our study population, with maxillary sinus being the most common site followed by nasal cavity. In DLBCL Epstein-Barr virus and autoimmune disease are thought to play a role. [1, 12, 13]However EBV genomes are more frequently detected in the NK/T-cell lymphoma specifically nasal NK/T-cell than in the B-cell or T-cell lymphoma. [6]

Clinical presentations of sinonasal lymphoma vary according to the histological type and the site oftumor. Most of the low-grade lymphomas are associated with sinonasal mass along with obstructive symptoms and/or lymphadenopathy. [14] The high-grade lymphomas (38% of NHL in the sinonasal tract) present with aggressive signs and symptoms including nonhealing ulcer, cranial nerve manifestations, facial swelling, epistaxis, pain, bony destruction or proptosis.[14]B-cell lymphomas are more likely to have a primary site of origin in the paranasal sinuses and present as a mass with typical presenting symptoms including nasal obstruction, nasal discharge, epistaxis and pain or swelling of the nose or face. Patients may also demonstrate signs due to infiltration of local structures, such as cranial nerve palsies or diplopia and proptosis due to intra-orbital or skull base extension. In contrast, T cell and NK cell NHL are more likely to have a primary site of origin in the nasal cavity and present as lethal midline granuloma with destructive lesions such as septal perforations, non-healing ulcers and fistulae. [8]Our patients presented with nasal obstruction, rhinorrhoea, facial swelling, headache and bone destruction. Nasal obstruction and rhinorrhoea were seen in the majority of our patients. Extranasal dissemination occurs rarely in Lymph nodes. At presentation, 2 patients have associated nodal disease and 2 patients have B-symptoms in our study.

Histopathology and immunohistochemistry examination should be performed to ensure accuratediagnosis and histological grading of lymphoma. Bone marrow biopsy should be done to rule out any marrow involvement by the disease.[15] Chest X-ray, CT or MRI scans of the thorax and the abdominal cavity should be done routinely for correct staging. [16-18]

Treatment for sino-nasal NHL primarily includes chemotherapy and / or radiation therapy.[1] Role of surgery is limited to establish the diagnosis only.[1,19] Most frequently administered drugs include doxorubicin, vincristine, prednisone, 6-mercaptopurine, rituximab, bendamustine and methotrexate.[1,20,21] Intrathecalmethotrexate is used if the disease has spread or may spread to the brain.[22] Radiation therapy is the primary treatment modality for localized disease (Stages I and II), especially for low-grade lymphomas.[1,19,20] Combination chemotherapy with or without radiation is used for more advanced disease and for intermediate- and high grade lymphomas.[1,19-21]

American studies report that nasal NK/Tcell lymphomas have an outcome similar to that of DLBCL, whereas Asian studies showed nasal NK/T-cell lymphoma carries poor prognosis. [23] Some studies suggest that conventional combined treatment (CHOP chemotherapy + radiotherapy) is ineffective for the NHL of the sino-nasal tract (especially NHLs of the nasal cavity), NHLs with tumor cells positive for T-cell markers, NHLs with stage higher than Stage IIE and NHLs with B symptoms.[24,25] Some other stated that radiation therapy alone has been argued to be effective for early-stage disease.[1,26]

Our data indicates that B-cell lymphomas have better survival in patients who received chemotherapy followed by radiation therapy and also in patients without B symptoms. We have limited number of patients presenting with involvement of PNS alone so we are unable to comment on survival benefit in these patients as compared to patients with combined involvement of PNS& nasal cavity. However, survival was not significant in one patient despite multi modalities treatment including surgery, chemotherapy, radiotherapydue to its high grade; and in another patient with follicular intermediate grade who received chemotherapy alone. In this study, only one elderlypatient received external beam radiation therapy alone, leaving the data underpowered to comment on its effectiveness as monotherapy.

It is noteworthy that substantial differences existed in the patterns of failure. Although it was reported that locoregional failure rates were similar among the three subtypes, striking differences were apparent in patterns of systemic failure which were higher in the patients with B-cell or NK/T-cell lymphoma than those in patients with T-cell lymphoma. Moreover, the sites of initial relapse also varied among the three immunophenotypic subtypes. In sinonasal B-cell lymphomas most distant relapses occurred in the nodal and extranodal sites below the diaphragm, such as in the paraaortic lymph nodes or GI tract, whereas patients with NK/T cell lymphomas showed an increased risk of systemic dissemination to the skin, GI tract, testes, soft tissue, spleen, and central nervous system. [6] In our study relapse frequently occurred in loco-regional site with one patient having CNS metastasis. CNS recurrence of sinonasal DLBCL with standard chemotherapy has a poor prognosis.

However, DLBCL is an aggressive lymphoma, initial response to treatment is good but this entity also shows aggressive behaviourwith a prolonged course with remissions and exacerbations. 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.[19] Patients with lymphomas of high histopathologic grade and recurrent or disseminated disease have the worst prognosis.[19] It was documented that B-cell lymphoma seemed to carry the favourable prognosis as compared to NK/T-cell lymphoma, although it is inferior to T-cell lymphoma. Extremely poor prognosis of NK/T-cell

lymphomas is due to its aggressive clinical course, frequent treatment failure of radiotherapy and/or chemotherapy.[6]

In summary, our data suggests that primary B-cell sinonasal lymphoma exhibits different clinical profile, patterns of failure and treatment outcomes. Despite that combined chemotherapy followed by external beam radiation is beneficial in these patients and have good survival.Even though the classifications of primary sinonasal lymphomas are complex and still debated, our results support that the recognition of these distinct subsets, diagnosed both morphologically and immunophenotypically, is very important and clinically relevant in terms of predicting potential behaviour and prognosis. Early diagnosis and staging are essential for effective treatment, and lymphomas should always be kept in the differential diagnosis of lesions of the nasal cavity and PNS.

Several new classes of therapies are being actively investigated and there is unmet need to improve patientsoutcome. Newer modalities like novel monoclonal antibodies, antibody drug conjugates, immunomodulatory agents, intracellular pathway inhibitors, immune checkpoint inhibitors and epigenetic regulators appears to be a valuable treatment option for refractory and advanced lymphoma.

Table: 1 Demographic and Disease-Specific Characteristics of Patients with sinonasal lymphoma [no. (%)]

Age mean, years37
Male 4(57%)
Female 3(43%)
Primary site,
NC only 0(0%)
NC + PNS 5 (71%)
PNSonly 2 (29%)
Cervical lymphadenopathy 2 (29%)
Systemic B symptoms 2(29%)
Ann Arbor stage,
Stage II 7 (100%)
Treatment modality
Chemotherapy + radiotherapy 3 (43%)
Chemotherapy, only3 (43%)
Radiation therapy, only.1 (14%)
Surgery1 (14%)

Table 2. Summary of patientscharacteristics and treatment with outcome.

Age/ sex	ECOG	Site	Clinical presentation	B symptoms	Histopathology diagnosis	Stage	Treatment	PFS month	OS month
35/F	1	Maxilla + Nasal cavity (NC)	Nasal obstruction Rhinorrhoea headache		NHL	II E	Chemotherapy Radiotherapy	270M	275M
2/M	1	Maxilla+NC	Nasal obstruction Facial swelling	Fever Weight loss	NHL high grade Lymphoblastic	II E	chemotherapy	8M	12M
55/F	1	Maxilla +NC	Nasal obstruction Rhinorrhoea Headache Facial swelling Non healing ulcer Bone destruction		NHL	II E	Chemotherapy Radiotherapy	54M	60
65/ M	1	NC+Maxilla +Ethmoid+Sph enoid+Frontal	Nasal obstruction headache Rhinorrhoea Bone destruction		NHL Diffuse High grade	II E	chemotherapy	12M	16M
11/ M	1	Maxilla + Ethmoid	Nasal obstruction Rhinorrhoea Facial swelling Cervical lymphadenopathy	Fever Weight loss	NHL Follicular lymphoma	II E	chemotherapy	14M	19M
55/ M	1	Maxilla	Facial swelling Cervical lymphadenopathy		NHL high grade	II E	Surgery Chemotherapy Radiotherapy	10M	15M
89/F	1	NC + Ethmoid+Maxilla + Sphenoid	Nasal obstruction Rhinorrhoea Facial swelling		NHL high grade	II E	Radiotherapy	3 M	5 M

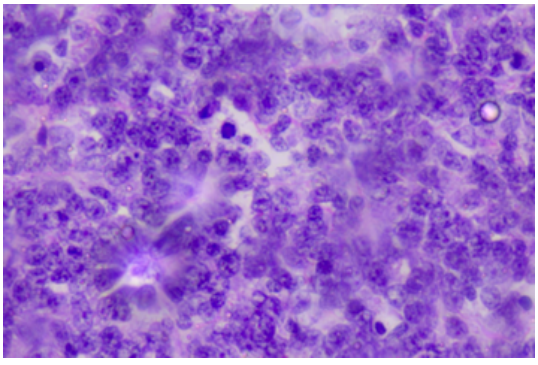

Figure :1 DLBCL H & E image 40 X showing diffusely scattered pleomorphic cells with prominent nuclei.

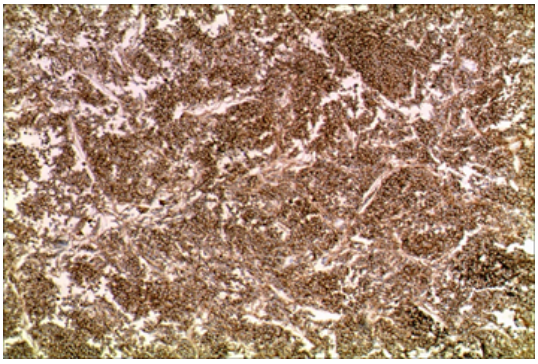

Figure :2 DLBCL Immunohistochemistry showing LCA positive

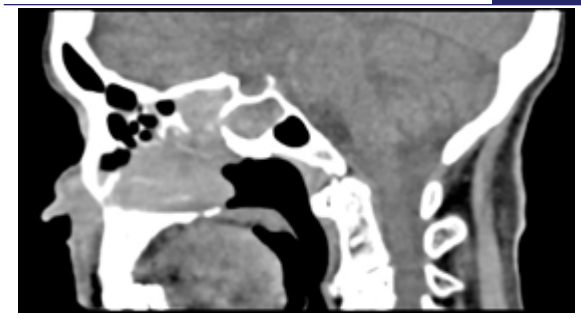

Figure : 3 CT scan- Sagittal view showing disease involving nasal cavity, ethmoid and sphenoid sinuses.

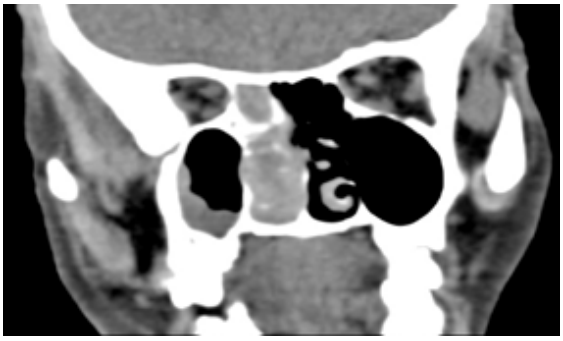

Figure : 4 CT scan- Coronal view showing disease involving nasal cavity, ethmoid and maxillary sinuses.

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