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RESEARCH ARTICLE

RETROSPECTIVE ANALYSIS OF PRIMARY EXTRANODAL NON HODGKINS LYMPHOMA- 3 YEARS STUDY AT A TERTIARY CARE INSTITUTE.

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Abstract

Backgound: A variable number of non-Hodgkin lymphomas (NHLs) arise primarily from sites other than lymph nodes or the bone marrow and even from sites which normally contain no native lymphoid tissue. Indeed, extranodal lymphomas can arise in almost every organ. The incidence of primary extranodal lymphomas is increasing substantially all over the world.

Methods: The study was carried out in the Department of Pathology, S.G.P.G.I.M.S, Lucknow. A total of 231 cases of non hodgkins lymphoma were registered over a period of 3 years. The demographic and clinical features, laboratory parameters, imaging findings, histopathology, and immunophenotyping were documented. The lymphomas were grouped as extranodal and nodal. The data were tabulated in a Microsoft Excel sheet, and descriptive analysis was done.

Results: Primary extranodal NHLs constituted 43% (100/231) of all NHLs. The B symptoms were less common in pENL compared to nodal NHL. Gastrointestinal tract (GIT) constituted the most common extranodal site (40/100, 40%), and diffuse large B-cell lymphoma (DLBCL) was the most common histological subtype. Majority (99/100, 99%) of the patients with pENL were immunocompetent.

Conclusions: Primary extranodal NHL constituted nearly half of patients diagnosed to have NHL at our center with the GIT being the most common site of presentation and DLBCL being the most common histology. A strong suspicion of NHL at an extranodal site with appropriate pathological and immunophenotyping evidence is needed to establish the diagnosis of a pENL.

Introduction:-

Lymphomas can affect any organ in the body, and present with a wide range of symptoms. They are traditionally classified as Hodgkin's lymphoma and non-Hodgkin lymphoma. Non-Hodgkin lymphoma (NHL) is a group of malignant lymphoproliferative disorders with heterogeneous clinical and histological characteristics. Non Hodgkins lymphoma arise from lymphocytes at various stages of development, and the characteristics of the specific lymphoma subtype are those of the cell from which they originated. [1] When NHL originates from tissues other than

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lymph nodes or even from sites that do not contain lymphoid tissue, they are referred to as primary extranodal lymphomas (pENLs). [2-4]The definition of pENL is rigorously limited to extranodal disease at one or multiple anatomical sites in the absence of any nodal manifestation, although it does allow the existence of a 'minor' nodal component along with 'clinically dominant' extranodal involvement.[5] Various studies have reported incidence rates of pENLs ranging from 10 to 48%.[2,3] The diagnosis of pENLs is a diagnostic challenge to the clinicians and pathologists due to their varied clinical presentations, morphological mimicry, and molecular alterations.

Over the last four decades, the incidence of the lymphomas arising in the extranodal sites has shown a rapid increase, especially in the central nervous system, the gastrointestinal tract (GIT) and the skin. This may be attributed to both improved diagnostic procedures and environmental factors such as chronic infections, immunosuppressive disorders such as AIDS, autoimmune disorders, and immunosuppressive treatments.[6] Although there are many case reports and series with extranodal lymphoma of the different sites of the body, the literature on pENL as a group is limited. This is primarily because these tumors, although numerous when considered together, have a widespread distribution throughout the body and so it is difficult to assemble adequate series of any given site. [2] With this purpose, the present study was undertaken to document our experience of this particular disease entity and to ascertain the incidence, anatomical distribution, histological subtypes, and clinical manifestations of pENL from a tertiary care institute in north India.

Material and methods:-

This was a retrospective study conducted in the Department of Pathology over a period of 3-year. During this period, 231 NHL were diagnosed. Of them, 100 cases were pENLs. All cases with extranodal lymphoma were diagnosed on the basis of either operated histopathological specimen or biopsy and tissue was processed routinely in 10% formalin and sections were stained with hamatoxylin and eosin. Immunohistochemistry (IHC) was performed using a panel of antibodies depending on the morphology. Molecular diagnostic techniques such as cytogenetics/fluorescence *in situ* hybridization were not performed in any of the cases due to lack of facilities. Data pertaining to patients' demography, ethnicity, occupation, clinical presentation, immune status, routine complete blood count, and microbiological (HIV, EBV, H. Pylori , HCV, and HBV) status were obtained from the medical records.

The inclusion criteria for the patient to be considered in the study was the Dawson Criteria (1961)[7], i.e.

1. Absence of palpable superficial lymph nodes on first physical examination
2. Absence of mediastinal lymphadenopathy detected on plain Chest X-ray
3. Dominant lesion at extranodal sites
4. Involvement of lymph nodes only in the vicinity of the primary lesion
5. White blood cell (WBC) count within normal range.

The exact definition of extranodal lymphoma is controversial, the lymphomas of tonsils and Waldeyer's ring, thymus, spleen, appendix, and Peyer's patches may be regarded as originating from lymphatic tissues and not considered as extranodal lesions.[8] Nonetheless, most of the researchers and studies separate nodal from extranodal rather than lymphatic from extralymphatic disease, and the term extra nodal lymphoma is generally indicative of a presentation outside lymph node areas. So in our study we included these sites as extranodal. Again the inclusion of stage III and IV lymphomas as primary extranodal lymphomas is debatable and only stage I and II presentation is considered as primary extranodal disease. However, since many extranodal lymphomas have the potential to disseminate, this approach may result in an incomplete picture. On the contrary, extranodal involvement in a disseminated disease may represent a secondary spread. Clearly, any chosen definition of pENL inevitably introduces a selection bias due to the extensive variability in the disease presentation.

Results:-

Primary extranodal NHL constituted 43.29% (100/231) of all NHL studied during this period. The mean age at presentation for the pENL was 50.0 years, (range 5–86 years). There were 72 male and 28 female in the pENL group. The peak incidence was in the fifth and sixth decade in the pENL group.

Abdominal pain associated with vomiting (34/100, 34%) was the most common presenting symptom in patients with pENL. The B symptoms were less common in patients with pENL(34% only) compared to those with nodal NHL. Only one patient with pENL was seropositive for HIV. No patient was positive for HBV and HCV infection.

Among the patients in pENL group, 58 patients underwent a major surgical procedure for the diagnosis (GIT, central nervous system [CNS], spleen and kidney) while 42 patients were diagnosed based on image-guided biopsy only. LDH was raised in 74%of the cases and was in normal range in rest of the 26% cases. 18% of the cases showed minor loco-regional lymph node involvement. Marrow infiltration was assessed in 75% of the patients by means of bone marrow biopsy, 18.6%(14) of these showed presence of marrow infiltration.

The GIT was the most common site of pENL (40/100, 40%) (stomach 20, large intestine12 and small intestine 8) was the commonest site affected in our study. Although controversy exists regarding inclusion of waldeyer's ring and spleen as extranodal site, we included them in our study.

Table 1:-Distribution of the cases according to the site localization.

Site	No. of cases	Site	No. of cases
GIT	40	Adrenal gland	3
Thyroid	6	Eyelid	3
Vertebrae	6	Orbit	3
Soft tissue	6	Sinonasal tract	3
CNS	5	Kidney	2
Spleen	6	Breast	2
Waldeyer's ring	5	Prostate	1
Liver	4	Parotid	1
Testis	4		

In the pediatric population, there were seven cases. The age ranged from 5 to 10 years with Male: Female ratio of 2.5:1. Sites involved were ileo-caecal region in 3 cases, jejunum in 1 case and orbit in 2 cases. Histologically, there were four cases of Burkitt lymphoma (BL), two cases of lymphoblastic lymphoma (LL).

According to the WHO 2008 classification diffuse large B-cell lymphoma (DLBCL, not otherwise specified), Burkitts lymphoma and marginal zone lymphoma were the three most common histological types observed. 91% were high grade lymphoma with high proliferation rate and only 9 % were indolent or low grade lymphoma comprising of small B cell lymphoma and extranodal marginal zone lymphoma of MALT type.

Table 2:-Distribution of the cases according to the histopathological diagnosis.

	Lymphoproliferative disorder	No. of cases
1	DLBCL(NOS)	68
2	Burkitt's Lymphoma	4
3	Marginal Zone lymphoma	4
4	Small B cell lymphoma	3
5	Peripheral T Cell Lymphoma, NOS	3
6	NK/T Cell lymphoma	3
7	Burkitt's like lymphoma	2
8	Lymphoblastic lymphoma	2
9	T Cell Rich B cell lymphoma	2
10	Anaplastic Large Cell lymphoma	1
11	T Cell PTLD	1
12	Cases not classified	7
	Total	100

IHC for CD20 was positive in 85 patients (85%), these were B cell lymphoma and 8 patients (8%) were positive for CD3 and were categorized as T cell lymphoma. 7 % cases could not be classified due to various reasons such as scanty tissue with insufficient IHC workup and equivocal IHC results in absence of a repeat biopsy.

Of the 100 cases, follow up was available in 40 cases. The duration of follow up was 3 months to 3 years. Of the 40 cases, 23 cases were in remission. 4 cases presented with a relapse of the disease. 11 subjects died over a variable period of time. Two of the patients presented with widely disseminated advanced disease.

Discussion:-

Primary extranodal Non- Hodgkins lymphoma is a heterogeneous group of lymphoma comprising of a variety of histological types, molecular abnormalities and clinical pictures(depending on the site of involvement) that can be present. Correct diagnosis and appropriate treatment of this diverse group is also complicated by the relative rarity of many of the subtypes involved. Moreover, in comparison with nodal presentation, B- and T-cell lymphomas diagnosed at extranodal sites, many times, have quite different outcomes and require different therapeutic approaches due to specific organ-related problems. This retrospective study was conducted in the Department of Pathology, S.G.P.G.I.M.S. with the aim to study the histomorphological spectrum of primary extranodal non hodgkins lymphoma and there organ wise distribution. The study group included 100 cases of pENL.

In our study age range of the patients was between 5-86 years with a median age of 50 years. Maximum patients belonged to the age group of 41 to 60 years. In the study conducted by Ananth Pai et al[9], the median age for pENL was 48.2 years with a age range of 5 to 81 years. Similarly in a study by Mishra et al[10] the age of peak incidence was noted in the fourth to fifth decade of life(age range 2-75 years). In the present study, as well as most of the previous studies show that males are more affected than females.

In our study B symptoms were seen in only 34% of the patients as compared to study by Sandhu et al[11] in which 43.2% showed presence of B symptoms.

In the present study maximum number of cases were that of DLBCL(NOS) followed by Burkitts lymphoma and marginal zone lymphoma. This was in accordance with all previous studies[9-13] wherein DLBCL has emerged as the most common type of pENL, although the incidence is different in each of them. Our study showed an incidence of 43.2% whereas it was 44% in a pioneer study from north India, 22% in a study conducted by Padhi et al[13] from southern India and 54.7% in a study by Jayanti et al[14] from western India. The regional variation suggests differences in genetic and geographic factors. Also this variation should be attributed to the referral bias seen in hospital based studies, not truly representative of population demographic profile.

Also in our study follicular lymphoma were conspicuously absent in the extra nodal sites. This could again be due to geographic variation and molecular expression profiling in follicular lymphoma as suggested by Biagi & Seymor[15]. Although in a study by kakoti et al the third most common subtype following DLBCL and PTCL.

In our study the most common site involved was the gastrointestinal tract, stomach being the most common subsite followed by colon and duodenum as compared to the other studies in India[12], Pakistan[17] and china[18] which reported head and neck to be the commonest site. Other unique site encountered in our study were thyroid, vertebrae , soft tissue and adrenal gland.

Female genital tract and skin did not feature in our study which may be attributable to the referral bias.

In the GIT the most common subtype encountered in our study was DLBCL which was in concordance with other studies followed by burkitt's lymphoma (4 cases), due to inclusion of pediatric population in our study. This was followed by low grade marginal zone lymphoma of the MALT type of which there were two cases. One case each of T cell non-hodgkin's lymphoma and in one case the patient had undergone renal transplantation twice over a span of 12 years. He had a drug history of cyclosporine, azathioprine, wysolone intake. He then presented with chronic diarrhoea for 2 years along with h/o pain abdomen & vomiting. USG was suggestive of small intestinal intusucception which was confirmed intra-operatively. A segment of jejunum was excised which showed a mass with features of Monomorphic T Cell Post Transplant Lymphoproliferative disorder.

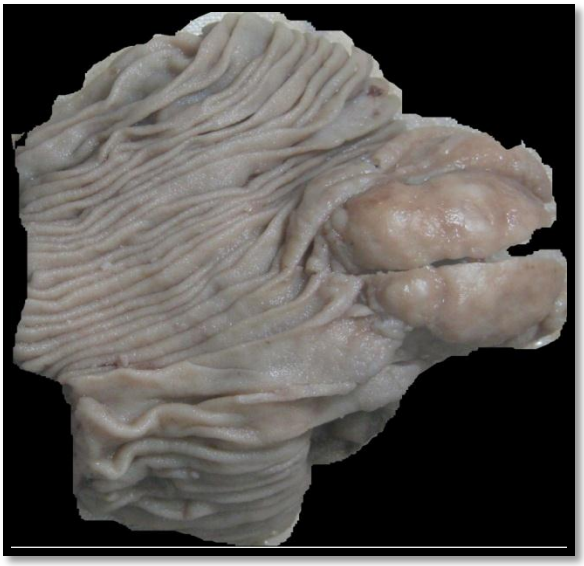


Figure 1a

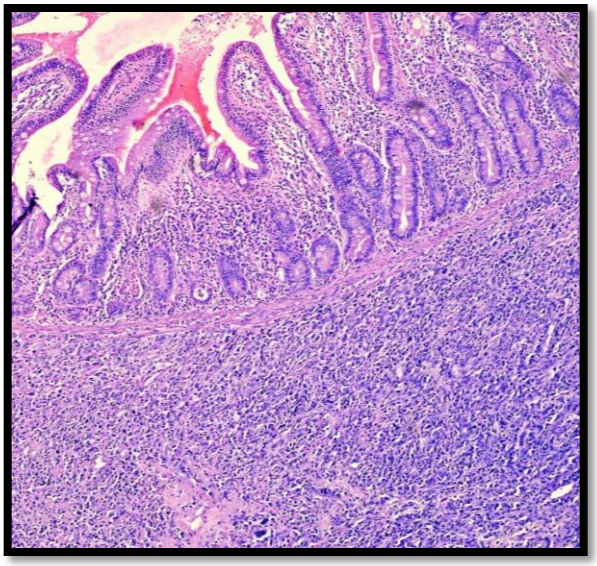


Figure 1b

Figure 1a:-A case of Monomorphic T Cell Post Transplant Lymphoproliferative disorder presenting as ileal mass

Figure 1b:-HE staining shows mucosal infiltration by intestinal monomorphic post-transplantation lymphoproliferative disorders (PTLD)

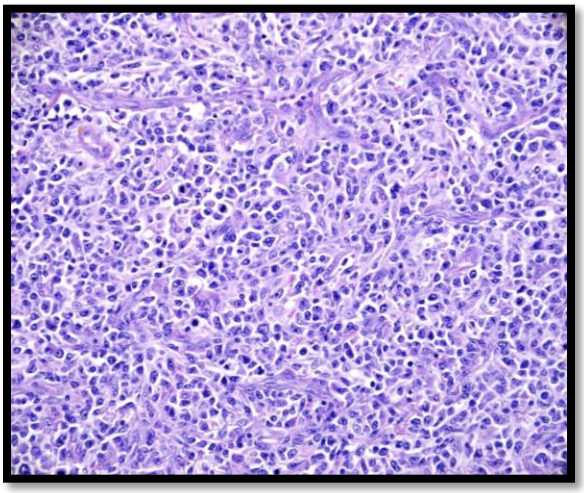


Figure 1c

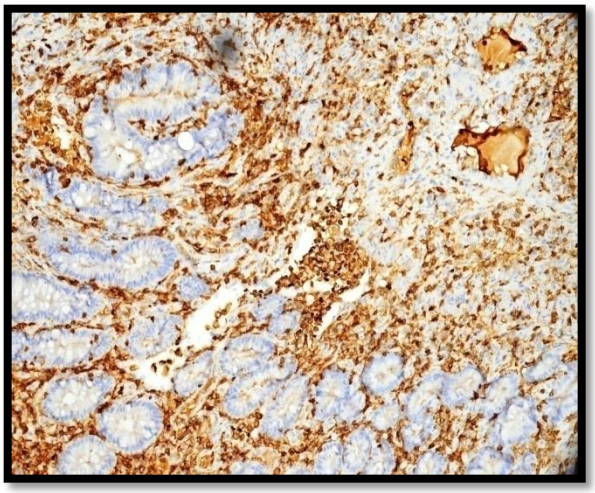
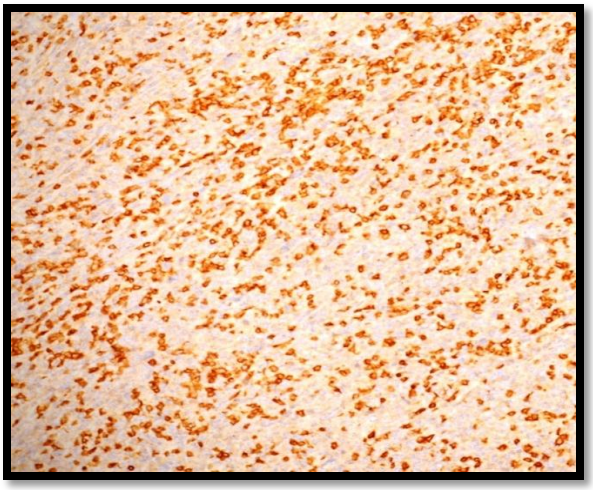


Figure 1d

Figure 1c:-Infiltrate comprising of predominant monomorphic atypical lymphoid cells.

Figure 1d:-The atypical lymphoid cells were diffusely positive for LCA.



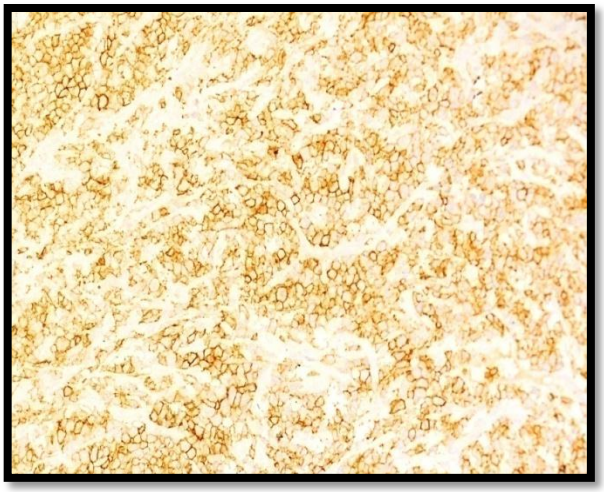
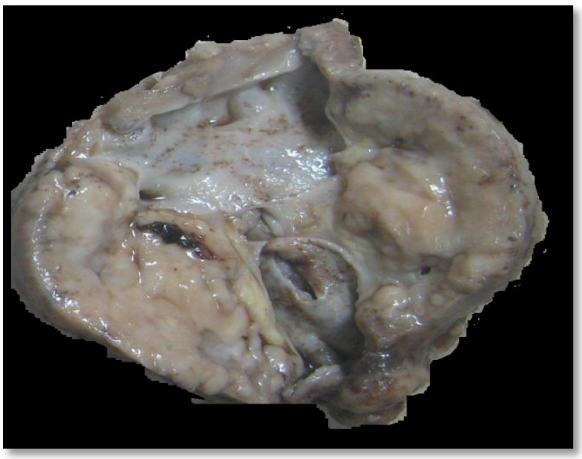


Figure 1e **Figure 1f**

Figure 1e & f:-The cells are positive for CD3 and CD43.



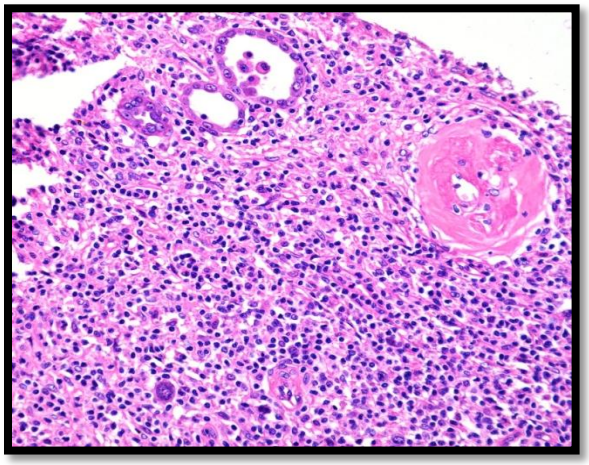
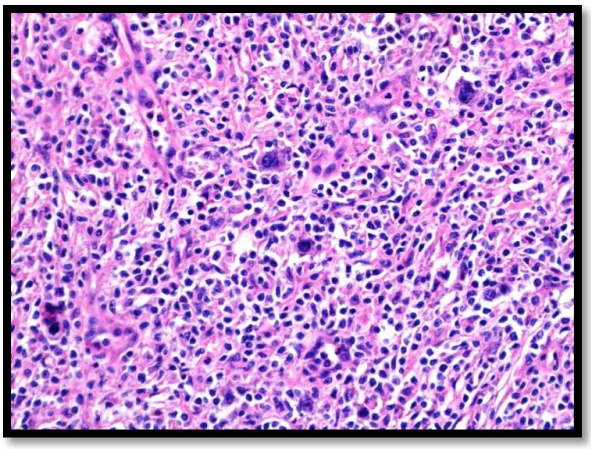


Figure 2a **Figure 2b**

Figure 2a:-Subcapsular nephrectomy specimen showing a tan grey fleshy mass.

Figure 2b:-Polymorphous infiltrate of cell was noted which was infiltrating and destroying the glomeruli, tubules and interstitium.



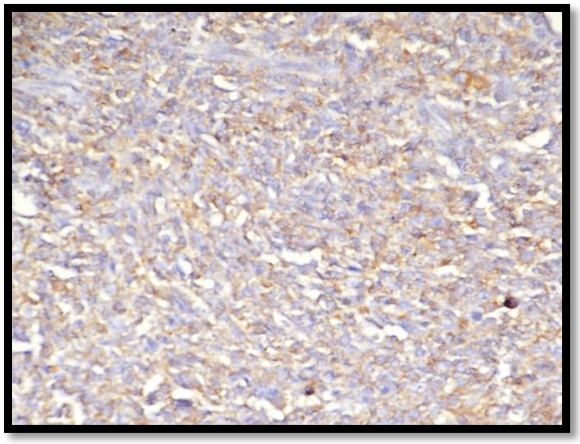


Figure 2c **Figure 2d**

Figure 2c:-Bizarre and pleomorphic malignant cells in a background of abundant T cells and histiocytes.

Figure 2d:-The cells are diffusely positive for LCA.

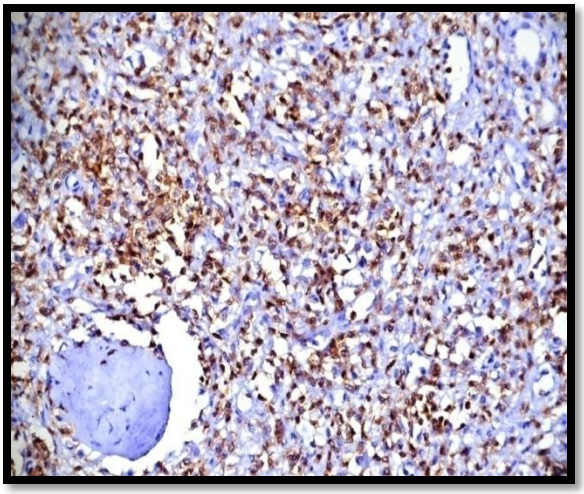


Figure 2e

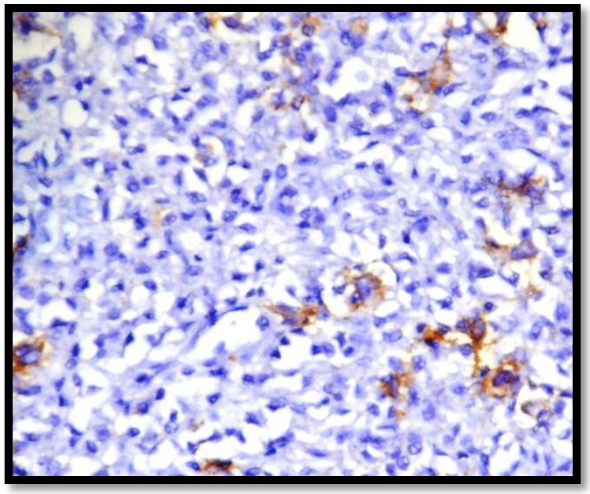


Figure 2f

Figure 2e & f:-The background cells are positive for CD3 and the scant malignant cells are positive for CD20. This finding was in concordance with other studies done by Arora N et al[19] and Raina et al[20] who also reported most cases of DLBCL amongst the cases of gastrointestinal non hodgkins lymphoma. Although Chandran et al[21] in their study had shown lymphoblastic lymphoma as the commonest GI lymphoma.

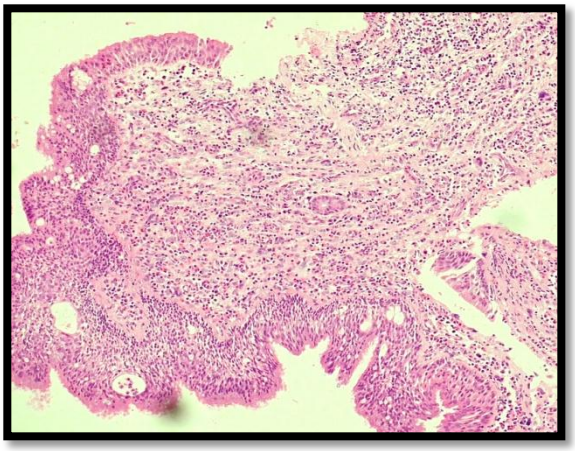


Figure 3a

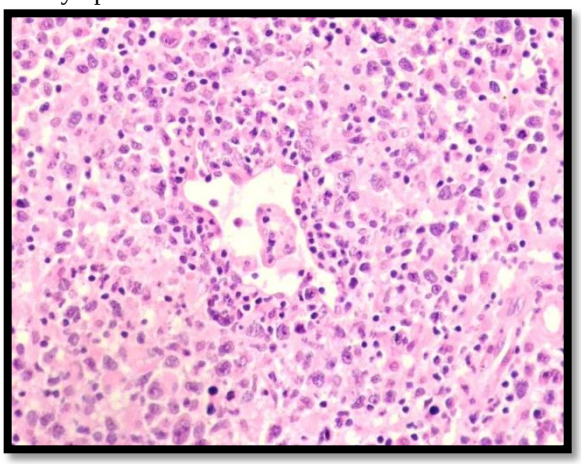


Figure 3b

Figure 3a:-Dense atypical lymphoid infiltration underlying the nasal mucosa.
Figure 3b:-Angioinvasion and destruction by malignant cells.

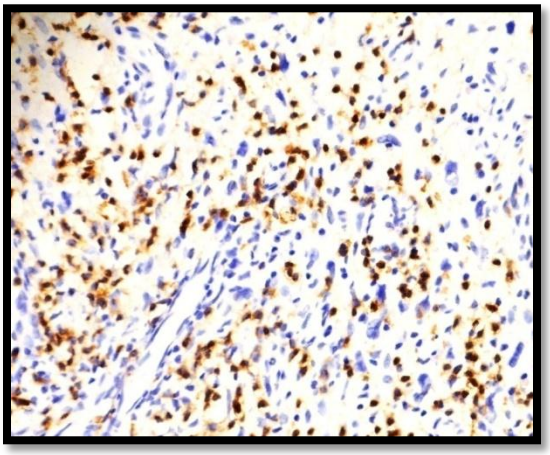


Figure 2c

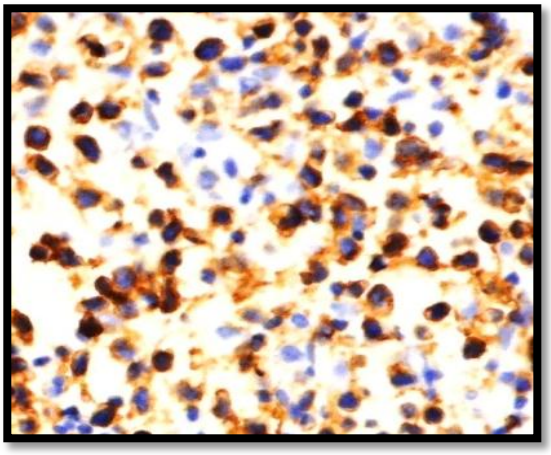


Figure 2d

Figure 2c & 2d:-Tumour cells are positive for CD3 and CD56.

Table 3:-Comparision of various Indian studies on Primary Extranodal Non Hodgkin's lymphoma:-

Author, Place	No of cases (NHL)	Duration of study	Extra Nodal NHL(n)%	Sites – Common	Sites – Less common	Histopathology (M.C.)
Singh et al[12], Delhi	241	3	106(44%)	Head and neck (tonsil), GIT (stomach)	Brain, Skin Bone, Testis, UB	Diffuse large cell lymphoma
Padhi et al[13], Pondicherry	308	5	66(22%)	Brain, GIT , Nose and nasopharynx+ paranasal sinus	Bone, Testes, Spleen, vulva, Lacrimal gland, Kidney	DLBCL, MALT B-NHL
Kakoti et al[16], Assam	257	4	80(31.1%)	Head and neck(tonsil),	GIT, orbit	DLBCL, PTCL, FL
Jayanti et al[14], Rajasthan	128	2	70(59.7%)	GIT	CNS, head and neck	DLBCL, PL, SLL
Mishra et al[10], Pondicherry	300	3	68(22%)	Head and neck, GIT	Soft tissues, Kidney	DLBCL, PTCL, MALT
A Pai et al[9], Tirupati	114	4	41(35.9%)	GIT, NPNS	Testis, FGT, thyroid	DLBCL, MALT
Present study, Lucknow	231	3	100	GIT, Thyroid, Vertebral	Spleen, soft tissue, CNS	DLBCL, Burkitts lymphoma, Marginal zone lymphoma

Conclusion:-

Primary Extranodal lymphoma are a group of heterogeneous group of hematolymphoid malignancy. Not only it comprises of a diverse group of diseases with different clinical course and outcome but also different anatomical distributions. There are studies from different parts of india and world with different set of findings because of this heterogeneity. Also there are many debating issues which will have to be addressed such as the definition of the term to include extranodal lymphatic sites such as the tonsil and Waldeyer's ring (WR)[22]. The staging system is also an issue which has to be addressed as the designation of stage III and IV lymphomas as primary extranodal NHLs is indeed questionable since extranodal involvement in the presence of mainly nodal or disseminated disease may represent secondary extranodal disease spread.

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