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Case Series

Primary extra – nodal DLBCL at rare sites: A case series

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ABSTRACT

Background: Lymphomas can originate from either nodal or extra-nodal sites, with an increasing number of patients presenting with extra-nodal non-Hodgkin's lymphoma (NHL). Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of primary extra-nodal NHL, constituting 71–81.3% of cases. DLBCL, a prevalent aggressive NHL, can manifest in various extranodal locations such as the gastrointestinal tract, thyroid, testis, breast, and skin. It can also originate in lymph nodes before spreading to extranodal sites. The heterogeneity of extranodal DLBCL leads to varied clinical presentations and prognoses depending on the affected organs.

Case Series Overview: This case series examines instances of primary extra-nodal DLBCL occurring at rare sites. Through detailed clinical evaluations and pathological examinations, the series aims to highlight the diagnostic challenges and therapeutic approaches for these uncommon presentations. In this case series we have described primary extra-nodal DLBCL in rare sites like thyroid, cervix, liver, breast and intraventricular region. Each case is meticulously documented, focusing on the patient's clinical history, the site of lymphoma involvement, diagnostic procedures, treatment modalities, and outcomes.

Discussion: The discussion addresses the complexities of diagnosing primary extra-nodal DLBCL due to its rarity and diverse presentation. The series underscores the importance of thorough clinical and pathological assessments in identifying these cases. The heterogeneity in clinical outcomes emphasizes the need for tailored therapeutic strategies. Moreover, the series explores the immunohistochemical profiles and genetic markers that might aid in better understanding the disease's behavior and improving patient management.

Conclusion: Primary extra-nodal DLBCL at rare sites presents significant diagnostic and therapeutic challenges. This case series contributes valuable insights into the clinical and pathological spectrum of the disease, advocating for personalized treatment approaches to enhance patient outcomes.

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1. Introduction

Lymphoma may arise from a nodal or extra-nodal origin, and the number of patients with extra-nodal non-Hodgkin's lymphoma (NHL) is rapidly increasing. The most common pathological type of primary extra-nodal non-hodgkin's lymphoma is diffuse large B-cell lymphoma (DLBCL), representing 71–81.3% of cases. Diffuse large B cell lymphoma (DLBCL) is one of the most prevalent histological subtypes of aggressive non-Hodgkin lymphoma (NHL).[1] Extra nodal occurrences account for up to one-third of DLBCL cases. Extranodal sites includes gastrointestinal tract, thyroid, testis, breast, and skin.[2] Additionally, DLBCL can originate in lymph nodes and subsequently disseminate to extranodal sites. Extranodal DLBCL exhibits high heterogeneity in both clinical presentation and prognosis in different organs. Many studies are concentrating on explaining its correlation between

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incidence, clinicopathological features, immunohistoprofile and molecular characteristics within specific organs. Hence extranodal DLBCLs emerge as distinct entities, as evidenced by variations in molecular pathogenesis, clinical presentation, and natural history.[2]

We are reporting 5 cases of primary extranodal DLBCL in rare sites.(Table 1)

All patient was diagnosed to have Extranodal Diffuse large B cell lymphoma of Germinal center B type after immunohistochemistry following Hans algorithm.(Table 2)

2. Case 1

45 year old male with hard nodular neck swelling involving right lobe and isthmus of thyroid.

USG neck showed a TIRAD4 neoplastic nodule. FNAC done showed florid lymphocytes with absent follicular epithelial cells. Hashimoto thyroiditis and lymphoma was considered. Hence, a biopsy was suggested. The patient underwent tru cut biopsy. It showed a neoplasm composed of cells arranged in sheet. Cells have hyperchromatic nucleus, distinct nucleoli and scant cytoplasm. Necrosis and mitosis also noted.

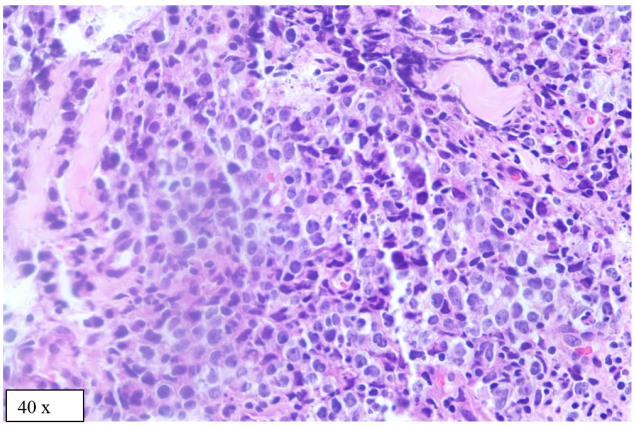

Figure 1: H& E of Thyroid: Cores of thyroid tissue with a neoplasm composed of cells arranged in sheet. Cells have hyperchromatic nucleus, distinct nucleoli and scant cytoplasm. Necrosis and mitosis noted

2.1. Primary diffuse large B cell lymphoma of thyroid

Primary thyroid lymphomas are predominantly of Non-Hodgkin's B cell type. The two most common subtypes are Diffuse large B cell lymphoma which accounts for 50-70%of cases followed by mucosa associated lymphoid tissue lymphoma accounting for 10-50%of cases. Majority of these patients presents with rapidly enlarging neck swelling.[3] While fine-needle aspiration (FNA) remains a crucial tool in managing thyroid diseases, but its effectiveness in diagnosing Primary Thyroid Lymphomas (PTL) is limited. Fine needle aspiration alone may lead

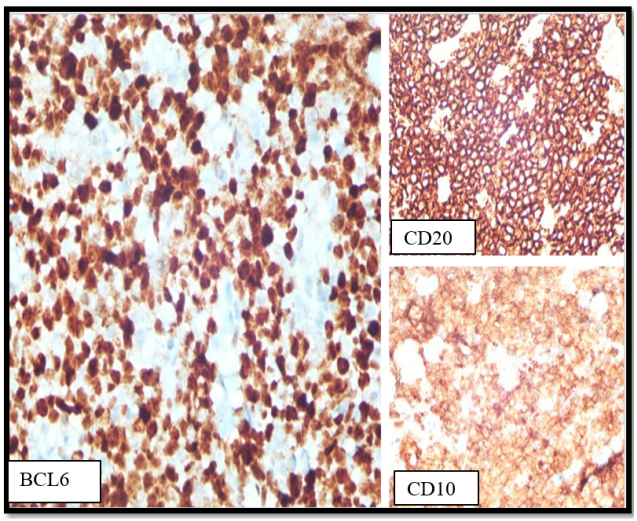

Figure 2: Immunohistochemistry of Primary extranodal DLBCL thyroid

to misdiagnosis of Hashimoto's thyroiditis. Furthermore, preexisting Hashimoto's thyroiditis is a well-acknowledged risk factor that predisposes individuals to the development of Primary Thyroid Lymphoma (PTL). Therefore, it is imperative to exercise utmost care to prevent the oversight of the potential occurrence of Diffuse Large B-cell Lymphoma (DLBCL). The identification of a monotonous population of atypical lymphocytes plays a crucial role in differentiating DLBCL from Hashimoto's thyroiditis.[4] Recent studies have shown that combining fine needle aspiration (FNA) with immunocytochemistry improves the accurate diagnosis of diffuse large B-cell lymphoma (DLBCL).[5] Biopsy of thyroid though not routinely done, it should be done in a case where lymphoma is suspected, in order to make a prompt diagnosis.[6] Primary thyroid lymphomas can be categorized as germinal center B-cell (GCB) or non-germinal center B-cell (non-GCB) type based on HAN's classification. In our case, it was identified as the non-GCB subtype.[7] Generally, primary thyroid DLBCLs have a more favourable prognosis compared to DLBCLs originating in other endocrine organs.[2] Our patient received the CHOP regimen and is currently under regular follow-up. After 18 months of treatment, the patient is doing well without any signs of relapse.

3. Case 2

47 year old female with complaints of irregular bleeding and dysmenorrhea. On examination had a pedunculated polypoidal mass in cervix. USG pelvis done showed bulky heteroechoic cervix with increased vascularity. Patient underwent punch biopsy which showed endocervical tissue with a neoplasm composed of cells with hyperchromatic nucleus arrange of diffusely. On suspecting lymphoma,

Table 1: Patient characteristics according to the primary involved site

Case	Age	Gender	Site	Symptoms
1	45	Male	Thyroid	Neck swelling
2	47	Female	Cervix	Irregular bleeding and dysmennorhea
3	57	Female	Liver	Upper abdominal pain
4	28	Female	Intraventricular region	Headache and generalised tiredness. History of seizures
5	58	Female	Breast	Incidentally detected

Table 2: Immunohistochemistry profile

Case	Site	CD20	CD10	BCL2	BCL6	MUM1	cMYC
1	Thyroid	Positive	Positive	Negative	Positive	Negative	Negative
2	Cervix	Positive	Negative	Negative	Positive	Negative	Negative
3	Liver	Positive	Positive	Negative	Negative	Negative	Negative
4	Intraventricular region	Positive	Positive	Positive	Positive	Negative	Negative
5	Breast	Positive	Negative	Positive	Positive	Negative	Positive

Immunohistochemistry was performed which lead to the diagnosis DLBCL.

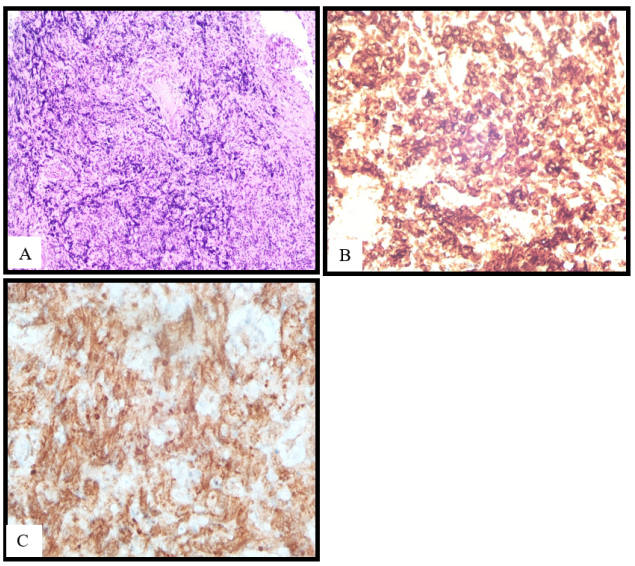

Figure 3: A): Shows endocervical tissue with a neoplasm composed of cells with hyperchromatic nucleus arranged diffusely (H & E 20X); **B**): CD20; **C**): BCL6.

3.1. Primary diffuse large B cell lymphoma of cervix.

Primary female genital lymphomas are exceptionally uncommon neoplasm comprising merely 0.2% to 1.1% of all extra-nodal instances. There is a lack of comprehensive studies on lymphomas affecting the uterine cervix, and the available data are primarily in the form of case reports. Diagnosis of cervical diffuse large B-cell lymphoma (DLBCL) is often challenging due to its rarity.[8] Pap smears may not be effective for diagnosis in the early stages as the lymphoma cells infiltrate the cervical stroma and the overlying epithelium is intact and normal.[9] Clinically, these lesions can present as bulky exophytic mass lesions. Cervical lymphoma is typically diagnosed across a broad age range, spanning from 20 to 80 years, with most cases occurring in individuals aged between 40 and 59 years. Histologically, primary cervical lymphomas can be mistaken for chronic inflammatory processes because of the dense lymphocytic infiltrate. However, certain features like a monomorphous population of lymphoid infiltrate, diffuse growth pattern, surrounding sclerotic stroma, and intact overlying epithelium can aid in the diagnosis of primary cervical lymphoma. The histological diagnosis in our case initially indicated a poorly differentiated malignancy. However, upon further examination using immunohistochemistry, it was subsequently determined to be diffuse large B-cell lymphoma of germinal centre type. Due to the rarity of lymphoma of cervix, it can be misdiagnosed as poorly differentiated carcinoma or as small cell carcinoma. however small cell carcinoma and poorly differentiated carcinoma exhibit some degree of nuclear moulding or cellular cohesion indicating their epithelial nature(9). When encountering small cell neoplasms or poorly differentiated tumors in this area, it is important to consider the possibility of lymphoma. The prognosis of cervical primary lymphomas is challenging to establish due to the scarcity of cases. Currently our patient is on treatment with R- CHOP regime.

4. Case 3

57 year old female came with complaints of upper abdominal pain for 2 weeks . CECT showed a space occupying lesion in liver measuring 7.6x5.3 cm lesion involving seg2/3/4 and was suggestive of hepatic adenoma or hepatocellular carcinoma. AFP was 5.1, CA19.9

was 5.5 and CEA was 1.6. She then underwent left hepatectomy. Showed a greyish white, firm and grossly circumscribed tumour measuring 10.5 x 8.0 x 5.0 cm. Microscopically a neoplasm composed of cells arranged diffusely. Cells have hyperchromatic nucleus with occasional prominent nucleoli. Morphologically lymphoma was a strong possibility and since radiologically a diagnosis of hepatocellular carcinoma was given IHC was done to confirm.

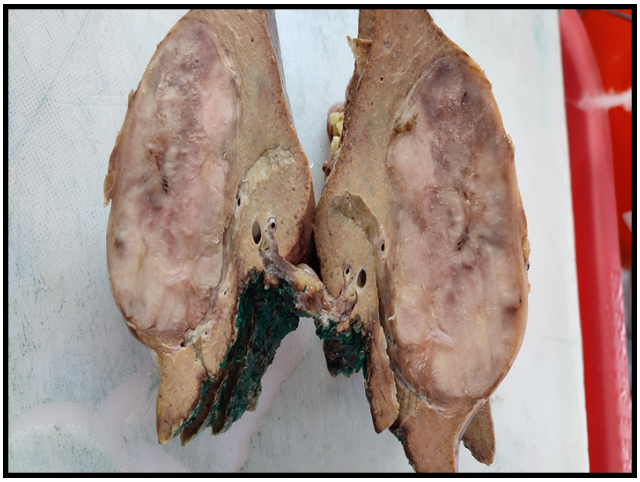

Figure 4: Shows greyish white, firm and circumscribed tumour measuring 10.5 x 8.0 x 5.0 cm in size

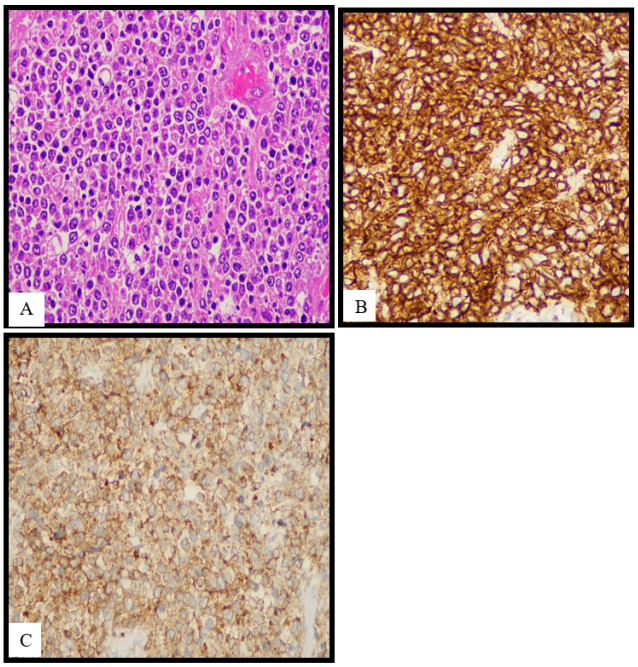

Figure 5: A): Shows liver tissue with a neoplasm composed of cells arranged diffusely. Cells have vesicular nucleus with prominent nucleoli (H&E, 40x); **B):** CD20; **C**): CD10

4.1. Primary diffuse large B cell lymphoma of liver

Ata and Kame first described the primary hepatic lymphoma (PHL) in 1965.[10] PHL is defined as lymphoma confined to the liver without any involvement of other organs or leukemic changes in the peripheral blood for at least 6 months after diagnosis. Since the incidence of hepatic involvement in NHL ranges from 16% to 22%, it is crucial to conduct careful investigations to exclude primary disease elsewhere. Most common type of primary NHL in the liver is diffuse large B cell lymphoma. The clinical presentation may vary, with abdominal pain being the most common symptom, and hepatomegaly the most prevalent clinical finding.[11] Lesions can present as solitary, multiple, or diffusely infiltrating, and may even be absent on radiological imaging. Consequently, they can be misdiagnosed as hepatic adenoma, HCC, metastatic carcinoma, or other infiltrative lesions such as tuberculosis, sarcoidosis, etc.[12] Elevated liver enzymes may occur in cases of primary NHL of the liver but normal levels of AFP, CA19.9 and CEA can aid in distinguishing it from hepatocellular carcinoma and metastatic carcinoma. However, liver biopsy is essential to arrive at a definite diagnosis. In our case there was a suspicion of hepatocellular carcinoma radiologically, hence patient underwent hepatectomy rather than a biopsy. As with nodal and other extranodal large B-cell lymphomas, chemotherapy is the primary treatment for primary hepatic diffuse large B cell lymphoma.[13] Our patient is currently on the chop regime.

5. Case 4

28 year old female with past history of seizures in 2012 and 2022 came with complaints of generalized tiredness and nausea with occasional headache for past 1 week. Imaging showed a well defined hypodense lesion with lobulated margins measuring 5.3 x 5.4cm around pineal region in midline. A diagnosis of pineal germinoma was given. Patient underwent fronto parietal craniotomy and biopsy was sent for histopathology. It showed a neoplasm composed of sheets of medium to large cells with round nuclei, small nucleoli and amphophilic cytoplasm. Keeping lymphoma as strong possibility immunohistochemistry was done which lead to diagnosis.

5.1. Primary diffuse large B cell lymphoma of intraventricular region

Central nervous system (CNS) lymphoma, whether primary or secondary, constitutes a relatively uncommon subgroup within non-Hodgkin lymphoma. Primary central nervous system lymphoma specifically encompasses cases localized to the CNS parenchyma, dura, leptomeninges, cranial nerves, spinal cord, or the intraocular compartment, particularly in immunocompetent individuals.[14] Diffuse large B-cell lymphomas stand out as the predominant

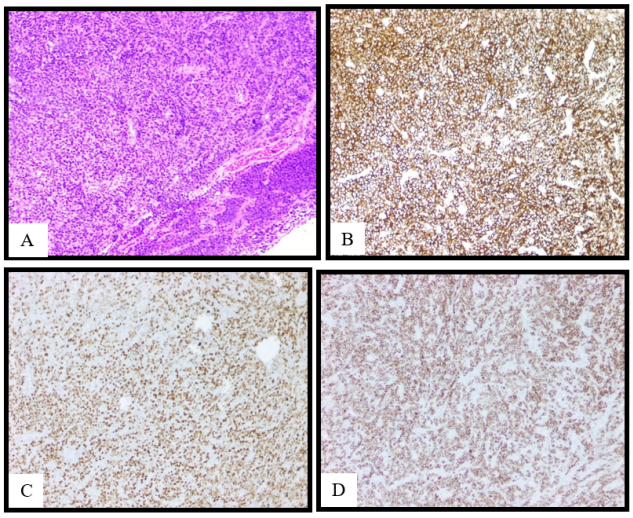

Figure 6: A): Shows a neoplasm composed of sheets of Medium to large cells with round nuclei, small nucleoli and amphophilic cytoplasm (H & E, 10x); **B)**: CD20; **C)**: BCL6; **D)**: BCL2

subtype among primary central nervous system lymphomas, constituting approximately 2-3% of all brain tumours and 4-6% of extranodal lymphomas. They are mainly situated in cerebral hemispheres, thalamus, basal ganglia, corpus callosum, periventricular region, and cerebellum, these lymphomas mostly manifest as solitary lesions.[15] Our patient was started on R-CHOP regimen and is currently doing well.

6. Case 5

58 year old female presented with incidentally detected right breast lump. On examination there was a well localised hard swelling. Imaging showed a BIRAD4a lesion, well defined anechoic lesion with internal solid area. FNAC done showed diffusely arranged atypical cells having hyperchromatic nucleus and scant cytoplasm. Mitosis and necrosis noted. A diagnosis of poorly differentiated malignant neoplasm was given. Following which trucut biopsy was done which showed a neoplasm composed of cells with uniform, hyperchromatic nucleus and prominent nucleoli arranged diffusely.

6.1. Primary diffuse large B cell lymphoma of breast

Primary breast lymphomas are infrequent, making up less than 0.5% of all malignant neoplasms in the breast and approximately 2% of extranodal lymphomas. SEER data indicates a notable rise in their incidence over the past few decades. Patients are usually middle aged or elderly women presenting with unilateral painless breast lump. Clinically these lesions may mimic breast carcinoma. Primary lymphoma of the breast can be three types-diffuse large b cell lymphoma, extranodal marginal zone

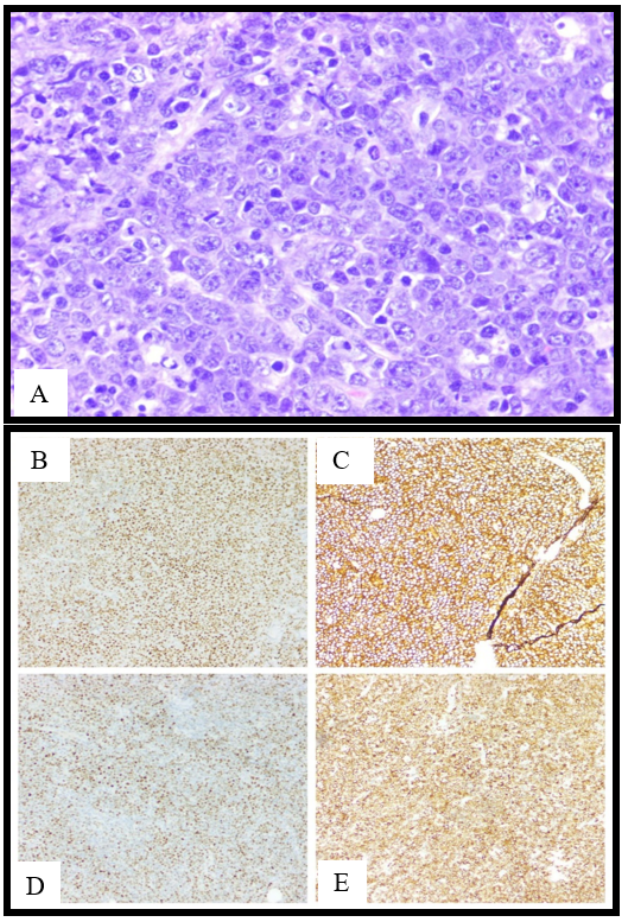

Figure 7: A): Shows a neoplasm composed of cells with uniform, hyperchromatic nucleus and prominent nucleoli arranged diffusely (H&E, 40x); B: BCL6; **C)**: CD20; **D)**: c-Myc; E: BCL2.

lymphoma of mucosa associated lymphoid tissue and follicular lymphoma.[16,17] The imaging findings of PBL are variable and at times may mimic breast cancer. Fine needle aspiration cytology may differentiate lymphoma from breast carcinoma, but it lacks architectural detail necessary to accurately classify lymphoma subtype. Hence a biopsy specimen is necessary for the diagnosis and subtyping of Primary DLBCL of breast.[18] Histologically it is characterized by medium-sized neoplastic cells with blastic nuclear features infiltrating the breast parenchyma in a noncohesive single-file pattern, resembling the invasive lobular pattern. In invasive lobular carcinoma, neoplastic cells exhibit a low nuclear grade, and immunohistochemical markers such as cytokeratin and ER are positive, while being negative for CD45, CD20, and CD3. In cases of primary breast lymphoma, local surgical excision may not confer the benefits of systemic therapy. Hence, radical excision is not recommended. Patients who have undergone radical mastectomy under the presumption of breast carcinoma must promptly initiate comprehensive chemotherapy and

radiotherapy. So, it is crucial to differentiate PBL from breast carcinoma by needle core biopsy to prevent unnecessary radical surgery. DLBCL bears the worst prognosis among the various subtypes of primary breast lymphomas. Chemotherapy stands out as an effective treatment for primary breast DLBCL. R-CHOP remains the primary treatment regimen in the first line. Following this, radiotherapy may be considered, as most data suggest that this combined modality can enhance survival rates and diminish local recurrence. [19]

7. Conclusion

Given the high heterogeneity of extranodal DLBCLs, ranging from clinical characteristics to prognosis, studies frequently concentrate on correlating DLBCL occurrence with its molecular characteristics in specific organs. Such investigations yield novel insights for the treatment of extranodal DLBCLs. The IHC algorithm developed by Hans and Tall divides DLBCL into three subtypes - Germinal centre B cell-like (GCB), Activated B-cell like (ABC) and unclassified subtype. Based on molecular studies, subtypes characterized by recurrent mutations have been identified. These are double-hit and triple-hit lymphomas, characterized by concurrent rearrangements of MYC, BCL2, and/or BCL6. Patients with these mutations typically have more aggressive disease course and a poorer prognosis following frontline treatment with R-CHOP, particularly in cases with advanced-stage disease.

In our case series all were of subtype germinal centre B cell like and except the breast case none had MYC rearrangement.

8. Souce of Funding

None.

9. Conflict of Interest

None.

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