Original Article

Extranodal Non-Hodgkin's Lymphoma: A Case Series

Sushama Gurwale, Charusheela R. Gore, Kunjal Mukesh Karia, Sourabh P. Paranjape, Padmakar R. Bardapurkar, Harsh Kumar, Archana C. Buch

Department of Pathology, Dr. D. Y. Patil Medical College, Hospital and Research Centre, Dr. D. Y. Patil Vidyapeeth, Pune, Maharashtra, India

Abstract

Introduction: Primary extranodal lymphoma (pENL), a type of Non-Hodgkin's lymphoma (NHL) are the group of malignant neoplasms that arise from tissues other than lymph nodes and alsofrom the sites devoid of normal lymphoid tissue. The incidence of extranodal lymphoma (ENL) has an increasing trend and it accounts for one-fourth of all NHL. Any anatomical site of the body can be source of origin for the ENL.The presence of distinct clinical features in many variants of pENL has varied etiology, some may be associated with microbial infection, immunodeficiency syndrome, auto-immune diseases etc. **Case Report:** We highlight case series of 13 patients presenting with pENL which we encountered in the span of three years. The diagnosis of these cases was made on histopathology and immunohistochemistry. **Discussion:** The term ENL encompasses a variety of morphological variants, molecular alterations, clinical presentations; thereby posing a diagnostic challenge. They require varied therapeutic approach due to organ specific problems. These cases are discussed in order to emphasize on the increased incidence of these primary extranodal lymphomas.

Keywords: *Extranodal lymphoma, non-Hodgkin's lymphoma, primary lymphoma*

Introduction

Non-Hodgkin's lymphoma (NHL) is the lymphoproliferative malignant neoplasms having varied histomorphological and clinical characteristics. The nodal type of NHL is the ones that arise from the lymphoid organs, while the lymphomas that arise from tissues other than the lymph node or the sites devoid of lymphoid tissue are the primary extranodal type.[1] The extranodal lymphoma (ENL) is of two types; primary and secondary. The secondary ENL is the presentation of lymphoma first in lymph nodes and involving the extranodal sites subsequently.[2] The incidence of primary ENL (pENL) is increasing over the past two decades, and ENL accounts for 25% for all NHL.[3] The frequency of ENL varies in the different parts of the world with the incidence of pENL more where lymphomas are encountered more.[2,4] They are of a diagnostic challenge to the clinicians, pathologists due to varied epidemiology, morphology, clinical presentations, and etiology.[1,3] The most common histological type of ENL noted is diffuse large B-cell lymphoma type (DLBCL) followed by peripheral T-cell lymphoma and MALToma.[1] The occurrence of Hodgkin's lymphoma at extranodal sites is rarely seen.[2]

Case Report

The pENL cases that we came across in 3 years time period are 13. Their detailed clinical presentation and approach to diagnosis is mentioned in Table 1.

Discussion

Primary extranodal lymphoma accounts for a substantial percentage of NHL. Primary ENL forms a heterogeneous group of tumors arising from sites other than lymph nodes, spleen, or bone marrow and also from the sites having no lymphoid tissue.[1,4,5] The exact definition of extranodal lymphoma is controversial in the presence of both nodal and extranodal disease. Krol *et al*. proposed the definition of pENL that included all patients of extranodal NHL, with or without disseminated disease, where extranodal component predominated.[6] ENL is said to be primary ENLs if they meet the following criteria laid by Dawson *et al*.[7]

- Absence of palpable lymphadenopathy
- Absence of mediastinal lymphadenopathy on X-ray chest
- Presence of lesion at extranodal site
- Involvement of lymph nodes in the areas adjacent to the primary lesion

How to cite this article: Gurwale S, Gore CR, Karia KM, Paranjape SP, Bardapurkar PR, Kumar H, *et al.* Extranodal non-Hodgkin's lymphoma: A case series. Clin Cancer Investig J 2018;7:137-42.

Address for correspondence:
Dr. Charusheela R. Gore, Department of Pathology, Dr. D. Y. Patil Medical College, Hospital and Research Centre, Dr. D. Y. Patil Vidyapeeth, Pimpri, Pune - 411 018, Maharashtra, India.
E-mail: shantugore@gmail.com

Access this article online

Website: www.ccij-online.org

DOI: 10.4103/ccij.ccij_61_18

Quick Response Code:

Table 1: pENL case sheets

Age (years) Sex	Site	Clinical presentation	Clinical diagnosis	Diagnostic modality		Final diagnosis
				Histopathology	IHC	
70 male	CNS	Hippocampal SOL	High grade astrocytoma	DLBCL	Tumour cells positive for LCA CD20, BCL 2, BCL 6 Negative for CD 3 Ki67: 90%	DLBCL
75 male	CNS	Left parafalcine SOL	Meningioma	DLBCL	LCA and CD 20: Diffuse positive CD 3 and CD30: Negative Ki67: 60% to 70%	DLBCL
52 female	Thyroid	Old case of Rt Ca breast with thyroid swelling (left > right)	Follicular thyroid neoplasm Metastasis from Ca breast	High grade NHL with Hashimoto's thyroiditis	Tumour cells positive for LCA CD20, BCL 2, Negative for CD 3, CD 30 and CD 10 Ki67: 70%-80%	Diffuse high grade BCL
55 female	Thyroid	Enlarged thyroid	Lymphocytic thyroiditis with colloid goiter	DLBCL	CD45, CD20: Positive CD 3, Synaptophysin, chromogranin: Negative	DLBCL
70 male	Anorectalmass	Ulcerated anorectal growth	Ca Rectum	Malignant round cell tumor	CD79a: Positive in some tumor cells LCA: Weak positive CD138, Mum1: Diffuse positive in tumor cells PANCk, CD 20, Chromogranin, HMB45, CD30: Negative	Plasmablastic lymphoma
46 male	Testis	Lt undescended testis with abdominal pain since 2 months	Lt undescended testis	DLBCL	CD45, CD20: Positive Ki 67: 80%-90%	DLBCL
65 male	Testis	Swelling left hemiscrotum since one month	Ca testis	Small round cell tumor s/o lymphoma	CD 20, CD 45, BCL2 positive CD3, CD 30 negative Ki67 80%-90%	DLBCL
24 female	Ovary	Acute abdominal pain for 2 days	Left twisted ovarian cyst	Burkitt lymphoma	LCA, CD20 and LMP1:Positive CD3, CD30, EMA, CD117: Negative Ki67: >95%	Burkitt lymphoma
62 female	Adrenal	Abdominal pain for 2 months	Adrenal cortical carcinoma	DLBCL	LCA, CD20: Diffuse positive CD3, CD5, CD10, synaptophysin, chromogranin, CK, EMA: negative	DLBCL
21 male	Lateral chest wall	Rapidly enlarging mass in chest wall	Soft tissue tumor	Round cell tumor	LCA, CD20: Positive BCL2 negative for tumor cells, CD15, panCK, desmin: Negative Ki 67: 90%	DLBCL
18 male	Pelvic mass	Lump and pain in lower abdomen	Soft tissue tumor	DLBCL	LCA, CD20: Positive CD 3, CD30: Negative Ki67: 90%	DLBCL

Contd...

Table 1: Contd....

Age (years) Sex	Site	Clinical presentation	Clinical diagnosis	Diagnostic modality		Final diagnosis
				Histopathology	IHC	
75 male	Left nasal cavity mass	Swelling over forehead since 4 months	Soft tissue sarcoma	Poorly differentiated carcinoma Non-Hodgkins lymphoma	CD45, CD20: Positive panCK: Negative Ki 67: 80%-90%	DLBCL
25 male	Skin	Whitish lesions with generalized scaling all over the body since 6-7 years	Pityriasis Lichenoid chronicus Mycosis fungoides	Mycosis Fungoides	CD8: Positive with loss of CD7 expression CD4 positive in few cells	Mycosis fungoides

CNS: Central nervous system, LCA: Leucocyte common antigen, EMA: Epithelial membrane antigen, DLBCL: Diffuse large B-cell lymphoma type, SOL: Space occupying lesion, IHC: Immunohistochemistry, BCL: B-cell lymphomas

- Normal white blood cell count.

The increasing incidence of primary ENL since the last 2 decades is attributed to the improved diagnostic procedures and changes amended in the classification system.[4,5] Primary ENL forms one-third of the bulk of all NHL.[5] The frequency of ENL varies with geographical distribution, ethnicity, anatomical localization, and morphology.[2,3] Extranodal NHL can arise from any anatomic site of the body such as gastrointestinal tract, head and neck, skin, central nervous system, bone, thyroid, testis, breast, adrenals, pancreas, and genitourinary system. Among all the anatomic locations, the gastrointestinal tract is the most common site, followed by head and neck.[2,8] However, in our study, we have found head and neck as the predominant region of involvement. pENL has a varied clinicopathological picture with unknown exact cause. It is usually multifactorial and is seen in association with immunodeficiency syndromes, autoimmune diseases, environmental agents, bacterial, and viral infections.[2]

The majority of pENL are of B-cell lineage with diffuse large cell type as the predominant type seen in approximately 50% of the cases of pENL. In our case series, we also have similar findings with DLBCL accounting around 70% of cases. The B-cell and T-cell lymphoma at the extra-nodal site have different clinical outcome than those at nodal site, thus requiring different treatment modalities and approach.[5] The patients with pENL involving rare sites have poor therapeutic outcome because of its complex behavior, organ-specific problems.[3,4] The independent prognostic variables of pENL are the age of the patient, stage of the lymphoma, performance status and serum lactate dehydrogenase (LDH) levels.[3]

Primary central nervous system lymphoma (PCNL) is defined as lymphoma arising in and confined to the cranial-spinal axis (brain, eye, leptomeninges and spinal cord). There is increased incidence in immunocompromised and immunodeficient hosts. Primary central nervous system (CNS) lymphoma is thought to arise from late germinal center or postgerminal center lymphoid cells and localizes to the CNS because of a poorly understood neurotropism. Presenting signs and symptoms are neuropsychiatric signs, increased intracranial pressure, seizures, and ocular symptoms. Seizures are less common than with other types of brain tumors, probably because PCNSL involves predominantly subcortical white matter rather than epileptogenic gray matter.[9] Blood tests for HIV, complete blood cell count, basic metabolic profile, and LDH level are also recommended. Testicular ultrasonography should be considered in men. Contrast-enhanced cranial magnetic resonance imaging (MRI) and postcontrast cranial computed tomography (CT) if MRI is contraindicated. Lumbar puncture is done for cell count, protein and glucose measurement, cytology, immunoglobulin heavy chain gene rearrangement studies, and flow cytometry studies. Ophthalmologic examination including slit-lamp evaluation, CT of the chest, abdomen, and pelvis, and bone marrow biopsy should be performed. The available treatment options for PCNSL include corticosteroids, chemotherapy (CHOP), and radiation.[8] Two cases of PCNL, both in elderly males, were noted in the present study.

Malignant lymphomas represent 4%–5% of all thyroid gland neoplasms. The most common presentation of thyroid lymphoma is a rapidly enlarging, painless goiter. Other symptoms such as dyspnea, dysphagia, and hoarseness may arise as a result of the pressure effects of the mass.[10] Typically, it presents in the seventh decade of life, with males being affected 5–10 years earlier than females. Women are more commonly affected reflecting the strong association between thyroid gland lymphoma and Hashimoto's thyroiditis, which also most commonly affects women.[8,11] The relative risk of developing thyroid gland lymphoma in patients with Hashimoto's thyroiditis is estimated to be 67–80 times greater than the general population. DLBCL and mucosa-associated lymphoid tissue-lymphoma are the most common types of lymphoma.[11] Our both cases of thyroid pENL were females with the lymphoma arising in the background

of Hashimoto's thyroiditis, thus reconfirming the strong association between these two. Thyroid ultrasound and fine needle aspiration cytology, using flow cytometry and immunohistochemistry, remain the main modalities used to confirm the presence of lymphoma. Treatment and prognosis are dependent on accurate histological classification.[10]

Plasmablastic lymphoma is an aggressive NHL classically occurring in individuals infected with HIV. It has a predilection for the oral cavity and jaw.[8,12] However, recent case reports have shown lymphoma in the stomach, lung, nasal cavity, cervical lymph nodes, jejunum, and anorectal region in HIV-negative individuals.[13] The WHO classified plasmablastic lymphoma as a variant of DLBCL.[11] We had one case of plasmablastic lymphoma in a seronegative elderly diabetic male presenting with anorectal mass. Morphologically, plasmablastic lymphomas are characterized by a monotonous proliferation of plasmablasts and/or immunoblasts with relatively few morphological features of mature plasmacytic differentiation.[12] Plasmablastic lymphomas have a postgerminal center B-cell/plasma cell phenotype. They express MUM1/IRF4, CD38, and CD138/syndecan-1 but are frequently negative for CD20 and PAX5/BSAP[8] [Figure 1].

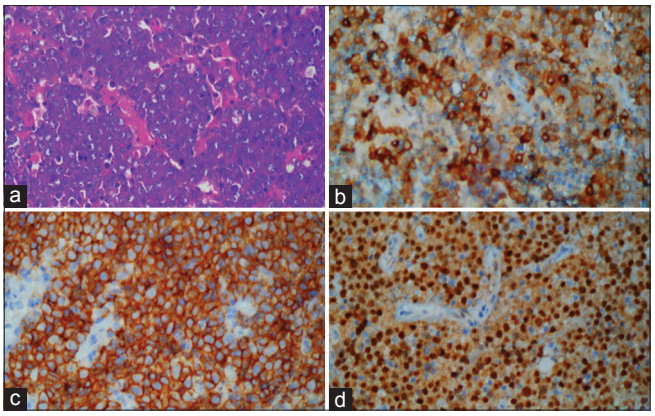

Figure 1: Plasmablastic lymphoma: Monotonous proliferation of plasmablastic cells having coarse chromatin and inapparent nucleoli (a) (H and E, ×400). Immunohistochemistry (IHC, ×400) CD 79a focal positive (b), CD138 cytoplasmic positivity (c), MUM1 shows nuclear positivity in tumour cells (d)

Primary malignant lymphoma of the testis represents 5% of all testicular tumors and only 1%–2% of all NHL, with an estimated incidence of 0.26/100,000/year.[5] Lymphoma, however, is still the most common testicular tumor in men >60 years of age. It is usually bilateral, and the predominant histological type is DLBCL.[14] We have encountered two cases pENL in testis, and both were DLBCL [Figure 2]. Orchidectomy is both diagnostic and therapeutic providing local tumor control, but it is not always curative. Primary testicular lymphoma has been recognized as a highly lethal disease, with an overall 5-year survival rate ranging from 16% to 50%.[5] Our cases, unfortunately, were lost to follow-up.

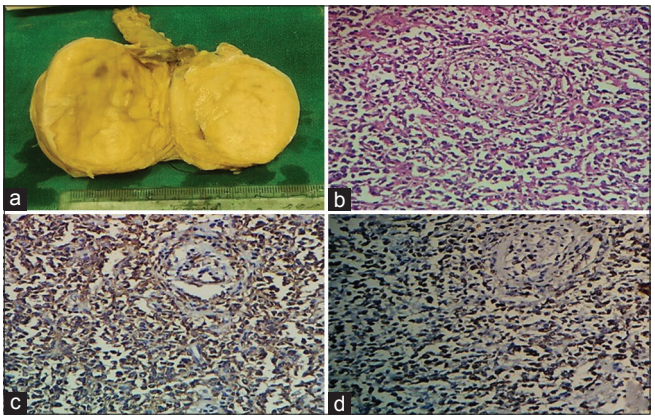

Figure 2: Diffuse large B-cell lymphoma Testis: Normal testicular parenchyma is replaced by yellowish white vaguely nodular firm tumour mass (a). Diffuse proliferation of large lymphoid cells with entrapped seminiferous tubule (b), (H and E, ×400) Immunohistochemistry (IHC, ×400) shows CD20 positivity (c), and BCL2 positivity (d) in the tumour cells

Primary lymphoma of the ovary accounts for 0.5% of all NHLs and 1.0% of all ovarian tumors. Burkitt lymphoma is the most frequent subtype of NHL in childhood and accounts for approximately 34% of cases, but primary ovarian Burkitt lymphoma is extremely rare. The ovary is the most frequent site of NHL in the female genital tract, and Burkitt lymphoma has been reported to account for approximately 19% of adnexal lymphomas. The single patient in our series is an adult female presented with acute abdomen and clinically thought of twisted ovarian cyst, which turned out to be a case of Burkitt lymphoma [Figure 3].

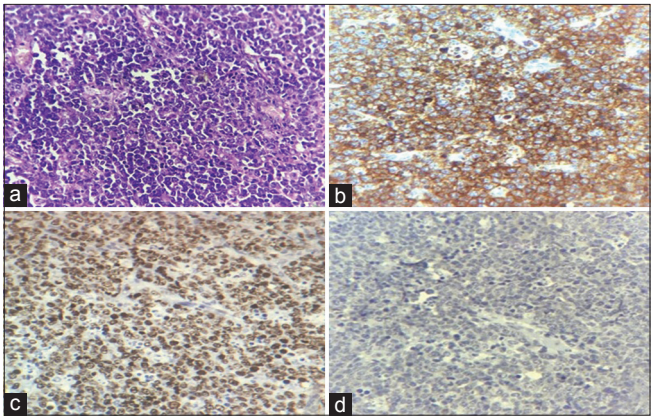

Figure 3: Burkitt's lymphoma ovary: Diffusely arranged noncohesive monomorphic population of round tumor cells having noncleaved nuclei with basophilic cytoplasm. Tingible body macrophages noted in the background (a), (H and E, ×400). Immunohistochemistry (IHC, ×400) tumor cells are positive for leukocyte common antigen (b) with Ki 67 proliferation index >95% (c) and negative for epithelial membrane antigen (d)

Fox and Langley proposed the following criteria for the diagnosis of a primary ovarian lymphoma.[15]

- Clinical confinement of the lymphoma to the ovary and a lack of evidence of lymphoma elsewhere on the complete investigation at the time of diagnosis

- The peripheral blood and bone marrow should not contain any abnormal cells
- If further lymphomatous lesions occur at sites remote from the ovary then at least several months should have elapsed between the appearance of the ovarian and extraovarian lesions.

There are two forms of Burkitt lymphoma: Endemic and sporadic. Burkitt lymphoma is the most rapidly growing tumor. Although it has been associated with a 60%–85% 5-year survival rate in advanced-stage disease, its prognosis can be very poor when the ovary is involved.[15]

Unilateral or bilateral NHL arising primarily in the adrenal glands is extremely rare. Patients usually present in the sixth decade of life and are more common in men. Presenting symptoms are nonspecific. Adrenal insufficiency is present in 50%–70% of these patients. We have also seen one case of primary DLBCL in an elderly female who presented with pain in abdomen. There was no adrenal insufficiency noticed. The most common hypothesis for the origin of these tumors is hematopoietic tissue rests in the adrenal gland akin to adrenal myelolipoma.[16,17] The most common subtype is the diffuse large B-cell type. T-cell and angiocentric large cell lymphoma Type B are the exceptions. The standard therapeutic modalities are combination CHOP with or without surgery. Some investigators suggest that surgical de-bulking with subsequent CHOP for large masses provides a better response rate. Alternatively, radiotherapy can be given to bulky lesion with the idea of preventing local recurrence.[16] The prognosis is grave with the survival period <5 months in the group of primary adrenal lymphoma.[17]

Mycosis fungoides is the most common type of cutaneous T-cell lymphoma and represents nearly 50% of all primary cutaneous lymphomas. It occurs mostly in elderly adults (age ≥55 years) but can also be seen in children and young adults. The male-to-female ratio is about 2:1. There is usually a prolonged clinical course with the evolution of patches and plaques to tumor stage in some patients. Our case was a young adult male who presented with whitish scaly lesions all over the body since 7 years morphologically the neoplastic lymphoid infiltrate is epidermotropic and composed predominantly of small to intermediate sized atypical lymphocytes with enlarged hyperchromatic, cerebriform nuclei, and clear cytoplasm (haloed cells). These atypical lymphocytes often colonize the basal layer of epidermis singly or in a linear fashion, forming a "string of pearls"[18] [Figure 4].

Conclusion

Our study constituted 13 cases of pENL with head and neck being predominant region of involvement (five cases), followed by genital organs (three cases) and CNS and thyroid (two cases each). The pENL involving adrenal gland, nasal cavity, and skin were also seen. The majority of pENLs were DLBCL. Although this is a relatively small series of cases, we have come across rare cases of lymphomas at unusual sites such as plasmablastic lymphoma in anorectal region and Burkitt's lymphoma primarily involving ovary, which prompted us to share our experience.

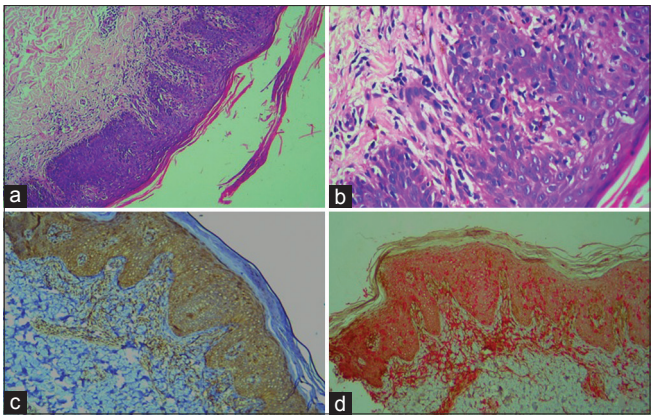

Figure 4: Mycosis fungoides: Lichenoid lymphocytic infiltrate involving papillary dermis and epidermis with hyper and parakeratosis (a), (H and E, ×100). The neoplastic lymphocytes are medium sized, hyperchromatic with irregular nuclei (b), (H and E, ×400).Immunohistochemistry (IHC, ×400) loss of CD 7 expression (c) with magenta colored CD8 cells and brown colored CD4 cells (d)

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Mishra P, Das S, Kar R, Jacob SE, Basu D. Primary extranodal non-Hodgkin lymphoma: A 3-year record-based descriptive study from a tertiary care center in Southern India. Indian J Pathol Microbiol 2015;58:296-300.
2. Mehta J, Thakrar MP, Matadeen M, Mittal A, Gupta K. Primary extranodal non-Hodgkin lymphoma: A 2-year retrospective analysis from a tertiary care centre in Rajasthan. Int J Med Res Prof 2016;2:76-80.
3. Pai A, Kannan T, Balambika RG, Vasini V. A study of clinical profile of primary extranodal lymphomas in a tertiary care institute in South India. Indian J Med Paediatr Oncol 2017;38:251-5.
4. Padhi S, Paul TR, Challa S, Prayaga AK, Rajappa S, Raghunadharao D, *et al.* Primary extra nodal non Hodgkin lymphoma: A 5 year retrospective analysis. Asian Pac J Cancer Prev 2012;13:4889-95.
5. Zucca E. Extranodal lymphoma: A reappraisal. Ann Oncol 2008;19 Suppl 4:iv77-80.
6. Krol AD, Le Cessie S, Snijder S, Kluin-Nelemans JC, Kluin PM, Noordijk EM. Primary extranodal non-Hodgkin's lymphoma (NHL): The impact of alternative definitions tested in the Comprehensive Cancer Centre West population-based NHL registry. Ann Oncol 2003;14:131-9.
7. Dawson IM, Cornes JS, Morson BC. Primary malignant lymphoid tumours of the intestinal tract. Report of 37 cases with a study of factors influencing prognosis. Br J Surg 1961;49:80-9.

8. Vega F, Lin P, Medeiros LJ. Extranodal lymphomas of the head and neck. Ann Diagn Pathol 2005;9:340-50.
9. Gerstner ER, Batchelor TT. Primary central nervous system lymphoma. Arch Neurol 2010;67:291-7.
10. Walsh S, Lowery AJ, Evoy D, McDermott EW, Prichard RS. Thyroid lymphoma: Recent advances in diagnosis and optimal management strategies. Oncologist 2013;18:994-1003.
11. Campo E, Chott A, Kinney MC, Leoncini L, Meijer CJ, Papadimitriou CS, *et al*. Update on extranodal lymphomas. Conclusions of the workshop held by the EAHP and the SH in Thessaloniki, Greece. Histopathology 2006;48:481-504.
12. Ferry JA. Extranodal lymphoma. Arch Pathol Lab Med 2008;132:565-78.
13. Brahmania M, Sylwesterowic T, Leitch H. Plasmablastic lymphoma in the ano-rectal junction presenting in an immunocompetent man: A case report. J Med Case Rep 2011;5:168.
14. Cheah CY, Wirth A, Seymour JF. Primary testicular lymphoma. Blood 2014;123:486-93.
15. Miyazaki N, Kobayashi Y, Nishigaya Y, Momomura M, Matsumoto H, Iwashita M, *et al*. Burkitt lymphoma of the ovary: A case report and literature review. J Obstet Gynaecol Res 2013;39:1363-6.
16. Dutta P, Bhansali A, Venkatesan R, Mittal BR, Kumar V. Primary adrenal lymphoma. Endocrinologist 2005;15:340-2.
17. Ho CH, Chueh SC, Pu YS, Chen SC, Yu HJ, Huang KH. Primary adrenal lymphoma – A rare entity with grave prognosis. JTUA 2009;20:168-72.
18. Song SX, Willemze R, Swerdlow SH, Kinney MC, Said JW. Mycosis fungoides: Report of the 2011 Society for Hematopathology/European Association for Haematopathology Workshop. Am J Clin Pathol 2013;139:466-90.