

# Varied Clinical Presentation of Non Hodgkin Lymphoma

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## Abstract

*Objective:* Lymphomas with involvement of soft tissues as an ulcer or sore as a primary event are very rare. We present varied cases like ALCL, Angioimmunoblastic lymphoma, Marginal zone lymphoma, PTCL and DLBL with soft tissue involvement and compared with the database of ten years. *Case report:* In this article we describe our experience with soft tissue non-Hodgkin lymphomas (NHL) diagnosed and treated in our institution over a 1 year period. The most common histologic subtype was diffuse large B cell lymphoma (DLBCL) followed by ALCL. *Conclusions:* Though indolent soft tissue B-cell NHLs appear to have a good outcome, soft tissue DLBCLs, ALCL and AITCL represent an anatomic-clinical entity with aggressive features, and dismal prognosis.

## Keywords

Diffuse Large B-cell Lymphoma, ALCL, AITCL, Non-hodgkin Lymphoma, Soft Tissue Lymphoma, T-Cell Lymphoma

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## 1. Introduction

Lymphomas with involvement of soft tissues as an ulcer, sore, nasal mass, breast lump and soft tissue swellings as a primary event are very rare. We present varied cases of extranodal lymphomas which presented as soft tissue masses and were diagnosed as ALCL, Angioimmunoblastic T cell lymphoma, PTCL and DLBL with soft tissue involvement.

## 2. Case Presentations

Lymphoma presenting as a soft tissue mass is rare and thus may be confused with the more common soft tissue sarcoma. Clinical and radiographic features that favor extranodal soft tissue lymphoma over sarcoma include pain and tenderness, lymphadenopathy (particularly when confluent radiologically), ipsilateral extremity swelling, and elevated lactate dehydrogenase. In this article we describe our experience with soft tissue non-Hodgkin lymphomas (NHL)

diagnosed and treated in our institution over a 1 year period.

59 years male with a colonic growth with thickened wall. Histology revealed monomorphic population of lymphoid cells arranged in sheets with occasional follicle formation. The cells have high NC ratio with scant cytoplasm, vesicular nuclei, and prominent nucleoli. CD 20 was diffusely membranous. Final diagnosis was Diffuse large B cell lymphoma.

A 26 yrs old young male presenting as a nonhealing ulcer in the leg which was diagnosed by FNAC and by histology as Anaplastic Large Cell Lymphoma. Sections show tumor comprising of sheets of pleomorphic large tumor cells with high NC ratio and prominent nucleolus with few cells having multiple nucleoli. Wreath like cells seen. Brisk mitotic activity with areas of necrosis seen. Immunohistochemistry shows CD45, CD30, CD3 positive, Alk negative. Ki67

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labelling > 90%.

64 and 80 yrs old male patients with a nasal mass which was diagnosed as Diffuse large B cell lymphoma with immunohistochemistry showing CD20 positive.

A 40 years old lady with a shoulder and chest wall mass reported as DLBCL. Similarly a 34 years old female presented with a large Jaw swelling which was reported as DLBCL.

A 34 yrs old male presenting with an axillary mass whose histopathology shows Angioimmunoblastic T cell lymphoma. (Fig.1).

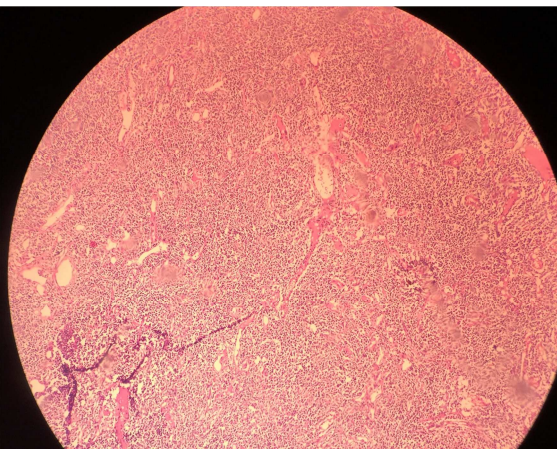


Fig. 1. Gross and Microscopy of angioimmunoblastic lymphoma in a axillary mass.

In this way we reviewed 50 cases of extranodal lymphomas over 1 year period of which soft tissue lymphomas were 25, GI 10, Breast 5, Nasal 5, CNS 5. The most common subtype was Diffuse large B Cell Lymphoma. The patients were started on chemotherapy and are on regular follow up. Moreover, we systematically review the available data from the literature in the past 2 decades, considering all the published series and case reports available in last two decades using a PubMed access. The most common histologic subtype was diffuse large B cell lymphoma (DLBCL) followed by ALCL.

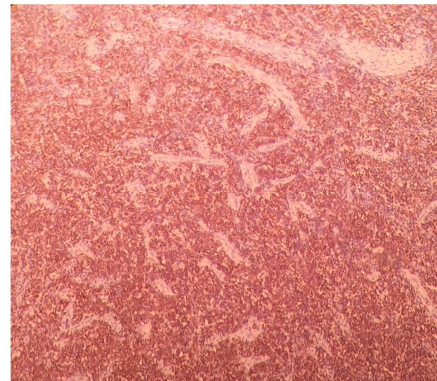
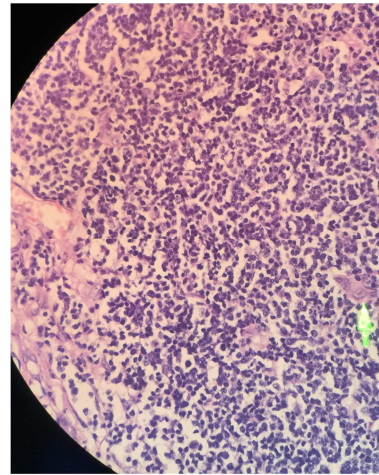


Fig. 2. Hematoxylin and eosin stained section and CD 20 positivity of Diffuse large B cell lymphoma in a colonic tumor.

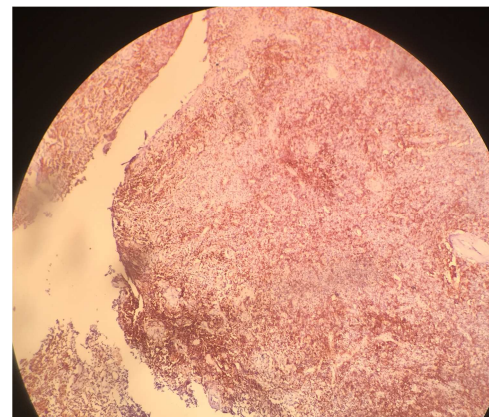
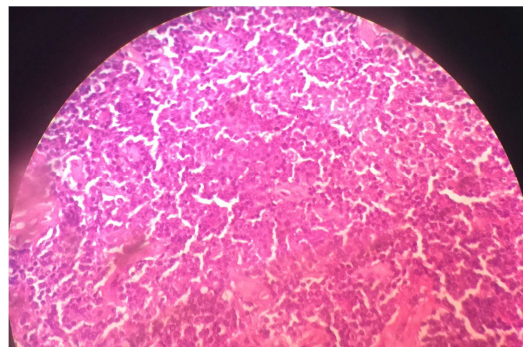


Fig. 3. Hematoxylin and eosin stained section and CD 20 positivity of Diffuse large B cell lymphoma in a nasal mass.

### 3. Discussion

At least one quarter of non-Hodgkin's lymphomas (NHL) arise from tissue other than lymph nodes and even from sites which normally contain no lymphoid tissue. These forms are referred to as primary extranodal lymphomas [1, 2]. Since these tumours, numerous when considered together, are widely distributed throughout the body, it is difficult to find adequate series of any given site. Moreover, many historical series were published before the recognition of mucosa-associated lymphoid tissue as the origin of many extranodal lymphomas and in general, classification of primary extranodal lymphomas was similar to that of nodal lymphomas, without consideration that their origin could be different. Hence, the literature lacks uniformity in histopathological classification. The first attempt to eliminate this problem was made with the proposal of the Revised European American Lymphoid Neoplasms (REAL) classification [3]. The definition of primary extranodal lymphoma, particularly in the presence of both nodal and extranodal disease, remains a controversial issue. Operationally, lymphomas can be considered as extranodal when, after routine staging procedures, there is either no or only 'minor' nodal involvement along with a clinically 'dominant' extranodal component, to which primary treatment must often be directed. Extranodal NHL of soft tissues is a rare disease and is described in only 0, 1% of the cases [1]. The biopsy is necessary to define the diagnosis. Surgery in soft tissue lymphoma is still controversial. Damron et al. are convinced that lymphoma is a non-surgical disease in which chemotherapy and/or radiotherapy are adequate therapeutic strategies and they do not recommend the surgical excision since it would remove a clinical barometer of responsiveness to medical treatment. Biopsy should be only performed to confirm the nature of the lesion, especially in differential diagnosis with soft tissue sarcoma. On the contrary Bozas et al. described a case of abdominal wall mass (10 × 18 cm) situated between the abdominal muscles and in which a wide excision was performed followed by immunochemotherapy. Belaabidia et al. also described a case of muscle lymphoma of biceps femoris (17 × 14 × 7 cm) in which treatment was wide surgery followed by chemotherapy.

It has recently been demonstrated that NHLs on the whole are showing a rapid increase in incidence, and over the past 20 years extranodal disease increased more rapidly than nodal disease. The greatest increases have been observed for the lymphomas of the central nervous system, followed by lymphomas of the gastrointestinal tract and the skin. In addition to the AIDS epidemic, other predisposing factors,

such as other viral infections, immunosuppressive treatments, or environmental factors, might explain the increased incidence of extranodal lymphomas. Gastrointestinal localisations represent the most common form of extranodal lymphoma. Other frequent and clinically important sites include the CNS and the skin. However, extranodal lymphomas can arise in almost every organ. Signs and symptoms at presentation depend largely on the localisation; generally, patients with extranodal lymphomas tend less often to present B symptoms than do patients suffering from lymphomas arising in the nodal regions. The outcome can be different in the disparate specific sites of primary extranodal lymphomas. This is partially due to differences in natural history, but mainly to differences in management strategy which are related to organ-specific problems. Testis and thyroid lymphomas are more often seen in elderly patients, while a significantly higher incidence of hepatic and intestinal lymphomas is related to younger age. Salivary gland and thyroid lymphomas are significantly more common in females, while intestinal and pulmonary lymphomas are more often found in males. NHL of the stomach, salivary glands and thyroid are more frequently localised, whereas extranodal lymphomas of the lungs, liver, bones and testes are often widespread. With respect to histological classification, aggressive subtypes (usually diffuse large B-cell lymphomas) are predominant in NHL of CNS, testes, bone, liver, and to some extent the stomach. Certain extranodal sites have characteristic patterns of either B-cell (e.g. gastric marginal zone lymphoma, MALT type) or T-cell disease (e.g., cutaneous lymphoma clearly comprises a wide range of lymphomas of T-cell origin, even though a subset of B-cell cutaneous lymphomas does exist).

### 4. Primary Gastrointestinal Lymphomas

The gastrointestinal (GI) tract is the most frequently involved extranodal localisation in NHL. In hospital based and population-based series published thus far, GI-NHL accounts for 4-20% (on average 12-13%) of all NHL and 30-40% of all extranodal cases. In the Western world, the most common locations are the stomach (approximately 50-60%) and the small intestine (approximately 30%) [1]. Infection by *Helicobacter pylori* has been cited as an environmental factor of possible aetiological relevance in those cases of gastric NHL deriving from the so-called mucosa-associated lymphoid tissue (MALT) [4-8]. Less epidemiological information is available on intestinal localisations. Patients with coeliac disease have a highly increased risk of developing the so-called enteropathy-associated T-cell lymphoma (EATCL) and

some authors even favour the hypothesis that adult-onset coeliac disease is itself a form of low-grade lymphoma [1]. Presenting symptoms are generally due to the local lesion (pain, obstruction, haemorrhage). Compared with nodal lymphomas, fewer patients with gastric lymphoma present with bone marrow involvement or elevated LDH levels. Fever and night sweats are uncommon. Weight loss, however, is common, although this is more often a consequence of the localisation of the primary lymphoma rather than a constitutional symptom of the disease. The optimal treatment of gastrointestinal lymphomas is still a controversial issue and depends on the histological type and stage of the disease [1]. Increasing evidence indicates that eradication of *H. pylori* with antibiotics can be effectively employed as the sole initial treatment in low-grade gastric MALT lymphoma provided that strict oncohaematological and endoscopic follow-up is carried out [4-6, 8]. However, it is still unknown whether *H. pylori* eradication will definitely cure the lymphoma. No treatment guidelines exist for the management of patients after failure of antibiotics and for the subset of cases in which no evidence of *H. pylori* can be found [4, 6]. It has been shown that the chance of a response to antibiotics is dramatically reduced in this latter group [4]. A choice can be made between conventional oncological modalities including chemotherapy, radiotherapy, surgery, alone or in combination. There are data suggesting that both chemotherapy and radiotherapy are effective, but, unfortunately, there are no published randomised studies to help the decision [4]. Combination chemotherapy is the treatment of choice for patients with locally advanced or disseminated aggressive (high grade) lymphomas. In a prospective study from the GELA French group including more than 700 patients with aggressive lymphomas treated with intensive chemotherapy, no difference in therapy outcome was observed between patients with an advanced aggressive nodal lymphoma and the subset of patients in which the lymphoma was deemed to have arisen in the gastrointestinal tract. The effectiveness of combination chemotherapy in advanced cases of gastrointestinal lymphomas has led to a reconsideration of the role of primary surgery in less advanced cases and new approaches have been advocated. It has been suggested by the results of some recent gastric lymphoma series (including the interim results of an ongoing large German trial with more than 250 GI-NHL patients) that chemotherapy, sometimes combined with radiotherapy, can be curative and that gastrectomy must be critically reconsidered. For primary intestinal lymphoma, however, there are as yet no studies which clearly demonstrate that surgery is unnecessary and combined modality treatment is widely considered the procedure of choice [1].

## 5. Primary Cutaneous Lymphomas

Primary cutaneous lymphomas can be defined as the presence of cutaneous localisations alone, with no nodal or systemic disease. They represent a very numerous group of extranodal lymphomas, accounting for approximately 10% of cases. Moreover, the skin is a relatively common site of dissemination of many nodal NHLs, especially those of T-cell phenotype. However, the clinical behaviour of primary cutaneous lymphomas is usually different from that of primary nodal lymphomas of similar histology involving the skin secondarily. Lymphoma on morphologic grounds alone: several types of primary lymphoma of the skin classified as high grade according to the Kiel classification or the Working Formulation very often show an indolent clinical behaviour. Therefore, only a combination of histologic, immunologic and clinical data can adequately define the primary cutaneous lymphoma entities. On this basis, a new classification scheme has recently been proposed by the EORTC cutaneous lymphoma study group. Lymphomas of the skin are more often of T-cell type, with mycosis fungoides and Sezary syndrome constituting around 65% of the cases. The other types of primary cutaneous T-cell lymphomas (CTCL) are less frequent and may be further characterised according to the specific expression of cell surface antigens such as CD30. They differ from mycosis fungoides in that the epidermotropism is usually absent (i.e. the neoplastic T-cells usually infiltrate the dermis and subcutaneous tissue but not the epidermis) [14]. Classification of primary cutaneous B-cell lymphomas is particularly controversial [1]. The subtypes, follicle-centre lymphoma of the head and trunk and immunocytoma of the EORTC classification, constitute over 90% of primary cutaneous B-cell lymphomas. This group includes a large percentage of diffuse large cell lymphomas which, in the scalp and in the trunk, despite their cytologically and histologically aggressive features, spread only very rarely beyond the skin and have a clinically indolent course. More aggressive is the clinical course of primary cutaneous large B-cell lymphoma of the leg. Moreover, cutaneous follicle-centre lymphoma appears to be distinctly different from the nodal counterpart both immunophenotypically and genotypically, lacking the chromosomal translocation (14; 18) and the expression of the common leukocyte antigen (CD 10). Extranodal marginal zone lymphomas (MALT type) of the skin have been described and the cutaneous immunocytoma may also be interpreted as a low-grade B-cell lymphoma of MALT type [1]. Since skin-associated lymphoid tissue (SALT) is usually devoid of B-cells, in analogy to the MALT concept in the stomach, an acquired SALT could represent the background for the development of the lymphoma. Furthermore, the

association of cutaneous B-cell lymphoma with acrodermatitis chronica atrophicans suggests that *Borrelia burgdorferi* might have a role similar to that of *H. pylori* in the stomach. Primary central nervous system lymphoma. Primary central nervous system lymphoma (PCNSL) is a disease distinct from other extranodal lymphomas in its biology, clinical features and response to treatment. PCNSL can be defined as lymphoma arising in and confined to the cranial-spinal axis (brain, eye, leptomeninges and spinal cord). Formerly a rare tumour, PCNSL is showing increased incidence both in immunocompromised (congenital, acquired or iatrogenic) high-risk groups and in the general population. Clinical and radiological characteristics of the disease in immunocompetent patients are very different from those observed in the AIDS-associated patients in whom the PCNSL often presents with an encephalopathic picture. PCNSL accounts for 1-2% of malignant brain tumours and 2-4% of all extranodal lymphomas. Secondary involvement of the central nervous system occurs in 5-30% of systemic non-Hodgkin's lymphoma [2]. PCNSL is usually disseminated within the nervous system at diagnosis, in approximately 40-50% of immunocompetent and in nearly 100% of AIDS patients. About 40% of patients have a demonstrable involvement of the spinal fluid and 20% of the eyes. In addition to the usual procedures staging requires contrast-enhanced computerised tomography scan and magnetic resonance imaging (MRI) with gadolinium of the brain and orbits, before steroids are started because of the rapid radiographic disappearance of tumour following the administration of steroids ('ghost tumour'), a peculiar feature of PCNSL, not shared by any other intracranial malignant tumour. Histologically, the vast majority of lymphomas are of diffuse large B-cell type in the immunocompetent patients. A surgical procedure more extensive than stereotactic biopsy is rarely indicated. Aggressive surgical decompression with partial or gross total removal of the tumour is of no benefit. Historically whole brain radiation has been the treatment of choice, but, despite different radiation schedules with good initial responses, over 90% of patients recur in the brain, often in sites remote from the initial ones. Systemic dissemination occurs in only 10% of the cases, and many of these have single localisations. The prognosis for unselected patients with immunocompetent PCNSL treated with radical irradiation alone is very poor, the 5-year survival rate is 5-10% with a median survival between 12 and 18 months. Several single institutions have reported encouraging results with systemic chemotherapy alone or combined with radiotherapy, with 5-years projected overall survival of 30-50% and median survival of 2-3 years. In general, the most recent studies seem to point out that radiation therapy alone is unable to provide significant long-term survival, may interfere with later chemotherapy and may increase the risk

of treatment-induced dementia. There is mounting evidence that initial chemotherapy should be the treatment of choice, reserving irradiation for resistant or relapsing disease [2].

A particular PCNSL is the primary ocular lymphoma. It should be pointed out that primary orbital and ocular adnexa lymphomas represents a different entity, most often of extranodal marginal zone histotype, and must not be confused with lymphoma of the eye. Primary ocular lymphoma — i.e. restricted to the globe, usually the vitreous body, retina, choroid — is exceedingly rare. Ocular involvement is often bilateral and more than half of the patients will later develop brain lesions. Radiotherapy to both eyes has been the standard treatment, and, like in the other PCNSL, the combination with systemic chemotherapy is being investigated [2].

In rare instances, PCNSL presents as a localized leptomeningeal disease in the absence of parenchymal brain involvement. Diagnosis is commonly obtained by positive CSF cytology or on meningeal biopsy. The therapeutic approach is similar to primary brain lymphomas. Prognosis is usually poor [2].

Primary extradural lymphoma represents approximately 1% of all localised NHLs, it most often presents with spinal-cord compression at thoracic level. The diagnosis is generally obtained at the time of decompressive surgery with diffuse large-cell lymphoma being the most common histology. Its inclusion among the PCNSL is controversial.

## 6. Conclusion

This study reports rare localization of cases of Non Hodgkin lymphoma in the soft tissues. Excision biopsy followed by chemotherapy allowed a good local and systemic control of the disease gives a good functional recovery. Lymphoma presenting as a soft tissue mass is relatively uncommon and can easily be confused with a wide variety of inflammatory conditions, more common neoplasias (sarcoma, plasmacytoma, metastasis) as well as infectious diseases (tuberculosis). Extranodal involvement by lymphoma has been described in every tissue of the body with multiple different appearances even within one organ system. Thus, it should be regularly included in the differential diagnosis of mass lesions.

## Clinical Message

Extranodal lymphomas are a rare entity that can mimic a wide range of conditions. It is important to have a high index of suspicion when assessing a mass and differential diagnosis should always include lymphoma.

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