Nodular lymphocyte predominant Hodgkin's lymphoma

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ABSTRACT

Objective: To describe the clinicopathological features, treatment, treatment outcome and sequelae of patients with nodular lymphocyte predominant Hodgkin's lymphoma (NLPHL) in a Saudi population.

Methods: This is a retrospective review of 29 patients with lymphocyte predominant Hodgkin's lymphoma treated at 2 major hospitals (King Khalid University Hospital and Security Forces Hospital) in Riyadh, Kingdom of Saudi Arabia from 1985 to 2000. Histological subtypes were confirmed by review of hematoxylin and eosin paraffin sections and immunochemistry. Details of clinical presentation, stage, treatment and results of treatment were analyzed.

Results: On pathological reappraisal of the 29 cases, 3 patients had nodular sclerosis Hodgkin's lymphoma and 4 patients were reclassified as lymphocyte rich classical Hodgkin's lymphoma. Twenty-two patients were identified to have nodular lymphocyte predominant Hodgkin's lymphoma (NLPHL). These patients comprised of 18 male and 4 female patients with a median age at presentation of 25 years. Nineteen (86%) patients had an early stage (Ann Arbor stage I and II) disease, 2 had stage III and one patient had a stage IV. The majority of the patients presented with peripheral lymphadenopathy and long duration of symptoms. For 16 patients, details of treatment and follow-up were available. All of these achieved a complete response to initial treatment. Four patients relapsed following the primary therapy.

Conclusion: Our results are consistent with the previous series reported from Western countries and confirm that patients with NLPHL have a characteristic clinical and pathological profile that distinguish it from other types of Hodgkin's lymphoma. The disease tends to run an unusual course and although most patients achieve an excellent response to therapy there is a tendency to relapse. Treatment remains controversial; however, recent understanding of the molecular pathogenesis of NLPHL could lead to modification of current therapeutic approach to this disease.

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The International Lymphoma Study Group, performed a complete reappraisal of the lymphoma classification system in 1994, the Revised European-American Lymphoma (REAL) classification and suggested that Hodgkin's disease comprised of 2 distinct lymphomas; namely classical Hodgkin's disease (nodular sclerosing, mixed cellularity, lymphocyte depleted and lymphocyte rich classical) and nodular lymphocyte predominant (NLP) type.[1] The REAL classification was later consolidated by the World Health Organization (WHO) working group in 1997.[2] Since then much has been learnt and it has been realized that Hodgkin's disease cell is a lymphoid cell that is clonal in nature. Thus, Hodgkin's disease is a true lymphoma deserving a name change to Hodgkin's lymphoma (HL).[3]

Nodular lymphocyte predominant Hodgkin's lymphoma (NLPHL) is a unique subtype of HL with characteristic morphologic, biologic and

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clinical features (**Table 1**).[4] It accounts for 3-5% of all HL cases. Morphologically, NLPHL has at least a partially nodular growth pattern with characteristic tumor cells called lymphocytic +/or histocytic (L&H) cells of B-cell lineage. Lymphocytic +/or histocytic cells differ from the Classic Reed-Sternberg cell (CRS), that they have vesicular polylobulated nuclei and distinct peripheral nucleoli, without perinuclear haloes. These cells are also called "popcorn" cells, due to its resemblance to an exploded kernel of corn.[5] In contrast, to classical HL cells, these atypical cells express B-cell associated antigens (CD19, CD20, CD22) but lack CD15 and CD30.[4,6] Recently, it has been observed that CD30 remains negative in L&H cells of NLPHL despite using enhanced antigen retrieval and, therefore, can be reliably used to distinguish NLPHL from classical HL. The value of epithelial membrane antigen in the diagnosis of NLPHL remains uncertain.[7] Clinically, patients with NLPHL show a striking male predominance and the male to female ratio is 3:1 or greater. The usual age reported at first diagnosis is 25-35 years.[8-9] Nodular lymphocyte predominant Hodgkin's lymphoma usually involves peripheral lymph nodes and in most series approximately 80% of patients have stage I and II disease at the time of diagnosis. Although more than 90% of all patients experience a complete remission (CR) upon first-line treatment, late and multiple relapses are more common than other types of HL. The cause of death in these patients is often described to be from non-HL, other cancers or complication of treatment, rather than HL.[10-12] Nodular lymphocyte predominant Hodgkin's lymphoma is considerably rare with an incidence rate for Western countries of 0.3 cases per 100,000.

Table 1 - Clinical features of nodular lymphocyte predominant Hodgkin's lymphoma (NLPHL) and classical Hodgkin's Lymphoma (HL).[4]

Features	Classical HL	NLPHL
Age distribution	Bimodal (NS)	Unimodal
Male gender (%)	NS: 50 MC: 70	70
Sites involved	Mediastinum, abdomen, spleen	Peripheral lymph nodes
Stage at diagnosis (%)	Often II or III	Usually I
B-symptoms (%)	40	<20
Course	Aggressive, curable	Indolent, late relapses
Risk of B-cell lymphoma	<1	2-3

According to the 1998-1999 report by National Cancer Registry (NCR) of Saudi Arabia, HL represents 3.4% of all 11,000 diagnosed cancers in Saudi Arabia. The annual incidence rate for HL as reported by NCR was 1.6/100,000, out of which only 4% were lymphocyte predominant.[13] In view of the rarity of this disease, it is hard to collect sufficient cases for meaningful analysis. We accumulated data from 2 major hospitals in Riyadh, Saudi Arabia, to study the clinical characteristics and pathological features of this intriguing disease from a Saudi perspective.

Methods. A list of patients diagnosed to have lymphocyte predominant Hodgkin's Lymphoma (LPHL) was obtained from the registries of King Khalid University Hospital and Security Forces Hospital, Riyadh, Saudi Arabia. From the years 1985 through 2000, a total of 29 patients were entered as LPHL. Hematoxylin and eosin stained paraffin sections obtained from conventionally prepared tissues were examined for confirmation of morphologic diagnosis according to REAL classification.[1] The diagnostic criteria for NLPHL used in this study included the following: L&H variants of CRS cells; background cells predominantly small mature lymphocytes; reactivity of L&H cells for CD20 and non-reactivity for CD15 and CD30. Features that excluded the diagnosis were: Frequent classic RS cells; frequent non-lymphoid inflammatory background cells; extensive fibrosis; reactivity of RS cells for CD15 or CD30 and non-reactivity for CD20. Monoclonal antibodies used were leucocyte common antigen (LCA), CD45 RO, CD3, CD20, CD15 and CD30.

Immunophenotyping was available for 19 patients. Using the above mentioned criteria for diagnosis, 7 cases initially considered to be LPHL according to Rye classifications were re-classified as classical HL. Three of these patients were considered to have nodular sclerosing HL and 4 patients were classified as lymphocyte rich classical HL. The remaining 22 patients were studied with regards to age, gender, Ann Arbor stage, the presence or absence of 'B' symptoms at diagnosis as well as the pattern and distribution of disease. All patients who were treated for NLPHL, underwent staging with history and physical examination, blood counts, chest x-rays, computerized tomography (CT) of thorax/abdomen and bone marrow biopsy. The various treatment modalities used, results of treatment, relapse pattern and follow-up of these patients were recorded.

The collected data were entered on a structured form and statistical analysis was carried out using Statistical Package for Social Sciences 10.0. All the values are represented as mean $\pm$ SD and percentage.

Results. Of the 22 patients studied, there were 18 (81.8%) males and 4 (18.18%) females, with a male to female ratio of 4.5:1. The mean age at presentation was 25±12.93 years (range 10-58 years). Mean duration of symptoms before the diagnosis of HL established was 17 months (range 2-72 months). The majority (86%) presented with early stage disease. Stage I comprised of 11 patients, and 8 had stage II disease. Two patients had a stage III at presentation and one was diagnosed with stage IV. Nodal presentation was predominantly cervical. Peripheral lymph node enlargement was reported in 20 (91%) cases. Two patients had mediastinal involvement, and only one patient had bulky disease (**Table 2**).

Overall 'B' symptoms (4 patients, 18%), abnormal chest x-ray (2 patients) and liver function abnormalities were rare. None of the patients had lymphopenia; however, 3 patients had anemia with hemoglobin values of less than 10.5 g/dL. One patient had leucocytosis (white cell count >18,000/m^2) while 2 other patients had hypoalbuminemia. Details of treatment were available for 16 patients, all of whom received standard treatment for HL according to the international protocols practiced at that time. Four patients received radiotherapy alone, 6 patients had chemotherapy alone, and 6 patients had chemotherapy aside from radiotherapy. All patients who received chemotherapy were administered by doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) protocol. One patient received mechlorethamine, vincristine, procarbazine and prednisone (MOPP) chemotherapy.[14,15] As a result of primary therapy all patients achieved complete response. These patients were followed-up in the clinic at 2 or 3 months intervals for 2 years, then at longer intervals. Follow-up studies included physical examination, chest x-ray and if indicated, a CT scan.

Overall, 4 patients had relapsed since initial therapy. The average time to relapse from complete remission was 57±28.61 months. Three of these patients had hypoalbuminemia, leucocytosis and anemia at the time of their original diagnosis; features which have been shown to indicate a worse prognosis.[16] The other characteristics of these patients are tabulated in **Table 3**. All of these patients underwent treatment and achieved complete response to treatment of relapsed disease.

Table 2 - Sites of presentation in 22 patients with nodular lymphocyte predominant Hodgkin's lymphoma.

Sites Involved	N (%)
Cervical lymph nodes	11 (50)
Axillary lymph nodes	5 (22.7)
Mediastinal lymph nodes	2 (9.1)
Supraclavicular/submandibular lymph nodes	2 (9.1)
Inguinal lymph nodes	2 (9.1)
Abdominal lymph nodes	1 (4)
Extranodal sites	
Bone marrow	1 (4.5)
Spleen	1 (4.5)
Liver	1 (4.5)

Discussion. Most previous studies of NLPHL were reported from Western countries. Our study confirms the unique and distinctive nature of NLPHL in a Middle Eastern population. In this study, NLPHL was mostly seen among young individuals with a notable male predominance. A

Table 3 - Characteristics of 4 relapsed patients.

Patient number	Age (years)	Gender	Initial stage	Initial site	Initial treatment	Time to relapse from diagnosis (months)	Site of relapse	Treatment of relapse	Outcome
1	41	Male	2B	Cervical, mediastinal, axillary	Chemotherapy	72	Cervical, axillary	Chemotherapy	Remission
2	17	Male	2A	Cervical, axillary, mediastinal	Chemotherapy	96	Cervical	Chemotherapy	Remission
3	14	Female	IIA	Cervical	Radiotx	36	Submandibular	Chemotherapy	Remission
4	18	Male	IVB	Axillary, bone marrow	Chemotherapy	24	Axillary	Radiotx	Remission

male to female ratio of 4.5:1 was considerably greater than the 1.5-2:1 ratio characteristic of classical HL. The majority of the patients were diagnosed at an early stage with a rather prolonged period of lymphadenopathy; namely, 42 months before diagnosis. Most patients presented with peripheral lymph node enlargement. Two patients had mediastinal lymph node involvement whereas only one patient had hepatic and splenic disease. These findings are similar to those previously described in literature (**Table 1**).[17-18]

Many authorities consider NLPHL to have a different pathobiology when compared to other classifications of HL. A multicenter retrospective study which investigated the clinical characteristics and course of LPHL patients reported that 27% of their patients had multiple relapses. This is significantly a higher percentage than the 5% relapses of classical HL. However, despite the frequent relapses, these patients had considerably superior survival compared to classical HL.[19] Among NLPHL patients, stage is an important prognostic factor for survival. The early stage at presentation indicates an excellent prognosis. However, survival and freedom from treatment failure are substantially worse for advanced stage patients. This implies that thorough staging at the time of diagnosis is mandatory for patients with NLPHL.[18] Review of the clinical course of our patients revealed that 4 out of 16 (25%) patients have relapsed since their original diagnosis and treatment. None of the patients with stage I disease has so far relapsed. Although some authors have reported a higher incidence of development of non-HL in patients with NLPHL, this was not demonstrated in our study. However, it is well-known that the natural history of NLPHL is exceptionally prolonged, therefore, a longer follow-up period might indicate a different result.[10,17]

The distinctive nature of NLPHL including an indolent course, early stage at presentation and an excellent overall prognosis suggests that when treating patients with this unique disease, one should consider tailoring therapy according to the individual patient. In order to minimize the toxicity and long term effects of treatment, patients with an early stage of disease should receive minimum possible therapy. This is supported by the results of some studies which suggested that freedom from treatment failure and survival was not significantly improved by intensification of chemotherapy or radiotherapy. It is for this reason that some experts advocate a conservative approach with a 'wait and watch' policy after excision biopsy for stage I-A disease.[19,20] However, the risk of late relapse, irrespective of initial therapy, necessitates a long term follow-up of these patients.

An exciting new avenue in the treatment of patients with NLPHL involves the use of monoclonal antibodies (Rituximab). This antibody acts against the B-cell antigen CD20 which is the antigen expressed by L&H cells. This therapy is already incorporated in the standard treatment for some CD20 expressing non-HL such as follicular lymphoma and diffused large B-cell lymphoma. For NLPHL there have been recent reports of excellent response to 'Rituximab' in relapsed cases.[21,22] With these encouraging reports, it is possible that in new protocols, immunotherapy may well-become one of the first line therapies for NLPHL in the near future.

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