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Case Report

Nodular Lymphocyte-Predominant Hodgkin Lymphoma or T-cell/Histiocyte Rich Large B-cell Lymphoma: The Problem in "Grey Zone" Lymphomas

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Abstract: Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) is a rare indolent B-cell lymphoma. However, its morphology can resemble T-cell/histiocyte rich large B-cell lymphoma (T/HRBCL), a subtype of more aggressive diffuse large B-cell lymphoma. More and more studies suggest that these two entities are closely related. In this report, a 59-year-old man with nodal NLPHL and concomitant T/HRBCL in the bone marrow is presented, the current progress in our understanding of these two closely related B-cell lymphomas reviewed and the problems in the diagnosis and differentiation of NLPHL and T/HRBCL discussed.
Key Words: Nodular lymphocyte-predominant Hodgkin lymphoma, T-cell/histiocyte rich large B-cell lymphoma, "grey zone" lymphoma

Introduction

Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) is characterized by a nodular proliferation of small lymphocytes with scattered large neoplastic cells [1]. In contrast to classical Hodgkin lymphoma (cHL), the neoplastic cells in NLPHL have a germinal center B-cell phenotype (CD20+/BCL6+) [2-4], indicating that NLPHL may be more closely related to B-cell non-Hodgkin lymphomas rather than cHL [5]. Due to its morphologic resemblance to lymphocyte-rich cHL and its distinct clinical course, however, NLPHL was classified as Hodgkin lymphoma in WHO classification [6]. Morphologically, like other Hodgkin lymphomas, it is characterized by rare large malignant cells in a background of reactive small lymphocytes within a nodular meshwork of follicular dendritic cells. The reactive small lymphocytes are mostly B-cells. $CD3^+$ and $CD57^+$ small T-cells often rim the singly distributed large neoplastic B-cells [6]. NLPHL is distinguished from cHL by its B-cell phenotype ($CD20^+$), expression of CD45, and negativity for CD15 and CD30.

T-cell/histiocyte rich large B-cell lymphoma (T/HRBCL) is a subtype of diffuse large B-cell lymphoma. Morphologically, it resembles NLPHL in that the neoplastic cells are rare components of the lesion [7]. On the other hand, it differs from NLPHL in which almost all B-cells in T/HRBCL are neoplastic cells that constitute only <10% of all the lymphoid cells [8]. The neoplastic cells diffusely infiltrate the tissue in a background of almost entirely reactive small T-cells with or without increased histiocytes. Small reactive B-cells are extremely rare.

In general, the presence of a nodular favors NLPHL, whereas a diffuse pattern is more common in T/HRBCL [6]. However, due to morphologic variations from case to case, and the overlapping features between NLPHL and T/HRBCL, it is sometimes impossible to distinguish these two entities; thus "grey zone lymphoma" is used to define some of those cases [9]. Because of the morphologic and immunophenotypic similarities between NLPHL and T/HRBCL, it is possible these two

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entities may represent different stages of the same disease. However, very different clinical courses between NLPHL and T/HRBCL warrant their distinction in clinical diagnosis [10-13]. NLPHL and T/HRBCL can occur subsequently or concomitantly [5, 13, 14]. NLPHL can also transform to T/HRBCL after a long indolent clinical course [14]. In this report, concomitant NLPHL and T/HRBCL are identified in a 59-year-old man; and the overlapping features and the diagnostic problems of these two entities are discussed.

Case Report

Clinical History

The patient was a 59-year-old gentleman presenting to the University of Maryland Medical Center (UMMC) with a lower back pain. MRI work-up revealed multiple osteolytic lesions in the L2 and L5 vertebral bodies. A subsequent bone scan showed significantly increased intake in the left sacroiliac joint and adjacent iliac bone, L2, L4 and L5 vertebrae, suspicious for metastatic disease. Since cancer was suspected, he underwent a computerized tomographic (CT) scan of the chest, abdomen and pelvis. Scan of the chest showed a 5.7 cm right axillary mass that was "suspicious for carcinoma." Biopsy of the axillary lesion was performed at the referring outside institution, which revealed NLPHL. Since NLPHL is an indolent disease and rarely involves bone marrow, a biopsy was also performed for the sacroiliac lesion at UMMC.

Histopathology

The H&E sections of the axillary lesion showed portions of lymph node completely effaced by a vaguely nodular lymphoid proliferation with scattered mottled areas under the low power magnification (**Figure 1A**). High power view showed that the mottled areas were composed of scattered large atypical cells with abundant cytoplasm, multilobated vesicular nuclei and prominent nucleoli, consistent with lymphocytic and histiocytic (L&H) cells (**Figure 1B**). A background of reactive small lymphocytes is present. Paraffin immuno-peroxidase stains showed that the large L&H cells were $CD20^+$ and $CD45^+$. These cells were negative for CD15 and CD30. The background reactive cells were primarily small T-cells with a few nodules of small B-cells. The $CD3^+$ and $CD57^+$ small T-cells formed rims around the

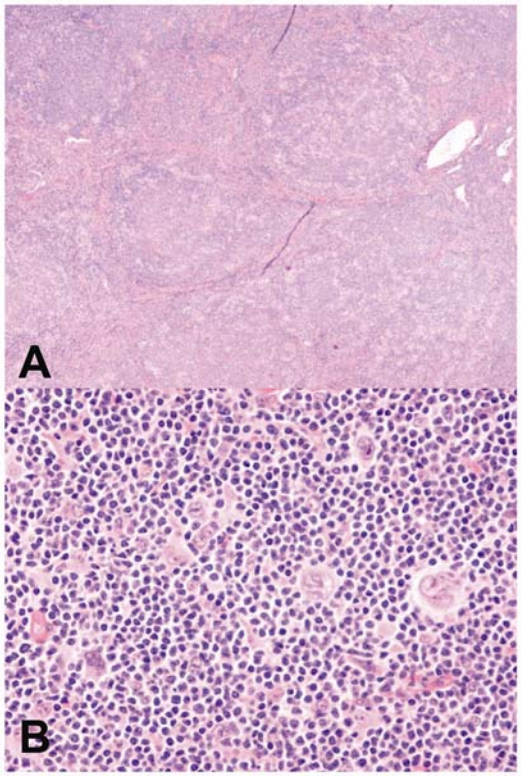

Figure 1 Nodular lymphocyte-predominant Hodgkin lymphoma. **A**. Vague nodules with mottled areas (H&E, 100x). **B**. Large atypical lymphocytic and histiocytic (L&H) cells in a background of reactive small lymphocytes (H&E, 1000x).

large neoplastic B-cells (not shown).

Biopsy of the sacroiliac bone lesion revealed a mildly hypercellular marrow with a diffuse infiltration of small lymphoid cells, focal crush artifact, and rare scattered large cells with abundant cytoplasm, hyperchromatic nuclei, and inconspicuous nucleoli (**Figure 2A**). Focal residual trilineage hematopoietic components were seen. Paraffin immuno-peroxidase stains revealed rare scattered large neoplastic cells to be CD20+ and the small lymphoid cells almost entirely CD3+ (**Figure 2B**). The large cells were also positive for CD79a (**Figure 2C**). These cells were negative for CD15 and CD30. Stain for CD21 was negative (not shown).

Clinical Follow-up

Based on the above findings, a diagnosis of NLPHL with transformation to T/HRBCL in bone marrow was made. The patient received 6 full cycles of Rituximab (R), Cyclo-phosphamide (C), Adriamycin (H), Vincristine

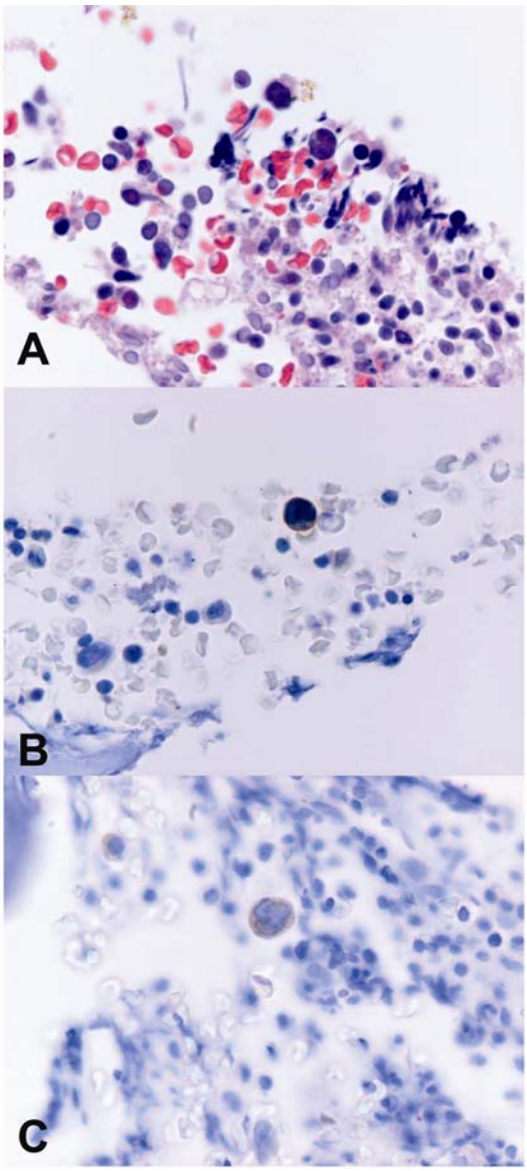

Figure 2 T-cell/histiocyte rich large B-cell lymphoma of the bone marrow. **A**. Singly distributed large atypical cells in a background of small lymphocytes (H&E, original magnification: 1000x). **B**. The large atypical cell is CD20+, whereas the background small lymphocytes are CD3+ (not shown) (immunoperoxidase, original magnification: 1000x). **C**. The large atypical cell is also positive for cytoplasmic CD79a (immunoperoxidase stain, 1000x).

(O) and Prednisone (P) (R-CHOP). Lymphadenopathy disappeared after 4 cycles of the RCHOP regimen. He is currently disease free and status post 6 cycles of R-CHOP 4 months after his initial diagnosis.

Discussion

The diagnosis of the sacroiliac lesion in this case was not straight forward. The hematopathologists attending the 2nd Atlantic Regional Hematopathology Meeting could not agree on the diagnosis at the beginning. The controversy was between "progressed NLPHL" involving the marrow or T/HRBCL in the marrow. Since the axillary nodal lesion was clearly NLPHL, one group believed that the sacroiliac lesion should also be NLPHL, considering the overlapping features of these two entities. The other group held that although the axillary and sacroiliac lesions were most likely of the same origin, the morphology and immunophenotyping favor T/HRBCL based on: 1) Rare large neoplastic B-cells in a background composed of almost entirely small T-cells; 2) The large neoplastic B-cells are CD79a+. Finally, a concensus diagnosis was NLPHL with concomitant transformation to T/HRBCL in the bone marrow. In addition, all the attendees agreed that the patient should be managed with intensified regimens. It was also speculated that NLPHL might had occurred in the axillary lymph nodes long before the bone lesions. Since the patient was asymptomatic, the tumor remained indolent until it eventually transformed and involved the lumbar vertebrae and sacroiliac bones. However, a concomitant occurrence of both an indolent NLPHL and an aggressive T/HRBCL cannot be excluded.

Relationship between NLPHL and T/HRBCL

NLPHL is an indolent B-cell lymphoma with distinct clinical features [6]. It usually occurs in young males and sometimes derives from progressively transformed germinal center (PTGC) B-cells. More and more reports showed that NLPHL will eventually transform into large B-cell lymphoma even 15 to 20 years after the initial diagnosis [5, 14]. T/HRBCL is one of the most common subtypes of large B-cell transformation from NLPHL [5, 15]. Based on the observation that PTGC is associated with NLPHL in either the same, previous or subsequent lymph node biopsies [16], it is currently believed that PTGC is the precursor of NLPHL [6]. Similarly, there are also many examples that NLPHL are clonally related to T/HRBCL [5, 18]. Therefore, from PTGC to NLPHL, and finally to T/HRBCL appear to be

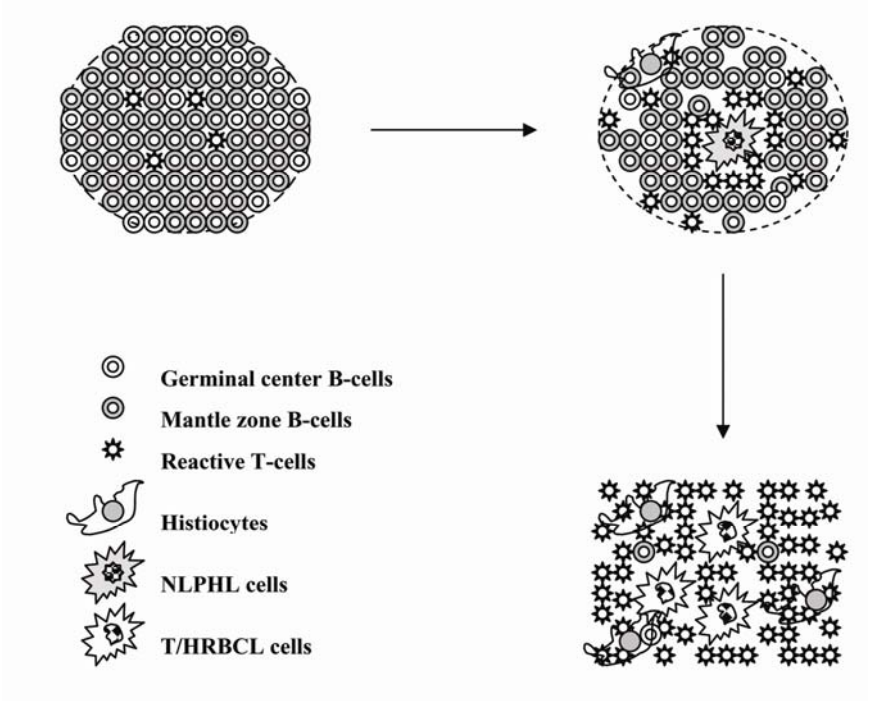

Figure 3 Natural course of progressively transformed germinal centers (PTGC), nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) and T-cell/histiocyte rich large B-cell lymphoma (T/HRBCL). PTGC occurs in response to aberrant antigen stimulation or cytokine secretion, which, if persists, could lead to dominance of one particular clone of germinal center B-cells. The clonal B-cells reside in the meshwork of follicular dendritic cells surrounded by reactive mantle zone B-cells and CD4+/CD57+ T-cells (NLPHL). These clonal B-cells could remain indolent for many years until additional genetic "hits" transform them into aggressive neoplastic B-cells (T/HRBCL).

the natural course of this disease (**Figure 3**).

The progression from NLPHL to T/HRBCL varies from months to years [5]. In the current case, the axillary lesion might have been there for a long time before it underwent large cell transformation in the bones. Recent findings that concurrent or evolving NLPHL and T/HRBCL could run in families suggest that common inheritable factors may determine the disease process [5]. Comparative genetic studies revealed numerous genomic imbalances in both NLPHL and T/HRBCL, with only a few overlapping recurrent genetic abnormalities in both entities [5]. These overlapping recurrent chromosomal abnormalities might be the genetic link between NLPHL and T/HRBCL. Identification and understanding of these abnormalities might help elucidate the pathogenesis and guide clinical management of these diseases.

Morphologic "Grey Zone"

As its name implies, NLPHL is characterized by a nodular growth pattern predominantly consisting of small lymphocytes, histiocytes and intermingled L&H cells; a diffuse pattern often indicates T/HRBCL [6]. Interestingly, nodular lesions with features of T/HRBCL have recently been reported [19]. Boudova and coworkers analyzed 235 tumors with a spectrum of morphology between NLPHL and T/HRBCL, and identified 17 cases that fell into the "grey zone" morphology. Two nodular patterns existed that might suggest either transformed NLPHL or T/HRBCL. In pattern A, neoplastic cells scattered loosely in a background of abundant histiocytes and cytotoxic T cells, but with only a scarce number of small B cells, resembled T/HRBCL at high magnification. In pattern B, cohesive clusters of large blasts in an inflammatory background could be seen, suggesting a morphologic transformation toward the pattern of DLBCL within the follicles. Although cases with these nodular patterns were frequently treated with intensified regimens, their prognosis is comparable to the classical NLPHL.

Immunophenotypic "Grey Zone"

Despite recent progress in immunologic markers, it is still a challenge to differentiate NLPHL from T/HRBCL in some cases. Even with global efforts of the most prominent contemporary hematopathologists, a "grey zone" could only be narrowed, but not be eliminated [20]. Extensive efforts have been made to develop criteria for the differentiation between NLPHL and T/HRBCL. Generally, CD79a and BCL2 expressions are more frequently identified in T/HRBCL than NLPHL [21, 22]. On the other hand, expression of PU.1, a transcription factor involved in B-cell development, was identified consistently in NLPHL, but not or only weakly in T/HRBCL [23]. However, this notion was challenged by a recent study [24]. Researchers also tried to define the features of the background small T-cells in NLPHL. Besides the characteristic rimming of neoplastic cells by CD3+/CD57+ T-cells on the paraffin section [6], CD4+/CD8+ T-cells are frequently increased in NLPHL [25]. It is currently believed that dysfunction of cytokines accounted for the increased CD57+ and CD4+/CD8+ T-cells in NLPHL [26]. Unfortunately, there are still no reliable immunological markers currently available for the clinical differentiation of NLPHL from T/HRBCL.

Clinical Management and Outcome

Clinical studies suggest that NLPHL be treated as cHL. Stage I/II NLPHL may even be managed by just "watch and wait" strategy. A recent large clinical trial involving 8298 Hodgkin lymphoma (394 NLPHL and 7904 cHL) patients suggested that the complete remission rate was similar to cHL even for the advanced stage NLPHL [27]. By contrast, T/HRBCL, as a subtype of DLBCL, is usually treated by R-CHOP. With the current stage-adjusted regimens, the overall survival for NLPHL is over 90%, whereas for T/HRBCL is only over 50% [19]. Such distinct clinical outcomes demand us to make the accurate diagnosis. Either under-treatment of T/HRBCL or over-treatment of NLPHL will have serious adverse consequences [15]. Even if NLPHL and T/HRBCL may indeed represent different stages of the same disease, recognizing and catching it at the right time point is critical for the patient survival. However, when bone marrow is involved (stage IV disease), whether it is "progressed NLPHL", T/HRBCL, or "grey zone" lymphoma, it should be managed similarly by intensified chemotherapy.

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