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Coexisting and clonally identical classical Hodgkin lymphoma and nodular lymphocyte predominant Hodgkin lymphoma

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Abstract

We report a case of concurrent nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) and classical Hodgkin lymphoma (cHL), nodular sclerosis subtype in an otherwise healthy 24 year-old male with a strong family history of cHL. The patient was found to have a parotid mass, which was diagnosed as NLPHL, and a thymic mass diagnosed as cHL, nodular sclerosis subtype concurrently. The lesion in the parotid showed features typical of NLPHL by morphology and immunophenotype. The LP cells were positive for PAX5, CD20, Oct2, weakly positive for CD30, and negative for CD15. The thymic lesion, diagnosed as cHL, nodular sclerosis subtype, showed prominent bands of fibrosis and HRS and lacunar cells positive for CD30 and CD15. These cells were variably positive for CD20 and negative for Oct2. PAX5 was weakly positive. Immunoglobulin gene rearrangement studies by PCR were performed on microdissected HRS and LP cells and shown to have identically sized peaks. NLPHL and cHL are two distinct diseases and are almost never seen concurrently. We present a case in which PCR analysis indicated that the tumor cells of these two distinct entities were clonally identical.

Keywords

Nodular lymphocyte predominant Hodgkin lymphoma; classical Hodgkin lymphoma; LP cell; Reed-Sternberg cell; familial lymphoma

INTRODUCTION

Nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) and classical Hodgkin lymphoma (cHL) are recognized as two distinct entities by the current 2008 WHO

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classification (26). Both Hodgkin/Reed-Sternberg (HRS) cells and lymphocytic and histiocytic (L&H), now termed lymphocyte predominant (LP) cells have been well accepted as being of B-cell origin (17). NLPHL and cHL differ in clinical presentation, immunophenotype, morphology, inflammatory background, and B-cell gene expression program. Clinically patients with NLPHL most often have localized peripheral lymphadenopathy without associated B-symptoms and no mediastinal involvement, while cHL of nodular sclerosis (NS) subtype most often presents with a mediastinal mass, with or without cervical lymphadenopathy, and a tendency to spread in a retrograde fashion following lymphatic drainage pathways.

NLPHL is associated with an increased risk for progression to diffuse large B-cell lymphoma (DLBCL) in 5-10% of cases, and both processes may be seen in the same anatomic site (5,9,25). cHL is associated with various forms of B-cell lymphoma at a lower rate (11). However, finding both NLPHL and cHL concurrently in the same patient is extremely rare. In 1993 Gelb *et al.* reported one patient with a composite lymphoma comprising NLPHL and cHL in a single anatomic site (8), as well as four cases in which NLPHL and cHL were sequential. Herein, we report a case in which NLPHL and cHL, NS were diagnosed concurrently in separate anatomic sites; moreover, PCR analysis of microdissected tumor cells showed that the two lesions were clonally related.

CASE REPORT

The patient is a 24 year-old male with no known significant past medical history, who presented with a 9 month history of a right post-auricular parotid, nickel-sized mass. The patient denied fever, chills, night sweats, pruritus, or weight loss. At initial evaluation, the mass was thought to be inflammatory and the patient received a course of antibiotics but the lesion did not decrease in size. The parotid mass was excised and grossly measured $3.0 \times 2.4 \times 1.8$ cm; it had a “fish flesh” consistency. A diagnosis of nodular lymphocyte predominant Hodgkin lymphoma was made. Computed tomography and FDG-PET scans were performed and showed a hypermetabolic thymic mass measuring approximately 2 cm. The thymus was excised and measured $9.0 \times 4.5 \times 1.5$ cm and weighed 19 grams; it contained a nodular lesion measuring 2.0 cm in greatest dimension. The lesion was diagnosed as classical Hodgkin lymphoma, nodular sclerosis subtype (cHL, NS).

The patient’s complete blood count and basic metabolic panel were within normal limits and he was seronegative for HIV. A bone marrow aspirate and biopsy were performed and showed a normocellular marrow with no morphologic evidence of lymphoma.

Further inquiry of the patient’s family history was noteworthy. The patient’s father had a past history of cHL and had been in complete remission for over 13 years. His paternal grandfather died at 67 years of acute myeloid leukemia and two paternal cousins also had a past history of cHL.

MATERIAL AND METHODS

Tissue samples, Immunohistochemistry, and In situ hybridization

The two biopsies were fixed in 10% neutral buffered formalin, embedded in paraffin, and stained with hematoxylin-eosin.

A panel of immunohistochemical stains were performed using commercially available antibodies, on formalin-fixed paraffin embedded (FFPE) sections according to previously published techniques (7,23) (Table 1).

In situ hybridization for EBER was performed on FFPE tissue sections using a FITC labeled oligonucleotide probe supplied by Ventana Medical Systems (Tucson, AZ) on an automated stainer (Ventana Benchmark). Visualization was achieved using the ISH iView system with Alk-Phosphatase and NT/BCIP substrate, with Fast red as contrast. A positive control was run with all cases and stained appropriately.

Laser assisted microdissection (LAM)

Five μm FFPE tissue sections were mounted on PEN membrane glass slides (catalog # LCM0522, MDS Analytical Technologies, Sunnyvale, CA, USA) and stained with Mayer's hematoxylin solution (catalog # MHS16-500ml, Sigma-Aldrich, St. Louis, MO, USA). HRS cells, LP cells, and background B-lymphocytes in the case of nodular lymphocyte predominant Hodgkin lymphoma, each yielding a minimum of 50 ng of DNA, were microdissected using Leica LMD 6000 (Leica Microsystems, Wetzlar, Germany).

Immunoglobulin PCR

DNA extraction was performed on FFPE with QiaCUBE extraction platform using their proprietary buffer and proteinase K digestion. PCR was performed using consensus primers directed to V_H framework (FR) III and joining region (J_H) of the immunoglobulin heavy chain gene (FRIII-IGH PCR) and to V_H FR region II and the joining region (FRII-IGH PCR), according to the method of Ramasamy *et al.* (21). Testing for the IGK locus was additionally performed using the Biomed II primer set described by van Dongen *et al.* and supplied by *InVivoScribe* Technologies (IGK@ Gene Clonality Assay-ABI Fluorescence Detection, Cat#: 1-102-0031) (29). These reactions interrogate rearrangements involving the V_K loci and J_K (tube A), the V_K locus and the κDE locus (tube B), and the κ -intron RSS locus and the κDE locus (tube B). The products from all reactions were separated by capillary electrophoresis on an ABI 3130xl Genetic Analyzer and the electropherograms analyzed using GeneMapper software version 3.7 (ABI).

RESULTS

Pathological Features

Pathologic review of the parotid mass showed effaced architecture by a vaguely nodular infiltrate containing scattered large atypical cells with multilobulated nuclei, vesicular chromatin, and small nucleoli, characteristic of LP cells in a background of small B-lymphocytes and histiocytes (Figure 1A, 1B). The LP cells were largely distributed singly, but focally formed small clusters in a vaguely nodular growth pattern. The LP cells were found to be strongly positive for Oct2, PAX5, and CD20 by immunohistochemistry (Table 1 and Figure 1C, D). Scattered cells were weakly positive for CD30 but negative for CD15. In situ hybridization for EBV (EBER) was negative. CD3 highlighted characteristic rosetting by small T-cells. The numerous background small B-cells were positive for CD20 as well as IgD.

The thymus gland contained a discrete nodule divided by broad fibrous bands, and containing clusters of HRS cells and lacunar cells in a background of small lymphocytes, histiocytes, and eosinophils (Figure 2A, 2B). There were interspersed Hassall's corpuscles and clusters of thymic epithelial cells. These HRS cells were weakly positive for PAX5 (Figure 2B inset), variably positive for CD20 and negative for Oct2. They were positive for CD30 and CD15 (Figure 2C, 2D). EBER was negative as well.

Molecular studies

Immunoglobulin gene rearrangement studies were performed by PCR for both heavy chain (IGH@) and kappa light chain (IGK@) loci on DNA isolated from whole mount tissue

sections. A polyclonal pattern was seen with FRII-IGH and FRIII-IGH for both lesions on whole mount tissue sections. However, the *IGK@* primers identified clonal peaks of identical size in DNA from both the NLPHL and cHL samples. To confirm that the clone was derived from the neoplastic cells, the PCR reactions were repeated on DNA isolated from microdissected LP cells and HRS cells, respectively (Figure 3A, Figure 3B). The prominent background small B-lymphocytes in the case of NLPHL were microdissected as well to determine whether those cells contained the same clonal rearrangement. DNA from the microdissected LP and HRS cells again showed the identical clonal rearrangements, whereas the small B-cells microdissected from the case of NLPHL were negative for a clonal rearrangement for both *IGH@* (not shown) and *IGK@* (Figure 3C). DNA quantity from laser assisted microdissection was insufficient for analysis by sequencing.

DISCUSSION

Having concurrent NLPHL and cHL is exceedingly rare (Table 2). Moreover, other reports have not examined the clonal relationship between the cells of NLPHL and cHL in those cases in which both processes were found in the same patient. Using microdissection techniques we report a novel case in which we show that the LP cells and the classical HRS cells contained the same sized *IGK@* gene rearrangement.

In 1993, Gelb *et al.* described a 22 year-old male in whom histological features of NLPHL and cHL, mixed cellularity subtype were identified in a single right submandibular lymph node (8). The patient achieved complete remission following radiotherapy alone. Those authors also described 4 other patients in whom the diagnoses of cHL and NLPHL were made sequentially (range of 3-18 years). In three of the four cases cHL preceded the diagnosis of NLPHL. Miettinen *et al.* reported two cases of NLPHL with subsequent biopsies of MCCHL, 5 and 17 years later (19). None of the other reports included cases with concurrent NLPHL and cHL. In none of the above reports were the authors able to examine the clonal relatedness of the two neoplasms.

LP and HRS cells are now believed to be derived from germinal center B-cells. In cHL, microdissection of the HRS cells from frozen tissue sections verified the B-cell origin of the cells, and showed that the *IG* genes were in a clonal configuration (15). HRS cells have been postulated to be derived from germinal center B-cells, based on the presence of somatic hypermutation and evidence of intraclonal diversity of the VH genes. LP cells are also known to have clonally rearranged immunoglobulin genes and are believed to be derived from antigen selected germinal center B-cells (2,13). *BCL6* associated translocations are frequent in LP cells and their frequent expression of BCL-6 by immunohistochemistry is another indication of their germinal center B-cell origin (22,27,30).

NLPHL and cHL are regarded in the WHO classification as separate diseases. A hallmark of cHL is downregulation of the B-cell program, such that most B-cell markers are not expressed in classic HRS cells. Some studies have suggested that NLPHL may be more closely related to the B-cell non-Hodgkin's lymphomas. However, recent work has shown surprising similarities with cHL (3). Using gene expression profiling of microdissected LP cells, Brune *et al.* demonstrated a close relationship between NLPHL and T cell/histiocyte-rich large B-cell lymphoma (THRLBCL), as anticipated. However, unexpectedly NLPHL, like cHL, showed evidence of suppression of the B-cell program, in contrast to DLBCL, Burkitt lymphoma (BL), or follicular lymphoma (FL) (3). In addition to diminished expression of B-cell specific transcription factors, other features shared in common between LP cells and HRS cells were constitutive NF- κ B activity and activation of the ERK signaling pathway. The occurrence of both forms of Hodgkin's lymphoma in a single patient may be further evidence of a close relationship. In addition, we show that both tumors

contained the same sized *IGK@* gene rearrangement, suggesting that NLPHL and cHL might in some cases arise from a common B-cell precursor.

Intriguingly, the patient has a strong family history of cHL. The father, paternal first and third cousins, all had cHL. The paternal grandfather and the first cousin both also had acute leukemia. These findings suggest an inherited susceptibility to developing a hematolymphoid neoplasm such as cHL in this family. Kerzin-Storarr *et al.* estimated a 4 fold increase in risk of cHL in first and second degree relatives affected with Hodgkin lymphoma. They estimated that 4.5% of cHL may be familial (12). Interestingly, 4 out of the 6 familial Hodgkin's cases were seen in a first degree male relative. This finding was later supported by a study from Bernard *et al.* in which they also found a male predominance in 9 familial Hodgkin's cases (1). Supporting a role for genetic factors in the development of Hodgkin's lymphoma, Mack *et al.* in a study of 432 twin pairs, found a greater risk for disease in monozygotic (10/179 twin pairs) as opposed to dizygotic twin siblings (0/187) of patients with Hodgkin's lymphoma (16). As for familial NLPHL, cases have been described infrequently and genetic studies are very limited (4,28).

In cHL, a clonal result for *IG* gene rearrangement studies is usually not detected in whole tissue sections likely due to the small percentage of tumor cells seen compared to the inflammatory background. Clonal rearrangements are usually only detected by isolation of individual HRS cells. However, detection of clonal *IG* gene rearrangements in past studies performed on microdissected HRS cells has been variable (6,10,14,18,20,24). The lack of clonal *IG* gene rearrangement in some of these studies is likely due to technical issues related to the success of the microdissection or the primer sets used at that time. In the present case, we performed PCR on DNA extracted from complete sections (results not shown) as well as DNA isolated from microdissected HRS and LP cells. Utilizing complete tissue sections from both the NLPHL and cHL case, *IGH@* showed a polyclonal rearrangement, while *IGK@* showed two distinct peaks of the same size suggesting a clonal rearrangement. *IGK@* performed on microdissected HRS and LP cells identified the same clonal peaks, a finding which further supports that the tumor cells shared the same clonal rearrangement. To rule out the possibility that the small B-lymphocytes in the background were the cause of this clone, we microdissected the background B-cells, which were polyclonal for *IGH@* and no specific peaks were seen with *IGK@*.

NLPHL and cHL are defined as two distinct entities by the WHO classification. They are similar in that they are both of germinal center B-cell origin, but differ in many other aspects. However, recent data from gene expression profiling has suggested that the two entities may be more closely related (3). Nevertheless, cases of coexisting NLPHL and cHL are exceedingly rare. In the reported case, an increased familial risk may explain the development of both lymphoma subtypes in the same patient.

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Figure 1. Nodular lymphocyte predominant Hodgkin lymphoma. A, Vaguely nodular architecture with scattered large atypical cells with multilobulated nuclei characteristic of LP cells (H&E). (B) Characteristic LP cells with multilobulated and “popcorn” nuclei (H&E). (C) Scattered LP cells strongly positive with Oct2 and (D) strongly positive with CD20.

Figure 2.

Classical Hodgkin lymphoma, nodular sclerosis subtype. A, Effacement of the thymic architecture by broad bands of fibrosis (bottom left) and scattered large atypical cells (H&E). (B) These cells have irregular nuclear contours, vesicular chromatin, and prominent nucleoli, characteristic of HRS cells in a background of small lymphocytes and eosinophils (H&E). These cells were weakly positive for PAX5 (inset) (C, D) and positive for CD30 and CD15, respectively.

Figure 3.

Nodular lymphocyte predominant Hodgkin lymphoma (A) in the parotid gland showing two intense peaks in the *IGK@* locus of 236 and 273 bps, consistent with a clonal process. (B) Intense peaks of identical size are also seen in the classical Hodgkin lymphoma, nodular sclerosis subtype, in the thymus. (C) The microdissected background small B-lymphocytes within the NLPHL are negative for a clonal process by both *IGH@* (not shown) and *IGK@* PCR.

Table 1

Immunohistochemical expression of HRS cells and LP cells in biopsies of thymus (cHL) and parotid lymph node (NLPHL)

Antibody	cHL	NLPHL
CD20	Negative	Positive
PAX5	Weakly positive	Positive
Oct2	Negative	Positive
CD30	Positive	Weakly positive
CD15	Positive	Negative
IgD	Negative	Negative
P53	Positive	Positive
EMA	Negative	Negative
EBER	Negative	Negative
Bcl-6	Negative	Positive

EBER indicates in situ hybridization for EBV, EMA, epithelial membrane antigen.

Nodular lymphocyte predominant Hodgkin lymphoma and classical Hodgkin lymphoma cases

Table 2

Authors (Year)	Age (years)	Sex	Initial diagnosis	Subsequent diagnosis	Time interval (years)
Miettinen <i>et al.</i> (1983)	21	M	NLPHL	MCCHL	5
	17	M	NLPHL	MCCHL	17
Gelb <i>et al.</i> (1993)	10	M	MCCHL	NLPHL	18
	30	M	NSCHL	NLPHL	10
	22	M	NSCHL	NLPHL	5
	27	M	NLPHL	NSCHL	3
	22	M	MCCHL and NLPHL*	N/A	0

NLPHL = nodular lymphocyte predominant Hodgkin lymphoma, MCCHL = classical Hodgkin lymphoma, mixed cellularity subtype, NSCHL = classical Hodgkin lymphoma, nodular sclerosis subtype, N/A = not applicable

* indicates concurrent diagnoses