

Progression of Nodular Lymphocyte-Predominant Hodgkin's Lymphoma to a High-Grade Lymphoma

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Abstract

Nodular lymphocyte-predominant Hodgkin's lymphoma (NLPHL) is a rare subtype of Hodgkin's lymphoma characterized by a nodular proliferation of large neoplastic B cells that are CD15 and CD30 negative. Although this neoplasm develops slowly and has a favorable prognosis with Stage I or II disease, it has a high rate of recurrence and patients tend to have repeated relapses [1]. Increasingly, reports have shown that a small percentage of patients with NLPHL may transform to a more aggressive lymphoma concurrently or many years later. This case highlights a 58 year-old man who developed NLPHL at age 33 and progressed to a high-grade malignant lymphoma 25 years later. The purpose of this report is to share this patient's unusual clinical course and provide a pertinent literature review of NLPHL.

Keywords: Lymphoma; Hodgkin's disease; Hematology/Oncology

Introduction

The World Health Organization (WHO) classifies Hodgkin's lymphoma into two different subtypes consisting of classical Hodgkin's lymphoma and nodular lymphocyte-predominant Hodgkin's lymphoma (NLPHL) [1]. NLPHL is much less common and accounts for only 5% of all Hodgkin's lymphomas [1,2]. Approximately 75 percent of patients are male and it is more common in African-Americans compared to Caucasians in the United States [3]. There is a bimodal age distribution in NLPHL with one peak in childhood and the other in adults 30 to 40 years of age [4].

The two subtypes differ in that classical Hodgkin's lymphoma contains Reed-Sternberg cells that stain positive for CD15 and CD30 whereas NLPHL has Reed-Sternberg cell variants, termed Lymphocyte Predominant (LP) or popcorn cells, that are CD15 and CD30 negative [1,5]. An additional distinguishing feature between the two is that LP cells stain positive for the B lymphocyte marker CD20, making NLPHL an unusual form of a B cell lymphoma [6]. Although many patients with NLPHL have favorable outcomes, there is increasing evidence that this subtype may progress to a more aggressive lymphoma, most commonly diffuse large B-cell lymphoma (DLBCL), concurrently or many years later [7,8].

The purpose of this case report is to highlight a patient's history involving this rare progression of NLPHL to a high-grade malignant lymphoma thought to have DLBCL features.

Case presentation

A 58 year-old African-American male originally presented in 1985 at age 33 with a right axillary mass. Biopsy of the mass and a thorough staging workup revealed Stage IA NLPHL. The patient received external beam radiation therapy (EBRT) of 40 Gy in 20 fractions to the mantle field. He was followed annually for 13 years without evidence of disease. In 1997, it was felt that he was essentially cured and no longer required follow-up.

In 2000, the patient presented to the emergency department with abdominal pain and hematuria. A CT scan revealed two densities along the ureter consistent with urolithiasis as well as right pelvic lymphadenopathy. Biopsy of the largest pelvic mass, measuring 2.8 by

6 cm, was consistent with recurrence of NLPHL. The patient declined the recommended chemotherapy and opted for radiation therapy alone. He received EBRT of 36 Gy in 20 fractions to the pelvic mass with a field covering the para-aortic and pelvic lymph nodes and was followed annually for 9 years without recurrence.

In 2009, the patient presented to the emergency department with intermittent back pain. A chest CT revealed a large mass involving the posteriolateral chest wall with osseous destruction of the right fifth rib. A PET scan demonstrated the subscapular mass with an SUV of 39.1 as well as multiple hypermetabolic nodules in the spleen, splenic hilum, celiac axis, porta hepatis, and paraaortic regions (Figure 1). FNA and core needle biopsy of the chest wall mass revealed a high-grade malignant lymphoma of large cell composition with an incomplete B cell immunophenotype based on a positive PAX-5 immunostain along with a negative CD20 stain and no B cells identified on flow cytometry (Figure 2, Figure 3). The pathologic features of the FNA and core biopsy of the chest wall mass indicated a "grey zone lymphoma" with features of both NLPHL and DLBCL. WHO defines grey zone lymphoma as an unclassifiable B-cell lymphoma with features intermediate between DLBCL and classical HL [1].

Shortly after the diagnosis, the patient started systemic therapy every two weeks with adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD) and was scheduled to complete 6 cycles, or 12 treatments. Imaging obtained after 4 cycles revealed resolution of the various sites of lymphadenopathy but persistence of the chest wall mass (Figure 4). ABVD was discontinued due to inadequate response

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to therapy. The patient began a "salvage" regimen with ifosfamide, carboplatin, and etoposide (ICE) and completed two cycles without complications. Imaging with a PET/CT at that point revealed dramatic improvement of the right posteriolateral chest wall mass (SUV 3.9) with no evidence of additional disease (Figure 5).

Due to persistence of the chest wall mass, the patient then completed a regimen of carmustine, etoposide, cytarabine, and melphalan (BEAM) followed by an autologous stem cell transplant (ASCT). BEAM is a high-dose chemotherapy used to treat relapsed Hodgkin's lymphoma and high risk non-Hodgkin's lymphoma [9]. BEAM is followed by ASCT due to its highly myelosuppressive nature. He underwent restaging at day 100 post-ASCT and had a complete remission (Figure 6). The patient continues in remission at eighteen months post-ASCT.

Discussion

The patient's demographic profile fits that which is typically seen with NPLHL: he is an African-American male who initially presented

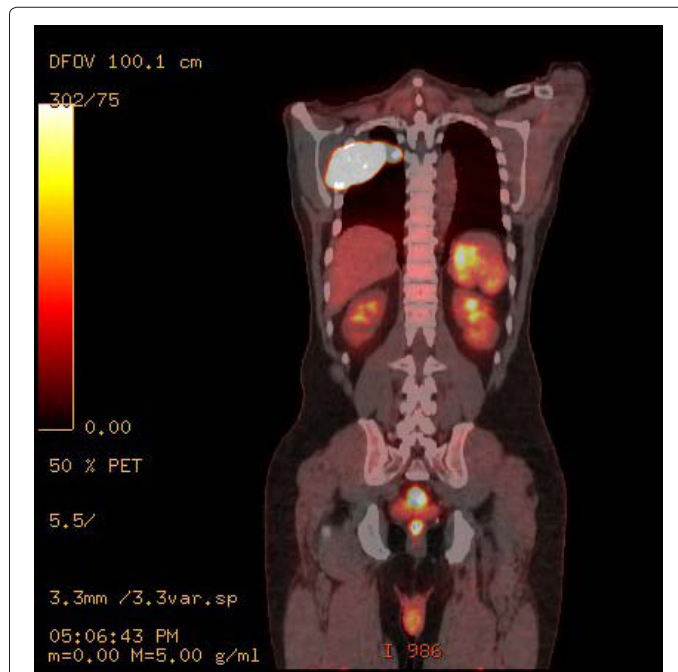


Figure 1: PET/CT prior to chemotherapy: Hypermetabolic postero-lateral right chest wall lesion with a maximal standardized uptake value (SUV). Multiple enlarged hypermetabolic nodules scattered throughout the mesentery, retroperitoneum, left inguinal region, and spleen.

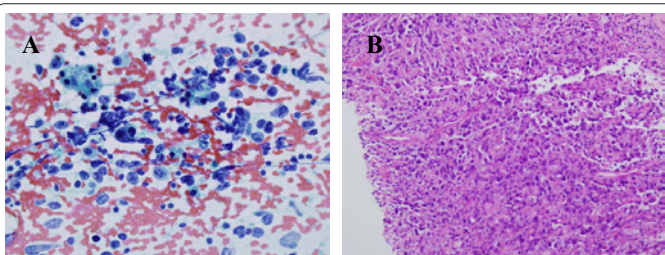


Figure 2: (A) FNA of chest wall mass showing large, highly atypical lymphoid cells with prominent macronucleoli (B) Core biopsy of mass showing malignant lymphoid tissue.

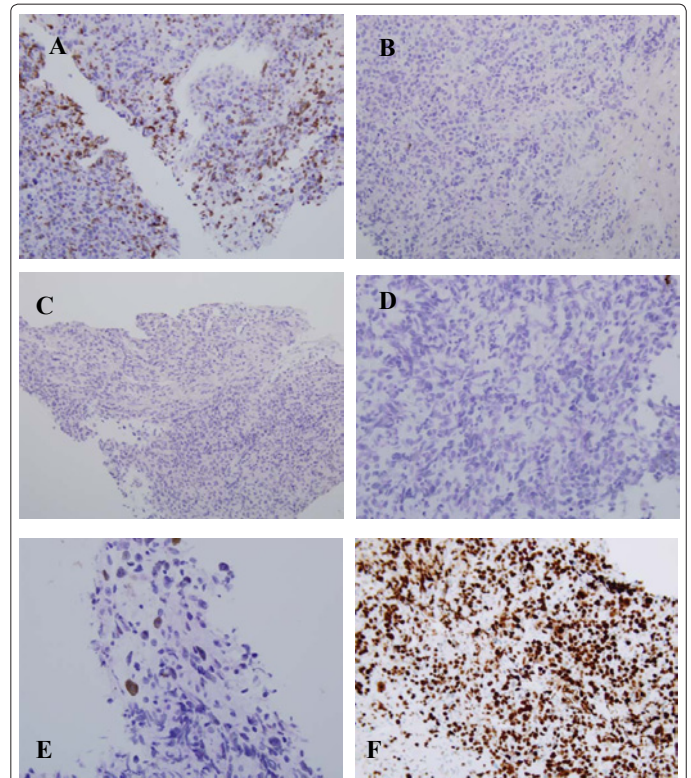


Figure 3: Immunohistochemical stains of chest wall mass (A) CD3 scattered positivity (B) CD 15 negative (C) CD 30 negative (D) CD 20 negative (E) PAX-5 positive (F) Ki-67 85% positive .

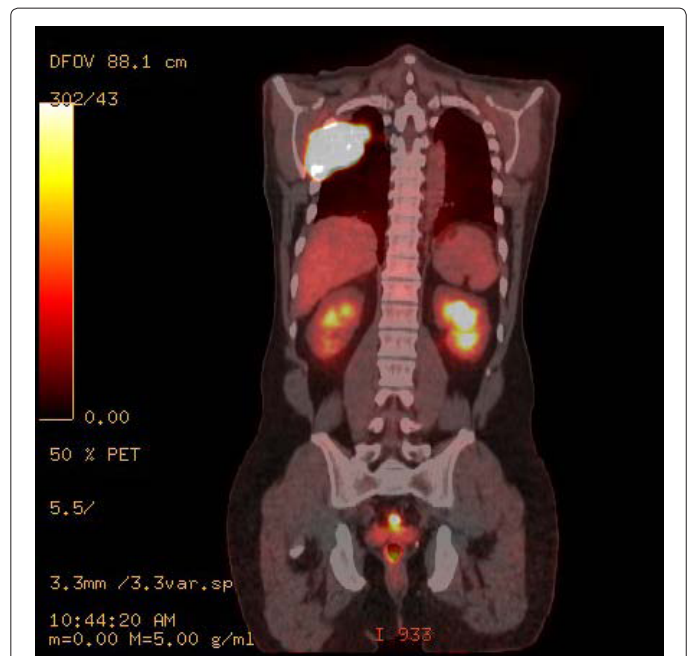


Figure 4: PET/CT following adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD): Stable hypermetabolic chest wall mass with resolution of previously described lymphadenopathy.

with Stage I peripheral lymphadenopathy in his thirties [1,3,4]. Patients commonly present with Stage I-II disease without B symptoms [10]. The presence of B symptoms, including fever, weight loss, and drenching

night sweats, are thought to occur in less than 15% of cases of NLPHL [4]. In a recent analysis of patients with NLPHL progressing to a high grade non-Hodgkin's lymphoma or DLBCL, common clinic features of patients undergoing transformation include males with Stage III-VI disease, extranodal involvement (liver, GI tract, soft tissue bone),

splenic involvement, elevated LDH and the presence of B symptoms [5].

Studies indicate that the LP cells in NLPHL represent a clonal tumor population of germinal center B cells [11-14]. Continuous immunoglobulin gene rearrangements and erroneous somatic hypermutation in the LP cells are thought to be involved in the pathogenesis of the histologic transformation to a high grade non-Hodgkin's lymphoma or DLBCL [15]. Genomic studies show that the gene rearrangements are rarely found in the neoplastic cells of NLPHL but are commonly found in patients who progress to DLBCL [16]. One rearrangement that is found in almost half of NLPHL cases involves the B-cell lymphoma 6 (BCL-6) gene [17,18].

Diagnosis of histologic transformation is ultimately dependent on biopsy with immunohistochemical analysis. The pathologic features of this patient's most recent FNA and core biopsy of the chest wall mass in 2009 indicate that he has a grey zone lymphoma with features of NLPHL and DLBCL. The lesion is considered high-grade due to the strong positivity of the proliferation marker Ki-67 and there is an incomplete B cell immunophenotype due to the positive PAX-5 stain and negative CD20. Large B cells are often difficult to identify on flow cytometry, which is most likely the reason why no B cells were identified. It is unknown whether the other hypermetabolic nodules seen on PET/CT were solely recurrence of NLPHL or also displayed features of the grey-zone lymphoma as biopsies of these areas were not done.

Increasing reports over recent years have shown that NLPHL has a continuous pattern of relapse and has the potential to evolve into a high-grade non-Hodgkin's lymphoma. In a study of 68 patients with NLPHL by Orlandi et al. [19] 18 patients relapsed as NLPHL while 5 developed non-Hodgkin's lymphoma. The cumulative risk of developing NHL at 10 years was 9%. In a more recent analysis of 146 patients with NLPHL by Biasoli et al. [20] the cumulative histologic transformation rate was 12%. Finally, in an analysis of 95 patients with NLPHL by Al-Mansour et al. [5] 14% patients progressed to an aggressive lymphoma and the risk of transformation increased with time from 7% to 30% at 10 and 20 years, respectively. The high recurrence and transformation rates support the need for continuous follow-up in patients as well as the importance of biopsy for a histologic diagnosis when a new mass appears.

The median time for histologic transformation varies. Biasoli et al. [20] demonstrated a median time of 4.7 years (range 0.4 to 18 years) whereas it was 8.1 years (range 0.35 to 20.3 years) in the study by Al-Mansour et al. [5]. The patient in this case report exceeds these ranges by having a 25 year lapse between diagnosis of NLPHL and transformation to a high-grade lymphoma. Independent of the time for transformation, patients who progress to DLBCL have a poorer prognosis compared to those with NLPHL. The overall survival rates after histologic transformation were similar in Biasoli et al. [20] and Al-Mansour et al. [5] at 60% and 62%, respectively. In a report of 21 cases from the Nebraska Lymphoma Study Group, Huang et al. [21] demonstrated there was no difference in survival outcomes between DLBCL arising from NLPHL versus DLBCL arising de novo.

While treatment algorithms exist for NLPHL, therapies for patients who histologically transform to a high-grade lymphoma or DLBCL are less clearly defined [22]. Treatment for patients diagnosed with stage I or II NLPHL without B symptoms consists of radiation therapy alone whereas stage I or II with B symptoms or stage III or

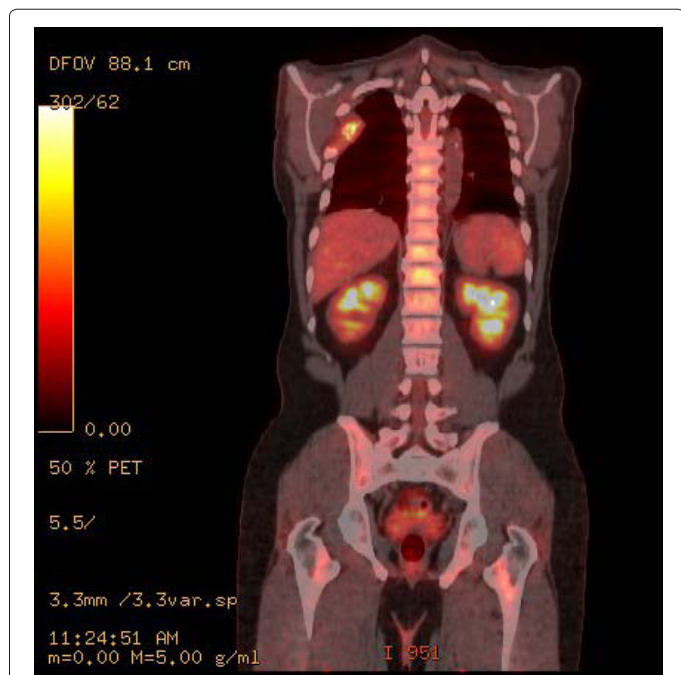


Figure 5: PET/CT following ifosfamide, carboplatin, and etoposide (ICE): Marked interval decrease in size and hypermetabolic activity of right chest wall mass.

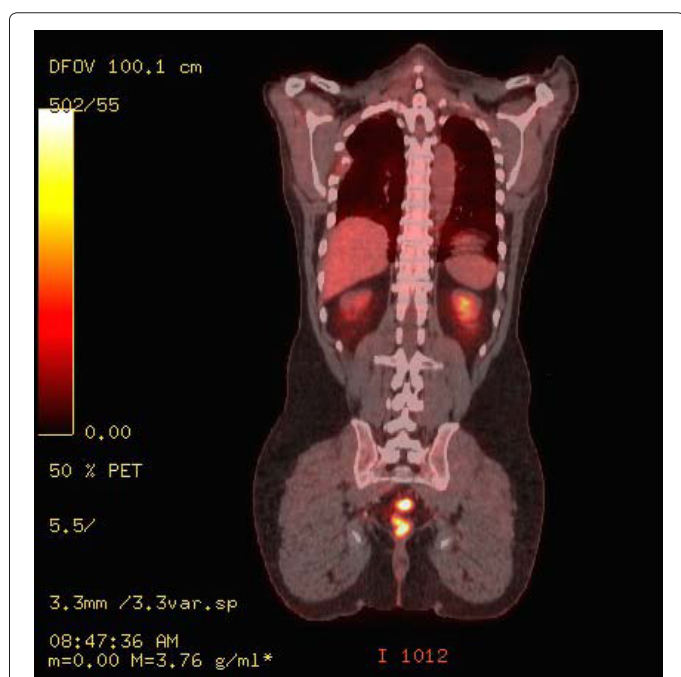


Figure 6: PET/CT day 100 post autologous stem cell transplant (ASCT): No appreciable residual soft tissue or significant metabolic activity at the postero-lateral right fifth rib. No evidence of disease progression.

IV disease are treated with chemotherapy +/- radiation [22]. Common chemotherapy regimens used to treat NLPHL include ABVD, CHOP (cyclophosphamide, vincristine, prednisone) and EPOCH (cyclophosphamide doxorubicin, etoposide, vincristine, prednisone) +/- rituximab or rituximab alone [22]. This patient was treated as if he had relapsed advanced stage classical Hodgkin lymphoma. He initially received ABVD opposed to more intensive high dose or salvage therapy as he did not have chemotherapy in the past. He eventually required salvage therapy with ICE and then BEAM followed by ASCT due to persistence of the chest wall mass. It is hypothesized that the chest wall mass was the only area that transformed to a high-grade lymphoma due to its resistance to therapy, although this cannot be confirmed as pathologic specimens from the other sites of recurrence were not obtained.

Conclusion

In summary, a small percentage of patients with NLPHL may progress to a high-grade non-Hodgkin's lymphoma, most commonly DLBCL. Due to the high recurrence rate and risk of transformation, continual follow-up and screening is required for these patients. Following a recurrence, biopsy is an important tool in determining if histologic transformation has taken place. Once transformation to aggressive non-Hodgkin's lymphoma has occurred, treatment with regimens appropriate to the transformed lymphoma subtype may be required for disease control.

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