Complete Response to Brentuximab Vedotin in a Transplant-Naïve Patient With Relapsed CD30-Positive Nodular Lymphocyte-Predominant Hodgkin Lymphoma

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A 20-year-old African American man initially presented to his primary care practitioner in 2005 complaining of swollen glands in his neck. Subsequent workup confirmed stage II A, nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) involving the neck. The large atypical cells were positive for CD20, CD45, and CD30. He was treated with 2 cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) followed by involved field radiation to his neck and Waldeyer's ring, to a complete response. He was followed for 3 years subsequently and then discharged from clinic.

In late 2011, he presented to Georgetown University Hospital for evaluation of a new posterior scalp mass. A positron emission tomography/computed tomography (PET/CT) scan revealed fluorodeoxyglucose (FDG) uptake in a left posterior scalp soft tissue nodule and in the left supraclavicular, left subpectoral, bilateral axillary, peripancreatic, left iliac, and bilateral inguinal lymph nodes. An area of increased metabolic uptake was also noted in a mid-thoracic vertebral body. Biopsy of the left occipital scalp mass revealed diffuse effacement of the lymph node architecture by a nodular proliferation of small-to-medium–sized lymphocytes. Some of the large cells had convoluted or cerebriform nuclei. The large atypical cells were positive for CD20, CD45, CD79a (weak), Pax5, bcl-6, MUM-1 (weak, focal), and CD30, and they were negative for all other markers tested (Figures 1 and 2). The morphologic and immunohistochemical findings were thought to be consistent with NLPHL. The patient was started on brentuximab vedotin (Adcetris, Seattle Genetics) at a dose of 1.8 mg/kg intravenously once every 3 weeks as a bridge to a possible autologous stem cell transplant (ASCT). The reason for initiating treatment with brentuximab was in view of the fact that this patient had NLPHL with CD30 positivity, a rare finding.

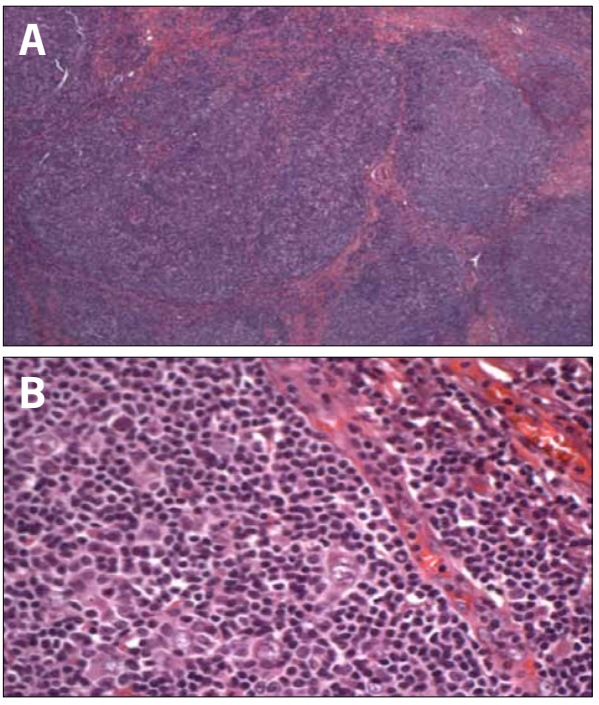

Figure 1. Hematoxylin and eosin [H&E] stains showing nodular atypical lymphoid proliferation in a patient with nodular lymphocyte-predominant Hodgkin lymphoma. Panel A shows a magnification of 40×. In Panel B, the higher magnification (400×) shows large, atypical popcorn-like cells.

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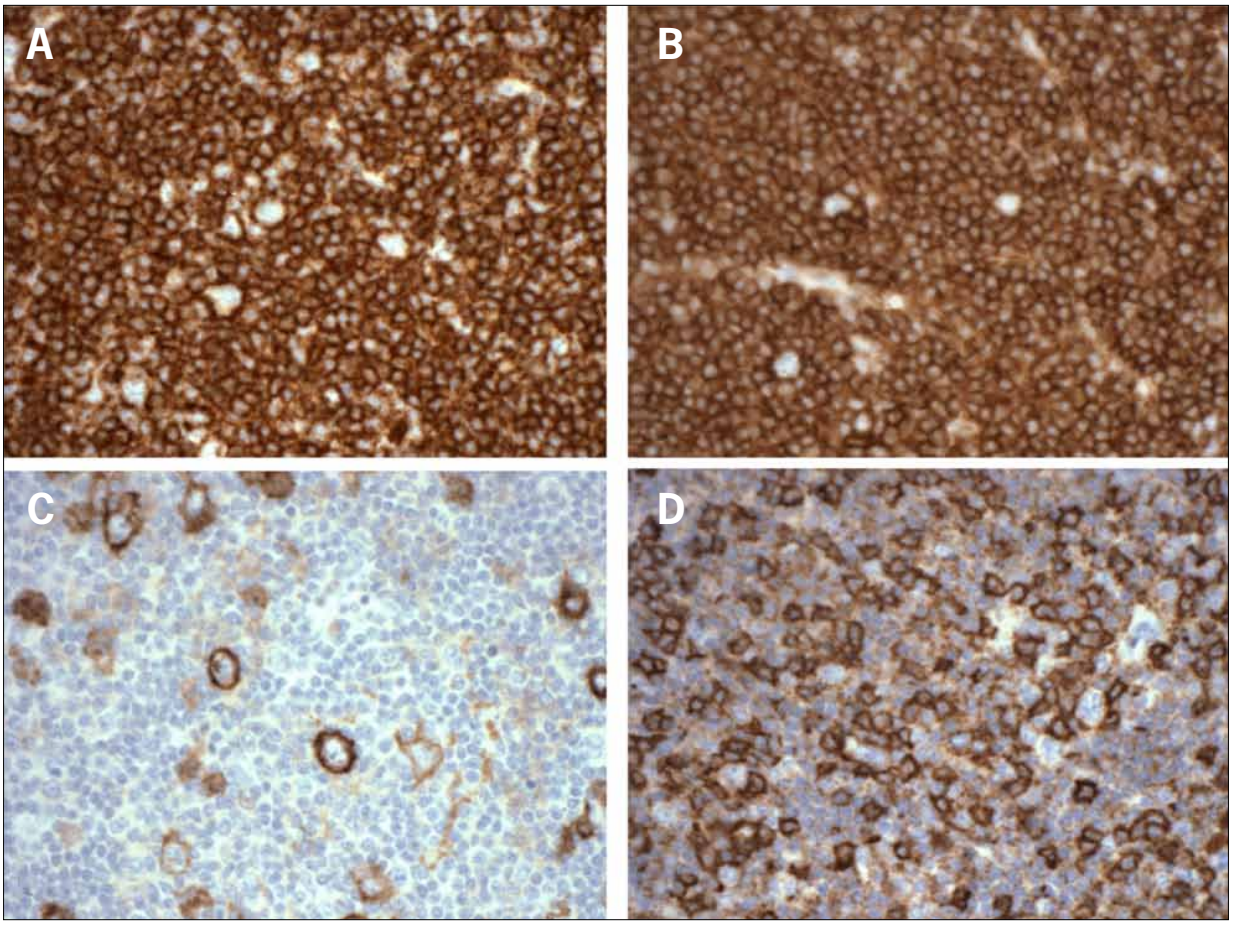

Figure 2. The large neoplastic cells and background small lymphocytes in the nodules are positive for CD20 (A) and CD45 (B). The large atypical cells are positive for CD30 (C), and negative for CD15. Many of these cells are rosetted by CD57-positive small T cells (D) (immunohistochemistry 400× magnification, each).

His first cycle of therapy was complicated by fevers of 100°F and mild headaches that began on day 9. CT of the brain and sinuses showed mild sinusitis. Serial blood cultures and a comprehensive septic workup were otherwise unremarkable. He was treated with a course of amoxicillin and clavulanate potassium with symptomatic relief. After 2 cycles of treatment, the patient had a PET/CT, which showed complete resolution of metabolic activity (Figure 3). He received his third cycle of brentuximab, and the transplant group decided to defer the procedure until the time of a subsequent relapse.

Discussion

NLPHL comprises 5% of all cases of Hodgkin lymphoma, and is more frequently seen in men with a slightly older average age at presentation than that associated with classical Hodgkin lymphoma (cHL). Patients frequently present with limited nodal disease involving the neck region with mediastinal sparing.[1] Characteristically, histology reveals neoplastic lymphocyte-predominant cells, which typically express B-cell–related antigens CD20 and CD79A, and leukocyte common antigen (CD45). Unlike cHL, lymphocyte-predominant cells are CD20-positive and CD15-negative, and only rarely express CD30 (7–10% of cases).[2,3] In the majority of cases, the CD30-positive cells were benign extrafollicular immunoblasts.[4] NLPHL has a different natural history than cHL in that it displays a more indolent course and can be associated with late relapses, including as diffuse large B-cell lymphoma.[2] Patients with NLPHL are usually treated with standard therapies used for cHL. Emerging evidence suggests that the anti-CD20 monoclonal antibody rituximab (Rituxan, Genentech/Biogen Idec) is an effective alternative therapy for relapsed and refractory NLPHL and is associated with a favorable toxicity profile.[5] As this patient's NLPHL also expressed CD30, the

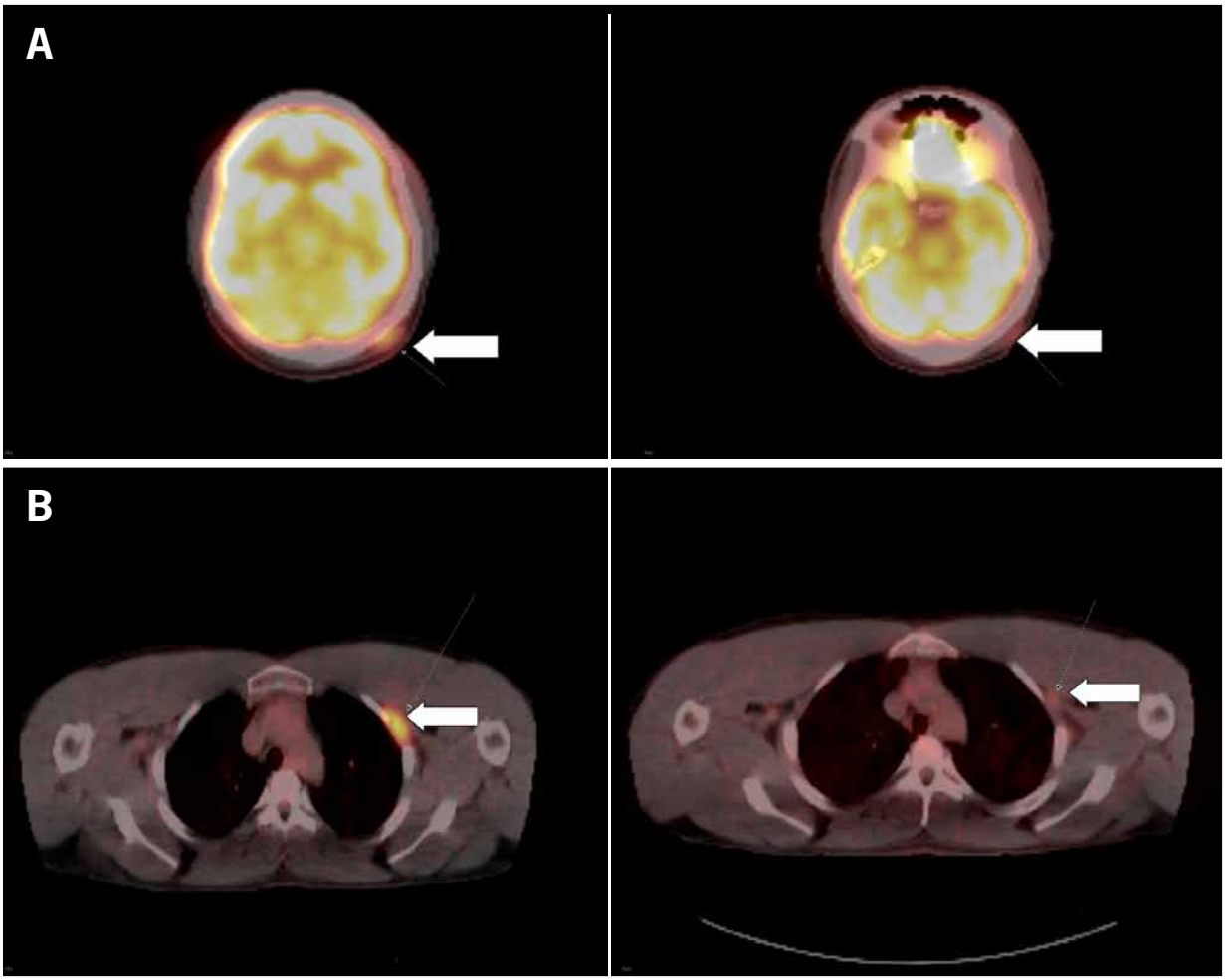

Figure 3. Pre- and post-treatment positron emission tomography/computed tomography imaging depicting response to treatment in the scalp (A) and left subpectoral regions (B).

decision was made to commence salvage chemotherapy with brentuximab vedotin.

Brentuximab vedotin is a chimeric anti-CD30 monoclonal antibody that is conjugated to 4 molecules of monomethyl auristatin E (MMAE), a synthetic anti-tubulin chemotherapeutic agent.[6] Brentuximab binds to CD30 and is promptly internalized and transported to lysosomes, which triggers release of MMAE and subsequent tubulin binding, culminating in cellular apoptosis.[7] In August 2011, the US Food and Drug Administration approved brentuximab for patients with cHL who had relapsed post-ASCT, or who had progressed on 2 prior chemotherapy regimens and were ineligible for ASCT. The evidence to date suggests that this drug is effective. In patients with refractory cHL treated with brentuximab, a 76% overall response rate was observed, with a complete response rate of 32%.[8] The median duration of response was 20.5 months. Brentuximab was well tolerated in this patient population,[6] and it is now being evaluated in the first-line and maintenance settings, whilst ongoing trials are assessing its efficacy as a salvage therapy prior to stem cell transplant. As salvage chemotherapy regimens often require inpatient admission and are associated with significant short-term and long-term toxicities, use of brentuximab in patients with relapsed CD30-positive malignancies could prove to be an attractive alternative.[6] It has been used successfully for this indication in patients with heavily pretreated CD30-positive lymphomas as a bridge to transplant.[9]

Whilst the standard treatment for relapsed cHL is salvage chemotherapy followed by an ASCT in patients with chemosensitive disease, an overall survival benefit has not been confirmed.[10] As NLPHL is relatively rare, limited information exists with respect to the utility of salvage chemotherapy and ASCT in this setting. An MD Anderson study reported that high-dose chemotherapy

and ASCT were highly effective in this subgroup, resulting in long-term remissions for the majority of patients.[11] However, it is difficult to extrapolate these data to our patient, who has a CD30-positive NLPHL.

With regard to further management of this patient, ASCT has been deferred at this point. Alternative options include completing a full course (16 cycles) of brentuximab, followed by observation or, perhaps, rituximab maintenance. The patient could then be transplanted at a later date if he were to subsequently relapse. Depending on the duration of remission, newer targeted agents may be available at that point.

To our knowledge, this case is the first to describe relapsed NLPHL with CD30 positivity that has been treated with brentuximab vedotin. This case raises several important issues. NLPHL has an indolent course and propensity to relapse late, which is unique to this subtype of Hodgkin lymphoma. Therefore, long-term follow-up is essential. Typically, NLPHL has been managed in a similar manner to cHL with successful outcomes, although often at the expense of long-term toxicities. In the era of molecular-targeted therapy and personalized medicine, it may be possible to avoid high-dose chemotherapy and autologous transplantation in NLPHL in favor of targeted therapies.

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Review

Treatment of Nodular Lymphocyte-Predominant Hodgkin Lymphoma—"DO NO HARM"

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O'Sullivan and colleagues describe a young man with a first relapse of nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) who achieved a complete response with 2 cycles of the anti-CD30 antibody-drug conjugate brentuximab vedotin (Adcetris, Seattle Genetics).[1] The patient's clinical course, including a 6-year interval from initial treatment to first relapse, is typical of NLPHL. However, as discussed, the biopsy revealed an unusual immunophenotype for NLPHL with expression of CD30. In contrast to classical Hodgkin lymphoma (cHL), the lymphocyte-predominant cells in NLPHL uniformly express CD20, but rarely express CD30. Expression of CD45 in the described case substantiates the diagnosis of NLPHL despite the rare phenotype.

There is no general consensus regarding therapy of NLPHL, either at diagnosis or relapse. Small patient numbers preclude randomized trials and hinder efforts to develop distinct treatment approaches for NLPHL. Historically, treatment of NLPHL paralleled that of cHL, with most patients treated using extended or regional field radiotherapy, with or without chemotherapy. In nearly all reports of long-term outcomes for patients with NLPHL, the majority of deaths are related to late effects of treatment, primarily cardiovascular disease and second malignancies, and not to Hodgkin lymphoma. In a series of 113 patients with early-stage NLPHL treated primarily with radiotherapy or combined modality therapy at the Dana Farber Cancer Institute between 1970 and 2005, only 3 of 113 patients died of Hodgkin lymphoma, while 10 patients died of second malignancy (6), cardiac disease (2), or unrelated causes (2).[2] These

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retrospective reports of long-term follow-up emphasize the importance of taking into account the often extremely indolent natural history of NLPHL when establishing a treatment plan. While a small percentage of patients with NLPHL will develop transformed DLBCL, most patients will enjoy a long survival, even in the setting of relapsed disease.

Currently, first-line therapy for early-stage NLPHL is either involved field radiotherapy (IFRT) or combined modality therapy with 2–4 cycles of chemotherapy followed by IFRT. First-line therapy for advanced-stage disease is combination chemotherapy. In patients requiring chemotherapy, the choice of regimen varies across centers. The British Columbia Cancer Agency advocates the use of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) based on a 10-year progression-free survival (PFS) rate of 91% for 56 patients with limited-stage NLPHL treated with ABVD alone (n=14) or in combination with radiotherapy (n=42).[3] However, these results are in contrast to a review of 37 NLPHL patients treated with chemotherapy, which showed 9 failures in 12 patients (75%) treated with ABVD or etoposide, vinblastine, and doxorubicin (EVA) compared to 8 failures in 25 patients (32%) treated with mechlorethamine, vincristine, procarbazine, and prednisone (MOPP) or MOPP/ABVD, suggesting perhaps that an alkylator-based regimen may be superior to ABVD in NLPHL, especially when given without radiotherapy, and implying an uncertain role for anthracyclines.[4]

The B-cell phenotype and uniform expression of CD20 in all cases of NLPHL has led to the investigation of rituximab (Rituxan, Genentech/Biogen Idec), an anti-CD20 monoclonal antibody, as a treatment option. Single-agent rituximab has been explored in small numbers of patients with NLPHL, both in the relapse setting and as primary therapy.[5-10] In all series, high response rates (88–100%) are reported, but early relapse is more common than described with radiotherapy or combined modality therapy. The German Hodgkin Lymphoma Study Group conducted small studies of single-agent rituximab in both newly diagnosed and relapsed NLPHL.[6,8,10] At a median follow-up of 63 months, the 5-year PFS for 15 patients with relapsed NLPHL was approximately 50%.[8] Importantly, the 5-year overall survival (OS) exceeded 90%. For 28 patients with newly diagnosed stage I NLPHL, the 3-year PFS and OS rates were 81% and 100%, respectively.[10] In a small series from Stanford, the use of maintenance rituximab appeared to prolong remission durations both in the upfront and relapsed settings.[7,9] Given the high relapse rate of single-agent rituximab, a combination of rituximab and chemotherapy is a logical approach for treating newly diagnosed or relapsed NLPHL. Recently, Fanale and colleagues reported a 100% response rate in patients with newly diagnosed NLPHL treated with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP; n=15) or R-CHOP + IFRT (n=5), with no relapses or transformations at a median follow-up of 42 months.[11] In the case presented, single-agent rituximab or a combination of rituximab and an alkylator-based regimen such as cyclophosphamide, vincristine, and prednisone (CVP) would also have been logical treatment choices given the patient's prior anthracycline exposure. Unless there is evidence of transformation, delaying aggressive approaches such as transplant for second or even later relapse is rational given the indolent nature of the disease and the very long expected survival, as evidenced by the 20-year survival rate of 85% reported in 38 patients with NLPHL treated at Stanford.[7]

In light of the CD30 expression, the authors elected to treat their patient with the targeted agent brentuximab vedotin. This promising new therapy for relapsed cHL is an antibody-drug conjugate composed of an anti-CD30 antibody (cAC10) conjugated to monomethyl auristatin E (MMAE), a potent antimicrotubule agent.[12] Brentuximab vedotin was approved by the US Food and Drug Administration in 2011 for patients with relapsed or refractory cHL following at least 2 prior lines of treatment and for patients with relapsed anaplastic large-cell lymphoma. In a pivotal phase II trial, brentuximab vedotin had an overall response rate of 75% and a complete response rate of 34% in 102 patients with relapsed or refractory Hodgkin lymphoma after autologous stem cell transplant (ASCT).[13] The median PFS was 5.6 months, and in patients who achieved a complete response, the median duration of response was 20.5 months. Common brentuximab vedotin toxicities include reversible peripheral sensory neuropathy (42%), neutropenia (19%), and diarrhea (18%). No febrile neutropenia or treatment-related deaths occurred in the phase II study.

Brentuximab vedotin is currently under study in other lymphomas that occasionally express CD30, but it has never been reported for NLPHL.[14] Responses have been seen in 7 of 15 patients with CD30-positive diffuse large B-cell lymphoma, 3 of 5 patients with angioimmunoblastic T-cell lymphoma, and 2 of 5 patients with grey zone lymphoma.[15] The rapid response to brentuximab vedotin seen in the accompanying case report is encouraging, but given the rarity of CD30 expression in NLPHL, this agent does not represent a feasible treatment option for the majority of patients with NLPHL. Obtaining insurance approval for off-label use of this very expensive drug (average wholesale price, approximately $18,000/dose) may also make it impractical, even in the cases that do express CD30. However, the authors' effort to choose a treatment with a modest toxicity profile and no known risks of serious late effects is exactly the approach we need for this indolent subtype of lymphoma.

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