A physician or group of physicians considers presentation and evolution of a real clinical case, reacting to clinical information and data (boldface type). This is followed by a discussion/commentary

Primary refractory Hodgkin lymphoma: Limited options and poor survival—but not always

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Our patient is a 32-year-old woman of Cape Verdean descent, who initially presented in February of 2010 with 1-month course of non-productive cough. She also stated that she had a few swollen lymph nodes on the right side of her neck for the past 6 months, which were initially sore, but never painful. She endorsed drenching night sweats and a 20-pound weight loss over the last 6 months, but denied any fever or chills. Her past medical history and family history were non-contributory. She is a cigarette smoker with a 10 pack-year history of cumulative smoking. After a course of antibiotics that had no effect on her lymphadenopathy, she had a cervical lymph node excisional biopsy.

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The differential diagnosis on this young woman with lymphadenopathy is broad and includes autoimmune such as systemic lupus erythematosus, chronic infections such as tuberculosis, and oncological processes. Given the presence of B symptoms, namely night sweats and 20-pound weight loss, I would favor an oncological condition such as lymphoma. The clinical picture is highly suspicious for Hodgkin lymphoma (HL), which has been associated with cigarette smoking based on a recent meta-analysis of epidemiological studies [1]. The differential diagnosis also includes follicular lymphoma (FL) and head and neck (H&N) cancer. FL, however, tends to present in older patients with B symptoms reported in only 20–30% of the cases. H&N cancer also tends to present in older individuals and has a strong male predominance. Given the 6-month clinical course, I would not favor more aggressive disorders such as Burkitt or diffuse large B-cell lymphoma.

The hematoxylin and eosin sections demonstrated a polymorphic lymphoid population focally intersected by broad areas of fibrosis. The lymphoid infiltrate consists of small-to-medium-sized lymphocytes with a background of scattered eosinophils, histiocytes, and neutrophils. Occasional large binucleated hyperchromatic cells with prominent nucleoli (Reed-Sternberg cells) are noted within this infiltrate. Per immunohistochemistry, the Reed-Sternberg cells are positive for expression of CD30 and CD15, and negative for CD3, CD20, ALK-1, granzyme B, cytomegalovirus (CMV), Epstein–Barr virus, and herpes simplex virus. These findings are diagnostic of classical HL, nodular sclerosing (NS) variant.

Not surprisingly, we have a pathological diagnosis of classical HL, NS variant. Although included in the group of classical HL, the NS variant is the most common, accounting for approximately 60% of the cases. The NS variant seems to be associated with a better prognosis than other variants such as mixed cellularity (MC) and lymphocyte-depleted (LD) HL. Based on a recent population-based study from the SEER database, patients with NS had higher relative survival and lower lymphoma-related death rates at 5 years than patients with MC or LD HL [2]. To complete this patient's staging and prognostic workup, a positron emission tomography/computed tomography (PET/CT) scan, bone marrow biopsy, echocardiogram, complete blood count (CBC) with differential, erythrocyte sedimentation rate (ESR), and serum albumin level would be recommended. The value of a bone marrow biopsy in the era of PET/CT scanning has recently been challenged [3]; however, it is our policy to perform unilateral bone marrow biopsies in all patients with lymphoma. An HIV ELISA test should be part of the workup as HIV infection has shown to increase the incidence rate of HL [4], although HL is not considered an AIDS-related malignancy.

Patient's PET/CT showed extensive lymphadenopathy involving the right side of her neck, mediastinum, and retroperitoneum, along with bilateral lung nodules, small low-density nodules within the spleen, and right adnexal region uptake (Fig. 1A). A bone marrow biopsy did not show evidence of involvement by HL. Her CBC showed white blood cell (WBC) count of 12.8 × 10^9/L, absolute lymphocyte count (ALC) of 1.9 × 10^9/L, hemoglobin 8.5 g/dL, and platelet count of 301 × 10^9/L. Her ESR was 90 mm/hr and her albumin level was 2.8 g/dL. Her echocardiogram showed an ejection fraction of 65%. Her HIV ELISA test was negative.

Based on the above information, the patient can be classified as stage IV HL with an International Prognostic Score (IPS) of 3. The IPS has proven to prognosticate freedom from progression (FFP) and overall survival (OS) in patients with HL [5]. According to this score, seven clinical factors are assigned 1 point: age ≥45 years, male sex, stage IV, WBC ≥15,000 × 10^9/L, ALC <600 × 10^9/L, hemoglobin <10.5 g/dL, and albumin <4 g/dL. The 5-year FFP rates ranged between 40% and 80% depending on how may adverse factors each group of patients presented. It is interesting to note that ESR >80 mm/hr was also an adverse prognostic factor in the above study; however, it was not included in the final model. Based on this study, the 5-year FFP and OS rates in patients with IPS of 3 were 60% and 80%, respectively. More recently, the prognostic value of the IPS has been re-evaluated. A Canadian study on patients with advanced HL treated with doxorubicin, bleomycin, vinblastine, and dacarbazine

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(ABVD) showed a narrower range of 5-year FFP between 62% and 88% [6], likely a reflection on the improvements on the administration of chemotherapy. Based on this study, patients with IPS of 3 had 5-year FFP and OS rates of 74% and 88%, respectively.

The next step is to begin therapy with a curative intent. There is an ongoing debate on which is the most appropriate initial therapy for patients with HL between ABVD, Stanford V, standard dose bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP), and escalated BEACOPP. A British randomized study compared the outcomes of patients with HL who received ABVD or Stanford V [8], and showed that there were no statistical differences on PFS, OS or toxicity between both approaches. An Italian randomized controlled study (RCT) has compared ABVD versus standard BEACOPP and showed that standard BEACOPP was associated with a better PFS but was also associated with higher toxicity rates and there was no difference in OS [7]. However, patients with an IPS $\geq$3 seemed to obtain a higher benefit with standard BEACOPP than with ABVD (Hazard ratio for progression 0.46), while no difference in survival was observed in patients with IPS $<$3. In a German RCT including approximately 1,200 patients with advanced HL, escalated BEACOPP has shown to induce higher response and survival rates when compared against standard BEACOPP and COPP-ABVD [9]. However, no RCTs have directly compared escalated BEACOPP versus standard ABVD. More recently, a network meta-analysis has shown a 10% improvement in 5-year OS rates seen with escalated BEACOPP over ABVD suggesting that escalated BEACOPP should be the standard of care in patients with advanced HL [10]. The risk of infertility associated with chemotherapy varies greatly between regimens. Specifically, in female patients, BEACOPP has been associated with infertility rates of 20–50% while ABVD with rates of $<$5% [11]. It is our policy and recommendation to discuss fertility impairment with the patient before initiating therapy.

A few days before starting chemotherapy, the patient developed facial swelling and engorged veins in the upper thorax and neck, consistent with superior vena cava (SVC) syndrome. She was hospitalized and started on ABVD. Being a mother of two, she declined egg harvesting. Within 1–2 weeks, her SVC symptoms gradually resolved. After completing four cycles of ABVD (June 2010), an interim PET/CT scan showed complete resolution of the lymphadenopathy above and below the diaphragm and decreased size and uptake within the lung lesions (Deauville score of 2). The lung lesions were considered inflammatory in nature. She then received two more cycles of ABVD. A PET/CT after completing six cycles of ABVD showed worsening of supraclavicular and mediastinal lymphadenopathy, and increased 18F-FDG uptake within lung nodules bilaterally (Fig. 1B). The patient was complaining of recurrence of her night sweats and underwent a biopsy of her supraclavicular lymphadenopathy that showed HL, NS variant (August 2010).

Unfortunately, this patient is showing evidence of disease progression concerning for an early relapse or perhaps primary refractory disease. A series of studies have described prognostic factors for survival at HL relapse. In these studies, a relapse seen within 12 months after completing initial therapy and advanced clinical stage at relapse were the most important adverse factors. In our case, the patient meets both criteria, which means that her 5-year OS rate would range between 20% and 30%, depending on the study [12–14]. In this specific scenario, our goal is still curative, and will encompass obtaining ideally a complete response (CR) with combination chemotherapy followed by high-dose chemotherapy with autologous stem cell rescue (ASCT). The level of evidence to support one regimen over another, however, is rather low. Most of the studies are small and not randomized [15]. In this situation, regimens such as ifosfamide, carboplatin, and etoposide (ICE), dexamethasone, cytarabine, and cisplatin (DHAP), etoposide, methylprednisolone, cytarabine, and cisplatin (ESHAP), or gemcitabine, vinorelbine, and liposomal doxorubicin (GVD) are all reasonable options. The addition of ASCT has been studied in two separate RCTs, both of which showed a 30%–50% improvement in PFS rate, but not OS, in patients with chemosensitive disease [16,17]. A model to prognosticate survival in relapse HL patients after ASCT has been published [18]. In this study, relapse $<$1 year of initial therapy, and presence of B symptoms and extranodal disease at relapse were considered adverse prognostic factors. Our patient actually has these three factors playing against her. The PFS rate at 43 months in patients like ours was 10%.

She received salvage chemotherapy with ICE (September 2010). After three cycles of ICE, she presented with fever and drenching night sweats. She then had a PET/CT showing progression of disease (Fig. 1C). She had a biopsy of one of the lung nodules that showed classical HL. She was started on third-line chemo with

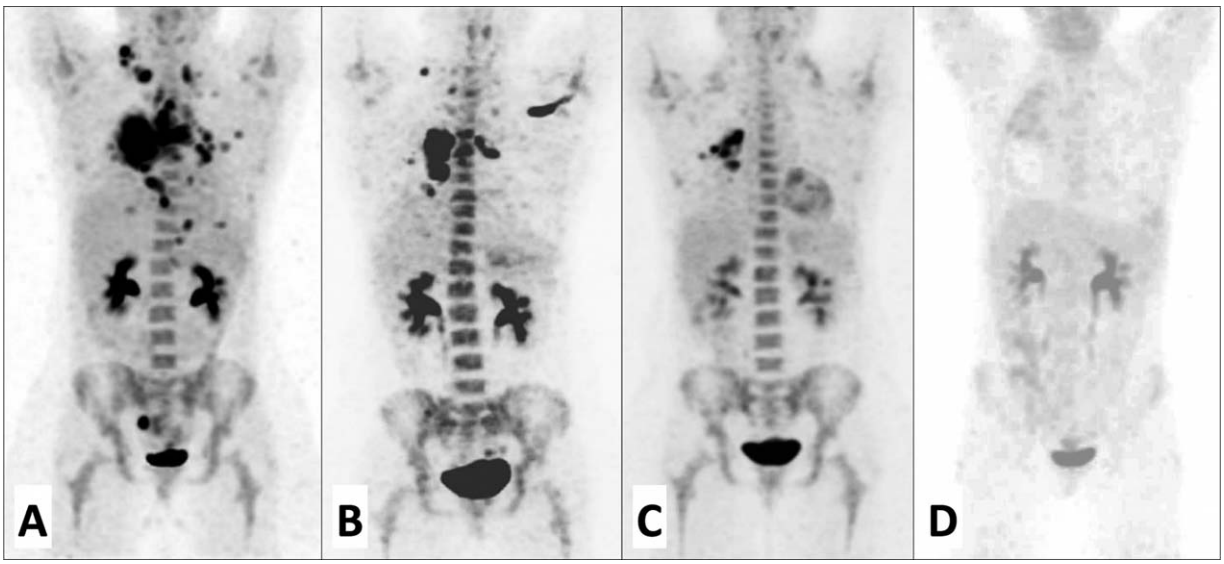

Figure 1. (A) PET/CT scan from February 2010 showing increased FDG avidity above and below the diaphragm before ABVD; (B) PET/CT scan from August 2010 showing increased FDG avidity after 6 cycles of ABVD; (C) PET/CT scan from December 2010 showing increased FDG activity after 3 cycles of ICE; (D) PET/CT scan from December 2011 showing no FDG avidity after 2 cycles of brentuximab vedotin.

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GVD (December 2010). After the first cycle of GVD, she was mobilized with cyclophosphamide, and then received BCNU, etoposide, cytarabine, and melphalan (BEAM) as conditioning regimen in preparation for autologous SCT. She then underwent autologous SCT in February 2011. On day 27, she had a PET/CT showing persistence of disease. Around day 45, she proceeded to receive an allogeneic SCT (March 2011). She received matched-related allogeneic stem cells with 10/10 HLA high-resolution match. The donor and recipient were ABO compatible and CMV negative. The conditioning regimen included fludarabine and busulfan. A restaging PET/CT on day 60 of allogeneic SCT showed persistence of disease (May 2011). She was initiated on salvage chemotherapy with oxaliplatin and cytarabine and, after three cycles, received two donor lymphocyte infusions (DLI) due to disease progression. The patient did not respond to DLI.

Our patient is now clearly showing refractory disease. A series of small studies have evaluated the role of SCT in this setting. A Spanish study evaluated the role of autologous SCT in 62 patients with primary refractory HL [19]. In this study, BEAM-like regimens were used for conditioning, and the 5-year OS was 26%. Similarly, a French study evaluated autologous SCT in 86 HL patients who either did not respond to frontline treatment, progressed within 3 months of completing therapy or showed evidence of progression during frontline therapy [20]. Although the 5-year OS for the entire group was 35%, the 5-year OS for patients with progressive disease during or shortly after autologous SCT was 19%. Similar results were found in other studies with 5-year OS rates in patients with chemoresistant disease ranging between 15% and 25% [21]. The data on allogeneic SCT after failing autologous SCT are even more scant. A Spanish study showed that patients with chemoresistant disease had a 3-year OS of approximately 20% following allo-SCT [22]. The current British guidelines do not support the use of autologous SCT or allogeneic SCT in patients who do not demonstrate an appropriate response [23]. However, in the NCCN guidelines [24], autologous SCT can be considered in patients who present with PET/CT scans with Deauville scores as high as 4. Additionally, the NCCN guidelines state that allogeneic SCT is an option for select patients as a category 3 recommendation. In this young woman, undergoing autologous and allogeneic SCT after minimal or no response to chemotherapy is not unreasonable.

Brentuximab vedotin (Adcetris®, Seattle Genetics, Seattle, WA) was approved by the FDA on August 19, 2011 for the treatment of patients with relapsed or refractory HL. She was then initiated on brentuximab vedotin at a dose of 1.8 mg/m^2 given IV every 3 weeks (September 2011). A PET/CT performed after two cycles showed a CR with no increased 18F-FDG uptake (Fig. 1D). Since then, the patient has been on brentuximab vedotin, with restaging scans every 6 months, without evidence of progression of disease for the last 2 years. Her only adverse events (AEs) related to therapy are grade 1 peripheral neuropathy, neutropenia, anemia, and thrombocytopenia. Earlier this year, WBC chimerism was 97% donor.

Discussion

HL affects about 9,000 new patients in the United States each year [25]. There is an increased incidence in young adults as well as in individuals 55 years and older [26]. There are no clearly defined risk factors for the development of this disease, and the cause of HL remains unknown. Factors shown to be associated with HL include familial factors, viral exposures, and immune suppression [26]. HL is composed of two distinct disease entities; the more commonly diagnosed classical HL and the rare nodular lymphocyte predominant HL [27]. NS, MC, LD, and lymphocyte-rich HL are subgroups under the designation of classical HL. The presence of malignant multinucleated giant Reed–Sternberg cells within the characteristic reactive cellular background is the pathologic hallmark of classical HL. Across all stages, >80% of patients are cured with combination chemotherapy and radiation [28]. However, up to 15% of patients with limited stage disease and 35%–40% of patients with advanced stage disease do not achieve CR initially or relapse within a few years after initial treatment [29]. High dose chemotherapy followed by autologous SCT in patients with relapsed and refractory HL provides a 50%–60% chance for a long disease-free survival [30]. Allogeneic SCT, though curative, is usually reserved for those patients who progressed after autologous SCT due to a treatment-related mortality of approximately 25% and long-term survival of 30%–40% [31]. Treatment options for patients relapsing post-transplant are limited and usually confined to clinical trials.

Brentuximab vedotin (SGN-35; Adcetris®) is an anti-CD30 antibody conjugated via a protease-cleavable linker to the potent anti-microtubule agent monomethyl auristatin E (MMAE). CD30 is a transmembrane protein that belongs to the tumor necrosis factor receptor superfamily, and it is normally expressed in activated T-cells, B-cells, and NK-cells [32]. The function of CD30, however, is poorly understood. Although no specific diseases have been associated with CD30 or CD30 ligand mutations, CD30-mediated signaling appears important for the regulation of the development of effector and memory T-cells. Following binding to CD30, brentuximab vedotin is rapidly internalized and transported to lysosomes where MMAE is released and binds to tubulin, leading to cell cycle arrest and apoptosis. Additionally, a small fraction of free MMAE diffuses out of the targeted CD30+ cells, inducing killing of the surrounding cells in the tumor microenvironment, which can support tumor growth. Brentuximab vedotin received accelerated FDA approval in August 2011 for use as a salvage therapy in cHL following failure of at least two prior therapies or after failure of autologous SCT.

The data on the use of brentuximab vedotin in primary refractory patients or in patients who have relapsed after autologous or allogeneic SCT are mounting. In an initial phase II study, 102 patients with relapsed or refractory HL were enrolled [33]. From these patients, 71% were primary refractory and 42% were refractory to their most recent prior therapy. Of note, 100% of the patients had been previously treated with autologous SCT. Patients who previously had received allogeneic SCT were excluded from this study. The ORR was 75% with a 34% CR rate and a time to CR of approximately 12 weeks. The authors state that patients who were considered primary refractory benefited from brentuximab vedotin but no additional data were provided. Grade 3 or higher AEs included neutropenia (20%) and peripheral sensory neuropathy (8%).

More recently, the German Hodgkin Study Group published their experience with 45 patients with relapsed and refractory HL treated with brentuximab vedotin [34], from which 28 (62%) were primary refractory and 29 (64%) were refractory to their last regimen. Additionally, 39 patients (87%) had already undergone autologous and/or allogeneic SCT. The ORR was 60% with a CR rate of 22%. In the 17 patients considered very high risk (i.e., primary refractory or early relapse plus refractory disease before brentuximab vedotin), the ORR was 59% with a CR in 18%, which appear similar to the whole group. However, the 12-month PFS and OS in this group was 14% and 68%, respectively, which was statistically different from 59% and 93%, respectively, seen in the low-risk group. The most common grade 3 or higher AEs were neutropenia (13%), thrombocytopenia (7%), fatigue (7%), and infections (7%).

A smaller study specifically evaluated the role of brentuximab vedotin on 25 patients with HL that experienced recurrence of disease after allogeneic SCT [35]. In these heavily pre-treated patients with a median of 9 previous lines of therapy, the use of brentuximab vedotin was associated with ORR and CR rates of 50% and 38%, respectively,

with a median time to response of 8 weeks and a median PFS of 8 months. The median OS was not yet reached at the time of the report. Grade 3 or higher AEs were limited to neutropenia (24%), anemia (20%), thrombocytopenia (16%), and hyperglycemia (12%).

As the treatment of primary refractory HL continues to evolve, several questions remain:

1. Is it possible to predict primary refractory disease at diagnosis? Several studies have now shown the prognostic value of an increased number of CD68+ tumor-associated macrophages (TAMs) within the HL microenvironment [36–38]. In one study, a high number of TAMs correlated with refractoriness to chemotherapy and early relapse [39]. However, other studies have challenged such prognostic value [40,41]. Another potential target for prognostication is plasma EBV DNA. One recent study, which will require further validation, found a relation between elevated plasma EBV DNA levels and resistance to therapy [42].
2. Would a PET/CT after two cycles of ABVD have impacted the therapy on our patient? Several retrospective and small prospective studies have shown a prognostic value of performing interim PET/CT scans after two cycles of chemotherapy in order to switch to more intensive regimens [43–45]. Patients with negative PET/CT scans at treatment interim experienced a significant better outcome than patients with positive PET/CT scans. It is important to note the high negative predictive value of PET/CT scanning (true negative); however, a positive PET/CT scan can be artifactual (false positive). In such cases, a biopsy is advocated to demonstrate persistence of disease [46]. For this reason, interim PET/CT scans to dictate treatment should be performed in the setting of a clinical trial. Specifically in our patient, the PET/CT scan after four cycles of therapy showed no abnormal 18F-FDG uptake (Deauville 2), and based on current NCCN guidelines [24], ABVD was continued to complete six cycles.
3. Now that this very high-risk, primary refractory patient is in remission, how long should brentuximab vedotin be continued? The answer to this question is rather unclear. In the pivotal phase II study, patients received brentuximab vedotin for a maximum of 16 cycles [33]. In other studies, the maximum number of cycles ranges between 12 and 16 cycles [34,35]. Given that the patient had a dramatic response to brentuximab vedotin and seems to be tolerating therapy well, we are considering therapy until progression or unacceptable toxicity.

In conclusion, primary refractory HL is associated with lower rates of response to conventional chemotherapy and portends a poor prognosis. However, the use of brentuximab vedotin in this setting has been associated with higher response rates and relatively benign toxicity profile than otherwise expected with conventional regimens. We presented the case of a patient with primary refractory HL whose disease was resistant to ABVD, ICE, and GVD, and relapsed shortly after autologous and allogeneic SCT, only to experience a long-lasting response to brentuximab vedotin.

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