Brentuximab Vedotin: First-line Agent for Advanced Hodgkin Lymphoma

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Abstract. *Hodgkin lymphoma (HL) is characterized by malignant Reed-Sternberg cells which express CD30. Current National Comprehensive Cancer Network guidelines for patients with advanced HL (stage III/IV disease) recommend adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD), or escalated bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) as first-line regimens. ABVD appears to be as effective, with fewer side effects, as escalated BEACOPP. Escalated BEACOPP leads to a greater progression-free survival but no difference in overall survival. Recent advancements in technology have enabled an exciting shift to molecular-targeted cancer therapy. Brentuximab vedotin, a CD30-directed antibody conjugate, specifically targets malignant HL cells. It is approved by the Food and Drug Administration for the treatment of systemic anaplastic large-cell lymphoma and refractory HL that has progressed after autologous stem cell transplant, or after two prior multiagent chemotherapy regimens among patients ineligible to receive a transplant.*

In this case report, we present a patient with advanced HL. Her grave condition was marked by respiratory failure, renal failure requiring hemodialysis, low cardiac ejection fraction and hepatic dysfunction with elevated bilirubin. Because of this, we felt she would not tolerate either ABVD or escalated BEACOPP. Brentuximab vedotin was given for three cycles followed by a modified BEACOPP regimen. The patient has done well and has been disease-free for one year.

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The mortality rate of Hodgkin lymphoma (HL) has fallen rapidly in the United States in the past five decades due to the development of multiagent therapies. Among adults, there are about 9,060 new cases with a reported death of 1,190 in 2012 (1). Current standard first-line regimens include adriamycin, bleomycin, vinblastine, dacarbazine (ABVD), bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, prednisone (BEACOPP) and Stanford V. Brentuximab vedotin, the first Food and Drug Administration (FDA)-approved agent for the treatment of HL in over three decades, has been well-studied in many trials as a second-line agent after prior failed chemotherapies. However, through our comprehensive literature research we did not find any study that reported the use of brentuximab vedotin as first-line agent. In this case report, we present a patient with advanced HL with multi-organ failures. The patient received brentuximab vedotin prior to modified BEACOPP and had a complete response.

Case Report

This 49-year-old female presented to the hospital with fevers of up to 39.4˚C for five days. Her complicated medical course had begun three months prior when she developed episodic fevers. This was initially attributed to an upper respiratory tract infection. One month later, while traveling to Lake Tahoe, she developed acute shortness of breath. During that admission, she was diagnosed with pulmonary emboli with extensive clot extending from her legs to the inferior vena cava (IVC). She subsequently underwent thrombolysis, thrombectomy and IVC filter placement while being placed on coumadin. She was anemic and during her outpatient work-up she developed high fevers which prompted her hospital admission.

In the Emergency Department, she had an abdominal/pelvic computed tomography (CT) which showed non-calcified retroperitoneal lymphadenopathy confluent in the left infrarenal region, calcified right-sided retroperitoneal node and a hypodense lesion of the liver. Her alkaline

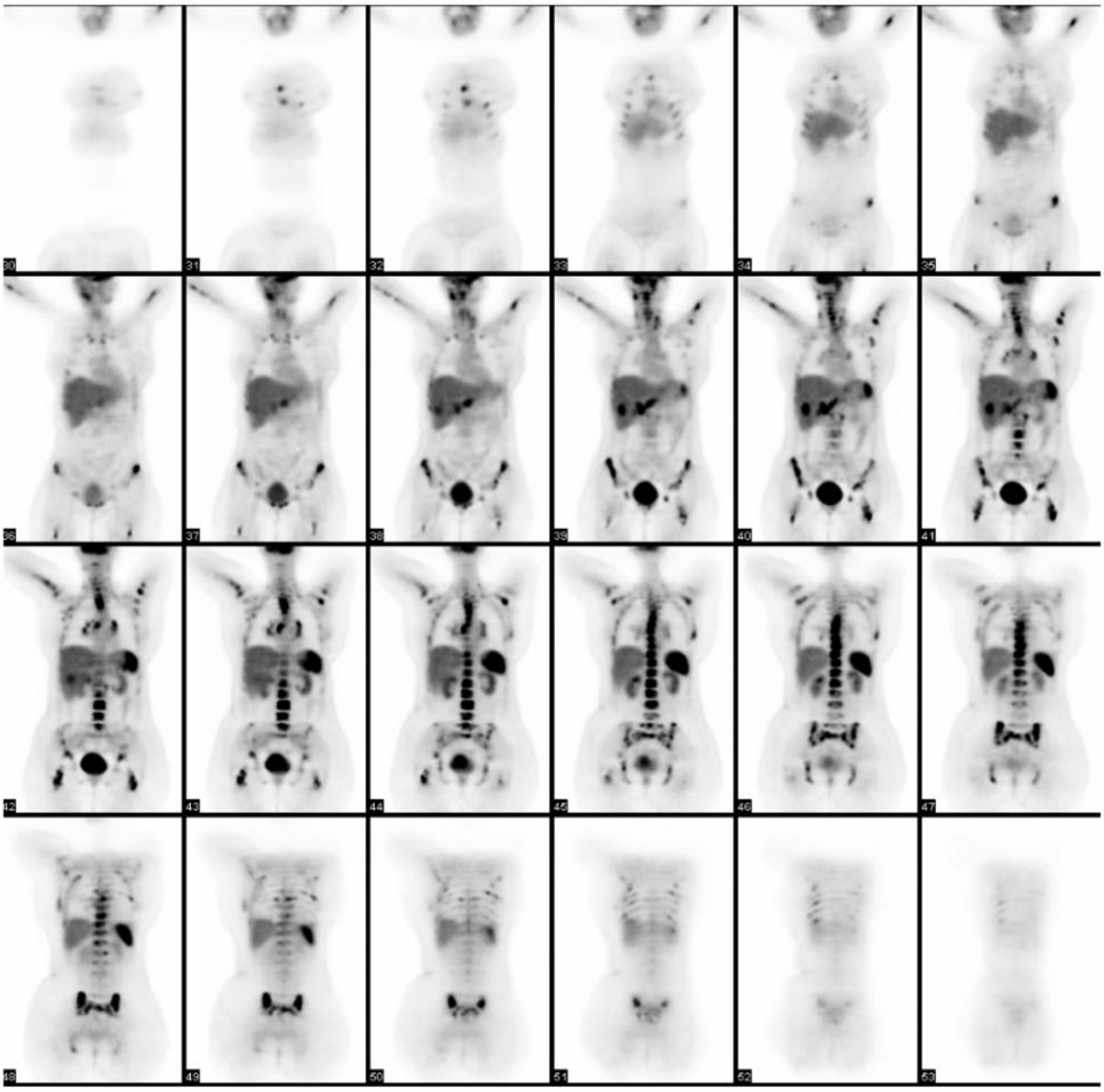

Figure 1. *Positron-emission tomography-computed tomography scan showed widespread, intense abnormal focus of fluorodeoxy-glucose uptake.*

phosphatase was elevated at 676 units/l but a previous magnetic resonance cholangiopancreatography (MRCP) was negative for a pancreatic mass or an obstructed biliary tract. She also had elevated aspartate transaminase (AST) (104 units/l), alanine transaminase (ALT) (55 units/l) and total bilirubin (2.5 mg/dl). In addition to an elevated white blood cell count of 15000K/μl, she continued to be anemic (hemoglobin of 9.5 g/dl) and thrombocytopenic ($95x10^3$/μl). She also developed acute renal failure (creatinine of 2.5 mg/dl). She was admitted to the hospital with the diagnosis of sepsis (bilateral pulmonary infiltrates, positive urinalysis, and metabolic acidosis with hypotension). She was appropriately placed on broad-spectrum antibiotic, zosyn and vancomycin. Given her classic Pel-Ebstein-type fevers and suspicious CT findings, lymphoma was also suspected. Subsequently, she rapidly developed respiratory failure secondary to pulmonary hemorrhage requiring intubation, renal failure requiring hemodialysis, and hepatic

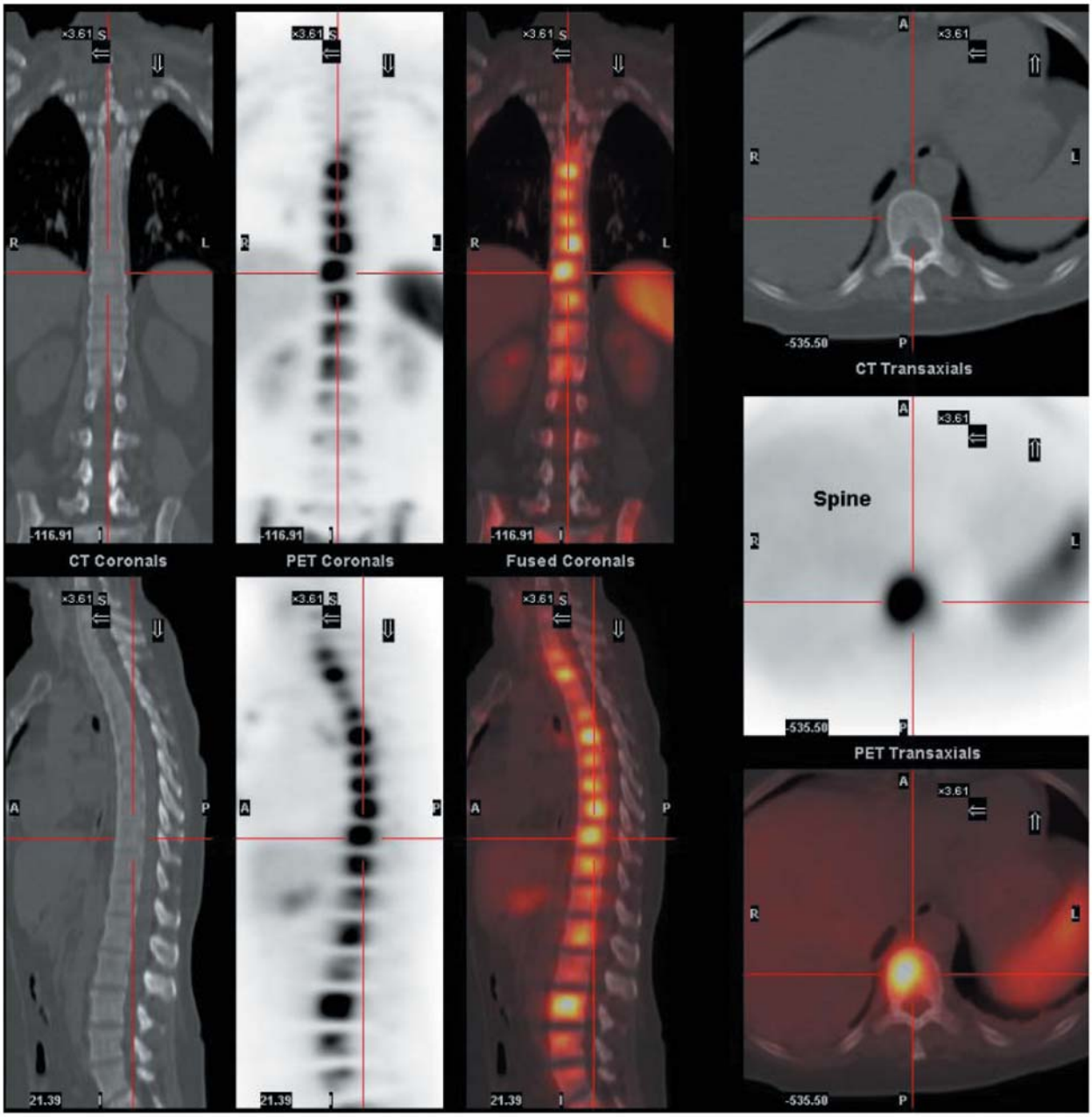

Figure 2. *Positron-emission tomography-computed tomography scan showed widespread, intense abnormal focus of fluorodeoxy-glucose uptake in the skeleton.*

dysfunction. Her cardiac output was compromised with a low ejection fraction of 44%. As part of her work-up, a bone marrow aspiration and biopsy of the iliac crest confirmed Hodgkin disease [immunohistochemical staining was positive for CD30 and paired box 5 (PAX5)]. A positron-emission tomography (PET)-CT scan showed intense abnormal focus of fluorodeoxy-glucose (FDG) uptake in an enlarged portocaval node adjacent to the pancreatic head. Additionally, widespread metastatic disease was suspected in the skeleton along with other adenopathy (Figures 1 and 2). Her rapidly deteriorating condition was thought to be secondary to multiple factors, sepsis (vancomycin-resistant enterococcus in urine culture) and advanced HL. Because of her extremely grave clinical condition and the fear that she might not tolerate a full course of standard chemotherapy, the decision was made to start her on brentuximab vedotin

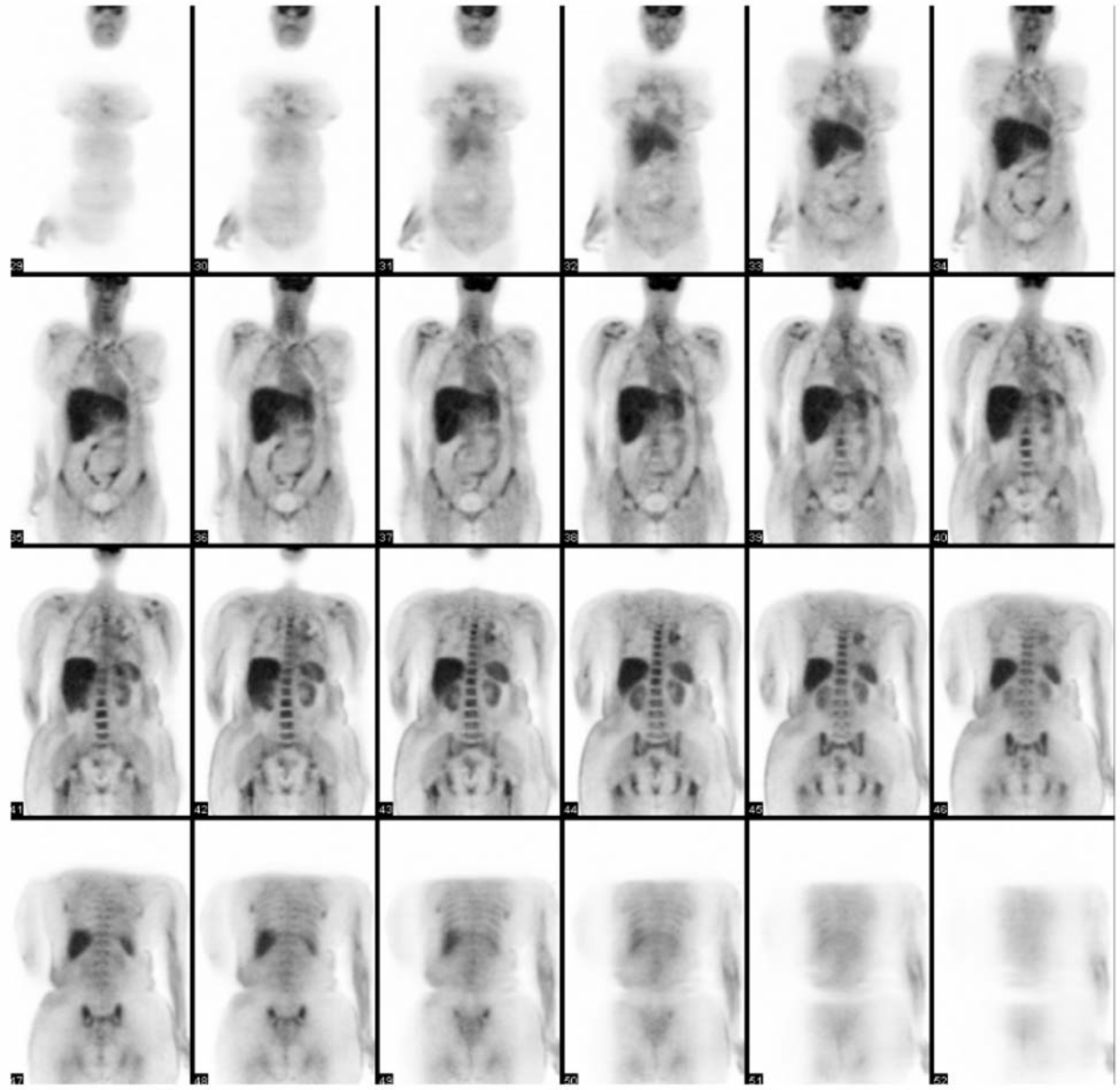

Figure 3. *A repeat positron-emission tomography-computed tomography 21 days after the first dose of brentuximab revealed complete resolution of increased fluorodeoxy-glucose uptake.*

(1.8 mg/kg intravenously). Twenty one days after the first dose, a repeat PET-CT revealed complete resolution of increased FDG uptake (Figures 3 and 4). She then received two more cycles of brentuximab vedotin (1.8 mg/kg intravenously) followed by three cycles of a modified regimen of BEACOPP (adriamycin, procarbazine and vincristine were omitted from the regimen secondary to renal dysfunction, pancytopenia and a low cardiac ejection fraction). She tolerated the therapy well, and her clinical condition gradually improved. At the time of discharge, four weeks later, she was off dialysis. Her liver function test normalized except for slightly elevated alkaline phosphatase level (251 units/l). The only complaint she had at discharge was minor peripheral neuropathy, which resolved subsequently. She had another PET-CT six months later, which demonstrated durable resolution of the initial disease. At her recent one year follow-up, she was disease-free.

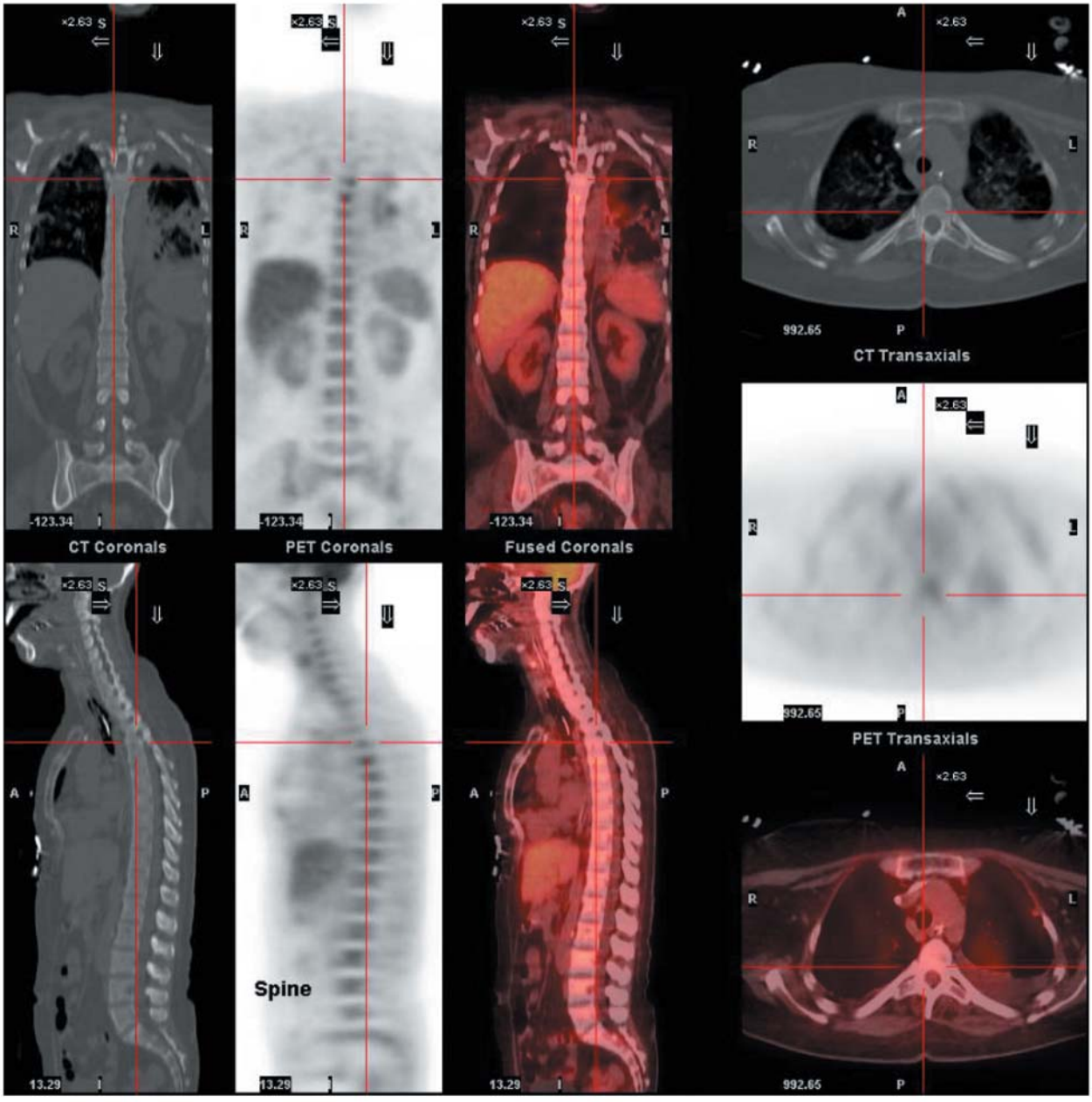

Figure 4. *A repeat positron-emission tomography-computed tomography 21 days after the first dose of brentuximab revealed complete resolution of increased fluorodeoxy-glucose uptake in the vertebral bodies.*

Discussion

Hodgkin lymphoma is characterized by malignant Reed-Sternberg cells which express CD15 and CD30. Before the successful development of multiagent chemotherapy, patients with advanced-stage HL had really poor prognosis. Mechlorethamine, oncovin, procarbazine, and prednisone (MOPP) regimen was the first combination utilized; however, ABVD became more popular given superior response rates and failure-free survivals in clinical trials. One of those studies directly compared MOPP *vs*. ABVD *vs*. MOPP alternating with ABVD. It showed that ABVD was superior to MOPP in terms of complete response rate (82% *vs*. 67%), failure-free survival at five years (50% *vs*. 61%) (2). The German Hodgkin Study Group (GHSG) developed the BEACOPP regimens rationally based on

principles of dose density/intensity and mathematical modeling (3). Several studies indicated that escalated BEACOPP achieved superior progression-free survival; however, the overall survival was not statistically significant. This could be explained by the high salvage rate among patients who had relapses from the ABVD regimen (4-6). Furthermore, escalated BEACOPP was associated with more acute toxicities, hematological side-effects and long-term secondary cancer. Current National Comprehensive Cancer Network (NCCN) guidelines for patients with advanced HL (stage III/IV disease) recommend ABVD or escalated BEACOPP or Stanford V (doxorubicin, vinblastine, mechlorethamine, etoposide, vincristine, bleomycin and prednisone) as first- line regimens.

Recent advancements in technology have enabled an exciting shift to molecular-targeted cancer therapy. Brentuximab vedotin is an antibody conjugate drug, linking an antibody to human CD30 that binds to malignant CD30 cells, releasing a microtubule-disrupting agent into the cells. Multiple prospective and retrospective studies confirmed the efficacy of brentuximab vedotin as a single agent in patients with relapsed/refractory CD30-positive HL (7). In a phase II multination open-label study, 102 patients with refractory HL were treated with brentuximab vedotin at 1.8 mg/kg every three weeks for a maximum of 16 cycles. The objective response was 75%, with a median progression-free survival of 5.6 months; 34% of the patients achieved a complete response and in these patients the median PFS was 21.7 months. These statistical numbers are impressive as the median number of prior chemotherapy regimens was 3.5 and all patients had failed autologous stem cell transplant (8).

In a phase I trial, the authors reported a tumor regression rate of 85% and an overall objective response rate of 59%, with 34% complete remission (9). In a retrospective analysis, the GHSG found an objective response rate of 60% including 22% complete remissions (10). The patients involved in the study were heavily pre-treated, with a median of four chemotherapy regimens. Notably, brentuximab vedotin is generally well-tolerated, with the most common side-effect being peripheral neuropathy; it affects about 53% of patient and 50% of patients have complete resolution of symptoms following treatment delay. Other common side-effects include nausea, fatigue, and neutropenia. Further follow-up is needed in order to determine the long-term side-effects of brentuximab.

The patient reported here presented with widespread HL. Her grave condition was compounded by heart failure, acute kidney injury requiring hemodialysis, and acute respiratory failure requiring mechanical ventilation. Her treatment options were limited given her poor comorbidities and toxicity profiles of the available first-line chemotherapy regimens. Therefore, brentuximab vedotin was given to the patient as an effort to control her disease while her other systems improved, hoping to administer standard chemotherapy. Surprisingly, she had a complete response, by PET-CT criteria, after one dose of treatment.

Brentuximab vedotin was well-received by the medical community. It marked the only new drug approved by the FDA in the last three decades for HL. However, its uses thus far are mainly restricted to relapsed/refractory HL. Given the impressive response rate and favorable toxicity profile for brentuximab vedotin in patients with relapsed/refractory HL, ongoing trials are incorporating its use into standard regimens such as ABVD (11). Other possibilities include using brentuximab vedotin as a single agent for early disease. As we learn more about molecular-targeted therapy, it will change our approach over treatment.

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