Lymphoma Rounds Leadership

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Hodgkin Lymphoma in Older Patients

Anem Waheed, MD, Tufts University School of Medicine
Andreas Klein, MD, Tufts University School of Medicine

A Rash Case of Peripheral T-Cell Lymphoma

Albert Yeh, MD, Fred Hutchinson Cancer Research Center, University of Washington
Sony Kilgore, MD, Kaiser Permanente

A Management of an Aggressive B Cell Lymphoma

Tracie Watson, DO, MS, Loyola University Chicago
Aadil Ahmed, MD, Loyola University Chicago
Scott Smith, MD, PhD, FACP, Loyola University Chicago

At the New England Lymphoma Rounds on September 26, 2018, Anem Waheed, MD, of Tufts University, discussed a case of Hodgkin lymphoma in an older patient. Andreas Klein, MD, of Tufts University, was the moderator.

Case Background

A 67-year-old male presented to a dermatologist with pruritus of the lower extremities. Additional complaints included marble-sized lymphadenopathy of the right neck, night sweats, dyspnea on exertion, fatigue, and weight loss. Past medical history is significant for type 2 diabetes, hypertension, hyperlipidemia and a 45-year history of cigarette use. He is a retired metal worker. Physical examination, performed following referral to a hematologist-oncologist, revealed excoriated regions of the skin of the lower extremities.

Continued on page 2
Hodgkin Lymphoma in Older Patients

Continued from page 1

1.5 to 2 cm right cervical lymphadenopathy and 3 cm right supraclavicular lymphadenopathy; neither axillary lymphadenopathy nor hepatosplenomegaly were present. Initial laboratory studies revealed WBC of 19,900 with an absolute neutrophil count of 17.8 and an absolute lymphocyte count of 0.4, hemoglobin of 11.5 g/dL with an MCV of 75, platelet count of 557/µL, elevated ESR and ferritin, serum albumin of <4 g/dL and LDH of 307 U/L.

Diagnosis
CT scan of the neck, chest, abdomen and pelvis revealed: lymphadenopathy in the right supraclavicular region measuring 7.5 X 4.2 X 5.8 cm; multiple enlarged lymph nodes in the mediastinum, axilla and retroperitoneum; multiple ill-defined hepatic masses, including a right hepatic lobe mass of 5 x 4.2 cm. PET scanning revealed increased FDG-avidity in the regions of the enlarged lymph nodes. Bone marrow aspiration and biopsy were hyper-cellular for age (60% cellularity). An excisional biopsy of the mass in the right hepatic lobe revealed effaced architecture with nodular proliferation of large atypical lymphoid forms. Reed-Sternberg cells were noted. Immunohistochemical staining revealed CD30+, CD15+, CD45- status, consistent with classical Hodgkin lymphoma, nodular sclerosis subtype, stage 4 disease.

Case Evolution
An incidental finding on the CT scan of the neck revealed severe left internal carotid artery stenosis, which was subsequently confirmed by a carotid duplex ultrasound study which showed 80-99% stenosis of the left internal carotid artery. One week after the diagnosis of Hodgkin lymphoma, the patient underwent a left carotid endarterectomy and developed complications of a hematoma that required evacuation, and left leg weakness of unclear etiology. The patient presented to Tufts Medical Center for outpatient evaluation in the oncology clinic from an inpatient rehabilitation facility. At his initial clinic visit, he was assessed to have an international prognostic score (IPS-7) of 7 and an ECOG performance status of 2.

The patient was enrolled into a multicenter, open-label phase 2 study for older, previously untreated patients with Hodgkin lymphoma. He completed the study, receiving 2 cycles of brentuximab vedotin (BV) every 3 weeks, 6 cycles of doxorubicin, vinblastine, dacarbazine (AVD), followed by 4 additional cycles of BV every 3 weeks. Currently, the patient is 70 years old and in clinical remission.

Discussion
Although the median age of diagnosis for Hodgkin lymphoma is 39 years, up to 20% of patients are over 60 years of age at the time of diagnosis. An older age at the time of diagnosis correlates with decreased overall survival at 5 and 10 years, compared with patients diagnosed at younger ages. The etiology of the poorer outcomes for older patients is not completely understood, but contributing factors are believed to be the...
Hodgkin Lymphoma in Older Patients

Continued from page 2

presence of significant comorbidities, poorer performance status, possible differences in disease biology (an increased incidence of mixed cellularity is noted in older patients compared with younger patients), and an inability to tolerate full-dose chemotherapy. Furthermore, older patients are underrepresented in clinical trials, so there is less clinical experience available for this age group.

A retrospective multicenter analysis of 95 patients with Hodgkin lymphoma, median age 67 years, found that at diagnosis 26% were considered unfit by their treating physician, 17% had a geriatric syndrome (defined as dementia, incontinence, or other syndrome), and 13% had loss of activities of daily living. Standard chemotherapy (ABVD or AVD) was administered to 67 of the 95 patients, with an overall response rate of 85% and a clinical remission rate of 73%; the incidence of bleomycin lung toxicity was 32% and the associated mortality rate was 25%. Two factors that predicted poorer overall survival were age greater than 70 years and loss of activities of daily living at the time of diagnosis.

When data for 44 patients older than 60 years were selectively analyzed in a study comparing the first line treatments for Hodgkin lymphoma, ABVD and Stanford V (mechlorethamine, doxorubicin, vinblastine, vincristine, bleomycin, etoposide), no survival difference and similar toxicities were demonstrated. However, for the older patients, the mortality rate was high at 18%, 5-year overall survival was 58%, and 24% developed bleomycin lung toxicity, reinforcing that older patients have a poorer prognosis and more difficult course compared to that of younger patients.

The multicenter phase 2 study in which the presented patient was enrolled included data on sequential treatment with brentuximab vedotin followed by AVD for 48 patients aged 60 years or older, of whom half were greater than 70 years. The overall response rate was 95%, the clinical remission 93% and, at 2 years, the overall survival was 93% (Figure 1), all of which are much improved compared with other trials of older patients with Hodgkin lymphoma.

Figure 1. Kaplan-Meier curves for event-free survival, progression-free survival, and overall survival.

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A Rash Case of Peripheral T-Cell Lymphoma

At the Seattle Lymphoma Rounds on February 20, 2018, Albert Yeh, MD of the University of Washington, discussed a case of peripheral T-cell lymphoma. Sony Kilgore, MD, of Kaiser Permanente, discussed the pathology. Nina Lamble, MD, of the University of Washington, was the moderator.

Case Background
A 71-year-old retired clergyman presented to the dermatology clinic at the University of Washington in May 2016 with a chronic, severely pruritic, erythematous rash of the scalp, anterior and posterior trunk, upper extremities, and posterior aspect of the lower extremities. Past medical history is notable for coronary artery disease, pacemaker for heart block and transient ischemic attack. Multiple skin biopsies, analysis of peripheral blood by flow cytometry and Sezary cell count were not informative in regard to the etiology of the rash.

Diagnosis
The patient was admitted to the hospital in crisis 16 months after the initial presentation and was diagnosed with a small bowel obstruction. Upon exploratory laparotomy, he was found to have extensive mesenteric lymphadenopathy. Excisional biopsy and evaluation of sampled lymph nodes revealed complete effacement of the normal nodal architecture. Immunostaining demonstrated diffuse CD4+ status (Figure 1) and flow cytometry revealed CD2+, CD3+, CD5+, CD7+ status, both of which supported the diagnosis of T-cell lymphoma. Punch biopsy of the left chest wall, in the region of the diffuse and persistent rash, revealed subtle infiltration of lymphocytes into the epithelium and dermis, which were CD3+ and CD4+ by immunostain (Figure 2). Bone marrow biopsy revealed 2% involvement with lymphoma. Although it was difficult to precisely classify this case, it was ultimately regarded as a systemic T-cell lymphoma, stage 4, as opposed to a cutaneous T-cell lymphoma that had generalized and involved soft tissue.

Case Evolution
The patient received 2 cycles of cyclophosphamide, doxorubicin, etoposide, vincristine and prednisone (CHOEP), with less...

Continued on page 5
A Rash Case of Peripheral T-Cell Lymphoma

Continued from page 4

doxorubicin in the first cycle because of poor functional status. During the second cycle of the full CHOE regimen, he did very poorly with complications of sepsis, clostridium difficile infection and a prolonged hospital stay. ECOG status dropped to 3 prior to discharge. Further therapy with belinostat, a histone deacetylase (HDAC) inhibitor indicated for treatment of relapsed or refractory peripheral T-cell lymphoma, was planned, but, in the interim, the patient suffered septic shock, skin desquamation, gastrointestinal bleeding and a subacute stroke. After a lengthy recovery period, treatment with belinostat was initiated. Disease progression with no evidence of response was noted after the first cycle. Following review of the limited number of available treatment options, the patient entered into a clinical trial with pralatrexate, a competitive inhibitor of dihydrofolate reductase, and leucovorin; however, he continued to decline and developed anasarca, worsening cutaneous symptoms, and recurrent infections. The patient was discharged to home hospice and he unfortunately passed.

Discussion
Diagnostic classification of T-cell lymphomas, with differentiation of peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS) and cutaneous T-cell lymphoma (CTCL), can be difficult. Among patients with PTCL-NOS, 49% present with nodal and extranodal disease (commonly the skin and gastrointestinal tract), 38% present with nodal disease only and 13% have extranodal disease only. Patients with CTCL can present with extracutaneous disease, including lymph node enlargement, and the more severe the skin involvement the more likely it is that this will occur. The diagnosis of CTCL is often preceded by a period ranging from months to years during which non-specific rash and skin findings are present.

PTCL-NOS is a heterogeneous classification that does not portend a clear treatment path. CHOP is a commonly used treatment regimen, often with the addition of etoposide. Subgroup analysis of several studies that compared CHOP with CHOP plus etoposide demonstrated that those who benefited from the addition of etoposide were younger than 60 years of age and with normal LDH. The addition of etoposide to the CHOP regimen has been demonstrated to improve progression-free survival but not overall survival and adds to toxicity. Analysis specific to PTCL-NOS is not available given the small number of patients enrolled in the comparison studies, but the overall survival rates on the order of months indicate a very poor prognosis.

A variety of single agent treatment options are available for treatment of relapsed or refractory PTCL, including belinostat, romidepsin, pralatrexate and brentuximab vedotin. Direct comparison studies between these agents are not available and early phase studies of combinations of agents are underway. At this time, clear delineation of approaches for relapsed and refractory PTCL remains an unmet clinical need. Intention of treatment, in terms of cure versus palliation, is a difficult but important boundary to consider and establish as early in the course of treatment as possible.
Management of an Aggressive B-Cell Lymphoma

At the Chicago Lymphoma Rounds on September 5, 2018, Tracie Watson, DO, MS, of Loyola University Chicago, discussed a case of aggressive B-cell lymphoma, with a focus on management strategies. Aadil Ahmed, MD, of Loyola University Chicago, discussed the pathology. Scott Smith, MD, PhD, FACP, of Loyola University Chicago, was the moderator.

Case Background

In November 2016, a 26-year-old female presented to the hospital with chest pain and a near syncopal event. Past medical history was significant for obesity, glucose intolerance, anemia and use of oral contraceptive therapy. An ST-elevation myocardial infarction (STEMI) with complete occlusion of the right coronary artery was noted and a stent placed. While evaluation by hematology did not reveal a familial disorder of coagulation underlying the occlusive disease, both iron and vitamin B12 deficiencies were noted.

Six months later, the patient returned to her primary care physician with complaints of swelling under her chin and a scratchy throat. Submental lymphadenopathy without fluctuance was apparent on physical exam. Monospot, throat culture and PPD all were negative. A CT scan of the neck revealed a 2-cm soft tissue mass with several smaller adjacent lymph nodes in the submandibular space. Fine needle aspiration of the mass revealed a reactive process.

Approximately 14 months after her initial presentation, the patient developed recurrent anemia with deficiencies of copper, chromium, vitamin B12 and vitamin D. Capsule endoscopy revealed multiple ulcerations of the small bowel, but the study was inconclusive.

In May 2018, the patient presented with shortness of breath, night sweats, weight loss and recurrent cervical lymphadenopathy and was admitted to the hospital by her cardiologist. CT scan of the chest revealed a moderate to large pleural effusion on the right side with internal mammary, supraclavicular and mesenteric lymphadenopathy noted. In addition, a follow-up scan demonstrated submental lymphadenopathy, with central necrosis (Figure 1), as well as supraclavicular lymphadenopathy (Figure 2). Laboratory evaluation showed microcytic anemia with thrombocytosis, LDH > 1,000 U/L, uric acid 14 mg/dl, EBV DNA with a copy number of >10⁶, and HIV status nonreactive.

Diagnosis

Analysis of pleural fluid obtained by thoracentesis revealed malignant cells. Evaluation of the bone marrow and CSF did not reveal evidence for lymphoma. Biopsy of the excised submental lymph node showed a diffuse lymphoid infiltrate with areas of necrosis, medium-size lymphoid cells with irregular nuclei, and a high proliferation rate. Expression of B-cell markers CD20, CD10, BCL6, and EBER were demonstrated by immunostaining and Ki67

Continued on page 7
Management of an Aggressive B-Cell Lymphoma

Continued from page 6

Three forms of Burkitt lymphoma have been identified: an endemic form, typically found in Africa and New Guinea, is generally associated with malaria and EBV infection; an immunodeficiency form that often follows HIV infection; and a sporadic form, that nevertheless is associated with EBV disease 20% of the time. At the molecular level, Burkitt lymphoma is associated with overexpression of c-MYC caused by translocation of the c-myc gene from chromosome 8 to either chromosome 2, 14, or 22.

At initial presentation, Burkitt lymphoma commonly includes findings at both nodal and extra nodal sites. Abdominal findings, such as lymphadenopathy with possible ascites, involvement of the distal ileum, stomach, cecum, kidneys, ovaries, or testes, are present in the majority of cases at the time of diagnosis. Approximately 20% of newly diagnosed patients present with bone marrow involvement and 15% with involvement of the central nervous system; such extra nodal involvements are more common in relapsed cases.

Burkitt lymphoma is highly aggressive and successful outcomes require prompt diagnosis and initiation of therapy. With an estimated doubling time of 25 hours, rapid dissemination of tumor occurs and patients frequently present with tumor lysis syndrome. Multiple approaches to treatment are used, including R-CHOP, R-EPOCH, R-Hyper-CVAD and the Magrath method (R-CODOX-M/R-IVAC). No consensus is yet available regarding a preferred method of treatment.

Multiple studies are underway comparing various treatment approaches, including a phase 3 study in Europe that compares dose-adjusted EPOCH-R with R-CODOX-M/R-IVAC (EudraCT Number: 2013-004394-27). Attendants at the conference expressed their view that the ability for dose adjustment is an important component of the EPOCH-R approach that leads to favorable outcomes in treatment.

Case Evolution
The patient received a cycle of rituximab plus etoposide phosphate, prednisone, vincristine sulfate, cyclophosphamide, and hydroxydaunorubicin (R-EPOCH) while molecular diagnostic studies were pending. During the first cycle, she developed gastrointestinal bleeding associated with ulceration of the distal transverse colon, attributed to a chemotherapy-induced mucosal injury. A PET scan performed following the completion of the first cycle of chemotherapy revealed a positive response to treatment with decreased size in lymphadenopathy, low F-18 fluorodeoxyglucose (FDG) uptake, and resolution of satellite nodules. Treatment with EPOCH-R, with the addition of intrathecal methotrexate, has continued until now. The patient is currently doing well part-way into cycle 5. Repeat testing revealed clearance of EBV infection.

Discussion
Burkitt lymphoma, a type of B-cell, non-Hodgkin lymphoma that has a median age of presentation of 30 years, is more commonly seen in younger patients. Within the non-Hodgkin lymphoma category, 30% of pediatric cases are Burkitt lymphoma, compared with 1% to 2% in the adult patient population.