Investigational Options for Refractory Lymphoma
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(Pathology) Oliver Graf, MD
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(Moderator) Reem Karmali, MD, MS
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T-Follicular Helper Lymphomas
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HIV-Associated DLBCL
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Investigational Options for Refractory Lymphoma

Presenters
Craig Boddy, MD, Northwestern University
(Pathology) Oliver Graf, MD, Northwestern University
(Moderator) Reem Karmali, MD, MS, Northwestern University

At the Chicago Lymphoma Rounds on May 10, 2017, Craig Boddy, MD, of Northwestern University, discussed a case of refractory lymphoma, focusing on emerging therapies. Oliver Graf, MD, of Northwestern University, discussed the pathology. Reem Karmali, MD, MS, of Northwestern University, was the moderator.

Case Background
A 48-year-old male was undergoing a hernia repair surgery when surgeons found a mildly enlarged mesenteric lymph node. A biopsy was obtained and the patient was referred to hematology/oncology.

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**Diagnosis**

CT staging showed minimal mesenteric adenopathy with the largest node measuring 1.5 cm. No other sites of adenopathy were noted. Lactate dehydrogenase (LDH) was normal. A biopsy of the excised mesenteric lymph node showed an effaced architecture with nodular growth pattern with enlarged back-to-back follicles. A lymphocytic infiltrate spread into the soft tissue. On higher power, the follicle center showed a monotonous population of centrocytes with scant cytoplasm, cleaved nuclei, and condensed chromatin. Few admixed centroblasts were noted. Flow cytometry showed monotypic B-cells that were kappa-restricted surface Ig light chain, CD10+, CD5-, and CD20+. The patient was diagnosed with grade 1/2 follicular lymphoma (FL), with a follicular lymphoma international prognostic index (FLIPI) score of 0.

No treatment was started at this time. A CT scan performed 6 months after diagnosis showed stable mesenteric adenopathy. Two years after diagnosis, the patient developed intermittent left flank pain and a rash consistent with herpes zoster that was treated with valacyclovir and prednisone. The rash resolved but the pain persisted and he developed night sweats. A physical exam showed normal vital signs with no palpable adenopathy, hepatosplenomegaly, or rash. Abnormal laboratory findings included a hemoglobin level of 11.5 g/dL, albumin of 3.3 g/dL, and LDH of 276 U/L (increased from 190 U/L). A CT scan showed new retroperitoneal adenopathy including a paraspinal mass measuring 4-5 cm; the mesenteric lymph node was unchanged.

Analysis of a core biopsy performed on the retroperitoneal mass showed extensive necrosis with an atypical infiltrate. On intermediate power, small blue cells and a fibrotic background were visible. Higher-power microscopy showed collections of large cells with irregular nuclear outlines, some with prominent nucleoli. IHC staining showed a large B-cell lymphoma with extensive necrosis. Flow cytometry showed monoclonal kappa-restricted surface Ig light chain, CD19+, CD20+, CD10+, and CD5- B-cells. A bone marrow biopsy was negative. As this occurred in 2009, fluorescence in situ hybridization (FISH) analysis was not yet available. Overall, the findings were consistent with transformation of FL to large B-cell lymphoma.

**Case Evolution**

The patient received 6 cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone plus rituximab (R-CHOP) plus 4 cycles of intrathecal methotrexate, which induced a complete response by CT scan. The remission lasted for 7 years until 2016, at which point the patient, then 58 years old, presented with abdominal pain and night sweats. No palpable adenopathy or hepatosplenomegaly was detected on physical exam. LDH was significantly elevated at 625 U/L. CT and positron emission tomography (PET)/CT scans showed a large, 11-cm retroperitoneal mass (Figure 1) that on

Figure 1: PET/CT demonstrating an 11-cm retroperitoneal mass, which was confirmed as relapsed transformed FL on biopsy.

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The Rock ‘n’ Roll Marathon is an exciting, 29-city, international run series, offering 5k, 10k, half marathon and full marathon options. This year, LRF is proud to offer 25 charity spots for participants to run and raise funds to support our mission. Participants will receive a free race entry, an LRF race jersey, and fundraising assistance from the Foundation.
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magnetic resonance imaging (MRI) appeared to invade the T12 and L1 vertebral bodies. A biopsy confirmed relapse of transformed FL; FISH was negative for MYC/BCL-6 gene rearrangements.

The patient received salvage chemotherapy with 2 cycles of ifosfamide, carboplatin, and etoposide with rituximab (R-ICE) with intrathecal methotrexate, which resulted in a partial remission with isolated disease to the large paraspinal mass.

At this point, clinical trial options were discussed, but the patient did not consent to participate in a clinical trial. Radiation therapy was administered to the isolated mass with a plan to proceed to allogeneic stem cell transplant if a good response was attained. Three weeks after completing radiation therapy, the patient developed new back pain and new paraspinal masses were detected by MRI, which were fluoro-deoxyglucose (FDG)-avid on PET scan. The patient then consented to participate on a clinical trial of chimeric antigen receptor (CAR) T-cell therapy. The patient’s T-cells were collected and he received steroids while waiting 6 weeks for the CAR T-cells to be prepared. He received his CAR T-cells and one month later, restaging PET/CT demonstrated a complete response (Figure 2).

Discussion
Transformation from FL to large-cell lymphoma occurs in about 2-3% of patients with FL per year. For patients with advanced-stage, asymptomatic, nonbulky FL, prospective, randomized data have not shown that rituximab reduces the risk of transformation compared with watch-and-wait. Looking at outcomes in the rituximab era, survival is similar in patients with de novo DLBCL and those with treatment-naive transformed FL; however, outcomes are worse in patients with transformed FL who were previously treated for their FL.

A variety of investigational strategies are being evaluated for patients with relapsed/refractory B-cell lymphoma including CAR T-cell therapy, the SYK inhibitor TAK-659, the dual histone deacetylase (HDAC) and phosphoinositide (PI3) kinase inhibitor CUDC-907, and GSK2816126, an inhibitor of EZH2 methyltransferase. Lenalidomide plus rituximab could also be considered as an off-study, non-FDA approved option for transformed large B-cell lymphoma.

CAR T-cell constructs target CD10 for B-cell malignancies with several products currently undergoing investigation in clinical trials for patients with relapsed/refractory NHL. These trials have shown durable responses in patients with relapsed/refractory DLBCL and transformed FL.

Figure 2. PET/CT demonstrating a CR approximately one month after administration of CAR T-cell therapy.

In 2017, the Lymphoma Research Foundation issued nearly 600 Continuing Education certificates from 18 activities totalling nearly 900 credit hours for healthcare professionals.
T-Follicular Helper Lymphomas

Presenters
Lauren Pinter-Brown, MD, FACP
University of California, Irvine
(Pathology) Amy Chadburn, MD
Weill Cornell Medicine

At the National Lymphoma Rounds Summit held on October 16, 2016, Lauren Pinter-Brown, MD, FACP, of the University of California, Irvine, presented the case of a patient with angioimmunoblastic T-cell lymphoma (AITL), a malignancy now categorized by the World Health Organization by the umbrella designation of T follicular helper (TFH) lymphoma. Amy Chadburn, MD, of Weill Cornell Medicine, discussed the pathology.

Case Background
A 78-year-old female had recently been diagnosed with stage IIB breast cancer and was receiving adjuvant chemotherapy when she lost 40 pounds and developed severe myalgia, prompting discontinuation of anastrozole. Within 6 months of discontinuing treatment, she developed autoimmune hemolytic anemia (AIHA) requiring transfusion. She reported a history of melanoma and endometrial carcinoma.

Diagnosis
A physical exam revealed an enlarged left axillary node. A needle core biopsy was obtained and pathological findings were consistent with AITL, with expression of TFH-related antigens fall into a new umbrella category of nodal T-cell lymphoid neoplasms, neoplasms that express at least 2 or 3 of these antigens, according to the 2016 revision of the World Health Organization classification of lymphoma. AITLs and in cases of peripheral T-cell lymphoma, not otherwise specified, recurrent mutations that are observed in a significant proportion of cases, including the T-cell receptor genes, which are detectable in the majority of patients, and clonal immunoglobulin genes found in about one-third of cases.

There are important differences between AITL and follicular T-cell lymphoma but excludes cutaneous neoplasms that may sometimes be associated with cutaneous T-cell lymphomas, neoplasms that express at least 2 or 3 of these antigens. There have been few clinical trials in patients with T-follicular helper lymphoma, although some strategies have been evaluated, including monoclonal antibodies, cytokine inhibitors, and demethylating agents. There have focused on characterizing the incidence of specific recurrent mutations in T-cell lymphoma subtypes, with the aim of identifying potential therapies and identifying prognostic factors.

Pathological features of AITL include partial effacement of the nodal architecture, proliferation of arborizing high endothelial venules, a polymorphic infiltrate often with increased follicular dendritic meshwork, and EBV-positive Reed-Sternberg-like B-lineage cells. AITL can help explain some of the clinical features observed including polyclonal hypergammaglobulinemia, AIHA, autoimmune serology, and B-cell malignancies. Clonal T-cell receptor genes are detectable in the majority of patients, and clonal immunoglobulin genes found in about one-third of cases.

Outcomes for patients with AITL specifically, and peripheral T-cell lymphomas (PTCL) in general, remain poor in comparison to B-cell lymphomas. Although responses to chemotherapy often occur, these are generally short-lived. There is a real need to understand the biology of these malignancies to identify potential targets for therapy.

AITL usually exhibits phenotype of follicular T helper cells: PD-1, CD10, CXCL13, BCL6

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T-Follicular Helper Lymphomas

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Genetic studies of heterogeneous T-cell lymphomas have revealed recurrent mutations that are observed in a significant proportion of AITLs and in cases of peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS) that have a TFH phenotype. These include mutations and/or abnormalities in TET2, IDH2, DNMT3A, RHOA, and CD28, and gene fusions including ITK-SYK and CTLA4-CD28. According to the 2016 revision of the World Health Organization classification of lymphoid neoplasms, neoplasms that express at least 2 or 3 of these TFH-related antigens fall into a new umbrella category of nodal T-cell lymphoma with TFH phenotype. This category includes AITL and follicular T-cell lymphoma but excludes cutaneous neoplasms that may have a TFH phenotype.

Although follicular T-cell lymphoma and AITL share a TFH phenotype, there are important differences between the two. Compared with AITL, follicular T-cell lymphoma tends to be more localized, is often diagnosed at an earlier stage, and is associated with fewer systemic symptoms. It also generally lacks the enlarged follicular dendritic cell meshwork and prominent high endothelial venules of AITL. Significant research efforts have focused on characterizing the incidence of specific recurrent mutations in T-cell lymphoma subtypes, with the aim of identifying potential therapies and identifying prognostic factors.

There have been few clinical trials in patients with T-follicular helper lymphomas, although some strategies have been evaluated, informed by the molecular features involved. Brentuximab vedotin has shown activity in patients with CD30+ relapsed AITL. Newer strategies include inducible costimulator (ICOS) blockade, interleukin-21 (IL-21) blockade, and CXCL13 blockade. A phase 1b study of the checkpoint inhibitor nivolumab in patients with relapsed/refractory hematologic malignancies showed some activity in PCTL—partial responses were observed in 2 of 5 patients (40%). Other potential strategies to explore include cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibition and the use of epigenetic modifiers such as histone deacetylase inhibitors or demethylating agents.

13th Mantle Cell Lymphoma Scientific Workshop

LRF’s Mantle Cell Lymphoma Scientific Workshop, held regularly since 2003, is the Foundation’s longest running scientific program, encouraging collaboration and the sharing of research developments between the world’s leading MCL researchers, including LRF MCL Consortium members, MCL grantees, and scientists from the United States, Canada, and Europe. Since its inception, the MCL Workshop has helped researchers make significant strides in understanding MCL biology, evaluating potential new therapies, and optimizing the use of currently available therapies.

The 13th Mantle Cell Lymphoma Scientific Workshop will be held April 25 and 26, 2018 in Atlanta, GA.
HIV-Associated DLBCL

At the New England Lymphoma Rounds on September 13, 2017, physicians from the University of Vermont presented a case of diffuse large B-cell lymphoma (DLBCL) in an HIV-positive patient. The case was moderated by Julian Sprague, MD, PhD, and presented by Saranya Kodali, MD, with pathology reviewed by Sahar Nozad, MD.

Case Background
In November 2014, a 61-year-old male presented to the hospital with confusion; he had been diagnosed with HIV/AIDS a month prior. He had a history of intravenous (IV) drug abuse and hepatitis C virus (HCV) infection. Past medical history included hypertension, congenital hearing loss, and gout. Medications included lisinopril/hydrochlorothiazide and Bactrim prophylaxis. His father was diagnosed with prostate cancer at age 70 and his mother was diagnosed with endometrial cancer at age 60.

Diagnosis
Upon physical exam, the patient was thin; his abdomen was diffusely tender to palpation, most pronounced in the right upper quadrant, with hepatomegaly. He had confusion and oriented x 1. His Eastern Cooperative Oncology Group (ECOG) performance status (PS) was 3. A laboratory workup revealed anemia (hemoglobin 7.9 g/dL), mild hyponatremia, a CD4+ cell count of 139 cells/mm3, lactate dehydrogenase (LDH) of 2169 U/L, aspartate aminotransferase (AST) of 76 IU/L, and alkaline phosphatase of 268 U/L.

An MRI of the brain showed no masses; an MRI of the spine was nonspecific. An ultrasound of the liver showed multiple enhancing lesions, which were confirmed with MRI. An ultrasound-guided biopsy of the liver revealed DLBCL with no MYC rearrangements.

A CT scan of the chest, abdomen, and pelvis showed large lesions in the right lobe of the liver with no lymphadenopathy. Bone marrow biopsy was negative for bone marrow involvement by DLBCL, but it showed hypercellularity with mild trilineage dysplasia including hypogranular neutrophils and erythroid lineage changes that raised the possibility of myelodysplastic syndrome (MDS) (Figure 1).

An initial lumbar puncture revealed small, kappa-predominant CD19+ cells. A repeat lumbar puncture 8 days later showed 5% of lymphocytes being atypical and large. The suspicious B-cells were CD19+, CD20+ cells that did not express light chains. The patient was diagnosed with stage IE DLBCL with inconclusive cerebrospinal fluid (CSF) analysis.

Case Evolution
In November 2014, the patient was initiated on chemotherapy with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) as well as highly active antiretroviral therapy (HAART). CNS prophylaxis with intrathecal (IT) methotrexate was initiated because of the atypical lymphocytes in the CSF, the reported 10% risk for meningeal involvement in AIDS-related NHL, and the high frequency for lymphomatous involvement of multiple extranodal sites with HIV.

In January 2015, the patient presented with new right foot drop. Positron emission tomography (PET) imaging showed resolution of lymphoma in the liver and a destructive mass in the left talus bone. He continued on R-CHOP with IT methotrexate.

In March 2015, at cycle 6, the patient was referred to neurology as his neurological status was not improving. An electromyogram (EMG) showed severe bilateral denervation in the lumbar roots concerning for CNS involvement. A lumbar puncture showed a small population of kappa-restricted B-cells. An MRI of the lumbar spine showed diffuse enhancement of cauda equina; PET scan was negative. The patient appeared to have worsening neurological function.

In May 2015, the patient had clinical, radiographic, and EMG evidence of secondary CNS lymphoma. He received high-dose methotrexate, IT and intravenous (IV) rituximab, and oral temozolomide for 6 cycles, which resulted in negative CSF cytology and improvement in the spine by MRI. His HIV viral load was well controlled on HAART.

In October 2015, the patient underwent ASCT with busulfan, thiotepa, and cyclophosphamide (Bu/TT/Cy). His post-treatment course was uneventful, and his PS improved to 1. An initial PET showed complete remission. He was discharged after a protracted hospital stay.

The patient did well until January 2017, when he developed fevers and neutropenic fever and MRSA bacteremia and died the following month after a protracted hospital stay.

Others. In June 2017, the patient presented with new right foot drop. Positron emission tomography (PET) imaging showed resolution of lymphoma in the liver and a destructive mass in the left talus bone. He continued on R-CHOP with IT methotrexate.

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Bone Marrow 2014

Figure 1. Initial peripheral blood and bone marrow aspirate smears, patient with HIV-associated DLBCL.

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**HIV-Associated DLBCL**

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The patient did well until January 2017, when he developed fevers and severe cytopenia (WBC 1600/μL, Hb 7.5 g/dL, platelets 61,000/μL). A bone marrow biopsy showed MDS with excess blasts (complex karyotype with monosomy 7, del 5q) (Figure 2). The patient was hospitalized with neutropenic fever and MRSA bacteremia and died the following month after a protracted hospital stay.

**Discussion**

R-CHOP is considered to be a safe regimen for patients with DLBCL and HIV/AIDS. A prospective analysis demonstrated that concurrent rituximab plus infusional etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (R-EPOCH) is also safe to use in this population and is associated with an improvement in event-free survival and overall survival compared with R-CHOP.

Secondary CNS involvement develops in approximately 2-10% for patients with aggressive non-Hodgkin’s lymphoma. CNS prophylaxis should be considered for patients with aggressive B-cell lymphoma at high risk of CNS involvement. The CNS International Prognostic Index (CNS-IPI) can help select patients at higher risk; factors include age > 60 years, elevated LDH, ECOG performance status > 1, stage III/IV disease, extranodal involvement exceeding 1 site, and involvement of kidneys/adrenal glands. Patients with at least 4 risk factors should be considered for CNS prophylaxis.

Other factors that have been associated with an elevated risk of CNS relapse include involvement of selected organs (breast, testis, uterus, epidural, or kidney/adrenals), MYC/BCL2 dual-expressing DLBCL (particularly activated B-cell type), CD5+ DLBCL, intravascular large B-cell lymphoma, and IgM-secreting DLBCL. Although the case patient had only 3 CNS-IPI risk factors (age > 60, elevated LDH, and ECOG PS >1), he also had atypical lymphocytes in the CSF and so was started on CNS prophylaxis with IT methotrexate. The efficacy of IT methotrexate as CNS prophylaxis was questioned given no improvement in overall survival and no efficacy in reducing the CNS recurrences.

Secondary CNS lymphoma can be treated with high-dose chemotherapy with IV methotrexate and cytarabine; ASCT has demonstrated substantial activity. This patient did well for about a year after ASCT but unfortunately died from MDS related complications. Lots of questions remain unanswered for this case including the efficacy of IT methotrexate as CNS prophylaxis, the role of CSF cytology and flow cytometry in adequately diagnosing CNS involvement, MDS in the late stages, and whether this is therapy related/de novo in the setting of underlying immunosuppression from HIV/AIDS.

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**Figure 2. Bone marrow biopsy section with CD34 Immunohistochemical staining and peripheral blood smears from 2017**
Lymphoma Research Foundation
Wall Street Plaza
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