Optimizing Therapeutic Approaches in NK/T-Cell Lymphomas

In his discussion of NK/T-cell lymphomas, Matko Kalac, MD, PhD, of Columbia University Medical Center, presented two different cases of rare NK/T-cell lymphoma: one with a “more typical” presentation and one less common presentation, each requiring consideration of different factors before identifying the best treatment approach.

Case Background

The first case involved a 40-year-old male with no past medical history who presented in May 2015 with a sore throat and cervical lymphadenopathy. He was prescribed valacyclovir and levofloxacin, which resolved the sore throat but not the lymphadenopathy. His family history revealed no history of malignancy. He had no notable social history, medications, or allergies.

The second case involved a 70-year-old man with a history of lower back pain, osteoarthritis, erectile dysfunction, hypertension, depression, and dyslipidemia. In March 2015 he presented with swelling of the right testicle. His family history included a mother with colon cancer at age 46. He had no notable social history.

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Medications included low-dose aspirin, atenolol, pravastatin, sildoxan, valaxantr, HCTZ, ezetimbe, and zolpidem. He had no known drug allergies.

**Diagnosis**

On exam the first patient was found to have palpable submandibular and bilateral non-tender superficial cervical lymphadenopathy. He had no organomegaly and his exam was otherwise normal. His body mass index (BMI) was 20.6 kg/m². Notable laboratory findings included mild anemia, an elevated lactate dehydrogenase (LDH) (232 U/L), and ERB positivity (7741 IU/mL). A CT scan of the neck, chest, and abdomen confirmed bilateral cervical lymphadenopathy and generalized prominence of the lymphoid tissue in the hypopharynx. No enlarged mediastinal or abdominal lymph nodes were identified. An ear, nose, and throat (ENT) exam reported bogginess of the nasopharynx. A PET/CT scan showed active disease on both sides of the neck and some linear activity posterior to the nasopharynx (Fig. 1).

The first patient underwent right testicular ultrasound that revealed a large hypoechoic mass with detectable vascularity. The left testicle was normal. His physical exam was otherwise normal with no organomegaly and no notable laboratory findings. Histologic analysis of excised testicle showed a diffuse stromal proliferation of medium-sized mature cells with irregular nuclei and inconspicuous nucleoli. This was characteristic of NK/T-cell lymphoma. The first patient showed multiple fragments of predominately necrotic tissue. Focal areas were viable and revealed an atypical lymphoid infiltrate composed of medium to rare large cells with irregular nuclei, mature chromatin, inconspicuous nucleoli and minimal cytoplasm. These atypical cells were positive for CD3, CD56, TIA1, granzyme B (variable), perforin (minority) and EBV-ISH (Fig. 2).

Both patients were diagnosed with extranodal NK/T-cell lymphoma. The second patient underwent a testicular ultrasound that revealed a large hypoechoic mass with detectable vascularity. The left testicle was normal. His physical exam was otherwise normal with no organomegaly and no notable laboratory findings. Histologic analysis of excised testicle showed a diffuse stromal proliferation of medium-sized mature cells with irregular nuclei and inconspicuous nucleoli. Although this type of presentation in an older male is often first thought to be diffuse large B-cell lymphoma (DLBCL), the immunohistochemical or centrolamellar morphology typical of DLBCL was not present. However, there was substantial angioinvasion that is characteristic of NK/T-cell lymphoma. The sample was surface CD3-negative (CD3-positive in the cytoplasm), CD56-positive, CD34-negative, CD8-negative, TIA-1-positive, perforin-positive, granzyme B-positive, and ERB-positive with a high proliferative index (Fig. 2).

**Case Evolution**

The first patient received 2 cycles of GELOX (gemcitabine, l-asparaginase, oxaliplatin) and attained a complete response. He is planning to have radiotherapy to the neck area (56 Gy total) and subsequently receive an additional 2 cycles of GELOX. The second patient underwent right orchectomy, which was followed by treatment using the SMILE regimen (methotrexate, leucovorin, ifosfamide, mesna, dexamethasone, etoposide, and L-asparaginase) for 3 cycles followed by 30 Gy of radiotherapy to the left testicle in 10 fractions. A PET/CT scan at 3 months post-treatment showed a complete response.

**Discussion**

NK/T-cell lymphomas are predominately extranodal EBV-associated lymphomas that are uncommon in the U.S. and Europe and have a higher incidence in Asia and Latin America. They most often occur in the nose and upper aerodigestive tract but can occur in other sites, including the skin, gastrointestinal tract, testes, and bone marrow.

NK/T-cell lymphomas that present without an apparent nasal primary tumor were previously referred to as “nonnasal.” However, it is now understood that these tumors are frequently associated with occult nasal primary tumors. It is important to confirm the NK/T-cell lymphoma diagnosis using either PET/CT scans and/or random punch biopsies of the nasopharynx in patients with an “extranasal” diagnosis and no evidence of disease on visual inspection of the nasopharynx.

Many prognostic models have been used to risk stratify patients with NK/T-cell lymphomas, including the International Prognostic Index and the Italian Prognostic Index for PTCL-U (IPT), the International Peripheral T-cell Lymphoma Project (IPTCLP), which have been considered suboptimal. The Korean Prognostic Index, which was developed primarily in an Asian population, appears to have better prognostic value. The index includes LDH level, regional lymph node involvement, B-symptoms, and Ann Arbor stage. More recently, Dr. Seok Jin Kim and colleagues reported on the PINK and PINK-E prognostic indices. These models appear to correlate even better in this specific patient population. PINK-E is important because it incorporates ERB positivity, which was found to be an independent prognostic factor for overall survival.

Radiation therapy has an important role in the management of localized NK/T-cell lymphoma; however, it alone appears to be insufficient for attaining long-term disease control. The dose administered and the extent of the field are important parameters in assessing the overall efficacy of radiation therapy in this disease. Inclusion of all sinuses and the nasopharynx, as opposed to targeting only the primary lesions, has been associated with lower local relapse rates. Although there are several effective systemic therapies for the disease, it is clear that CHOP is not an effective regimen for patients with NK/T-cell lymphomas. A variety of newer regimens have demonstrated marked activity. The SMILE regimen has demonstrated efficacy and is now commonly recommended, albeit, the regimen is associated with significant toxicity. The DeVIC regimen (dexamethasone, etoposide, ifosfamide and carboplatin), administered at two-thirds of the initially reported dose, has also demonstrated efficacy in combination with radiation therapy and appears less toxic than SMILE, though the concurrent radiation therapy is associated with substantial mucositis and poor oral intake for weeks after completion of therapy. More recently, the GELOX regimen (gemcitabine, oxaliplatin, and L-asparaginase) has demonstrated high response rates in combination with sequential radiation therapy in patients with early-stage extranodal NK/T-cell lymphomas.

The NK/T-cell lymphomas are a rare group of lymphoid malignancies that require a true multimodality approach involving highly specialized hematopathologists, radiation oncologists, radiologists, and medical oncologists. The focus of many of the emerging treatment algorithms is to reduce the substantial toxicity and co-morbidities associated with concurrent or sequential radiotherapy, while simultaneously improving long-term disease control. With the right tailored approach, most patients can expect a successful treatment outcome.

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Fig. 1. PET/CT scan of a patient with extranodal NK/T-cell lymphoma shows metabolically active disease present on both sides of the neck (maximum SUV, 11)

Fig. 2. Histologic analysis of extranodal NK/T-cell lymphoma

Karthik Ganapathi, MD, PhD, of Columbia University reviewed the pathology. A random nasopharyngeal biopsy from the first patient showed multiple fragments of predominately necrotic tissue. Focal areas were viable and revealed an atypical lymphoid infiltrate composed of medium to rare large cells with irregular nuclei, mature chromatin, inconspicuous nucleoli and minimal cytoplasm. These atypical cells were positive for CD3, CD56, TIA1, granzyme B (variable), perforin (minority) and EBV-ISH.
Mantle Cell Lymphoma Post-Ibrutinib

**Presenter**
Jeffrey Barnes, MD, PhD
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**Case Background**
In 2010, a 63-year-old man presented with lymphocytosis, thrombocytopenia, and splenomegaly. He was referred to hematology.

**Diagnosis**
A bone marrow analysis of the bone marrow suggested infiltration by a CD5-positive, CD20-positive, cyclin D1-positive lymphocytic infiltrate. Ki-67 and SOX11 expression was not yet available at that time. Based on the clinical and laboratory findings, he was diagnosed with mantle cell lymphoma (MCL).

**Case Evolution**
The patient received initial therapy with the Nordic regimen of dose-intensified induction immunomcytotoxic chemotherapy with rituximab plus cyclophosphamide, vincristine, doxorubicin, and prednisone (R-CHOP) alternating with high-dose cytarabine, followed by high-dose chemotherapy with BEAM (carmustine, etoposide, cytarabine, and melphalan) with rituximab in vivo-purged autologous stem cell transplant (ASCT).

Five years later, at age 68, the patient presented with leukocytosis. He was seen at an outside institution where clinicians were concerned that he had developed treatment-related acute myeloid leukemia (AML). However, a review of the peripheral blood smear indicated that the atypical lymphocytes with blast features were consistent with MCL blasts. At this time, his absolute lymphocytosis count was 97,000 cells/mm³, hematocrit was 27, and platelet count was 44,000 cells/mm³. His performance status was excellent.

There was concern that the patient could have a blastoid variant that would not respond well to many therapies. The patient was not interested in an allogeneic transplant.

He received ibrutinib and developed the expected lymphocytosis, which subsequently resolved. For 6 months, he felt good and had normal blood counts. However, he then developed a relapse with a WBC of 20,000 cells/mm³, no detectable neutrophils, a hemoglobin of 20, and a platelet count of 6,000 cells/mm³².

The patient then enrolled onto a trial of a CD20-targeting bispecific T-cell-engaging (BITE) antibody. His WBC count was 30,000 cells/mm³ with no neutrophils and a platelet count of 6,000 cells/mm³. He had diffuse bone marrow involvement and an enlarged spleen. The BITE antibody induced a dramatic response with resolution of most bone marrow disease and normalization of blood cell counts (Fig. 3). The patient developed severe cytokine release syndrome with tumor lysis requiring multiple doses of tocilizumab. After 4 weeks, he had progression of cutaneous lesions (Fig. 4). A second induction course of the BITE antibody was not effective and the patient developed disease progression with multiple cutaneous tumors, including some large lesions (> 20 cm). At this time, his WBC was 5 cells/mm³; he had no longer progression dependent, and his platelet count was approximately 120,000 cells/mm³.

He was given 1 cycle of dose-reduced bendamustine/rituximab. The regimen induced a transient response in the cutaneous tumors but the tumors reoccurred before the next cycle. T-cells have been isolated from the patient in preparation for chimeric antigen receptor (CAR) T-cell therapy. During the waiting period, the patient received subcutaneous bortezomib. His CAR T-cell infusion is forthcoming.

**Discussion**
Faculty discussed various aspects in the treatment of MCL, starting with the selection of initial therapy. Evidence suggests that some patients with MCL may have a long natural history and do not require immediate therapy. MCL in these patients is typically Ig-hypermutated and SOX11-negative. For patients requiring therapy, available regimens vary based on transplant eligibility. For transplant-eligible patients, an intensive cytarabine-containing regimen followed by ASCT is appropriate. Other initial combination regimens could include rituximab plus bendamustine, R-CHOP, or VR-CAP, which is the R-CHOP regimen but with bortezomib substituting for vincristine.

For patients not eligible for transplant, options to consider include R-CHOP followed by maintenance rituximab and bendamustine/rituximab. Although many patients not eligible for transplant are also not candidates for R-CHOP, there are circumstances in which a patient ineligible for ASCT could receive R-CHOP. However, the randomized, phase III German Stil trial showed the superiority of bendamustine/rituximab versus R-CHOP in patients with MCL. The role of rituximab maintenance after R-CHOP is unclear.

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Outcomes tend to be poor for patients with blastoid variants. For a patient who has already received cytarabine-based therapy, ASCT, and ibrutinib, options to consider could be rituximab/bendamustine, VR-CAP, lenalidomide, bortezomib, or a clinical trial of a novel agent such as immunotherapy. Cytoxans could limit the use of some options such as lenalidomide as well as enrollment in some trials. However, trials for some immunotherapies, such as the BITE antibody trial in which the patient enrolled, have no hematologic requirements.

**References**

**Stem Cell Transplantation Guides Now Available**
The Lymphoma Research Foundation recently released its first ever transplantation guide, titled Understanding the Stem Cell Transplantation Process. This comprehensive patient booklet represents a first-of-its-kind framework, offering in-depth and up-to-date information regarding stem cell transplantation as a treatment option for various lymphoma subtypes, as well as a unique lymphoma cancer care plan.

The transplantation booklet is designed to provide patients and caregivers a better understanding of when a stem cell transplantation may be a viable treatment option, as well as what to expect if transplantation becomes a part of their cancer care planning.

As with all of LRF’s booklets and fact sheets, the Understanding the Stem Cell Transplantation Process booklet is available at no-cost to patients and their loved ones, and can be found on lymphoma.org/publications, as well as through the LRF Helpline at (800) 500-9976.
Patient was diagnosed with gastric DLBCL, intestines. A staging bone marrow biopsy chest, and abdomen, and in areas of the small stomach, in lymph nodes in the neck, observed.

Detected by fluorescence in situ hybridization protein expression, no Myc translocation was DLBCL. Although the cells had high c-Myc consistent with an activated B-cell (ABC)-like Bcl-6-positive, and strongly MUM1-positive, showed the infiltrate was CD10-negative, lymphoma (DLBCL). Additional staining infiltrating cells were large, irregularly infiltrating cells throughout the tissue sample. An upper endoscopy showed multiple diagnosis and reported occasional alcohol use. The weight loss. He attributed the weight to poor appetite and dysphagia. Past medical history included diabetes mellitus, chronic obstructive pulmonary disease, hypertension, and pulmonary vascular disease. He reported no remarkable family history. He was a long-time smoker and reported occasional alcohol use. The patient was referred to gastroenterology for evaluation.

Diagnosis

An upper endoscopy showed multiple ulcers. Analysis of a biopsy showed atypical infiltrating cells throughout the tissue sample. Infiltrating cells were large, irregularly shaped, CD20-positive and Ki-67-high (>-95%), consistent with diffuse large B-cell lymphoma (DLBCL). Additional staining showed the infiltrate was CD10-negative, Bcl-6-positive, and strongly MUM1-positive, consistent with an activated B-cell (ABC)-like DLBCL. Although the cells had high c-Myc protein expression, no Myc translocation was detected by fluorescence in situ hybridization (FISH). However, a Bcl-6 translocation was observed.

A PET/CT scan showed intense uptake in the stomach, in lymph nodes in the neck, chest, and abdomen, and in areas of the small intestine. A staging bone marrow biopsy showed no lymphoma involvement. The patient was diagnosed with gastric DLBCL, stage III/IV or IV (depending on the staging system).

Case Evolution

The patient started chemotherapy with standard rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP), which was well tolerated aside from mild gastrointestinal toxicity and a self-limiting episode of shortness of breath. H. pylori eradication therapy was not administered, as its benefit is unclear in patients such as the case patient with lymph node involvement both above and below the diaphragm.

A restaging PET/CT scan after 4 cycles of therapy showed a complete metabolic response (Fig. 5). The patient completed 6 cycles of R-CHOP. He was referred to radiation oncology for consolidative radiation and received 36 Gy in 20 fractions to the site of initial bulky disease in the stomach. Radiation therapy was well tolerated. The patient remained in remission 6 months after completing treatment.

Discussion

Primary gastric lymphomas account for 20-30 percent of extranodal non-Hodgkin’s lymphomas. The two most common gastric lymphoma subtypes are DLBCL and mucosa-associated lymphoid tissue (MALT) lymphoma. Both can be both associated with H. pylori infection; thus, eradication therapy is a standard component of primary gastric lymphoma treatment. The role of eradication therapy in patients with systemic disease with gastric involvement is less clear.

Aggressive lymphomas with primary lesions located in the stomach are less likely than others to cause disseminated disease but are still associated with a worse prognosis.

Fig. 5. Complete metabolic response to standard R-CHOP in a patient with primary gastric DLBCL.
Lymphoma Rounds Leadership

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