At the Seattle Lymphoma Rounds on May 1, 2019, Nikhil Kamat, MD, of the Seattle Cancer Care Alliance, discussed a case of chronic lymphocytic leukemia (CLL), focusing on the spectrum of available therapies. Mazyar Shadman, MD, MPH, of the Seattle Cancer Care Alliance, was the moderator.

**Case Background**

A 62-year-old man was diagnosed with CLL, Rai stage 0, in 2010 and was placed under clinical surveillance. In 2013, he developed bulky lymphadenopathy.

**Diagnosis**

Molecular analyses revealed deletion of 13q by fluorescence in situ hybridization (FISH) and unmutated immunoglobulin heavy chain variable region (IGHV) status. The patient...
received six cycles of chemoimmunotherapy with fludarabine, cyclophosphamide and rituximab (FCR), achieving a complete clinical response.

**Case Evolution**
The patient relapsed in 2016 with cytopenias. A bone marrow biopsy revealed 80% CLL without evidence of myelodysplastic syndrome (MDS) or other primary bone marrow disorder. Repeat FISH demonstrated a new finding of deletion of 17p, persistence of 13q, and no cytogenetics. The patient started ibrutinib therapy with a complete clinical response and a mild adverse effect profile, noting mild arthralgias without any functional disability.

In mid-2018, the patient noted progressive lymphadenopathy. Repeat FISH showed persistent 17p and 13q deletion without complex cytogenetics. Venetoclax with an escalated ramp-up was started. Ibrutinib was continued concurrently, and the patient was referred to the Seattle Cancer Care Alliance and the Fred Hutchinson Cancer Research Center for consultation regarding CAR T-cell therapy in March 2019.

**Discussion**
Molecular analyses by FISH, cytogenetics, and karyotyping, with special attention to chromosomes 17p/TP53, 12, 13q, and IGHV mutation status, are essential to prognostication and therapeutic decision-making for management of CLL. The importance of repeating FISH analysis at each point of disease progression was highlighted because of CLL’s tendency to accumulate mutations with subsequent lines of therapy (Malickova et al, Leukemia 2015 PMID 25287991, Landau et. al. Cell 2013, PMID 23415222). Those with unmutated IGHV have poorer responses to chemotherapy (FCR, bendamustine-rituximab [B-R]) but have similar responses to those with IGHV mutation if treated with ibrutinib (Kipps, International Conference on Malignant Lymphoma, 2017).

Among chemotherapy regimens, FCR is associated with an increased risk of myelodysplastic syndromes and development of therapy-related acute myeloid leukemia (AML) and MDS. In the event of cytopenia at a time of relapse, a bone marrow biopsy was recommended to rule out this possibility.

Major advances in CLL management have occurred since the advent of ibrutinib. For many patients, high risk disease is better controlled with pathway ibrutinib therapy in 17p deletion/TP53 mutated disease, which confers an 80%, 5-year progression-free survival in treatment-naïve individuals. Predictably, a less robust response is observed in patients with relapsed or refractory disease (Ahn, Blood, 2018).

Venetoclax, a selective BCL-2 inhibitor, has been demonstrated to have activity against CLL in patients who have relapsed or are refractory to ibrutinib, with a median progression-free survival of about two years (Jones, Lancet Oncology 2017 PMID 29246803). Inpatient acceleration of the usual 5-week dose ramp-up of venetoclax as well as continuation of ibrutinib therapy for as long as feasibly possible were discussed as emerging evolutions in clinical practice that may influence practical management of this disease when transitioning from ibrutinib to venetoclax.

The appropriate timing for consideration of CAR T-cell therapy for patients with refractory or relapsed CLL was discussed. Detailed studies of outcomes for CAR T-cell treatment of CLL demonstrate preliminary data that is encouraging but still nascent. An algorithm prepared by the European Group for Bone Marrow Transplantation (EBMT) and European research initiative on CLL (ERIC) was reviewed as seen in Figure 1. The review included 24 patients, limiting the power of its results. An important observation from this cohort of patients, including what line of treatment should follow CAR T-cell therapy, is no consensus agreement about the appropriate timing as of yet. One view presented is that it is acceptable to consider cellular therapy for patients with high-risk mutations who fail one prior course. It could also be viewed as an appropriate time to consider a referral for CAR T-cell therapy, it may be viewed as an appropriate reference for patients with refractory or relapsed disease (Figure 2).

**Figure 1:** Fred Hutchinson’s study of IGH sequence patients and their treatment plan.

**Figure 2:** In CLL patients with high-risk disease defined by P53 aberration, the optimal referral time for cellular therapy (CAR-T or CAR-NK) was reviewed as seen in Figure 1. The review included 24 patients, limiting the power of its results. An important observation from this cohort of patients, including what line of treatment should follow CAR T-cell therapy, is no consensus agreement about the appropriate timing as of yet. One view presented is that it is acceptable to consider cellular therapy for patients with high-risk mutations who fail one prior course. It could also be viewed as an appropriate time to consider a referral for CAR T-cell therapy, it may be viewed as an appropriate reference for patients with refractory or relapsed disease (Figure 2).
CARTography of CLL Therapies

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The clinical experience with CAR T-cell therapy in refractory B-cell malignancies from the Fred Hutchinson Cancer Research was reviewed as seen in Figure 1. The review included 24 patients, limiting the power of its results. An important observation from these data is that response to CAR T-cell treatment is more successful in patients with minimal residual disease negative in the bone marrow at day 28. Many questions remain for this cohort of patients, including what line of treatment should follow CAR T-cell therapy and when it should be instituted.

Fred Hutchinson Schema for High-Risk CLL

Figure 2: In CLL patients with high-risk disease defined by P53 aberration, the optimal referral time for cellular therapy (CAR-T or allogeneic transplant) is not clear. We suggest that patients be referred for an initial assessment of comorbidities, donor status and discussion about cellular therapies after failing the first line of treatment, which is usually a Bruton Tyrosine Kinase (BTK) inhibitor.
Marginal Zone Lymphoma in a Patient with Autoimmune Disease and Iatrogenic Immune Suppression

Presenters
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Amy Chadburn, MD
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Peter Martin, MD,
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At the New York Lymphoma Rounds: Marginal Zone Edition on April 17, 2019, John Allan, MD of Weill Cornell Medicine, discussed a case of marginal zone lymphoma in a patient with autoimmune disease and associated immune suppression. Amy Chadburn, MD, of Weill Cornell Medicine, discussed the pathology. Peter Martin, MD, of Weill Cornell Medicine, served as the moderator.

Case Background
A 74-year-old woman with a several-year history of Sjögren’s syndrome with waxing and waning fatigue and shotty lymphadenopathy presented with a flare of her disease. Imaging demonstrated an increase in adenopathy, while labs revealed a monoclonal Immunoglobulin M (IgM) and a cryoglobulin with a cryocrit in the 4-6% range. She developed cutaneous vasculitic ulcers in her legs as well as mononeuritis multiplex necessitating treatment with prednisone, hydroxychloroquine, and mycophenolate treatment.

Case Evolution
Two years later, a bronchial pneumonia required reduction of immunosuppression. A bone marrow biopsy performed during this time revealed a hypocellular marrow in the IgM plasmacytoid cells, but findings were not sufficient to support the diagnosis of a lymphoproliferative disorder.

To treat the persistent cryoglobulinemia and associated increasing symptoms arising from the leg ulcers and neuropathy, four weekly doses of rituximab were administered, with significant improvement in both cryoglobulin levels and symptoms. Treatment was repeated the following year, again with a good response.

The following year, a recrudescence of symptoms, elevation of IgM levels and cryocrit values of 4% to 6% prompted a course of treatment with rituximab and cyclophosphamide. Her clinical symptoms and laboratory values improved, but the benefits were short-lived, as symptoms and laboratory abnormalities returned within a year. Treatment was escalated, and the patient underwent plasmapheresis followed by treatment with bendamustine and rituximab (BR). Both laboratory values and clinical symptoms improved.

Recent symptoms occurred eight months later, and the patient presented with fatigue and new palpable lymph nodes in the axilla. Imaging by positron emission tomography (PET) CT scan revealed markedly hypermetabolic diffuse lymphadenopathy (SUVmax 67.2) and lesions within the liver and bone, indicating a marked change in severity of disease. Laboratory evaluation revealed white blood cell (WBC) count of 6,100/µL, hemoglobin 12.3 g/dL, platelets 216,000, and normal liver and renal function. Serum protein electrophoresis showed a bclonal IgM spike. Lactate dehydrogenase (LDH) was elevated, and cryoglobulins were elevated at 4%. Antibodies to hepatitis C virus were negative.

A lymph node biopsy was performed. Examination of the specimen revealed

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diffuse effacement of the normal lymph node architecture by predominately plasmacytoid cells, plasma cells and small lymphocytes admixed with a few scattered larger transformed cells. Flow cytometry showed monotypic B cells that expressed surface kappa immunoglobulin light chain and exhibited a low level of CD20 expression, the latter finding reflective of prior rituximab therapy. Immunostaining confirmed the low level of CD20 expression, but also showed strong CD79A, CD38 and cytoplasmic kappa expression, indicative of a significant B-cell / plasma cell presence (Figure 1). In addition, a significant number of associated CD3/CD5-positive T cells were present. A polymerase chain reaction (PCR) analysis demonstrated the presence of a monoclonal B-cell population, indicative of a B cell neoplasm. The diagnosis of nodal marginal zone lymphoma was made.

Because of the history of long-term immunosuppressive treatment, in situ hybridization for the presence of the Epstein-Barr virus (EBV) was performed. A large number of EBV-positive cells were demonstrated (Figure 1, lower right). In addition, cells positive for the EBV-associated protein, LMP-1, indicating latency II EBV infection were present. The case was reclassified as an iatrogenic immunodeficiency associated lymphoproliferative disorder, EBV-positive marginal zone lymphoma.

Therapy with ibrutinib was initiated. A follow-up PET CT scan after two months revealed a mixed response with clear evidence of increased disease in specific areas, and ibrutinib treatment was discontinued.

She was enrolled into a clinical trial with a CD3/CD20 bispecific antibody. Cytokine release syndrome was observed with initial infusions of the study drug which remained low grade, managed with conservative measures and expectantly resolved with continued treatment and repeat doses on protocol. She eventually achieved a complete response. Treatment with plaquenil and prednisone are successfully controlling ongoing symptoms of Sjogren’s syndrome.

Discussion

Iatrogenic immunodeficiency associated lymphoproliferative disorder lesions are quite rare. Initially described in patients treated with methotrexate being treated for rheumatoid arthritis or dermatomyositis, these lesions have a tendency to occur in extranodal sites and are often EBV-positive. Initially EBV-positive marginal zone lymphoma was described in renal transplant recipients; however, it is now evident that EBV-positive marginal lymphomas can occur in patients with immunosuppression from a variety of causes, including treatment for autoimmune disorders or with chemotherapy.

In order to counter the impression that all EBV-positive marginal lymphomas are responsive to treatment, a participant shared his experience with three cases that occurred in children following transplantation. All three cases progressed into aggressive unresponsive disease, and two of the patients died. Another participant echoed that the presented case should serve as a reminder that marginal zone lymphomas, particularly of the bronchial or gastric type, are not necessarily indolent diseases.
Fever of Unknown Origin

At the New England Lymphoma Rounds on February 6, 2019, Luke Mantle, MD of Baystate Medical Center, discussed a case of a fever of unknown origin. Majd Jawad, MD of Baystate Medical Center, discussed the pathology. Syed Ali, MD, and Armen Asik, MD of Baystate Medical Center, were the moderators.

Case Background
A 66-year-old man presented to his primary care physician in July 2018 with complaints of progressive fatigue, weight loss, night sweats and low-grade fever. Past medical history was significant only for untreated hypertension. Family history included first degree relatives with breast cancer and colon cancer. Physical examination was unrevealing, except for the presence of a 1-2 cm palpable posterior cervical lymph node. Laboratory evaluation demonstrated an unremarkable complete blood count (CBC), elevated inflammatory markers including erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), lactate dehydrogenase (LDH) 330 U/L, and negative blood cultures and TB testing result. An extensive infectious disease workup only revealed prior infection with cytomegalovirus (CMV) and Epstein-Barr virus (EBV); viral antibody studies were negative for HIV, hepatitis A, B, C, and a panel for tick-borne diseases was also negative.

The patient was referred to a local hematologist. An ultrasound of the abdomen showed mild splenic enlargement and an 11-mm cystic lesion of the right hepatic lobe, which was confirmed by an abdominal CT scan. Biopsies of the bone marrow and the posterior cervical lymph node were not diagnostic.

Progressive clinical decline, including further weight loss, fever, and reduced energy levels, prompted referral to Baystate Medical Center in October 2018 for further evaluation.

Diagnosis
Computed tomography (CT) scan of the chest, abdomen and pelvis demonstrated increased hepatosplenomegaly and hyperattenuating splenic lesions but no lymphadenopathy. Evaluation of tissue obtained by biopsy of a splenic lesion was not diagnostic. Fevers continued during this hospitalization, prompting empirical treatment with prednisone, 20 mg daily. Improvement followed, and the patient was discharged.

Recurrent symptoms, including nausea, fever and rigor, prompted a return to Baystate Medical Center. Palpable hepatosplenomegaly to 2 cm below the costal margin was noted, but not general lymphadenopathy or cutaneous manifestations. CBC demonstrated the new onset of significant anemia and thrombocytopenia, with hemoglobin of 8.8 g/dL and platelet count of 37,000. Abnormal liver function with alanine aminotransferase (ALT) predominance, direct hyperbilirubinemia, LDH of 560 U/L, ferritin 2500 mg/L and soluble IL-2 receptor level of 18,000 U/mL were reported, prompting consideration of hemophagocytic lymphohistiocytosis as a possible diagnosis.

Histological evaluation of a bone marrow biopsy (Figure 1) revealed CD20+, CD3- cells in a linear arrangement within sinusoidal spaces and vessels. Evaluation of tissue obtained by liver biopsy (Figure 2) revealed infiltration with middle to large size mononuclear cells with prominent nucleoli. Immunostaining revealed CD20+, CD3-, CD10-, BCL6+, Myc1 positive status, leading to the diagnosis of non-germinal center large B-cell intravascular lymphoma. Rearrangements in the Myc, BCL2, and BCL6 genes were not demonstrated by fluorescence in situ hybridization (FISH) analysis.

Case Evolution
Positron emission tomography (PET) scan revealed hypermetabolic areas in the spleen, liver, thoracic and lumbar spine, and subcutaneous nodules. Chemoimmunotherapy with R-CHOP (rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, prednisone), modified because of hyperbilirubinemia, was administered in mid-December.

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2018-2019 Lymphoma Rounds at a Glance

- Professionals Participated in the Program Series: 2,500
- Lymphoma Cases Were Presented: 74
- Academic Institutions and Community Centers Participated: 61
- Lymphoma Rounds Programs Held: 23

2018. Hemophagocytic cells were found in the bone marrow and high-dose dexamethasone was started as treatment for hemophagocytic lymphohistiocytosis. Improvement in both fever curve and liver function followed. After the first course of chemotherapy, the patient developed typhlitis and pseudomonas bacteremia, necessitating a delay in the second course of treatment. Liver function and soluble IL-2 receptor levels improved with treatment, and CT scan of the abdomen demonstrated improvement in hepatosplenomegaly. At a rehabilitation facility following the second round of chemotherapy, the patient again developed fevers and pseudomonas bacteremia. On January 18, 2019, altered mental status and dyspnea occurred and bilateral cavitary pneumonia was diagnosed by CT scan of the chest. Right hemiplegia developed the next day. MRI scan of the brain showed significant new changes in the central pons, possibly secondary to intravascular lymphoma. The patient continued to decline and expired on January 22, 2019.

**Discussion**

Intravascular lymphoma, a rare disease of clonal lymphocyte proliferation, is difficult to diagnose and often found only on post-mortem evaluation. The median age of diagnosis is 70 years and a higher incidence is noted in Asia. Typical presenting clinical features include fever of unknown origin, central nervous system (CNS) or cutaneous involvement, elevated LDH, anemia and thrombocytopenia. The clonal population is typically CD20+ but can be CD5+, and most are categorized as non-germinal centered type.

Randomized clinical trials regarding the treatment of intravascular lymphoma are not available, so retrospective case series must be relied upon for guidance. An older small case series demonstrated a 59% response rate and 33% three-year overall survival using anthracycline based chemotherapy regimens. The addition of rituximab further improved the response rate to 91% and the three-year overall survival to 81%, according to a small retrospective case series from 2008. Because up to 25% of relapses occur in the CNS, high dose methotrexate treatment as prophylaxis is an important consideration, a point about which several conference attendees expressed agreement. The Asian variant, typically associated with hemophagocytic lymphohistiocytosis, has a particularly poor prognosis and life expectancy of 2 to 8 months without treatment.

Figure 2: Histology and immunoprofile of lymphoid tissue from the submental lymph node showing sheets of monomorphic, small to medium sized cells in a background of apoptotic debris.