Indy Hematology Review® 2023
TOWNHALL CASE PRESENTATION

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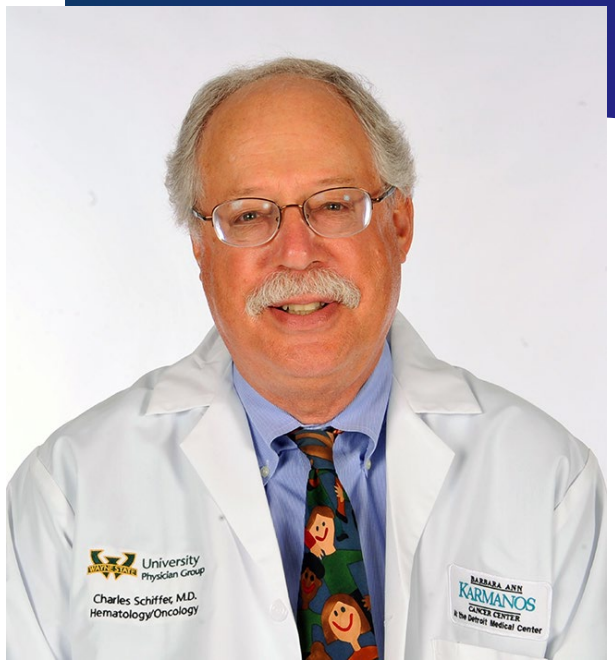
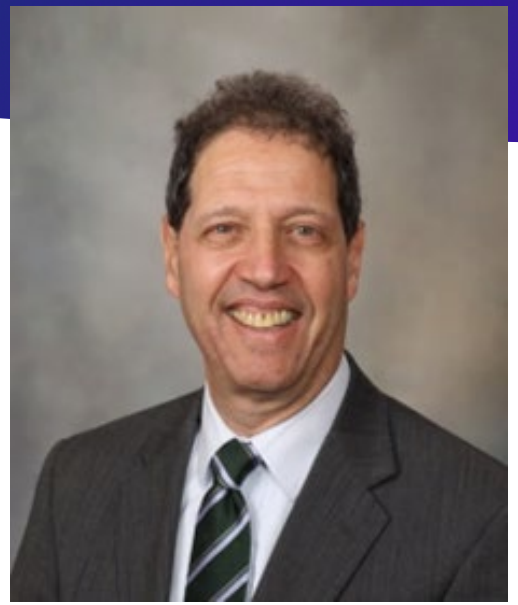
Hematologic Malignancies Town Hall



Charles Schiffer, MD
Emeritus Professor of Oncology and previously the Joseph Dresner Chair for Hematologic Malignancies Wayne State University School of Medicine Detroit, MI



Morie Gertz, MD, MACP
Roland Seidler Jr. Professor, Art of Medicine
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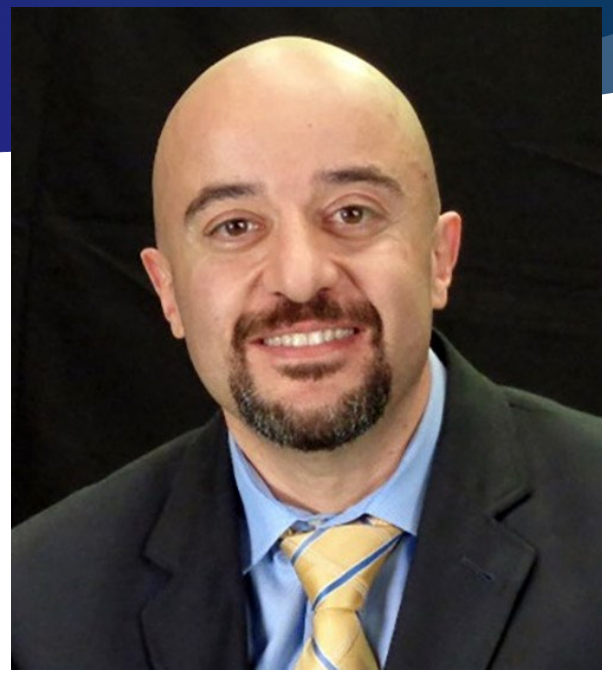
President, Enterprise Cancer Service Line Atrium Health; Executive Director of the NCI Comprehensive Cancer based at Wake Forest Baptist (Winston-Salem, NC



Rami Komrokji, MD
Vice Chair of the Malignant Hematology and Head of the Leukemia and MDS Section at the Moffitt Cancer Center Tampa
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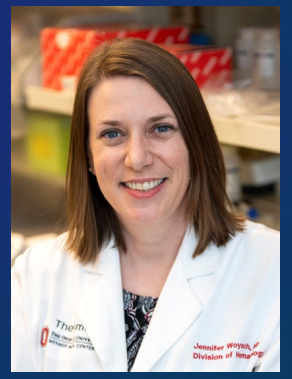
Hematologic Malignancies Town Hall

PLUS: Michael Weimann, MD, Saad Usmani, MD, Joseph Mikhael, MD, Matthew Lunning, DO, Steven Treon, MD, PhD, Tycell Phillips, Jennifer Woyach, MD,









CALR MUTATED ESSENTIAL THROMBOCYTOSIS

- 39-year-old woman who presents with abnormal CBC: WBC; 9.3, Hg; 12.5, HCT; 37.6, and a PLTs; 1405 with an unremarkable differential
- CALR mutation present, JAK mutation negative. LDH; normal at 447
- von Willebrand Factor antigen; normal at 52, von Willebrand Factor Ristocetin Co-Factor Activity (RIPA); low at 27%, and Factor VIII activity; low at 37%.
- BM biopsy: Hyperchromatic megakaryocytic morphology with atypical pleomorphic morphology, grade 1 of 3 reticulin fibrosis, and normocellular marrow with 80% trilineage hematopoiesis without increased blasts identified with a blast count of 0% with normal maturation of myeloid and erythroid elements. No lymphoid aggregate or plasma cell aggregates were identified.
- Diagnosis: CALR mutated prefibrotic primary myelofibrosis with increased thrombocytosis was rendered. Cytogenetics normal female karyotype.

DISSEMINATED CD30-POSITIVE CUTANEOUS T-CELL LYMPHOMA

- 43-year-old presents with a progressive maculopapular erythematous hyperpigmented rash, gradually becoming generalized over a one-year period.
- Skin biopsy: Possible lichenoid dermatitis without diagnostic features of a cutaneous lymphoproliferative process identified.
- Initial Therapy: Topical steroids and expectant monitoring for 6 months, but progressive and persistent symptomatology
- Repeat skin biopsy: Superficial perivascular dermatitis with lymphocytic epidermotropism with PAS special staining negative for fungal elements.
- Gene rearrangement studies: T-cell gamma gene rearrangement and T-cell beta gene rearrangement positive, consistent with clonality and consistent with a clonal T-cell population, findings consistent with clonal T cells.
- DIAGNOSIS: CD30-Positive Cutaneous T-cell Lymphoma.
- PMH: Type 2 DM., Hypothyroidism, Essential hypertension.
- Review of Systems: Pruritus and neck adenopathy.
- PET/CT scan; Splenic disease with hypermetabolic adenopathy of the axilla and left supraclavicular adenopathy compatible with disseminated disease.
- Bone marrow biopsy negative for metastatic disease with trilineage hematopoiesis

42-YEAR-OLD WITH NEWLY DIAGNOSED PH-POSITIVE ACUTE LYMPHOBLASTIC LEUKEMIA

- 42-year-old male presents to ED with worsening lower back pain, fatigue, SOB, bruising. Went to ED,
- LABS: WBC's 9.9, AND 400, plts 6, Hgb 8.4, 6% circulating lympoblasts. LDH elevated.
- CT c/a/p showed mild splenomegaly. MRI brain negative. MRI LS spine showed endplate enhancement of L2-L5 and T6, T9, but no solid nodules, no abnormal cord signal, no leptomeningeal metastases.
- Peripheral blood flow cytometry: 47% blast cells with a dim CD45()/CD34(+)/CD19(+)/CD20(-)/bright CD10(+)/HLADR(+)/CD38(/+) and TdT(+) immunophenotype.
- FISH testing positive for BCR/ABL 1 rearrangement in16% of cells examined.
- Bone marrow biopsy showed greater than 90% cellularity, with more than 95% blasts.
- Next generation sequencing confirmed presence of a BCR–ABL 1 fusion.
- PMH: Wolfe Parkinson White Syndrome, failed prior ablation. Had 3 episodes of SVT requiring adenosine, flecainide added to current meds of metoprolol and nifedipine.
- ECHO: Normal EF
- Oncocardiology consult: No cardiac contraindications to ponatinib, given probable benefits.

42-YEAR-OLD WITH NEWLY DIAGNOSED PH-POSITIVE ACUTE LYMPHOBLASTIC LEUKEMIA – PART 2

- Started Hyper-CVAD and imatinib (only TKI available in-house, on short notice).
- LP: Negative CSF analysis. Prophylactic intrathecal methotrexate and cytarabine initiated.
- BM bx ~day 18: < 5% blasts, WBC's 1.5, Hgb 9.6, Plts 210, ANC 570.
- Discharged shortly thereafter, changed from imatinib to ponatinib on day of discharge.
- Admitted one week later for total bilirubin 4.5, AST and ALT 3x ULN; LFT's had been completely normal day ponatinib started.
- CT: Mild intrahepatic biliary ductal dilatation with potential narrowing at the junction of the left and right lobe ducts, with mild beaded appearance of the left duct possibly consistent with junction of the left and right lobe ducts, with mild central beaded appearance of left duct, possibly consistent with cholangitis.
- Febrile at the time but not neutropenic, treated with IV antibiotics
- ERCP: Biliary strictures noted, underwent sphincterotomy and stent placement x 2, repeat ERCP recommended in 4 weeks, and began ursodiol.

STAGE IVB MANTLE CELL LYMPHOMA

- 55-year-old presents with progressive abdominal pain
- CT scan: Massively splenomegaly with extensive retroperitoneal adenopathy, lower paraesophageal and bilateral obturator lymphadenopathy.
- Bone marrow biopsy: Extensive involvement with a low-grade CD5 negative CD10 positive B- cell lymphoma, comprising of 60-70% cellularity by immunohistochemistry without evidence of large cell lymphoma.
- Molecular: Cyclin D1 expression, translocation of 11;14, supporting a diagnosis of Mantle Cell Lymphoma.
- Gene rearrangement negative for BCL6 ,MYC rearrangement or amplification of MYC, MALT1 rearrangement was not detected. IgH rearrangement was detected in addition to absence of translocation of 4,18.
- PET/CT scan: diffuse multifocal hypermetabolic lymphadenopathy below and above the diaphragm, associated with splenomegaly and marrow activity, consistent with Stage IV disease,
- DIAGNOSIS: Stage IVB Mantle Cell lymphoma
- Bendamustine/Rituximab x 5 cycles complicated by COVID pneumonia in PET-CR, then prolonged pancytopenia.
- Current Status: New mild PET avid adenopathy, resolved cytopenias.

IDH-2 MUTANT MDS WITH TRANSFORMATION TO AML

- 82-year-old man with a history of MGUS diagnosed in 2010 who was monitored expectantly and presents in December 2021 with pancytopenia: WBC: 2.3, Hg 9.8, PLTS: 68K, and ANC 920.
- Bone marrow biopsy: Markedly hypercellularity with left shifted granulocytic maturation and increased CD34+ blasts of ~ 5-9% and trilineage dysplasia with rare plasma cells and rare lymphoid aggregates and trace iron stores.
- Flow cytometry: CD34+, CD117+, HLA-DR+, CD33+, CD13+, and cMPO+ with NTdT-.
- Cytogenetics: 46XY normal male karyotype.
- NGS: Mutations of SRSF2, AXL1, and IDH2 and negative for FLT3, MPL1, and IDH1.
- Diagnosis: Myelodysplastic Syndrome with excess blasts type 1 with an IDH2 mutation.
- IV decitabine followed by oral decitabine/cedazuridine instituted in January 2022.
- Restaging bone marrow biopsy in July 2022: Morphologic complete remission and oral decitabine/cedazuridine continued.
- Secondary to persistent cytopenias in March 2023, repeat BM biopsy: 1. HYPERCELLULAR BONE MARROW WITH MULTILINEAGE DYSPOIESIS AND ~20% BLASTS; CONSISTENT WITH AN ACUTE MYELOID LEUKEMIA WITH MYELODYSPLASIA-RELATED CHANGES (AML-MRC). SEE COMMENTS. 2. FOCAL ATYPICAL CLUSTERS / AGGREGATES OF SMALL CD5(+) B-CELLS (5% CELLULARITY) AND MILDLY INCREASED RETICULIN FIBROSIS. Normal Cytogenetics, NGS pending.
- DIAGNOSIS: Transformation to Acute Myelogenous Leukemia

72-YEAR-OLD WITH IGVH UNMUTATED STATUS

- 72-year-old asymptomatic patient presents following a routine CBC in September 2020.
- WBC: 14.8, Hg:13.8, Plts: 202,000 with 61% lymphocytes, 1% reactive lymphocytes, an absolute lymphocyte count of 9,200 with an absolute neutrophil count of 4,000.
- Peripheral blood FISH test was performed which revealed the presence of a 13q deletion.
- Pertinent Past Medical History: GERD, HTN, Anxiety/Depression, Impaired glucose tolerance, BPH
- Molecular testing: IVGH unmutated status.
- Diagnosis: IVGH unmutated and 13q deleted chronic lymphocytic leukemia.
- Bone marrow biopsy which showed involvement with CLL with cytogenetics revealing a translocation between chromosome 6 and 13 of uncertain significance,
- In July 2022, the patient presented with progressive lethargy associated with progressive anemia and a rapidly increasing WBC count.
- WBC: 105.6, Hg: 10.5, Plts: 147

65-YEAR-OLD WITH TRANSFORMED FOLLICULAR LYMPHOMA

- 65-year-old presented 5 years prior secondary to progressive fatigue associated with new onset neck adenopathy and low-grade fevers.
- CT scan neck: November 2017: Bilateral cervical, left axillary and superior mediastinal adenopathy.
- CT scan of C/A/P: Generalized adenopathy
- Core needle lymph node biopsy: Follicular B-cell Non-Hodgkin's lymphoma, grade 1-2 of 3, without evidence of high-grade component.
- Labs: WBC: 5.4, Hg:13.8, Plts: 278, ANC of 2800. Creatinine of 0.76.
- PET CT scan consistent with disseminated disease.
- July 2022: Progressive disease, manifesting as progressive neck adenopathy, weight loss, fatigue, lethargy, associated with lymphomatous colitis and iron deficiency anemia and night sweats.
- PET scan: Progressive adenopathy and splenomegaly.
- Chemotherapy comprising of bendamustine and rituximab instituted in August of 2022.
- Following 4 cycles of BR, restaging PET/CT: disease response except for a new FDG avid right level 5 cervical lymph node maximum SUV18.2.
- Cervical LN biopsy: Transformed follicular B-cell non-Hodgkin lymphoma consistent with diffuse large B-cell lymphoma.
- Alternative chemotherapy comprising of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) chemotherapy in December 2022
- Following 2 cycles of R-CHOP chemotherapy: Persistent right neck adenopathy

25-YEAR-OLD WITH NEWLY DIAGNOSED CHRONIC PHASE CHRONIC MYELOID LEUKEMIA

- 25-year-old presents with progressive fatigue, low grade fevers, resulting in a CBC which revealed a WBC of 56.16K, Hg: 13, Plts: 254,000 with 38,808 neutrophils, increased metamyelocytes of 1,848, and myelocytes of 7,392, with monocytes of 606, eosinophils of 606, basophils of 3,080, and with 63% neutrophils, 3% metamyelocytes, 12% myelocytes, 15% lymphocytes, and 1% nucleated right blood cells.
- Peripheral smear: "Concerning for Myeloproliferative disorder/Acute leukemia".
- Additional labs: Cholesterol: 141, creatinine: 0.82, total protein: 7.2, and albumin: 5.1, and TSH: 2.94. Hepatitis and HIV serology negative.
- PMH: Unremarkable.
- Physical examination: Spleen not palpable.
- Peripheral blood flow cytometry: No significant pathology.
- FISH: 98.5% BCR-ABL translocation of 9;22.
- Bone marrow biopsy: Consistent with Chronic Myelogenous Leukemia, chronic phase, with blasts <5% of cellularity with mild focal reticulin fibrosis and increased stainable iron stores without ringed sideroblasts.
- Diagnosis of Chronic Phase, Chronic Myeloid Leukemia
- Splenic ultrasonogram: Enlarged spleen: measuring 14.8 x 14.1 x 0.8 cm. Splenic volume; 959.2 mL. No focal splenic lesions.
- Sokal Score of 0.5

NEWLY DIAGNOSED MYELOFIBROSIS

- 79-year-old female presents with chronic anemia
- Hg: 10.4, WBC: 5.8, PLTS: 419 with 68% neutrophils
- Lab results: folic acid vitamin B12 and iron studies normal.
- Given the above, the patient was placed on empiric iron therapy.
- Subsequent workup included serum protein electrophoresis, immunofixation, iron stores, B12 and folic acid stores, and reticulocyte count; all of which were normal except for reticulocytopenia.
- Bone marrow biopsy: Hypercellular marrow with 90% cellularity with increased/mild erythroid hyperplasia, with marked atypical megakaryocytic hyperplasia with moderate reticulin fibrosis (MF2) with less than 1% blasts. Cytogenetics revealing a 46XX normal female karyotype. FLT3 mutation evaluation was negative.
- Peripheral smear: Moderately hypochromic normocytic marrow without circulating blasts,
- FISH testing: negative for BCR/ABL.
- NGS testing: Pathogenic mutation of MPL gene detected, Variants of unknown clinical significance are detected in the following genes: BCORL1, CUX1 and JAK2.
- Extended JAK-2 exon 12-15: Positive for c.1831 T>G (p.L611V)mutation
- Splenic ultrasonography: moderately severe splenomegaly
- Diagnosis: Myelofibrosis.

NEWLY DIAGNOSED HIGH-RISK MYELOMA

- 59-year AAM presents with arising PSA.
- Pelvic MRI: BPH and with bone lesions concerning for metastases with the differential including multiple myeloma and prostatic carcinoma
- HEMATOLOGY CONSULT:
- SPEP and immunofixation: IgG kappa monoclonal protein with an M-protein of 2.2 g/dL, IgG of 3254 with an IgA of 77 and an IgM of 31.
- Free kappa of 448.07, free lambda of 13.87 with an abnormal kappa/lambda ratio of 32.3, and LDH was normal.
- Albumin 4.2, calcium normal at 9.6, and creatinine was normal at 1.1, Beta-2 microglobulin 2.49
- PET/CT scan: Lucent osseous lesions of the bone consistent with multiple myeloma and no evidence of metastatic prostatic carcinoma was identified.
- BM BIOPSY: 80% Plasmacytosis. FISH: deletion of TP53 20%, monosomy of chromosome 13 in 26% and a monosomy of chromosome 1 as well as FGFR3/4p, IGH/14q, and MAF/16q positivity in 20% of the nuclei.
- Diagnosis: ISS Stage I IgG kappa multiple myeloma with high-risk features including deletion of chromosome 17p.
- 4 cycles of Daratumumab/KRD: M-Protein: 0.03gm/dL, possible IgG Kappa, FKCL: 15.31,FLLC: 5, K:L Ratio: 3.06,
- Repeat BM Biopsy; Minor kappa-restricted plasma cell population (<5% of limited cellularity), trilineage hematopoiesis. 46,XY[20] NORMAL MALE KARYOTYPE
- MRD: + Residual Sequences Detected ESTIMATED MRD VALUE: 543 residual clonal cells per million nucleated cells (Range: 211 - 803) Total nucleated cells evaluated from this sample: 3,514,724

NEWLY DIAGNOSED PRIMARY CNS LYMPHOMA

- 71-year-old presents with progressive encephalopathy and mental status changes including increasing confusion, memory impairment, fatigue, anorexia, and weight loss of about a month
- MRI of the brain: focal encephalomalacia of the anteromedial right frontal lobe as well as increased T2 abnormalities of the left pallidium consistent with a neoplastic process.
- LP: WBC; 26, glucose; 63, protein; 78
- Cytology: Atypical lymphocytes consistent with a monoclonal B-cell population.
- Stereotactic biopsy of the brain: Diffuse large B-cell lymphoma.
- CT scan C/A/P: Negative for a primary neoplasm with nonspecific trace ascites and nonspecific fluid around the kidneys, mild perinephric stranding, and high-grade stenosis of the distal superior mesenteric artery and a questionable L2 spinal lesion.
- MRI of the spine which showed no obvious of metastatic disease and a benign hemangioma of L2 with degenerative disease of the spine and trace bilateral pleural effusions

PROGRESSVE UNTREATED WALDENSTROM MACROGLOBULINEMIA

- 62-year-old presents secondary to an elevated total protein and globulin fraction, raising the possibility of gammopathy 1 year prior.
- Laboratory results: Creatinine: 1.29, albumin: 3.4, globulin: 5, total protein: 8.4 with an albumin/globulin fraction of 0.7.
- SPEP: M-protein: 2.18 grams/dL, IgM: 4367, IgG: 399, IgA: 20 with a total globulin of 5.1
- Immunofixation: IgM monoclonal protein detected. WBC: 9.2, Hg: 12.6, PLTS: 446; ANC: 6974. The patient denies a previous history of any gammopathies or any major medical conditions.
- Pertinent Family History: Unremarkable for any malignancies.
- Bone marrow biopsy: low grade B cell lymphoma with 30% cellularity with associated kappa restricted plasma cells comprising 10-15% of the total cellularity. No evidence of amyloid deposition was noted. Additionally, CXCR4 (wild type) and MYD88 mutation positive.
- Current Status: Progressive anemia; Hg: 8.5, WBC: 7.9, PLTS: 365 on February with adequate iron, B12, folate stores. IgM: 4730, IgA: 16, IgG: 413, features consistent with disease progression

81-YEAR-OLD WITH NEWLY DIAGNOSED MYELOMA

- 81-year-old presents with progressive fatigue:
- WBC: 9.3, Hg: 9.4, Plt: 415, creatinine: 1.7, normal LDH of 124
- SPEP: IgG: 297, IgA: 6 and IgM:<5 with an albumin of 3.6
- Bone marrow biopsy:
- NORMOCELLULAR BONE MARROW WITH TRILINEAGE HEMATOPOIESIS AND ~20% LAMBDA-MONOCLONAL PLASMA CELL INFILTRATES;
- MYELOMA FISH: POSITIVE FOR DELETION 13q, TRISOMY 9, IgH GENE REARRANGEMENT, AND DELETION 16q.
- NO EVIDENCE OF AMYLOID DEPOSITION
- Cytogenetics: normal.
- Beta-2 macroglobulin: 4.45.
- Diagnosis: ISS Stage II lambda light chain myeloma.

NEWLY DIAGNOSED "ATYPICAL" CLL

- 71yo presents with leukocytosis.
- WBC: 25.4, Absolute lymphocyte count was elevated 11,000. Plts: 289,000; Hg:13.5
- PB Flow cytometry: Monoclonal B-cells, 42% B cells with a CD19/CD20 positive, FMC7 positive, CD5 negative, CD23 positive, CD38 positive, CD52 positive CD200 positive and lambda restricted immunophenotype consistent with mature B-cell lymphoid proliferation
- FISH: deletion of 17p
- IGHV is unmutated
- ECOG: 0.
- Bone marrow biopsy: low-grade B-cell lymphoproliferative disorder with nonspecific phenotype, 50 to 70% of cellularity, hypercellular bone marrow with trilineage hematopoiesis that is mature; and atypical lymphoid infiltrate. No definite morphologic features myelodysplasia or increase in blasts. Note that the stainable iron appears.
- BM Flow cytometry: Positive for CD19, CD20, CD23, CD45, CD11c, CD38, FMC7, surface lambda, but are negative for CD10, CD25,'s CD103. CD5 appears to be negative or partially dim in a small subset of clonal B cells.

RECURRENT CORE BINDING AML WITH LEUKEMIC MENINGITIS

- 53-year-old who presented in July 2020 with WBC 135,000. at that time; started on hydrea and leukopheresis;
- BM: AML with inversion 16. Blasts were 90% of nucleated cells seen. MYH11-CBFB fusion (t(16;16)(p13;q22)) or inv(16)(p13.1;q22), SKIN BIOPSY- leukemia cutis.
- Initial therapy: 7+3, Day 28 BM: 3-5% myeloblasts, but FISH was negative for CBFB rearrangement.
- Referred for AlloSCT. Pt elected consolidation chemotherapy, HiDAC.
- Repeat BM: End of consolidation negative, but CBFB/MYH11 persistence (0.01).
- June 2022: Evaluated by for AV replacement (open surgery) due to h/o AR; CBC: ANC 0.66/pancytopenic.
- ? Recurrent AML vs. a new Therapy Related AML.
- BM: Recurrent AML. Genomic Alteration: CBFB-MYH11 fusion
- Started on Dacogen + Venetoclax , Needs AVR prior to Allo Transplant
- Achieved Remission, underwent AV replacement, tolerated procedure well.
- Current Status: Presents with developed weakness in LE's
- Spine MRI were concerning for Leptomeningeal involvement.
- LP showed presence of blasts and eventually HSV viral cultures were positive.
- Diagnoses: with CNS relapse of AML based on flow results, and also HSV encephatlitis
- BM biopsy: Morphologic CR, MRD positive for CBFB-MYH11 fusion.

NEWLY DIAGNOSED AMYLOIDOSIS

- 56F with medical history of COPD, lung cancer in remission
- Multiple hospital visits: failure to thrive, chronic abdominal pain, nausea and vomiting and diarrhea.
- Echocardiogram: left ventricular hypertrophy with a speckled myocardium suggestive of amyloidosis; LVEF 75%.
- SPEP and IFE showed IgG lambda-restricted monoclonal protein, 0.7 g/dL, lambda light chains 599.7 mg/L, Kappa LC 26.4 mg/L, affected LC ratio: 22.7.
- CT scans negative for suspicious bone lesions.
- Abd fat pad biopsy negative.
- Bone marrow: Normocellular bone marrow (35-40%) with active trilineage hematopoiesis. Adequate iron stores. 5%% population of lambda restricted plasma cells compatible with a plasma cell dyscrasia.
- Congo Red: Positive for amyloid. cytogenetics.
- Cytogenetics: Normal Karyotype.
- Myeloma FISH: Abnormal Results - Gain(s) of 1q, loss of chromosome 13, rearrangement of IGH