Case 1

- 38 y.o. man presented to San Carlos urgent care with shortness of breath
- Chest X-ray showed left perihilar and right upper lobe infiltrates concerning for pneumonia
- Was treated with levofloxacin with resolution of fevers but continued to have a residual cough

Clinical Course

- Developed significant pruritis over his upper and lower extremities with associated excoriation
- Saw multiple dermatologists for this and was felt to have atopic dermatitis
- Hydroxyzine was prescribed but was not helpful
- Continued to have a mild cough and occasional low-grade fevers

Physical Examination

- General appearance: middle-aged man, pleasant and conversant, in no acute distress
- HEENT: conjunctivae clear, sclerae anicteric, MMM, no oropharyngeal lesions
- Neck: no thyromegaly no JVD
- Nodes: right anterior cervical and supraclavicular adenopathy up to 3 x 3 cm, left anterior cervical adenopathy up to 1.5 x 1.5 cm, no other palpable adenopathy
- CV: NRRR, normal S1 and S2, no murmurs, rubs, or gallops
- Pulm: CTAB, no wheezes, rales, or rhonchi
- Abd: soft, NTND, +BS, no palpable hepatosplenomegaly
- Ext: warm and well perfused, no lower extremity edema
- Neuro: alert and oriented, strength and sensation intact, gait smooth and symmetric
- Skin: warm and dry, excoriations over bilateral upper and lower extremities
- MSK: no active synovitis or joint deformities

Laboratory Evaluation

- WBC 20.7
- Hgb 14.2
- Plt 286

- WBC Diff:

80% PMNs

9% lymph

Normal ALC

- Na 141
- K 4.1
- Cl 100
- HCO3 26
- BUN 26
- Cr 0.8
- Glc 120

- Tbili 0.9
- AST 32
- ALT 46
- Alk phos 104
- Albumin 4.1

- HIV negative
- HepB negative
- HepC negative
- LDH 269
- ESR 16

Clinical course

- Developed more frequent fevers every 2-3 days and worsening cough
- Chest X-ray showed a right lower lobe consolidation and new right paratracheal and right hilar adenopathy. He was treated again with levofloxacin for presumed pneumonia without improvement in his symptoms
- Repeat chest X-ray showed more prominent right paratracheal and right hilar adenopathy. A subsequent CT scan of the chest showed extensive adenopathy in the neck, mediastinum, and upper abdomen
- Biopsy of a right supraclavicular node was done, as follows:

Pathology

LYMPH NODE, RIGHT SUPRACLAVICULAR, EXCISION (2/1/2018)
-- CLASSICAL HOGKIN LYMPHOMA (SEE COMMENT)

MICROSCOPIC DESCRIPTION: Histologic sections show occasional scattered large atypical cells with hyperchromatic nuclei with irregular nuclear contours. These atypical cells are intermixed with more abundant small mature appearing lymphocytes as well as scattered histiocytes, eosinophils, and neutrophils. The lesion contains bands of fibrosis.

ANCILLARY STUDIES: The provided stains were reviewed, with appropriate internal and external positive and negative controls available unless otherwise stated. The large atypical cells express CD30, CD15 (dim subset), and PAX5 (moderate to bright). The large atypical cells are negative for CD20, CD3, CD45, S100, and CKAE1/3. AFB and GMS stains are negative.

Initial PET/CT results

1. Extensive markedly FDG avid lymphadenopathy in the neck, chest and upper abdomen compatible with the diagnosis of Hodgkin's lymphoma.
2. FDG avid pulmonary nodules, also compatible with lymphomatous involvement.
3. Focal FDG avid uptake in T11 compatible with osseous lymphomatous involvement.
4. Diffuse moderate marrow uptake in the axial and proximal appendicular skeleton, may be related to lymphomatous involvement or marrow activation.

Additional workup

- PFTs showed DLCO 67% (reduced)
- Echo showed EF 64%

- *What treatment would you choose for this patient?*

  A-ABVD x 6 cycles

  B-A-AVD

  C-ABVD x 2 cycles and if PET-2 is negative, AVD x 4 cycles

  D- AVD x 6

Case 2

- 65-year-old female who presented with night sweats and 20 lb. loss
- Denied fevers
- Was having some left thigh pain when sitting down
- Reported back pain
- Noted a firm mass along the left side of her lower abdomen

Physical Examination

- ECOG 0
- General Appearance: not in acute distress
- Eyes: sclera anicteric
- ENT: Oropharynx clear, moist oral mucosa, no thrush
- Lymph: no nodes in the cervical, supraclavicular, infraclavicular, axillary.
- 2x2 palpable left inguinal node, 5 x 5 cm palpable left thigh mass starting just below the inguinal ligament
- Cardiac: Regular rate and rhythm, normal S1 and S2
- Lungs: Clear auscultation, normal symmetry and expansion
- Abdomen: soft and nontender, no palpable hepatosplenomegaly
- Ext: no edema
- Neuro: Alert and oriented x3, CN II-XII intact, no wide-based or antalgic gait

Laboratory Evalution

- WBC 11.8
- Hgb 7.5, MCV 88
- Plt 218

<u>WBC Diff:</u>

PMNs 86%

Lymph 14%

- Na 131
- K 3.1
- Cl 95
- HCO3 25
- BUN 7
- Cr 0.71
- Glc 119

- Tbili 0.4
- AST 10
- ALT 10
- Alk phos 87
- Albumin 3.8

- HepB negative
- HepC negative
- HTLV-1 negative

CT abdomen/pelvis

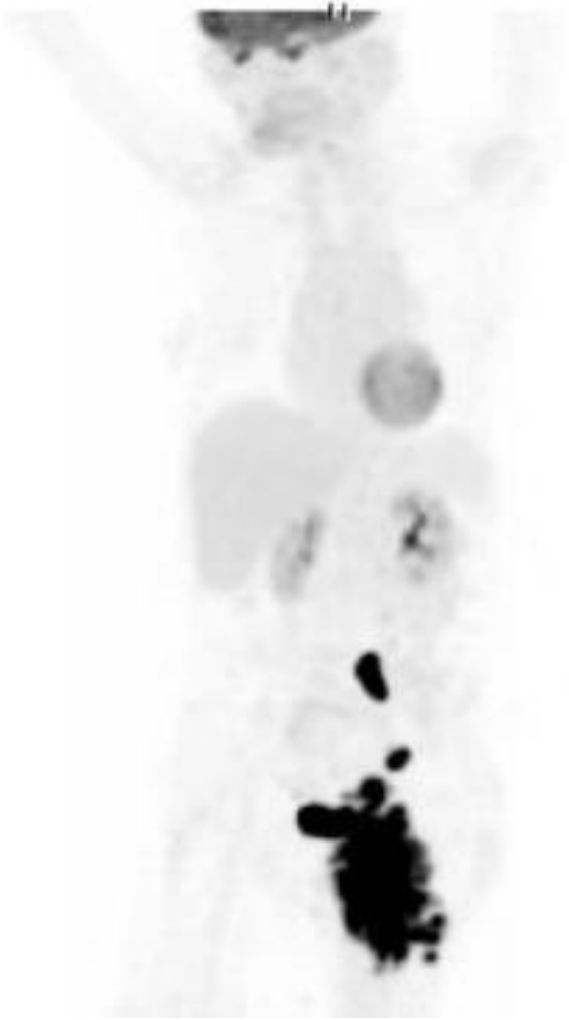
1. Abnormal retroperitoneal and mesenteric lymphadenopathy are seen. The findings are nonspecific but suspicious for lymphoma or nodal metastasis.
2. 7 x 4.4 cm left groin mass which may represent a large necrotic lymph node, primary tumor and/or metastatic disease.
3. Destructive left iliac bone mass with associated soft tissue mass. This finding is suspicious for metastatic disease, less likely primary tumor. T12, L2, L5 and S1 vertebral bodies also have findings suspicious for metastatic disease. The left sixth anterior rib is incompletely evaluated on this study however there is an associated soft tissue focus which may also represent metastatic disease.

MRI spine

- 1. Multiple osseous metastasis at T6, T7, T9, T11, L2, L5, S1 vertebral body and iliac with pathological compression fractures at T11, L2 and L5 vertebral bodies. Posterior tumor retropulsion at T11 resulting in moderate spinal canal narrowing.
  2. Severe right T10-T11 and T11-T12 and moderate right L5-S1 neuroforaminal narrowing due to paraspinal tumor infiltration.
  3. Extensive retroperitoneal metastasis and the left gluteal and bilateral iliopsoas muscle tumor infiltration.

Interval PET/CT

- Intensely hypermetabolic left common iliac, left pelvic sidewall, left external iliac, and left inguinal lymph nodes measuring up to 1.6 cm in the left common iliac region on image 165 with a 3D max SUV of 35.8.
- Moderately to intensely hypermetabolic soft tissue masses in the proximal medial left thigh measuring up to 5.9 x 7.6 cm on image 217 with a 3D max SUV of 23.4.



Inguinal node biopsy

DIAGNOSIS:
LYMPH NODE, LEFT GROIN, BIOPSY (WCRS17-33502; 8/18/17)
-- HIGH GRADE B-CELL LYMPHOMA WITH MYC AND BCL2 GENE REARRANGEMENTS (SEE COMMENT)
-- MYC AND BCL2 REARRANGEMENT POSITIVE BY FISH (BY REPORT)
-- BCL6 REARRANGEMENT NEGATIVE BY FISH (BY REPORT)

LYMPH NODE, LEFT GROIN, BIOPSY (WCRS17-33502; 8/18/17)
Sections from the lymph node show two cores, both with sheets of CD20 positive B-cells. In one core most B-cells show expression of Bcl-2, Bcl-6, CD10 and c-myc and lack MUM-1 and EBER. In the other core, B-cells express Bcl2, MUM-1 and EBER and lack Bcl6, CD10 and c-myc. Both populations are negative for Bcl-1, CD3, CD5 or TdT. Overall the findings are compatible with the diagnosis of a high grade B-cell lymphoma. By report, myc and Bcl2 gene rearrangements were detected by FISH and the Bcl6 rearrangement was not.

FISH results

Positive for MYC oncogene (8q24) rearrangement in 47% (47/100) of cells;
Positive for t(14;18) translocation in 36% (36/100) of cells
BCL6 rearrangement (3q27): Negative;
MYC rearrangement (8q24): Positive in 47% (47/100) of cells;
BCL2/IGH fusion or t(14;18) translocation: Positive in 36% (36/100) of cells.

Stomach biopsy

STOMACH, BIOPSY (SCHS17-24577; 9/3/17)
-- INVOLVED BY B-CELL LYMPHOMA
-- CMV GASTRITIS WITH ULCERATION AND MIXED INFLAMMATION
-- RARE FUNGAL HYPHAE IDENTIFIED ON GMS STAIN

STOMACH, BIOPSY (SCHS17-24577; 9/3/17)
Sections show atypical cells scattered throughout the lamina propria, which by morphology and immunophenotype are compatible with involvement by the patient's known B-cell lymphoma. Received and reviewed are immunostains for CD30, CD10, EBV, cMyc, CD20, Pax8 and CD15. The provided EBV stain is positive in scattered atypical cells. A provided CMV stain is also positive. An HSV stain is also reviewed and is negative.

Clinical course

- Flow cytometry of CSF was negative
- Diagnosis: stage IV double-hit DLBCL
- Started DA-R-EPOCH as inpatient
- Received 6 cycles
- Achieved complete response (CR1)
- Course was followed by biopsy proven-relapse after 6 months later:

- *How would you treat this relapsed DLBCL?*

  A- RICE followed by Autologous stem cell transplant

  B- RICE followed by Allogeneic stem cell transplant

  C- CAR T/Yescarta alone

  D-Yescarta followed by allo transplant if < CR

  E-Blinatumumab + Lenelidomide on PHI-79 clinical trial followed by Allo transplant

Case 3

65 year old M with newly diagnosed AML transfers in from an outside facility. He presented with cough, fatigue, dizziness, nausea and aches. Labs showed a WBC 90, Hgb 9, Plt 11, 80% circulating blasts, no TLS and mild DIC. BMBx showed 85% myeloblasts that express CD33.

Transfer is delayed due to bed availability and he is started on Hydroxyurea and allopurinol. During this time, cytogenetics return normal. FISH is negative, including t(15;17). Molecular studies are positive for IDH1 R132H (VAF 38.1%) and SRSF2 P95H (VAF 42.8%) mutations. TTE shows a normal LVEF. ECOG PS 0. He takes Tamsulosin for BPH. He has no history of liver disease, antecedent hematologic disease, or prior exposure to radiation or chemotherapy. He is fit and active.

Case 3

Assuming there is no available trial, what induction would you offer this patient who is fit and has intermediate risk cytogenetics and IDH1 and SRSF2 mutations?

1. 7+3
2. 7+3 plus fractionated gemtuzumab ozogamicin
3. 7+3 plus midostaurin
4. 7+3 plus ivosidenib
5. Liposomal Dauno/AraC (CPX-351)
6. Azacitidine plus venetoclax

Case 3

You then discover that he actually has a NPM1 mutation (VAF 42.8%) and FLT3-ITD mutation (allelic ratio 0.1). What induction regimen would you offer now?

1. 7+3
2. 7+3 plus fractionated gemtuzumab ozogamicin
3. 7+3 plus midostaurin
4. 7+3 plus ivosidenib
5. Liposomal Dauno/AraC (CPX-351)
6. Azacitidine plus venetoclax
7. Azacitidine plus sorafenib

Case

The patient is induced with 7+3 plus midostaurin. Day 22 marrow is hypocellular without increased blasts. Induction is complicated by febrile neutropenia but overall tolerated well. Upon count recovery, you plan a remission marrow. Besides getting an aspirate, core biopsy, standard flow cytometry and cytogenetics, which additional test(s) would you order?

1. AML FISH
2. MRD flow cytometry
3. NGS-based molecular profiling
4. NPM1 quantitative RT-PCR
5. None of the above
6. Just go ahead and check all the boxes on the order sheet
7. Order #2-4

Case

The patient has achieved a morphologic complete remission. Cytogenetics are normal. MRD flow cytometry is negative. NPM1 qRT-PCR is negative. NGS-panel is negative for NPM1, FLT3, IDH1 and SRSF2 mutations. He has biological siblings and is a potential transplant candidate although caregiver support is a possible limitation. How would you approach his post-remission care?

1. Allotransplant in CR1, bridge with up to 2-4 cycles of IDAC plus midostaurin consolidation
2. No allotransplant in CR1, give up to 2-4 cycles of IDAC plus midostaurin consolidation
3. No allotransplant in CR1, give 2 cycles of AraC plus danuorubicin plus gemtuzumab ozogamicin
4. No allotransplant in CR1, give cycles of azacitidine until relapse, undue toxicity or patient decision to stop
5. No allotransplant in CR1, give cycles of ivosidenib until relapse, undue toxicity or patient decision to stop

Case

The patient is consolidated with 2 cycles of IDAC plus midostaurin. He tolerates therapy exceptionally well so two additional cycles are given. A repeat BMBx is done after the 4th cycle and shows morphologic complete remission. Cytogenetics are normal. MRD flow cytometry is negative. NPM1 qRT-PCR is negative. NGS-panel is negative for NPM1, FLT3, and SRSF2 mutations but is now positive for IDH1 R132H (VAF 2%). Although previously hesitant to proceed with transplant, the patient is open to that now. He now has caregiver support and an identified matched related donor. What should we do now?

1. Observation/Surveillance
2. Start midostaurin maintenance
3. Start ivosidenib or clinical trial with a mIDH1 inhibitor
4. Start azacitidine
5. Salvage with FLAG-/+Ida
6. Proceed with allotransplant asap

Case # 4

- **67 yo man referred for evaluation of remote history of Von Willebrand Disease prior to hip replacement. Per patient: VWD was diagnosed at age 16 after need to re-stich 2 days after wisdom teeth extraction, appendectomy at 26, post op bleed required 4 units of pRBC, no other surgeries.**
- **His mother was a "bleeder", had hysterectomy at age 28. he has no children**

A - Reassure and proceed without any treatment.

B - Order DDAVP prior to surgery

C - Order VWF concentrate one dose prior to surgery and 10 follow up days

D – perform detailed bleeding history and laboratory workup

E - Order recombinant VWF prior to surgery and 10 days follow up days

Criteria in Condensed MCMDM-1VWD BQ (condensed ISTH BAT)

- Epistaxis
- Cutaneous symptoms
- Bleeding from minor wounds
- Oral cavity symptoms
- Gastrointestinal Bleeding
- Hematuria
- Tooth Extraction
- Surgery
- Menorrhagia

- Postpartum Hemorrhage
- Muscle Hematomas
- Hemarthrosis
- Central Nervous System Bleeding
- Other Bleeding (e.g. umbilical stump bleeding, Cephalohematoma, Conjunctival Hemorrhage, excessive bleeding after venipuncture)

Interpretation

- Abnormal cut-offs
  - Men >3
  - Women >5
  - Children >2

-Detailed review shows bleeding score over 4

-Labs show:

PT	13.2
PTT	32
Risto Activity	14%
VW Factor Ag	18%
Factor 8	98%

A - Reassure and proceed without any treatment.

B - Order DDAVP prior to surgery

C - Order VWF concentrate one dose prior to surgery and 10 follow up days

D - refer to nearest hemophilia treatment center

E - Order recombinant VWF prior to surgery and 10 days follow up days

Case # 5

37 yo lady with history of gastric bypass, diagnosis of Antiphospholipid Syndrome and unprovoked PE at 35 on anticoagulation with Rivaroxaban presents to ED with new SOB; imaging shows new PE. She is started on heparin gtt. Next step is:

A – Start her on warfarin – APS should not have been treated with DOAC

B – measure the Rivaroxaban level and adjust Riva dose

C – change to different DOAC

D – continue Rivaroxaban at the same dose

E – verify the APS diagnosis to decide about anticoagulation

Case # 6

- CC: abnormal labs:
- HPI: 58 y/o African American man presents to clinic after being referred by his PCP for abnormal labs. He feels well, but was noted to have a slight increase in his creatinine, and something to do with protein levels. He has no pain, change in bowel habits or urinary habits, though admits to foamy urine sometimes. He continues to work, denying fatigue or decreased physical capabilities. He hasn't had any dyspnea, palpitations, light headedness or dizziness.
- PMHx: Hypertension, requiring 2 medications, with a third medication added after most recent to PCP, diabetes controlled with metformin and Januvia
- PE: unremarkable

Case # 6 (cont)

- Labs:
  - CBC: WBC: 6.0, H/H: 11.8/35, plt: 230
  - Chem: Creat 1.4 (incr from baseline 1.2), Ca 8.2, alb 4.0, LDH 170 (wnl), total protein 8.5 (uln 8.3)
  - SPEP: m-spike 1.7, IFE: IgG Kappa
- Additional workup (at Hem/onc)
  - sFLC:
    - kappa: 136 (uln 19.5)
    - lambda: 30 (uln 25)
    - K:L: 4.5 (uln 1.65)
  - Skeletal Survey: no evidence of lytic lesions
  - UPEP: no monoclonal protein noted, mild albuminuria (too low to quantitate)

Case #6

- The Diagnosis and next steps in management
  A. Multiple myeloma
  B. Low risk MGUS
  C. High Risk MGUS
  D. Not sure yet – additional work-up is needed

Case #6

- A PET-CT is performed, identifying several small FDG lytic lesions throughout the axial skeleton
- Bone marrow biopsies reveals:
  - 40% kappa restricted plasma cells
  - +1q, +3, +7, t(11;14), del(17p)

Case #6

- What would be your first choice of induction therapy:
  A. RVd -> stem cell transplant -> lenalidomide maintenance
  B. RVd -> stem cell transplant -> bortezomib maintenance
  C. KRD -> stem cell transplant -> carfilzomib maintenance
  D. Rd indefinitely
  E. CyBorD -> bortezomib maintenance