MAYO CLINIC

Inpatient Cancer Care
ACP Puerto Rico Chapter Annual Meeting

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Question 1

A 55 year old gentleman was treated nine days ago with chimeric antigen receptor T cell therapy (CAR-T) for relapsed diffuse large B cell lymphoma. He presents to the clinic with fever, chills, and lightheadedness. He is having difficulty describing his symptoms, but he is clearly unwell.

Vitals: BP 85/60, HR 120, O2 sat 94%, Temp 39.0 C

Exam: unremarkable

Neuro assessment: word finding difficulty, altered handwriting

Labs:

Hg 11.0
WBC 1.0, 980 neutrophils
Plt 40,000

Ferritin: 1,235
CRP: 257
Cr: 1.2
LFT: normal

Question 1

- What is the likely cause of his presentation?
- A. Neutropenic fever with sepsis
- B. CNS relapse of disease
- C. Cytokine release syndrome
- D. Neurotoxicity from CAR-T
- E. C and D
- F. All of the above

Question 1

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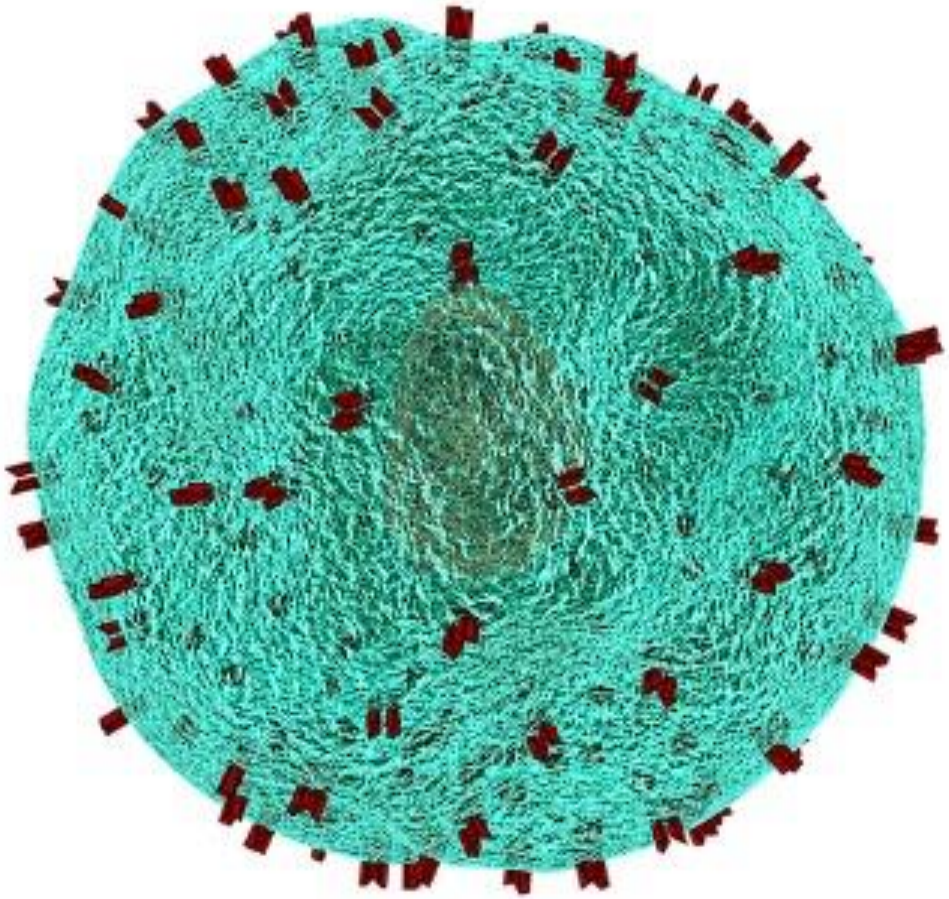
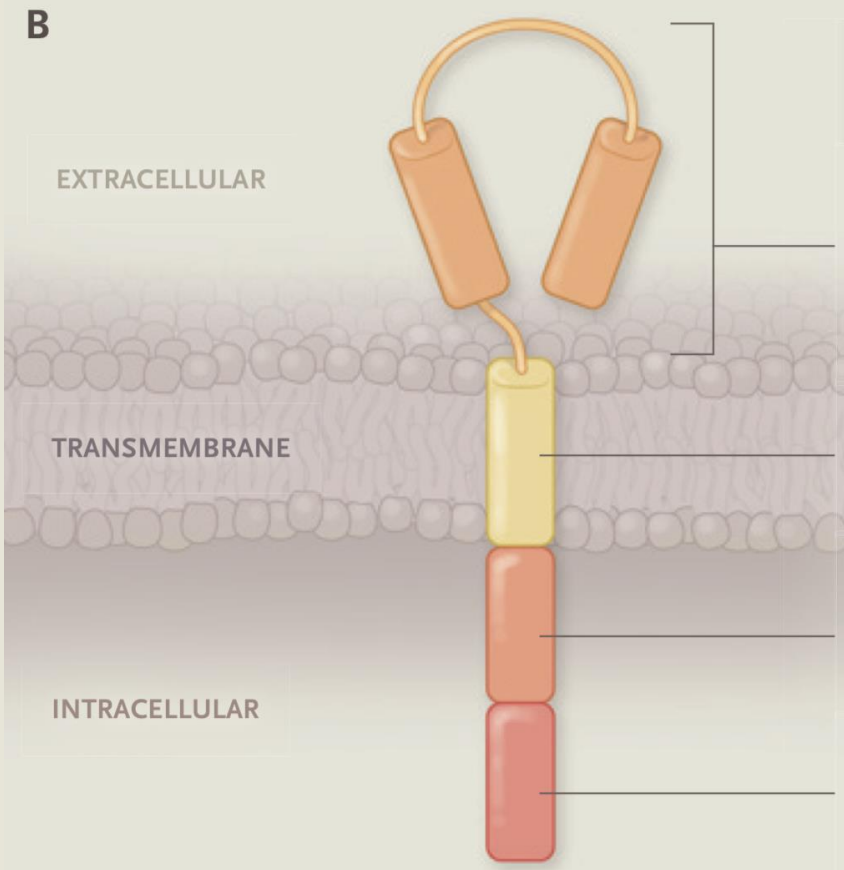
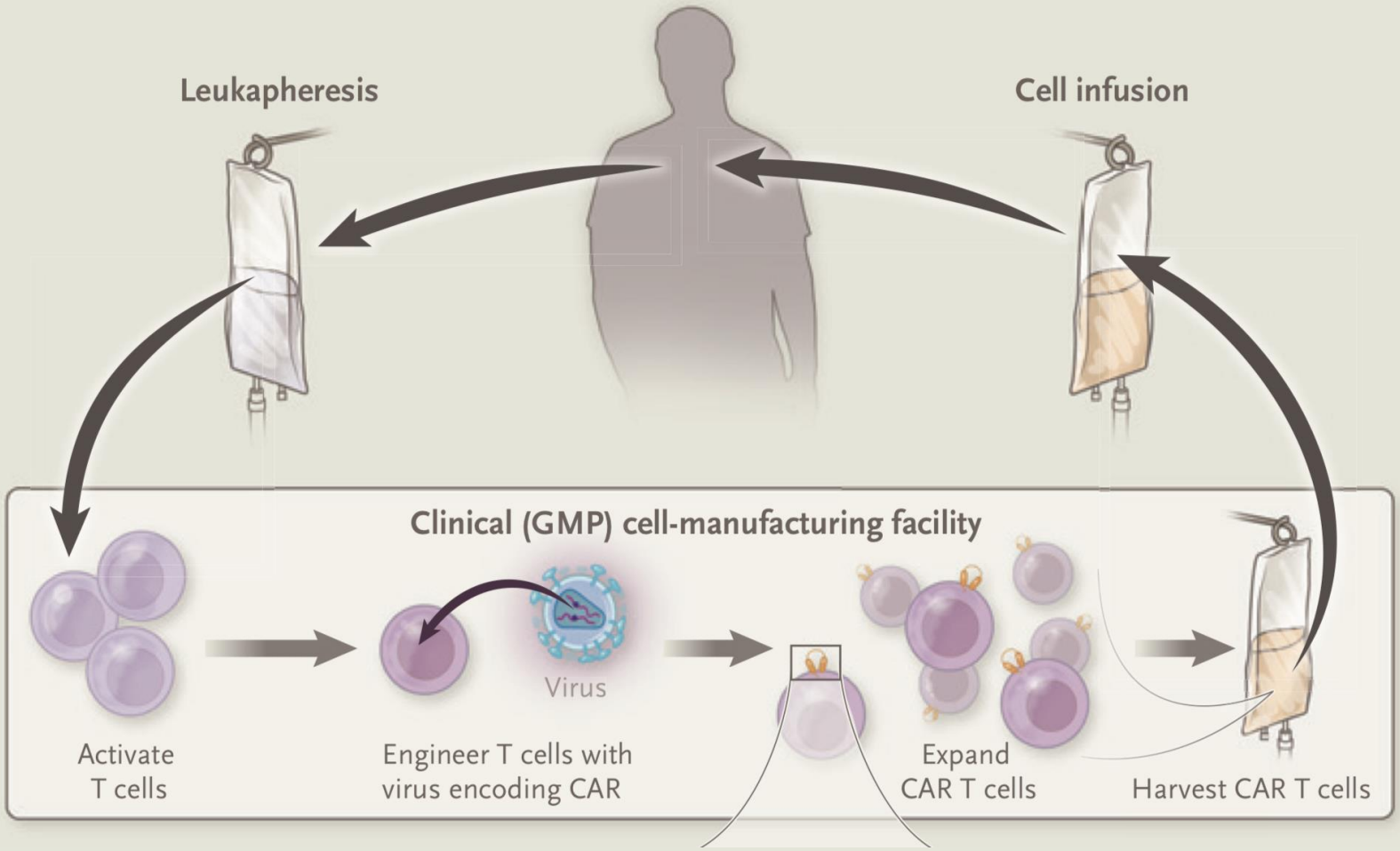




	Neelapu et al.	Schuster et al.
Anti-CD19 antibody variable domains	FMC63	FMC63
Transmembrane domain	CD28	CD8
Costimulatory domain	CD28	4-1BB
TCR signaling domain	CD3-ζ	CD3-ζ

Tran et al, NEJM 377;26

A

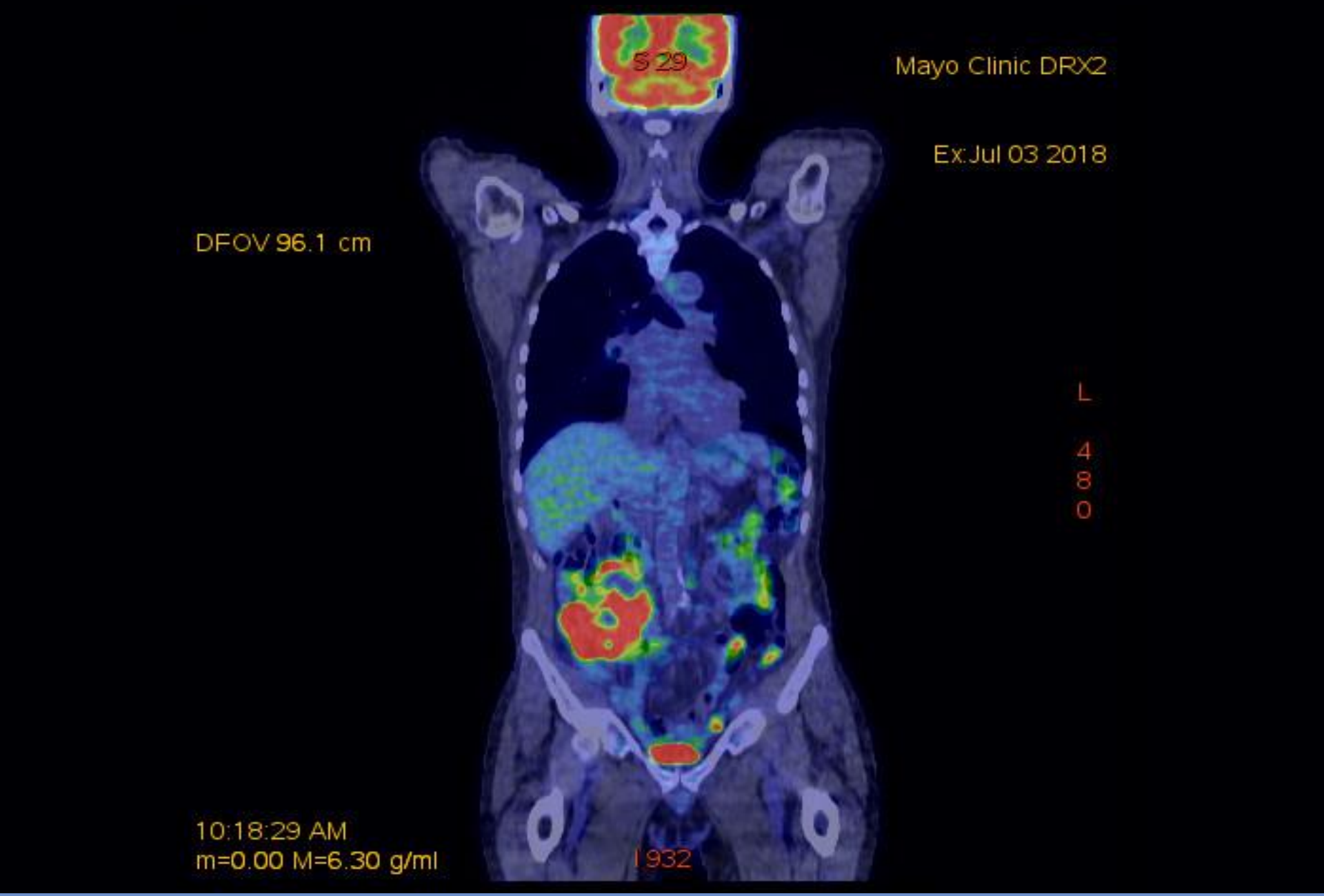


Tran et al, NEJM 377;26

Efficacy of CAR-T Therapy

Disease	Response Rates (%)	Notes	References
Adult B-Cell ALL*	83-93	High initial remission rates - ? Role of allogeneic SCT	Park et al., Davila et al., Turtle et al.
Pediatric B-Cell ALL*	68-90	About 25% of patients relapse with a CD19- leukemia, CD22 CAR-T may improve survival	Maude et al., Fry et al., Lee et al.
Diffuse Large B-Cell Lymphoma	64-86	40-50% of patients have a durable complete response	Turtle et al., Neelapu et al., Schuster et al.
Follicular Lymphoma	71	Of those that responded, 89% response maintained at median 28.6 month follow up	Schuster et al.

* Acute Lymphoblastic Leukemia



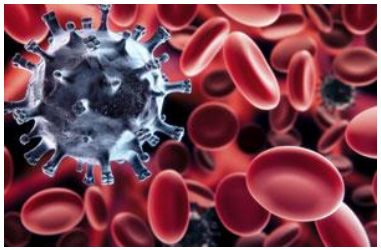
Toxicities from CAR-T Therapy

- Cytokine release syndrome
  - Typically occurs between day 3-5 after infusion of product
  - Second wave may occur day 9-14 after infusion
  - Characterized by hypotension, tachycardia, and hypoxia
  - Treated with tociluzimab
    - IL-6 receptor inhibitor
    - CRS resolves in hours

Toxicities from CAR-T Therapy

- Neurotoxicity
  - Occurs in same timeframe as CRS
  - Etiology is not well understood
  - Characterized by headache, wordfinding difficulties, tremor, somnolence
  - May worsen to cerebral edema
  - Treated with dexamethasone and antiseizure prophylaxis
    - Takes longer to resolve than CRS

Question 2



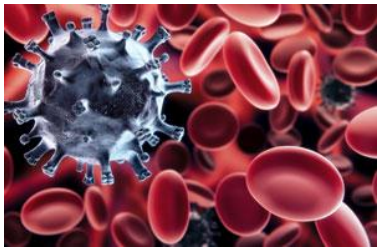
65 year old man admitted to the hospital with chest pain. Troponins were positive, and the patient underwent coronary angiography. Angiography was negative for stenosis.

ROS +ve for 25lb weight loss, occasional night sweats.

Exam: small, mobile rubbery lymphadenopathy in inguinal area bilaterally, 1-2cm in size

Labs:
Hg: 9.7
MCV: 84.7
WBC: 7.0
PLT: 455K
Smear: rouleaux +
ESR 137

Iron and TIBC slightly low
Cr: 1.0
SPEP: 2.3g/dL M spike in gamma region
Imm. Fix: monoclonal IgMλ, small IgMκ
IgG: 822 mg/dL
IgM: 3250 mg/dL
IgA: 52 mg/dL



Question 2

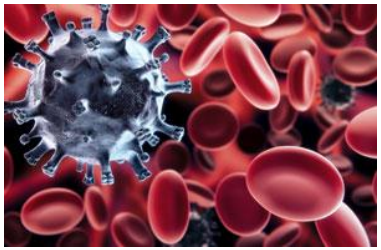
The patients' presentation is most consistent with which of the following diagnoses?

A. Waldenstrom Macroglobulinemia

B. Smoldering Waldenstrom Macroglobulinemia

C. Lymphoplasmacytic lymphoma

D. IgM MGUS



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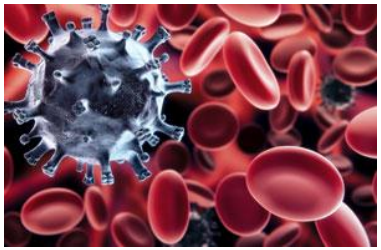
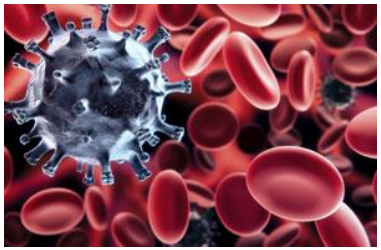
The Spectrum of Disease



	M Spike	BM involvement %	Sign/symptom of disease
IgM MGUS	<3g/dL	<10%	-
Smoldering Waldenstrom	>3g/dL	>10%	-
Waldenstrom macroglobulinemia	Any	>10%	+*
Lymphoplasmacytic lymphoma	-	+/-	+

*Fatigue, B symptoms, hyper-viscosity, neuropathy, lymphadenopathy, cytopenia

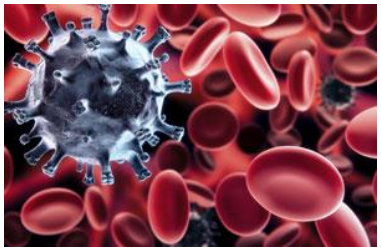
Waldenstrom Macroglobulinemia



- Lymphoplasmacytic lymphoma
  - Neoplasm of small b lymphocytes, plasmacytoid lymphocytes, and plasma cells

- Lymphoplasmacytic lymphoma with:
  - Bone marrow involvement
  - IgM monocolonal gammopathy
    - → Waldenstrom Macroglobulinemia

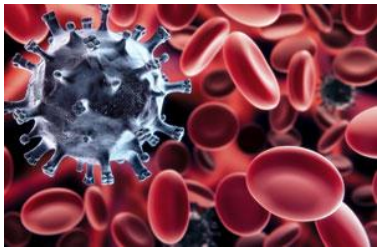
Waldenstrom Macroglobulinemia



Presentation:

Sign/Symptom	Present at Diagnosis
Fundoscopic abnormalities	34%
Hyper-viscosity	31%
Lymphadenopathy	25%
B symptoms	23%

Question 3



The patient is started on rituximab based therapy. On routine follow-up for the next cycle, he is admitted for excessive fatigue. He states that for the past week, the fatigue has been so bad, he has been limiting his activity, not leaving the house. He also is embarrassed to admit that he has fallen a couple of times in the past two days. He admits his vision has been a little blurry, but he's needed new glasses for a while, and his allergies have been particularly troublesome lately. Otherwise, he would like to receive his next cycle of treatment.

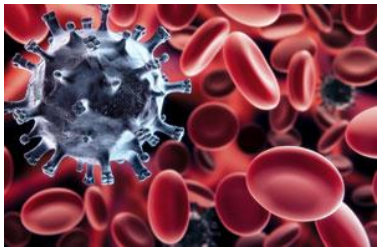
What is the next step in management?

A. Evaluation for neuropathy

B. Plasmapheresis

C. Placement in SNF

D. Continue chemotherapy



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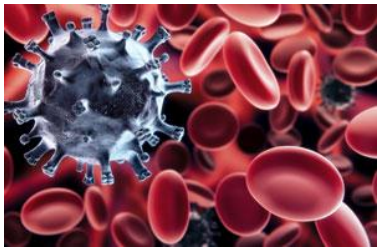
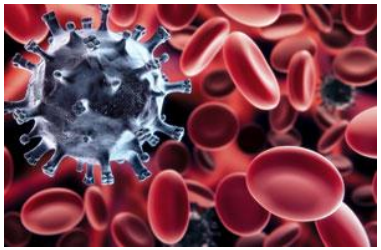
IgM Flare and Hyperviscosity



- Flare
  - Rise of serum IgM ≥25% rise from baseline
  - Occurs most commonly associated with rituximab
  - May take up to 4 months to resolve
  - May precipitate hyper-viscosity syndrome

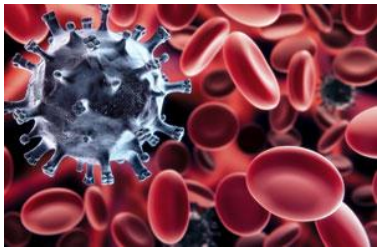


Hyper-viscosity Syndrome

- Can measure serum viscosity
  - Not precise, but clear correlation:

Serum Viscosity	Patients with hyper-viscosity symptoms
<3 CP	0%
>4 CP	67%
>5 CP	75%

Waldenstrom Macroglobulinemia

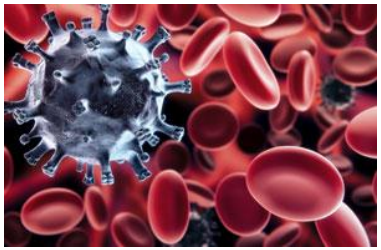


Treatment:

Asymptomatic → observe/follow*

Symptomatic → require treatment

- Rituximab based therapy

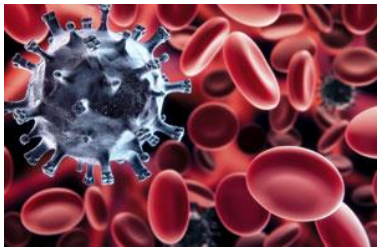


Question 4

A 65-year-old man was in his usual state of health until he began experiencing fatigue and shortness of breath.

Laboratory investigations reveal:

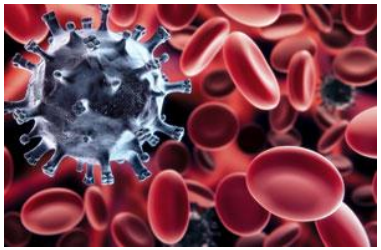
- Hg: 6 g/dL
- WBC: 40 $X10^9$/L
  - 60% blasts
- Plt: 52,000
- Fibrinogen: 205
- INR: 1.1



Question 4

He is admitted to the hospital and appropriate therapy has begun. Peripheral blood flow cytometry shows blasts that are CD19+ and CD20+ (amongst others). What type of leukemia is this phenotype most associated with?

- A. Acute Promyelocytic Leukemia (APL)
- B. FLT3+ Acute myelogenous leukemia (AML)
- C. Acute B Lymphoblastic Leukemia (ALL)
- D. Chronic Lymphocytic Leukeima (CLL)
- E. Mantle Cell Lymphoma (MCL)
- F. None of the above



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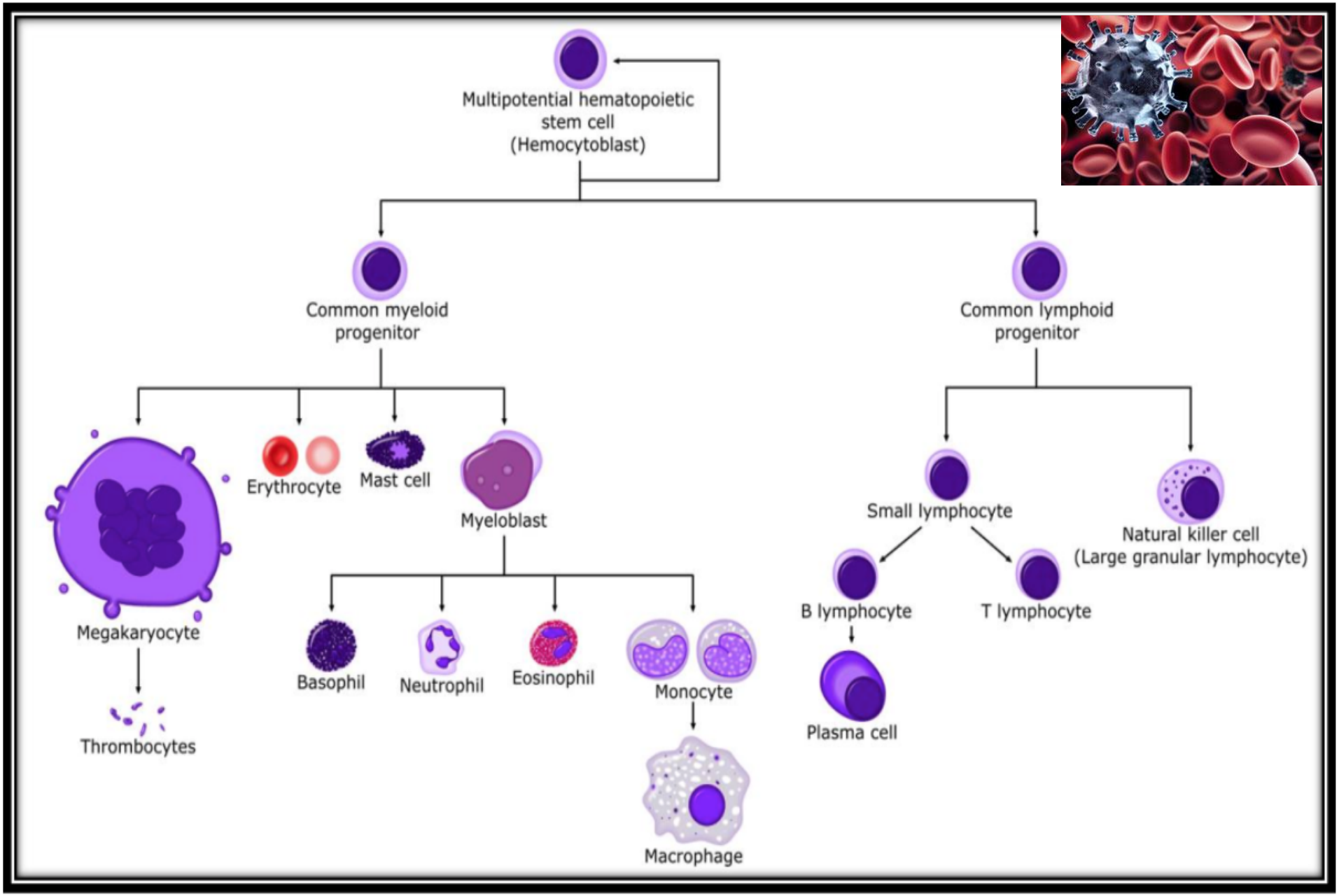
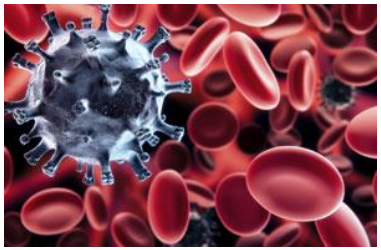
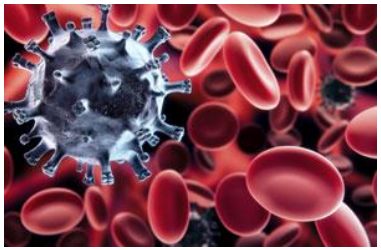




Question 4

- Lab calls to update testing results. His total WBC count is ***actually 240k.***
- Over the past 12 hours, profoundly fatigued, develops headache, and dyspnea.
- Evaluation reveals:
  - O2 sat: 88%
  - K+: 5.9
  - Uric acid: 8.3
  - PO4: 6.0

Cr: 1.4
INR: 1.3



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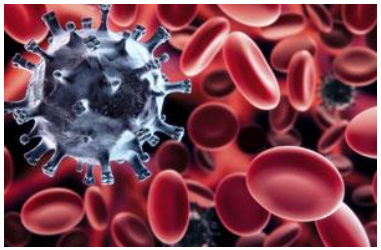
Her presentation is most consistent with:

- A. Spontaneous tumor lysis
- B. Blast crisis
- C. DIC
- D. Differentiation syndrome
- E. Neutropenic Fever



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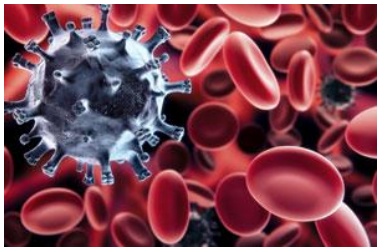
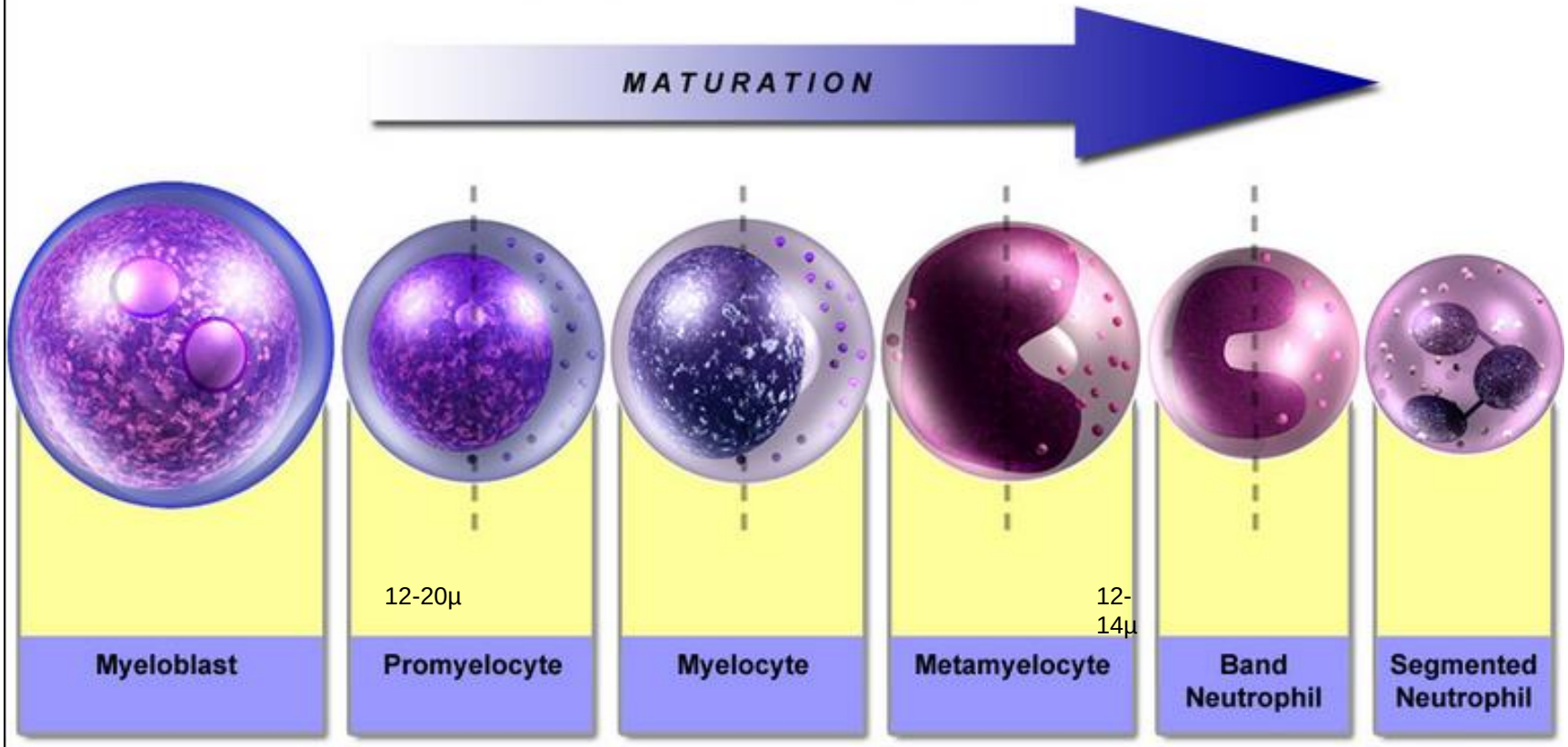
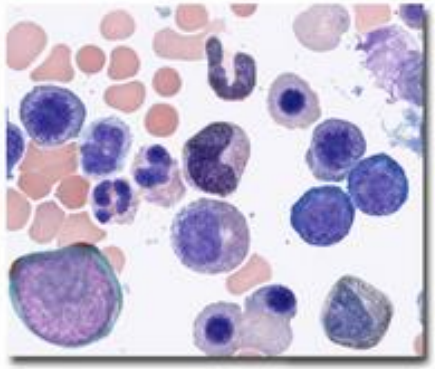


Blast Crisis

GRANULOCYTIC MATURATION DIAGRAM



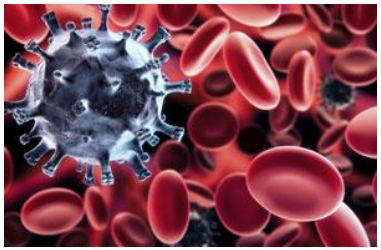
-Cell size generally decreases
-Nuclear volume generally decreases
-Nuclear maturation goes from round, fine chromatin to segmented, dark chromatin
-Nuclear-to-cytoplasmic ratio decreases
-No cytoplasmic granules to primary (azurophilic) granules to specific (secondary) granules



20 µm

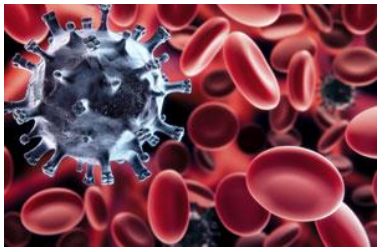
Rashidi H MD, Nguyen J MD et al. HematologyOutlines.com

Blast Crisis

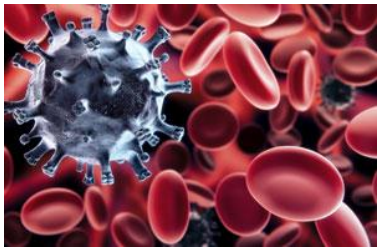


- Pseudo hypoxemia
- Pseudo hyperkalemia
- Blood transfusion may be hazardous because of increasing the blood viscosity
- Hydroxyurea
- Monitor for tumor lysis and DIC

Blast Crisis



WBC Counts as Indication for Leukapheresis	Symptomatic	Asymptomatic
Acute myeloid leukemia (AML)	>50,000	>100,000
Acute lymphoid leukemia (ALL)	>150,000	>300,000
Chronic myeloid leukemia (CML)	>150,000	No
Chronic lymphoid leukemia (CLL)	>500,000	No
Acute promyelocytic leukemia (APL)	No	No



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A 65 year old gentleman is diagnosed with chronic lymphocytic leukemia (CLL) and is initiated on ibrutinib. Two months after initiation of therapy, he sees you for routine follow up. Unfortunately, his lymphocyte count has ***increased*** from 25,000 to 35,000. He feels fatigued and has intermittent body aches.

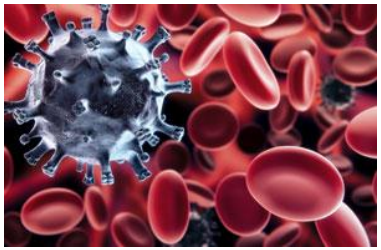
What is the next step in management?

A. Stop ibrutinib due to progressive disease

B. PET scan to evaluate for Richter's transformation

C. Continue ibrutinib despite symptoms

D. Peripheral blood flow cytometry to evaluate for ibrutinib escape



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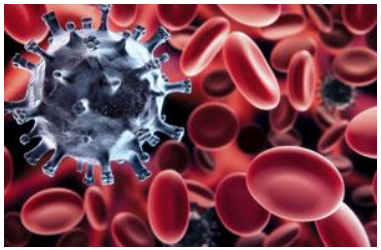
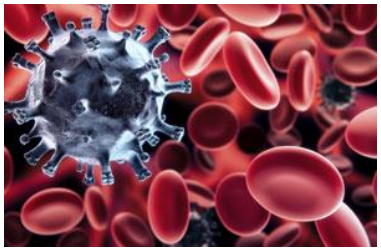


Ibrutinib side effects/toxicities

- Diarrhea
- Fatigue
- Body aches
- ***Elevation*** in lymphocyte count



Question 6

This same gentleman was admitted to the hospital after a fall and traumatic fracture to his left hip. He is scheduled for hip surgery later today. He has been on ibrutinib for the past 6 months, and his disease is well controlled.

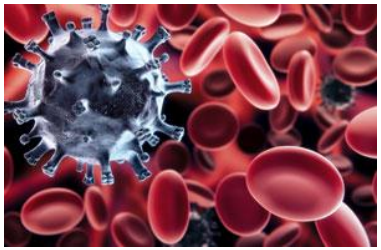
What would be the optimal management of his ibrutinib?

A. Continue and proceed with surgery

B. Hold ibrutinib for 24 hours then proceed with surgery

C. Hold ibrutinib and delay surgery for 4-7 days

D. Switch ibrutinib to another bruton tyrosine kinase (BTK) inhibitor.



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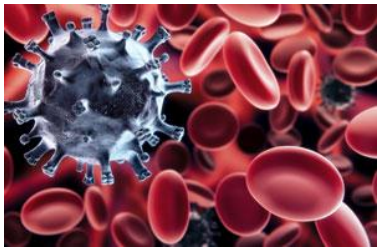

Ibrutinib and bleeding

- Half of patients will develop low grade ecchymoses and petechiae
  - Defect in platelet aggregation
- Major hemorrhage rates range from 1%-9%
  - May be spontaneous or periprocedural
- Therefore, elective surgeries should be performed before initiation
  - Emergency surgeries case by case

Review

- CART toxicities
- Hyperviscoscity syndrome
- Blast crisis
- CLL and Ibrutinib

Thank You

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