Approach to Lymphadenopathy

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Case 1

- 43 year old woman with no significant prior medical history presents for evaluation of enlarged cervical, axillary, and inguinal lymph nodes, notes generalized night sweats and intermittent fever with 10 lbs weight loss.
- On physical exam noted to have palpable bilateral cervical, axillary, and inguinal lymphadenopathy, largest 2.5 cm in diameter
- Labs significant for hemoglobin 10.5, mcv 90, wbc- 5.2, platelets 188
- Referred to hematology for further evaluation

Approach to Lymphadenopathy

- Broadly differential diagnosis includes:
  - Reactive process related to infection, trauma, auto-immune disorder, Rx
  - Malignancy
  - Rare non-malignant systemic disorders

Approach to Lymphadenopathy

- Localized versus generalized?
- Size?
- Associated constitutional symptoms (or pruritis)?

Generalized Lymphadenopathy – Differential Diagnosis

- HIV infection, EBV, CMV, tuberculosis or other mycobacterial infection, rheumatologic disease (including SLE), lymphoma, rare systemic disorders

Initial Work-up – Generalized Lymphadenopathy

- Minimum initial work-up: complete blood count, HIV testing, chemistry, Chest x-ray
- Consider serology for EBV, CMV, ANA if other relevant supporting symptoms
- Lymph node biopsy if evaluation non-diagnostic

Case 1 - Continued

- 43 year old woman with no significant prior medical history presents for evaluation of enlarged cervical, axillary, and inguinal lymph nodes.

- On evaluation by hematology testing for HIV 1 returned positive
- HIV RNA Viral load 841, 028
- EBV Viral capsid antigen IgG positive, negative monospot and IgM
- EBV Viral load by PCR 10,478
- Right axillary excisional lymph node biopsy performed with EBV positive cells, no evidence of malignancy

Case 2

- 32 year old woman with a history of seasonal allergies who notes painless firm mildly enlarged lymph node for the past eight years. She recently has relocated to the area. A palpable left anterior cervical lymph node measuring approximately ≤ 1 cm is noted on routine physical exam.

- She denies constitutional symptoms and ROS is otherwise negative. Physical exam is significant for no other areas of lymphadenopathy. No hepato-splenomegaly is appreciated. Labs are significant for negative HIV 1/2 serology and normal CBC, CMP, LDH.

- Referred to hematology for evaluation

Approach to Localized Lymphadenopathy

- Anatomic location and size important considerations
- Lymph nodes ≤ 1 cm very unlikely to be malignant[1]
- Lymph node size ≥ 3.4 cm associated with 6-fold higher likelihood of malignancy in recent series[2]
- Younger age, non smoker, and known rheumatologic condition associated with lower likelihood of malignancy[2]

[1]Ferrer R. *Am Fam Physician*. 1998;58(6):1313 [2]Nixon S. et al. *JCO Oncol Pract*. 2020 16(1):e29-e36

Case 2 – continued

- 32 year old woman with a history of seasonal allergies who notes painless firm palpable lymph node.
- Given the size (1 cm) and stability over time reassurance provided with routine annual primary care follow-up recommended

Localized Lymphadenopathy Approach

- Thorough history, including travel and sexual history, and physical exam crucial to guide work-up
- Empiric antibiotics not recommended, empiric corticosteroids should be avoided (compromise diagnostic yield if lymphoma present)
- Location also important to guide work-up
- Supra-clavicular location associated with high risk for malignancy
- Observation for 3-4 weeks reasonable in absence of red flags

Localized Lymphadenopathy Differential Diagnosis

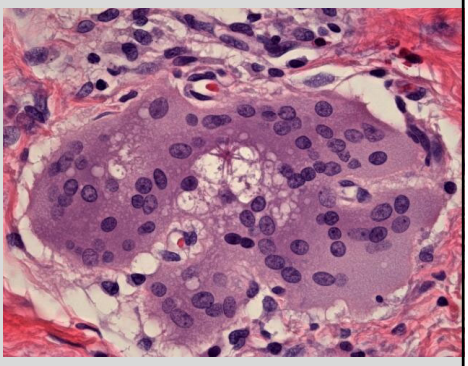
- Inguinal adenopathy:
  - Lower extremity trauma, infection
  - STI
  - Malignancy – lymphoma, skin of lower extremities (melanoma), cervical, vulvar, rectal, ovarian, penile cancer most common malignancies
- Axillary lymphadenopathy:
  - Infection or trauma in arms, breast, or chest wall
  - Cat scratch disease
  - Malignancy – breast, lymphoma most common malignancies

Localized Lymphadenopathy Differential Diagnosis

- Epitrochlear:
  - Infections of hand or arm, infections including syphilis or tularemia, lymphoma most common malignancy
- Sub-occipital, posterior auricular:
  - Most frequently related to scalp infection
- Cervical:
  - Head or neck infections, EBV or CMV infection, toxoplasmosis
  - Most common malignancy in older patients head and neck squamous cell carcinoma, lymphoma most common malignancy in younger patients

Uncommon Systemic Diseases Associated with Lymphadenopathy

- Castleman's disease – localized or multi-centric
- Kikuchi's disease – typically cervical localization with constitutional symptoms
- Kawasaki disease
- Kimura disease
- Progressive transformation of germinal centers
- Rasai-Dorfman disease
- IgG4 related disease
- Sarcoidosis



Multinucleated giant cell containing an asteroid, microscopy. | Wellcome Collection
https://wellcomecollection.org/works/daadvcez/images?id=tx3t62wk

Medications associated with risk for lymphadenopathy (less common)

- Quinidine
- Imatinib
- Allopurinol
- Antibiotics including penicillin, cephalosporines, sulphonomides
- Antihypertensives including hydralazine, atenolol, captopril
- Anti-epileptics including lamotrigine, carbamazepine

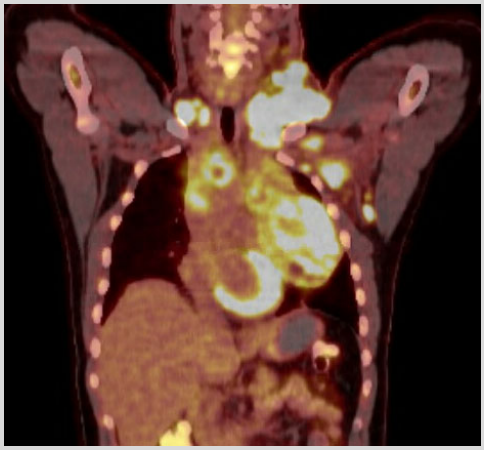
Painting, ca. 1900. Attribution 4.0 International (CC BY 4.0)
https://wellcomecollection.org/works/tebjpwj7/images?id=nhyp8u6g

Case 3

- 23 year old male with no significant prior medical history who presents with gradual enlargement of a mass of the neck for the past three months with associated pruritus and recent night sweats.
- On physical exam 4 x 3 cm left supraclavicular lymph node palpable, 2 x 2 cm bilateral cervical lymph nodes palpable
- Labs significant for normal hemoglobin (14.5), wbc 15.7 (left shift), mild thrombocytosis (397), elevated ESR (59)

Case 3 - continued

- CT Chest with 4.3 x 4.2 x 6.0 supraclavicular lymph node, 11.5 x 9.1 x 11.8 cm anterior mediastinal mass
- Core needle biopsy of supraclavicular lymph node consistent with classical Hodgkin's lymphoma



James Diagnostic Clinic

- Nurse practioner lead multi-modality clinic offering evaluation to coordinate diagnostic evaluation including biopsy in patients with suspected but unconfirmed malignancy

Considerations for Lymph Node Biopsy

- FNA useful for initial evaluation in cases of carcinoma, rarely diagnostic in cases of lymphoma
- For lymphoma excisional lymph node biopsy remains gold standard
- Core needle biopsy is alternative option for diagnosis and has become increasing common for logistical reasons
- Core needle biopsy may miss representative region and in some cases excisional biopsy is still necessary to establish the diagnosis

Hodgkin's Lymphoma Pearls

- Pruritis can be presenting symptoms (similar to other B symptoms such as fever, night sweats, weight loss)
- Histologic findings may be confounded by corticosteroids, granulomatous reaction may be seen without clear Reed-Sternberg cells, important to maintain suspicion in appropriate context

Summary Points

- HIV testing essential in initial evaluation generalized lymphadenopathy
- FNA useful in diagnosis of carcinoma but not sufficient in evaluation for lymphoma, core needle or ideally excisional lymph node biopsy necessary
- **Avoid empiric corticosteroids for undifferentiated lymphadenopathy**

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Novel Treatments in Lymphoma: CAR T-cells and Bispecific T-cell Engagers

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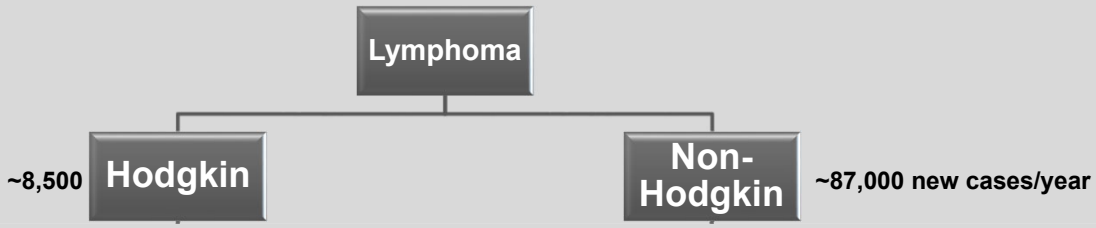
Outline

- Brief overview of lymphoma subtypes
- Treatment approach for diffuse large B cell lymphoma
- Treatment with CAR T cells and Bispecific T-cell engagers (BiTEs)
  - Mechanism of action
  - Efficacy
  - Toxicities
  - Future Directions

Lymphoma Classification (Simplified)



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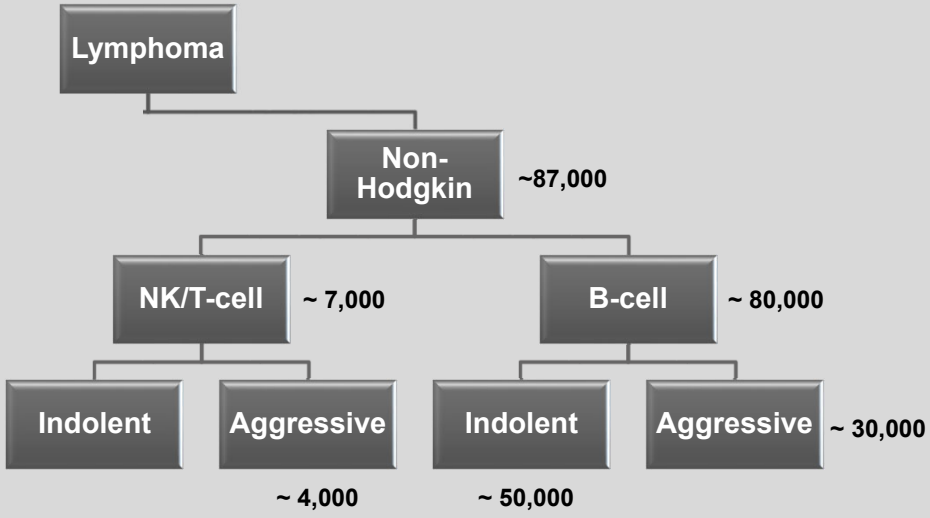


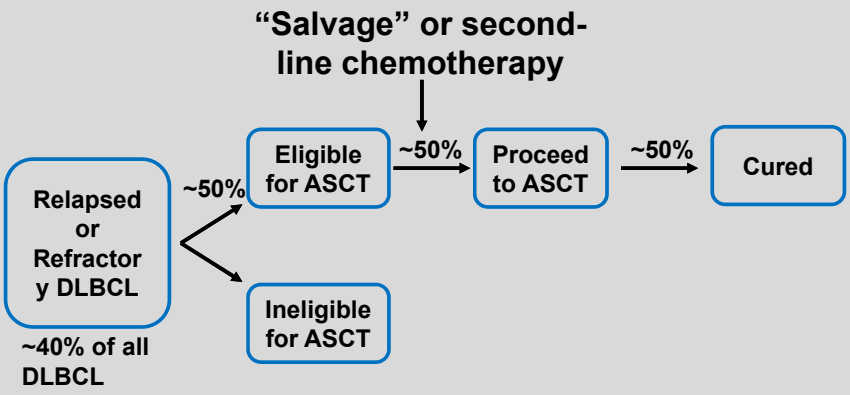
Diffuse Large B Cell lymphoma (DLBCL)

- Most common type of lymphoma, ~ 28,000 new cases annually in the USA
- Typical presentation: rapidly progressing lymphadenopathy, extranodal involvement is common, B symptoms (30%)
- Diagnosis based on pathology review (excisional biopsy > core-needle, not FNA)
- Staging work-up: LDH, HIV & remote hepatitis panel, PET/CT, echo, +/- bone marrow biopsy

DLBCL - Treatment

- Potentially curable regardless of stage
- Frontline treatment has been mostly the same for the last ~ 20 years: R-CHOP
  - Rituximab (anti-CD20 monoclonal antibody)
  - Cyclophosphamide
  - Doxorubicin (hydroxydaunomycin)
  - Vincristine (oncovin)
  - Prednisone (100 mg x 5 days)
- ~ 60% of patients with DLBCL are cured with R-CHOP

Treatment of Relapsed or Refractory DLBCL



Only a minority of patients with relapsed or refractory DLBCL get cured

ASCT = autologous stem cell transplantation

Adapted from Maddocks, K. American Society of Hematology. Education Program, 2020, 101–106.

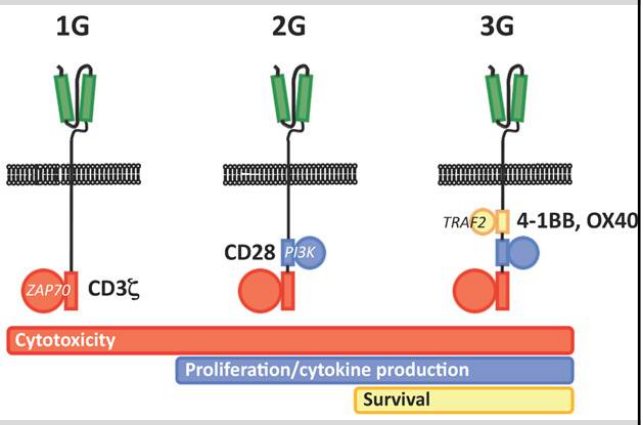
"New" Treatment Options for Relapsed/Refractory DLBCL

- **CAR T-cells. Three products FDA-approved**
- **Bispecific T cell engagers (BiTEs). Not approved (yet)**

- Bendamustine, rituximab + polatuzumab: FDA-approved June 2019
- Tafasitamab + lenalidomide: FDA-approved July 2020
- Selinexor: FDA-approved June 2020

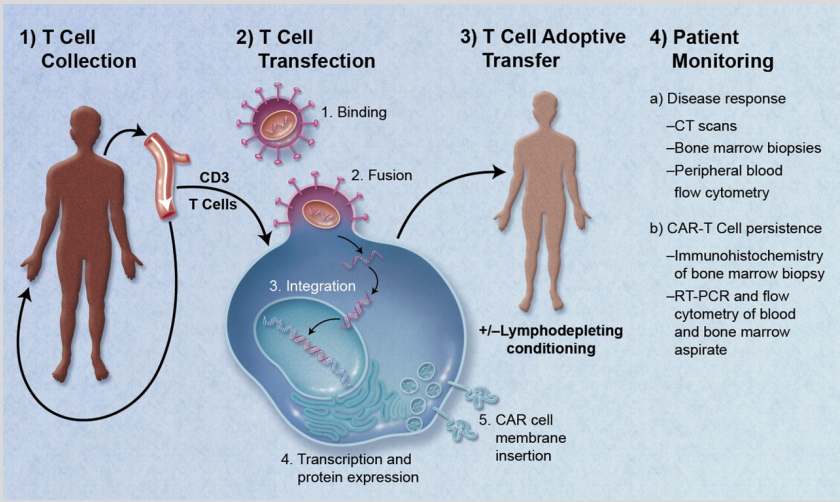
Chimeric Antigen Receptor (CAR) T cells

- T cells transfected by a viral vector to introduce a construct coding for a CAR into the T cell's DNA
- The CAR mediates binding to the target tumor antigen, independent of MHC, and subsequently activates the T cell and induces target cell killing



Casucci M & Bondanza A, J Cancer 2011; 2:378-382

Chimeric Antigen Receptor (CAR) T cells



Jacobson C & Ritz J, Blood (2011) 118 (18): 4761–4762

CAR T Cells

- Three CAR T cell products are currently approved in relapsed/refractory DLBCL:
  - Axicabtagene ciloleucel (axi-cel) (October 2017)
  - Tisagenlecleucel (tisa-cel) (May 2018)
  - Lisocabtagene maraleucel (liso-cel) (March 2021)
- All three are autologous anti-CD19 CAR T cells

- Other approvals (all anti-CD19)
  - Tisa-cel in pediatric and young adult patients with relapsed **acute lymphoblastic leukemia**
  - Brexucabtagene autoleucel in relapsed **mantle cell lymphoma** (July 2020)
  - Axi-cel in relapsed **follicular lymphoma** (March 2021)

Efficacy in Relapsed/Refractory DLBCL

	Tisa-cel	Axi-cel	Liso-cel
No of patients infused	93	101	269
Age, median (range)	56 (22-76)	58 (23-76)	63 (54–70)
≥3 prior therapies	52%	69%	51%
Prior ASCT	49%	21%	33%
Overall response rate	52%	83%	73%
Complete response (CR) rate	40%	58%	53%
Progression-free survival			
- All patients	-	2- year 39%	1-year 44%
- In CR	1-year 83%	2- year 72%	1-year 65%

Schuster SJ et al, NEJM 2018. Neelapu et al, NEJM 2017. Locke et al, Lancet Oncol 2019. Abramson et al, Lancet 2020.

CAR T-cell Toxicities

1. Cytokine release syndrome (CRS)
2. Immune effector cell-associated neurotoxicity syndrome (ICANS)
3. B-cell aplasia and hypogammaglobinemia
4. Prolonged myelosuppression and pancytopenia

Cytokine Release Syndrome

- Caused by the release of proinflammatory cytokines from T-cells and other immune cells
- Typically occurs in the first few days after CAR T-cell infusion
- Manifests with fever, tachycardia, hypoxia and hypotension
- Hemodynamic instability and end-organ dysfunction occur in severe cases (in up to 22% of patients)
- Management:
  - Intensive monitoring and supportive care
  - High-dose corticosteroids
  - Tocilizumab (anti-IL-6 receptor antibody)

Immune Effector Cell-associated Neurotoxicity Syndrome (ICANS)

- Pathophysiology is less-well understood, likely caused by a supraphysiologic immune-activation state.
- Commonly follows CRS
- Variable clinical presentations ranging from mild confusion and tremors to aphasia, obtundation, seizures, cerebral edema, and coma.
- Severe cases occur in up to 31% of patients.
- Management:
  - Supportive care
  - Corticosteroids
  - Antiepileptics

Future Directions

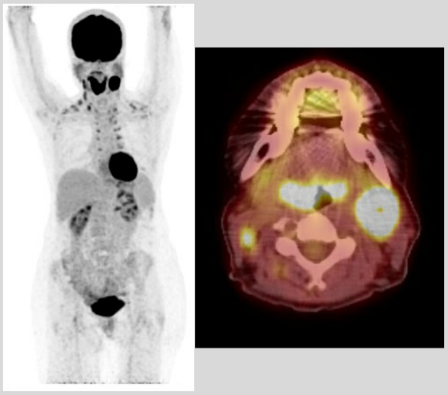
- "Third-generation" CAR-T: Dual costimulatory domains with enhanced proliferation and persistence capabilities
- Combination therapies to reduce immune evasion and CAR T-cell exhaustion
- Dual antigen targeting to reduce CD19-antigen loss (e.g. CD19/CD22 and CD19/CD20)
- "Armored" CAR T-cells: secrete proinflammatory cytokines or express ligands that stimulate not only CART but also other immune cells.
- Allogenic CAR T-cells and natural-killer (NK) CAR cells
- CAR T-cells in other hematologic malignancies (MM) and ? solid tumors.

Case Presentation

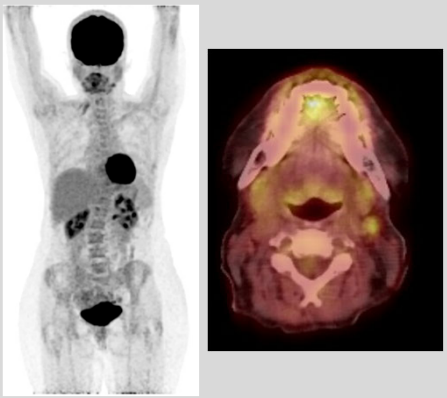
- A 57 year old female presented with rapidly progressing inguinal lymphadenopathy in 2018.
- Biopsy confirmed DLBCL, transformed from lymphoplasmacytic lymphoma
- PET/CT with diffuse lymphadenopathy above and below the diaphragm as well as bone marrow involvement (stage IV).
- Received R-CHOP x 6 cycles (achieved complete response)
- Underwent consolidative ASCT 2019
- Developed cervical lymphadenopathy in 2020. Biopsy confirmed DLBCL

Case Presentation #2

- Insurance denied coverage for CAR T-cells
- Enrolled on a phase I clinical trial of a CD20 x CD3 bispecific antibody



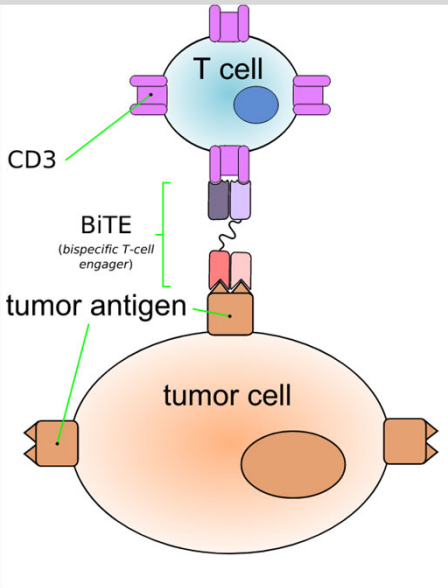
Baseline (at relapse)



Two months later

Bispecific T cell engagers (BiTEs)

- Small linker peptides connecting two different single-chain variable fragments with one fragment designed to bind to CD3 on T cells and the other to a tumor associated antigen
- The simultaneous binding of CD3 on T cells and the tumor associated antigen triggers T-cell mediated cytotoxicity of the malignant cell.



https://commons.wikimedia.org/wiki/File:BiTE_antibody_01.svg

Common Features of BiTEs

- Toxicity: Cytokine release syndrome (CRS)
  - Require inpatient stay initially
  - Mitigation strategies: Split and step-up dosing; Premedications: steroids; SQ formulation
  - Generally predictable and manageable; grade ≥3 CRS less common than with CAR-T
- "Off-the-Shelf" therapies
- Duration of treatment is still unclear
- Limited data on response durability

Summary of Efficacy and Safety of Bispecific Antibodies in r/r NHL

Bispecific Antibody	Population	ORR (n evaluable)	CR rate	CRS (Grade ≥3)
Odronextamab[1]	- r/r FL	90% (30)	70%	61% (7%)
	- r/r DLBCL, no prior CAR-T	55% (11)	55%	
	- r/r DLBCL, post CAR-T	33% (24)	21%	
Mosunetuzumab[2]	- r/r indolent NHL	63% (67)	43%	29% (1%)
	- r/r aggressive NHL	37% (124)	19%	
Epcoritamab[3]	- r/r FL	90% (10)	50%	59% (0%)
	- r/r DLBCL	68% (22)	46%	
Glofitamab[4]	- r/r indolent NHL	67% (18)	54%	64% (4%)
	- r/r aggressive NHL	61% (23)	54%	

1. Bannerji et al. ASH 2020. 2. Schuster et al. ASH 2019 3. Hutchings el al. ASH 2020. 4. Hutchings el al. ASH 2020

Future Directions

- ? Approval in B-cell NHLs
- In combination with chemotherapy and other novel agents
- In earlier lines of treatment (e.g. in elderly/frail patients with previously untreated DLBCL)