Case 11. NHL/HD/MM/ MS4th
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Abdallah Al-Abbadi.MD.FRCP.FRCPath
Feras Fararjeh MD

NHL/ HD(Lymphoma): common features

1- Lymph node enlargement: painless, decides stage

2- May be associated with B-symptoms: fever, night sweats, weight loss

3- Compression symptoms may occur

4- Extra-nodal involvement

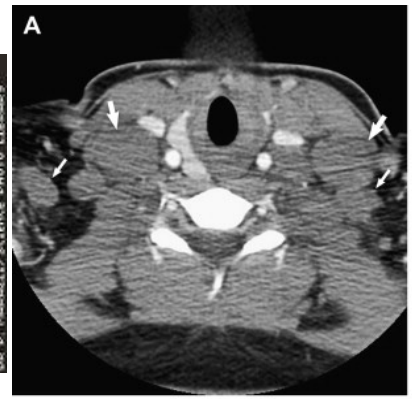
5- Needs LN BX for diagnosis

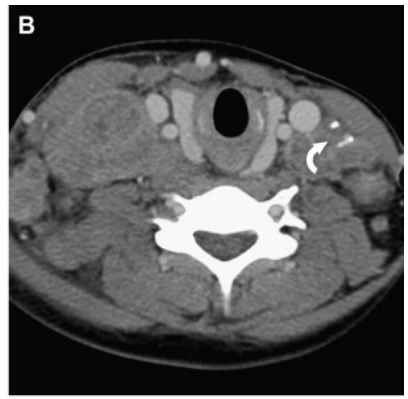
6- Each has different histology types

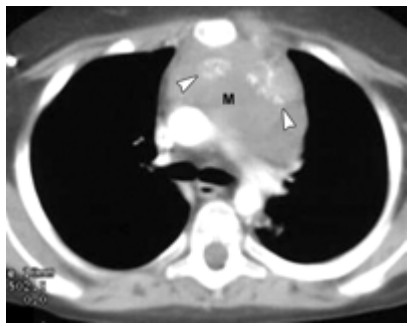
7- Both have similar staging system

Case 11: NHL

27 yr old male, presented with weight loss, low grade fever and profuse sweating for the last 6 wks.P/E, he had generalized lymphadenopathy, hepato-splenomegaly and enlarged tonsils.



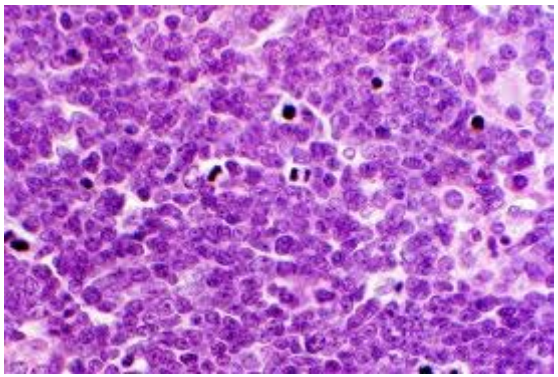


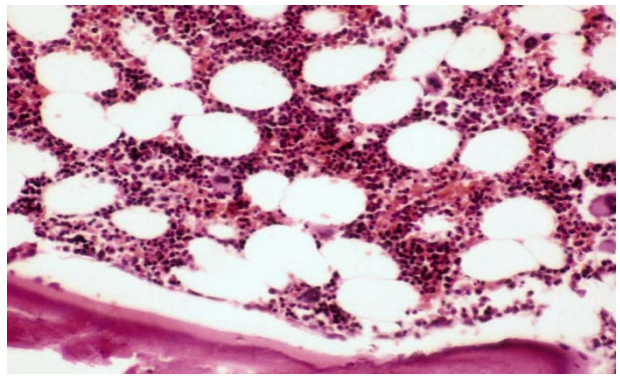


Case 11

Hb 10g/dl, MCV 100, WBC 14k, Normal diff, Plt 196k, LDH 820, S.uric .a 7.5, Creat, Ca, PO4 Nl,

LN.Bx

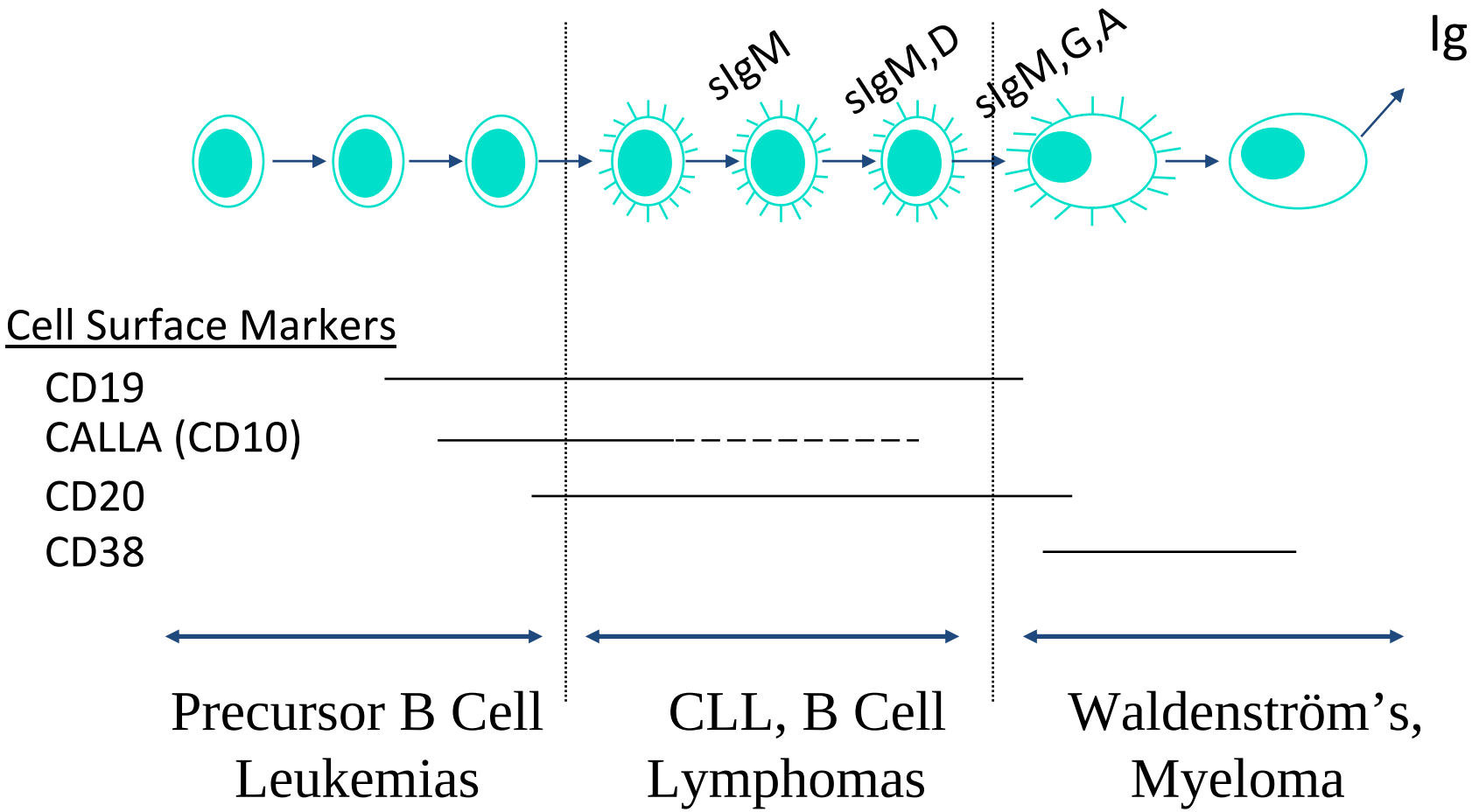




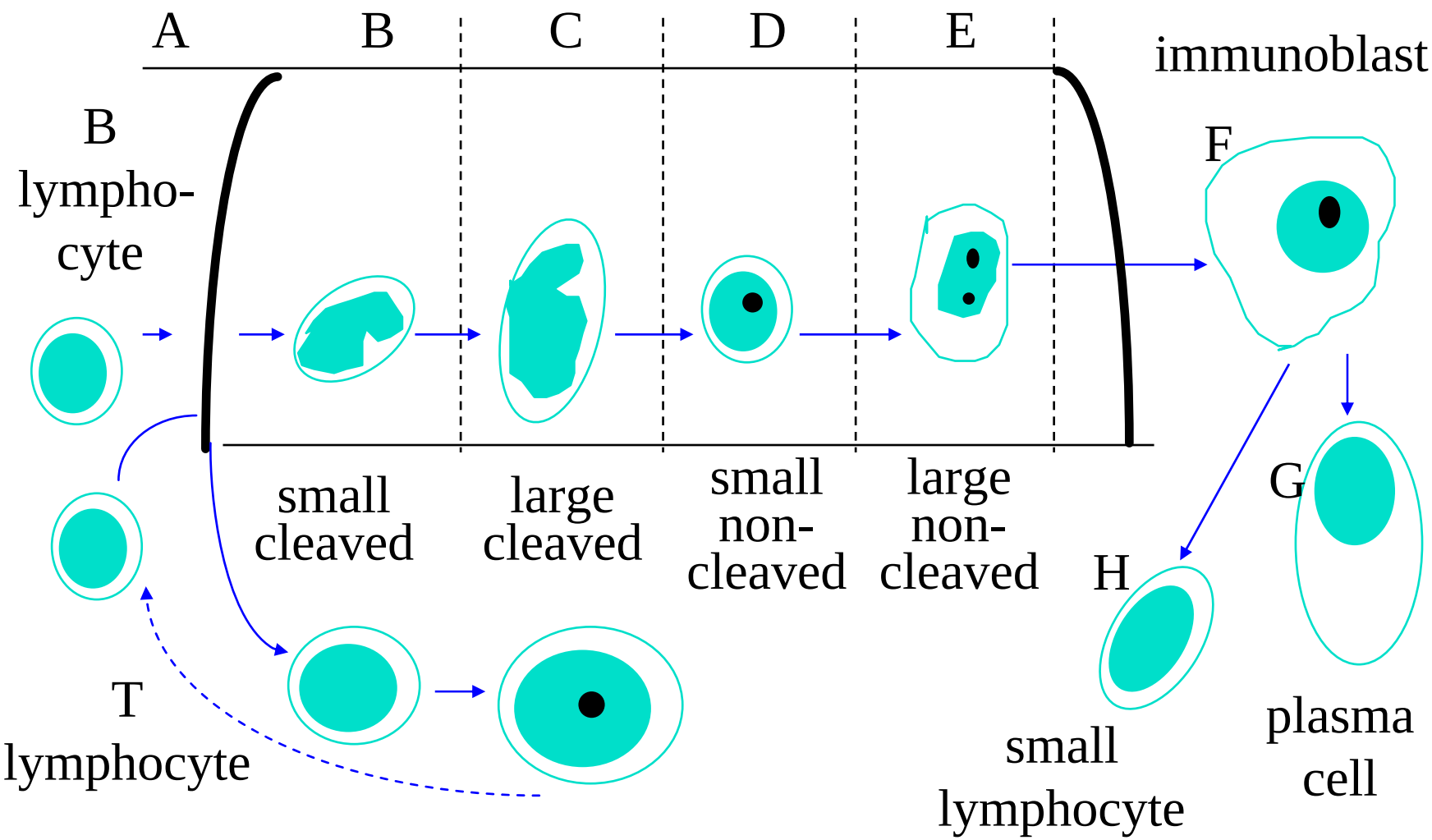
NHL

- The types of non- Hodgkin's lymphoma reflect the developmental stages of lymphocytes.
- Each type of lymphoma can be viewed as a lymphocyte arrested at a certain stage of development and transformed into a malignant cell.
- 85% B cell origin, the rest T or null cell.

B CELL DIFFERENTIATION



MATURATION IN LYMPHOID FOLLICLE



Etiology of NHL

- Idiopathic
- Immune suppression
  - congenital (Wiskott-Aldrich)
  - organ transplant (cyclosporine)
  - AIDS
  - increasing age
- DNA repair defects
  - ataxia telangiectasia
  - xeroderma pigmentosum

Etiology of NHL

- Chronic inflammation and antigenic stimulation
  - *Helicobacter pylori* inflammation, stomach
  - *Chlamydia psittaci* inflammation, ocular adnexal tissues
  - Sjögren's syndrome
- Viral causes
  - EBV and Burkitt's lymphoma
  - HTLV-I and T cell leukemia-lymphoma
  - HTLV-V and cutaneous T cell lymphoma
  - Hepatitis C

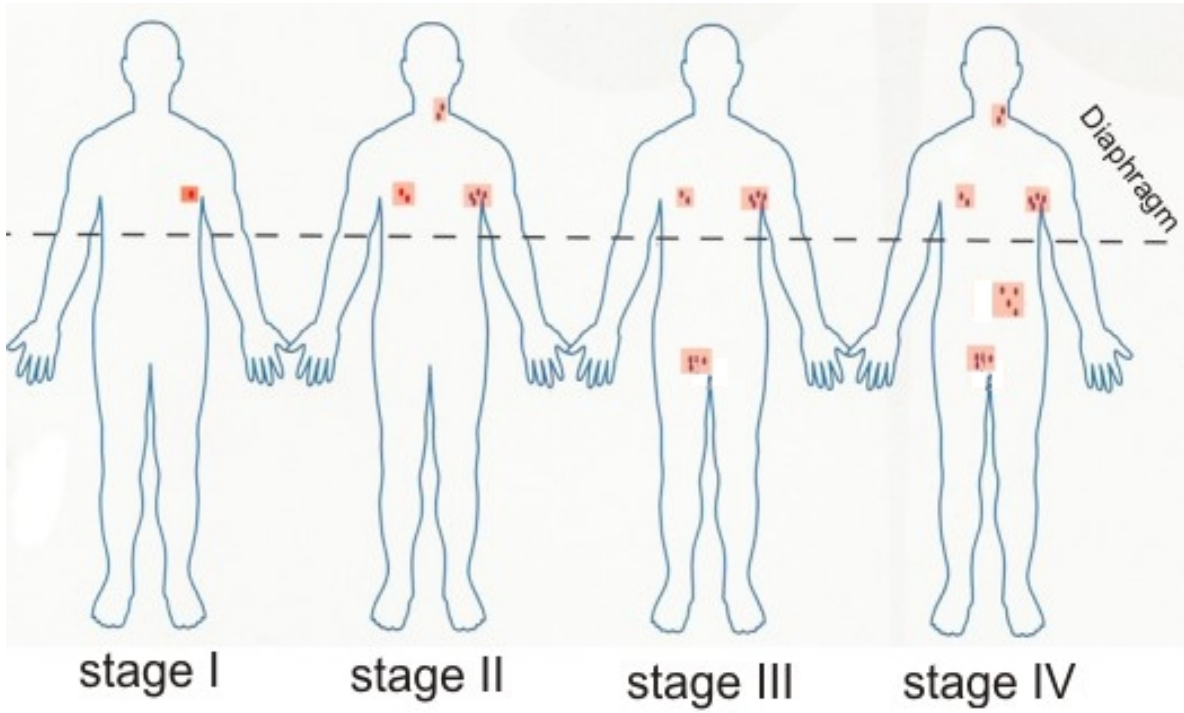
Diagnosis of NHL

- Chromosome changes
  - 14;18 translocation in follicular lymphoma
    - *bcl-2* oncogene
  - t(8;14), t(2;8), t(8;22) in Burkitt's lymphoma
    - *c-myc* oncogene
  - t(11;14) in mantle cell lymphoma
    - *cyclin D1* gene

Staging: Ann Arbor

I. 1 lymph node region or structure
II. >1 lymph node region or structure, same side of diaphragm
III. Both sides of diaphragm
IV. Extranodal sites diffuse, beyond “E” designation

Staging System for Lymphomas
(ANN ARBOR CLASSIFICATION)



Revised European-American Lymphoma (REAL) Classification: B-Cell Neoplasms

Indolent	Aggressive	Very Aggressive
• CLL/SLL	• PLL	• Precursor B-lymphoblastic lymphoma/Leukemia
• Lymphoplasmacytic/ IMC/WM	• Plasmacytoma/ Multiple myeloma	• Burkitt's lymphoma/ B-cell acute leukemia
• HCL	• MCL	• Plasma cell leukemia
• Splenic marginal zone lymphoma	• Follicle center lymphoma, follicular, grade III	
• Marginal zone lymphoma – Extranodal (MALT) – Nodal	• DLCL	
• Follicle center lymphoma, follicular, grade I-II	• Primary mediastinal large B-cell lymphoma	
	• High-grade B-cell lymphoma/Burkitt's-like	

Hiddemann. *Blood.* 1996;88:4085.

Prognostic factors in non-Hodgkin's lymphoma

- ***Adverse factors:***
- ***Age > 60 years***
- ***Stage III or IV, i.e. advanced disease***
- ***High serum lactate dehydrogenase level***
- ***Performance status (ECOG 2 or more)***
- ***More than one extranodal site involved***

Treatment Options in Advanced Indolent Lymphomas

- ***Observation only.***
- ***Radiotherapy to site of problem.***
- ***Systemic chemotherapy***
  - ***oral agents: chlorambucil and prednisone***
  - ***IV agents: CHOP, COP-R, FC-R***
- ***Antibody against CD20: rituximab***
- ***Stem cell or bone marrow transplant.***
- *New monoclonal antibodies*

Reasons to Treat in Advanced Indolent Lymphomas

- Constitutional symptoms
- Anatomic obstruction
- Organ dysfunction
- Cosmetic considerations
- Painful lymph nodes
- Cytopenias

Treatment Options:
Aggressive Lymphomas

Aggressive

- Diffuse large cell lymphoma, large cell anaplastic lymphoma, peripheral T cell lymphoma.

Very Aggressive

- Burkitt's lymphoma and lymphoblastic lymphoma.

Treatment Options for Aggressive Lymphomas

*potentially curable

*disseminates through bloodstream early

*must use systemic chemotherapy

- ❖CHOP-R x ?8 cycles
- ❖CHOP-R x 3 cycles followed by radiotherapy
- *Bone marrow transplantation for some cases
- *New monoclonal antibodies

Standard Treatment for Aggressive Lymphomas

- Systemic chemotherapy
  - CHOP-R
- ± Intrathecal chemotherapy
  - AIDS patients and CNS involvement
- ± Radiotherapy
  - Spinal cord compression, bulky disease

??BMT

Burkitt's Lymphoma

- Treated with multidrug regimen similar to pediatric leukemia/lymphoma regimens.
- BMT

Hodgkin's Disease/Lymphoma Treatment

With appropriate treatment about 85% of patients with Hodgkin's disease are curable

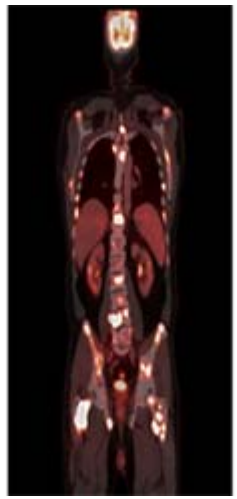
- **I A,B chemo.Radiation Therapy in selected cases**
- **II A Chemo.XRT in selected cases**
- **IIB; IIIA,B; IVA,B Chemo (+/- radiotherapy in selected cases)**

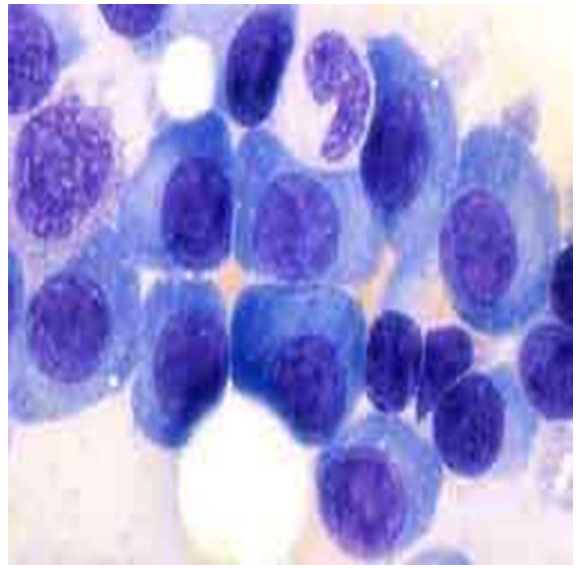
Chemotherapy Regimens for Hodgkins disease

- MOPP
  - **M**echlorethamine, **O**ncovin, **P**rocarbazine, **P**rednisone
- ABVD
  - **A**driamycin, **B**leomycin, **V**inblastine, **D**acarbazine
- BEACOPP
- BMT for relapse or resistance

Case 11 B: Multiple Myeloma

67 yr old male has been complaining of back pain for several months. He recently noticed exertional dyspnea. He was admitted because of sever pain in his arm.

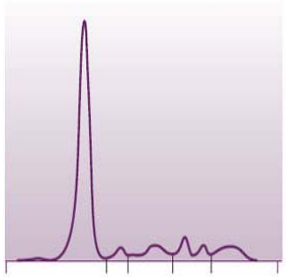




Case 11 B Investigation and Diagnosis

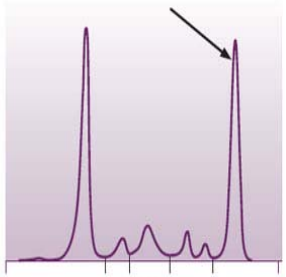
1- Hb 8 g/dl, normocytic normochromic, WBC 8K, Plt 180K, ESR 112mm/1st hr. Bld film. B2-microglobulin 6mg/l, serum albumin 3 g/dl,P/E 1gG 15 g/dl and IF/ igGK

2- Multiple myeloma igG/k stage III (C).



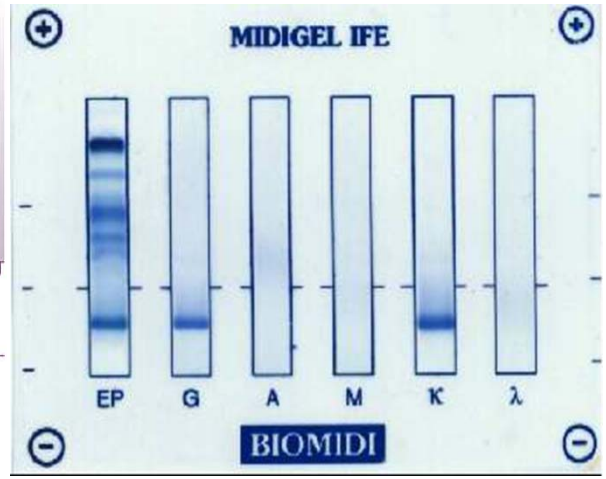
A/G 2.32
T.P.: 7

Fractions	%	Ref. %	g/dl	Ref. g/dl
Albumin	69.9	52.9–66.9	4.9	3.7–4.9
Alpha	3.5	3.0–5.8	0.2	0.2–0.4
Alpha 2	8.8	7.5–13.4	0.6	0.5–1.0
Beta	9.3	8.5–13.7	0.7	0.6–1.0
Gamma	8.5	8.8–19.2	0.6	0.6–1.4



A/G 0.67
T.P.: 8.2

Fractions	%	Ref. %	g/dl	Ref. g/dl
Albumin	40.2	52.9–66.9	3.3 L	3.7–4.9
Alpha	4.8	3.0–5.8	0.4	0.2–0.4
Alpha 2	11.0	7.5–13.4	0.9	0.5–0.9
Beta	7.8	8.5–13.7	0.6	0.6–1.0
Gamma	36.2	8.8–19.2	3.0 H	0.6–1.4



Clinical Features

- Symptoms related to BM infiltration: bone pain, osteolytic lesions and fractures, anemia, hypercalcemia
- Secretion of abnormal proteins: renal and neurological or visceral manifestations
- Hyperviscosity syndrome
- Recurrent infections
- Amyloidosis

Related organ or tissue impairment

B*uy* – Lytic bone lesions – visible on x-ray in **85**% of patients. **Hint** – Osteoclasts activated, not osteoblasts.

C – Hypercalcemia (Ca > 11 mg/dL)

A – Anemia (Hb < 10)

V – Hyperviscosity – especially common in the rare IgM secreting myeloma

I – Bacterial infections (>2)

A – Amyloidosis

R – Renal (Crt > 1.96 mg/dL): **HINT** – occurs 50% of the time because most often the light chains are toxic to the tubules.

These are the end organ manifestations of myeloma

Clinical features

- common tetrad of multiple myeloma is ***CRAB***
  - **C = Calcium (elevated)**
  - **R = Renal failure**
  - **A = Anemia**
  - **B = Bone lesions**

Active Multiple Myeloma

Both criteria must be met:

1- Clonal bone marrow plasma cells 10% or biopsy-proven bony or extramedullary plasmacytoma

2- Any one or more of the CRAB features

Smouldering MM

Both criteria must be met:

Serum monoclonal protein (IgG or IgA) 3 g/dL, or urinary monoclonal protein 500 mg per 24 h and/or clonal bone marrow plasma cells 10%–60%

Absence of myeloma defining events or amyloidosis Mu

Diagnosis and Staging Workup

- Bone marrow biopsy and aspirate
- Serum protein electrophoresis and immunofixation
- Skeletal survey/ MRI/PET Scan
  - Plain x-rays are better than bone scan.
  - Lytic lesions do not show up well on bone scan.
- Quantitative immunoglobulins

Prognostic Factors

International staging system

I (good prognosis)

Serum albumin > 3.5 g/dl

Serum β2 microglobulin < 3.5 mg/dl

II

Not I or III

III

β2 microglobulin: >5.5 mg/dl

Categories with Potential Prognostic Significance

Factor	Abnormality	Median Survival
	[illegible]	5 – 23 mos
Surface Markers	CD38+/CD45- [illegible] Peripheral blood	>10 cells/uL 37 mos
Kinetics	S phase 1- 3% S phase > 3%	22 mos 12 mos
Conventional cytogenetics	Deletion 13	15 mos
FISH	t(4;14)	29 mos

Gertz, Morie A. , (2007) 'Relevant prognostic features of multiple myeloma and the new International Staging System', Leukemia and Lymphoma, 48:3, 458 - 468

Treatment of Multiple Myeloma

<u>Standard Chemotherapy</u>

- Dexa and Thalidomide
- Dexa and Bortezomib(Velcade)/ Lenalidomide
- Melphalan and prednisone
- <u>High Dose Chemotherapy</u>

with Bone marrow transplant (auto)