VASILE MUSTEATA, MD, PhD, MPH,
associate professor;
Discipline of Hematology,
State University of Medicine
and Pharmacy "N. Testemitanu"

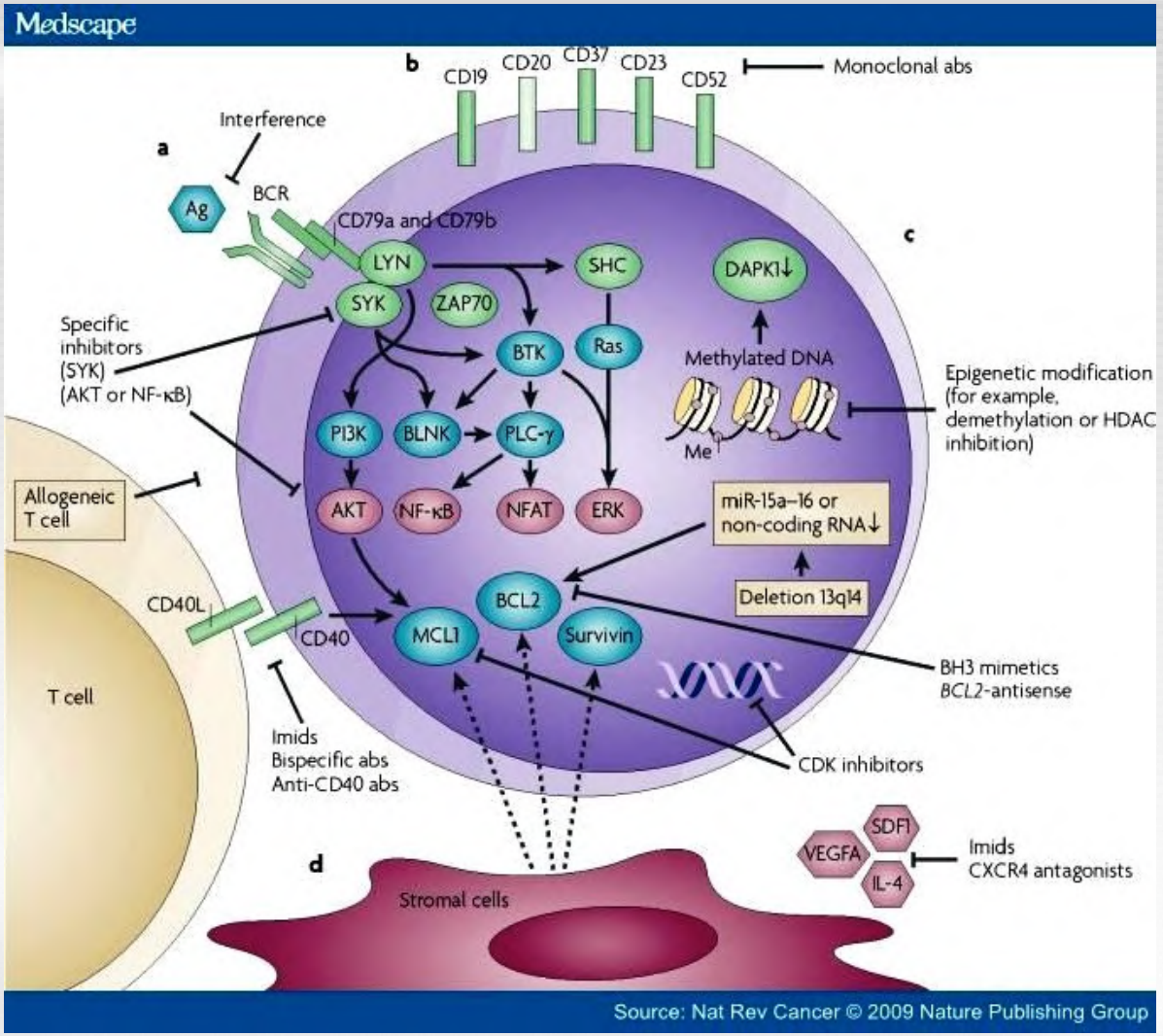
CHRONIC LYMPHOCYTIC LEUKEMIA
MULTIPLE MYELOMA
MACROGLOBULINEMIA WALDENSTRÖM

CHISINAU - 2020

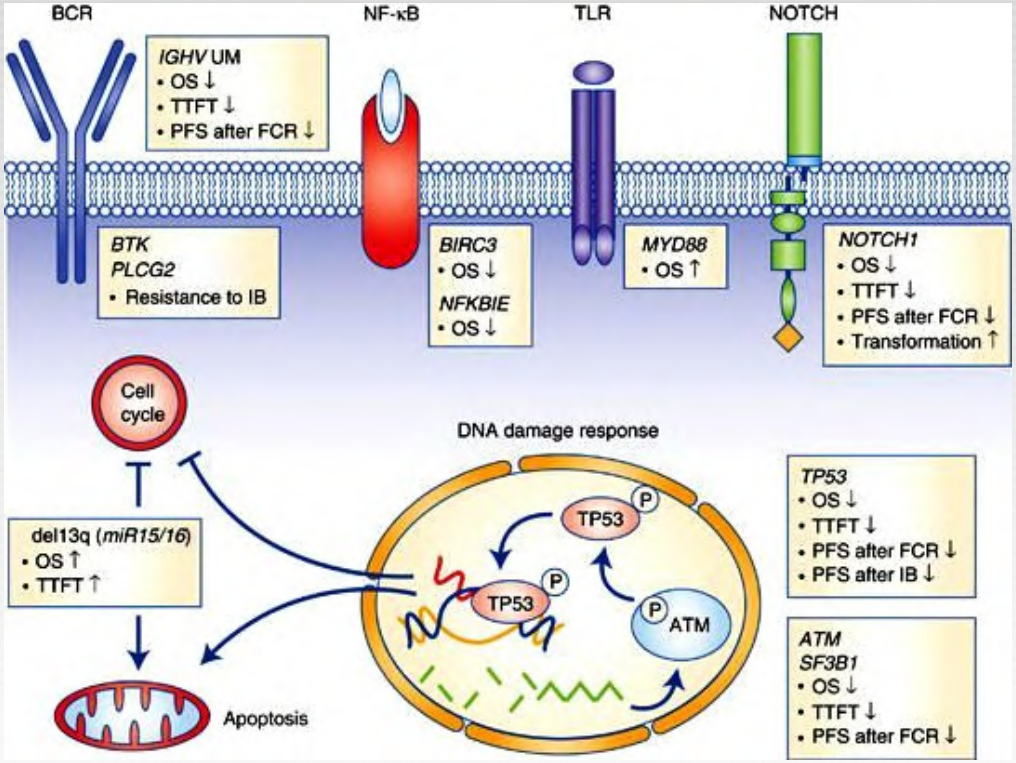
***CHRONIC LYMPHOCYTIC LEUKEMIA (*CLL*)* is a lymphoproliferative disorder, characterized by the accumulation of mature-appearing lymphocytes in the blood, marrow, lymph nodes, and in the spleen. CLL is the most common form of leukemias in North America and Europe, but is extremely rare in the Orient. The incidence of CLL in Moldova is 1.2, in USA – 1.3 – 2.2, in Poland – 1.0, in Japan – 0.08 per 100000 population. The disease typically occurs in older patients, with the highest incidence being in those aged 50 to 55 years, and affects men twice as often as women (Dighiero G., Travade P., Chevret S. et al., 1991).**

In most cases (94 - 95%), the cells are monoclonal B lymphocytes, although T-cell CLL can occur rarely (5 - 6%).

PATHOGENESIS OF CLL



PATHOGENESIS OF CLL



Source: British Journal of Cancer 2016, 114: 849–854

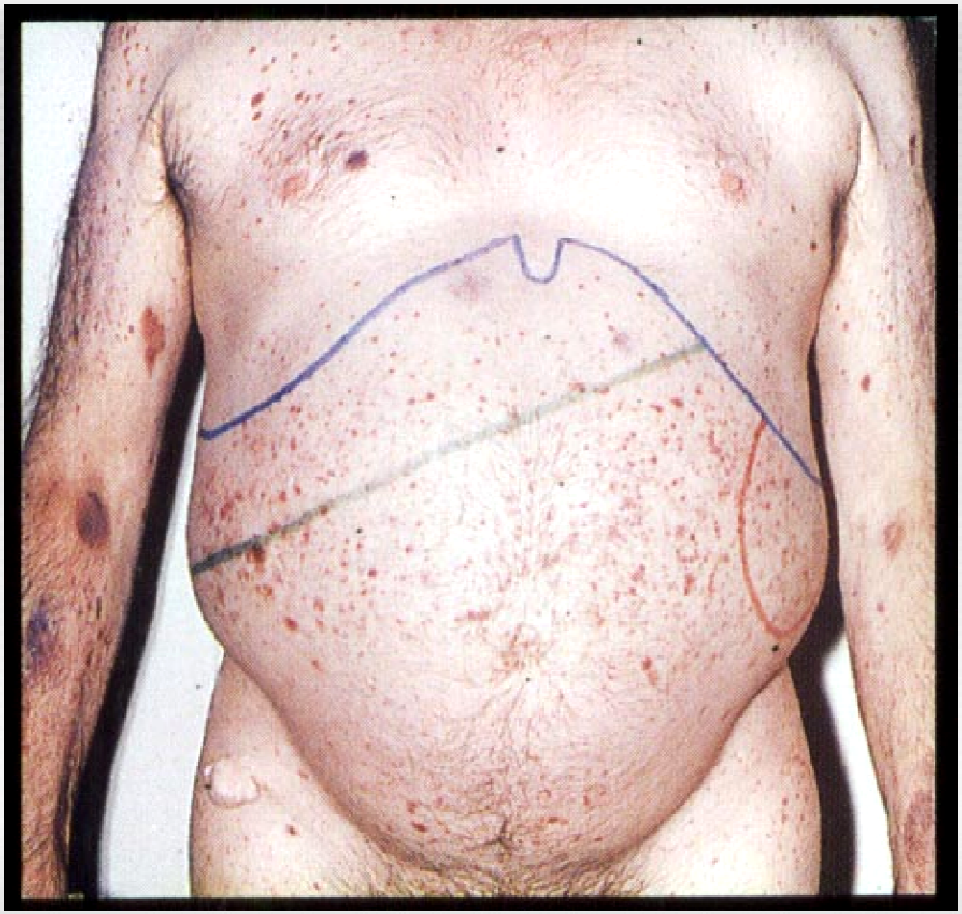
STAGING OF CLL

INITIAL STAGE: **Patients are asymptomatic. Lymph nodes, liver, and spleen are not palpable. Leukocyte count is less than 30.0 x 10^9/l. Moderate blood lymphocytosis (50 – 60%).**

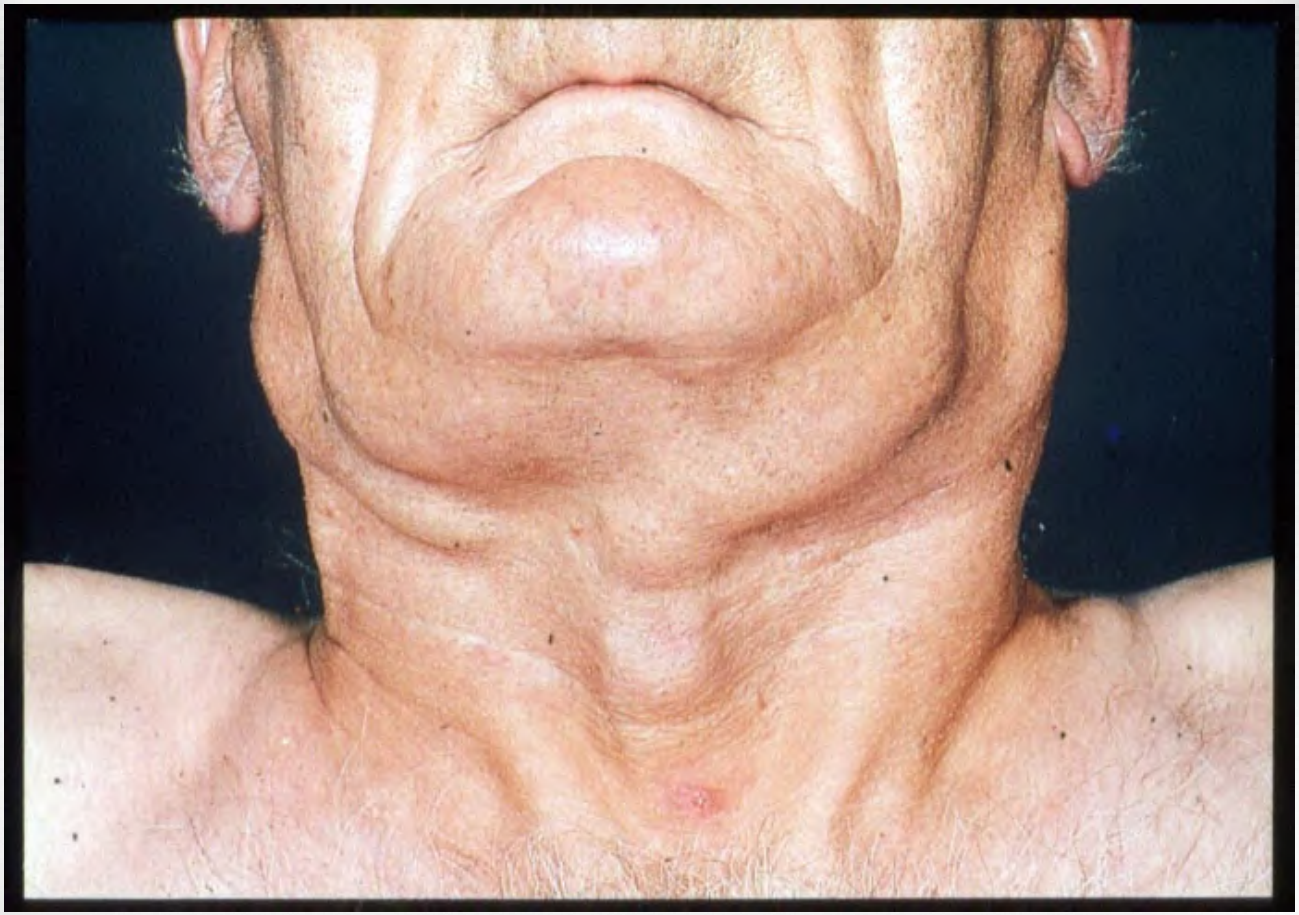
UNFOLDED STAGE: **The majority of patients are symptomatic, and have enlarged lymph nodes, as well as splenomegaly. The lymph nodes are usually discrete, elastic, freely movable and nontender. Hepatomegaly may occur. Leukocyte count exceeds 30.0 x 10^9/l and may reach 500 – 600 x 10^9/l. Lymphocyte count increases to 80 – 90%. Anemia and thrombocytopenia can develop during the course of the disease and are usually related to autoimmune destruction and to marrow infiltration by lymphoid cells.**

TERMINAL STAGE: **Somatic decompensation of patients. The lymph nodes, liver, and the spleen are considerably enlarged. Sarcomatous growth develops frequently. Blast crisis is uncommon.**

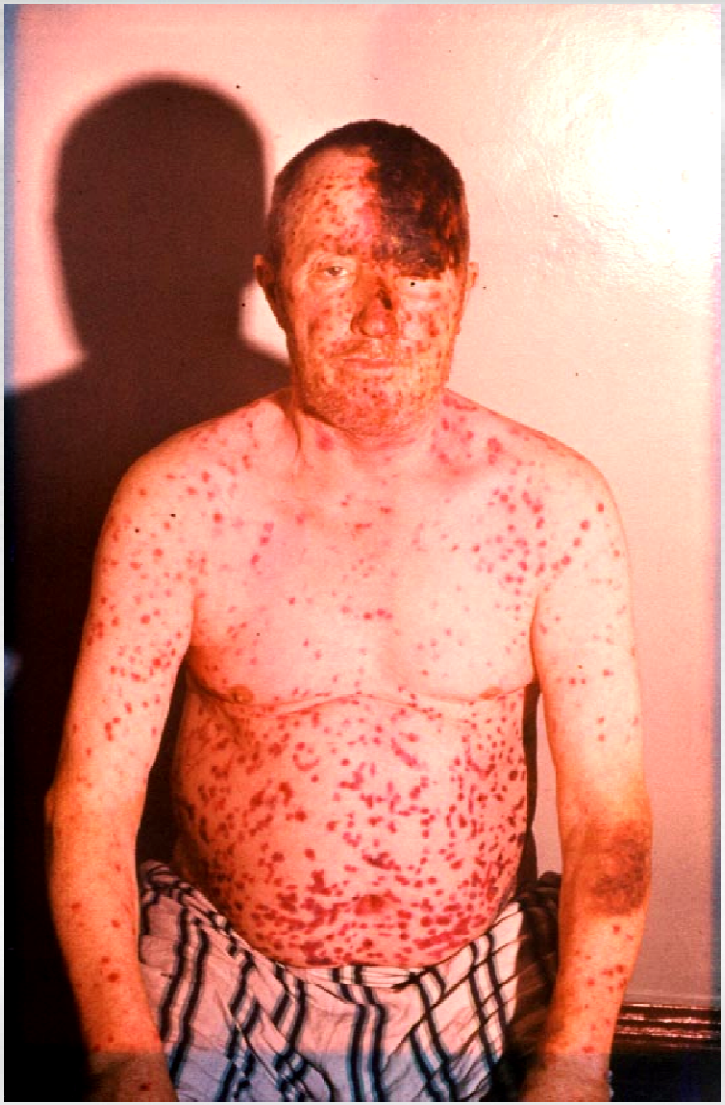
CLINICAL EXAMINATION OF PATIENT WITH CHRONIC LYMPHOCYTIC LEUKEMIA



LYMPH NODE ENLARGEMENT IN CHRONIC LYMPHOCYTIC LEUKEMIA



HERPES ZOSTER IN PATIENT WITH CHRONIC LYMPHOCYTIC LEUKEMIA



BLOOD COUNT IN CHRONIC LYMPHOCYTIC LEUKEMIA

Leucemie limfocitară cronică

Hemoglobina (g/l)	132	122	123
Eritrocite (10^{12}/l)	4,05	4,0	3,6
Leucocite (10^{9}/l)	22,8	45,0	145,0
Celule blastice (%)	—	—	—
Promielocite (%)	—	—	—
Mielocite (%)	—	—	—
Metamielocite (%)	—	—	—
Nesegmentate (%)	—	1	1
Segmentate (%)	7	9	8
Eozinofile (%)	1	—	—
Bazofile (%)	—	—	—
Prolimfocite (%)	—	—	1
Limfocite (%)	91	90	90
Monocite (%)	1	—	—
Trombocite (10^{9}/l)	312,0	360,0	180,0
VSH (mm/oră)	12	10	40

RAI CLINICAL STAGING SYSTEM FOR CHRONIC LYMPHOCYTIC LEUKEMIA

Risk group, stage	Features at diagnosis	Median survival (months)
Low risk		
Stage 0	Blood and marrow lymphocytosis	>120
Intermediate risk		
Stage I	Lymphocytosis and adenopathy	108
Stage II	Lymphocytosis and splenomegaly or hepatomegaly, with or without adenopathy	94
High risk		
Stage III	Lymphocytosis and anemia (Hb <11 g/dL)	60
Stage IV	Lymphocytosis and thrombocytopenia (platelets <100,000/μL)	60

*Modified from Dighero G, Binet J-L. When and how to treat chronic lymphocytic leukemia. N Engl J Med. 2000;343:1799–801.

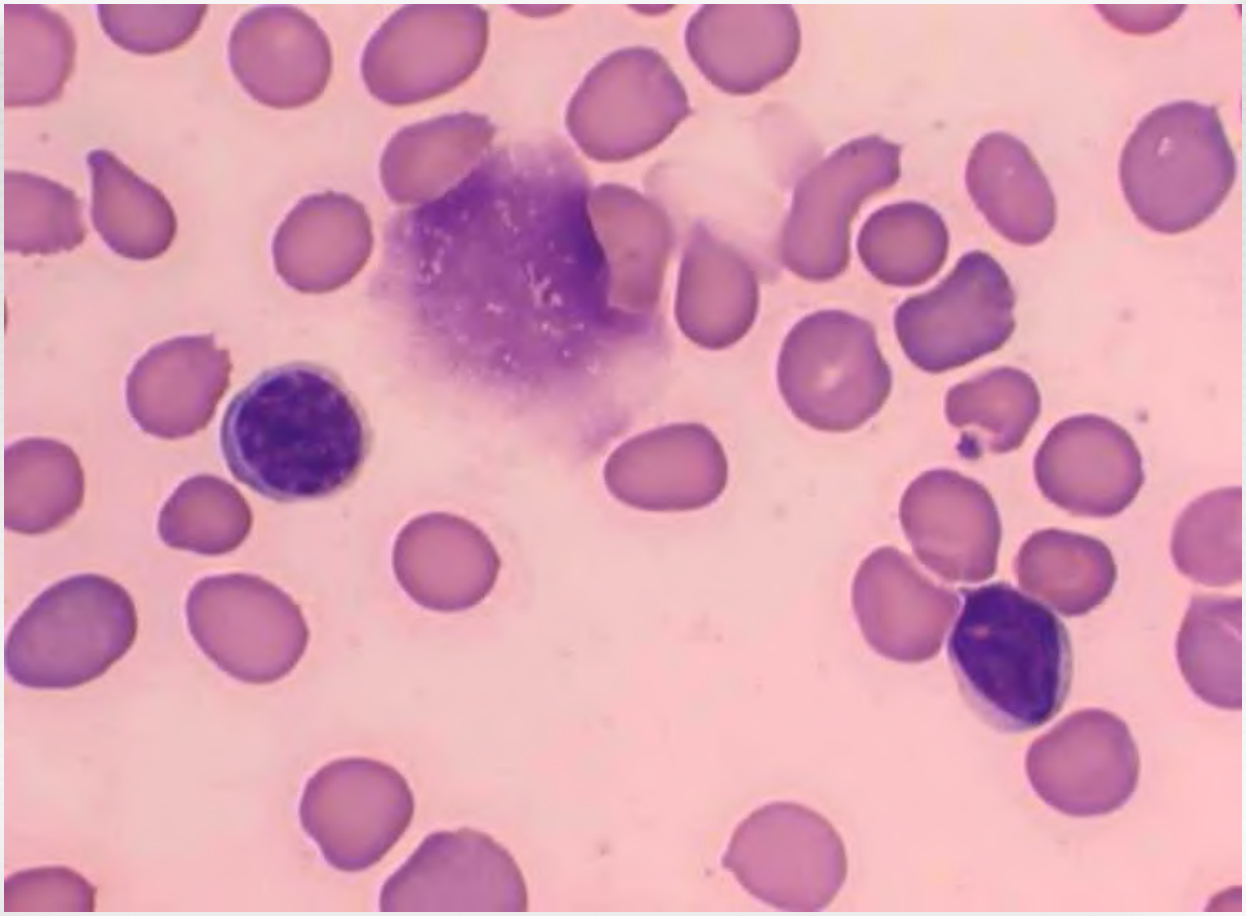
Rai KR. A critical analysis of staging in CLL. In: Gale RP, Rai KR (eds). Lymphocytic Leukemia. Recent progress and future directions. New York: Alan R. Liss, Inc. 1987, pp. 253–64.

BINET CLINICAL STAGING SYSTEM FOR CHRONIC LYMPHOCYTIC LEUKEMIA

Stage	Features at diagnosis	Median survival (months)
A	Blood and marrow lymphocytosis, <3 areas of palpable adenopathy	>120
B	Lymphocytosis, 3 or more areas of adenopathy	84
C	Same as Stage B, plus anemia (Hb <11 g/dL in men, <10 g/dL in women), or thrombocytopenia (<100,000/μL)	60

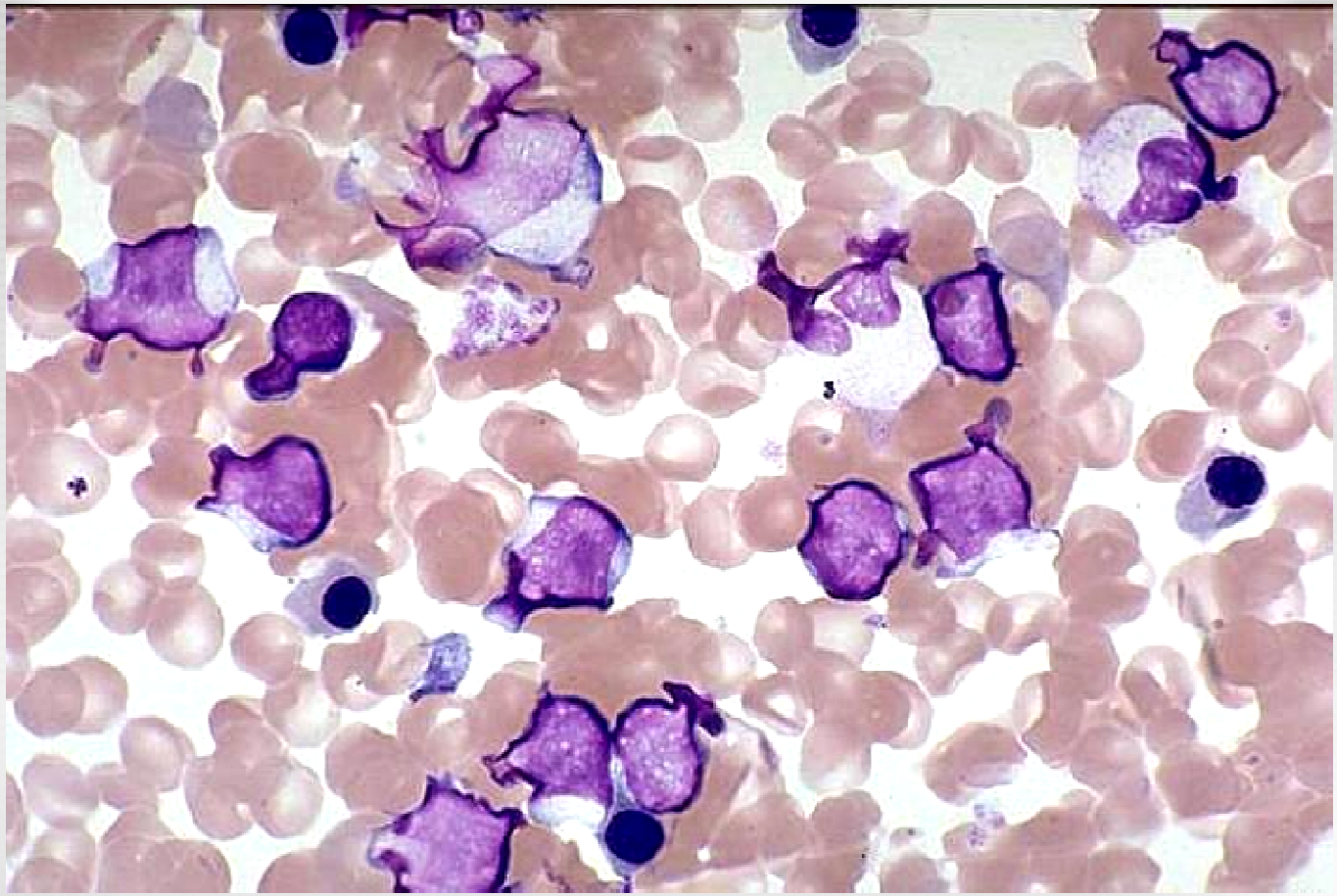
*From Dighero G, Binet J-L. When and how to treat chronic lymphocytic leukemia. N Engl J Med 2000;343:1799–801.

BLOOD SMEAR IN THE UNFOLDED STAGE OF CHRONIC LYMPHOCYTIC LEUKEMIA



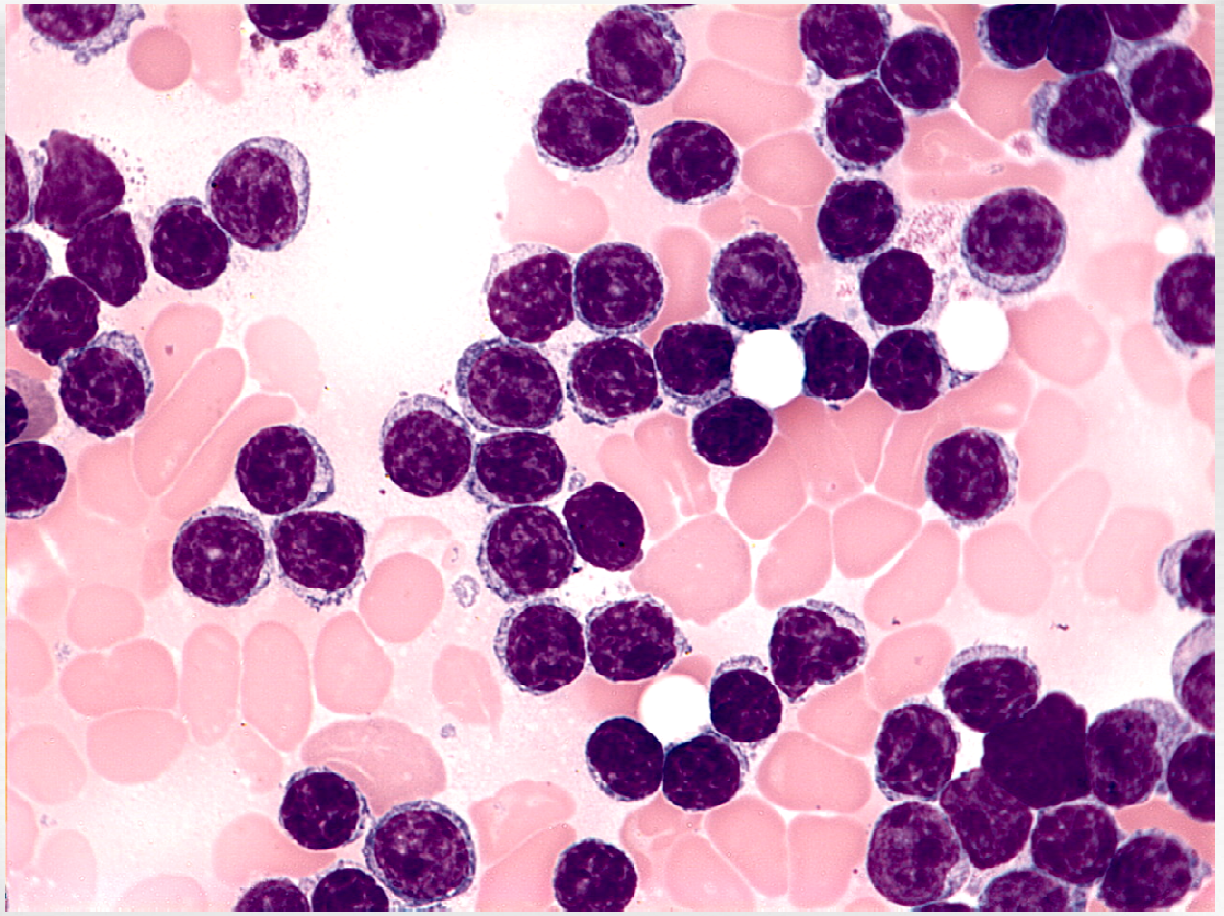
May-Giemsa staining, x 1000

BLOOD SMEAR IN THE UNFOLDED STAGE OF CHRONIC LYMPHOCYTIC LEUKEMIA



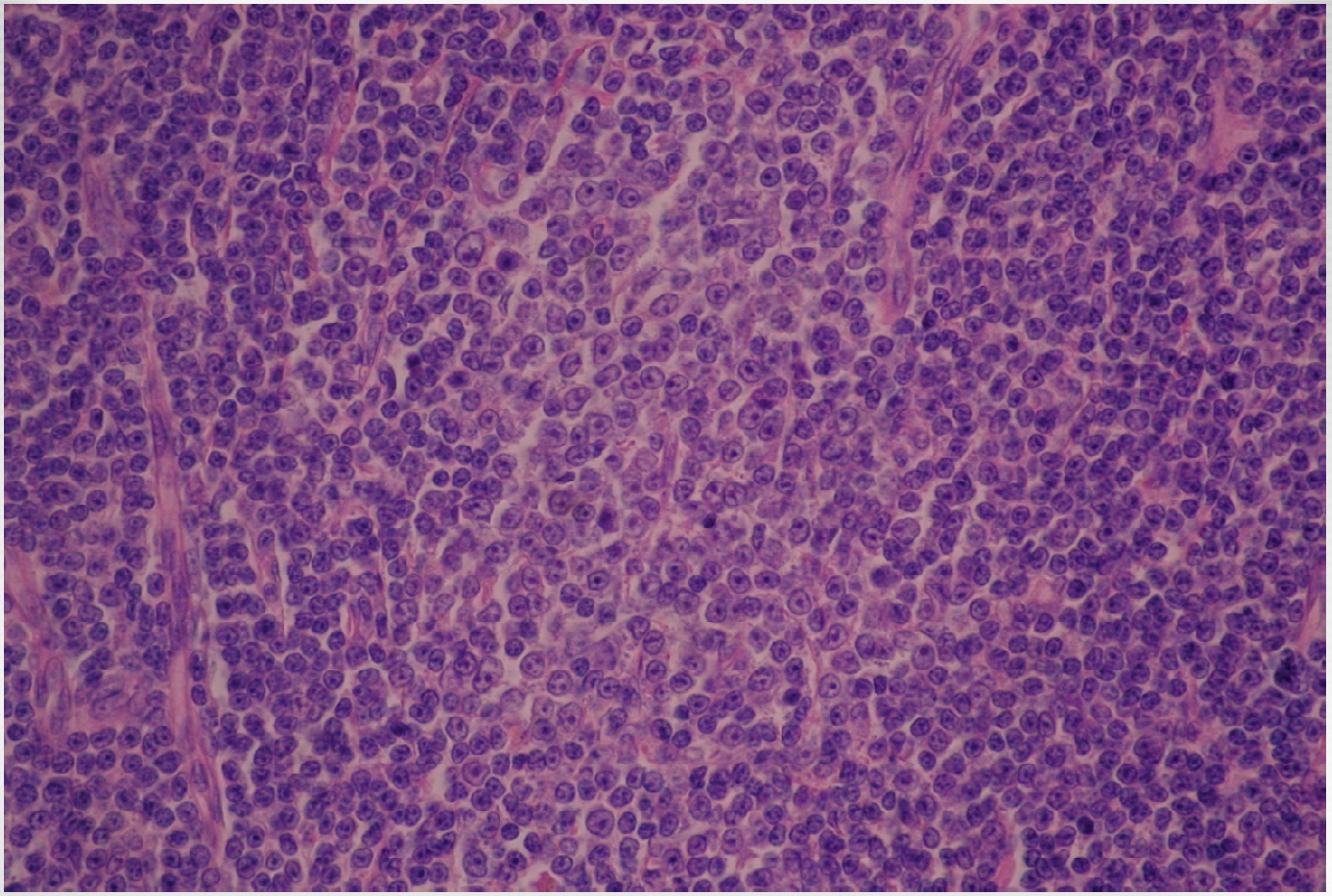
May-Giemsa staining, x 1000

BONE MARROW SMEAR IN THE UNFOLDED STAGE OF CHRONIC LYMPHOCYTIC LEUKEMIA



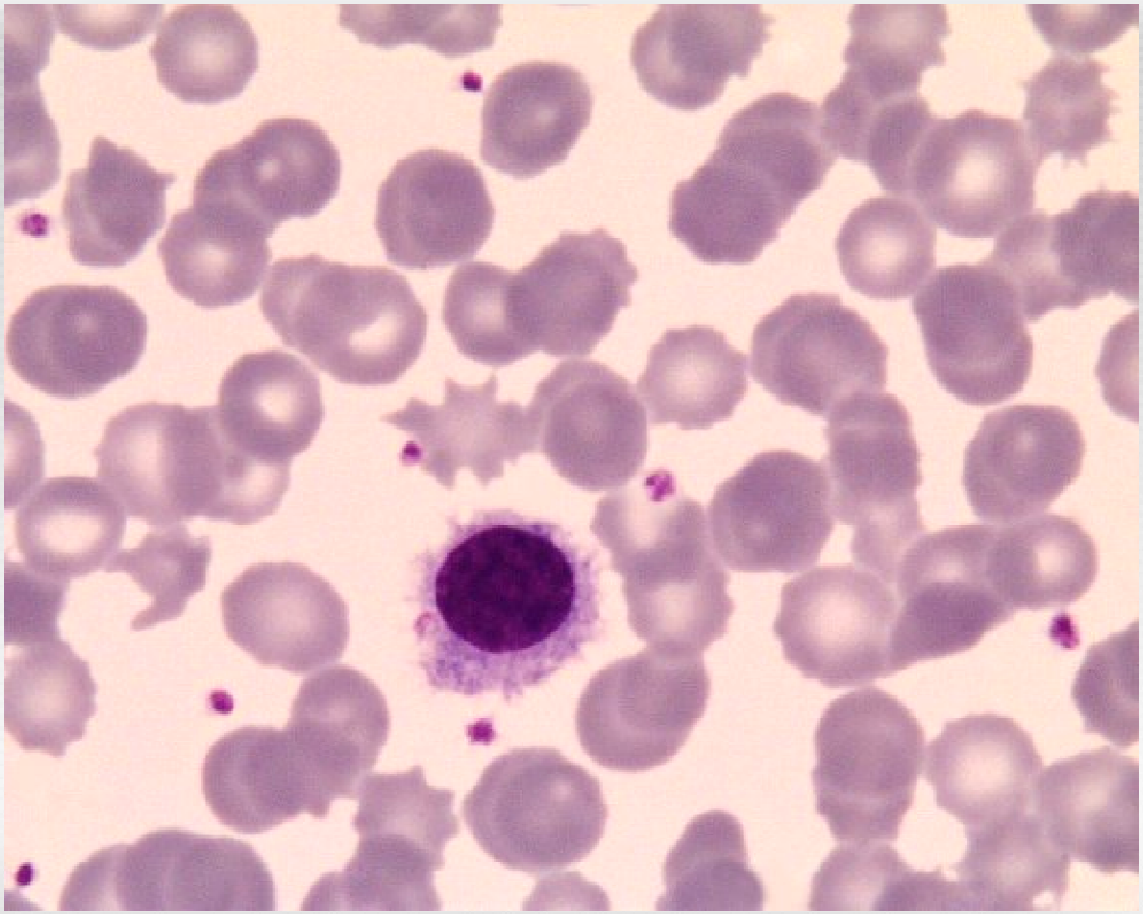
The high power view emphasizes the clumping of the chromatin which helps define mature lymphoid cells.
May-Giemsa staining, x 1000

BONE MARROW BIOPSY IN THE UNFOLDED STAGE OF CHRONIC LYMPHOCYTIC LEUKEMIA



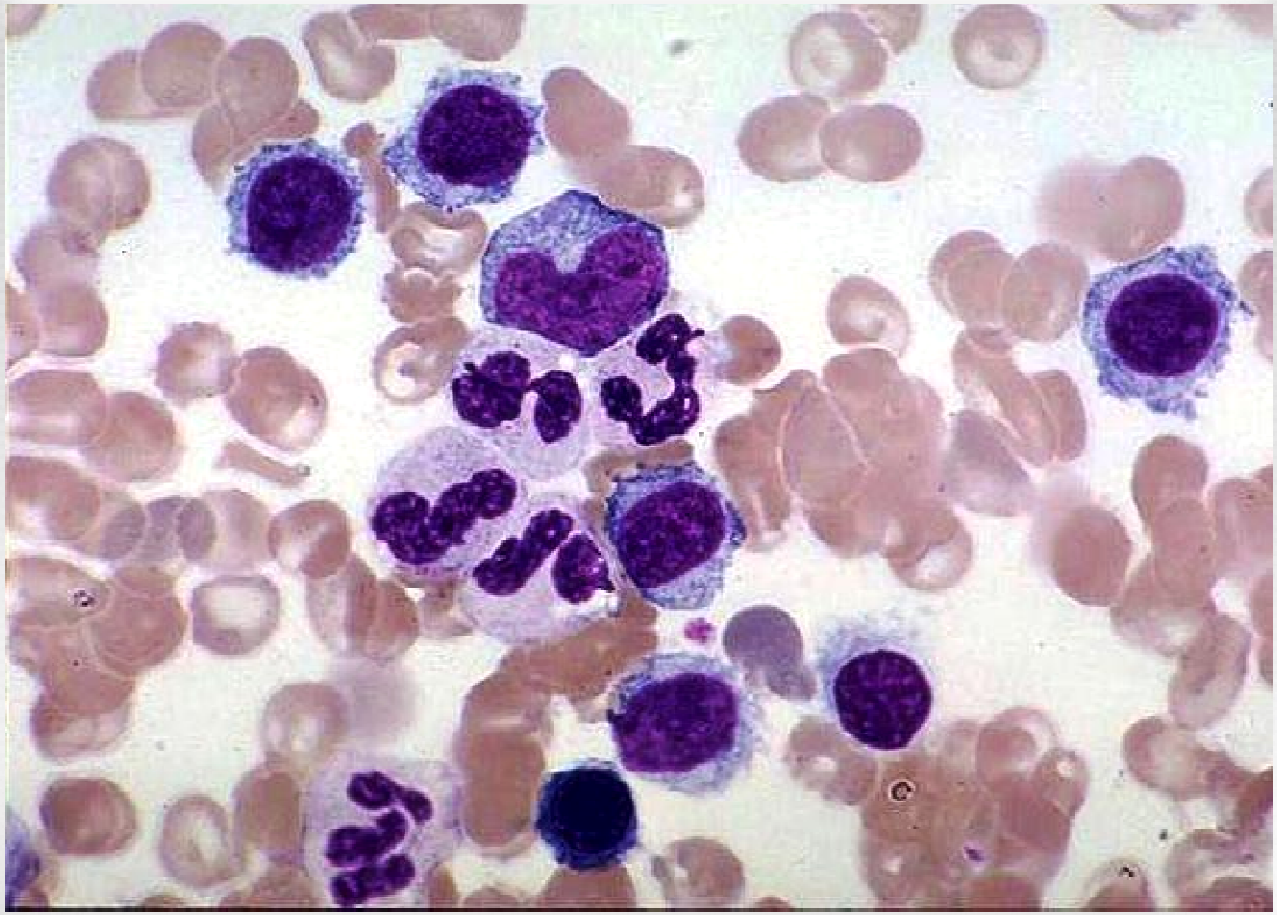
The high power view emphasizes the clumping of the chromatin which helps define mature lymphoid cells.
May-Giemsa staining, x 1000

BLOOD SMEAR IN THE UNFOLDED STAGE OF CHRONIC LYMPHOCYTIC LEUKEMIA



May-Giemsa staining, x 1000

BONE MARROW SMEAR IN HAIRY CELL LEUKEMIA



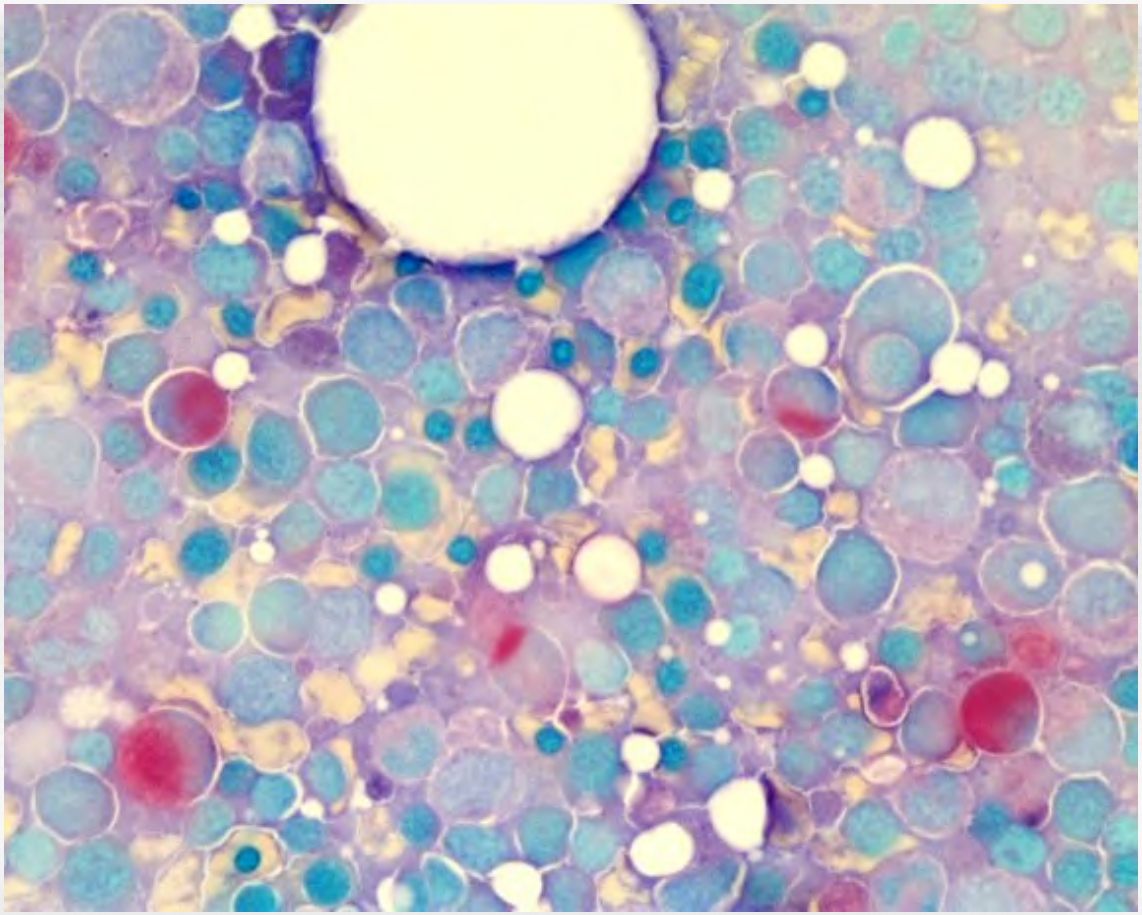
May-Giemsa staining, x 1000

FISH CYTOGENETICS: BIOLOGICAL AND CLINICAL CORRELATIONS IN CLL

Abnormality	(%)	Correlates		Median survival (years)
		Biological	Clinical	
Del(13q14) isolated	25–40	Mutated *IGHV* genes *MYD88* mutations	Good prognosis	>15
Trisomy 12	15–20	Atypical morphology (prolymphocytes) Atypical immunophenotype (CD20+FMC7+, CD11c+) *NOTCH1* mutations	Short treatment-free survival	~ 7.5
Del(11q22-23)	20–25	*ATM* mutations (30%) *BIRC 3* mutations	Tumoral forms Shorter time to progression. Longer PFS with FCR vs. FC or F	~ 6
Del(17p13.1)	5–3	Unmutated *IGHV* genes *TP53* mutations Clonal evolution Complex karyotype	Resistance to therapy	~ 4

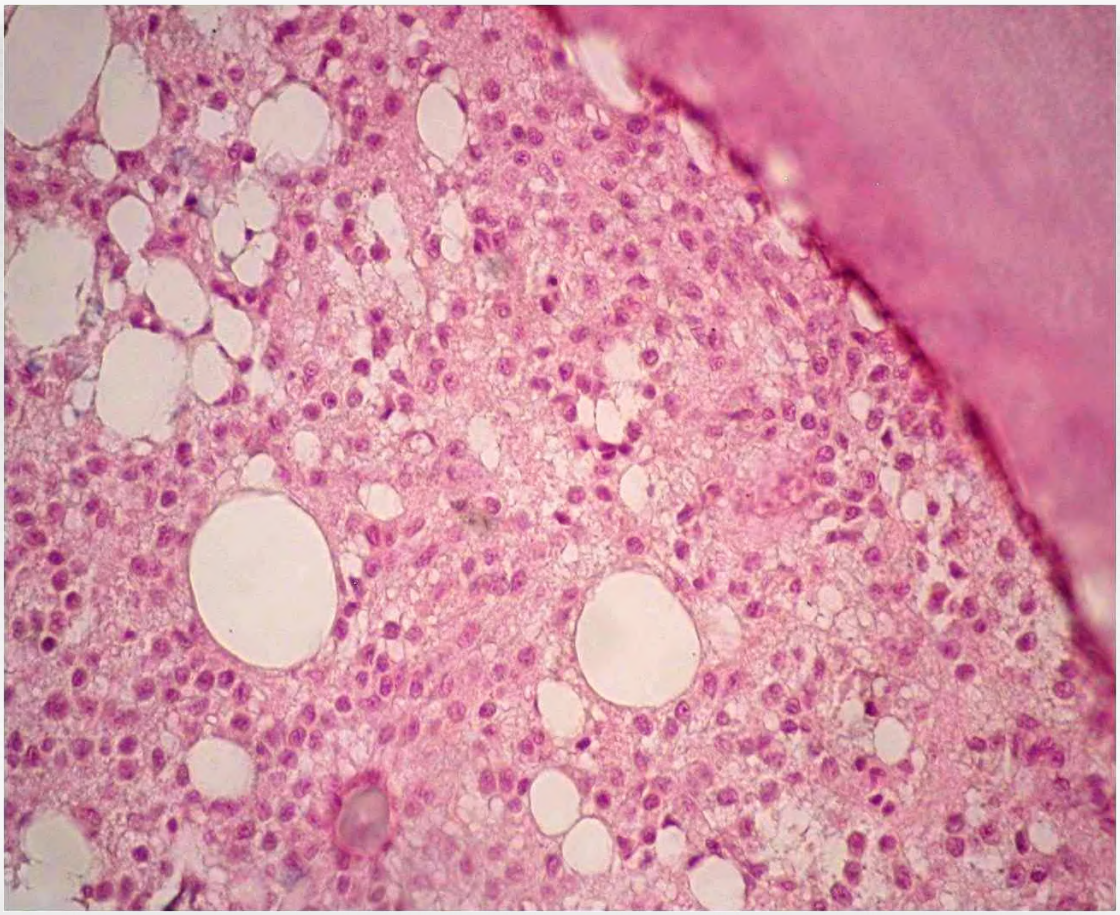
Source: Postgraduate Haematology, 7th Edition. Wiley Blackwell, 2016: 934 p.

BONE MARROW SMEAR IN HAIRY CELL LEUKEMIA



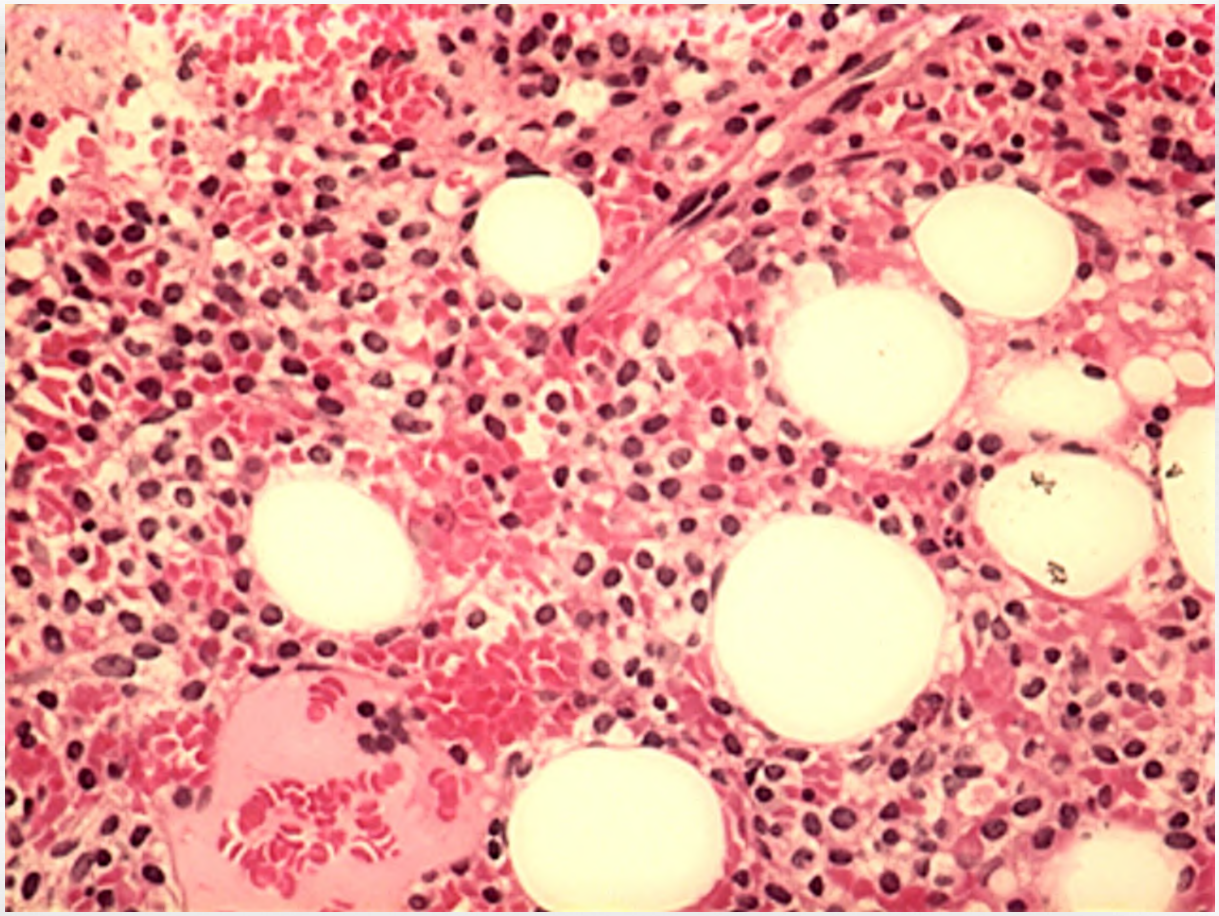
Tartrate-resistant acid phosphatase, x 1000

BONE MARROW BIOPSY IN HAIRY CELL LEUKEMIA



In the biopsy, the hairy cells have a clear area surrounding the nucleus creating a classic fried egg appearance

BONE MARROW BIOPSY IN HAIRY CELL LEUKEMIA



In the biopsy, the hairy cells have a clear area surrounding the nucleus creating a classic fried egg appearance

MANAGEMENT OF CHRONIC LYMPHOCYTIC LEUKEMIA BY STAGE, RISK CATEGORIES AND PHYSICAL FITNESS

(ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology, 2011; 22 (Supplement 6): vi50–vi54)

Stage	Fitness	Molecular cytogenetics	First-line therapy
Asymptomatic Binet A–B or Rai 0–II	Irrelevant	Irrelevant	None
Binet C or Rai III–IV, or symptomatic disease (any stage)	Go Go	No del(17p)	FCR
		del(17p)	FCR, A or FA→Allo SCT
	Slow Go	No del(17p)	Clb
		del(17p)	A
Relapse	**Fitness**	**Molecular cytogenetics**	**Relapse therapy**
Early (<12–24 months after monotherapy or <24–36 months after chemoimmunotherapy)	Go Go	No del(17p)	After chemoimmunotherapy: BR, A or FA→Allo SCT After monotherapy: FCR
		del(17p)	A or FA→Allo SCT
	Slow Go	No del(17p)	FCR[a], B, A, O, R + HDS
		del(17p)	A
Late (>12–24 months after monotherapy or >24–36 months after chemoimmunotherapy)	Go Go and Slow Go		Repeat first line

[a]Not recommended for patients refractory to fludarabine.

'Go go' defines patients with a good physical fitness and low co-morbidity burden, 'Slow Go' defines patients with impaired physical fitness and relevant comorbidity burden).

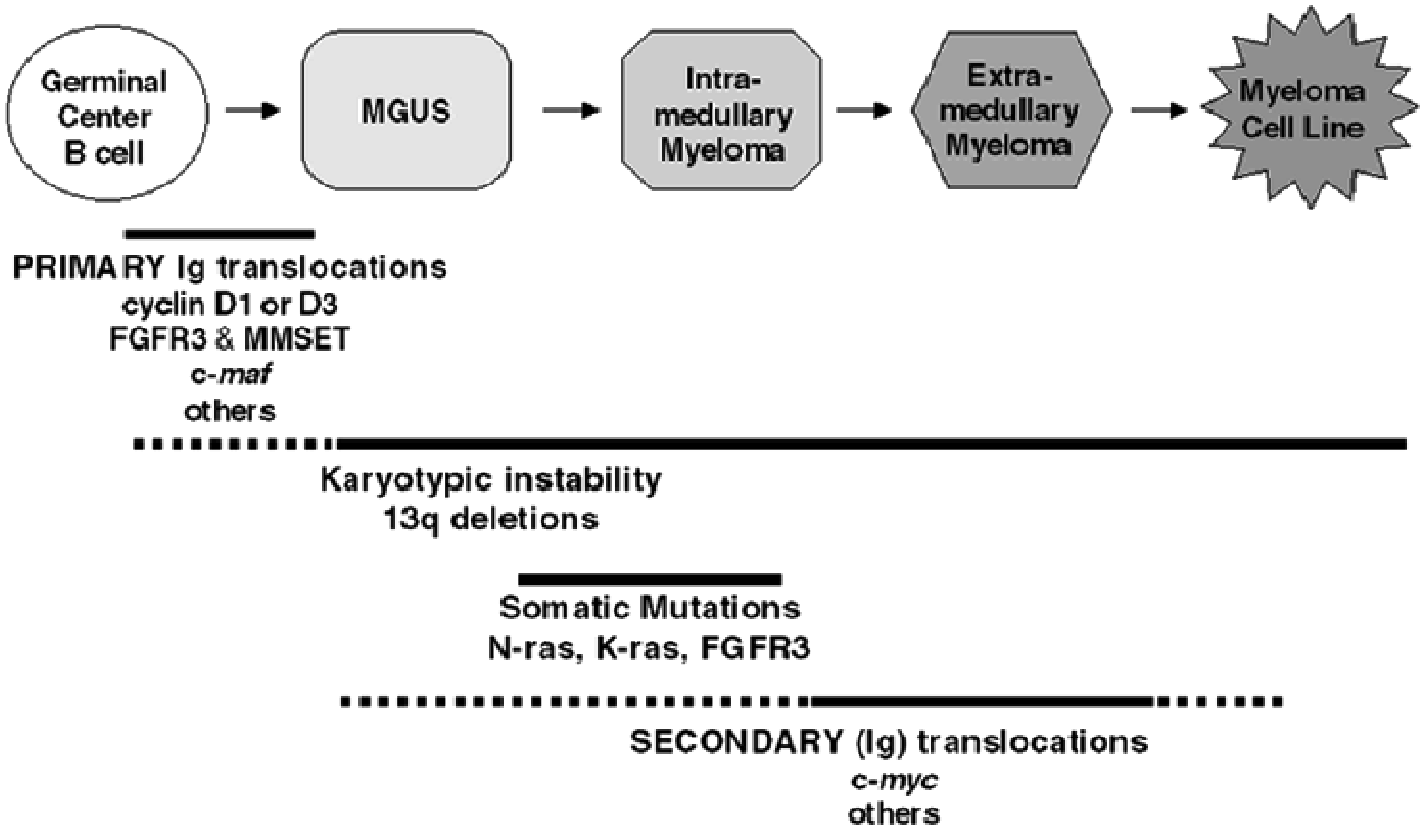
A, alemtuzumab; Allo SCT, allogeneic stem cell transplantation; B, bendamustine; C, cyclophosphamide; Clb, chlorambucil; F, fludarabine; HDS, high-dose steroids; O, ofatumumab; R, rituximab.

MULTIPLE MYELOMA (MM) **is is a malignancy of the plasma cell characterized by migration and localization to the bone marrow where cells then disseminate and facilitate the formation of bone lesions. The average, age adjusted incidence of MM is about 1 per 100 000 population. The annual incidence of myeloma, age-adjusted to the 2000 USA population, is 4.3 per 100 000. In Republic of Moldova, the incidence of MM is 0.6 per 100 000 population. The incidence rose progressively with age. The disease more commonly develops in persons over 40 years. In children MM is not registered. MM is twice as common in blacks compared with whites and slightly more common in males than females.**

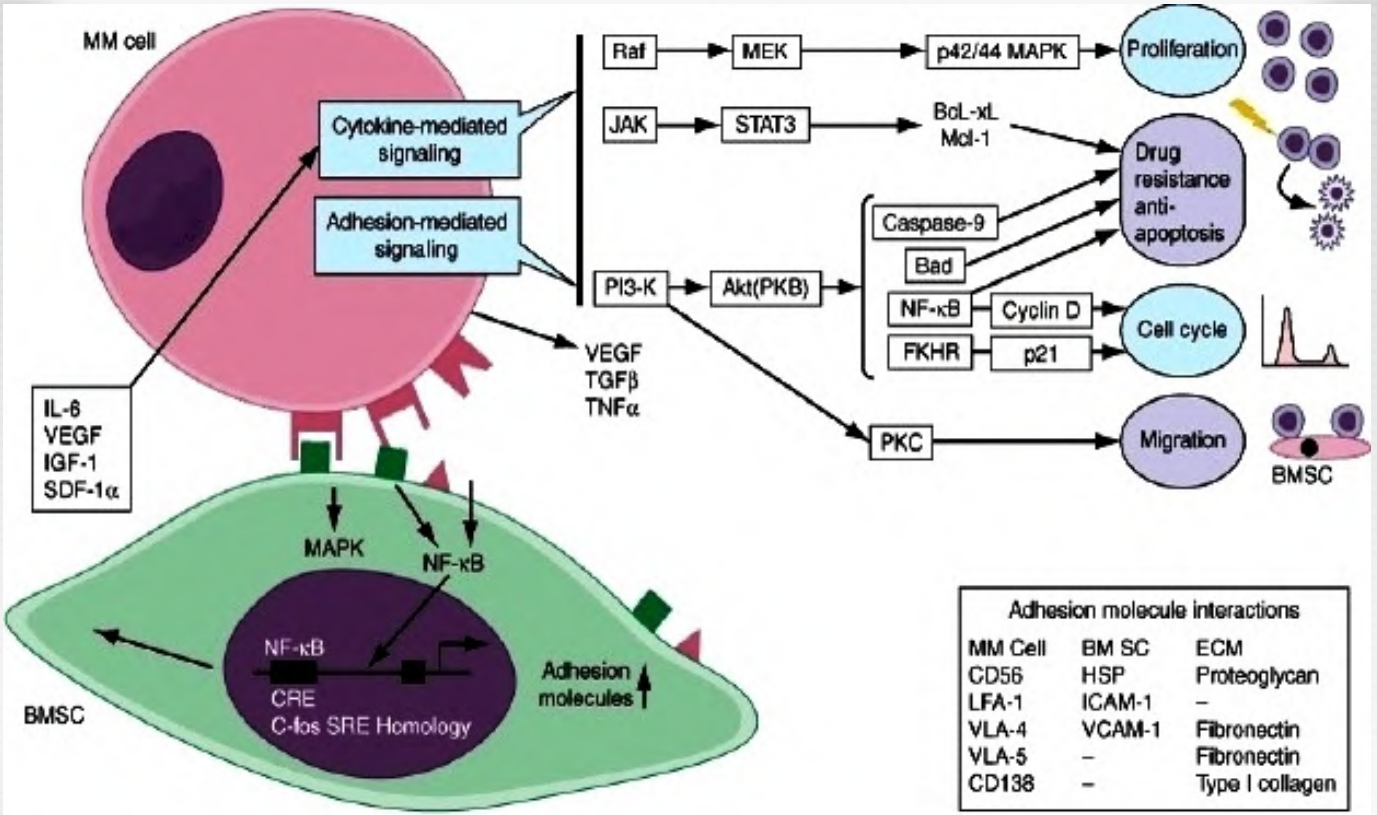
PATHOGENESIS. **MM originates in early B-cell precursors with idiotypic pre-switch rearrangements of the immunoglobulin gene. When such cells undergo malignant transformation, they proliferate to form a clone of identical cells which produce a typical monoclonal (M) protein identified as a "spike" by serum electphoresis. MM is a malignant plasma cell neoplasm that often is preceded by a common pre-malignant monoclonal expansion of plasma cells called monoclonal gammopathy of undetermined significance (MGUS). MGUS is reported to be present in 3% of the adult population and to progress to MM at a rate of 1% per year. Since MM is almost exclusively a tumor of plasma cells that have undergone the processes of somatic hypermutation and isotype switch recombination in germinal centers, the errors during these physiological processes may occur, leading to chromosome translocations involving the immunoglobulin genes.**

MULTI-STEP MOLECULAR PATHOGENESIS OF MM

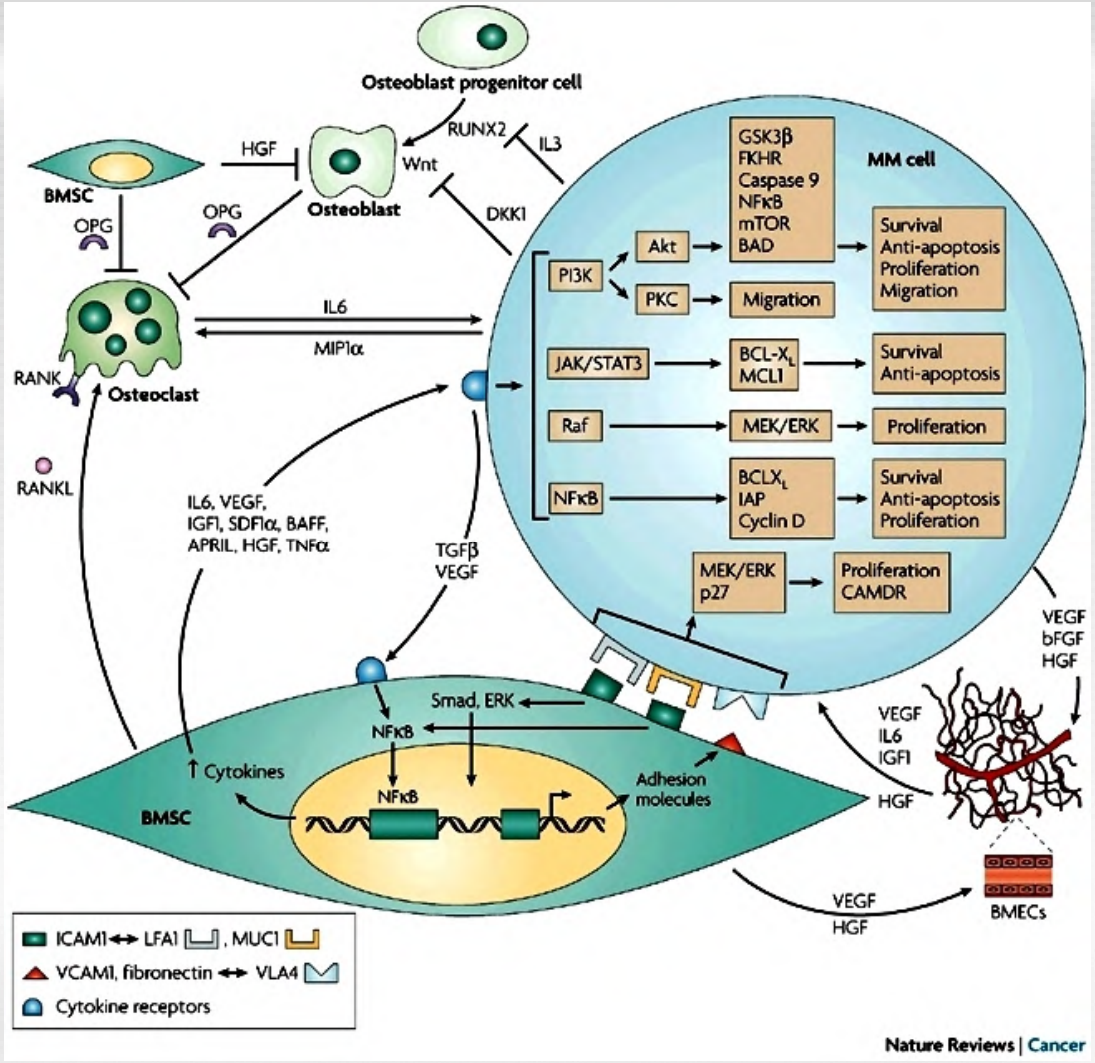
(American Society of Hematology. Dalton W.S. et al., Hematology 2001)



PATHOGENESIS OF MM

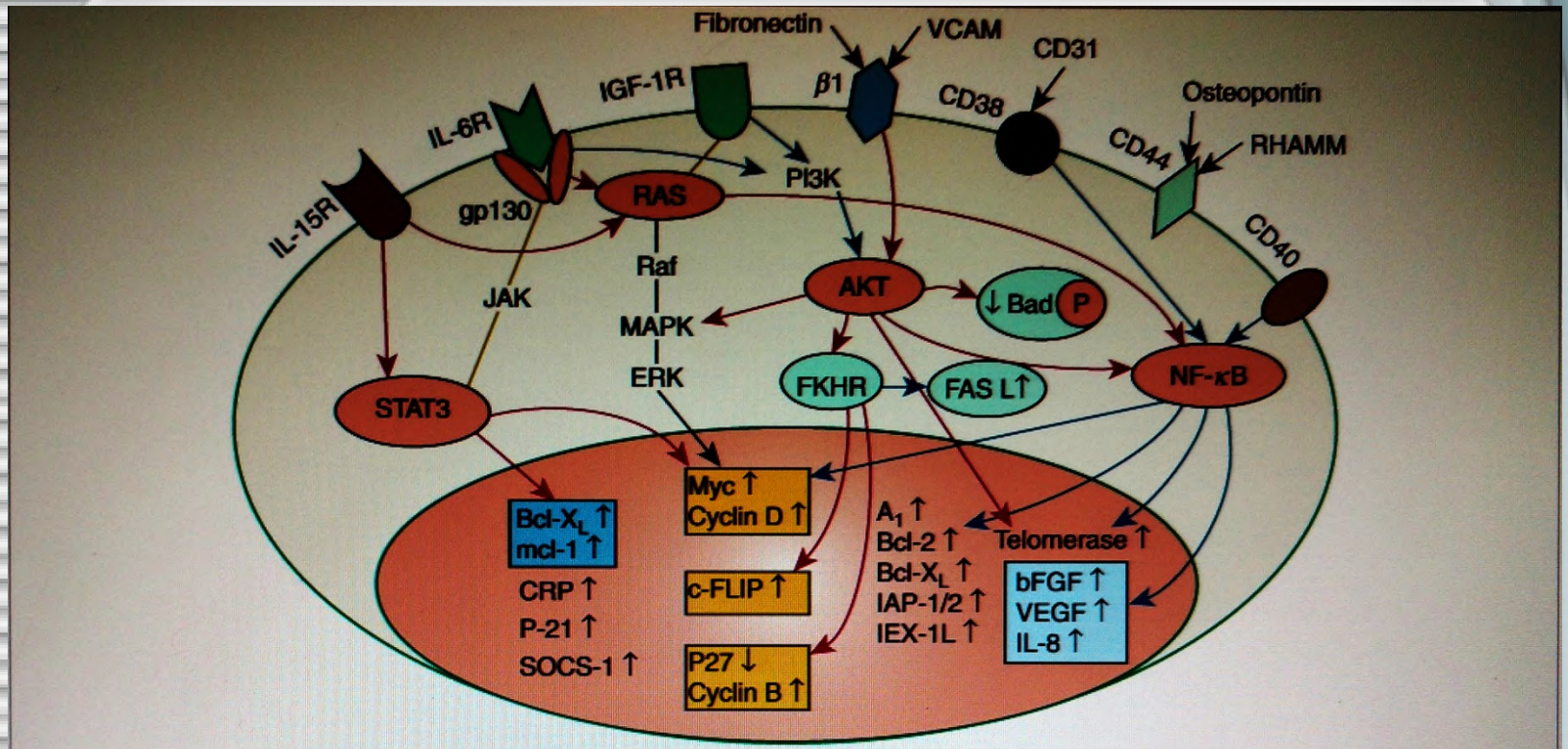


PATHOGENESIS OF MM



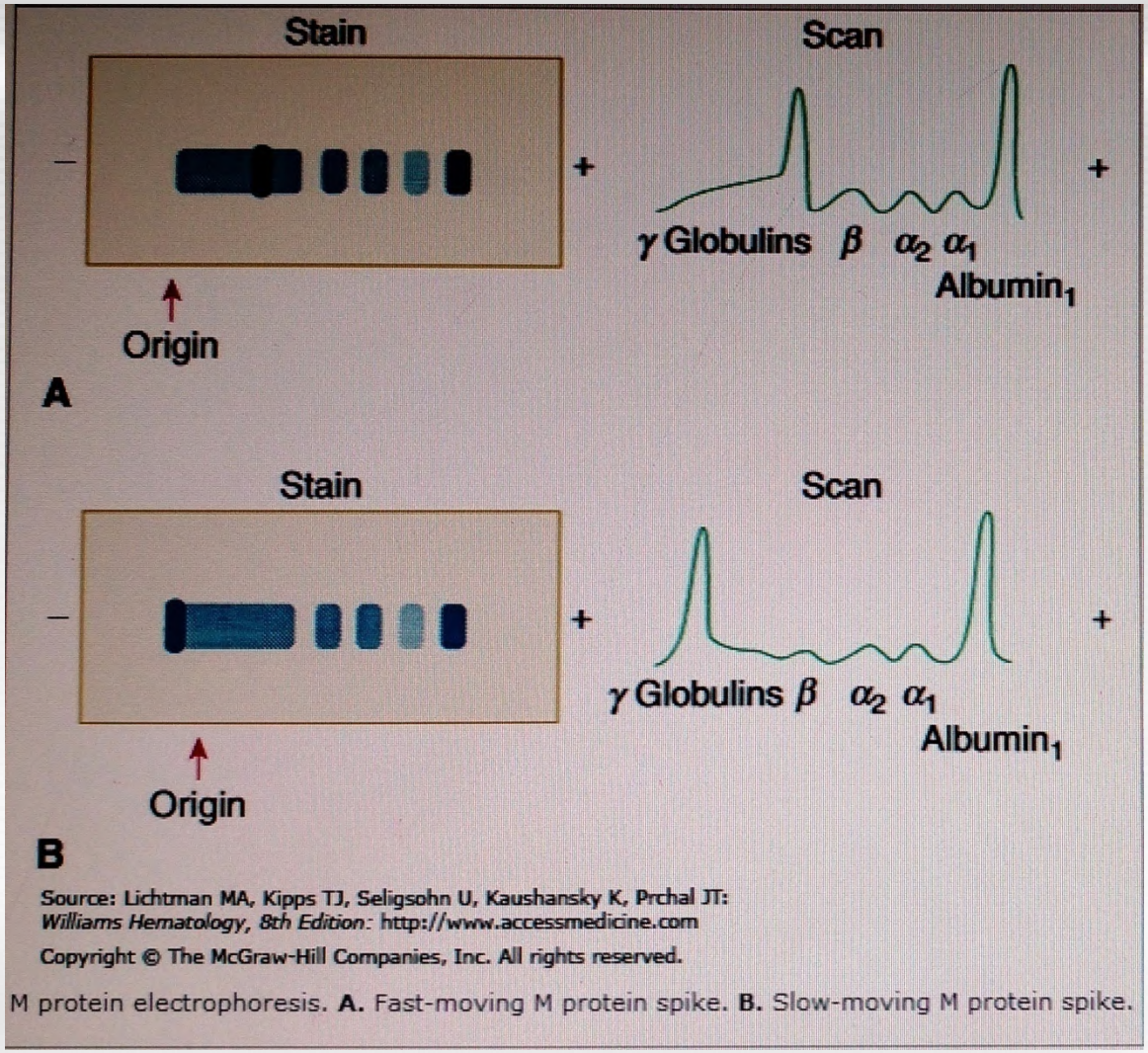
Source: Nature Reviews Cancer 2007 , 7: 585–598

PATHOGENESIS OF MM



The microenvironment provides factors engaging receptors present on myeloma cells, which promote their survival and proliferation. bFGF, basic fibroblast growth factor; CRP, C-reactive protein; ERK, extracellular response kinase; gp130, glycoprotein 130; IAP, inhibitors of apoptosis; IEX, immediate early response gene X-1; IGF, insulin-like growth factor; IL, interleukin; JAK, Janus kinase; MAPK, mitogen activated protein kinase; NF-κB, nuclear factor-κB; PI3K, phosphatidylinositol 3'-kinase; RHAMM, receptor for hyaluronan-mediated motility; SOCS-1, suppressor of cytokine synthesis 1; VCAM, vascular cell adhesion molecule; VEGF, vascular endothelial growth factor.

PATHOGENESIS OF MM



M protein electrophoresis. **A.** Fast-moving M protein spike. **B.** Slow-moving M protein spike.

COMMON LABORATORY FEATURES OF PLASMA CELL DISORDERS

(Pazdur R., Coia L.R., Hoskins W.J. et al., Cancer Management: A Multidisciplinary Approach. 8th Edition. New York: CMP Healthcare Media)

Multiple myeloma
Marrow plasmacytosis > 10%
Monoclonal immunoglobulin peak (usually > 3.0 g/dL)
Decreased levels of uninvolved immunoglobulins
Presence of Bence Jones protein
Lytic bone lesions or diffuse osteopenia

Smoldering myeloma
Same as multiple myeloma but without symptoms and;
Hemoglobin > 10.5 g/dL
Monoclonal immunoglobulin peak (< 4.5 g/dL)
Normal serum calcium and creatinine levels
No lytic bone lesions

Solitary plasmacytoma of bone (SPB)
Solitary bone lesion due to plasma cell tumor
Normal skeletal survey and MRI of the skull, spine, and pelvis
Normal bone marrow plasmacytosis
No anemia, hypercalcemia, or renal disease
Preserved levels of uninvolved immunoglobulins

Monoclonal gammopathy of unknown significance (MGUS)
Monoclonal immunoglobulin level < 3.0 g/dL
Bone marrow plasma cells < 10%
No bone lesions
No symptoms due to plasma cell dyscrasia
Usually preserved levels of uninvolved immunoglobulins

Amyloidosis without myeloma
Same as MGUS plus evidence of amyloidosis on biopsy

Screening and diagnosis

No screening measures for multiple myeloma have demonstrated any benefit.

The diagnosis usually requires the presence of bone marrow plasmacytosis and a monoclonal protein in the urine and/or serum (Table 1). One immunoglobulin class is produced in excess, whereas the other immunoglobulin classes are usually depressed.

DIAGNOSTIC CRITERIA OF PLASMA CELL DISORDERS

(Palumbo A. et al., International Myeloma Working Group guidelines. Leukemia (2009), 1–15)

Diagnosis	*Diagnostic criteria: all three required*
Symptomatic multiple myeloma[a]	Monoclonal plasma cells in the bone marrow ⩾10% and/or presence of a biopsy-proven plasmacytoma Monoclonal protein present in the serum and/or urine[b] Myeloma-related organ dysfunction (⩾1)[c] [C] Calcium elevation in the blood (serum calcium >10.5 mg/l or upper limit of normal [R] Renal insufficiency (serum creatinine >2 mg per 100 ml) [A] Anaemia (haemoglobin <10 g per 100 ml or 2 g <normal) [B] Lytic bone lesions or osteoporosis[d]
Monoclonal gammopathy of undetermined significance (MGUS)	Serum monoclonal protein low[e] Monoclonal bone marrow plasma cells <10% No evidence of end-organ damage attributable to the clonal plasma cell disorder: Normal serum calcium, haemoglobin level and serum creatinine No bone lesions on full skeletal X-ray survey and/or other imaging if performed No clinical or laboratory features of amyloidosis or light chain deposition disease
Smouldering or indolent myeloma[f]	Monoclonal protein present in the serum 3 g per 100 ml or higher or Monoclonal plasma cells 10% or greater present in the bone marrow and/or a tissue biopsy No evidence of end-organ damage attributable to the clonal plasma cell disorder: Normal serum calcium, haemoglobin level and serum creatinine No bone lesions on full skeletal X-ray survey and/or other imaging if performed No clinical or laboratory features of amyloidosis or light chain deposition disease
Solitary plasmacytoma of bone	Biopsy-proven plasmacytoma of bone in a single site only. X-rays and magnetic resonance imaging and/or FDG PET imaging (if performed) must be negative outside the primary site. The primary lesion may be associated with a low serum and/or urine M-component The bone marrow contains no monoclonal plasma cells No other myeloma-related organ dysfunction

Adapted with permission from Kyle and Rajkumar.[73]

[a]These criteria identify Stage IB and Stages II and III A/B myeloma by Durie/Salmon stage. Stage IA becomes smouldering or indolent myeloma.

[b]If no monoclonal protein is detected (non-secretory disease), then ⩾30% monoclonal bone marrow plasma cells and/or a biopsy-proven plasmacytoma required.

[c]A variety of other types of end-organ dysfunctions can occasionally occur and lead to a need for therapy. Such dysfunction is sufficient to support classifications myeloma if proven to be myeloma related.

[d]If a solitary (biopsy-proven) plasmacytoma or osteoporosis alone (without fractures) is the sole defining criteria, then ⩾30% plasma cells are required in the bone marrow.

[e]Low is defined as serum M protein <3.0 g per 100 ml.

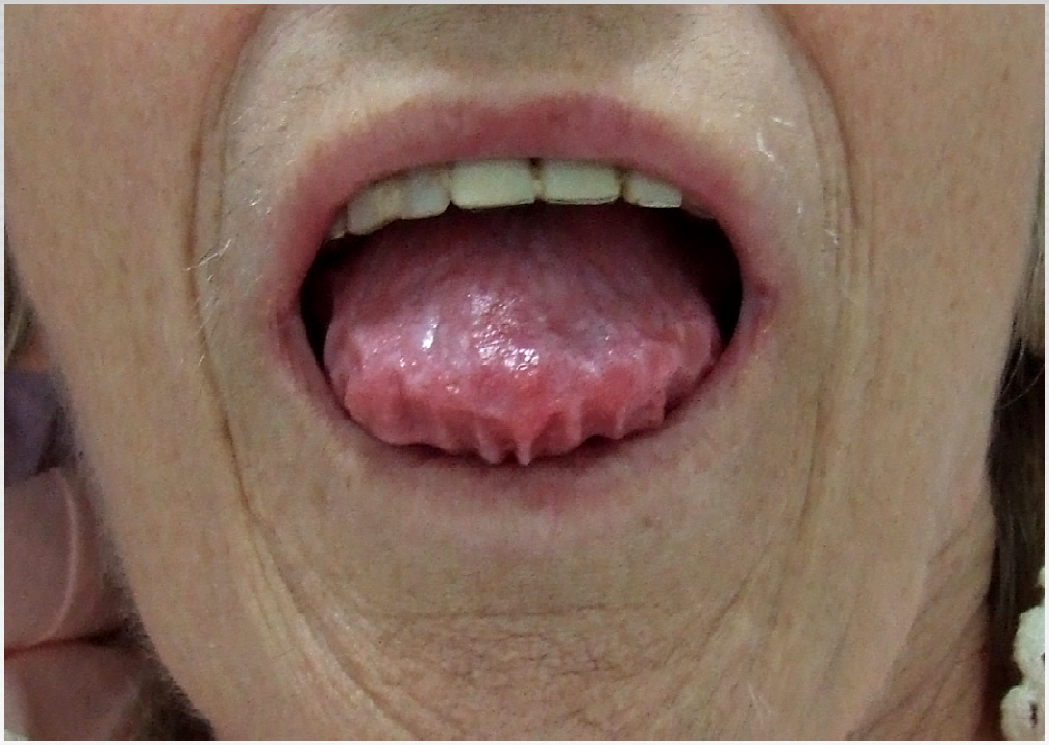
[f]These criteria identify Stage IA myeloma by Durie/Salmon stage.

MYELOMA STAGING SYSTEM (DURIE BGM, SALMON SE, 1975):

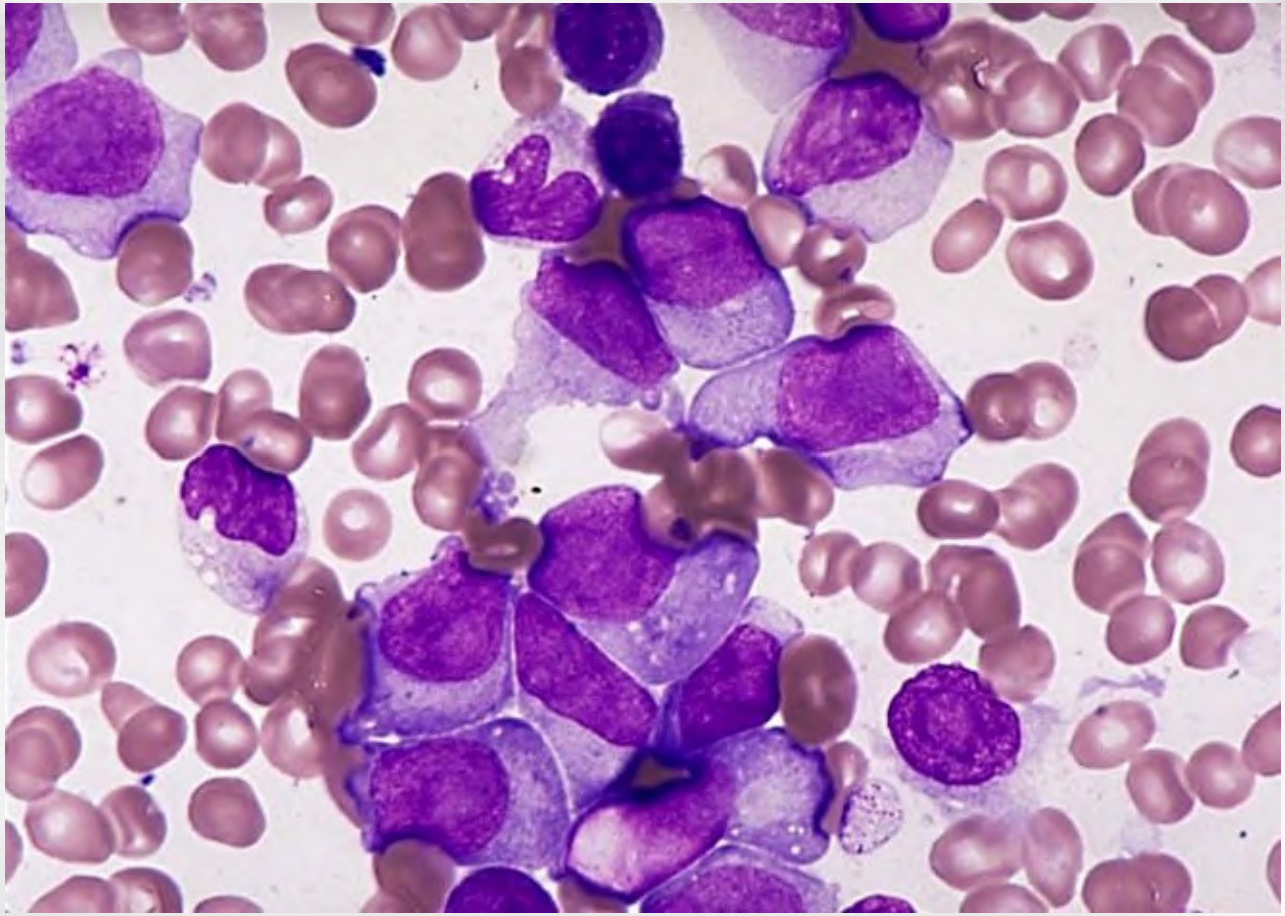
Stage	*Criteria*
I	*All of the following:* Hemoglobin value > 100 g/l. Serum calcium value normal. On radiograph, normal bone structure or solitary bone plasmacytoma only. Low M-component production rates IgG value < 50g/l IgA value < 30 g/l Urine light chain M-componenton electrophoresis < 4g/24h
II	*Fitting neither stage I nor stage III*
III	*One or more of the following:* Hemoglobin value < 85 g/l Serum calcium value > 12 mg/dl Advanced lytic bone lesions High M-component production rates IgG value > 70g/l IgA value > 50 g/l Urine light chain M-component on electrophoresis > 12g/24h

Subclassification: **A – Normal renal function; B – Abnormal renal function**

PARAAMYLOIDOSIS OF THE TONGUE IN MULTIPLE MYELOMA WITH LIGHT CHAINS

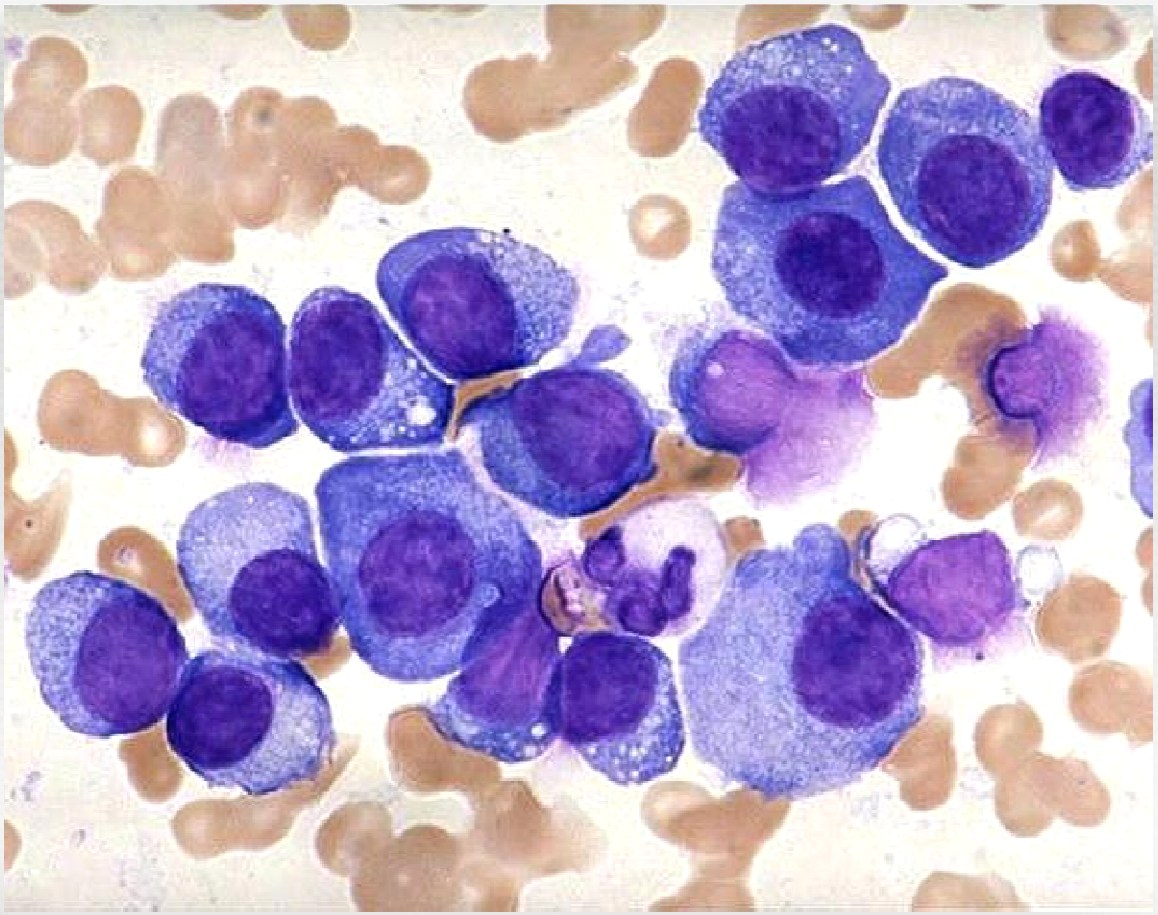


BONE MARROW SMEAR IN MULTIPLE MYELOMA



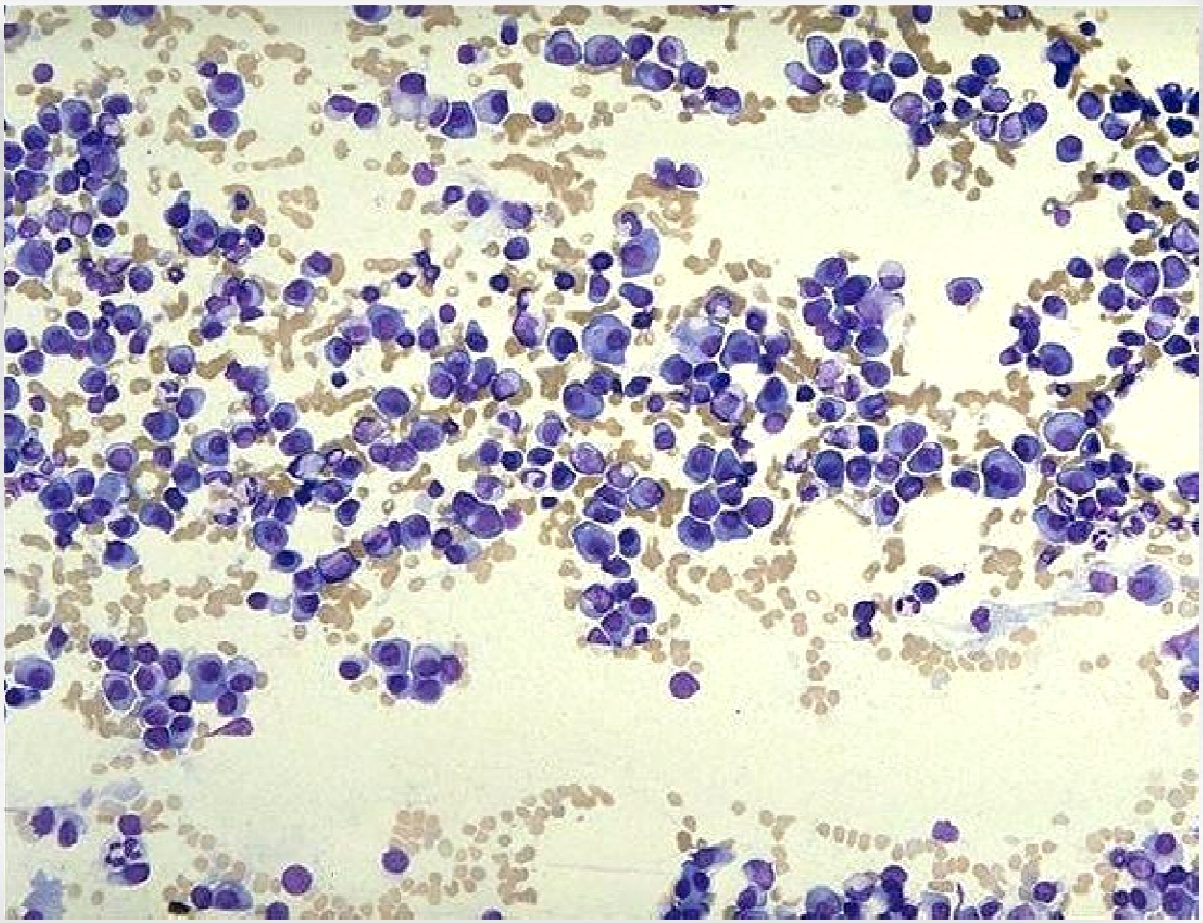
May-Giemsa staining, x 1000

BONE MARROW SMEAR IN MULTIPLE MYELOMA



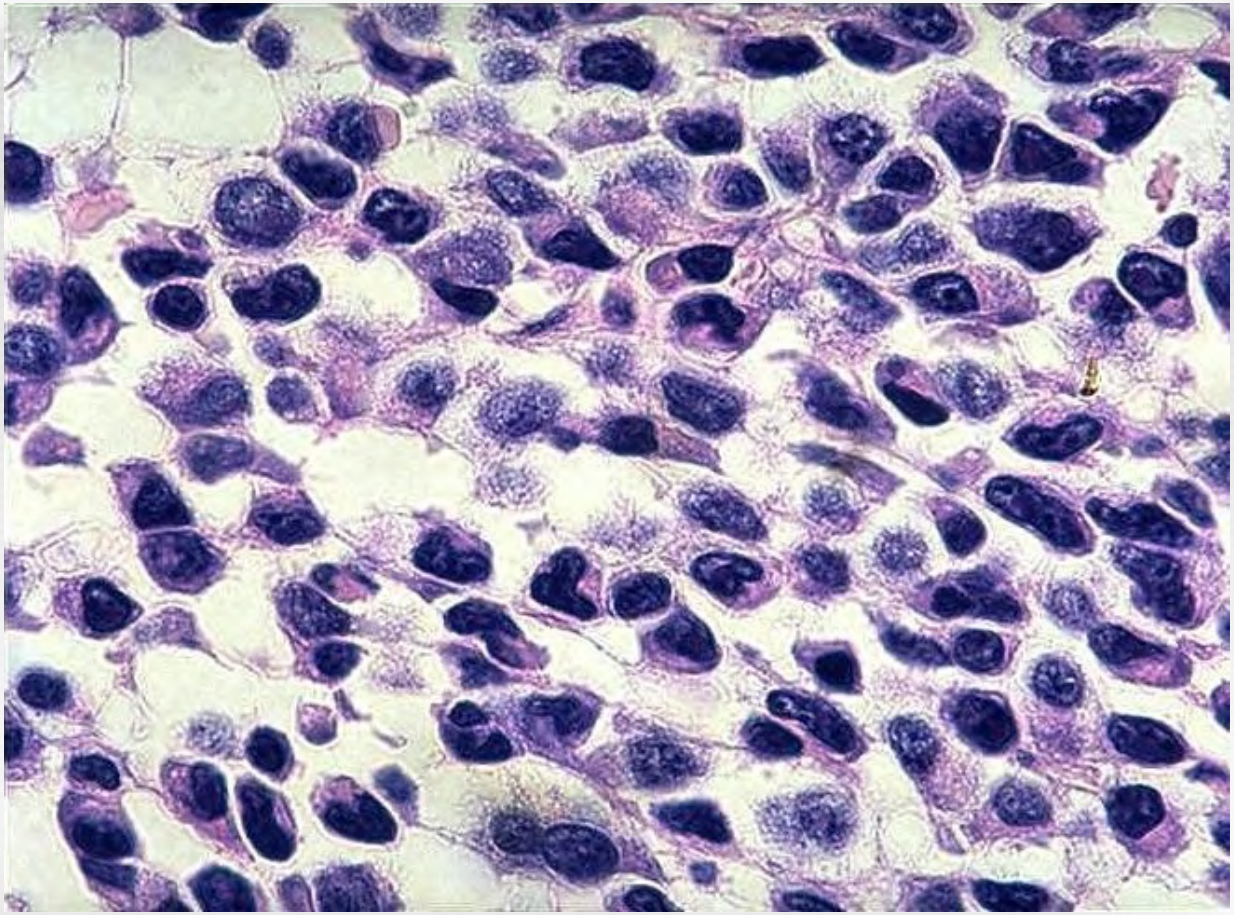
May-Giemsa staining, x 1000

BONE MARROW SMEAR IN MULTIPLE MYELOMA



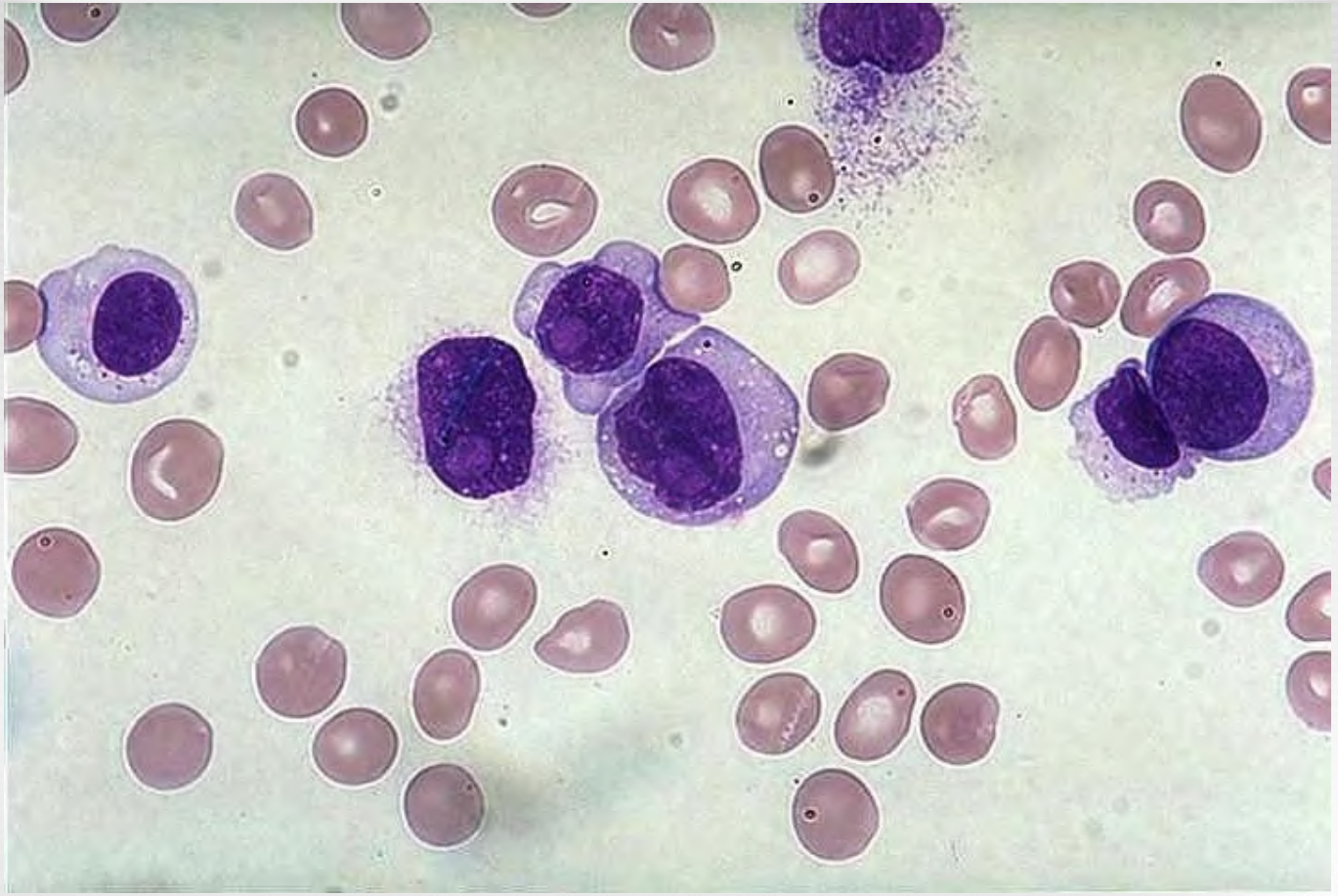
May-Giemsa staining, x 200

BONE MARROW BIOPSY IN MULTIPLE MYELOMA



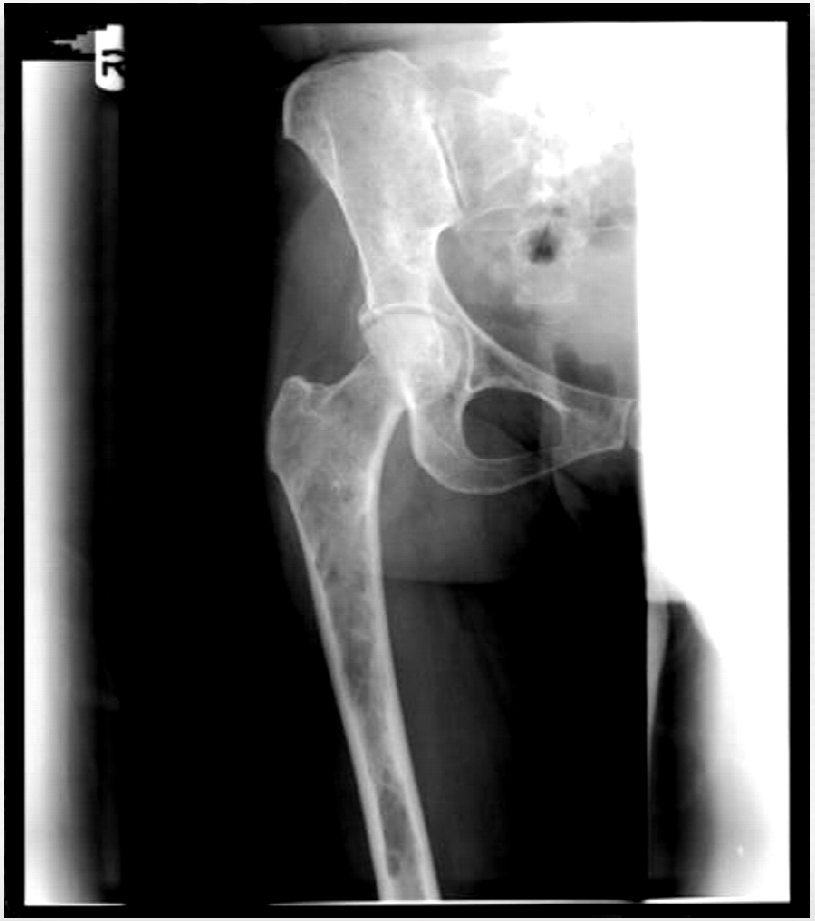
Clot Section, hematoxylin and eosin stain, x1000

BLOOD SMEAR IN MULTIPLE MYELOMA: LEUKEMIC CONVERSION



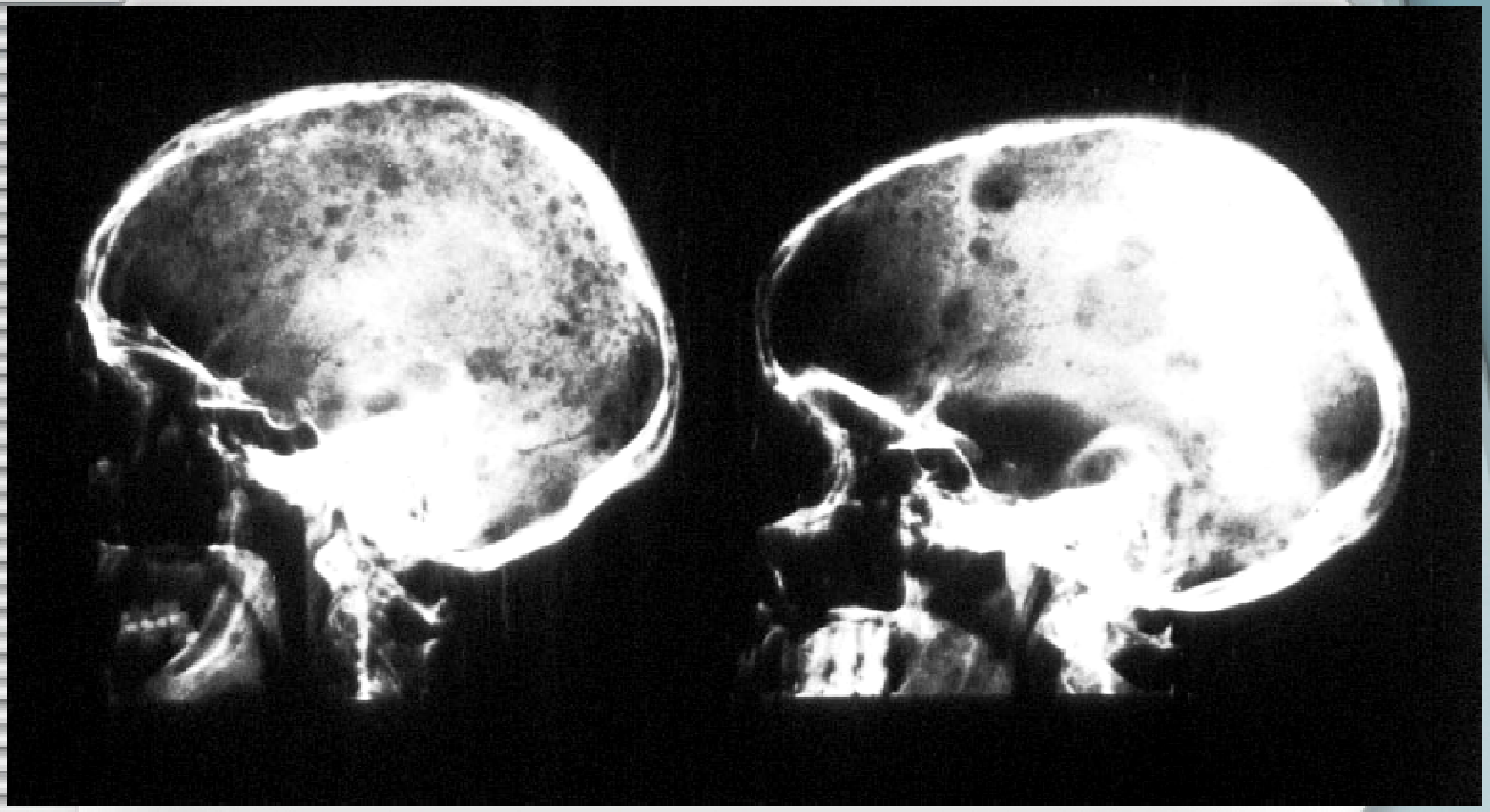
May-Giemsa staining, x 1000

X-RAY EXAMINATION IN MULTIPLE MYELOMA



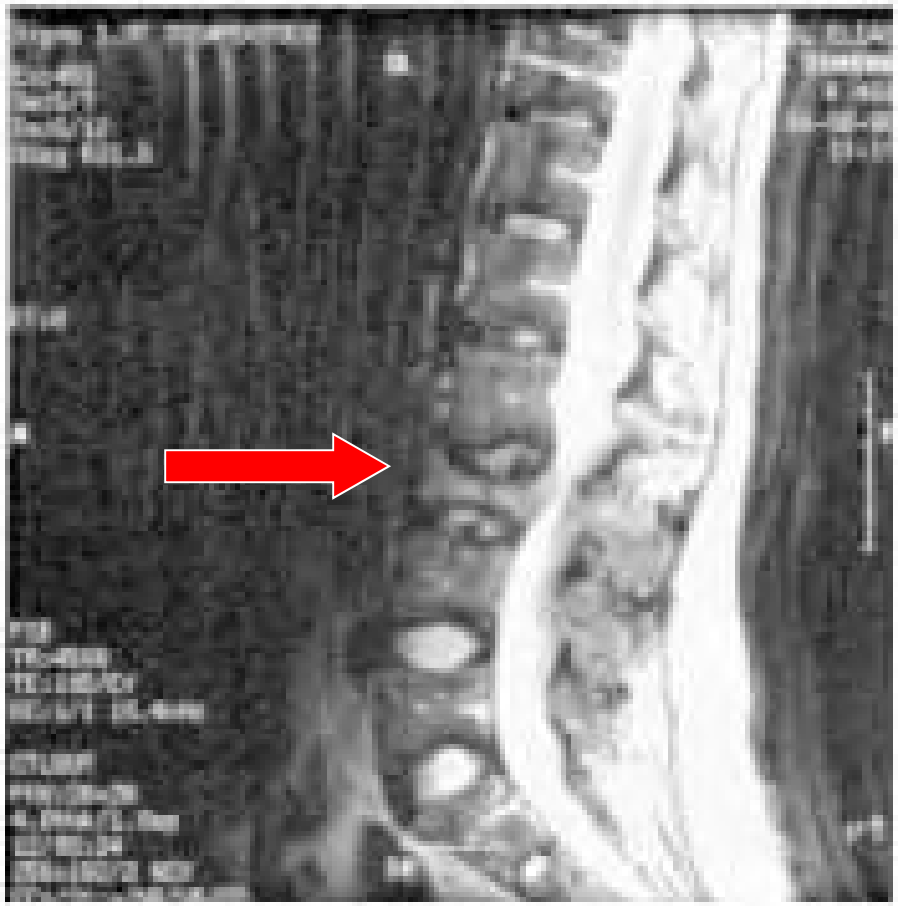
Skeletal survey demonstrates multiple osteosclerotic lesions

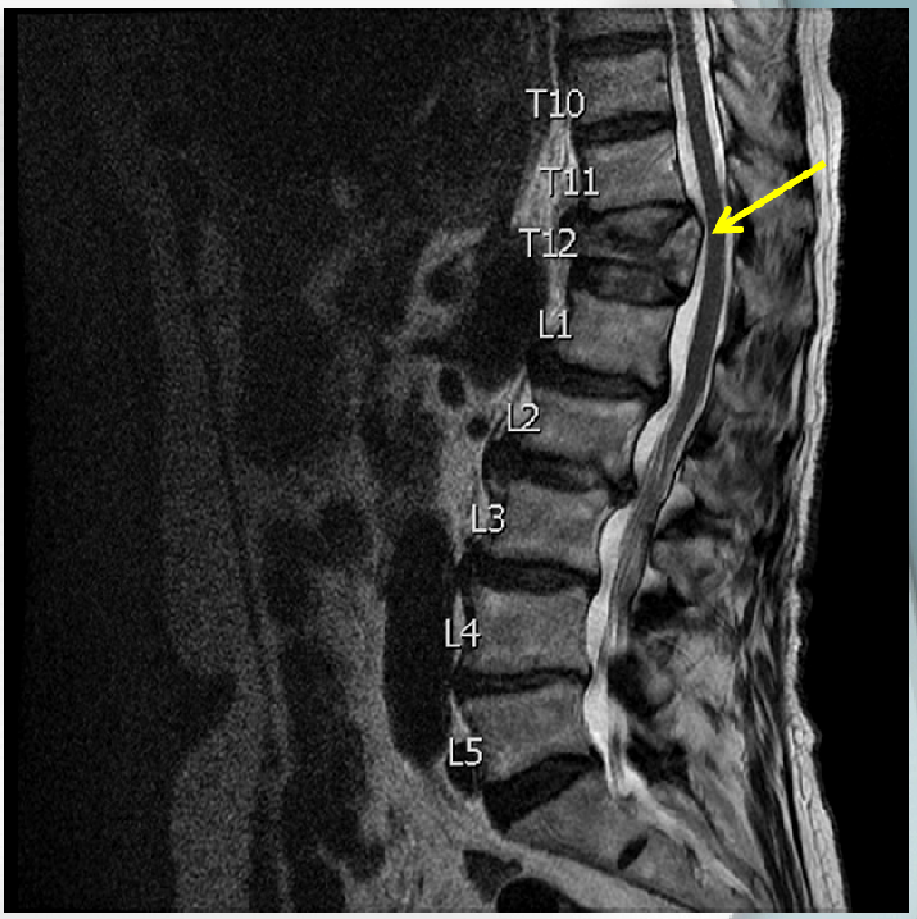
X-RAY EXAMINATION IN MULTIPLE MYELOMA



Skeletal survey demonstrates multiple osteosclerotic lesions

MAGNETIC RESONANCE IMAGING IN MULTIPLE MYELOMA

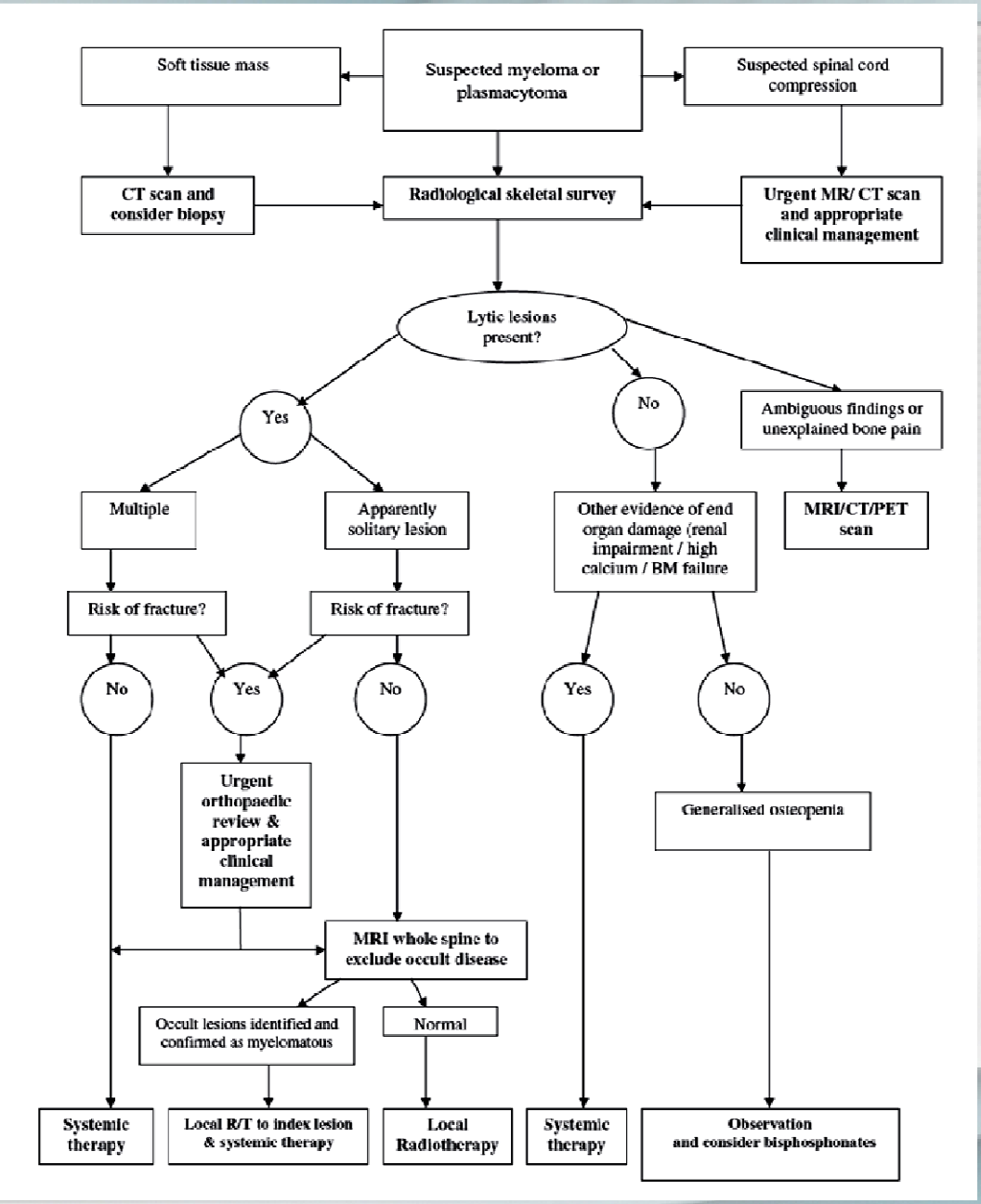




Compression fracture of the vertebra, with the intense bone pain, followed by the flaccid paraplegia

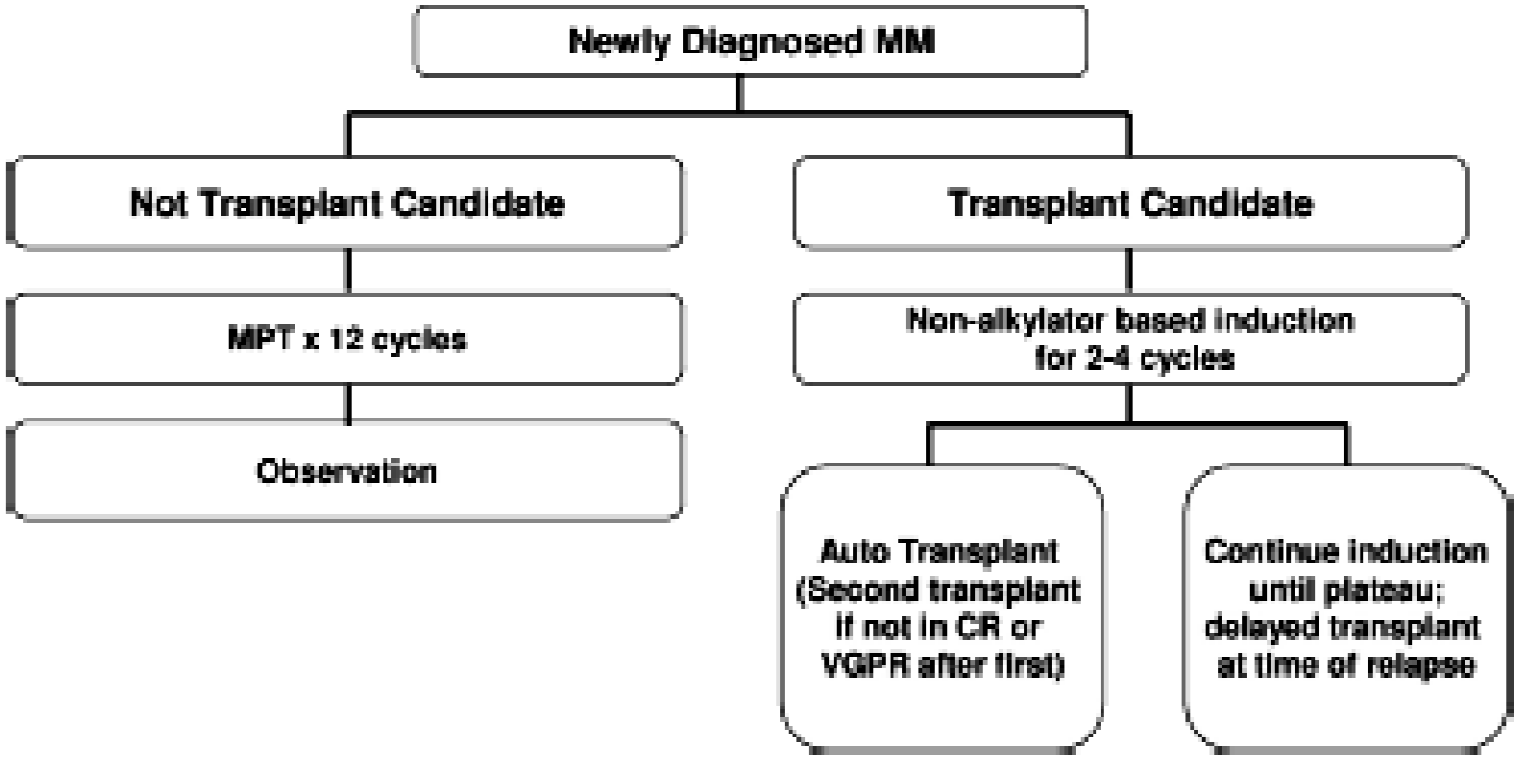
MANAGEMENT ALGORITHM IN SUSPECTED MULTIPLE MYELOMA OR PLASMACYTOMA

(2007 British Society for Haematology Journal Compilation , 2007 Blackwell Publishing Ltd, British Journal of Haematology, 137: 49–63)



TREATMENT ALGORITHM IN NEWLY DIAGNOSED MULTIPLE MYELOMA

(Kyle R.A., Rajkumar S.V. BLOOD, 2008; VOLUME 111, NUMBER 6: 2962 - 2972)



TREATMENT OPTIONS IN MULTIPLE MYELOMA

(Pazdur R., Coia L.R., Hoskins W.J. et al., Cancer Management: A Multidisciplinary Approach. 8th Edition. New York: CMP Healthcare Media)

Disease or patient status	Treatment approach
Initial therapy	
Candidates for high-dose therapy	
Dexamethasone	40 mg on days 1-4, 9-12, and 17-20 every 35 days or on days 1-4 every 2 weeks
Dexamethasone/thalidomide	Dexamethasone as above with thalidomide (200 mg/d)
VAD	Vincristine (0.5 mg/d IV) + Adriamycin (10 mg/m^2/d IV), both given as continuous infusion on days 1-4, along with dexamethasone (40 mg) on days 1-4, 9-12, and 17-20 every 35 days
High-dose melphalan and SCT following induction therapy	
Noncandidates for high-dose therapy	
Above options or	
MP	Melphalan (8 mg/m^2/d PO) + prednisone (100 mg/d PO) on days 1-4 every 4-5 weeks
Relapsed myeloma	
Resistant to thalidomide/ dexamethasone	Bortezomib (Velcade) Alkylating agent combination High-dose melphalan and SCT
Resistant to VAD or dexamethasone	Dexamethasone/thalidomide Alkylating agent combinations (MP, VBMCP) Cyclophosphamide/etoposide DCEP or EDAP High-dose melphalan and SCT Newer agents: Revimid (in clinical trials) and arsenic trioxide (Trisenox)

DCEP = dexamethasone, cyclophosphamide, etoposide, and cisplatin; EDAP = etoposide, dexamethasone, Ara-C, and cisplatin; G-CSF = granulocyte colony-stimulating factor; SCT = stem-cell transplantation; VBMCP = vincristine, BCNU, melphalan, cyclophosphamide, prednisone

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