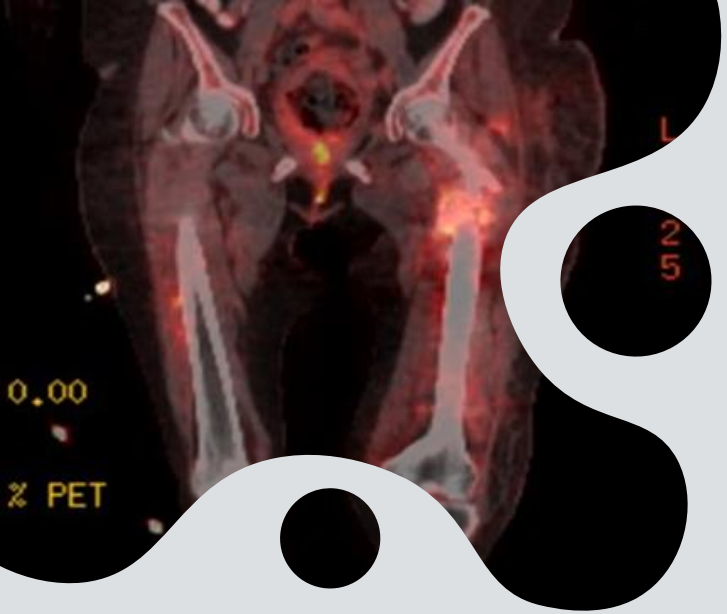
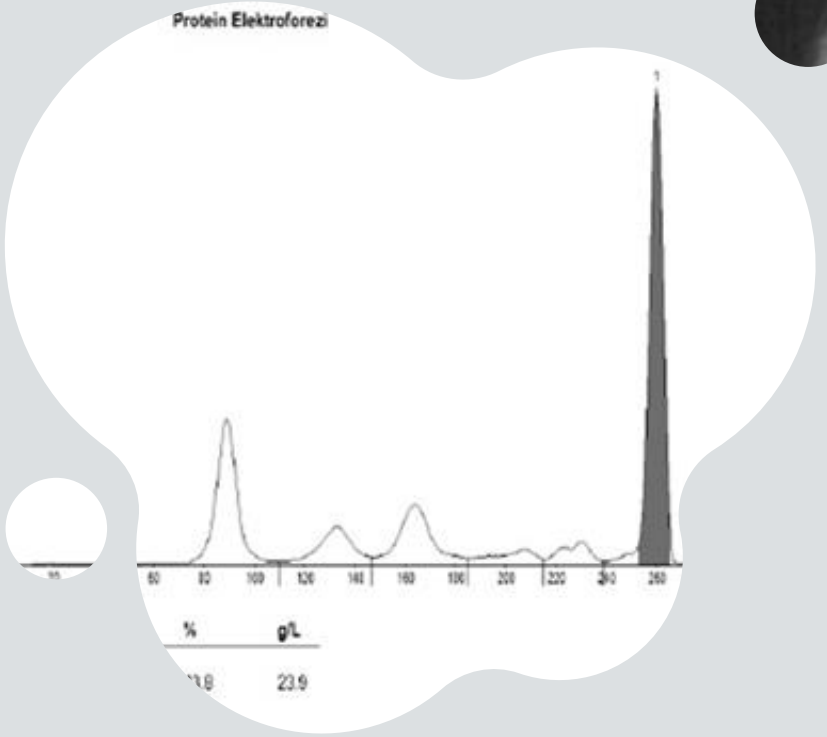
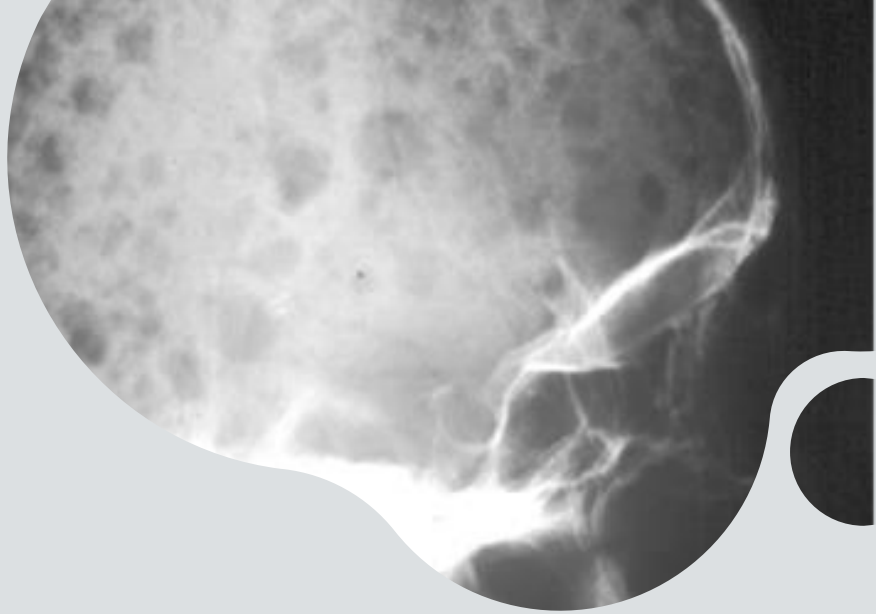




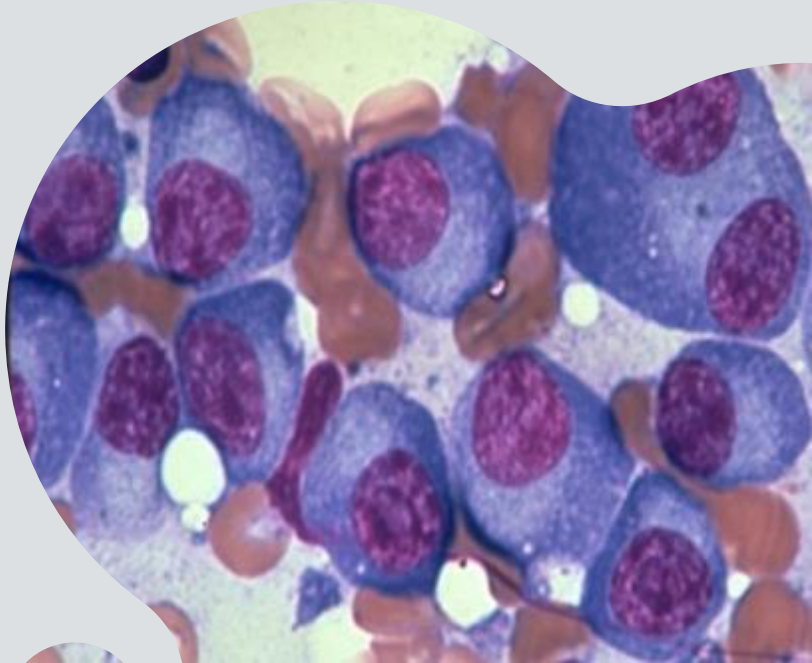


PARAPROTEİNEMİLERE YAKLAŞIM

DR. EMINE GULTURK

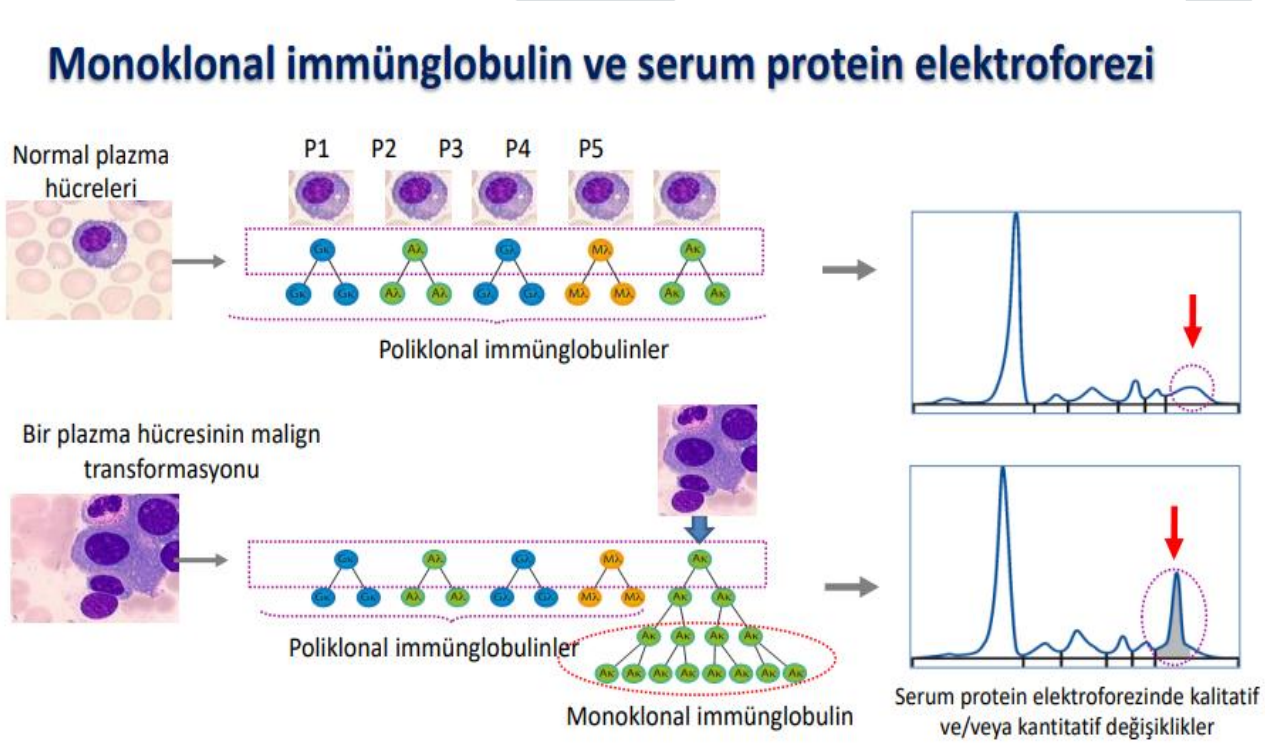
XII. İSTANBUL DAHİLİYE KLİNİKLERİ BULUŞMASI

12.11.2022



PARAPROTEİN

Monoklonal protein veya M bandı olarak da adlandırılan paraprotein, kanda veya idrarda bulunan ve en yaygın olarak plazma hücreleri veya olgun B lenfositlerin klonal proliferasyonundan kaynaklanan monoklonal bir immünoglobulin veya immünoglobulin hafif zinciridir.



Vaka 1

58 YAŞ KADIN HASTA

KRONİK HASTALIK VE İLAÇ KULLANIM ÖYKÜSÜ YOK

YAKINMA: 5 GÜNDÜR BULANTI, KUSMA-İSHAL. İSHAL GÜNDE 5-6 KERE BOL SULU KANSIZ-MUKUSSUZ.

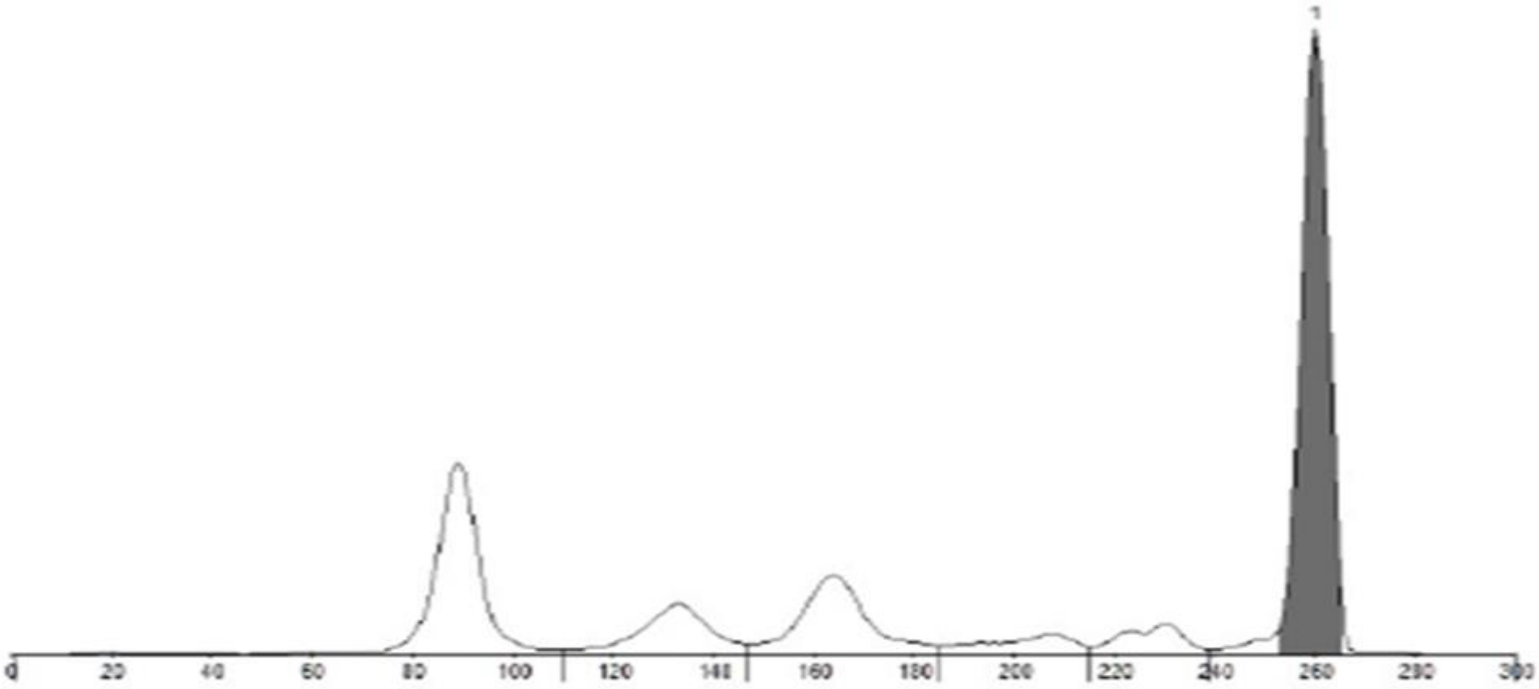
EVDE OĞLUNDA DA BİR HAFTADIR İSHAL OLDUĞU ÖĞRENİLDİ.

FM: DEHİDRATE GÖRÜNÜMLÜ, SOLUK

LAB: WBC 11.5 , NEU 6.12 , HB 8.4 , PLT 454, ÜRE 97 ,KRE 2.34 (BAZAL 6 AY ÖNCE 1), T PROT: 83.7, ALB: 20.2, CA: 9.74, NA 128 , K 3.43 , CRP 183

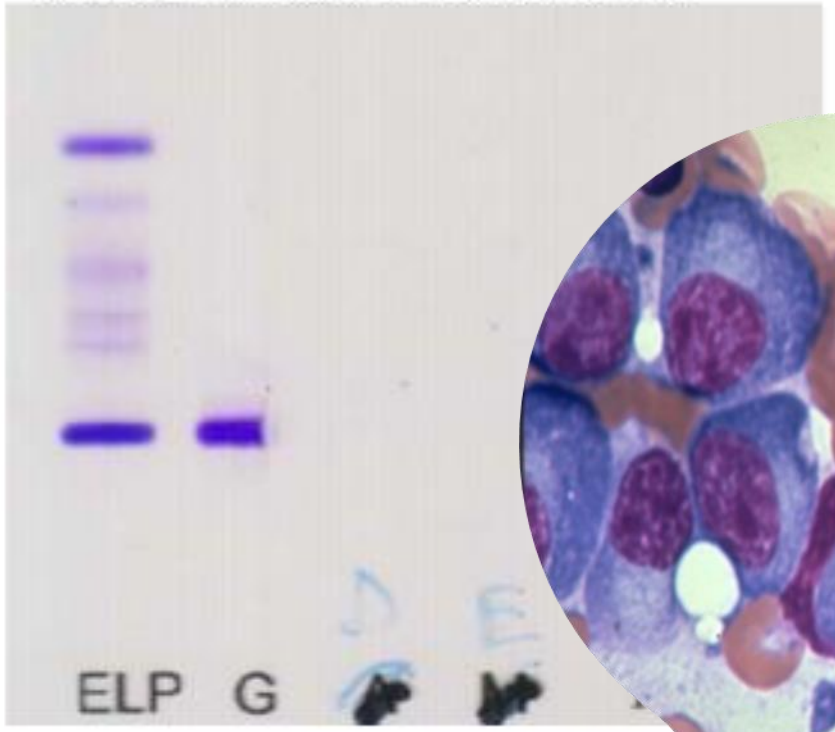
ADI SOYADI : [redacted] ID :512301138358 T.C. Kimlik No : [redacted]

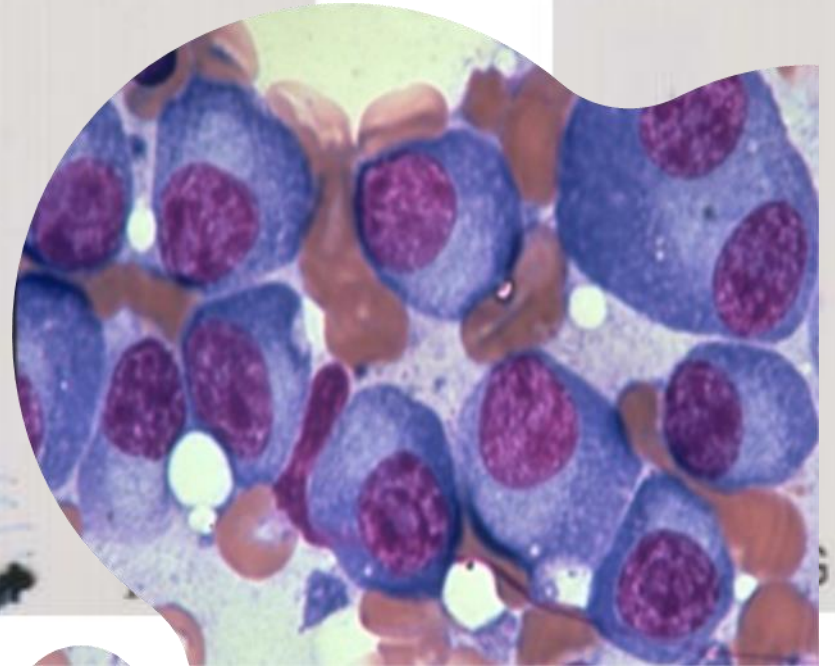
Protein Elektroforezi



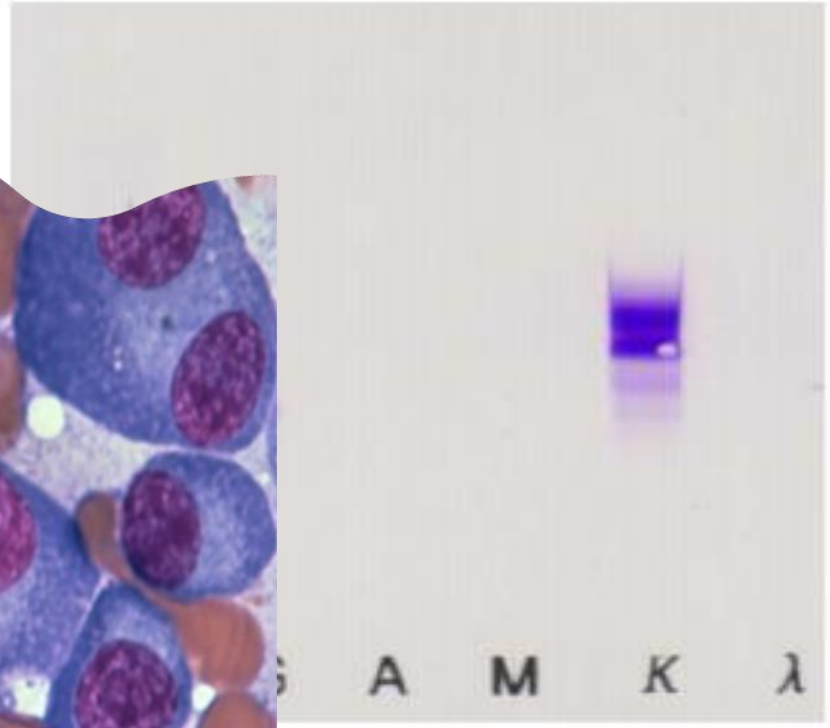
Pik	%	g/L
1	43.8	23.9

SERUM İMMUN ELEKTROFOREZİ





İDRAR İMMUN ELEKTROFOREZİ



VAKA-2

67 YAŞ ERKEK HASTA

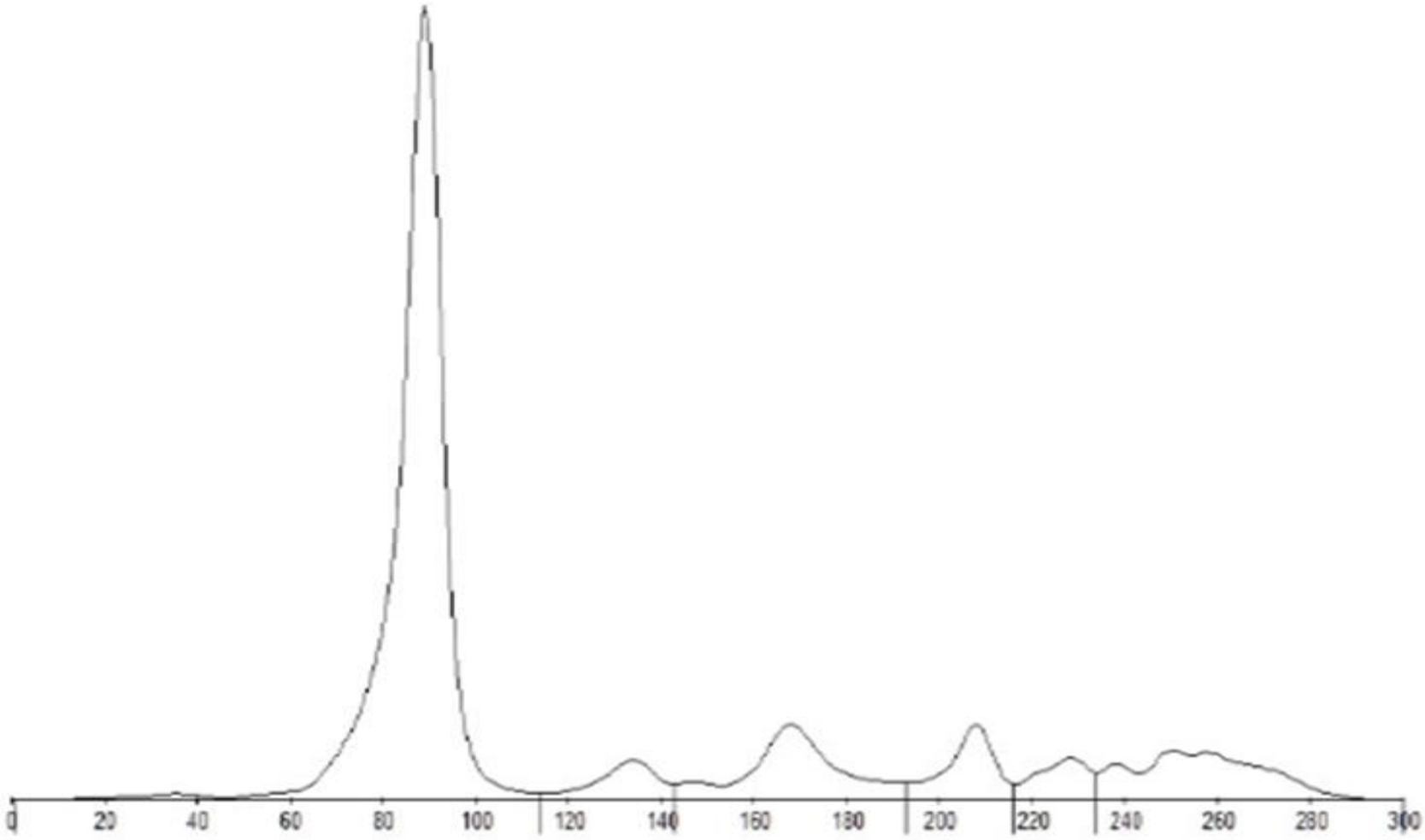
TİP II DM, HT, BPH TANILARI OLAN HASTA DÜZENLİ OLARAK DİYABET POLİKLİNİĞİNDEN TAKİPLİ

2020 YILINDAN BERİ KREATİNİN DEĞERLERİ 1,3-1,6 ARASINDA OLUP TİT ALBUMİN (-), SPOT İDRARDA MİKROALBUMİN 82 MG

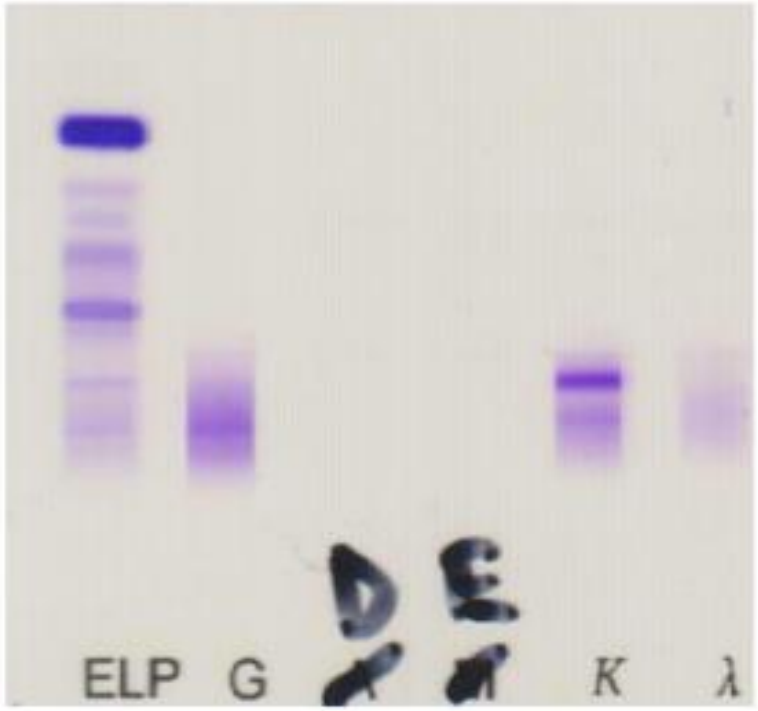
MAYIS 2022 DE DAHİLİYE KONTROLÜNDE KREATİNİN 2.2 SAPTANMASI ÜZERİNE NEFROLOJİ POLİKLİNİĞİNE YÖNLENDİRİLMİŞ.

FM: ÖZELLİK YOK

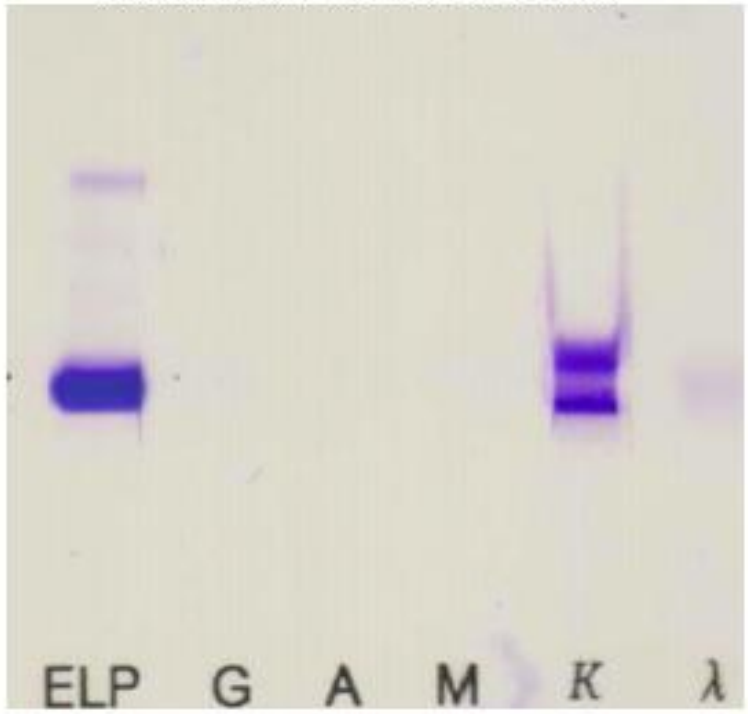
LAB: WBC 7.62 , NEU: 4.4 , HB11.4 , PLT 243, ÜRE 75 ,KRE 3,1 , T PROT: 67.7, ALB: 45.2, CA: 9.8, NA 137 , K 4.67. 24 SAATLİK İDRAR: 4,5 GR PROTEİN, 100 MG MA

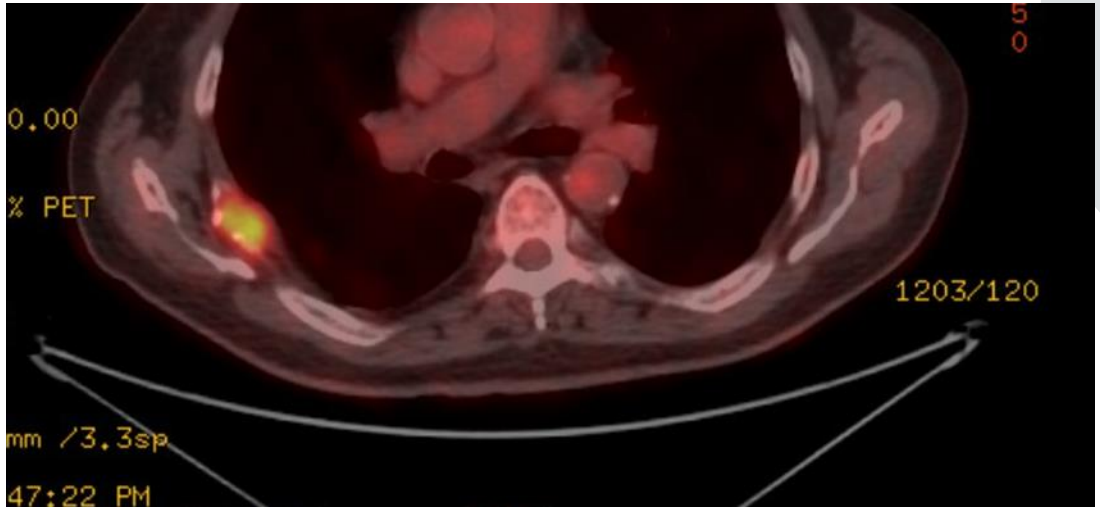

0
20
40
60
80
100
120
140
160
180
200
220
240
260
280
300

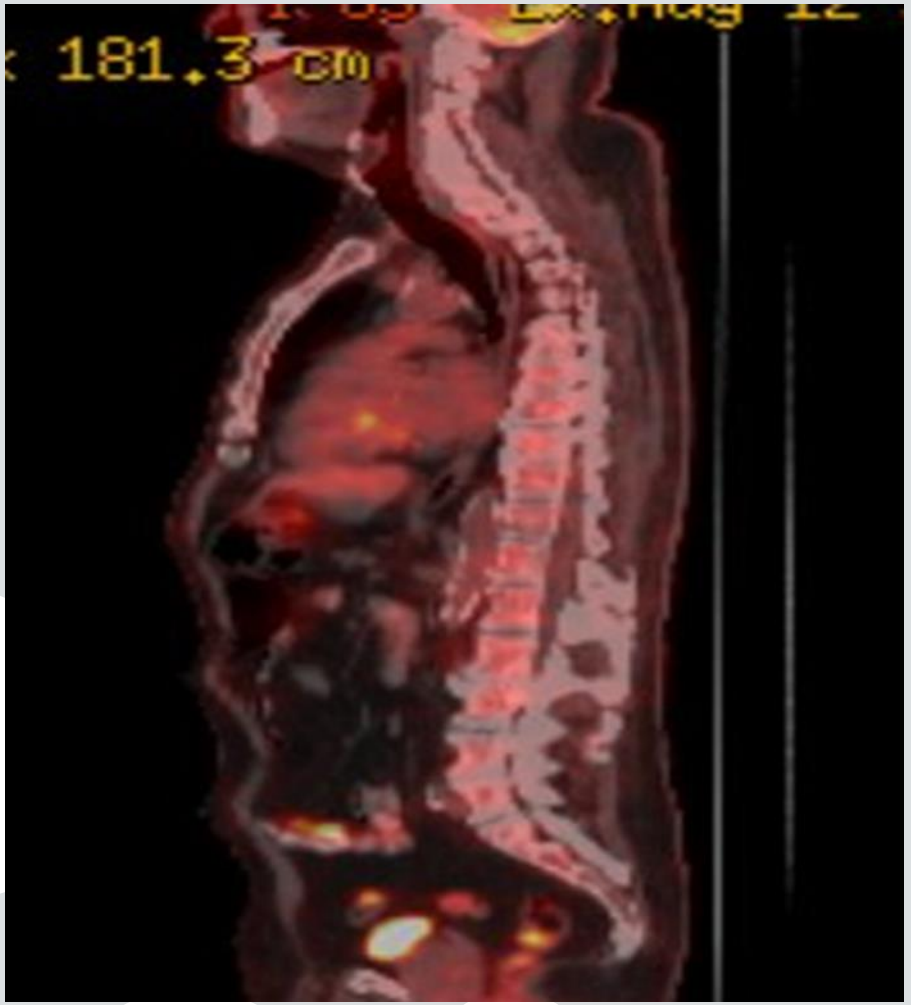
SERUM İMMUN ELEKTROFOREZİ



İDRAR İMMUN ELEKTROFOREZİ




5
0
0.00
% PET
1203/120
mm /3.3sp
47:22 PM


181.3 cm

VAKA-3

40 YAŞ ERKEK HASTA

ANEMİ, TROMBOSİTOPENİ NEDENİYLE YÖNLENDİRİLMİŞ.

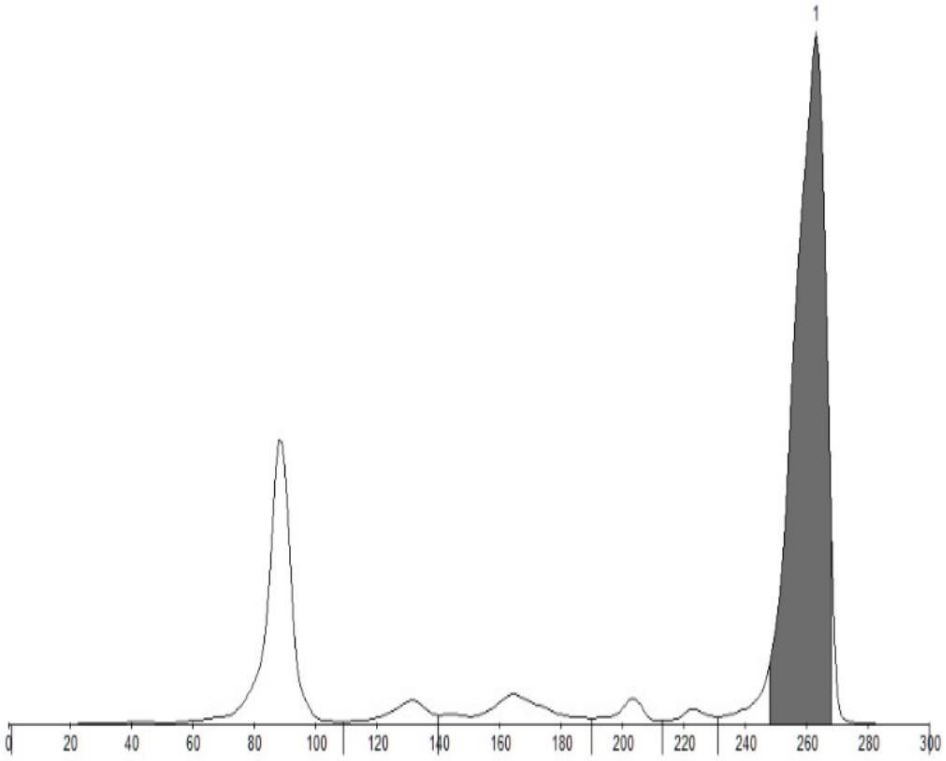
KİLO KAYBI, GECE TERLEMESİ VAR

FM: İNGUİNALE UZANAN DEV DALAK

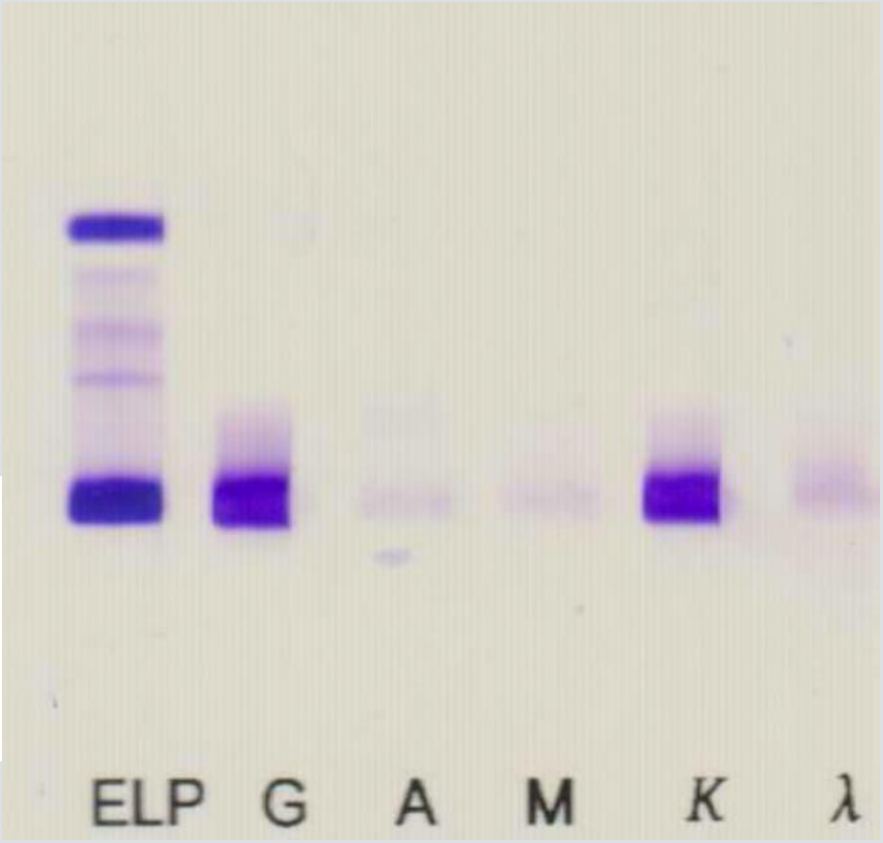
WBC 14,78 NEU 2,9 LYM 11,2 HGB 6,5 MCV 89 PLT 53BİN

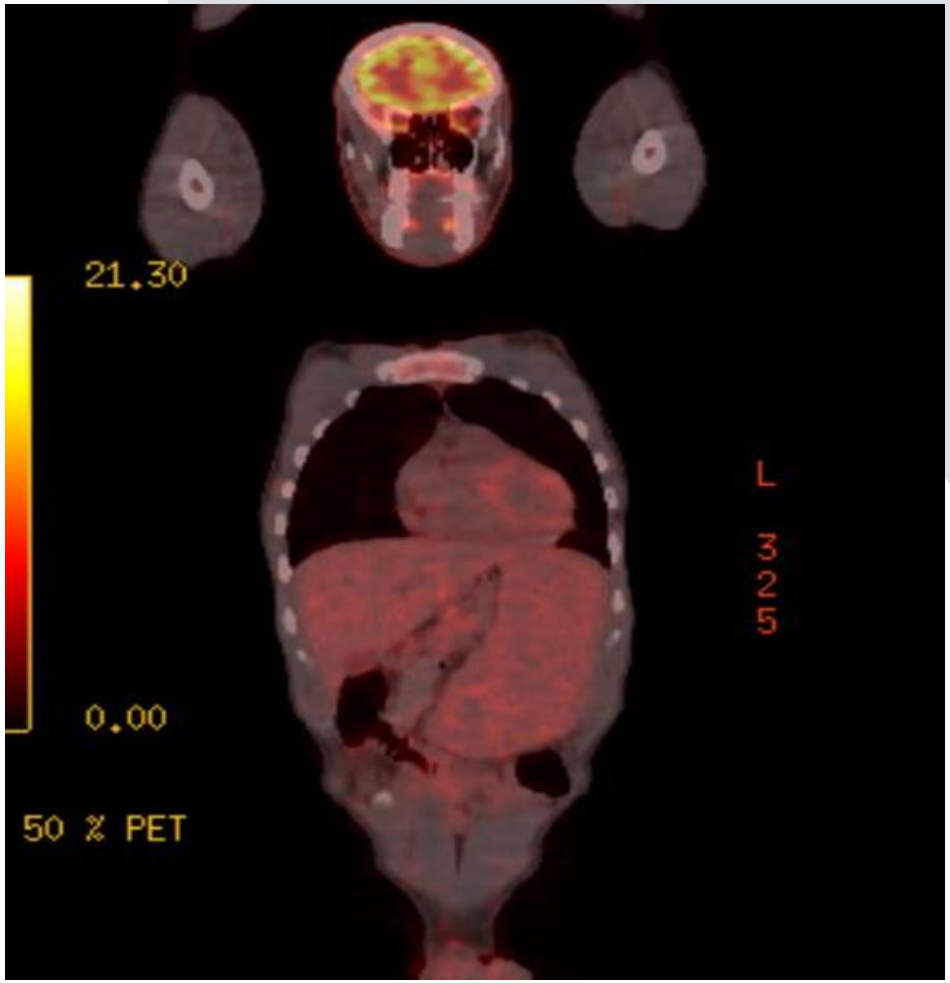
2019 WBC 15,45 NEU 5,15 LYM 9,28 HGB 14,2 MCV 87 PLT 172BİN

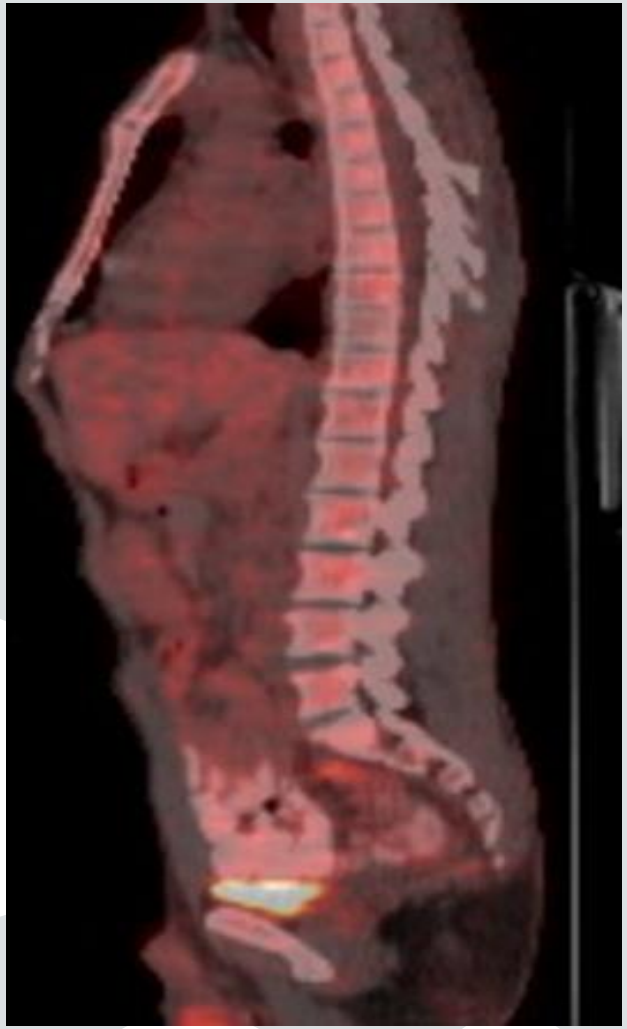
T. PROT: 13.1, ALB: 2.1

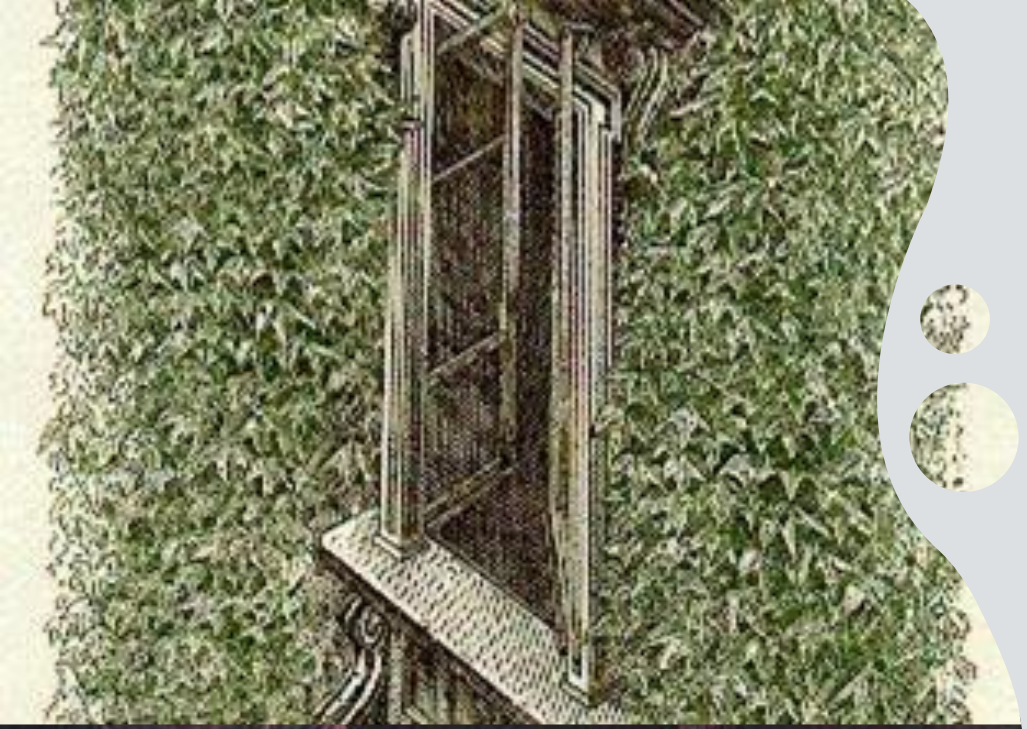


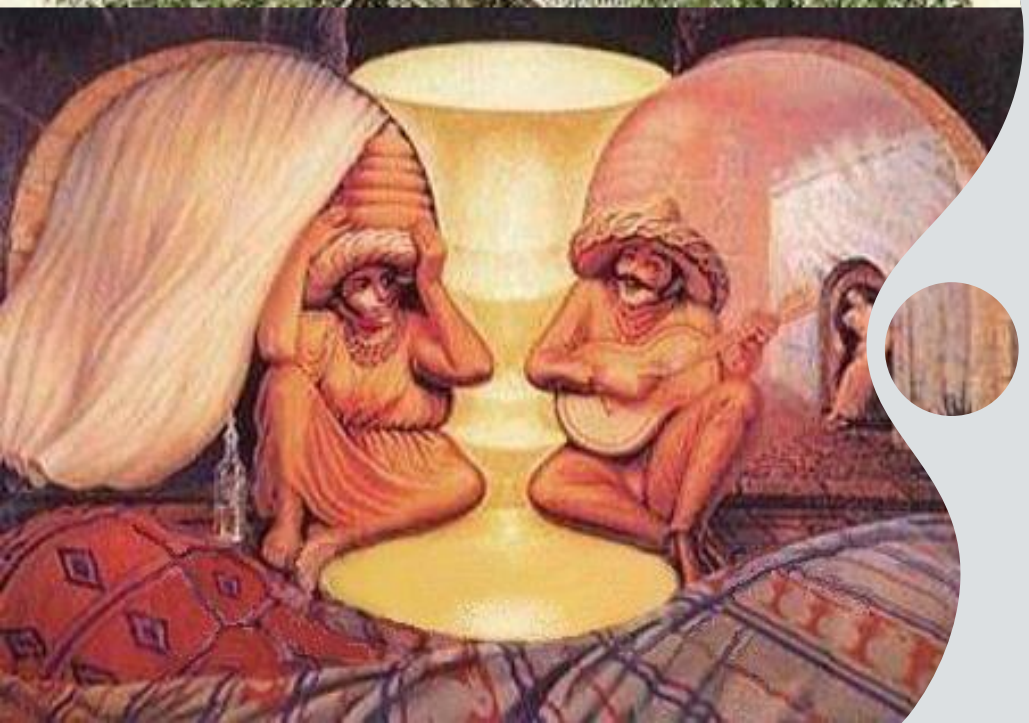
Pik	%	g/L
1	62.7	94.1




21.30
0.00
50 % PET
L
3
2
5



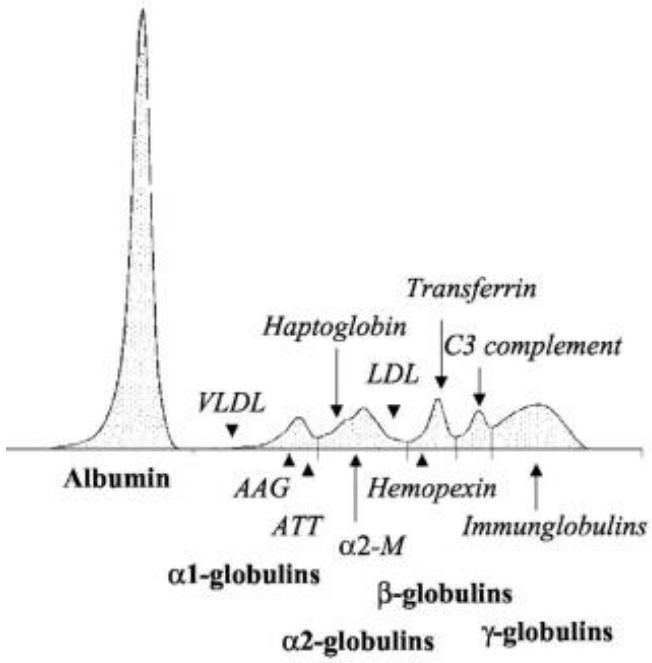


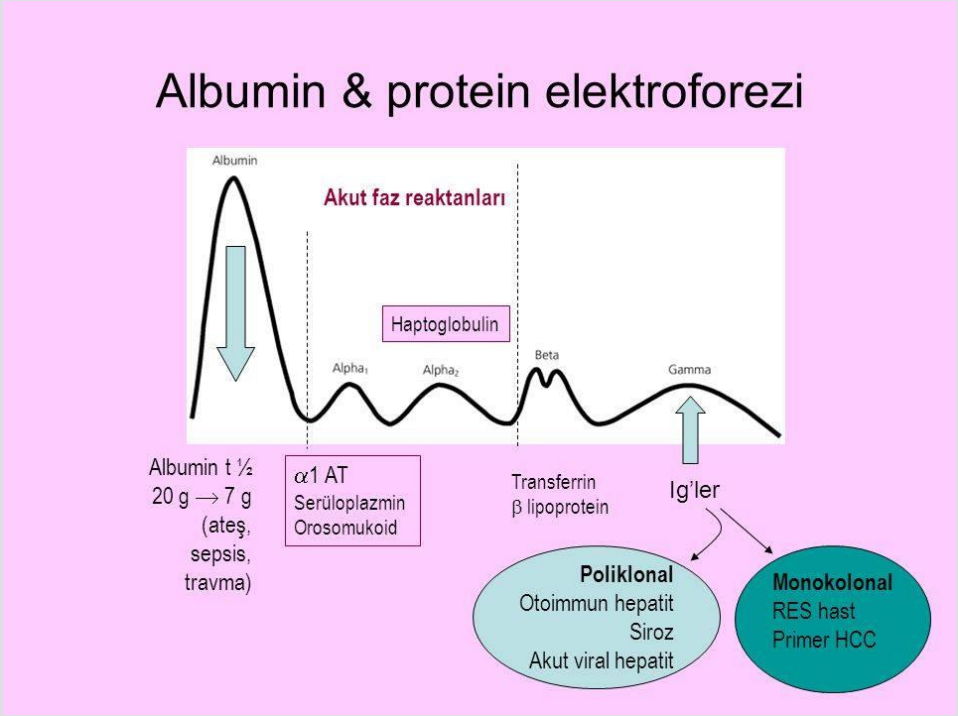


*HER MONOKLONAL GAMOPATİ MULTİPL MYELOMA DEĞİLDİR.

*MONOKLONAL GAMOPATİ SAPTANMAYAN PROTEİN ELEKTROFOREZİ İLE PLAZMA HÜCRE DİSKRAZİSİ DIŞLANAMAZ.

*PROTEİN ELEKTROFOREZİNE BAKAN HER KİŞİ FARKLI BİR AYRINTI GÖREBİLİR.





PROTEİN ELEKTROFOREZİ

Monoklonal gamopati ilişkili hastalıklar

Differential diagnosis for monoclonal gammopathy

Malignant

Plasma cell disease

- Monoclonal gammopathy of undetermined significance
- Multiple myeloma
- Smouldering multiple myeloma
- AL amyloidosis
- Other rarer malignant plasma cell disorders

B-cell (usually IgM) disease

- Lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia
- Chronic lymphocytic leukemia
- Small lymphocytic lymphoma
- Marginal zone lymphoma
- Other indolent lymphomas (rare)

Benign

Autoimmune/inflammatory disease

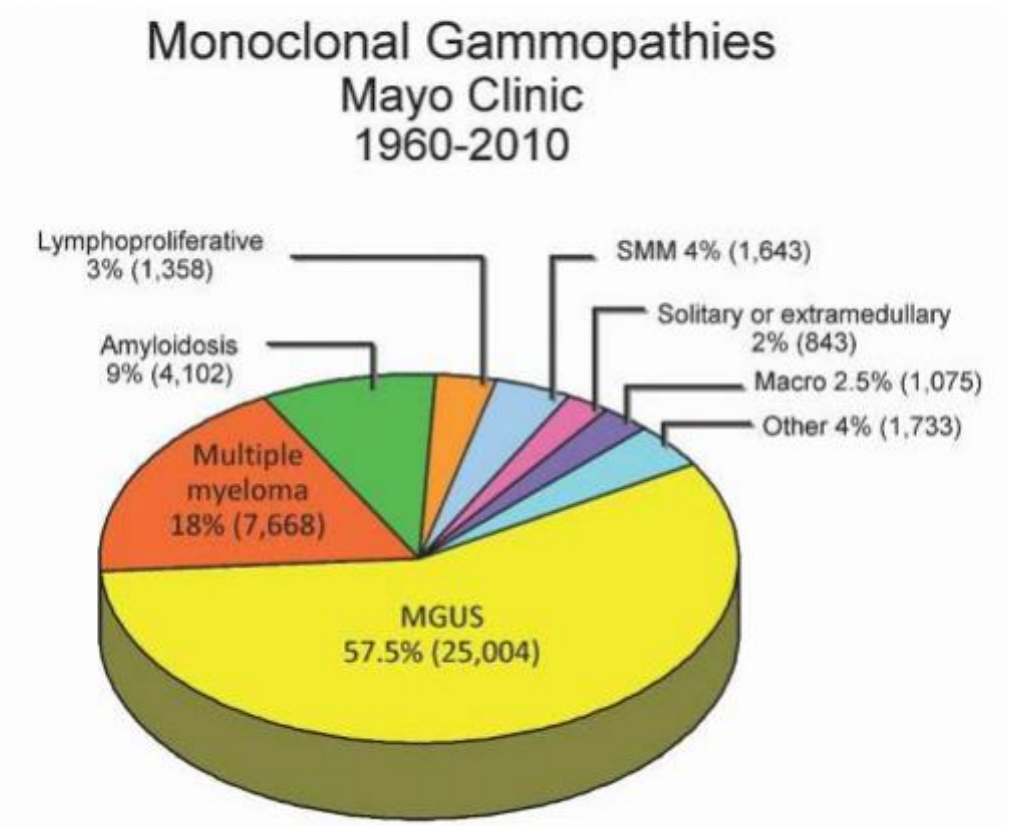
- Rheumatoid arthritis, ankylosing spondylitis
- Systemic lupus erythematosis, scleroderma, Sjogren syndrome
- Vasculitis, polymyalgia rheumatica
- Paraprotein-associated neuropathies

Infectious disease

- Viral infections (EBV, CMV, HIV, HBV, HCV)
- Severe acute infections
- Subacute or chronic infections (osteomyelitis, endocarditis, abscess)

Posttransplant effect

- Response to stem cell or solid organ transplantation



MGUS ile birliktelik gösterebilen klinik durumlar:

Dermatolojik: Edinsel C1 inhibitör eksikliği, Kriyoglobulinemi, Nekrobiyotik Ksantogranulom, **Schnitzler sendromu**

Endokrinolojik: İnsulin otimmün sendrom ,

Hematolojik: Edinsel Von Willebrandt sendromu, soğuk aglütinin hastalığı, TEMPI, İmmün Trombositopeni

Romatolojik: Skleromiksödem

Nefrolojik: Anti glomerüler bazal membran hastalığı, C3 glomerulonefriti, yoğun birikim hastalığı (Dense deposit disease), fibriller glomerulonefrit, immünotaktoid glomerulonefriti, hafif zincir proksimal tübülopatisi (Fanconi sendromu), membranöz nefropati, monoklonal immünoglobulin depo hastalığı, monoklonal gamopati ile birliktelik gösteren ilerleyici glomerulonefrit, AL, AH veya ALH amiloidoz, tip1 ve 2 kriyoglobulinemiler

Nörolojik: CANOMAD (kronik ataksi nöropatisi, oftalmopleji, IgM MGUS, soğuk aglütinin ve disialosyl antikorları),

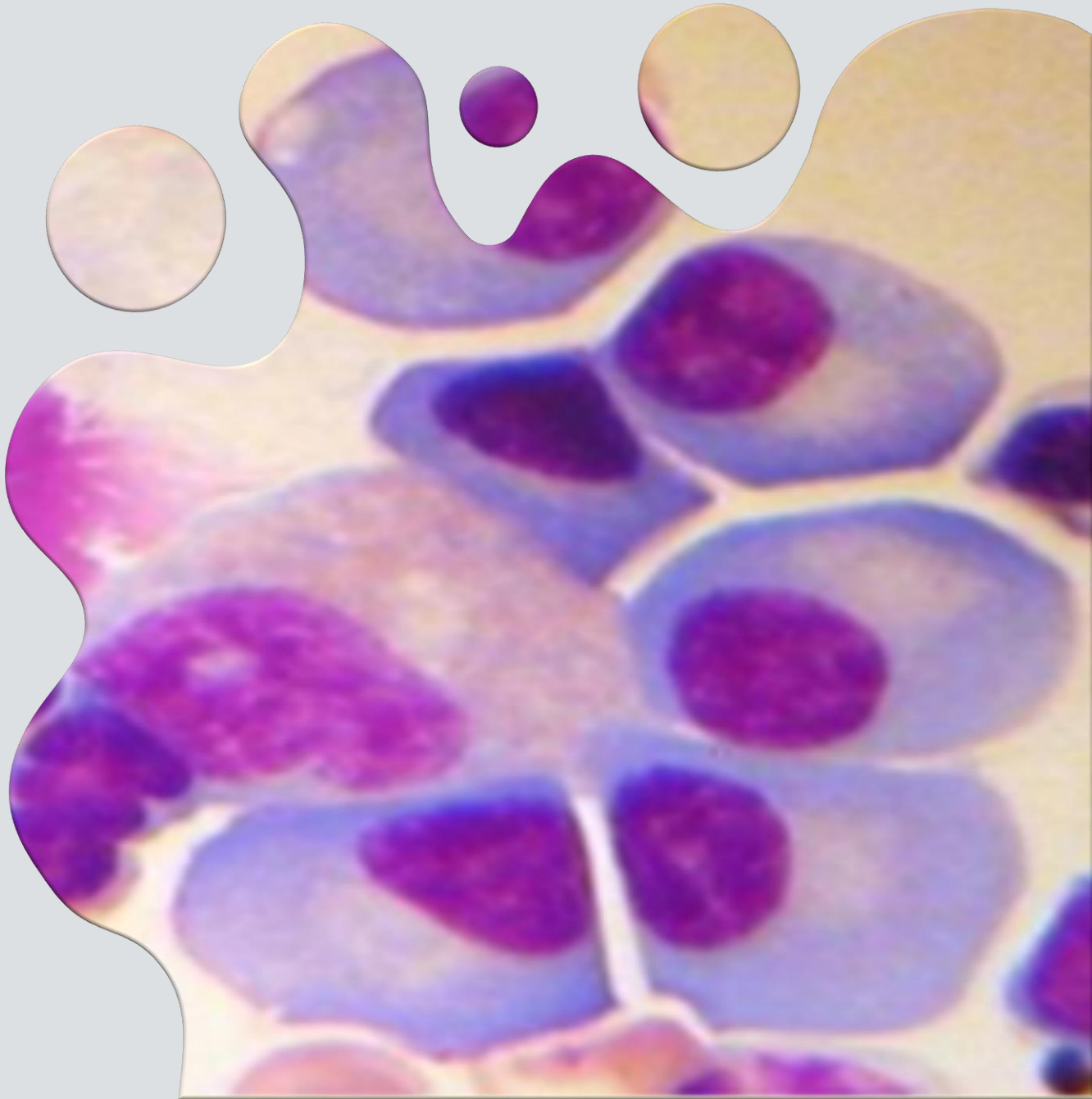
POEMS (Polinöropati, organomegali, endokrinopati, monoklonal gamopati (çoğunlukla lambda hafif zincir), deri değişiklikleri), sensorimotor nöropati, sporadik geç başlangıçlı nemalin myopatisi

Oftalmolojik : Korneal bakır birikimi, kristalin keratopatisi

Diğer: Kapiller sızma sendromu, kristal depolayan histiyositoz

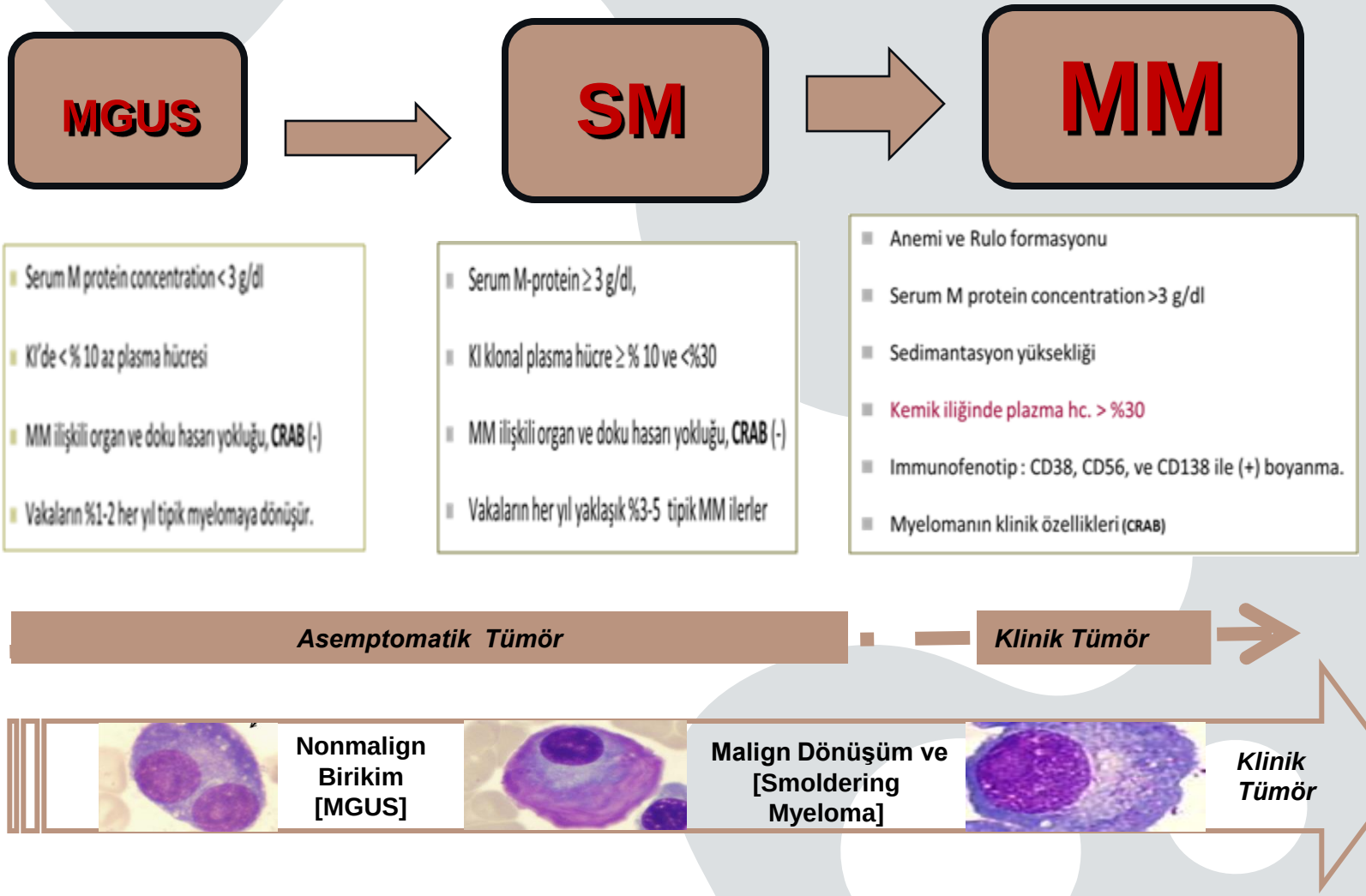
Multipl myeloma

B lenfosit hattında ortak progenitor hücreden kaynaklanan ve patolojik Ig (M proteini) salgılayan plazma hücrelerinin oluşturduğu bir hastalıktır.



Hastalığın Evreleri:

Her myelom olgusu, bir MGUS sürecinden geçerek ortaya çıkar.



Multipl Miyelom: Epidemiyoloji

Tanı yaşı ortalama 60 – 73

- Olguların % 2'si < 45 yaş

Risk faktörleri

- Yaş
- Erkek cinsiyeti
- Afrika kökenli
- Mesleki olarak zirai ilaçlar, böcek ilaçları, petrol ürünleri,
- Ağır metaller, plastikler, asbeste maruz kalmak
- Aile hikayesi riski artırır
- MGUS varlığı riski artırır
- Radyasyona maruz kalmak

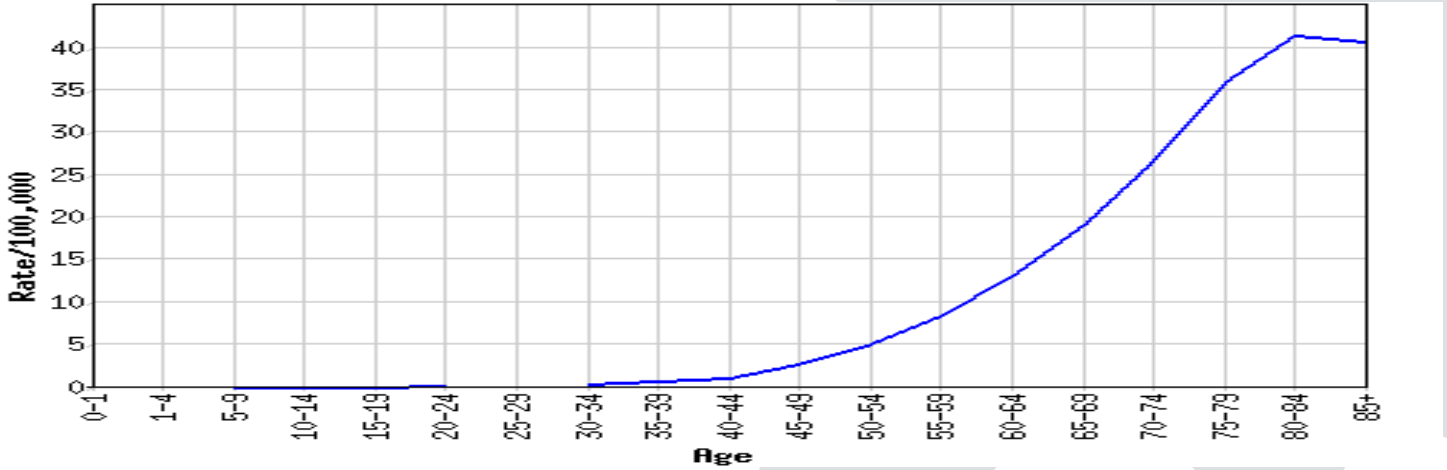
≈7500

Yeni vaka

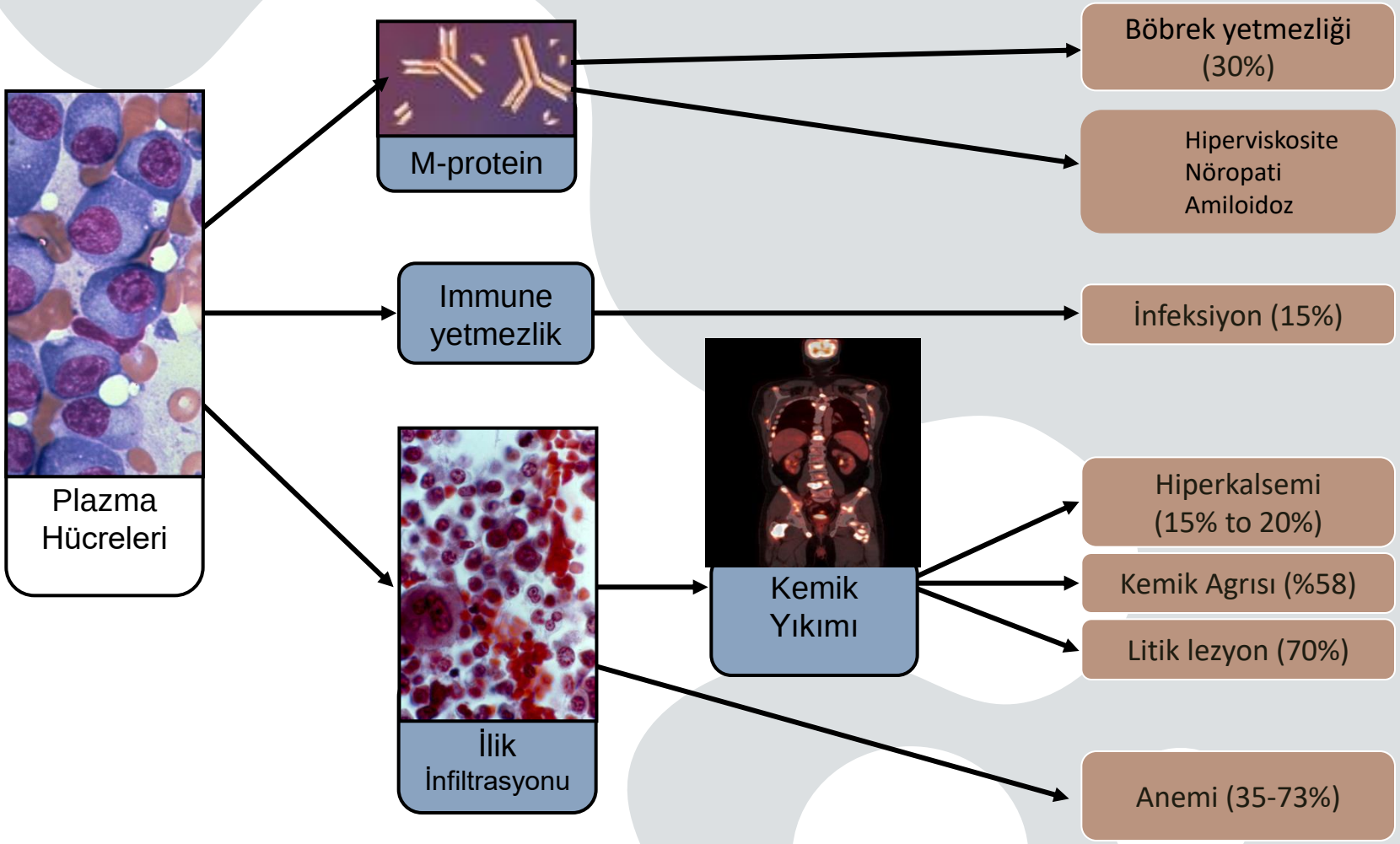
Klinik Bulgular

Rutin kontrol sırasında semptomsuz vakalarda, anemi, sedimantasyon yüksekliği, proteinüri şeklinde saptanırken;

Geç dönem vakalar kemik ve eklem ağrısı, renal (myelom böbreği) yetmezlik ve nörolojik semptomlar (hipervizkosite) ile başvurur.



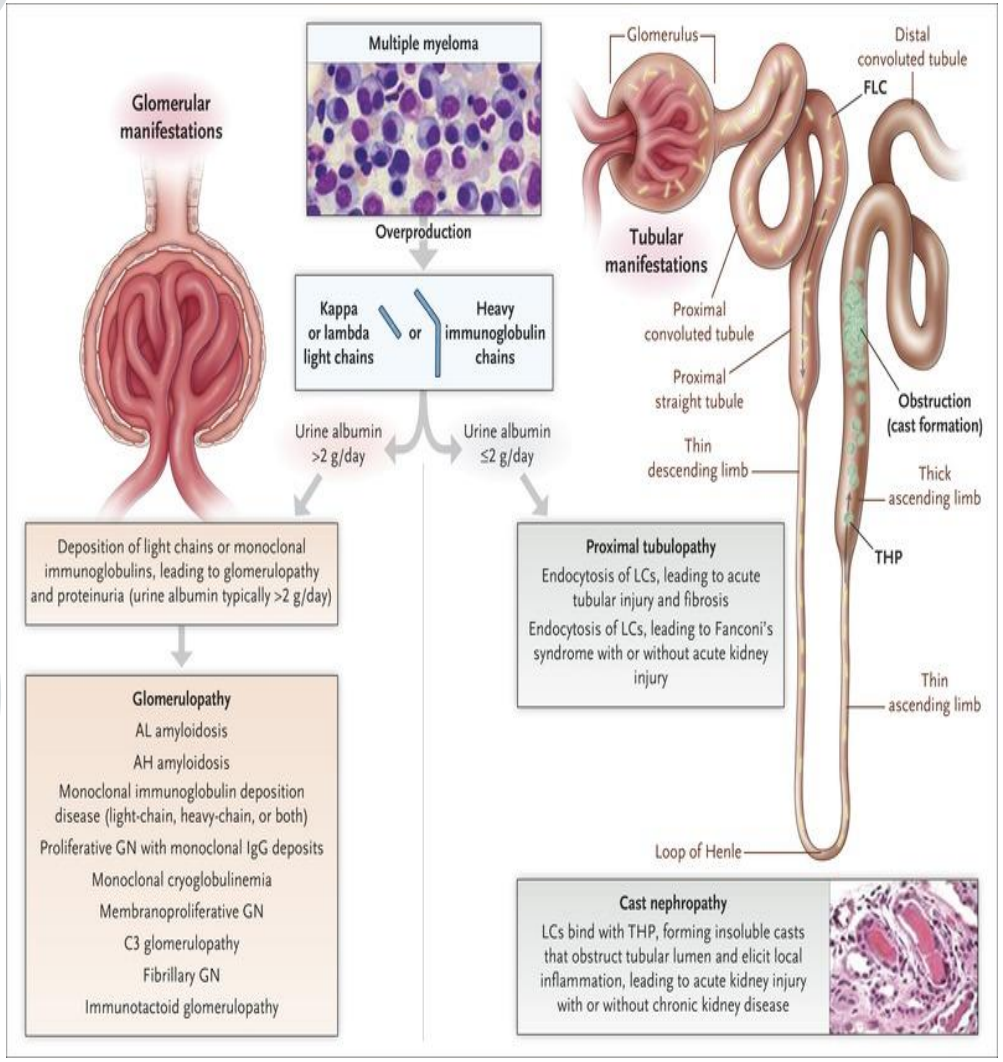
Klinik Bulgular



Hoffman R. Hematology: basic principles and practice, 5th edition; 2008. Ropper AH, et al. N Engl J Med. 1998;338:1601-1607.

Klinik Bulgular:
Renal yetmezlik: %25-50

- Renal bulgular teşhis esnasında vakaların % 25'inde mevcut iken; hastalığın seyri sırasında % 20 vakada daha renal yetmezlik bulguları gelişir.
- Çok sayıda faktör sorumludur. Hiperkalsemia, hiperürisemi, dehidratasyon ve tekrarlayan enfeksiyonlar renal yetersizliği tetikler.
- Renal yetmezliğin temel sebebi distal tübülüslerde hafif zincir presipitatlarının (Bence Jones proteini) birikmesidir
- Tedavi ile renal yetmezlik bulguları % 50 vakada geri dönüşümlü olabilir.



Klinik Bulgular:
Anemi: 70- 80%

Normokrom/normositik

Myelofizitik (malign hücre infiltrasyonu)

Plazma hücrelerinin ürettiği inhibitör sitokinler...

Endojen eritropoetin (EPO) üretiminin yetersizliği veya suprese edilmiş EPO cevabı sonucu kemik iliğinde yetersiz kırmızı küre üretimi sonucu oluşur.

Renal yetmezlikli hastalarda anemi daha şiddetli olabilir.

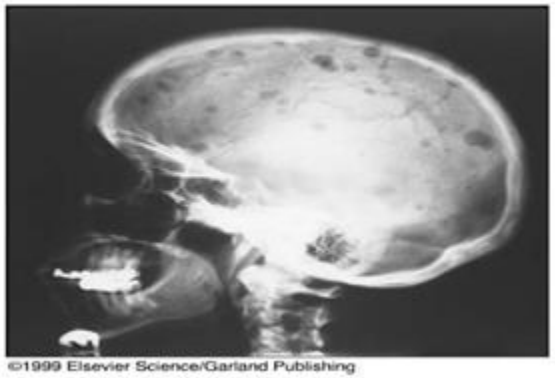
Lökopeni ve trombositopeni sadece İleri vakalarda

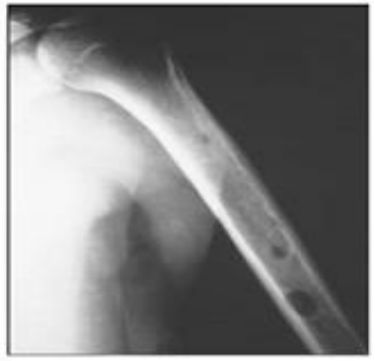
Klinik Bulgular:

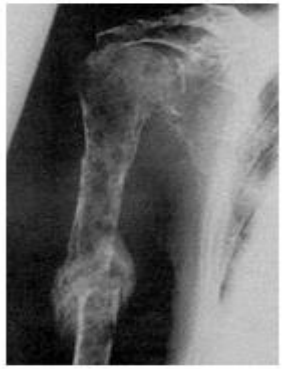
Kemik ağrısı ve kemik lezyonları

- Plazma hücreleri infiltre ettiği kemiklerde osteoklastik hiperaktiviteye yol açar.
- Kemik rezorbsiyonu IL-6 ve IL-1ß tarafından uyarılan osteoklastlarca yönlendirilir.
- Hareketle ortaya çıkar; İlk teşhiste vakaların % 70'ine yakınında litik kemik lezyonları ve/veya fraktürler saptanır.
- Tipik lezyon "Zımba ile delinmiş manzarası" olup; kemik iliği yapımının aktif olduğu kafa kemikleri, vertebralar ve femurda multifokal litik lezyonlara yol açar.

  Yük taşıyan kemiklerin kompresyonu, uzun kemiklerin fraktürleri ortaya çıkar.







Klinik Bulgular:

Hiperkalsemi % 20-30

Vakaların % 20'sinde ilerleyici kemik lezyonlarına bağlı olarak kemikten seruma Ca^{++} salınımı sonucu oluşur.

Hiperkalsemi hastalığın progresyon ve proliferasyonu için önemli bir göstergedir.

Hastalığın tedavisi ile birlikte hiperkalsemi düzelir.

Klinik Bulgular :

Enfeksiyonlara yatkınlık (AC-ÜS)

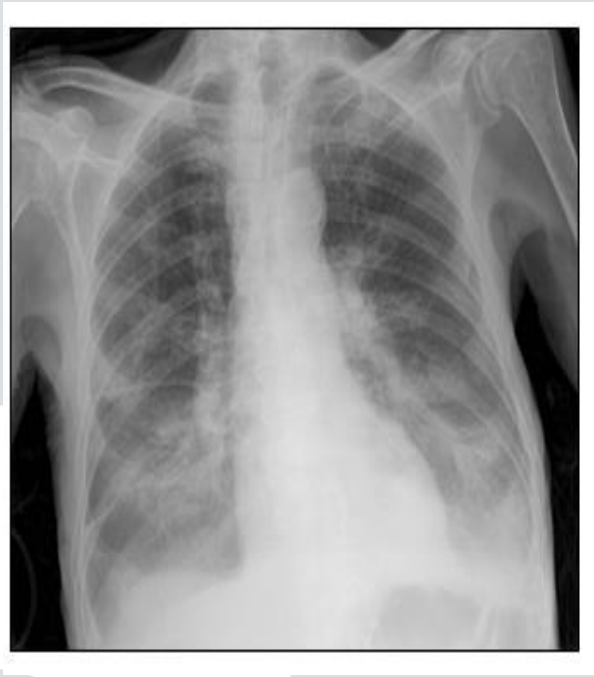
Diffüz Hipogamaglobinemi.

Zayıf AK cevabı ,

Nötrofil disfonksiyonu

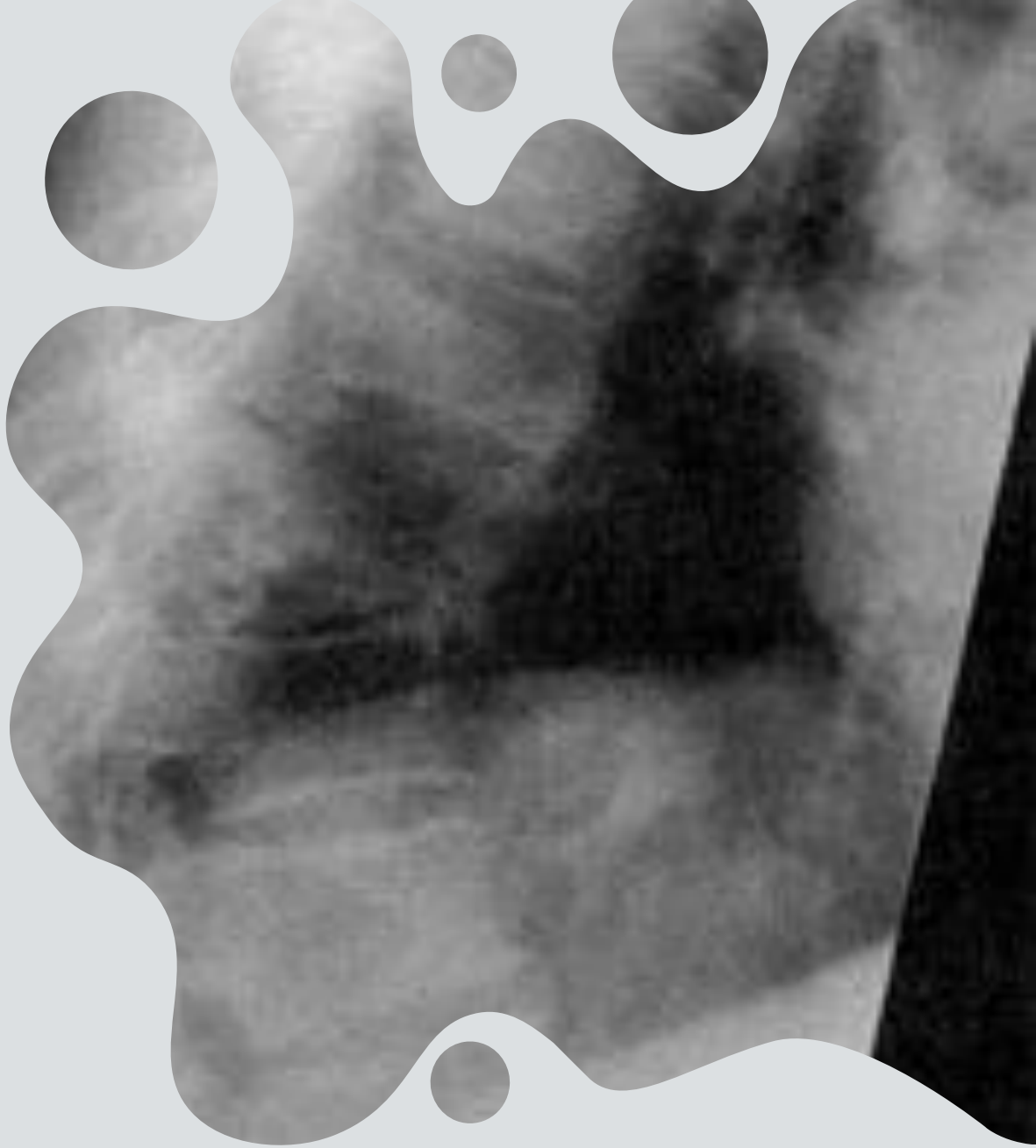
Pneumococcus, S.aureus, GN aeroblar

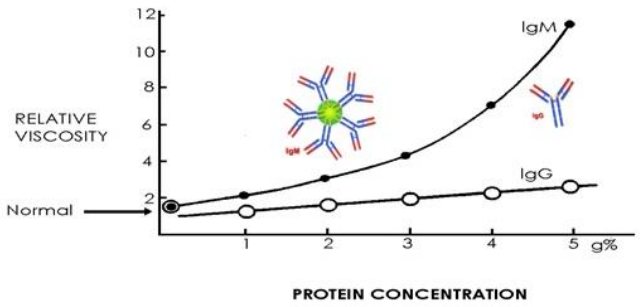
Pneumonia,Pyelonephrits



Klinik Bulgular :
Spinal Kord Kompresyonu

- Tümörün invaze ettiği vertebralardan direk invazyon veya intervertebral foremen içine büyüme sonucu oluşur.
- Vakaların % 10-15 inde; hastalığın erken evrelerinde veya geç relaps evresinde saptanır.
- MR ile acil olarak kord kompresyon bölgesi görüntülenmeli; radyoterapi ve yüksek doz glukokortikoid tedavisi başlanmalıdır





Klinik Bulgular:

Hiperviskosite

Vakaların % 5 kadarında saptanır.

En sık IgM alt tipi ile birliktedir

Hipervizkosite hemorajik bir komplikasyon olmaksızın da kanamalara, oküler lezyonlara ve nörolojik semptomlara (baş dönmesi, somnolens v.s.) yol açar.

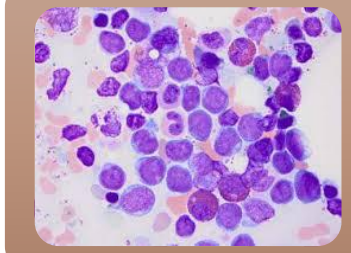
BAŞLANGIÇ TESTLERİ

Tam kan sayımı, periferik yayma

Biyokimya

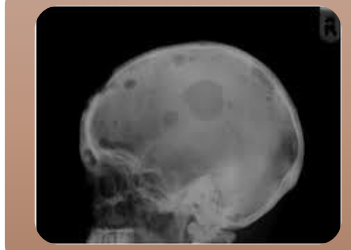
B2 mikroglobulin ve albümin

Elektroforez, immunofiksasyon, serbest hafif zincirler



Kemik iliği aspirasyon biyopsisi

- FISH
- Sitogenetik



Kemik survey

PET CT veya MRI

Kemik iliği plazma hücreleri > %10 veya biyopsi ile kanıtlanmış plazmasitoma ve aşağıdakilerden biri

CRAB

Hiperkalsemi: >11mg/dL

Kemik iliğinde %60 veya daha fazla plazma hücresi

Böbrek yetmezliği: Cr >2mg/dL veya klirens <40ml/dk

Hafif zincir oranı >100

Anemi: Hgb de >2g/dL azalma or Hgb < 10g/dL

MRI ile saptanan lezyonlar ≥5mm

Kemik lezyonları: ≥1 kemik lezyonu CT, PET veya x ray, osteopeni

STAGING SYSTEMS FOR MULTIPLE MYELOMA[a]

Stage	International Staging System (ISS)	Revised-ISS (R-ISS)
I	Serum beta-2 microglobulin <3.5 mg/L, Serum albumin ≥3.5 g/dL	ISS stage I and standard-risk chromosomal abnormalities by FISH[b] and Serum LDH ≤ the upper limit of normal
II	Not ISS stage I or III	Not R-ISS stage I or III
III	Serum beta-2 microglobulin ≥5.5 mg/L	ISS stage III and either high-risk chromosomal abnormalities by FISH[b] or Serum LDH > the upper limit of normal

M stemleri

[a] Palumbo A, Avet-Loiseau H, Oliva S, et al. Revised International Staging System for Multiple Myeloma: A Report from International Myeloma Working Group. J Clin Oncol 2015;33:2863-2869.

[b] Standard-risk: No high-risk chromosomal abnormality. High-risk: Presence of del(17p) and/or translocation t(4;14) and/or translocation t(14;16).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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Multiple Myeloma

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NCCN Categories of Evidence and Consensus: All recommendations are category 2A unless otherwise indicated.

See NCCN Categories of Evidence and Consensus.

NCCN Categories of Preference:
All recommendations are considered appropriate.

See NCCN Categories of Preference.

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INITIAL DIAGNOSTIC WORKUP[a]

- History and physical (H&P) exam
- CBC, differential, and platelet count
- Peripheral blood smear
- Serum BUN/creatinine, electrolytes, liver function tests, albumin,[b] calcium, serum uric acid, serum LDH,[b] and beta-2 microglobulin[b]
- Creatinine clearance (calculated or measured directly)[c]
- Serum quantitative immunoglobulins, serum protein electrophoresis (SPEP), and serum immunofixation electrophoresis (SIFE)
- 24-h urine for total protein, urine protein electrophoresis (UPEP), and urine immunofixation electrophoresis (UIFE)
- Serum free light chain (FLC) assay
- Whole-body low-dose CT scan or FDG PET/CT[d,e]
- Unilateral bone marrow aspirate and biopsy, including immunohistochemistry (IHC) and/or multi-parameter flow cytometry
- Plasma cell fluorescence in situ hybridization (FISH)[b] panel on bone marrow[f] [del(13), del (17p13), t(4;14), t(11;14), t(14;16), t(14:20), 1q21 gain/1q21 amplification, 1p deletion][g]
- NT-proBNP/BNP[h]

Useful In Certain Circumstances

- If whole-body low-dose CT or FDG PET/CT is negative, consider whole-body MRI without contrast to discern smoldering myeloma from multiple myeloma (MM)
- Tissue biopsy to confirm suspected plasmacytoma
- Plasma cell proliferation
- Serum viscosity
- Human leukocyte antigen (HLA) typing
- Hepatitis B and hepatitis C testing and HIV screening as required
- Echocardiogram
- Evaluation for light chain amyloidosis, if appropriate (See NCCN Guidelines for Systemic Light Chain Amyloidosis)
- Single nucleotide polymorphism (SNP) array on bone marrow,[f] and/or next-generation sequencing (NGS) panel on bone marrow[f]
- Consider baseline clone identification and storage of aspirate sample for future minimal residual disease (MRD) testing by NGS
- Assess for circulating plasma cells as clinically indicated

CLINICAL FINDINGS

- Solitary plasmacytoma → See Primary Treatment (MYEL-2)
- Smoldering myeloma (asymptomatic)[i] → See Primary Treatment (MYEL-3)
- MM (symptomatic)[i] → See Primary Treatment (MYEL-4)
- Monoclonal gammopathies of clinical significance
  - For Monoclonal Gammopathy of Renal Significance see MGRS-1
  - For Monoclonal Gammopathy of Neurological Significance see MGNS-1

[a] Frailty assessment should be considered in older adults. See NCCN Guidelines for Older Adult Oncology.
[b] These tests are essential for R-ISS staging. See Disease Staging and Risk Stratification for Multiple Myeloma (MYEL-A).
[c] See Management of Renal Disease in Multiple Myeloma (MYEL-J).
[d] Skeletal survey is acceptable in certain circumstances. However, it is significantly less sensitive than whole-body low-dose CT and FDG PET/CT. If whole-body FDG PET/CT or low-dose CT has been performed, then skeletal survey is not needed. FDG PET should always be performed with CT.
[e] See Principles of Imaging (MYEL-B).
[f] CD138-positive selected sample is strongly recommended for optimized yield.
[g] 1q21 amplification is defined as ≥4 copies detected by FISH, and a gain is defined as 3 copies of 1q21.
[h] If NT-proBNP is not available, BNP can be performed.

TEŞEKKÜR EDERİM