KEMİK İLİĞİ YETMEZLİĞİ

Prof. Dr. Işınsu Kuzu

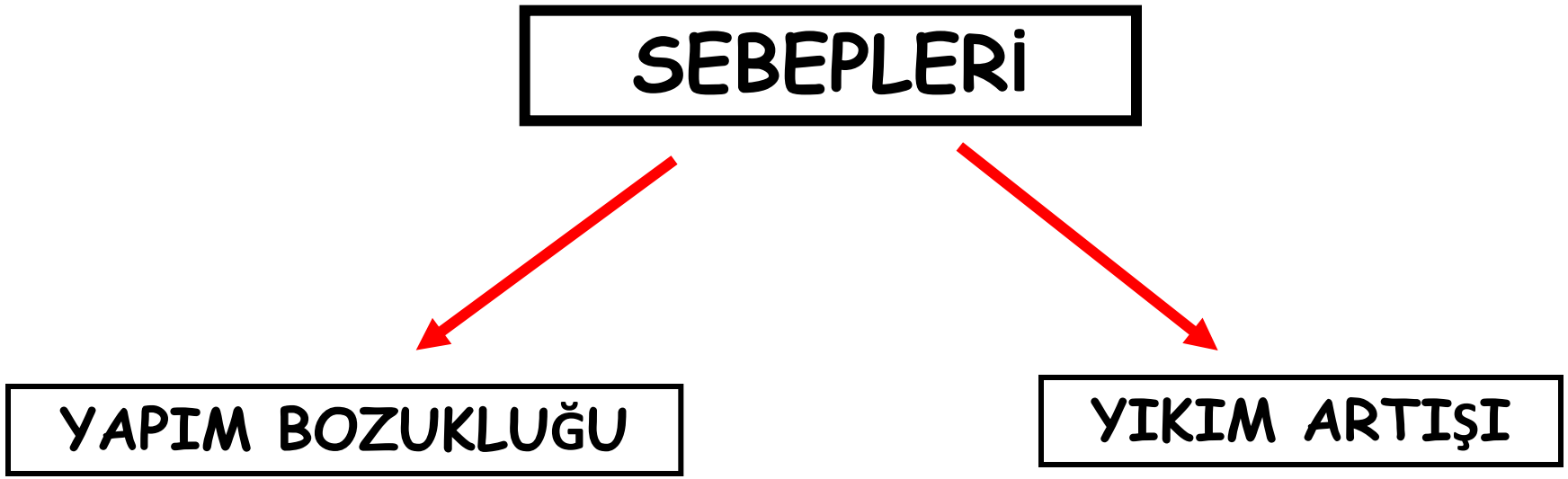
Patoloji Anabilim Dalı

13 Mart 2017

DÖNEM III MODÜL IV

SİTOPENİ

Kemik iliği kaynaklı hücrelerin periferik kanda sayıca azalması



YAPIM BOZUKLUĞU

YIKIM ARTIŞI

Nerede görürüz?

YAPIM BOZUKLUĞU

KEMİK İLİĞİ

YIKIM ARTIŞI

Nerede görürüz?

YAPIM BOZUKLUĞU

KEMİK İLİĞİ

YIKIM ARTIŞI

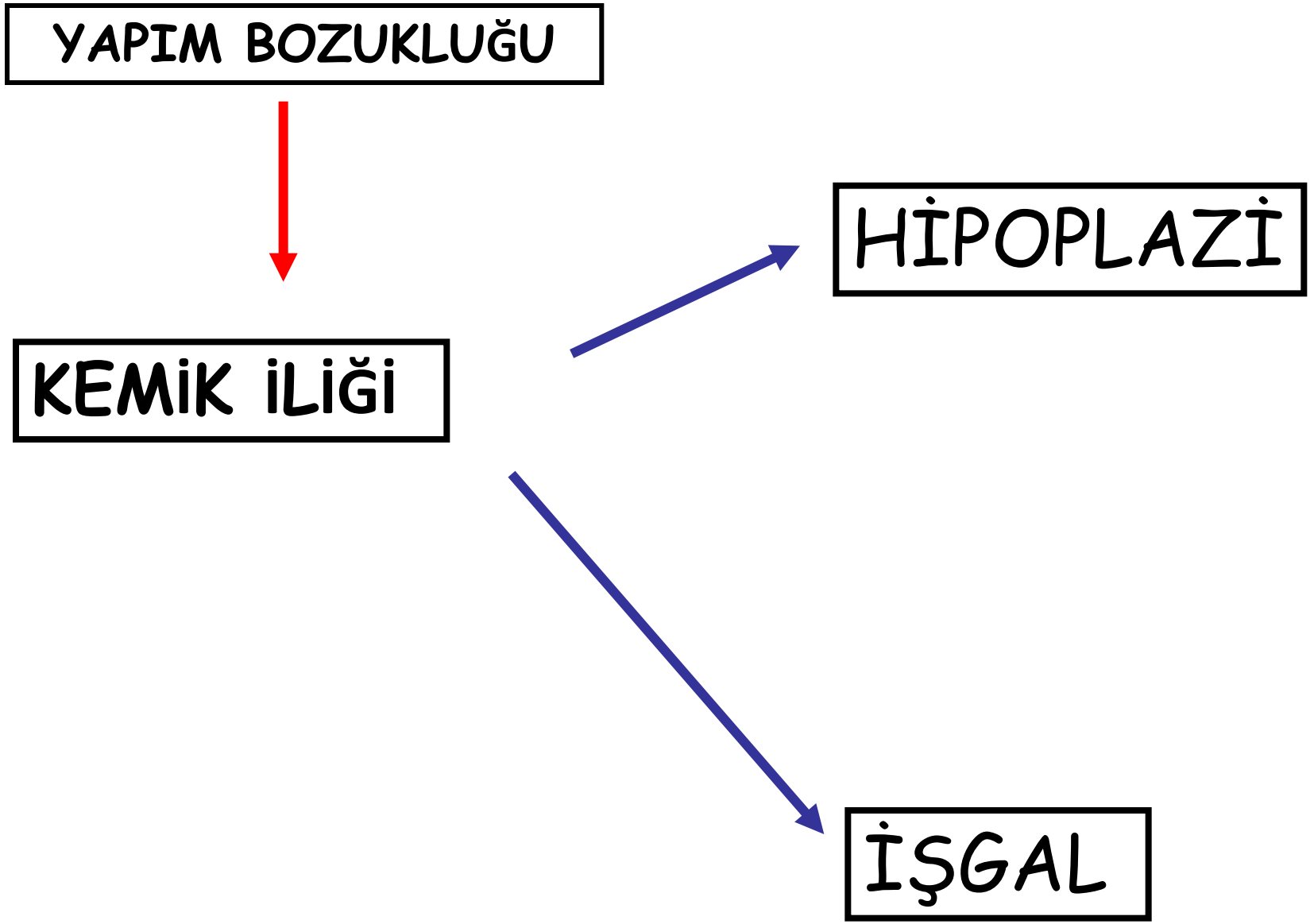
1.DALAK
2.PERİFERİK DAMARLAR
3.KEMİK İLİĞİ

Nerede görürüz?

YAPIM BOZUKLUĞU

KEMİK İLİĞİ

Ne görürüz?



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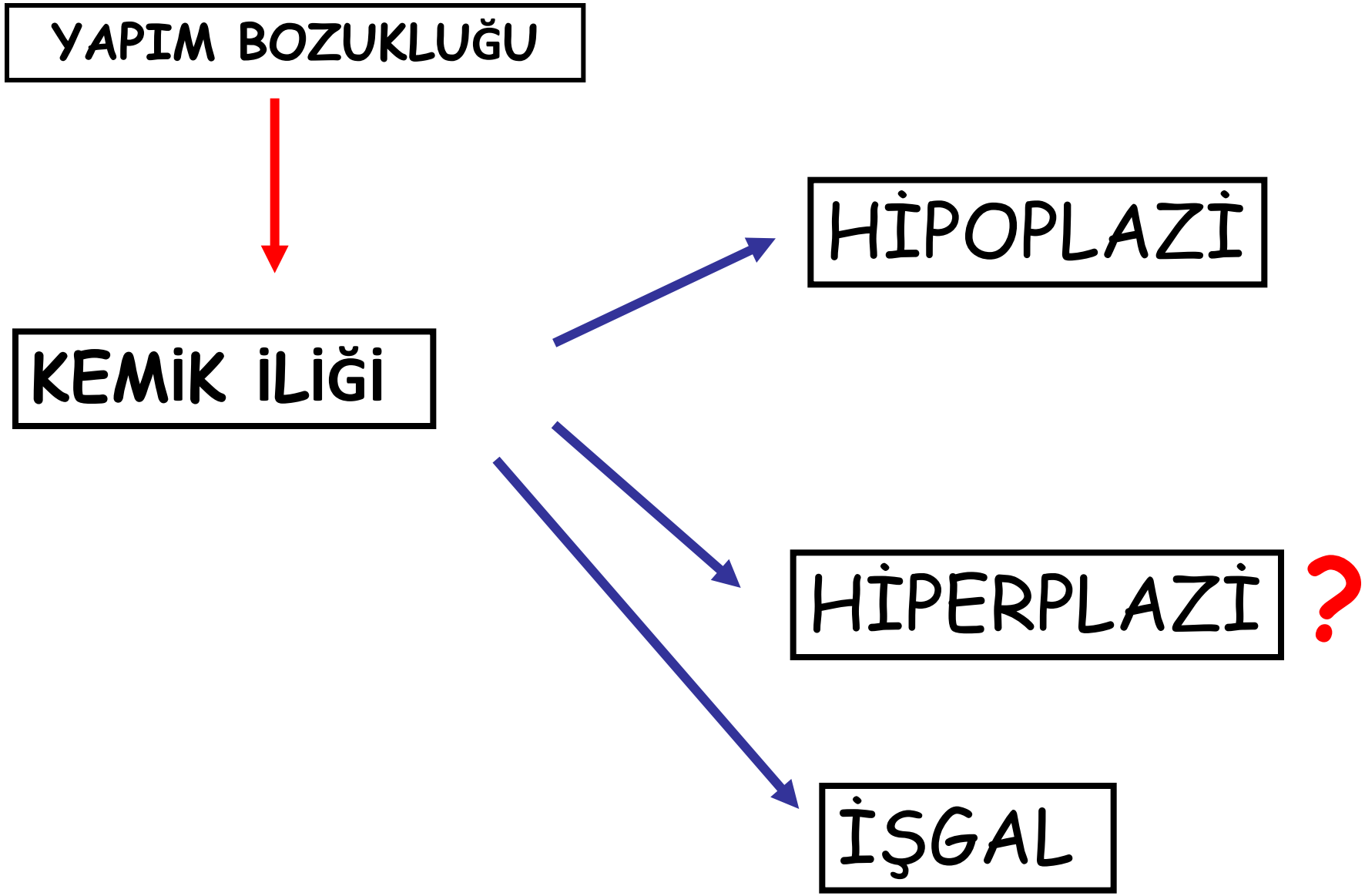


Ne görürüz?

YAPIM BOZUKLUĞU

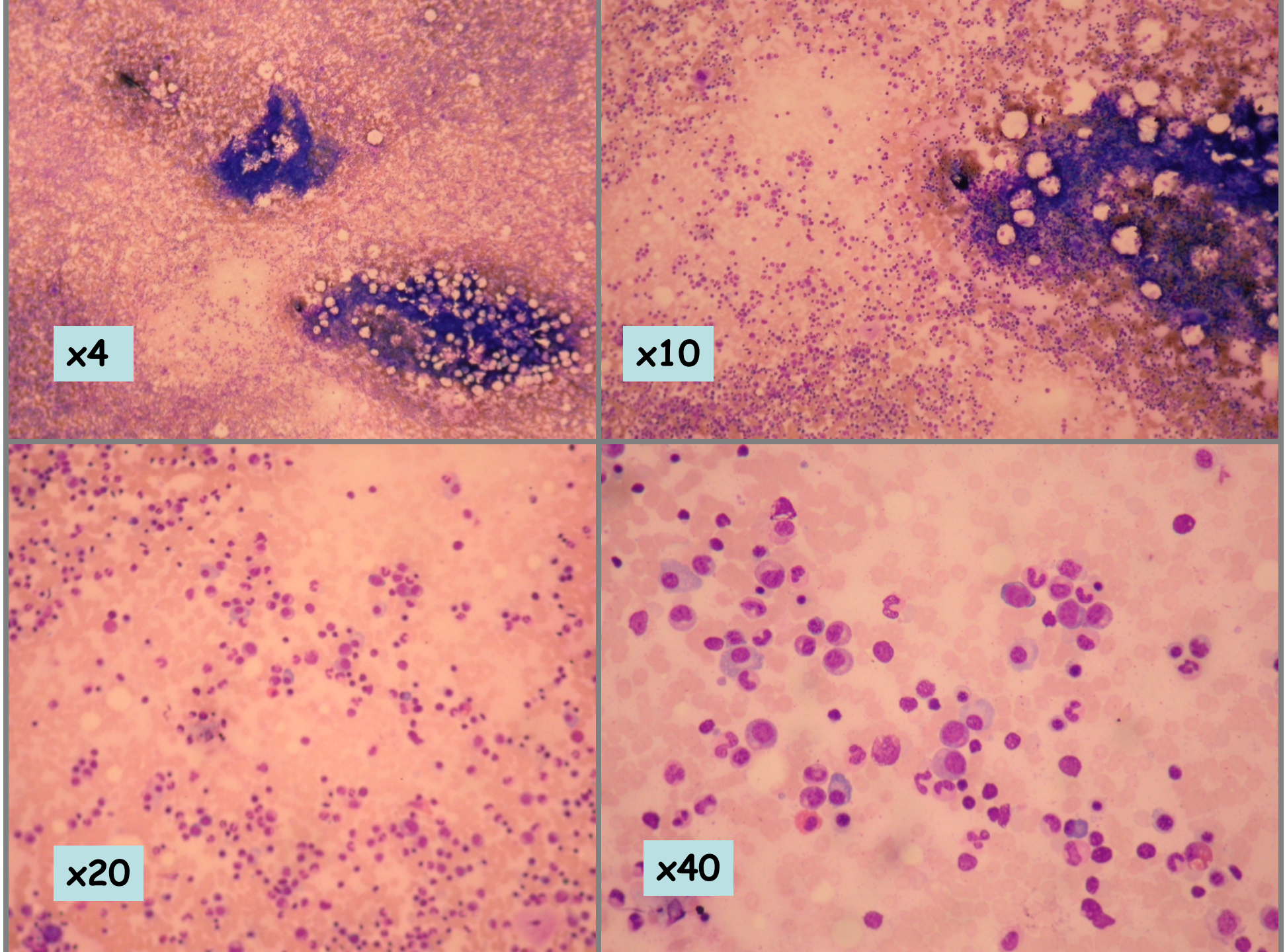
KEMİK İLİĞİ

HİPOPLAZİ

HİPERPLAZİ ?

İŞGAL

Ne görürüz?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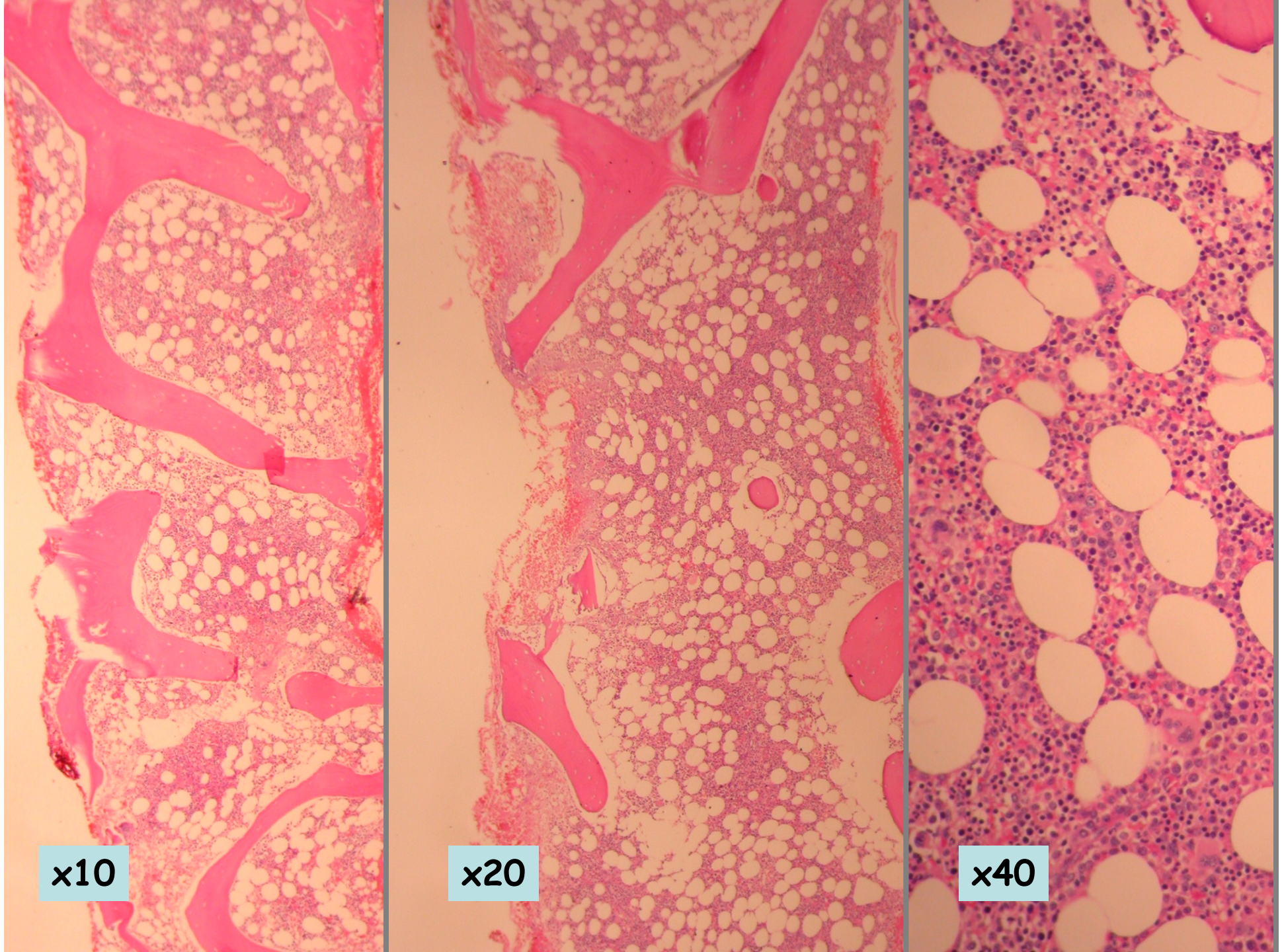
x10
x20
x40


x10
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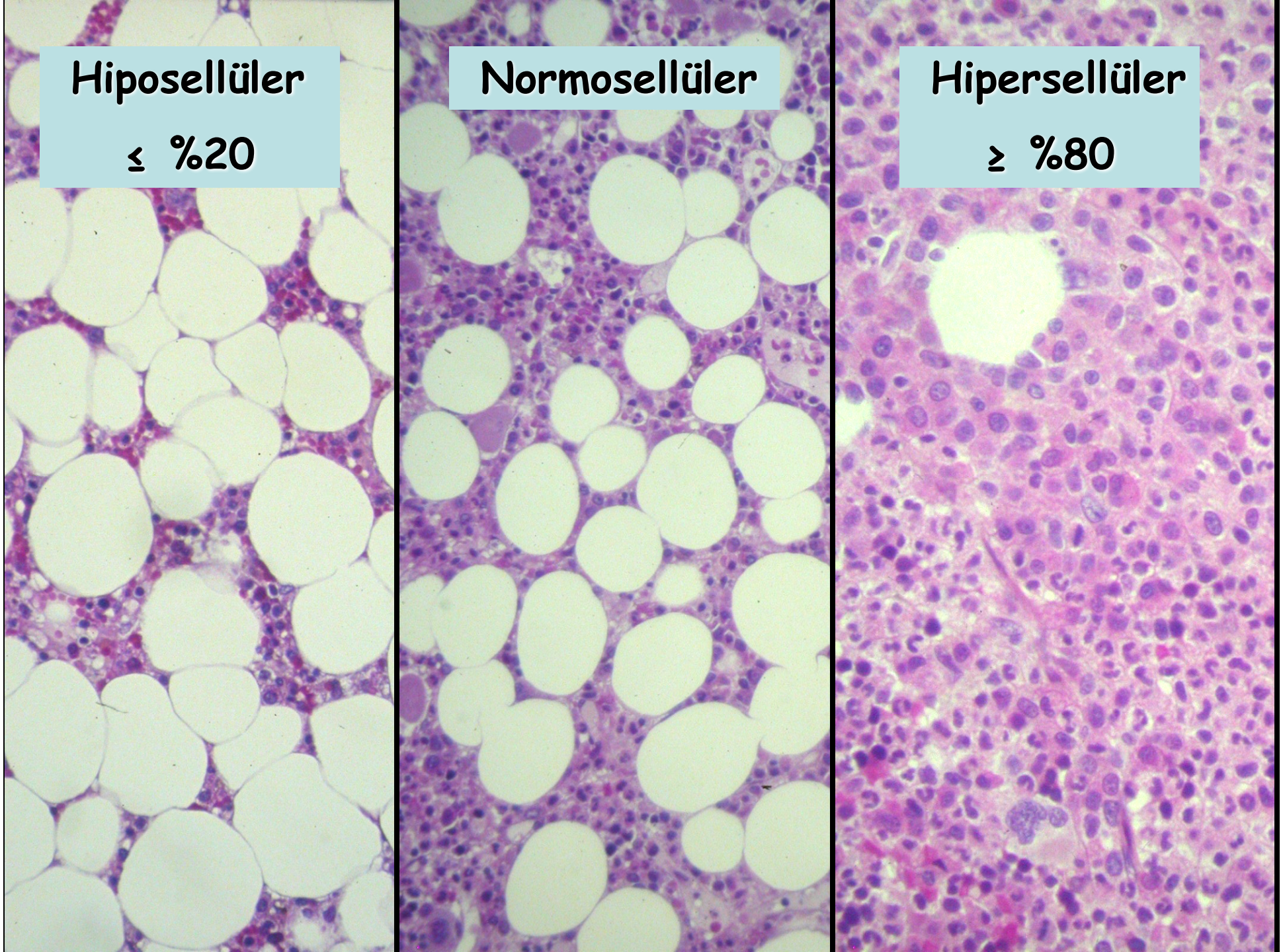
Kemik İliğinin Normal Sellülaritesi

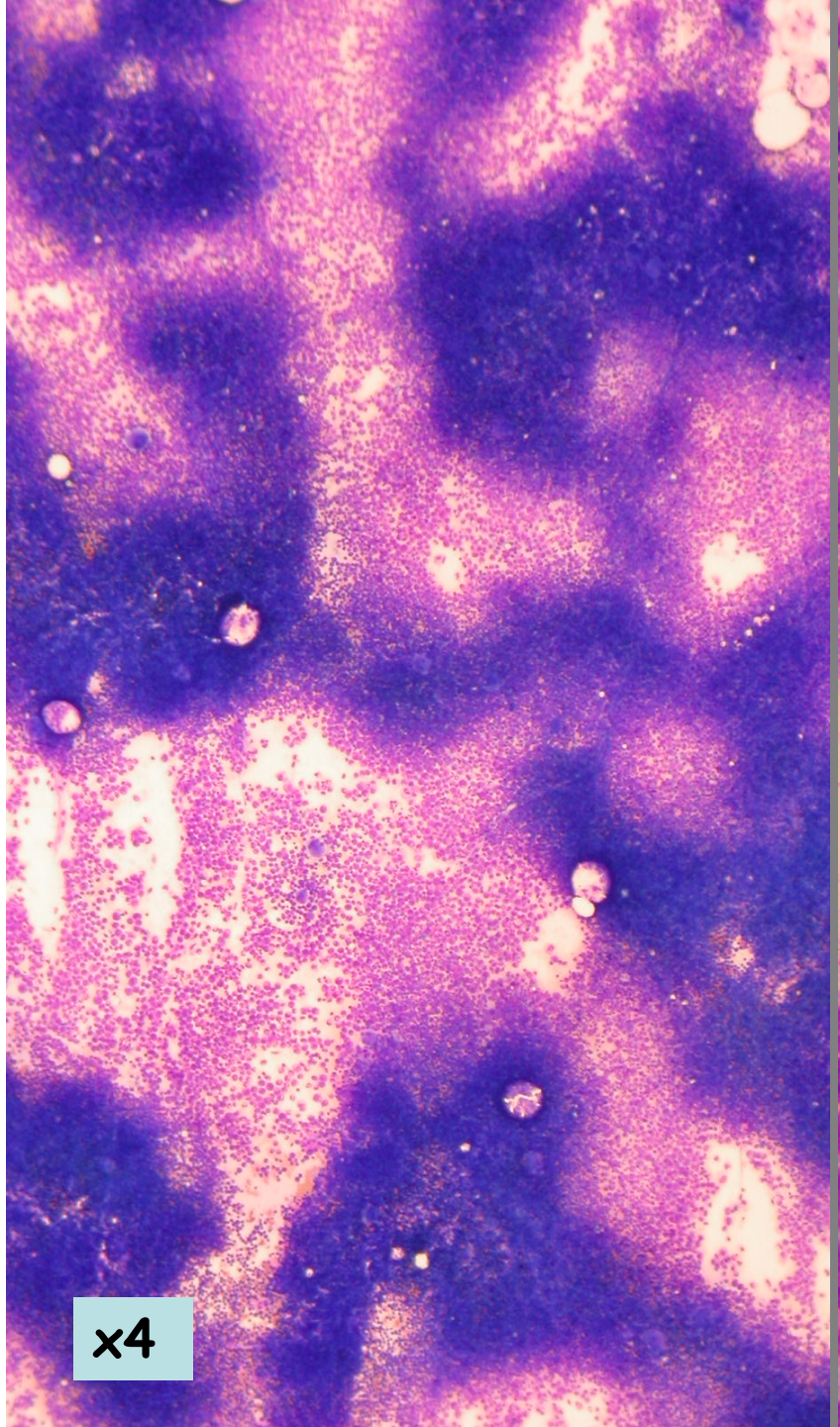
- Çocuklarda %65-100
  - Yenidoğanlarda %100
  - İlk dekadda %80-90
  - İkinci dekadda %65-85

- Erişkinlerde %25-75
  - 20 yaş %65-80
  - 30 yaş %50
  - 60 yaş %40
  - >70 yaş %25-30

Erişkin kemik iliği aspirasyonunda hücre tiplerinin oranları

Hücre tipleri	%
Myelomonositik seri	
Myeloblastlar	0-2
Promyelositler	2-5
Myelositler (nötrofilik)	9-16
Metamyelositler	7-23
Bantlar	8-15
Nötrofiller	4-10
Myelositler (eosinofilik)	0-2
Bant	0-2
Matür	0-2
Monositler/makrofajlar	0-3
Bazofiller	0-1
Mast hücreleri	0-2
Eritroblastlar	15-37
Megakaryositler	0,5-2
Lenfositler	8-24
Plazma hücreleri	3-6


Hiposellüler
≤ %20
Normosellüler
Hipersellüler
≥ %80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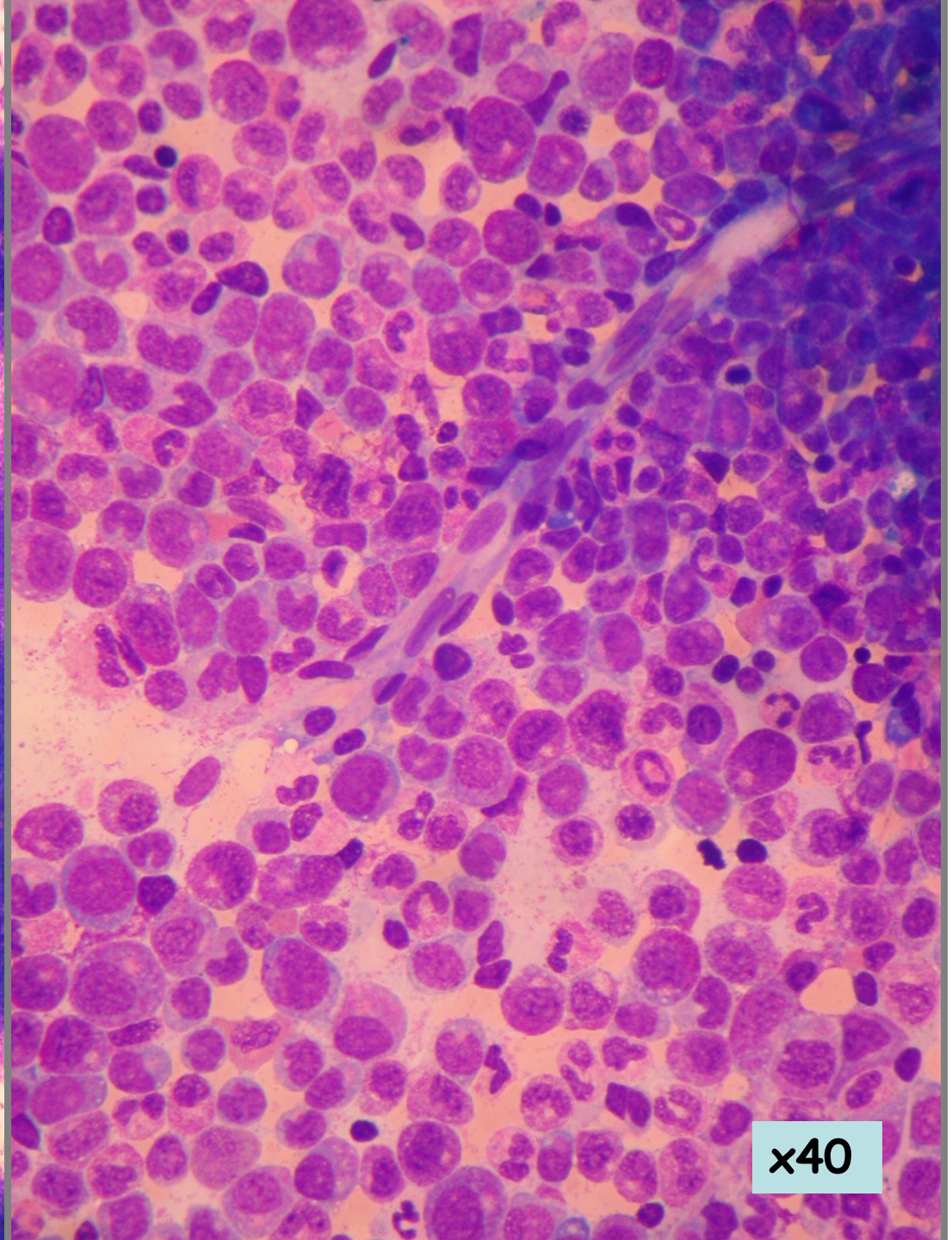
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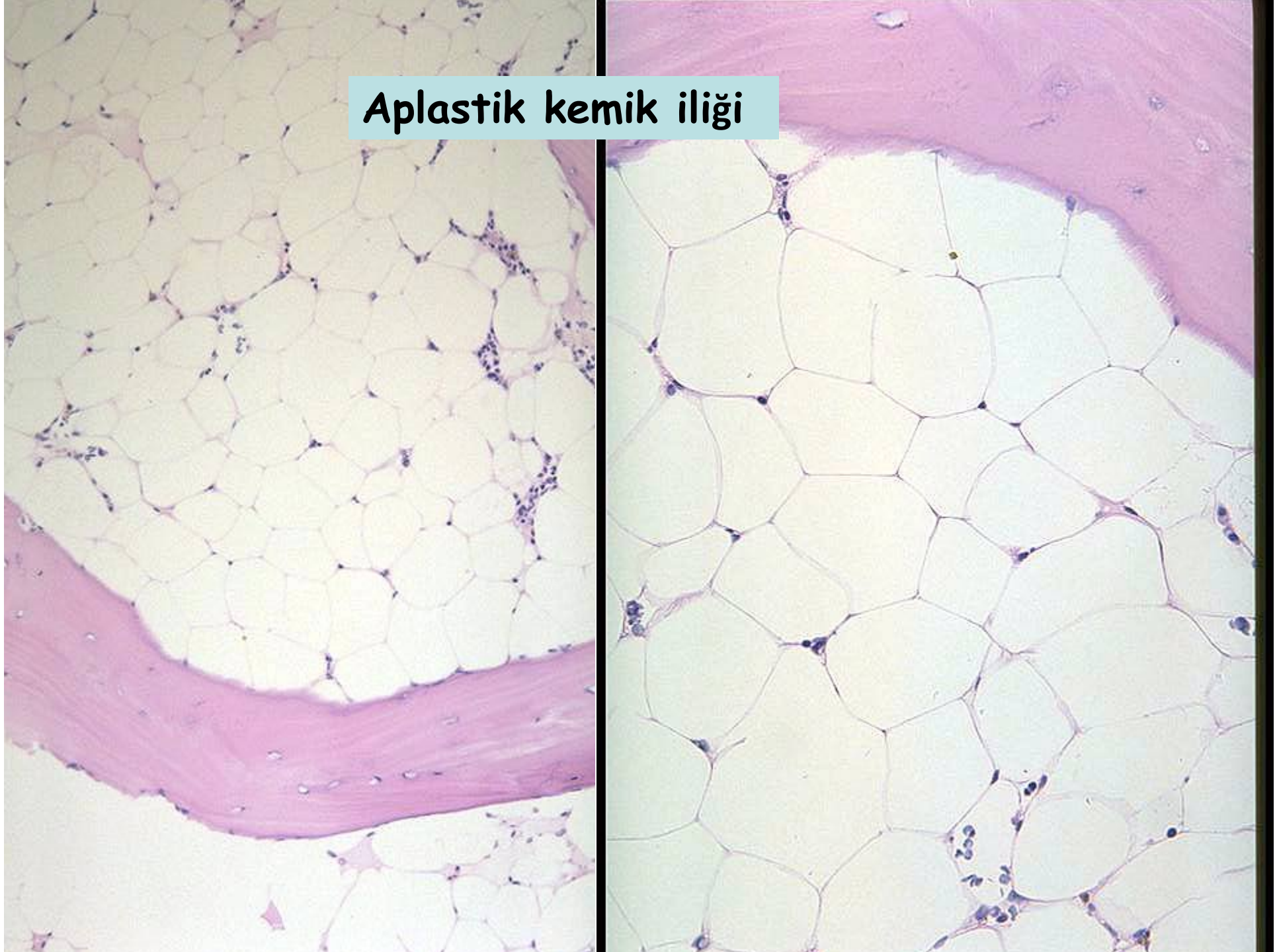
Aplastik kemik iliği



SİTOPENİ

ERİTROİD SERİ = ANEMİ

MYELOİD SERİ = LÖKOPENİ

TROMBOSİTER SERİ = TROMBOSİTOPENİ

ERİTROİD SERİ NORMAL DEĞERLER

Ölçümler	Erkek	Kadın
Hemoglobin (gm/dL)	13.6-17.2	12.0-15.0
Hematokrit (%)	39-49	33-43
Eritrosit # ($\times 10^6/\mu L$)	4.3-5.9	3.5-5.0
Retikülosit sayısı # (%)	0.5-1.5	
Ortalama Eritrosit Hacmi (fl) **MCV**	82-96	
Ortalama Eritrosit Hemoglobini (pg) **MHC**	27-33	
Ortalama Eritrosit Hemoglobin Konsantrasyonu (gm/dL) **MCHC**	33-37	
Eritrosit dağılım genişliği **RDW**	11.5-14.5	

ANEMİLER

ERİTROSİTLERİN NORMAL ORANLARININ ALTINDA SAYIDA OLMASI

- Çoğalma bozukluğu
- Olgunlaşma bozukluğu
  - Çekirdek
  - Sitoplazma
- Yıkım artışı
- Kan Kaybı

ANEMİLER

- **Çoğalma bozukluğu Kalıtsal**

Kök hücre azlığı Fankoni, telomeraz bozuklukları

Eritroblast olgunlaşması: Thallassemi Sendromları

- **Çoğalma bozukluğu Edinsel = Kazanılmış**

Beslenme : B12 , Folat (DNA sentezi =Çekirdek)
Demir (Hemoglobin Sentezi =Sitoplazma)

Büyüme Faktörü : Böbrek yetmezliği, kronik hastalık

İmmun progenitör hasarı: Aplastik anemi, izole formlar

Primer tümörler : MDS, Lösemi,

Sekonder tümör -enfeksiyon : Metastaz -Fibrozis -Granülom

Enfeksiyonlar (Eritroid): Parvovirus B19

Çeşitli : Endokrin ve karaciğer bozuklukları

ANEMİLER

Kan kayıpları : Akut-Kronik

Yıkım Artışı (Hemoliz) :

Kalıtsal Hastalıklar:

Membran defekti: Herediter sferositoz

Enzim eksiklikleri: G6PD, Glutatyon Sent,Pürivat Kin, Hekzokinaz

Hemoglobin Anomalileri: Globin sentezi: Thalassemi Send

Yapısal : Sicle cell, stabil olmayan hemoglobinopatiler

Kazanılmış

Genetik defekt: Fosfoditilinozitol ilişkili glikolipid (PNH)

Antikor ilişkili: Otoimmun, transfüzyon, ilaç….

Mekanik: TTP, Hemolitik üremik Syd,

Kardiyak travmatik : Kapak

Enfeksiyon: Malarya,

Toksik Kimyasal: Sepsis, Yılan sokması, Kurşun zehirlenmesi

Membran lipidleri: KC hasarı

Sekestrasyon : Hipersplenizm

ANEMİLER

- **Çoğalma bozukluğu**

*Eritroid seride hipoplazi

*Kemik iliğinin neoplastik hücrelerle işgali

*Fibrozis ile işgal

ÇOĞALMA BOZUKLUĞU

APLASTİK ANEMİ

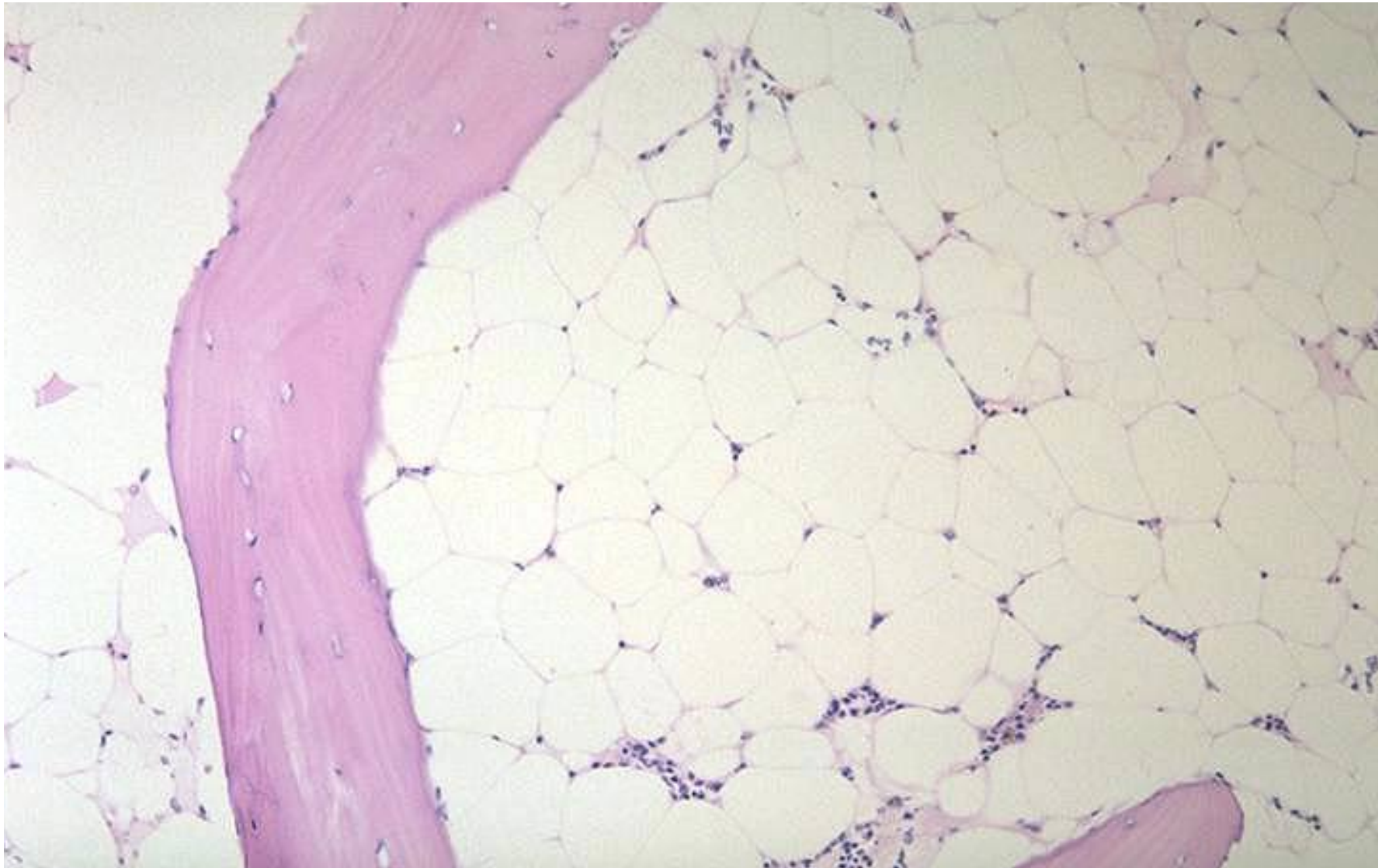


TABLE 14-7 Major Causes of Aplastic Anemia

APLASTİK ANEMİ

- **Acquired**
  - Idiopathic
  - Acquired stem cell defects
  - Immune mediated
- **Chemical Agents**
  - Dose related
    - Alkylating agents
    - Antimetabolites
    - Benzene
    - Chloramphenicol
    - Inorganic arsenicals
  - Idiosyncratic
    - Chloramphenicol
    - Phenylbutazone
    - Organic arsenicals
    - Methylphenylethylhydantoin
    - Carbamazepine
    - Penicillamine
    - Gold salts
- **Physical Agents**
  - Whole-body irradiation
- **Viral Infections**
  - Hepatitis (unknown virus)
  - Cytomegalovirus infections
  - Epstein-Barr virus infections
  - Herpes zoster (varicella zoster)
- **Inherited**
  - Fanconi anemia
  - Telomerase defects

APLASTİK ANEMİ

1- Kemik iliği progenitor hücrelerinin immun kökenli ⟹ T hücre yanıtı

2- İntrinsik kök hücre anomalisi

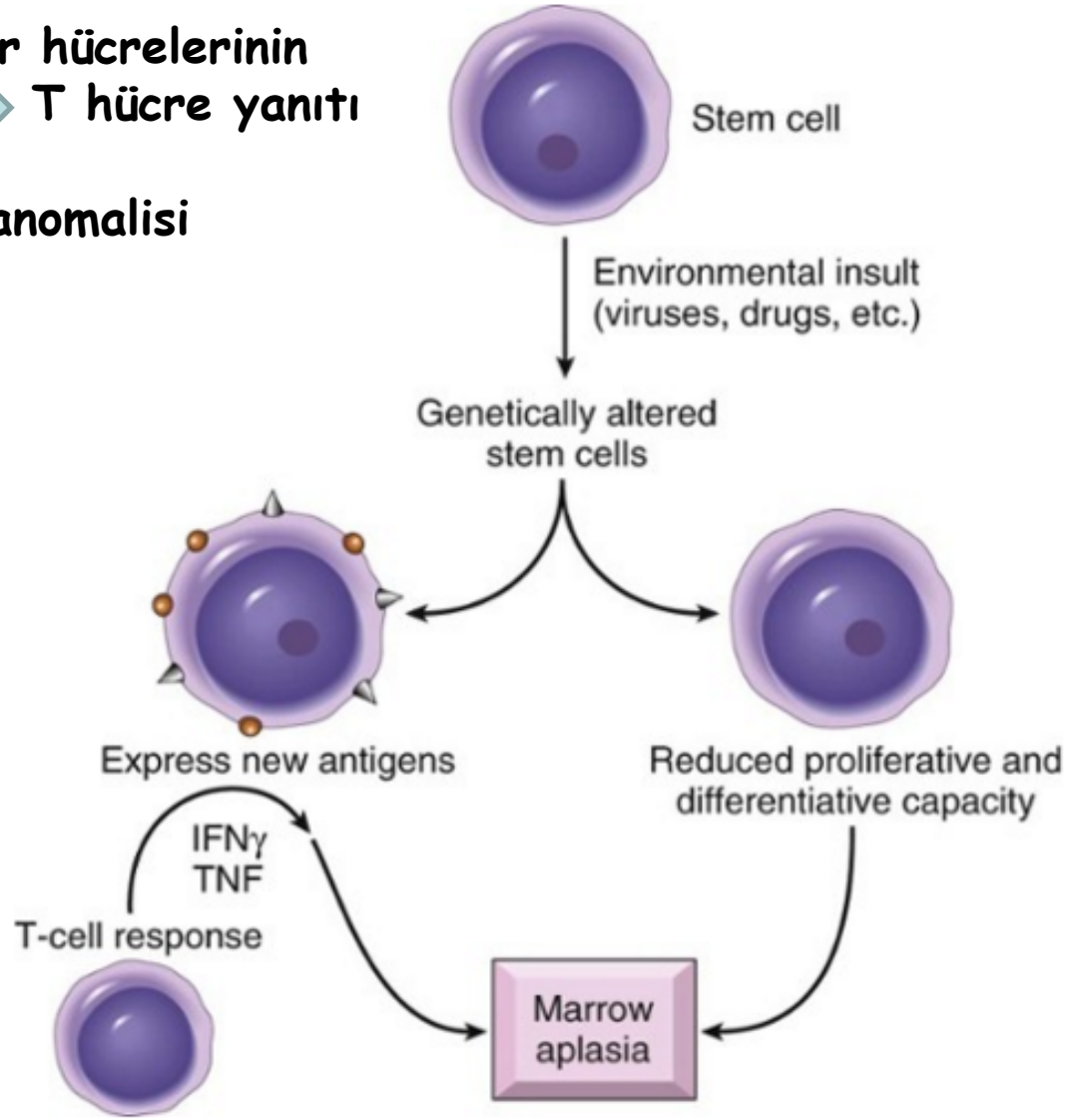


FIGURE 14-24 Pathophysiology of aplastic anemia. Damaged stem cells c

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SADECE ERİTROİD SERİYİ İLGİLENDİREN

Pure Red Cell Aplasia

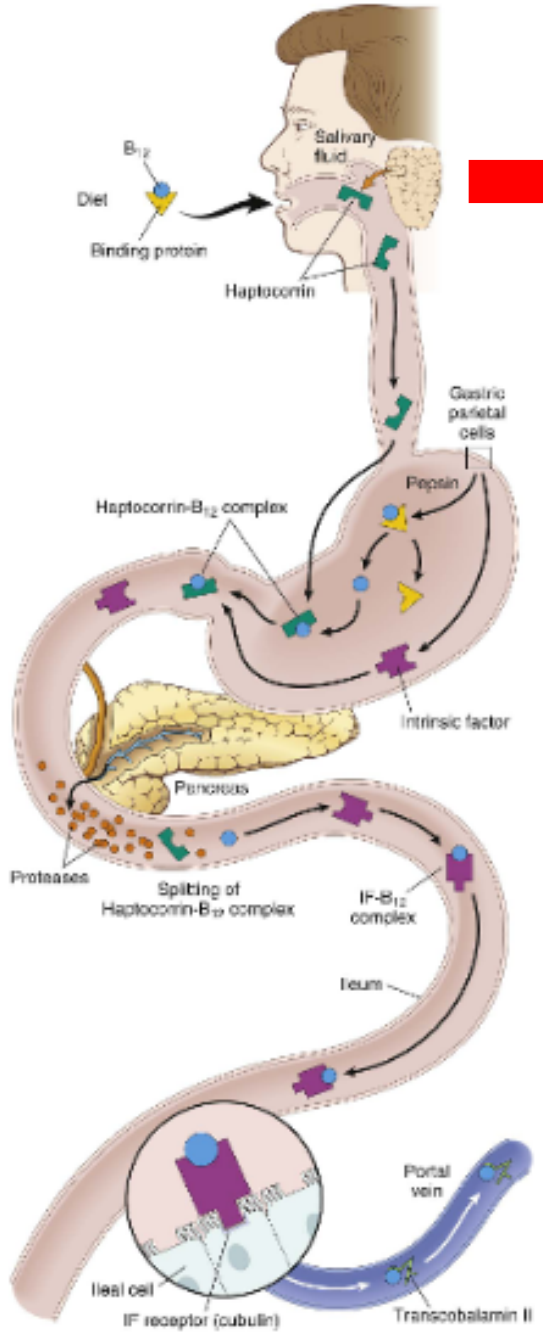
- Acute: Parvovirus B19 infection (may persist in immunosuppressed patients)
- Chronic: Associated with thymoma, large granular lymphocytic leukemia, presence of neutralizing antibodies against erythropoietin, and other autoimmune phenomenon

ANEMİLER

- **Olgunlaşma bozukluğu (çekirdek, sitoplazma)**

Kongenital: *Thalassemi, Kongenital Diseritropoetik A
*Transkobalamin III eksikliği,
*Metionin sentez eksikliği.

Edinsel: *Beslenme: Demir, Vit B12, Folat
*Myelodisplastik sendrom (MDS)
*Alkol ile oluşan



B12 vitamini

Decreased Intake
Inadequate diet, vegetarianism
Impaired Absorption
Intrinsic factor deficiency
Pernicious anemia
Gastrectomy
Malabsorption states
Diffuse intestinal disease (e.g., lymphoma, systemic sclerosis)
Ileal resection, ileitis
Competitive parasitic uptake
Fish tapeworm infestation
Bacterial overgrowth in blind loops and diverticula of bowel

FOLİK ASİD

Decreased Intake
Inadequate diet, alcoholism, infancy
Impaired Absorption
Malabsorption states
Intrinsic intestinal disease
Anticonvulsants, oral contraceptives
Increased Loss
Hemodialysis
Increased Requirement
Pregnancy, infancy, disseminated cancer, markedly increased hematopoiesis
Impaired Utilization
Folic acid antagonists
Unresponsive to Vitamin B_{12} or Folic Acid Therapy
Metabolic Inhibitors of DNA Synthesis and/or Folate Metabolism (e.g., Methotrexate)

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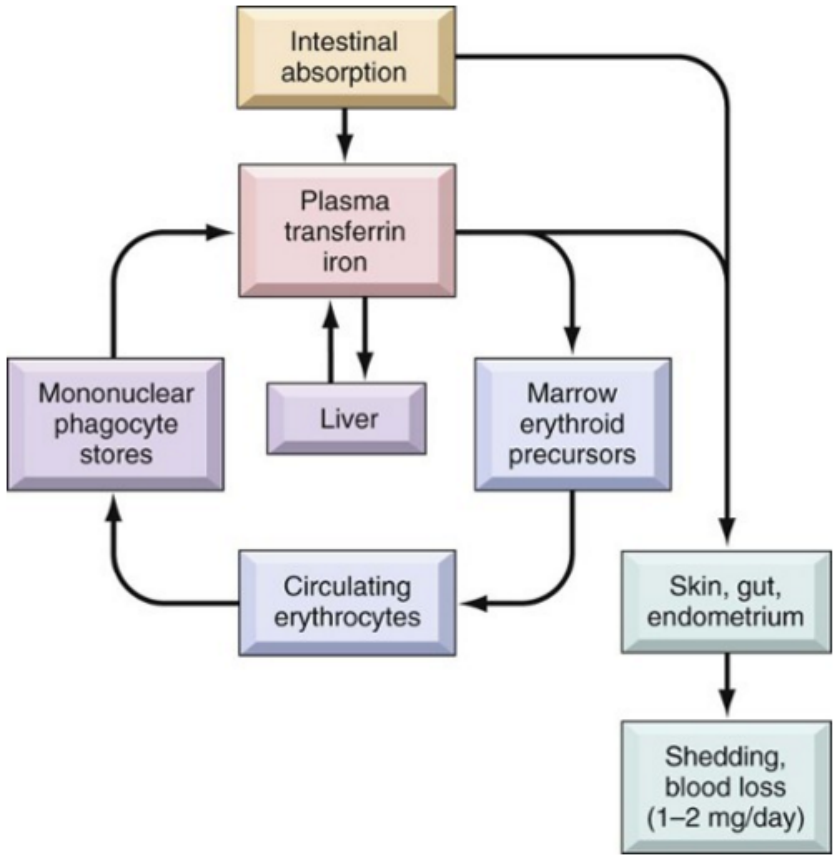
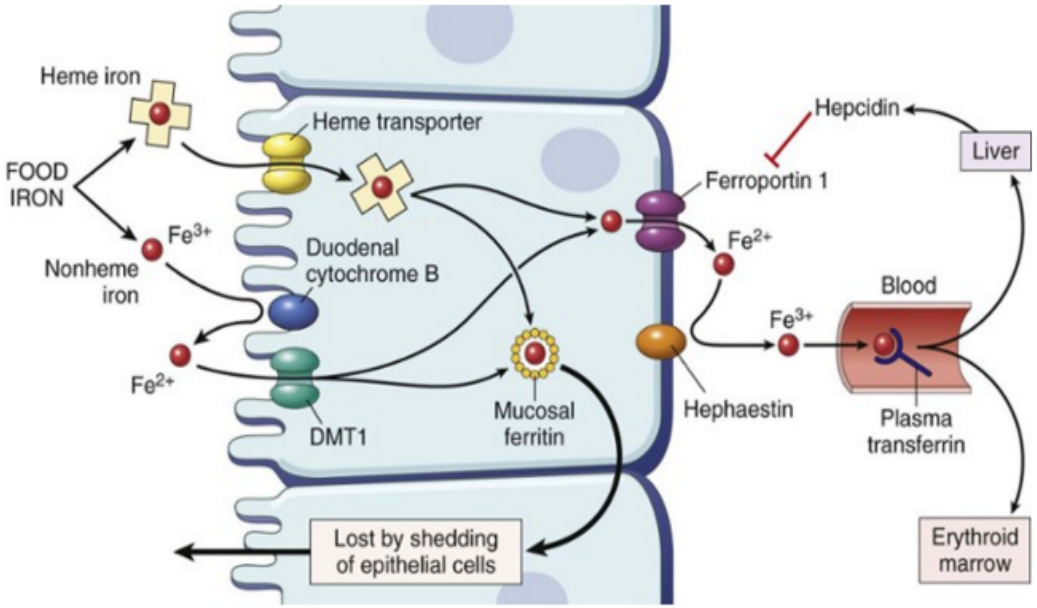
DEMİR DÖNGÜSÜ





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ANEMİLER

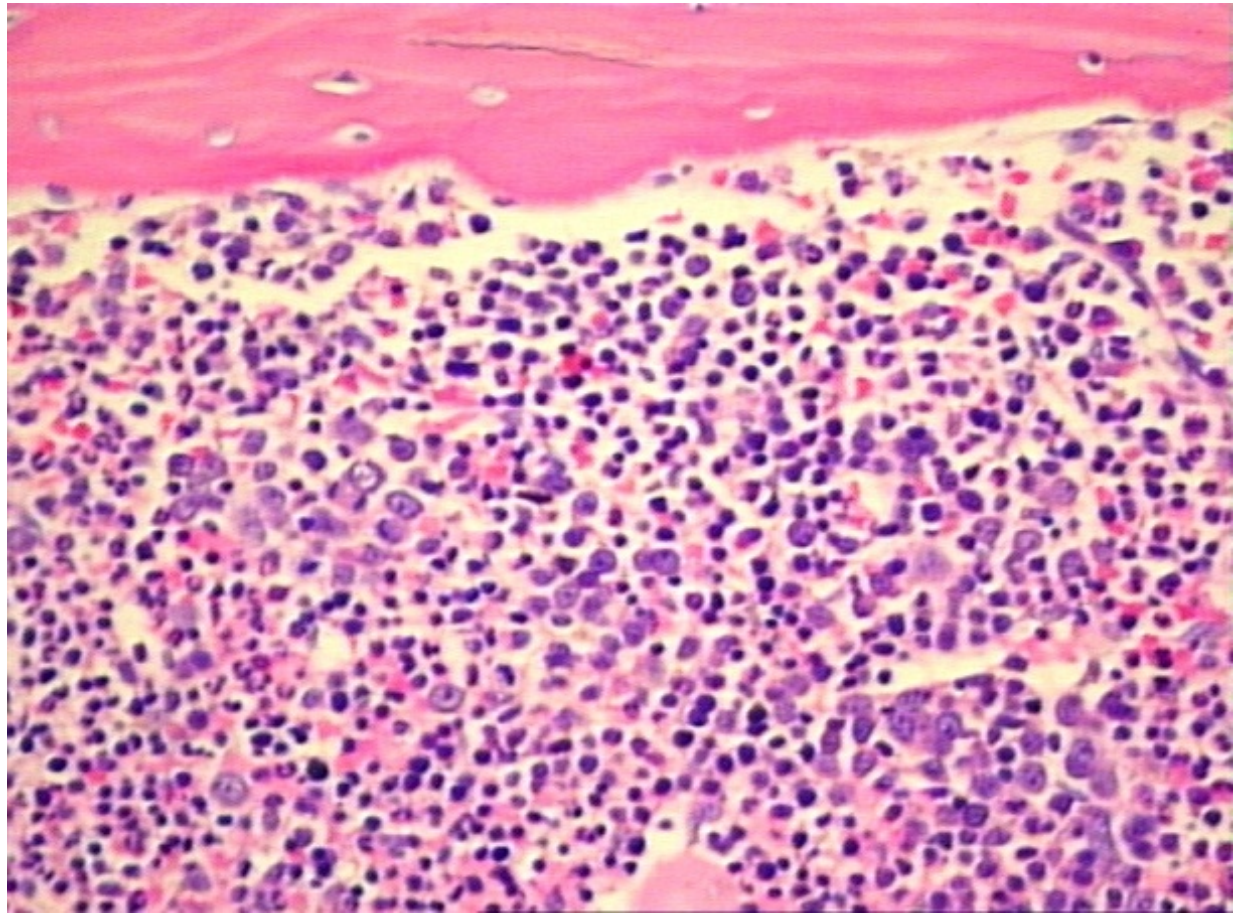
Olgunlaşma bozukluğu

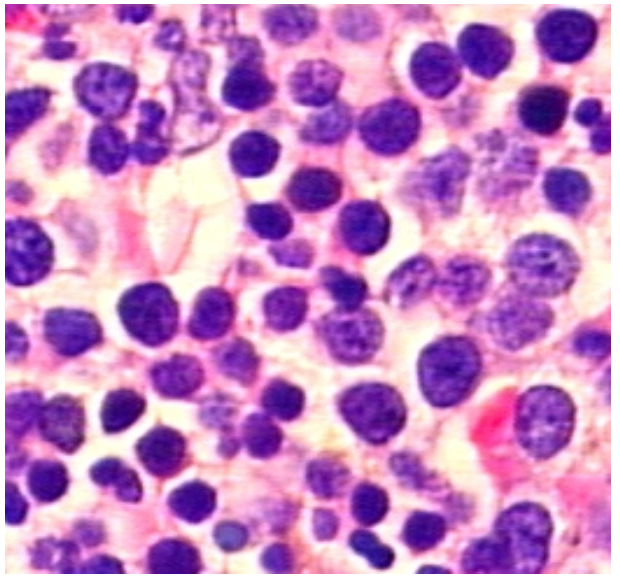
- **Çekirdek:** MAKROSİTOZ
  Megaloblastik değişiklikler
  Eritroid hiperplazi; inefektif hematopoez ve kemik iliğinde hücre ölümü

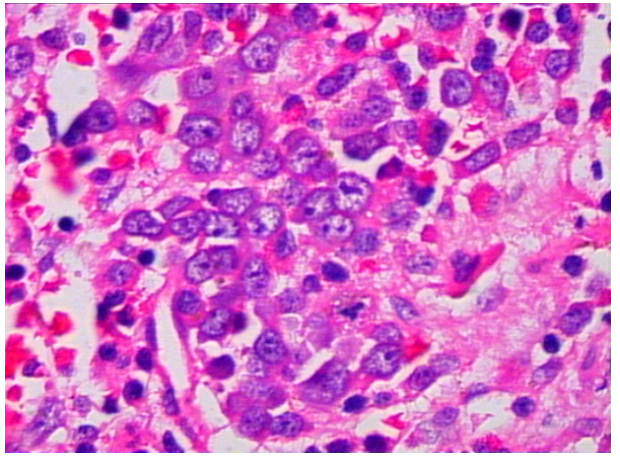
- **Sitoplazma:** MİKROSİTOZ
  Eritroid hiperplazi ve inefektif hematopoez

ÇEKİRDEK OLGUNLAŞMA BOZUKLUĞU

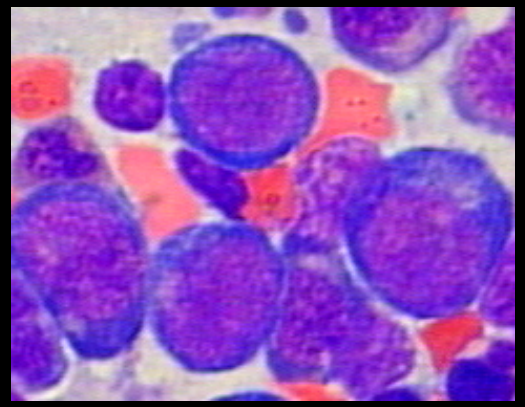
Myelodisplastik Sendrom (MDS)

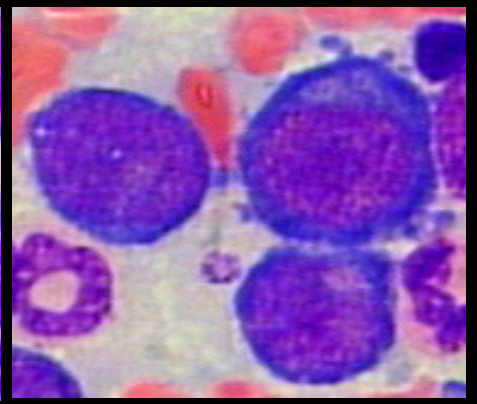


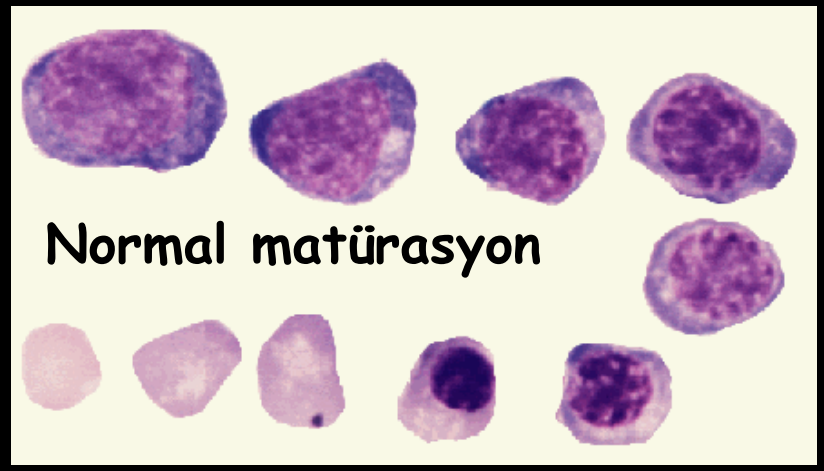




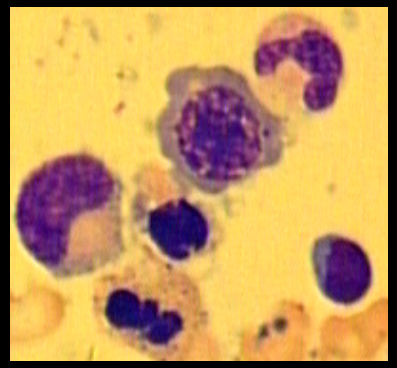
Diseritropoez

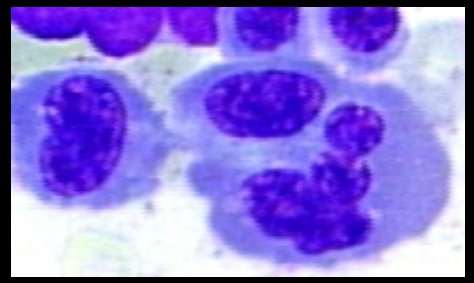




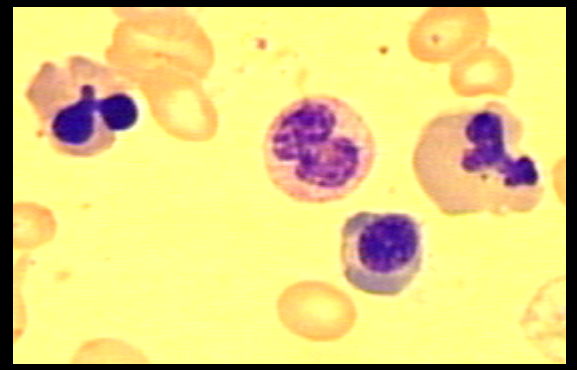


Megaloblastik değişiklikler

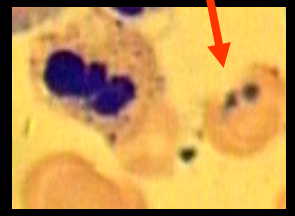




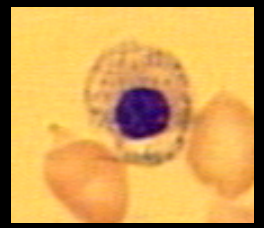
Çekirdek morfoloji bozukluğu

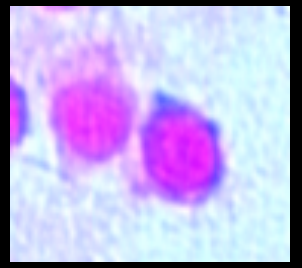


Howell-Joly

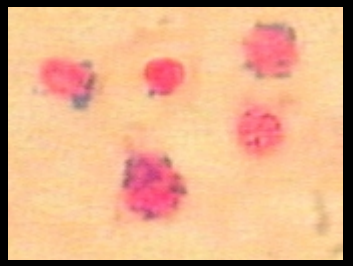


Bazofilik Noktalanma





Ring Sideroblast



ANEMİLER

- **Yıkım artışı**

Kongenital:

*İntrinsik eritroid bozukluklar:
Herediter sferositoz,
G6PDH eksikliği,
Sickle cell anemi

*Edinsel: *İntrinsek eritrosit bozuklukları: PNH
*Ekstrinsek(çevresel) :
Immun hemolitik anemi
Otoimmun, ilaç ilişkili, HÜS,
Clostridium sepsisi, TTP

PAROKSİSMAL NOKTURNAL HEMOGLOBİNÜRİ (PNH)

- **Eritrosit membranında glycosylphosphatidylinositol (GPI).**
- **Hematopoetik kök hücrelerde GPI-linked proteinlerin somatik mutasyonu (PIGA mutasyonu) : compleman aktivasyonu kontrolü bozukluğu**

1- decay-accelerating factor : CD55;

2- membrane inhibitor of reactive lysis **:CD59;** (Kompleman alternatif yolunun kendiliğinden aktivasyonunun engellenmesi)

3- C8 binding protein.

Hastalarda : Hemoliz kan PH sının düştüğü ile geceleri genellikle olur. Hemoglobinüri olmadan kronik hemoliz !

Tromboz riski yüksektir.

OTOİMMUN HEMOLİTİK ANEMİ

Warm Antibody Type (IgG Antibodies Active at 37°C)
Primary (idiopathic) Secondary Autoimmune disorders (particularly systemic lupus erythematosus) Drugs Lymphoid neoplasms
Cold Agglutinin Type (IgM Antibodies Active Below 37°C)
Acute (mycoplasmal infection, infectious mononucleosis) Chronic Idiopathic Lymphoid neoplasms
Cold Hemolysin Type (IgG Antibodies Active Below 37°C)
Rare; occurs mainly in children following viral infections

ANEMİLER

Yıkım Artışı

Periferde : Eritrosit şekil bozuklukları:

Retikülosit artışı,
Trombositopeni
Mikroanjiyopati.

Kemik iliğinde: Eritroid hiperplazi

NÖTROPENİ

- **Çoğalma bozukluğu:** Myeloid elemanların azalması
- **Olgunlaşma Bozukluğu:** Nötrofil öncülerinin olgunlaşması sorunu ;
  inefektif granülopoez
  Kemik iliğinde yıkım artışı
- **Hayatta kalma sorunu:** Genç formların Kemik iliğinde kalma sorunu
- **Dağılım anomalisi:** Periferik dokularda nötrofil göçü nedeniyle periferde azalma, Kemik iliğinde hiperplazi.

TROMBOSİTOPENİ

- Yapısal bozukluklar: Kongenital hastalık
- Edinsel Bozukluklar:

Aplastik anemi
Neoplastik infiltrasyon
Viral enfeksiyonlar

- Edinsel klonal bozukluklar :

Paroksismal Nokturnal Hemoglobinüri (PNH)
Myelodisplastik Sendrom (MDS)
Akut Myeloid Lösemi (AML)
Myeloproliferatif Neoplaziler (MPN)

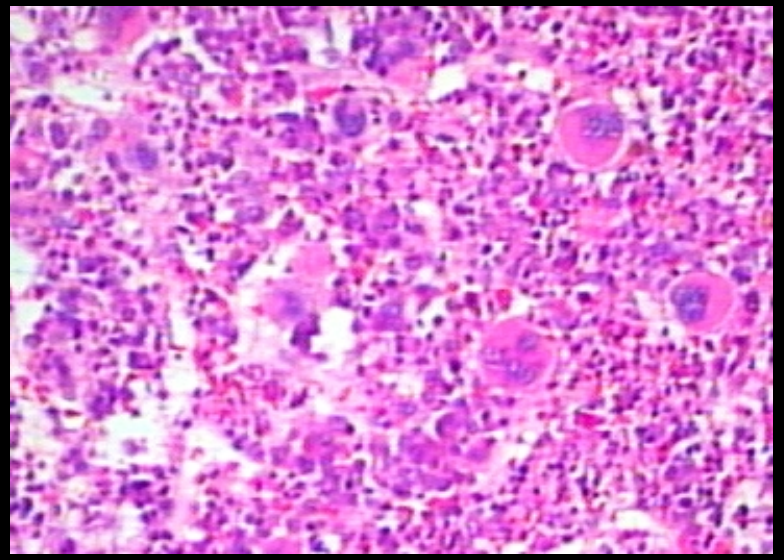
TROMBOSİTOPENİ

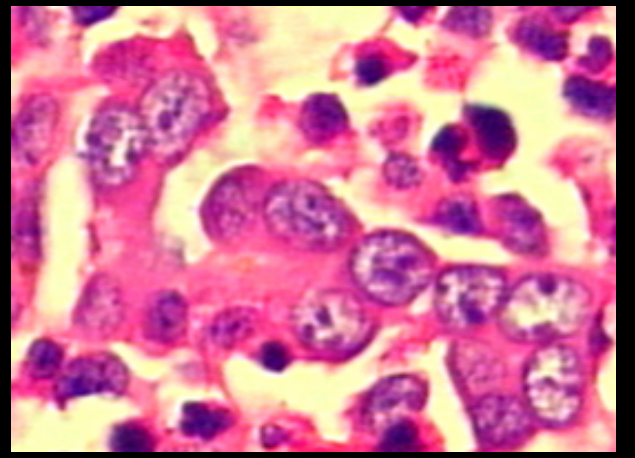
- Yapısal bozukluklar
- Edinsel Bozukluklar
- Yapısal klonal bozukluklar
- Edinsel klonal bozukluklar

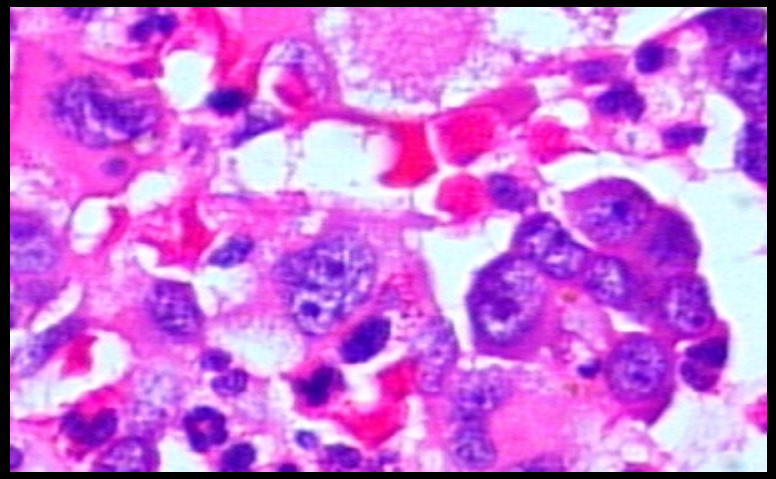
MEGAKARYOSİT SAYISI AZALIR
MEGAKARYOSİT SAYISI NORMALDİR
MEGAKARYOSİT SAYISI ARTMIŞTIR.

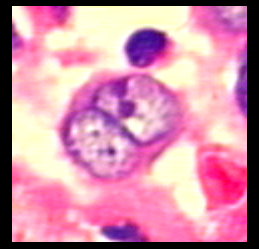
Dismegakaryopoez

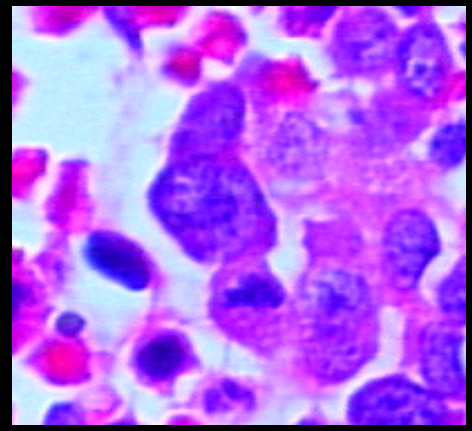
Paratrabeküler alanlara göç ve gruplaşma











Lobulasyonun azalması
Mikromegakaryosit

Erişkin kemik iliği aspirasyonunda hücre tiplerinin oranları

Hücre tipleri	%
Myelomonositik seri	
Myeloblastlar	0-2
Promyelositler	2-5
Myelositler (nötrofilik)	9-16
Metamyelositler	7-23
Bantlar	8-15
Nötrofiller	4-10
Myelositler (eosinofilik)	0-2
Bant	0-2
Matür	0-2
Monositler/makrofajlar	0-3
Bazofiller	0-1
Mast hücreleri	0-2
Eritroblastlar	15-37
Megakaryositler	0,5-2
Lenfositler	8-24
Plazma hücreleri	3-6

Kemik iliğinin primer neoplastik hastalıkları

Table 1.01 The myeloid neoplasms: major subgroups and characteristic features at diagnosis.

Disease	BM cellularity	% Marrow blasts	Maturation	Morphology	Haematopoiesis	Blood counts	Organomegaly
MPN	Usually increased, often normal in ET	Normal or slightly increased; <10% in chronic phase	Present	Granulocytes, erythroid precursors relatively normal, megakaryocytes abnormal	Effective	Variable; one or more myeloid lineage usually initially increased	Common
Myeloid/lymphoid neoplasms with eosinophilia and abnormalities of *PDGFRA*, *PDGFRB* or *FGFR1*	Increased	Normal or slightly increased; <20% in chronic phase	Present	Relatively normal	Effective	Eosinophilia (>1.5×10⁹/L)	Common
MDS	Increased, occasionally normocellular or hypocellular	Normal or increased; <20%	Present	Dysplasia in one or more myeloid lineage	Ineffective	Cytopenia(s)	Uncommon
MDS/MPN	Increased	Normal or slightly increased; <20%	Present	Usually one or more lineages dysplastic; JMML often has minimal dysplasia	May vary among lineages	Variable, WBC usually increased	Common
AML	Usually increased	Increased >20%, except in some cases with specific cytogenetic abnormalities or in some cases of erythroleukaemia	Varies, usually minimal	May or may not be associated with dysplasia in one or more lineages	Ineffective or effective	WBC variable, usually anaemia and thrombocytopenia	Uncommon

MPN, myeloproliferative neoplasms; MDS, myelodysplastic syndromes; MDS/MPN, myelodysplastic/myeloproliferative neoplasms; AML, acute myeloid leukaemia; ET, essential thrombocythaemia; JMML, juvenile myelomonocytic leukaemia; WBC, white blood cells.