

MONONÜKLEOZ SENDROMU: NASIL TANIRIM? NASIL TEDAVİ EDERİM?

Mononükleoz Sendromunun Klinik Tanı ve Tedavisi

KLİMİK Ankara Aylık Toplantıları

27 Şubat 2013

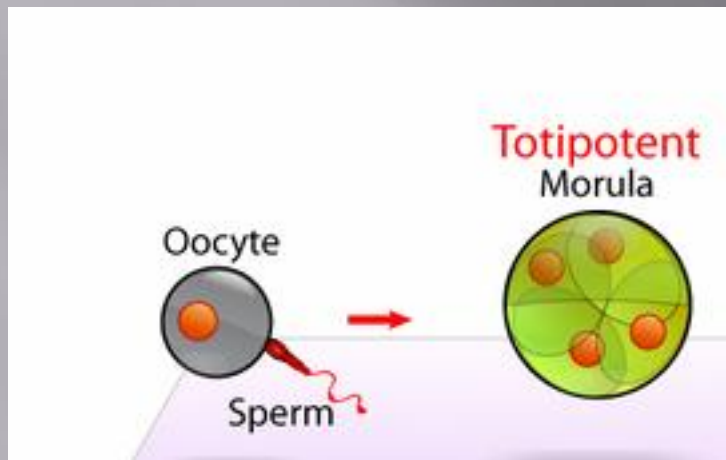
Ediz Tütüncü

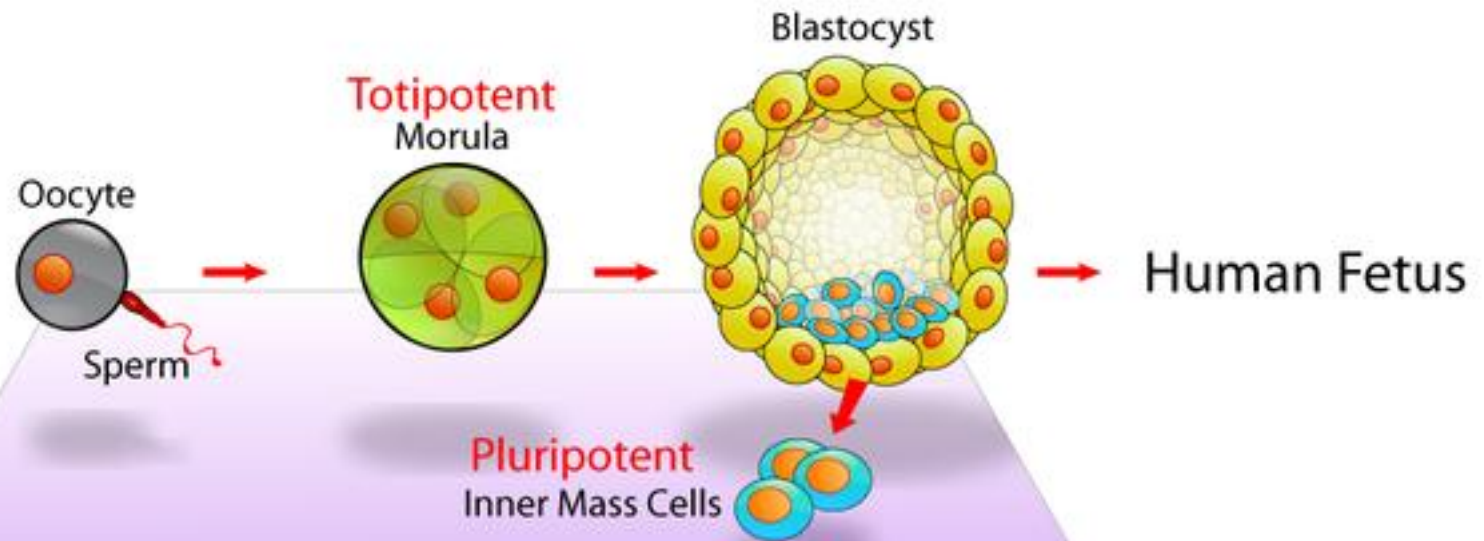
Sunum planı

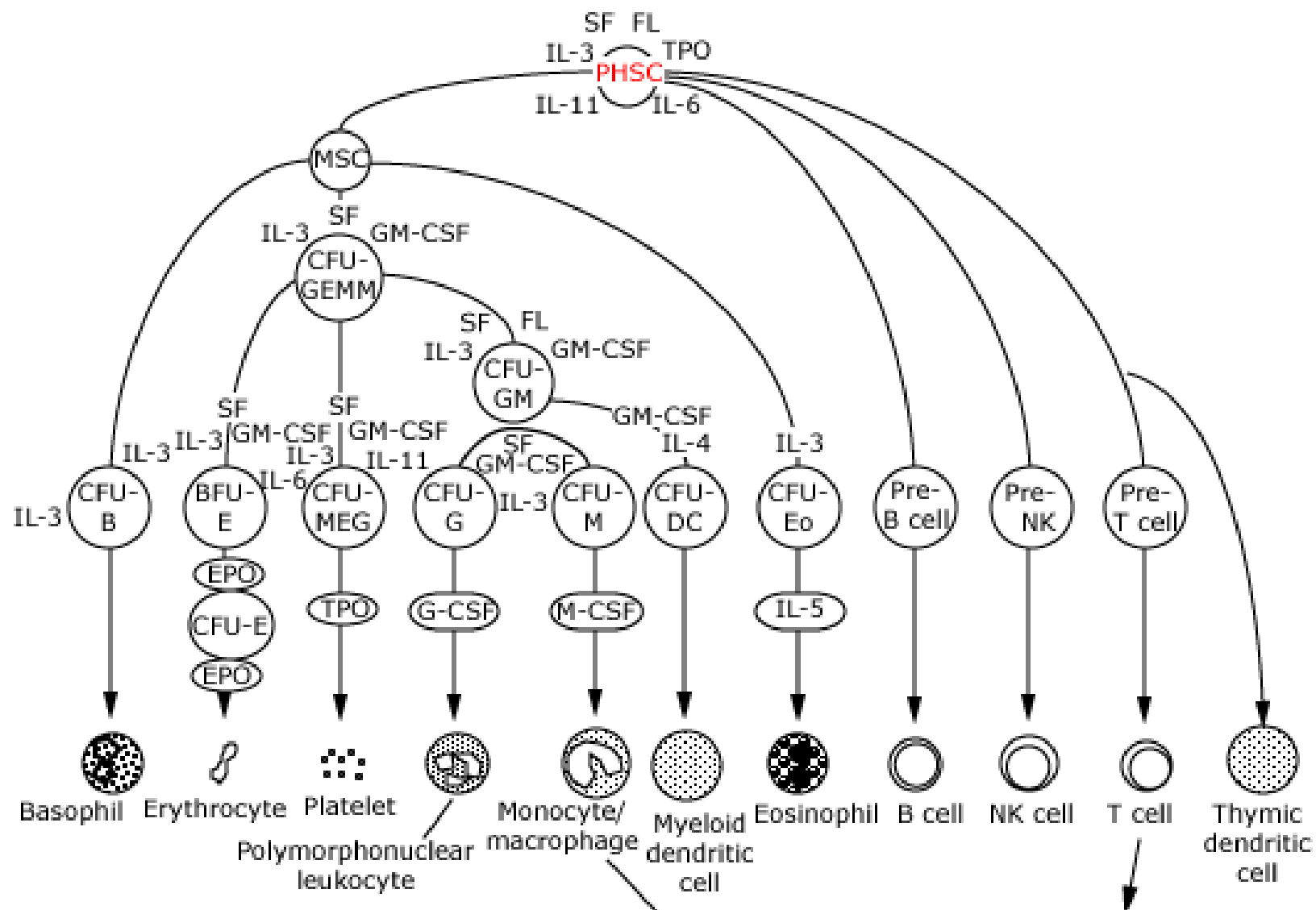
Mononükleoz sendromu nedir?

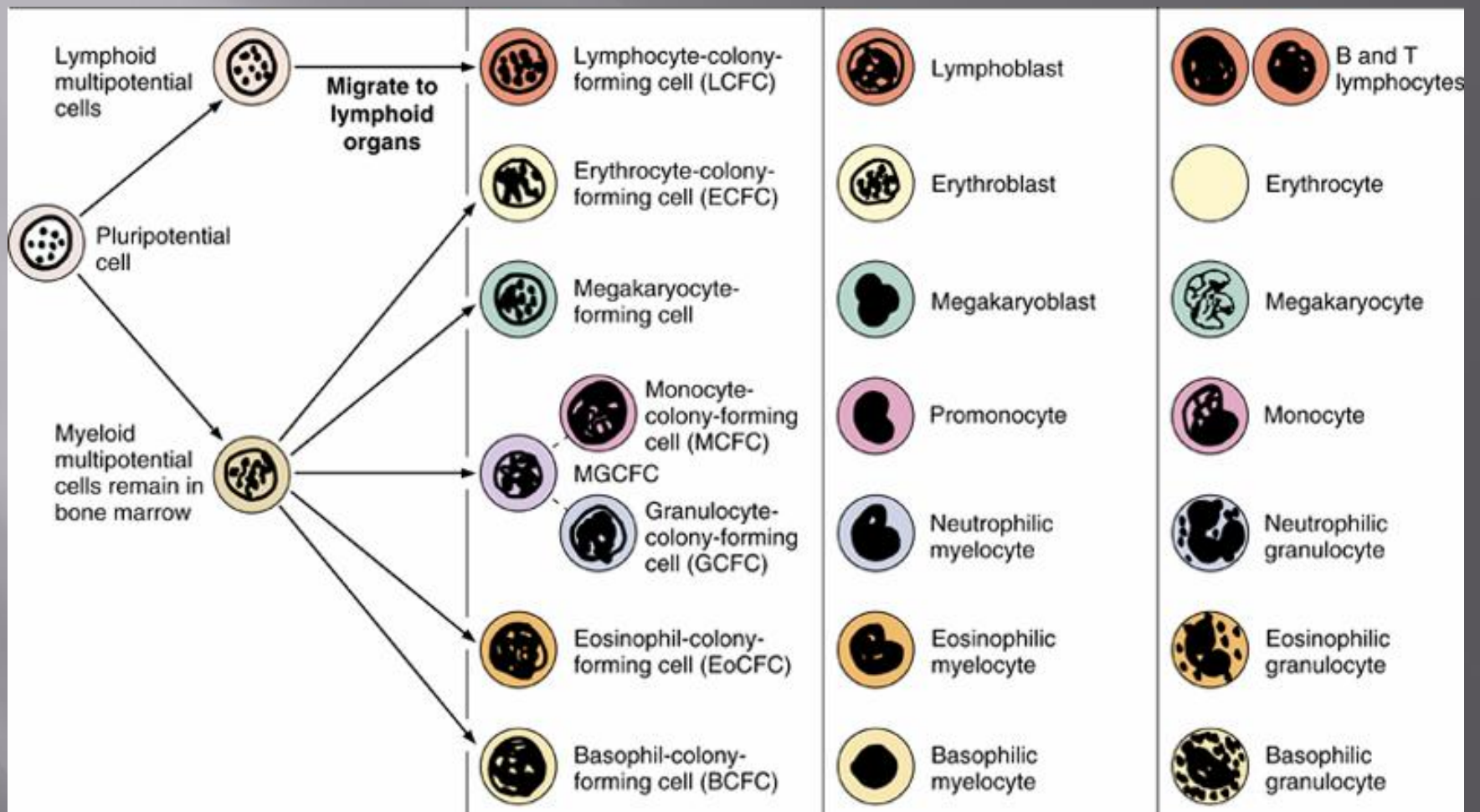
Nasıl tanırım?

Nasıl tedavi ederim?









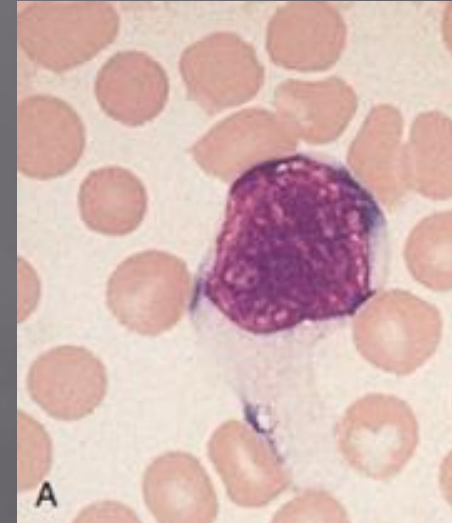
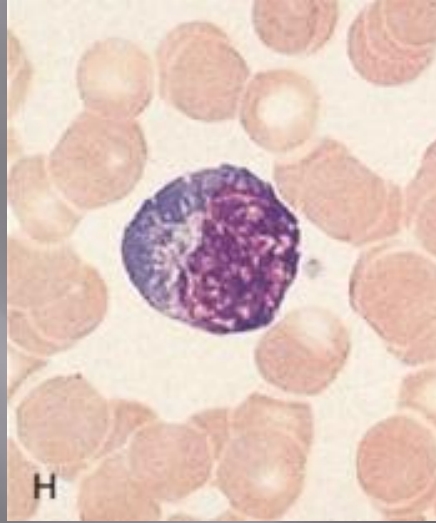
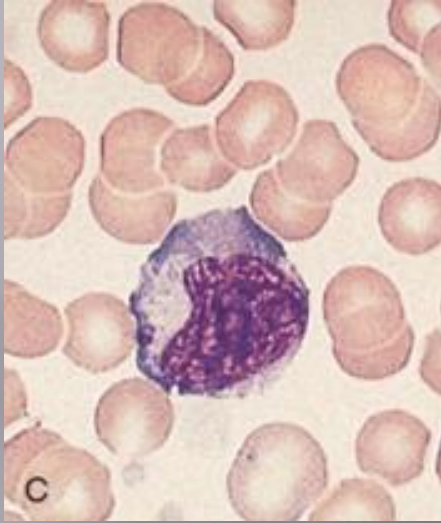


5 major

Nötrofil (60%)
Lenfosit (30%)
Monosit (7%)
Eosinofil (2%)
Basofil (1%)

Lenfosit subpopülasyonları

T hücreleri (CD3+) %60-80
 Th (CD4+) %60-70
 Tc (CD8+) %30-40
B hücreleri (CD20+) %10-20
NK hücreleri (CD56+) %5-10



1910-1920

Spontan remisyon gelişen lösemi olguları

MONONUCLEAR LEUCOCYTOSIS IN REACTION TO ACUTE INFECTIONS

("INFECTIOUS MONONUCLEOSIS")

By THOMAS P. SPRUNT and FRANK A. EVANS

(From the Division of Clinical Pathology of the Medical Clinic, The Johns Hopkins University and Hospital)

A mononuclear leucocytosis in children is not unusual, and when it occurs is a simple lymphocytosis showing almost exclusively normal lymphoid forms or cells varying but slightly from them in morphological characteristics. In adults also one may encounter occasionally a mononuclear leucocytosis, but the picture presented is different from that seen in children in that the increase in leucocyte count is due largely to pathological forms of diverse morphology, probably all lymphoid in origin but not proven so. Such a blood picture may be seen in a variety of conditions, but among them there are some that show not only the same blood picture but other signs and symptoms so much alike that they seem to constitute a group by themselves.

During the past few years we have observed several cases in adults presenting the symptoms of an acute infection, a moderate enlargement of the lymph nodes and of the spleen, and a mononuclear leucocytosis instead of the more usual increase in the polymorphonuclear leucocytes. Similar cases have been described by Türk,¹ Lüdke,² Marchand,³ Cabot,⁴ Sanders⁵ and others, and most of these authors emphasize the resemblance of such cases to acute leukæmia. Türk considered this group of cases as a key to the understanding of

ings, and especially in hæmatology, gives these cases a well-defined position as a fairly clear-cut clinical group, whether or not they may form an entity from the viewpoint of etiology. A better appreciation of this syndrome is desirable, not only for the sake of accuracy in diagnosis but also because in this relatively benign affection a favorable prognosis may be given.

CASE I

H. C. Medical No. 31625. White woman, unmarried. Age 23 years. Medical student. Admitted to the hospital October 24, 1913. Discharged November 18, 1913. Acute febrile disease without local manifestations except marked lymphocytosis and slight enlargement of lymph nodes and spleen. Recovery.

Complaint.—Headache and backache.

Family History.—Unimportant.

Personal History.—The patient had had measles and scarlet fever in childhood, smallpox in 1907—mild, and frequent attacks of inflammatory rheumatism, the last one four years ago. Until the tonsils were removed five years ago, there were repeated attacks of tonsillitis. Otherwise the personal history was negative.

Present Illness.—The patient had been feeling badly for several days, but was not sick. The day before admission there appeared suddenly an occipital headache and chilly sensations. When the patient was admitted to the hospital she had headache, aching in the back and some pain in the left side.

1920

6 sağlıklı genç erişkinde ateş, LAP, ileri derecede halsizlik ve güçsüzlük

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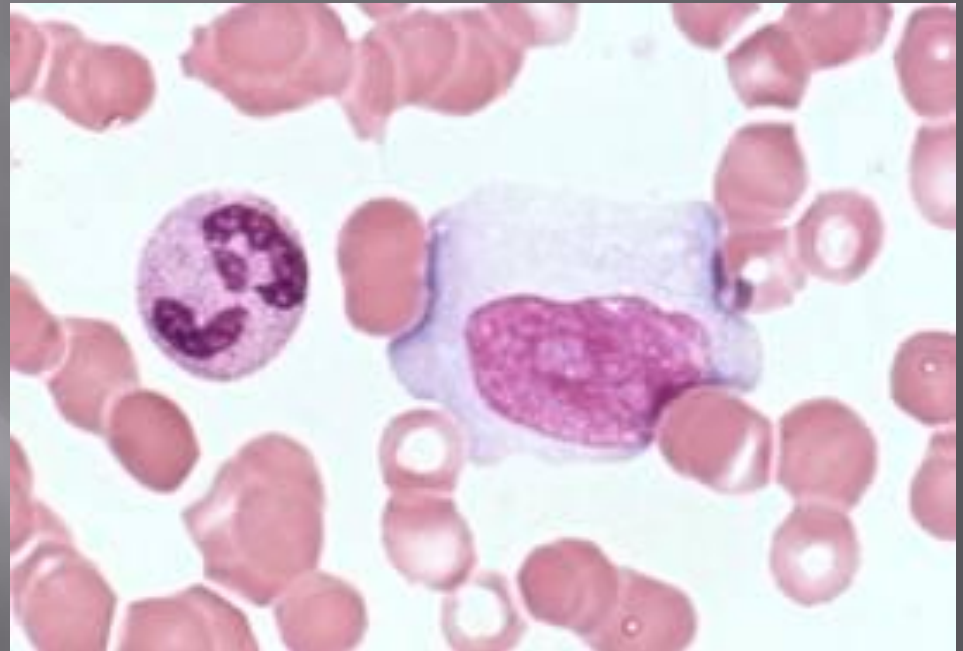
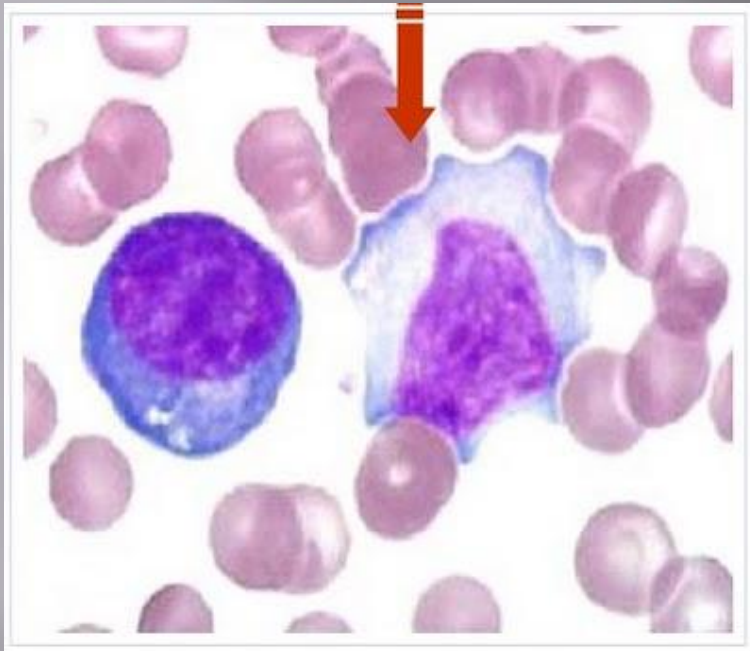
(From the Division of Clinical Pathology of the Medical Clinic, The Johns Hopkins University and Hospital)

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Princeton University.



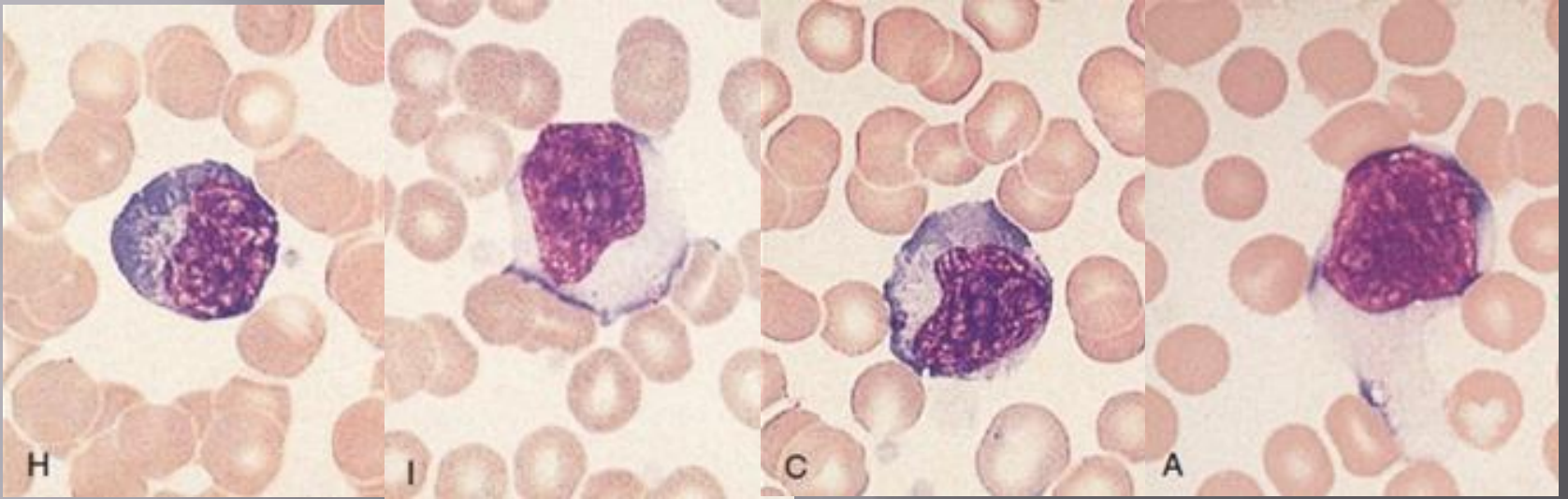
The Eighty Nine Memorial
to
David Bobaird.

Atipik lenfositlerin
monosit sanılması nedeniyle...



Atipik lenfositlerin daha detaylı tanımlaması...

Downey H, McKinlay CA. Acute lymphadenosis compared with acute lymphatic leukemia. *Arch Intern Med* 1923;32:82-112.



Büyük, vakuoller içeren geniş sitoplazma,
çekirdekte hafif blast benzeri kromatin yapısı,
Lenfositlerin kenarları komşu eritrositlerce itilmiştir

□ **SHORT COMMUNICATION** □**Causes of Infectious Mononucleosis-like Syndrome in Adult Patients**

Toshio Naito, Nagako Kudo, Akihiro Inui,
Naomi Matsumoto, Naoto Takeda, Hiroshi Isonuma,
Takashi Dambara and Yasuo Hayashida

Key words: infectious mononucleosis, atypical lymphocyte,
HHV-6, HIV, parvovirus B19

(DOI: 10.2169/internalmedicine.45.1725)

Infectious mononucleosis (IM) is a common disease in young adults, typically presenting as fever, sore throat, rash and lymphadenopathy. Diagnosis is based on clinical findings and the presence of atypical lymphocytes. Although

Table 1. Causes of Mononucleosis in 40 Adult Patients

Pathogen	Number (%)
EBV	17 (42.5)
CMV	11 (27.5)
HHV-6	2 (5.0)
Parvovirus B19	2 (5.0)
HIV-1	1 (2.5)
Unknown	7 (17.5)

primary HIV-1 infection was screened by PCR for RNA and



REVIEW

Diagnostic Evaluation of Mononucleosis-Like Illnesses

Christopher Hurt, MD,^a Dominick Tammaro, MD^b

^a*Department of Medicine, Division of Infectious Diseases, University of North Carolina at Chapel Hill, School of Medicine, Chapel Hill, NC;* ^b*Department of Medicine, Division of General Internal Medicine, Brown Medical School, Providence, RI.*

ABSTRACT

Clinicians face a diagnostic challenge when a patient with the classic fever, pharyngitis, and lymphadenopathy triad of infectious mononucleosis has a negative “spot” heterophile antibody test. This screening test, although commonly considered sensitive for the presence of Epstein-Barr virus (EBV) infection, may be negative early after infection. A growing number of pathogens have been reported to cause heterophile-negative mononucleosis-like illnesses, including cytomegalovirus (CMV), human herpesvirus 6 (HHV-6), human immunodeficiency virus (HIV), adenovirus, herpes simplex virus (HSV), *Streptococcus pyogenes*, and *Toxoplasma gondii*. Other infectious and noninfectious disorders also may present in ways that mimic

ÇOCUKLUK ÇAĞINDA MONOSİTOZ SENDROMLARI

Adalet Meral Güneş

Uludağ Üniversitesi Tıp Fakültesi, Pediatrik Hematoloji Bilim Dalı, Görükle, Bursa

Mononükleer Fagosit Sistemi

Bu sistem kemik iliğinde monoblastlar, promonositler, periferik kandaki monositler ve hem serbest hem de dokuya fiske makrofajları içerir. Vasküler endotel hücreleri, retiküler hücreler, ve dendritik hücreler mononükleer fagositer sisteme dahil edilmez iken, yapılan in vivo çalışmalar monositlerin dendritik hücrelere de dönüşebildiğini göstermiştir. Bu nedenle daha önce retikü-

Vücut Başlıkları

Pleural makrofaj

Peritoneal makrofaj

İnflamatuvar Doku

Epitelyum hücreleri

Eksuda makrofajları

Çok nukleuslu dev hücreler

CHAPTER 53

The Mononucleosis Syndromes

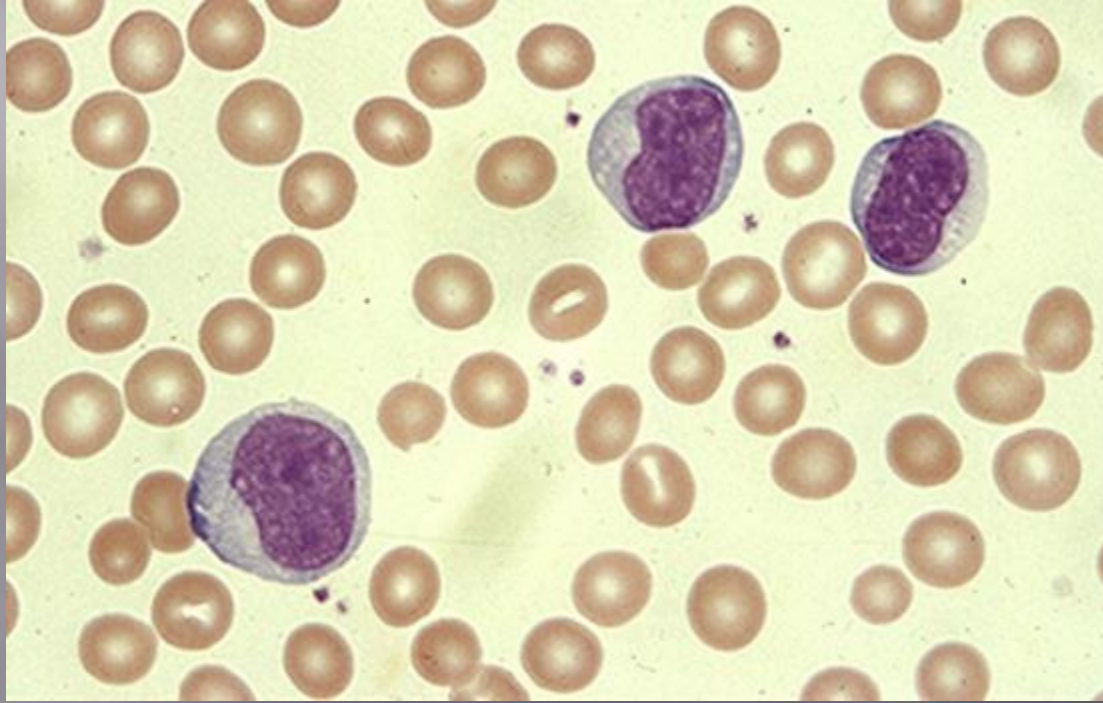
İnfeksiyöz bir etkene karşı gelişen lenfositoz

Hoagland kriterleri

>%50 lenfosit

>%10 atipik (reaktif) lenfosit

Mononükleoz



EBV

EBV
dışı

İnfeksiyöz
mononükleoz

Ateş
Farenjit
LAP

Mononükleoz
sendromu

CHAPTER 53

The Mononucleosis Syndromes

Epstein-Barr virus

Hepatit A

Cytomegalovirus

Adenovirus

HIV

Toxoplasma gondii

Human herpes virus-6

Bartonella henselae

Metapneumovirus

GABHS

Rubella

Diagnostic Evaluation of Mononucleosis-Like Illnesses

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^aDepartment of Medicine, Division of Infectious Diseases, University of North Carolina at Chapel Hill, School of Medicine, Chapel Hill, NC; ^bDepartment of Medicine, Division of General Internal Medicine, Brown Medical School, Providence, RI.

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Kollajen doku hastalıkları

Sarkoidoz, Still hastalığı, SLE

Maligniteler

Hodgkin hastalığı, Non-Hodgkin lenfoma

ilaç reaksiyonları

Karbamazepin, minosiklin, fenitoin

İnfeksiyöz mononükleoz

Epstein-Barr virus

Human herpes virus-4

Çİ DNA genom, ikozahedral kapsid,
lipid zarf,

184 kb genom 100 protein

Bulaş

Seropozitif bireylerin oral sekresyonlarına
öpüşme, gıda paylaşma, yakın temas sonrası
maruziyet ile

Major zarf glikoproteini gp350 ile CD21 molekülü arasındaki ilişki,
gp42 ile MHC sınıf II arasındaki ilişki koreseptör görevi görüyor

EBV B hücrelerini infekte ediyor

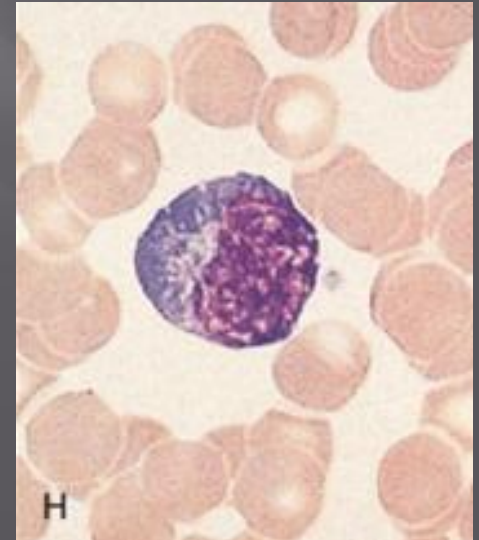
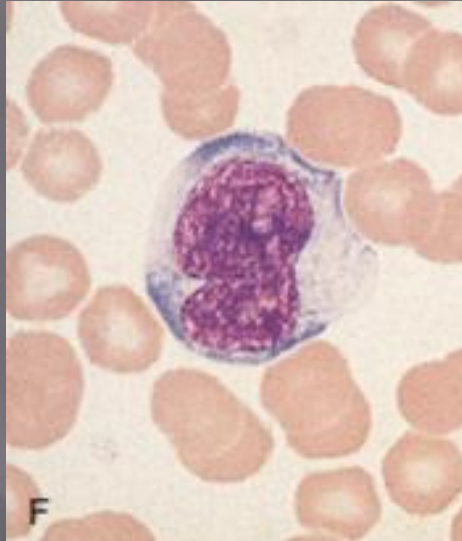
Epitelyal hücre tropizmi,
Tonsillerde B lenfositlerin infeksiyonu

Transformasyon / İmmortalizasyon

EBV ile infeksiyon sonrası poliklonal B lenfosit proliferasyonu

B lenfositlerdeki yaygın infeksiyon yoğun bir CD8+ sitotoksik T lenfosit yanıtını tetikler.

Atipik lenfositoz



İnfekte B lenfositler temizlenir ancak milyonda 1-50 B lenfosit immün yanıttan kurtulur ve ömür boyu sürececek olan infeksiyonun rezervuarı haline gelir.

EBV Persistence in Memory B Cells In Vivo

Gregory J. Babcock,* Lisa L. Decker,*
Mark Volk,† and David A. Thorley-Lawson*‡

*Department of Pathology
Tufts University School of Medicine
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and Rowe, 1992), which is dispensable for immortalization but may play a critical role in the maintenance of latency in resting cells.

The presence of latent EBV in resting B cells creates a paradox—how does EBV, which drives infected cells

Mukozal (tonsiller) lenfoid dokuda B lenfositlerinin EBV ile infeksiyonu, bu hücrelerin “latent blastoid evre”ye girerek hafıza B hücrelerine dönüşmesine yol açar.

Latent olarak infekte hücrelerdeki periodik reaktivasyonlar ile infeksiyöz EBV virionları tükürüğe geçer.

Uterin serviksten EBV izolasyonu cinsel bulaş?

Gelişmekte olan ülkelerde EBV infeksiyonu çocukluk çağında edinilir, yetişkinlerin %90-95'i infeksiyonu geçirmiştir.

ABD'de 5 yaşta serokonversiyon ~ %50
İkinci serokonversiyon dalgası ikinci dekatta

İnsidans 45/100000/yıl
15-24 yaş arasında zirve

EBV labil bir virüstür, çevresel kaynaklardan izole edilemez.

Duyarlı birey ile asemptomatik olarak virüsü yayan kişinin yakın teması gerekir



Boğaz ağrısı
Halsizlik
Baş ağrısı
İştahsızlık
Myalji
Titreme
Bulantı

LAP
Farenjit
Ateş
Splenomegali
Hepatomegali
Palatal enanem
Döküntü



Klinik triad

Ateş

Boğaz ağrısı

LAP

Mononükleoz
sendromu

Epstein-Barr virus

Hepatit A

Cytomegalovirus

Adenovirus

HIV

Toxoplasma gondii

Human herpes virus-6

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Epstein-Barr virus %50-90

Cytomegalovirus %5-7

Human herpes virus-6 %9

GABHS %3-4

T. gondii <%3

HIV <%2

Acute HIV Infection among Patients Tested for Mononucleosis

To the Editor: Acute infection with human immunodeficiency virus type 1 (HIV-1) is associated with a self-limited, mononucleosis-like illness in the majority of persons. Symptoms may include fever, pharyngitis, lymphadenopathy, rash, oral and genital ulcerations, orthostasis, and gastrointestinal problems. Although many patients seek medical attention during acute HIV-1 infection, the diagnosis is often missed.¹ In the early symptomatic stage, the standard enzyme-linked immunosorbent assay (ELISA) is negative for HIV-1, but tests for plasma HIV-1 RNA or plasma p24 antigen are positive. We hypothesized that health care providers are likely to perform testing for heterophil antibodies to Epstein-Barr virus in patients with the acute retroviral syndrome.

Akut EBV infeksiyonu öntanısıyla test edilen 563 örneğin 11(%2)'inde HIV RNA pozitifliği

Mononükleoz sendromu

Farengeal form

- boğaz ağrısı
- EBV

Glandüler form

- LAP
- *T. gondii*

Tifoidal form

- letarji, ateş
- CMV

CMV mononükleoz

en sık ikinci mononükleoz etkeni,
farenjit daha hafif, eksuda görülmez,
uzamış ateş,
gi semptomlar ön planda,
anikterik hepatit

HHV-6

Roseola infantum-ekzantem subitum
daha hafif ancak uzamış ateşli
dönem,
bilateral, ağrısız, anterior ve
posterior servikal LAP
LAP 3 aya kadar uzayabilir

HIV

40 °C'ye ulaşan ateş, farenjit, myalji,
artralji, baş ağrısı,
ağrısız aksiller, servikal, oksipital LAP
mukokutanöz ülserasyonlar,
sentrifugal makülopapüler döküntü

T. gondii

hafif sistemik semptomlar,
ağrısız servikal, oksipital LAP,
farenjit,
makülopapüler döküntü

Heterofil antikorlar,
akut EBV infeksiyonu sırasında
infekte hücrelerin yüzeyinde eksprese
edilen kompleks bir glikoprotein yapıya
karşı gelişen IgM sınıfı antikorlardır.

Türdeş olmayan hayvanların eritrositleri ile
çapraz tepkime verirler.

Normalde insan serumlarında, koyun eritrositlerini düşük titrelerde aglutine eden antikorlar bulunabilir.

İM'da ise, koyun eritrositlerini aglutine eden yüksek titrede antikor oluşur.

1932 Paul-Bunnell

İM hastalarının serumlarının yüksek dilüsyonlarda bile koyun eritrositlerini aglütine etmesi

SEROLOGIC DIAGNOSIS OF INFECTIOUS MONONUCLEOSIS

ISRAEL DAVIDSOHN, M.D.
CHICAGO

Infectious mononucleosis has been known under different names since 1889, when it was described by F. Pfeiffer¹ as glandular fever. Thirty-four years later, Tidy and Daniel² and Downey and McKinlay³ described the characteristic blood changes and inaugurated the hematologic diagnosis of infectious mononucleosis. The blood changes are very helpful in the recognition of the disease, but they are not pathognomonic. Similar changes are found in several clinically unrelated diseases, particularly acute infections of the pharynx. Furthermore, in the early stages of infectious mononucleosis the characteristic elevation of the mononuclear cells may be absent and the blood picture may show merely a slight to moderate increase of the total number of white cells with a normal differential

Forssman type. Further information may be found in reviews of the subject.⁷

It was shown by proper absorption tests that the antibodies against sheep red cells in normal persons and after horse serum therapy are of the Forssman type and by analogy it was assumed by many writers that the antibodies in infectious mononucleosis are also of that type.

In February 1934 I presented before the Chicago Pathological Society a modification of the technic of the agglutination test for infectious mononucleosis that has greater speed and precision than the older technic that I employed previously in the study of serum disease.⁸ I now began a study of the nature of the heterophilic antibodies in infectious mononucleosis and a preliminary report of my studies was given at the meeting of the American Society of Clinical Pathologists in June 1935.⁹ It is of interest that similar investigations were carried on independently of each other by C. A. Stuart and his associates,¹⁰ and by Bailey and Raffel.¹¹

1937 Davidsohn

Guinea pig böbrek ve sığır eritrositleri kullanarak “ayırt edici aglütinasyon”u tanımlamıştır.

Forsmann antikorlarından ayrımı

	Absorbe edilmemiş	Kobay böbrek abs.	Sığır eritrositleri
İnfeksiyöz mononükleoz	++++	+++	0
Serum hastalığı	+++	0	0
Forssman Ak	+	0	+

Ayırt edici aglütinasyon ile serum hastalığı ve Forssman antikorları, kobay böbrek özütü ile absorbe edilir.

Bu işlem sonrası >1:40 titre, kliniği uyan hastada İM için kuvvetli kanıttır.

Horse agglutinins in infectious mononucleosis¹

III Criterion for differential diagnosis

C. L. LEE, F. ZANDREW, AND I. DAVIDSOHN

*From the Department of Pathology, The Chicago Medical School,
University of Health Sciences, and Department of Experimental Pathology,
Mount Sinai Hospital Medical Center, Chicago, Illinois 60608*

At eritrositlerinin kullanımı ile sonuçlar daha iyi...

Heterofil Ak testi

yetişkin ve adolesan İM olgularında
>%90 pozitifdir,
1. haftada %25 yalancı negatif,
semptomların 2-5. haftasında,
düşük düzeylerde 12 aya kadar
saptanabilir

Ticari monospot kitlerinin

duyarlılığı %70-92,
özgüllüğü %96-100.

EBV spesifik antikorlar
yapısal proteinlere_VCA
yapısal olmayan proteinlere_EA
_EBNA

EBV spesifik antikorların saptanması, heterofil antikorların >%90 pozitif saptanması nedeniyle nadiren gerekir.

VCA IgM

- klinik tablonun başlangıcında pozitiftir,
- 4-8 hafta saptanabilir düzeylerde kalır,
- akut EBV infeksiyonu için tanısaldır.

VCA IgG

- klinik tablonun başlangıcında pozitiftir,
- ömür boyu saptanabilir düzeylerde kalır,
- epidemiyolojik amaçlarla kullanılır.

Anti-EA-D

- indirekt immünfloresan ile çekirdek ve sitoplazma difüz boyanır,
- akut EBV infeksiyonunda %70 pozitifdir,
- VCA'dan daha geç yükselir, daha geç kaybolur,
- VCA IgG ile birlikte pozitifliği akut infeksiyonu düşündürür,
- Varlığı ve titresini klinik hastalığın süresi ve ciddiyeti ile koreledir.

Anti-EA-R

- indirekt immünfloresan ile sadece sitoplazma boyanır,
- nadiren pozitif saptanır,
- yaklaşık 2 yıl saptanabilir düzeylerde kalır.

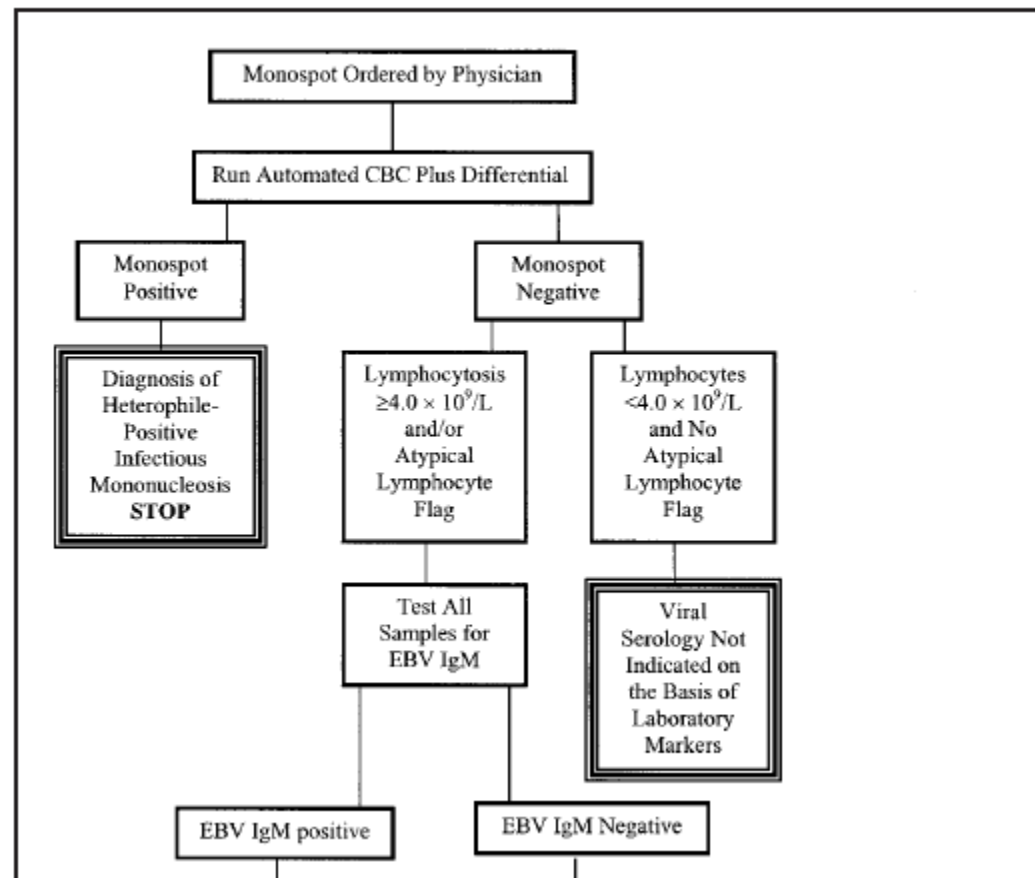
EBNA

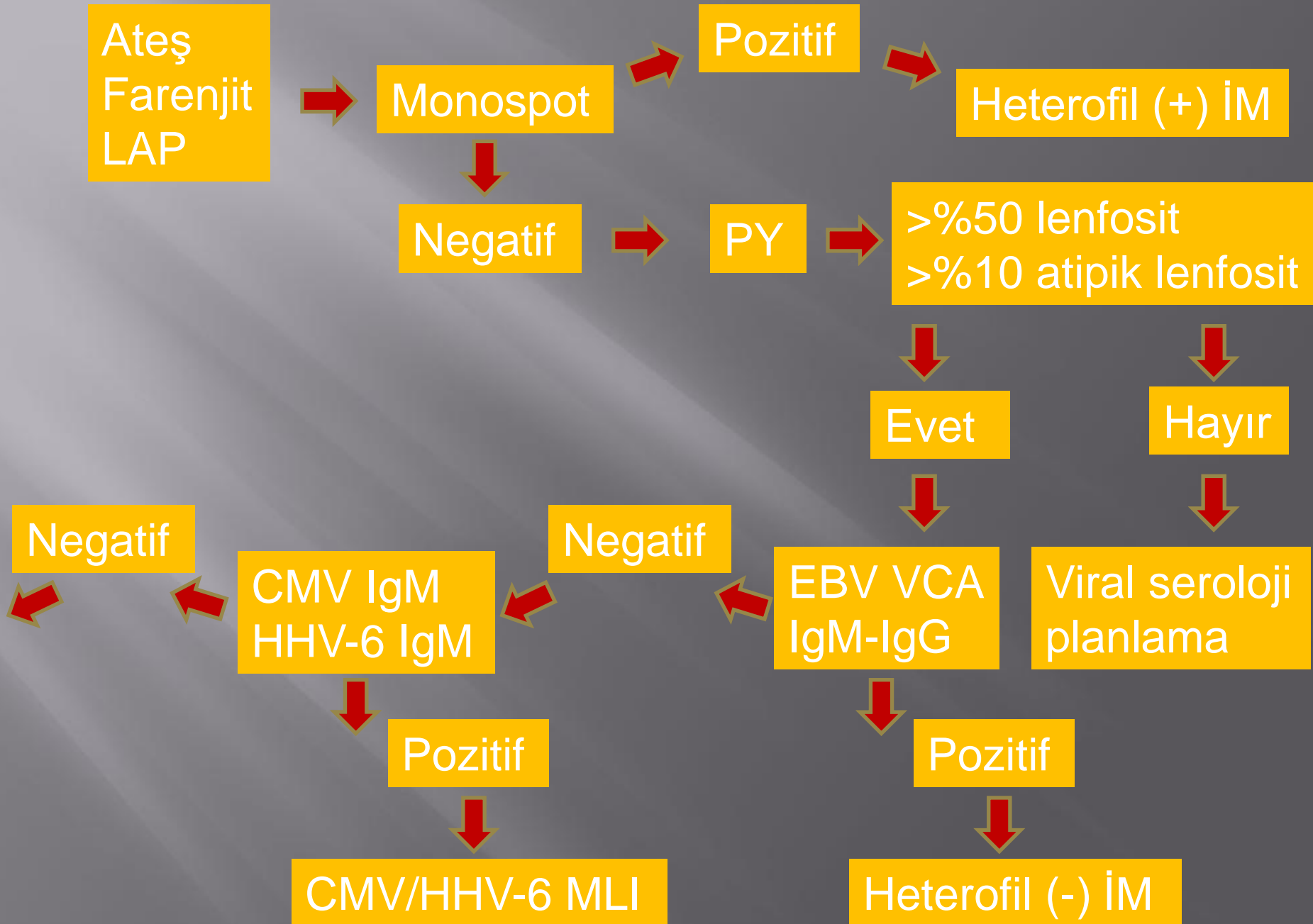
- klinik hastalığın başlangıcından 3-4 hafta sonra saptanır,
- VCA pozitif hastada serokonversiyonu akut infeksiyon lehinedir,
- ömür boyu saptanabilir düzeylerde kalır.

Proportion Positive for Epstein-Barr Virus, Cytomegalovirus, Human Herpesvirus 6, *Toxoplasma*, and Human Immunodeficiency Virus Types 1 and 2 in Heterophile-Negative Patients With an Absolute Lymphocytosis or an Instrument-Generated Atypical Lymphocyte Flag

Yotis F. Tsaparas, BSc; Malcolm L. Brigden, MD, FRCPC; Richard Mathias, MD, FRCPC; Eva Thomas, MD, FRCPC; Janet Rahoul, PhD; Patrick W. Doyle, MD, FRCPC

Figure 3. An algorithm for investigating heterophile-negative infectious mononucleosis.





Diğer tanısal testler

- HIV EİA, Western blot, HIV RNA
- *T. gondii* IgM, IgG, avidite
- Viral hepatit serolojisi
- Adenovirus EİA, PCR, viral izolasyon
- Rubella IgM
- Streptokokal hızlı antijen saptama testleri,boğaz kültürü
- Kemik iliği incelemesi ve biyopsi

İM kendini sınırlayan bir hastalıktır, ciddi komplikasyonlarla nadiren karşılaşılır.
Semptomatik tedavi yeterlidir.

Asetaminofen
Tuzlu su ile gargara

Splenomegali varlığında aktivite kısıtlaması önerilir.

Acyclovir for Treatment of Infectious Mononucleosis: A Meta-analysis

DONATO TORRE¹ and ROBERTO TAMBINI²

From the ¹Department of Infectious Diseases, Regional Hospital, Varese, and the ²Department of Infectious Diseases, Ospedali Riuniti, Bergamo, Italy

A meta-analysis of 5 randomized controlled trials (RCT), involving 339 patients with acute infectious mononucleosis (IM) treated with acyclovir (ACV) was performed. ACV was given intravenously in 2 RCTs, which included patients with more severe disease, and orally in the remaining 3 RCTs, which included patients with mild to moderate IM. Both clinical and virological endpoint data available from RCT were evaluated in this study. There was a trend towards clinical effectiveness of ACV treatment, but no statistically significant results were achieved. In contrast, a significant reduction in the rate of oropharyngeal EBV shedding was observed at the end of the therapy (overall OR: 6.62; 95% CI: 3.56–12.29; $p < 0.00001$). However, no difference in EBV shedding was observed 3 weeks later. There was no significant difference on adverse events in the groups of patients treated with ACV or placebo. In conclusion, clinical data do not support use of ACV for the treatment of acute IM, despite good virological activity of this drug. There is a need for more effective treatment of EBV infection.

5 randomize kontrollü çalışmanın metaanalizi
İM tedavisinde asiklovirin belirgin yararı yok.

Acyclovir and Prednisolone Treatment of Acute Infectious Mononucleosis: A Multicenter, Double-Blind, Placebo-Controlled Study

**Elsa Tynell, Elisabeth Aurelius, Astri Brandell,
Inger Julander, Martin Wood, Qing-yun Yao,
Alan Rickinson, Börje Åkerlund, and Jan Andersson**

*Department of Infectious Diseases, Karolinska Institutet, Danderyd and
Huddinge University Hospitals, and Department of Immunology,
Arrhenius Laboratories for Natural Sciences, University of Stockholm,
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Birmingham Heartland Hospital, and Department of Immunology,
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Ninety-four patients with infectious mononucleosis and symptoms ≤ 7 days were randomized to treatment with oral acyclovir (800 mg 5 times/day) and prednisolone (0.7 mg/kg for the first 4 days, which was reduced by 0.1 mg/kg on consecutive days for another 6 days; $n = 48$), or placebo ($n = 46$) for 10 days. Oropharyngeal Epstein-Barr virus (EBV) shedding was significantly inhibited during the treatment period ($P = .02$, Mann-Whitney rank test). No significant effect was observed for duration of general illness, sore throat, weight loss, or absence from school or work. The frequency of latent EBV-infected B lymphocytes in peripheral blood and the HLA-restricted EBV-specific cellular immunity, measured 6 months after onset of disease, was not affected by treatment. Thus, acyclovir combined with prednisolone inhibited oropharyngeal EBV replication without affecting duration of clinical symptoms or development of EBV-specific cellular immunity.

Hafif ve orta ağırlıkta seyreden olgularda asiklovir ve steroid kombinasyon tedavisi hastalık süresi, boğaz ağrısı, kilo kaybı, işgücü kaybı açısından yarar sağlamaz.

Acyclovir and Prednisolone Treatment of Acute Infectious Mononucleosis: A Multicenter, Double-Blind, Placebo-Controlled Study

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Prednison 60-80 mg/gün, 7-14 gün
üst solunum yolu obstrüksiyonu,
immün hemolitik anemi,
immün trombositopenik purpura,
santral sinir sistemi tutulumu

CMV

immün yetmezliği olmayan hastalarda
tedavi önerilmez.

T. gondii

immün yetmezliği olmayan hastalarda
tedavi önerilmez.

HIV

ART

Sonuç olarak,

Ateş, farenjit, LAP ve eşlik eden lenfositozun saptandığı hastalarda öncelikli olarak EBV infeksiyonu düşünülmeli, İM tanısı doğrulamayan olgularda etyolojiye yönelik incelemeler yapılarak takip ve tedaviye yön verilmelidir.