POEMS sendromu

Dr. Tayfur Toptaş
Marmara Üniversitesi

HOD, 20 Eylül 2019, KKTC

Aus der Nervenheilanstalt Maria-Theresien-Schlössel in Wien.

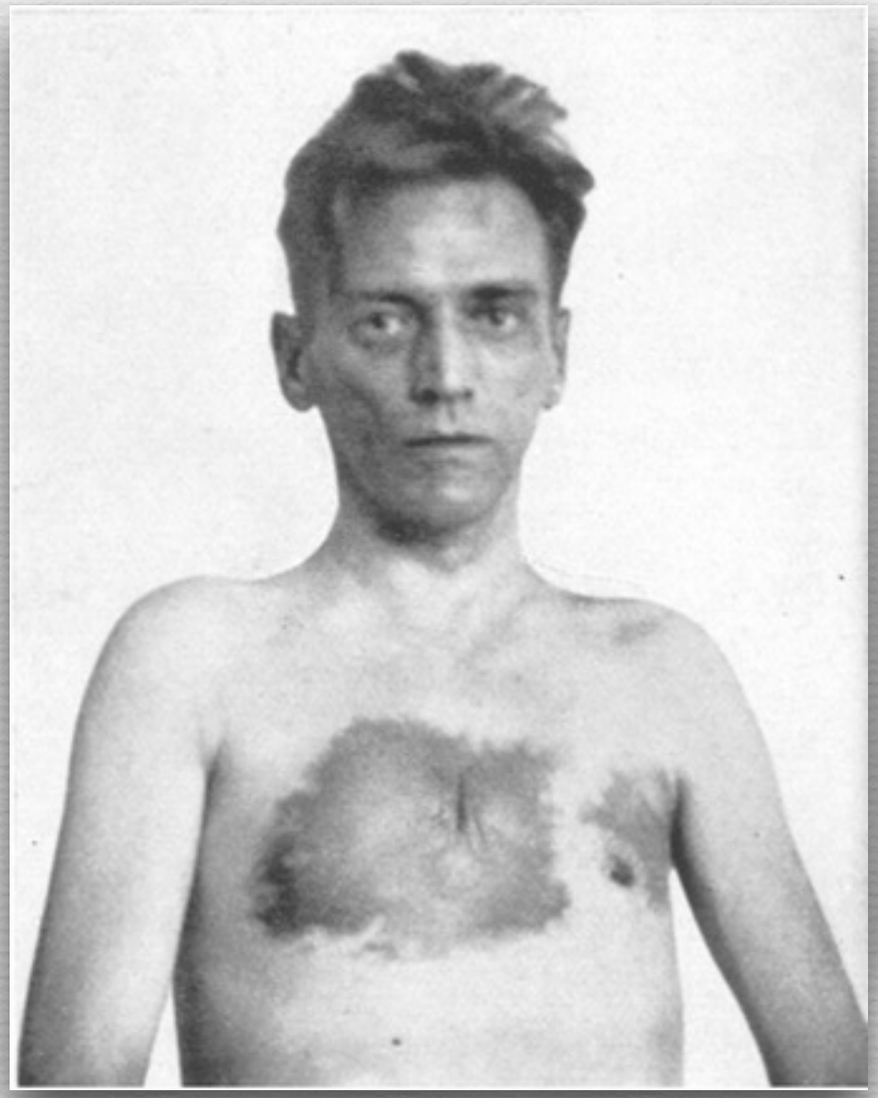
Myelom und Nervensystem.

Über eine bisher nicht beschriebene mit eigentümlichen Hautveränderungen einhergehende Polyneuritis bei einem plasmazellulären Myelom des Sternums.

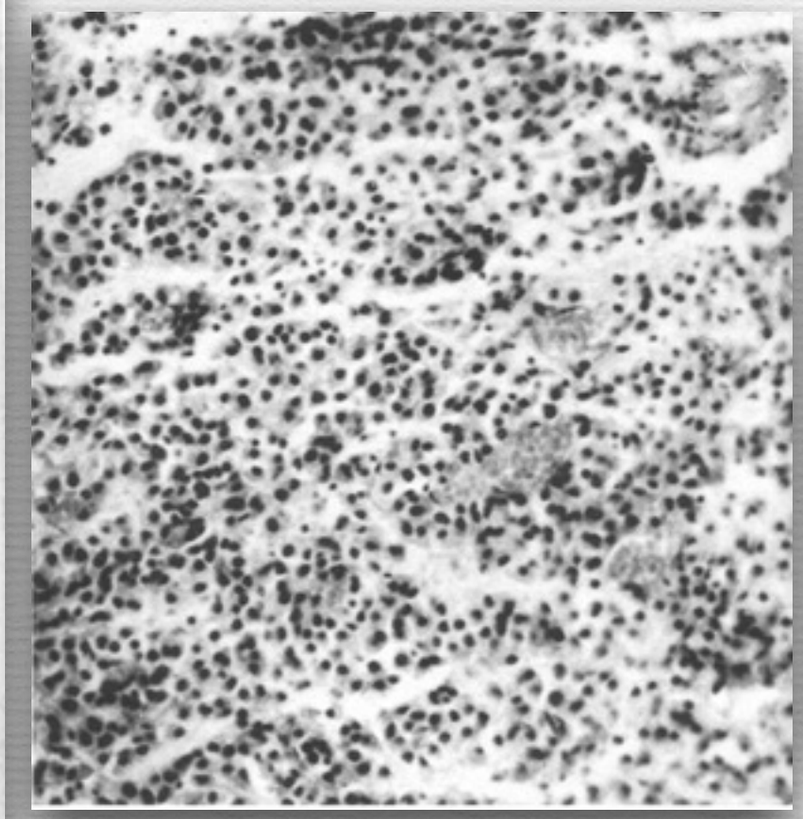
Von

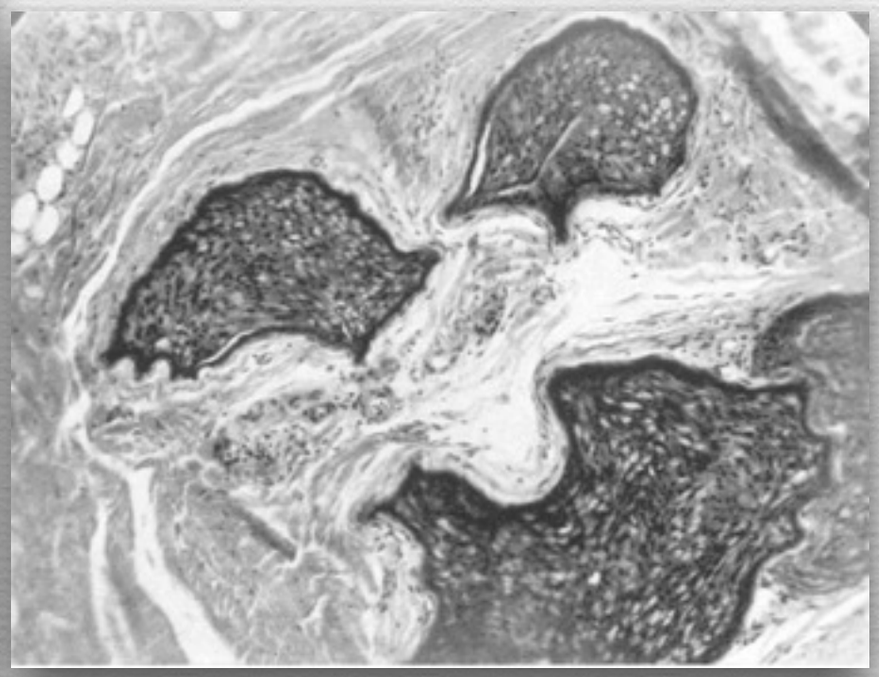
Dr. **I. Scheinker.**

39, E, pareztezi, güç kaybı, hiperpigmente lezyon



Plazmasitom





Scheinker I, J Neurology 1938;147:247

PERIPHERAL NEURITIS IN MYELOMATOSIS

BY

R. S. CROW, M.B., Ch.B., M.R.C.P.

*Senior Medical Registrar, Bristol Royal Infirmary**

[With Special Plate]

appeared in the region of the right acromion process and slowly increased in size. During that year his wife was concerned about a darkening of his skin and noted a "shininess" of his finger-nails.

In February, 1955, he first experienced a sensation of coldness and prickling in both feet with pain on walking. Thereafter weakness of the ankles and increasing numbness of the lower legs developed. Pain in the feet occurred even at rest, and there was oedema of the ankles in the evening. During the first half of 1955 he lost 17 lb. (7.7 kg.) in weight.

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Medicine

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Plasma Cell Dyscrasia with Polyneuropathy, Organomegaly, Endocrinopathy, M Protein, and Skin Changes: The POEMS Syndrome

Report on Two Cases and A Review of the Literature[1]

P. A. BARDWICK, N. J. ZVAIFLER, G. N. GILL, D. NEWMAN, G. D. GREENWAY, and D. L. RESNICK

POEMS sendromu

Crow Fukase sendromu

Osteosklerotik miyelom

PEP (plazma hücreli diskrazi, endokrinopati, polinöropati) sendromu

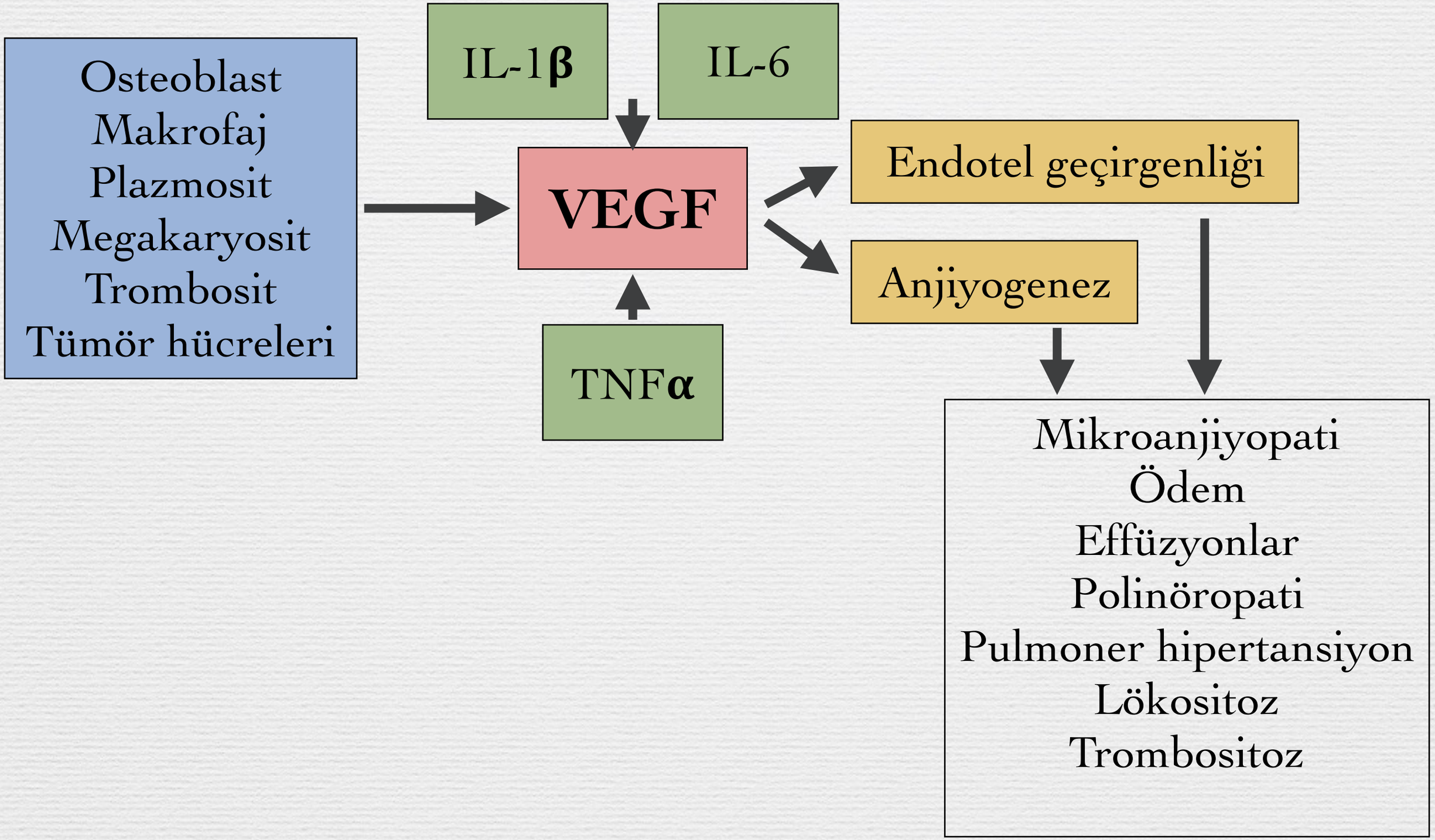
Takatsuki sendromu

Patogenez

- Açık değil
- **Miyelomdan farklı**

1. Başlıca: **<u>nöropati</u>**, endokrinopati, sıvı yüklenmesi
2. Kemik ağrısı, renal yetersizlik, plazma hücre artışı **<u>yok</u>**
3. VEGF **<u>yüksek</u>**
4. Prognoz **<u>daha iyi</u>**
5. **<u>Lambda</u>** zincir hakim (>%95)

Dispenzieri A, Am J Hematol 2019



Dispenzieri A, Am J Hematol 2019

Osteoblast
Makrofaj
Plazmosit
Megakaryosit
Trombosit
Tümör hücreleri

IL-1β

IL-6

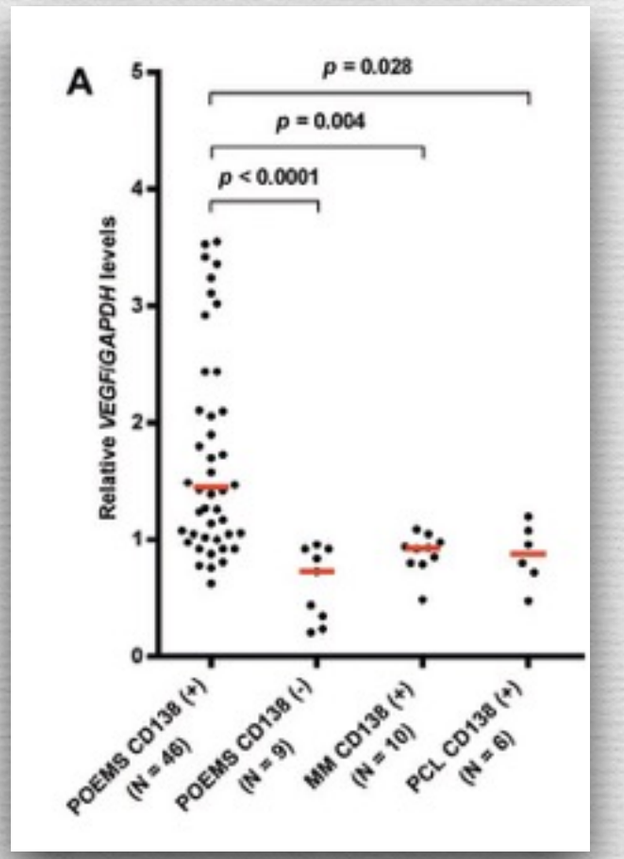
VEGF

TNFα

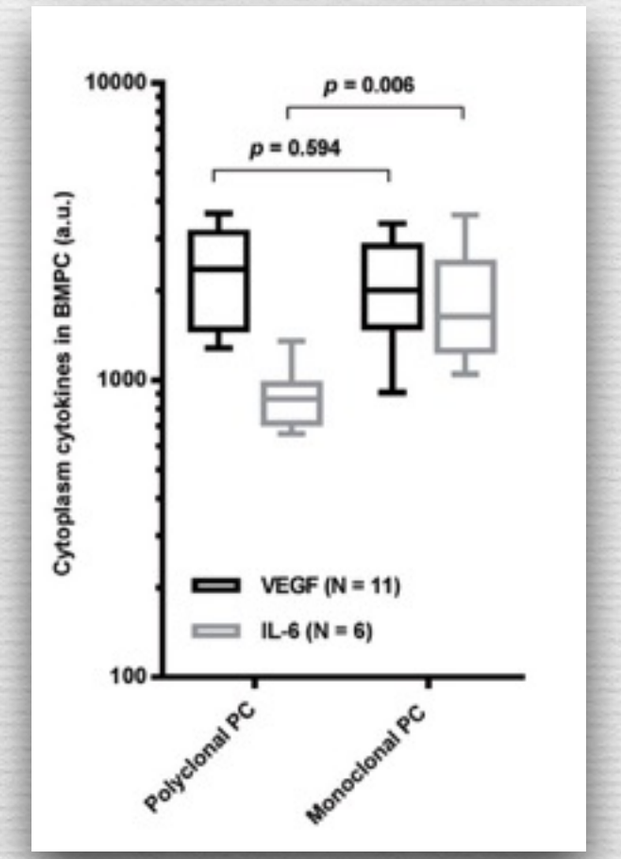
Endotel geçirgenliği

Anjiyogenez

Mikroanjiyopati
Ödem
Effüzyonlar
Polinöropati
Pulmoner hipertansiyon
Lökositoz
Trombositoz



VEGF mRNA ifadesi



VEGF ve IL-6 düzeyi

Dispenzieri A, Am J Hematol 2019

Wang C, Leuk Res 2016

Osteoblast
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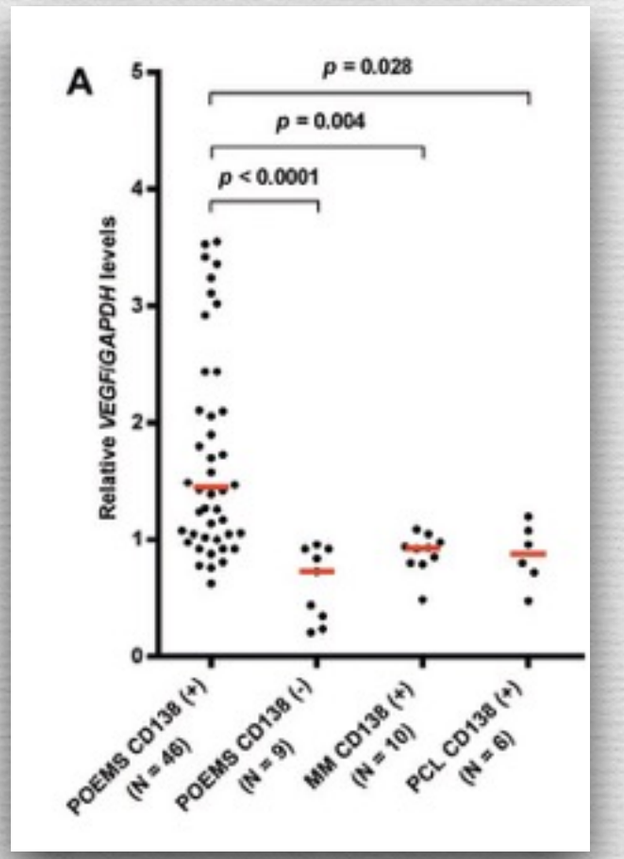
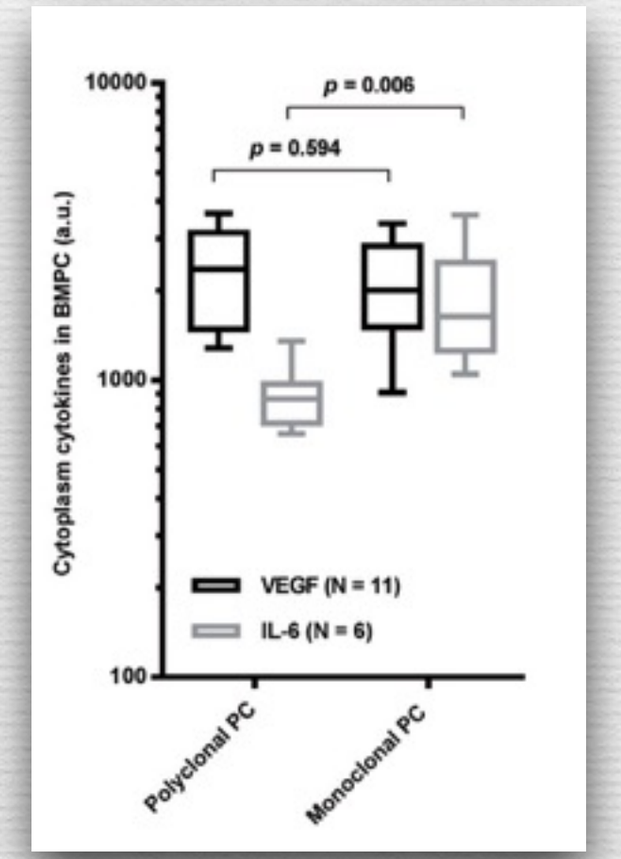


VEGF mRNA ifadesi



VEGF ve IL-6 düzeyi

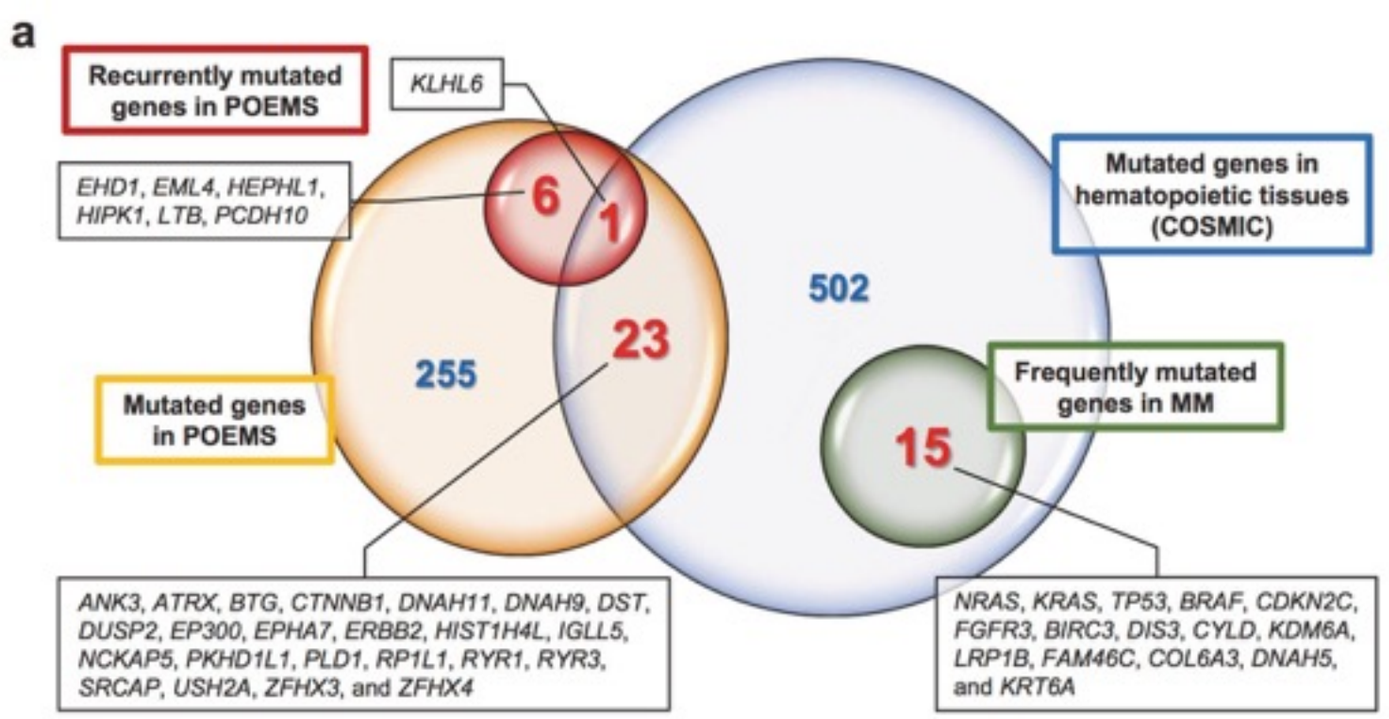
IL-6 ve IL-12 hastalık aktvitesiyle ilişkili

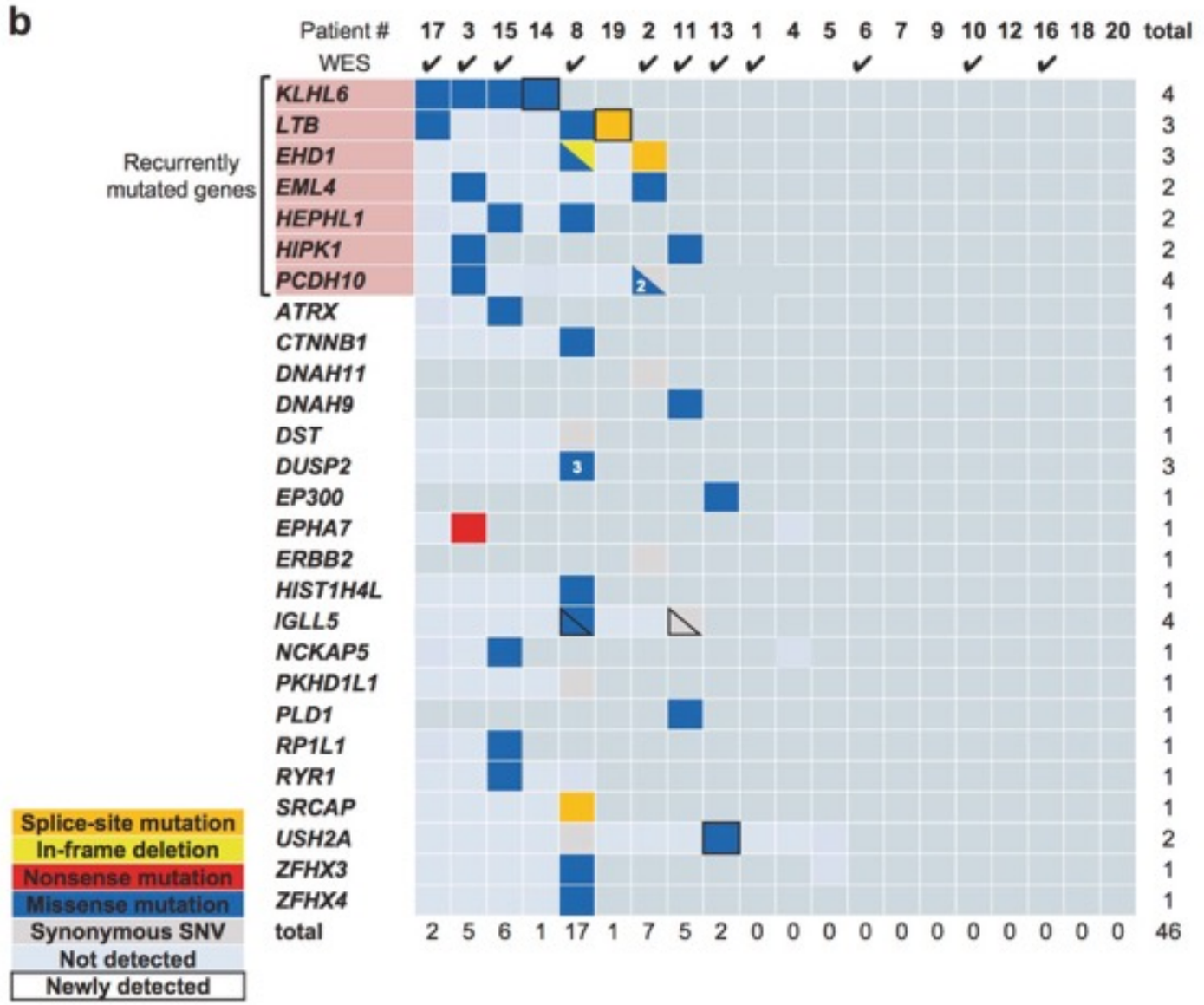
Dispenzieri A, Am J Hematol 2019

Wang C, Leuk Res 2016

Somatik mutasyon profili MM'den farklı

Nagao Y, Leukemia 2019





Epidemiyoloji

- Japon, N=392 (2012-2015)
- Prevalans: 0.3/100,000
- Ortanca yaş: 54 (21-84), ≤65y: %84
- E/K:~1.5
- Nöroloji/Hematoloji:60/40

Suichi T, Neurology 2019

Klinik

1. POEMS tanısı için tüm özellikler şart değil
2. POEMS içinde yer almayan önemli özellikler
    - *P*apilödem,
    - *E*kstravasküler sıvı yüklenmesi,
    - *S*klerotik kemik lezyonları
    - *T*rombositoz/Eritrositoz
3. POEMS'in Castleman varyantı

Dispenzieri A., Am J Hematol 2019

Klinik

Polinöropati	%100
Organomegali (HM, SM, LAP)	%67
Castleman hastalığı	%19
Endokrinopati	%66
Gonadal aks bozuklukları	%34
Monoklonal plazma hücre hastalığı	%100
Deri değişiklikleri	%78
Hiperpigmentasyon	%68

Nakanishi T, Neurology 1984

Dispenzieri A, Blood 2003

Suichi T, Neurology 2019

Klinik

Papilödem	%34
Ekstravasküler sıvı yüklenmesi	%62
Periferik ödem	%60
Sklerotik ± litik kemik lezyonları	%92
Trombositoz	%30
Eritrositoz	%15
Pulmoner hipertansiyon	%10
BOS proteini artışı	%100
VEGF yüksekliği*	%86

Nakanishi T, Neurology 1984

Dispenzieri A, Blood 2003

Suichi T, Neurology 2019

Periferik nöropati

- Olmazsa olmaz
- Ayaklarda başlar: uyuşma, soğukluk hissi, parestezi
- Önce duysal, sonra motor.
- Distal, simetrik, progresif, proksimale yayılım
- Otonomik nöropati, kranyal sinir tutulumu beklenmez
- Tekerlekli sandalye veya yatağa bağımlı: %30
- Aksonal dejenerasyon ve demiyelinizasyon

Dispenzieri A., Am J Hematol 2019

Suichi T, Neurology 2019

Organomegali

- Masif organomegali beklenmez
- LAP: Castleman

Dispenzieri A., Am J Hematol 2019

Suichi T, Neurology 2019

Endokrinopati

- Hipogonadizm: %70
- Adrenal aks bozuklukları: adrenal yetersizlik
- Hiperprolaktinemi
- Jinekomasti/galaktore
- *DM: toplumda sık*
- *Hipotiroidi: toplumda sık*

Dispenzieri A., Am J Hematol 2019

Suichi T, Neurology 2019

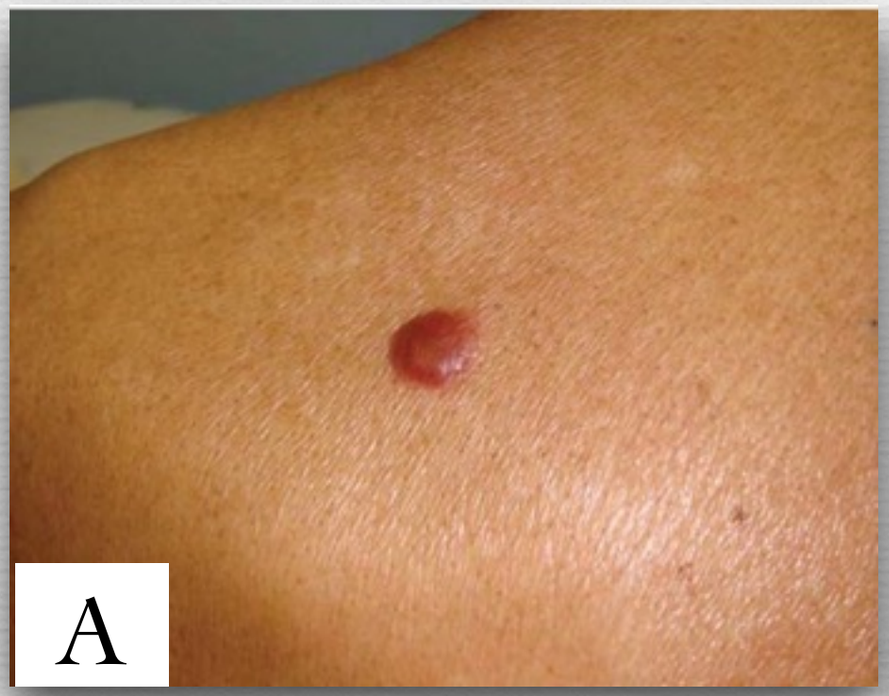
Monoklonal gammopati

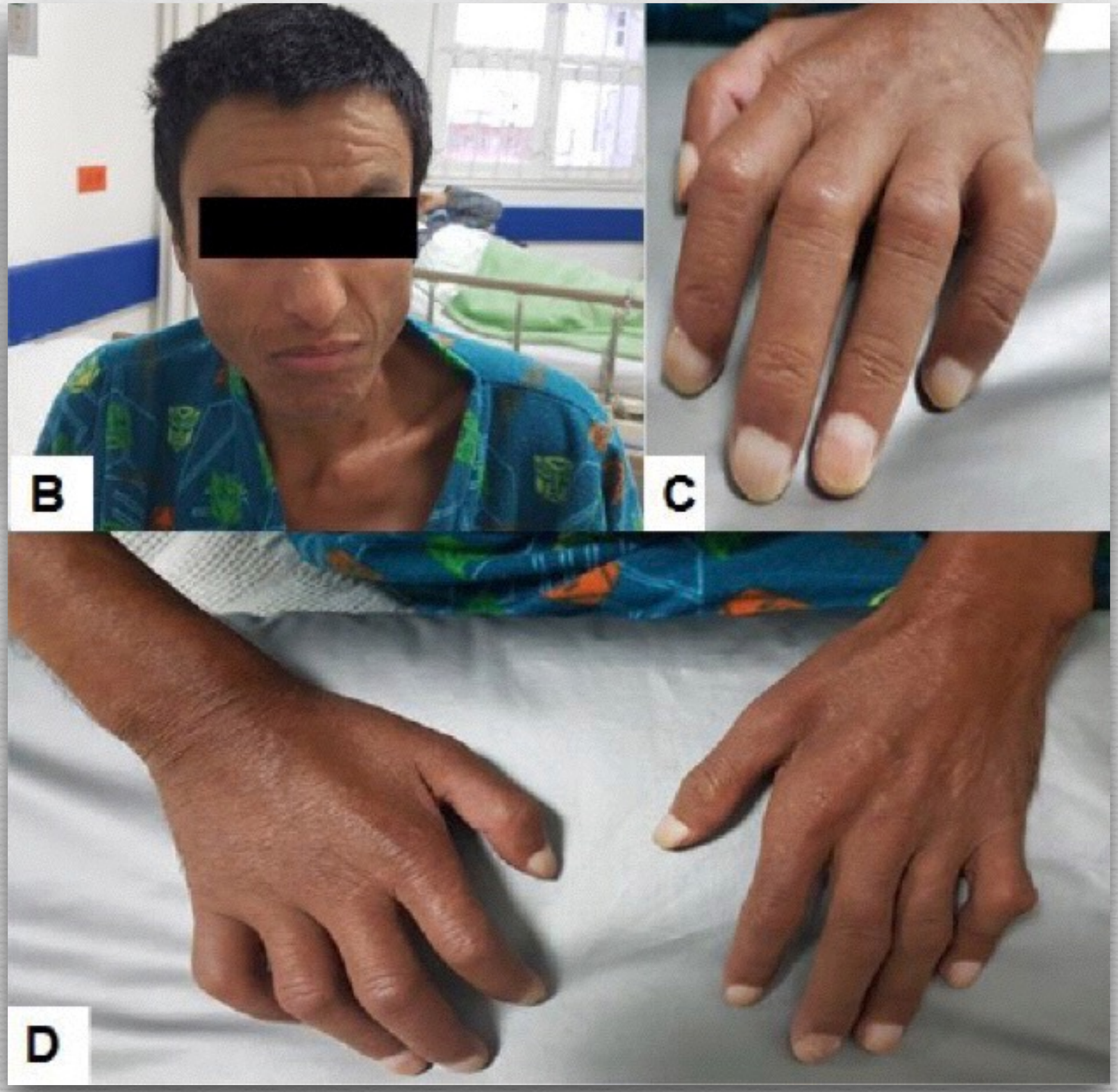
- M proteini <2 g/dL: %93
- Hemen hemel her zaman: lambda
- IgG/IgA/IgM: %52/%47/%1
- Ortanca plazma hücre oranı: %2.4
- Plazma hücre oranı >%10: <%15

Dispenzieri A., Am J Hematol 2019

Suichi T, Neurology 2019

Deri değişiklikleri



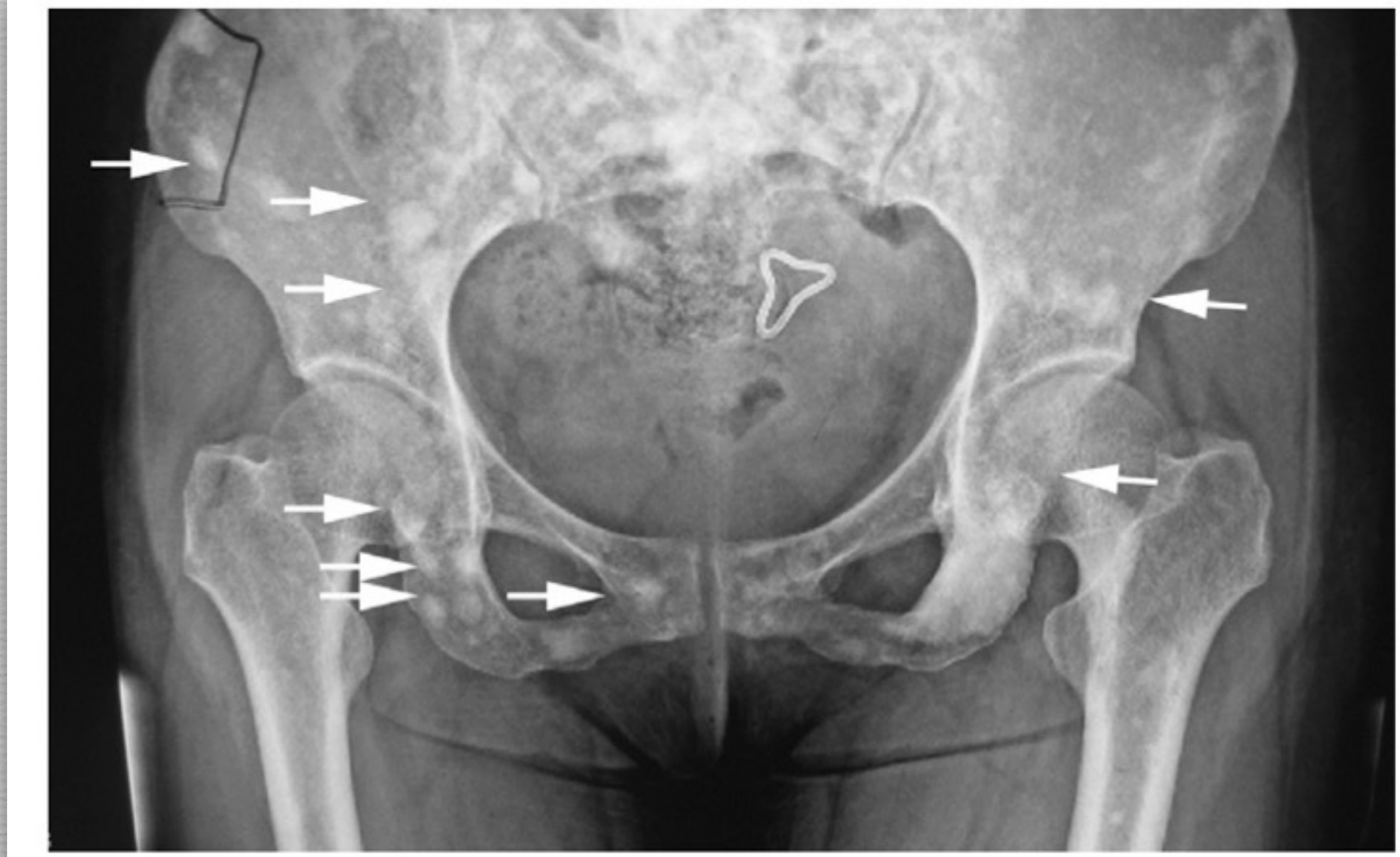


Glomeruloid hemanjiyom (%47)	**A**
Hiperpigmentasyon (%23)	**B**
Clubbing/leukonichia (%6/%30)	**C**
Hiperkeratoz	**D**
Skleroderma görünümü (%26)	**D**

Tedaviye yanıtlı

Enciso L, J Clin Case Rep 2017

Osteosklerotik kemik lezyonları



Dispenzieri A., Am J Hematol 2019

Shi X, Clin Lymph Myeloma Leukemia 2015

Kimde şüphelenilmeli?

Tedaviye dirençli
assit/periferik ödem

Açıklanamayan
polinöropati

Açıklanamayan
organomegali/
jinekomasti

POEMS

Dispenzieri A., Am J Hematol 2019

Tanı

Zorunlu majör kriterler	**1.** Periferik nöropati (tipik olarak demiyelinizan)
1 + 2	**2.** Monoklonal plazma hücre proliferatif hastalığı (~%95 lambda)
Diğer majör kriterler	**1.** Castleman hastalığı
Herhangi biri	**2.** Osteosklerotik kemik lezyonları
	3. VEGF yüksekliği (3-4 x üst sınır)
Minör kriterler	**1.** Organomegali (HM, SM, LAM)
Herhangi biri	**2.** Ekstravasküler sıvı yüklenmesi (periferik ödem, assit, plevral efüzyon)
	3. Endokrinopati (adrenal, *tiroid*, hipofiz, gonadal, paratiroid, *pankreatik*)
	4. Deri değişiklikleri (hiperpigmentasyon, hipertrikoz, glomeruloid
	hemanjiyomlar, beyaz tırnaklar, pletora, akrosiyanoz)
	5. Papilödem
	6. Trombositoz/eritrositoz
Ek özellikler	Hiperhidroz, çomak parmak, kilo kaybı, pulmoner HT, ishal,
	restriktif akciger hastalığı, vitamin B12 düşüklüğü

Dispenzieri A., Am J Hematol 2019

Tanısal değerlendirme

TEST	BASE-LINE	EVERY 3-6 MONTHS	EVERY 1-2 YEARS
History and review of systems			
Detailed neurologic history (numbness, pain, weakness, balance, orthostasis)	X	X	
History regarding menstrual and sexual function	X	X	
Skin pigment, thickening and texture, body hair quantity and texture, color of distal extremities, and development of cherry angiomata	X	X	
Physical exam			
Neurologic exam	X	X	
Funoscopy	X		X
Organomegaly, lymphadenopathy, extravascular volume overload	X	X	
Skin (see above)	X	X	
Blood			
Complete blood count (hemoglobin, platelet)	X	X	
Serum protein electrophoresis, quantitative immunoglobulin and immunofixation	X	X	
Vascular endothelial growth factor	X	X	
Testosterone, estradiol, fasting glucose, glycosylated hemoglobin, thyroid stimulating hormone, prolactin	X	X*	X
Follicle stimulating hormone, luteinizing hormone, adrenocorticotropin hormone, cortrosyn stimulation test, serum cortisol, parathyroid hormone	X*	X*	
Other studies			
24 hour urine total protein, electrophoresis, and immunofixation	X		X
Bone marrow aspirate and biopsy (test for kappa/lambda by IHC)	X		X*
Electrophysiologic study (nerve conduction studies)	X		X*
Sural nerve biopsy	X*		
Echocardiography to assess right ventricular systolic and pulmonary artery pressures	X		X†
Pulmonary function tests including DLCO	X		X†
Skeletal CT and/or PET/CT for bone lesions, organomegaly, effusions	X	X*	

* As clinically indicated
† Only if affected
IHC, immunohistochemistry; DLCO, diffusion capacity of carbon monoxide

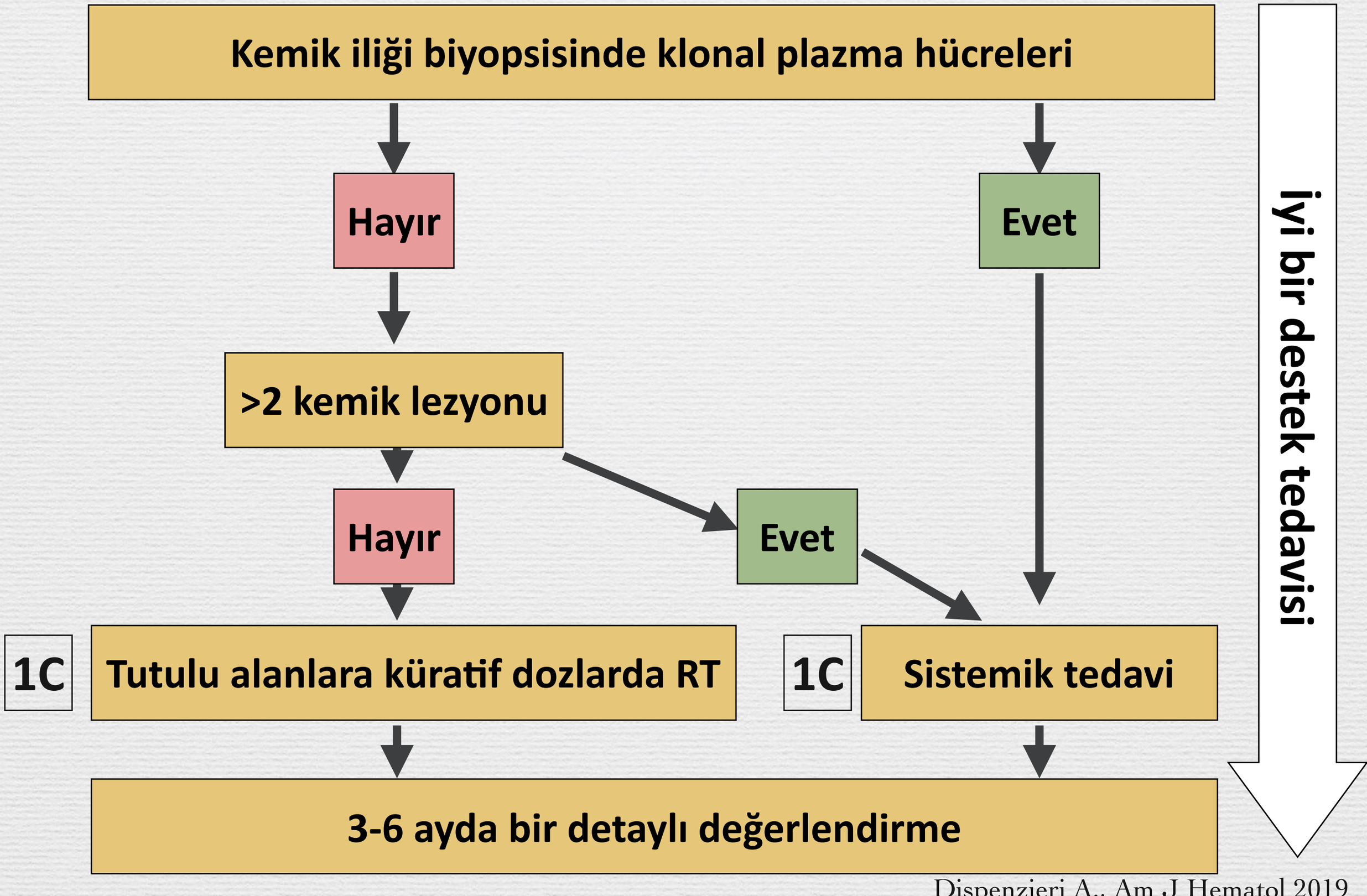
Dispenzieri A., Am J Hematol 2019

Risk değerlendirmesi

- Mayo Clinic: albümin< 3.2 g/dL, ileri yaş, tedavi ile hematolojik yanıt alınamaması
- Çin: >50 yaş, plevral efüzyon, pulmoner HT, eGFR<30 mL/dk
- Castleman
- Sıvı yüklenmesi, papilödem, pulmoner semptomlar, çomak parmak, VEGF yüksekliği

Dispenzieri A., Am J Hematol 2019

Tedavi algoritması



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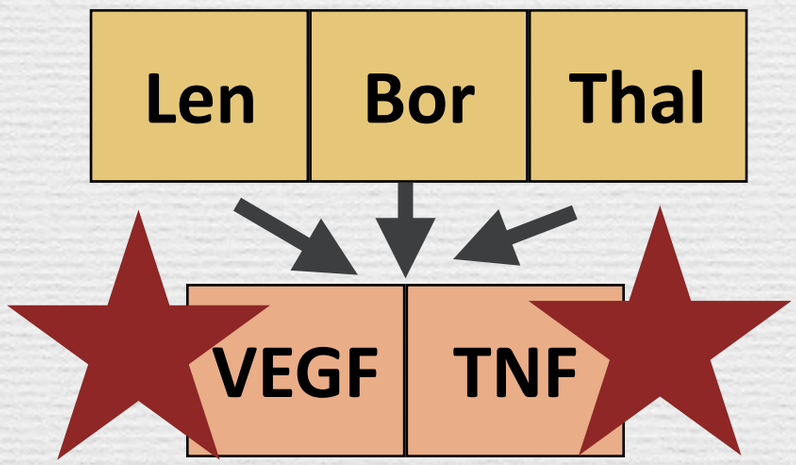
Tedavi seçenekleri

Tedavi	Sonlanım
Radyoterapi	küratif + semptomatik; 10-y OS: %70, 6-y PFS: %62, başarısızlık 12 ay
Mel-Dex	12 siklüs: hematolojik yanıt: %81, VEGF ve nörolojik yanıt: %100 (**1A**)
Kortikosteroidler	%50'de belirgin klinik düzelme
Cy-Dex	En az %50'de belirgin klinik düzelme
OKIT	Tümünde anlamlı klinik iyileşme, 10-y OS: %89, 6-y PFS: %72. (**1A**)
Thal-Dex	İyi yanıt alınan olgular var, birinci basamak değil (**1B**)
Len-Dex	%75-95 klinik iyileşme ve VEGF yanıtı, 3-y OS: %90, PFS: 75 (**1A**)
Bortezomib	Hematolojik ve VEGF yanıtları %100, nöropati! (**1B**)
Bevacizumab	Sonuçlar tutarsız, ölümler bildirilmiş.



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Yanıt değerlendirmesi

PARAMETER	EVALUABLE	Complete response	Improvement	Progression [a]
Plasma VEGF	2x ULN	Normal [b]	50% reduction from baseline [b]	50% increase from lowest level
Hematologic	M-spike 0.5 g/dl [c], 1.0 g/dL [d,e]	Negative serum & urine IFE & bone marrow [b]	50% reduction of M-spike from baseline [f]	25% increase from lowest level, which must be >0.5 g/dL
PET/CT	At least one lesion with FDG SUV_{max} [g]	No FDG uptake	50% reduction in sum of SUV_{max} [g]	30% increase of sum of SUV_{max} [g] from lowest level, which must be at least 4 SUV_{max} [g] OR appearance of new FDG avid lesion
mNIS $+7_{POEMS}$	All patients	…	↓ 15% change from baseline (a minimum of 10 points)	↑ 15% change from lowest value (a minimum of 10 points)
Ascites / effusion / edema	Present	Absent	Improved by 1 CTCAE grade from baseline	Worsened by 1 CTCAE grade from lowest grade
ECHO RVSP	≥40 mm Hg	…	<40 mm Hg	
Papilledema	Present		Absent	Worsening by 1 CTCAE grade
DLCO	<70% predicted	≥70% predicted	…	Worsening by 1 CTCAE grade

IFE = immunofixation; ECHO RVSP, echocardiogram right ventricular systolic pressure; DLCO, diffusing capacity of carbon monoxide

[a] Any progression event (VEGF, hematologic, or clinical) will be considered progression, assuming change is attributable to disease and not an adverse event. To document progression, option exists for repeating value. If confirmed, progression date is first date of suspected progression.

Dispenzieri A., Am J Hematol 2019

“Teşekürler”