İmmünglobülin G4 İlişkili Hastalık

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İç Hastalıkları - Romatoloji Bilim Dalı

Sunum planı

- Tanım
- Epidemiyoloji
- Patogenez
- Klinik
- Tanı
- Tedavi

Ig G4 İlişkili Hastalık- tanım :

- **«Fibroinflamatuar»** immun aracılı bir hastalık
- Her organı/anatomik lokalizasyonu etkileyebilir
- Organ hasarı !

- 2001- 2003 te ilk defa tanımlanmış

- Hamano H, Kawa S, Horiuchi A, et al. High serum IgG4 concentrations in patients with sclerosing pancreatitis. N Engl J Med 2001;344:732–8.

- Kamisawa T, Funata N, Hayashi Y, et al. A new clinicopathological entity of IgG4-related autoimmune disease. J Gastroenterol 2003;38:982–4.

IgG4 ilişkili hastalığın komponenti olarak kabul edilen eski tanımlamalar

- Mikulicz sendromu (sialadenit, dakroadenit)
- Küttner sendromu (izole submandibular bez hastalığı)
- Riedel tiroidit
- Multifokal fibrosklerozis
- Retroperitoneal fibrozis (Ormond hastalığı)
- Otoimmun pankreatit tip 1
- Mediastinal fibrozis
- Periaortitis ve periarteritis
- İnflamatuvar aortik anevrizma
- İdiyopatik hipokomplementemik tubulointerstisyel nefrit
- İnflamatuvar psödotümör (orbita, akciğer, böbrek)

**Recommendations for the nomenclature of IgG4-related disease and its individual organ system manifestations. Arthritis Rheum. 2012*

Epidemiyoloji

- 5.-7. dekatlarda, prevelans 5/100 000
- **Erkek** baskın
- Klinik başvuru şekli – cinsiyet:

Alerjik hastalık öyküsü, Mikulicz sendromu (sialadenit ve dakriyoadenit), tiroidit => kadınlarda

Otoimmün pankreatit, retroperitoneal fibrozis, sklerozan kolanjit =>erkeklerde

- Sigara >> RPF !*
- Premalign olduğu kanıtlanmamış*

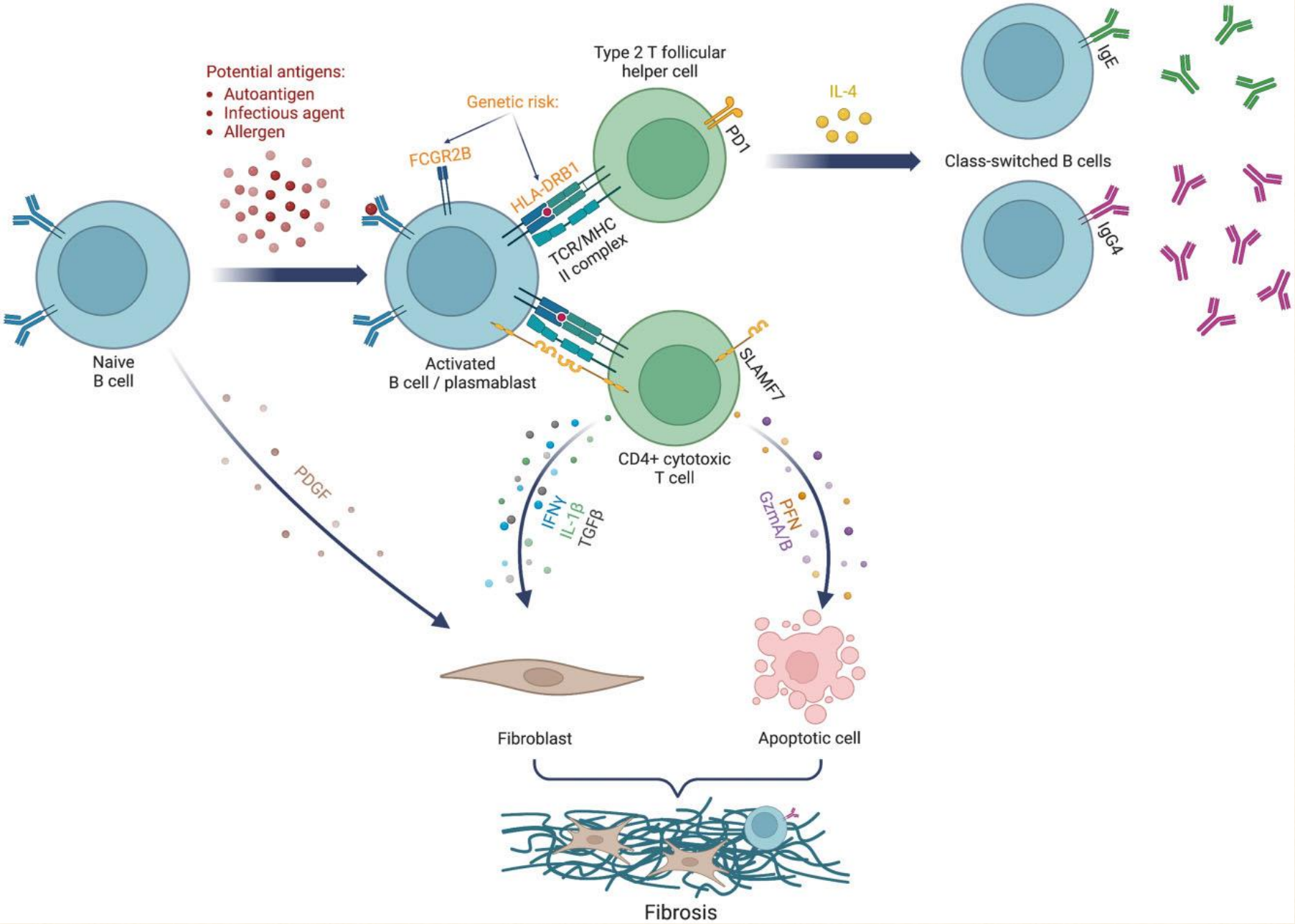
** Clinical Perspectives on IgG4-Related Disease and Its ClassificationAnnu. Rev.Med. 2022*

Patogenez

- CD4+ ve Tip 2 T foliküler helper hücreleri
- İnflamatuar faz : otoantijenlerin CD4+ T helper ve sitotoksik T hücreleri tetikleyici rol oynadıkları düşünülmektedir

➢ granzim ve perforin; bunun yanı sıra IL-1B, IL-6, TGF-beta ve interferon gamma gibi fibroziste rol oynayan sitokinlerin salınımı gerçekleşir

- Fibrotik faz : Aktive olan lenfositler ve plazmoblastların da etkisiyle tutulum olan bölgede fibroblast akvitasyonu ve kollajen üretimi



Current and future advances in practice: IgG4-related disease. Rheumatol Adv Pract. 2024 Apr

Patogenez

- Ig G4 ün rolü: Patojenik ?? İmmün aktivasyona kompansatuar yanıt?
- Ig G4: non- inflamatuar /anti inflamatuar

komplemanı aktive etme yeteneği çok düşük ve aktive edici Fc reseptörüne düşük afinitede bağlanma gösteren bir molekül

- Yüksekliği organ tutulumu ve nüks riskleri ile ilişkili*

**Predictors of disease relapse in IgG4-related disease following rituximab. Rheumatology (Oxford). 2016*

Klinik

- Sistemik; ama bazen organ sınırlı
- Tüm organlar etkilenebilir: kitle, hipertrofi, organomegali, duvar kalınlaşması şeklinde
- Asemptomatik saptanan radyolojik ve histolojik bulgular olabilir
- Genellikle **subakut** seyirli
- Konstitüsyonel semptomlar gözlenmez (Kilo kaybı>> ekzokrin pankreas?)
- **Atopi:** alerjik şikayetler sık(%40) (IgE ve eozinofil yüksekliği)

Table 1. Patterns of presentation

Pattern	Pancreato-hepatobiliary disease	Retroperitoneum and aorta	Head- and neck-limited disease	Mikulicz and systemic disease
Typical manifestations	Autoimmune pancreatitis, sclerosing cholangitis	Retroperitoneal fibrosis, aortitis, large vessel disease	Salivary and/or lacrimal gland enlargement, adnexal orbital involvement	Classic symmetric lacrimal, salivary gland enlargement with involvement in the chest and/or abdomen
Male predominance	Yes	Yes	No	Yes
Age, mean, years	63	58	55	63
Serum IgG4 concentration	Elevated	Normal to mildly elevated	Elevated	Very high
Examples of potential mimics	Pancreatic cancer, autoimmune pancreatitis type 2, primary sclerosing cholangitis	Lymphoma, Erdheim–Chester disease, GCA	SS and other autoimmune CTD, granulomatosis with polyangiitis, lymphoma	

Clinical phenotypes of IgG4-related disease: an analysis of two international cross-sectional cohorts. Ann Rheum Dis 2019

Klinik- Abdomen ve Pelvis:

- **Tip 1 Otoimmün Pankreatit:** %60

➢Kitle, ağrısız tıkanma sarılığı; **!** pankreas kanseri ayırıcı tanı **!**

➢Akut, rekürren olabilir

➢Çoğunda IgG4 ile ilişkili sklerozan kolanjit, lenfadenopati, tükürük veya gözyaşı bezi tutulumu eşlik eder

➢pankreasın yaygın genişlemesi, "sosis“ şeklindeki pankreas

- **Sklerozan kolanjit:**

➢Tıkanma sarılığı

Klinik- Abdomen ve Pelvis:

- **Retroperitoneal fibrozis:** Tüm RPF lerin %30-60*ı

40-60 yaş ; E:K= 3:1

infrarenal aorta, iliak arterler, üreterleri de içerecek şekilde

Ağrı, obstrüktif üropati > hidronefroz, alt ekstremite ödemi

Diğer sekonder RPF etiyoloji: ilaç enfeksiyon malignite

**Overview of IgG4-related aortitis and periaortitis. A decade since their first description.Autoimmunity Reviews. 2020*

Klinik- Abdomen ve Pelvis:

- **Aortit ve Periaortit:** IgG4 te %20-30

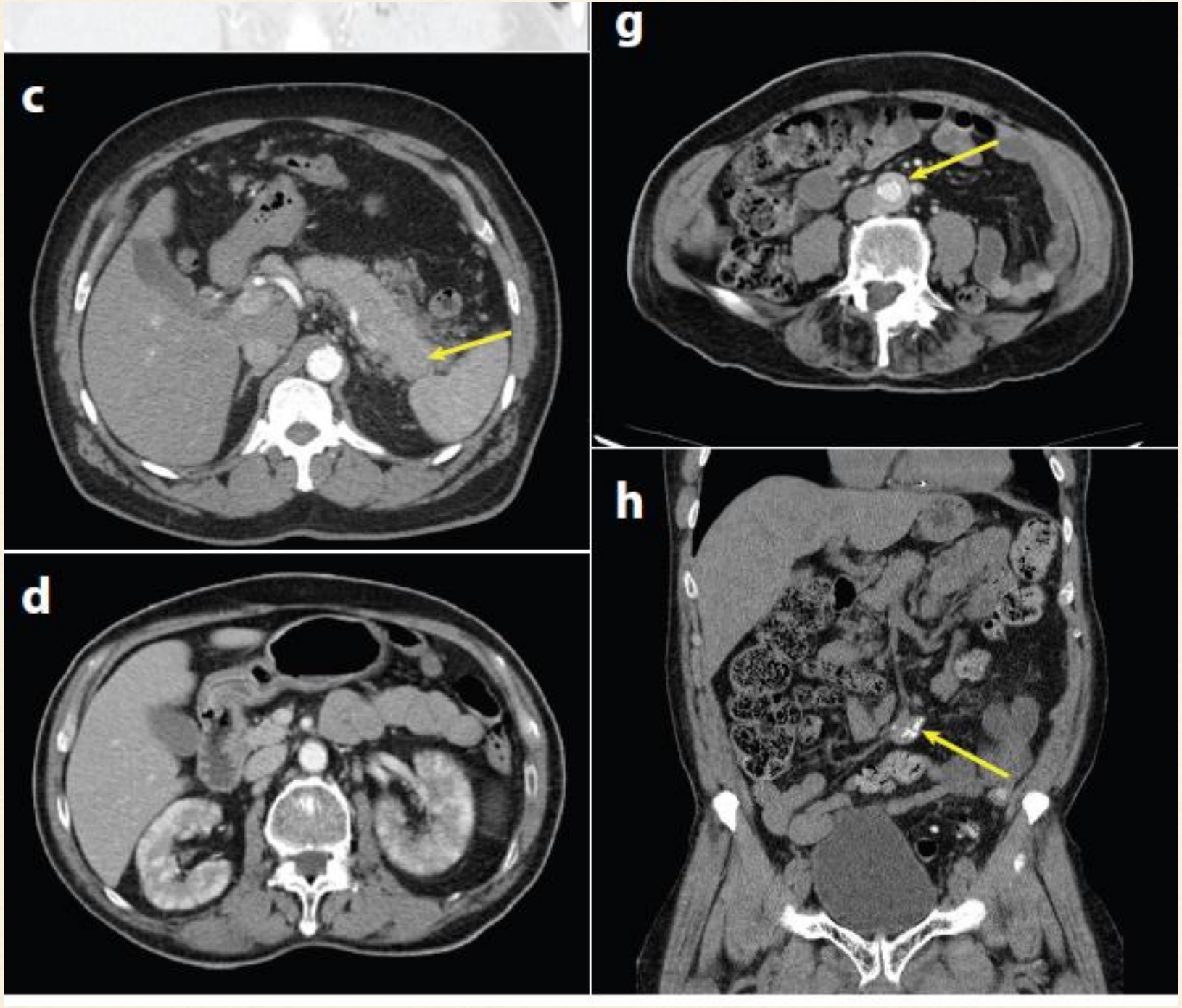
Ağrı, **!** Anevrizma

- **Böbrek :**

Tübülointerstsiyel nefrit (TIN)

membranöz glomerülonefrit

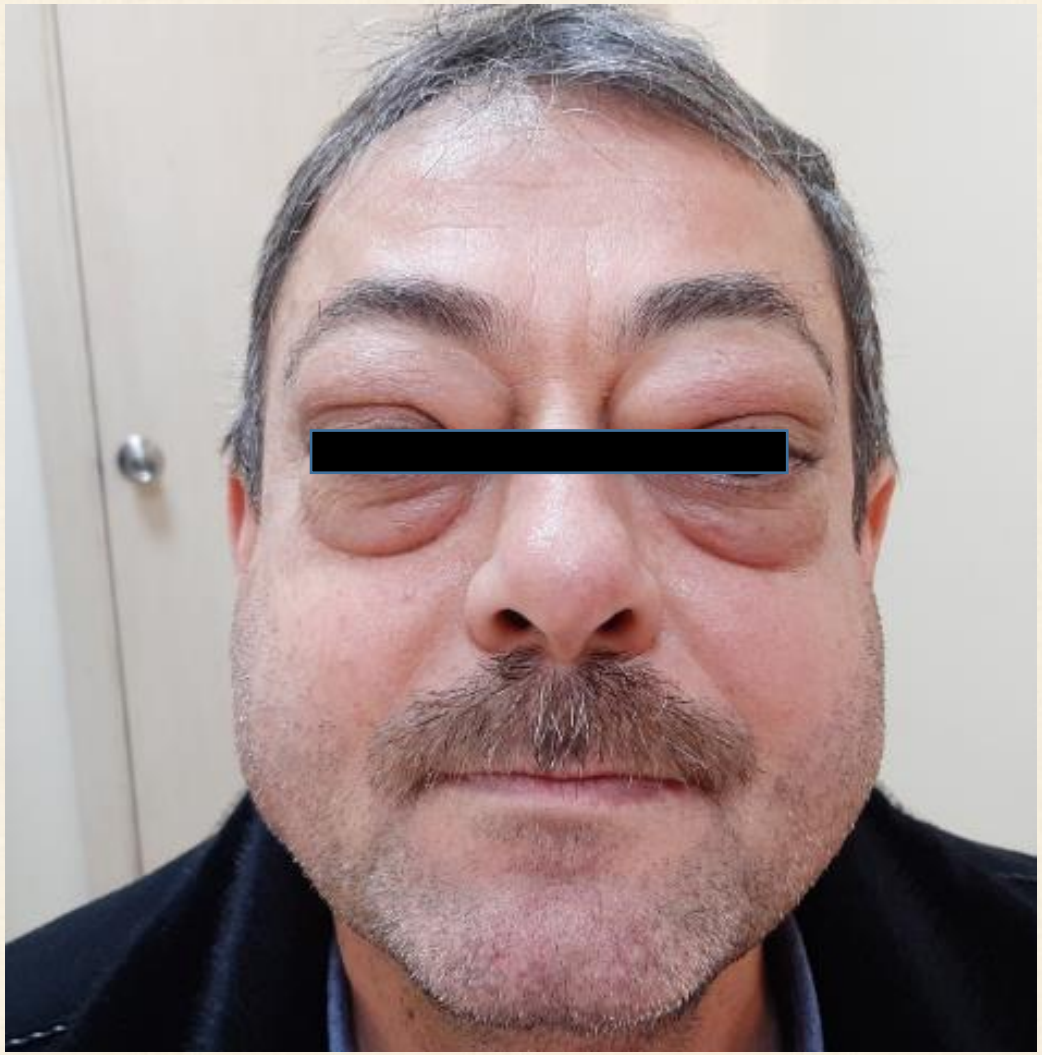
- Prostatit



Clinical Perspectives on IgG4-Related Disease and Its Classification.Annu. Rev.Med. 2022

Klinik- Baş boyun: %30

- Lakrimal ve tükürük bezlerinin simetrik ağrısız tutulumu **(Mikulicz)**
- Submandibular en sık
- Sikka
- Bazen ekstraoküler kaslar, orbital yağ dokuları, göz kapakları, trigeminal sinir dalları gibi diğer dokular ve nazolakrimal kanal da tutulur, **Orbital psödotümör**
- **Propitozis** (orbital miyozite bağlı)
- **Riedel tiroiditi :** «Fibrozan» sert tiroid



Klinik- Lenfadenopati: %30-55

- Ağrısız ama bası yapabilir
- En sık mediastinal, aksiller, abdominal, servikal
- En sık «sistemik tutulumlu Mikulicz»e eşlik ediyor
- PET CT’de görüntü reaktif LAP ye benzer
- Kötü progroz (yüksek relaps risk) ile ilişkili

Lymphadenopathy in the rheumatology practice: a pragmatic approach. Rheumatology (Oxford). 2024 May 3;63(6):1484-1493

Klinik- Akciğer, Plevral, Kalp:

- Tutulum çok çeşitli
- İnterstisyel akciğer hastalığı, nodül, kitle
- Plevral kalınlaşma, efüzyon
- Perikardial kalınlaşma, perikardit
- Koroner arterit, koroner stenoz ve anevrizma

Klinik- Diğer nadir tutulumlar:

- **SSS:**

Hipertrofik pakimenenjit

Hipofizit

- Hepatik pseudotümor, hepatopati

- Sklerozan mastit , memenin inflamatuvar psödotümörleri

TANI

ZOR

Tanı

«Karakteristik» histopatolojik

+

Klinik

+

Serolojik

+

Radyolojik bulgular

(Hiç birisi tek başına yeterli değil!)

2019 ACR EULAR sınıflandırma kriterleri*:

- Temel giriş kriteri =Bu sınıflandırma kriterlerini karşılamak için hastaların öncelikle IgG4-RD'den etkilenen **tipik bir organın (klinik, radyolojik veya histopatolojik) dahil olduğunu göstermesi gerekmektedir.**

- Tipik organ = gözyaşı bezleri, major tükürük bezleri, orbita, akciğer, paravertebral yumuşak doku, retroperitoneum, aort, pankreas, safra yolu, böbrekler, meninges ve tiroid bezi

*The 2019 American College of Rheumatology/European League Against Rheumatism Classification Criteria for IgG4-Related Disease. Arthritis Rheumatol. 2020 Jan;72(1):7-19

Table 4 The 2019 American College of Rheumatology/European League Against Rheumatism classification criteria for IgG_4-RD

Step	Categorical assessment or numerical weight
Step 1. Entry criteria	
Characteristic* clinical or radiological involvement of a typical organ (eg, pancreas, salivary glands, bile ducts, orbits, kidney, lung, aorta, retroperitoneum, pachymeninges or thyroid gland (Riedel's thyroiditis)) OR pathological evidence of an inflammatory process accompanied by a lymphoplasmacytic infiltrate of uncertain aetiology in one of these same organs	**Yes**† or No
Step 2. Exclusion criteria: domains and items‡	Yes or **No**§
Clinical	
Fever	
No objective response to glucocorticoids	
Serological	
Leucopenia and thrombocytopenia with no explanation	
Peripheral eosinophilia	
Positive antineutrophil cytoplasmic antibody (specifically against proteinase 3 or myeloperoxidase)	
Positive SSA/Ro or SSB/La antibody	
Positive double-stranded DNA, RNP or Sm antibody	
Other disease-specific autoantibody	
Cryoglobulinemia	
Radiological	
Known radiological findings suspicious for malignancy or infection that have not been sufficiently investigated	
Rapid radiological progression	
Long bone abnormalities consistent with Erdheim-Chester disease	
Splenomegaly	
Pathological	
Cellular infiltrates suggesting malignancy that have not been sufficiently evaluated	
Markers consistent with inflammatory myofibroblastic tumour	
Prominent neutrophilic inflammation	
Necrotizing vasculitis	
Prominent necrosis	
Primarily granulomatous inflammation	
Pathologic features of macrophage/histiocytic disorder	
Known diagnosis of the following:	
Multicentric Castleman's disease	
Crohn's disease or ulcerative colitis (if only pancreatobiliary disease is present)	
Hashimoto thyroiditis (if only the thyroid is affected)	

If case meets entry criteria and does not meet any exclusion criteria, proceed to step 3.

Step 3. Inclusion criteria: domains and items¶	
Histopathology	
Uninformative biopsy	0
Dense lymphocytic infiltrate	+4
Dense lymphocytic infiltrate and obliterative phlebitis	+6
Dense lymphocytic infiltrate and storiform fibrosis with or without obliterative phlebitis	+13
Immunostaining**	0–16, as follows:
	Assigned weight is 0 if the IgG_4+:IgG+ ratio is 0%–40% or indeterminate and the number of IgG_4+ cells/hpf is 0–9.‡‡ Assigned weight is 7 if: (1) the IgG_4+:IgG+ ratio is ≥41% and the number of IgG_4+cells/hpf is 0–9 or indeterminate or (2) the IgG_4+:IgG+ ratio is 0–40% or indeterminate and the number of IgG_4+ cells/hpf is ≥10 or indeterminate. Assigned weight is 14 if: (1) the IgG_4+:IgG+ ratio is 41%–70% and the number of IgG_4+ cells/hpf is ≥10 or (2) the IgG_4+:IgG+ ratio is ≥71% and the number of IgG_4+ cells/hpf is 10–50. Assigned weight is 16 if the IgG_4+:IgG+ ratio is ≥71% and the number of IgG_4+ cells/hpf is ≥51.
Serum IgG_4 concentration	
Normal or not checked	0
>Normal but <2× upper limit of normal	+4
2–5× upper limit of normal	+6
≥>5× upper limit of normal	+11
Bilateral lacrimal, parotid, sublingual and submandibular glands	
No set of glands involved	0
One set of glands involved	+6
Two or more sets of glands involved	+14
Chest	
Not checked or neither of the items listed is present	0
Peribronchovascular and septal thickening	+4
Paravertebral band-like soft tissue in the thorax	+10
Pancreas and biliary tree	
Not checked or none of the items listed is present	0
Diffuse pancreas enlargement (loss of lobulations)	+8
Diffuse pancreas enlargement and capsule-like rim with decreased enhancement	+11
Pancreas (either of above) and biliary tree involvement	+19
Kidney	
Not checked or none of the items listed is present	0
Hypocomplementemia	+6
Renal pelvis thickening/soft tissue	+8
Bilateral renal cortex low-density areas	+10
Retroperitoneum	
Not checked or neither of the items listed is present	0
Diffuse thickening of the abdominal aortic wall	+4
Circumferential or anterolateral soft tissue around the infrarenal aorta or iliac arteries	+8

Tanı:

- Kriterler klinik pratikte hastamıza tanı koymak için düzenlenmemiştir

- Toplam puanın ≥20 olması, sınıflandırma kriterlerini karşılar

Table 1 Key exclusion criteria from the ACR/EULAR classification criteria for IgG4-related disease (26)

Clinical findings	Comorbid conditions
Fever	Multicentric Castleman disease
No objective response to glucocorticoids	Crohn disease or ulcerative colitis[b]
Serological findings	Hashimoto thyroiditis (if only the thyroid is affected)
Leukopenia and thrombocytopenia	**Pathological findings**
Peripheral eosinophilia	Cellular infiltrates suspicious for malignancy
Autoantibodies with high specificity[a]	Markers of myofibroblastic tumor (e.g., ALK1, ROS1)
Cryoglobulinemia	Prominent neutrophilic inflammation
Radiological findings	Necrotizing vasculitis
Findings suspicious for malignancy	Prominent necrosis
Rapid radiological progression	Granulomatous inflammation
Long bone abnormalities of Erdheim–Chester disease	Markers of macrophage or histiocytic disorder[c]

*The 2019 American College of Rheumatology/European League Against Rheumatism classification criteria for IgG4-related disease

Histopatoloji:

- Tipik morfolojik özellikler:

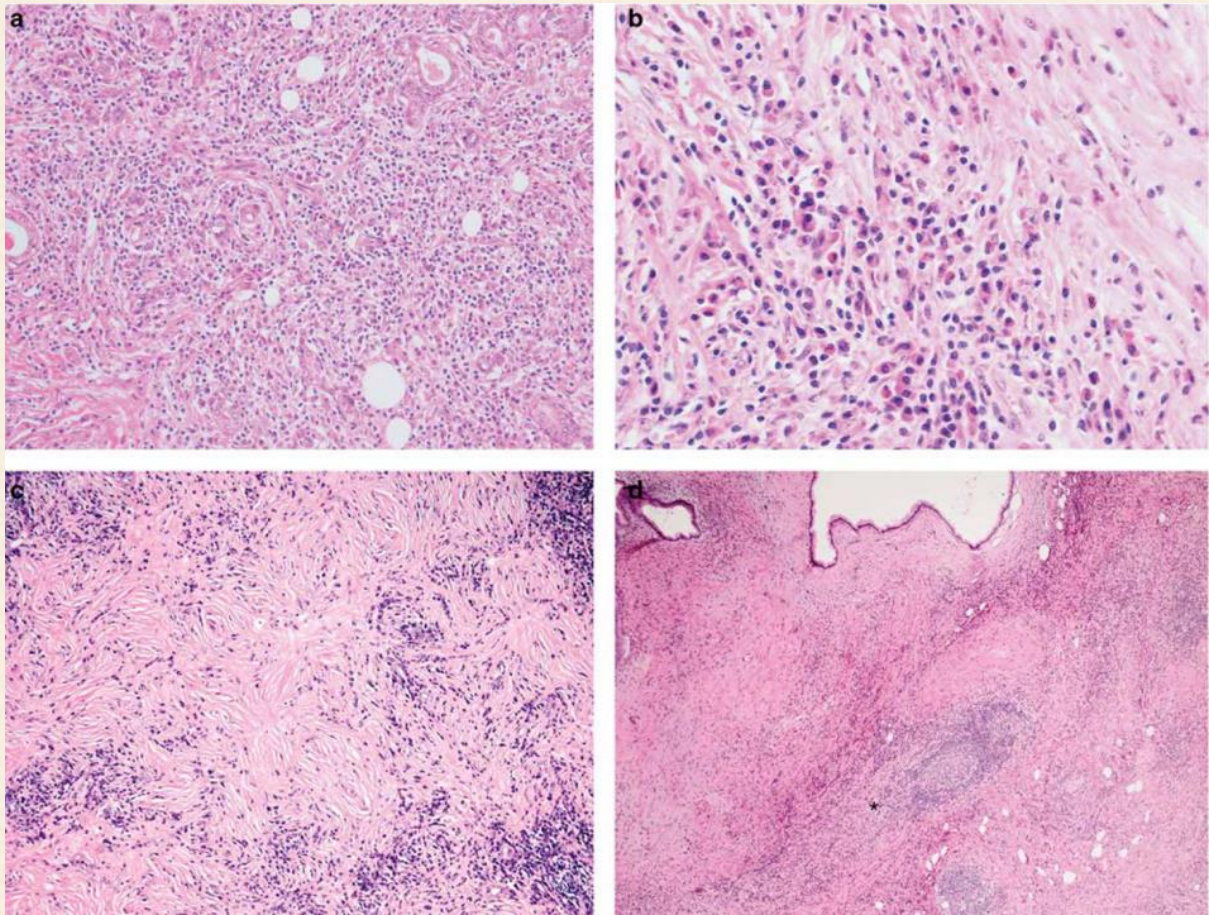
➢ yoğun lenfoplazmositik infiltrasyon

(tipik: IgG4+/IgG+ plazma hücreleri>40%)

➢ storiform fibroz

➢ obliteratif flebit

hafif-orta şiddette eozinofil inflitrasyonu sık



Seroloji:

- Serum IgG4 yüksekliği (>135mg/dL) tutulu fenotipine göre: %50-%90

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Seroloji:

- IgG4 yüksekliği spesifik değil;
  - Lenfoma, lösemi, MM
  - EGPA, SLE, sarkoidoz
  - Enfeksiyonlar: *Staphylococcus aureus, Mycobacterium*
- Serum IgG4 > x 5 kat = PPV %75*
- Hastalık aktivitesi ile ilişkili

- Ayrıca : yüksek IgG1 IgE, eozinofili; düşük C3, C4

**The Positive Predictive Value of a Very High Serum IgG4 Concentration for the Diagnosis of IgG4-Related Disease. J Rheumatol. 2023 Mar;50(3)*

Table 7 Differential diagnosis of IgG4-related disease, by body region or organ

Head and neck	Chest	Pancreatohepatobiliary system
ANCA-associated vasculitis	Lung malignancy	Pancreatic malignancy
EGPA	Mesothelioma	Cholangiocarcinoma
Sarcoidosis	Inflammatory myofibroblastic tumor	Hepatocellular carcinoma
Lymphoma	Lymphoma	Primary sclerosing cholangitis
Amyloidosis	ANCA-associated vasculitis	Lymphoma
Sjögren syndrome	EGPA	**Mesentery and retroperitoneum**
Graves disease	Sarcoidosis	Sarcoma
Idiopathic orbital inflammation	Mycobacterial infection	Lymphoma
Erdheim–Chester disease	Endemic fungal infection	Erdheim–Chester disease
Rosai–Dorfman disease	Interstitial lung disease	Amyloidosis
Other histiocytosis (e.g., AAPOX)	Erdheim–Chester disease	Idiopathic retroperitoneal fibrosis
Allergic disease (e.g., allergic rhinitis)	Multicentric Castleman disease	**Meninges and pituitary**
Inflammatory myofibroblastic tumor	Lymphomatoid granulomatosis	ANCA-associated vasculitis
Kimura disease	**Great vessels**	Sarcoidosis
Infectious sinusitis	Giant cell arteritis	Behçet disease
Kidneys	Takayasu arteritis	Erdheim–Chester disease
Drug-induced TIN	Behçet disease	Langerhans cell histiocytosis
Membranous nephropathies	Cogan syndrome	Rosai–Dorfman disease
ANCA-associated vasculitis	Infectious aortitis	Lymphoma
Sjögren syndrome	Atherosclerosis	Dural carcinomatosis
Sarcoidosis	**Prostate**	Infectious pachymeningitis
Renal cell carcinoma	Benign prostatic hyperplasia	Intracranial hypotension
	Prostate cancer	Lymphocytic hypophysitis

* *Clinical Perspectives on IgG4-Related Disease and Its ClassificationAnnu. Rev.Med. 2022*

Tedavi:

- **Glukokortikoidler** ilk ve en etkin seçenek: en az 40mg (~0.6-1mg/kg/gün)

  (yanıtsız ise tanı sorgulanmalı!)
- Yaygın ve relaps riski yüksek hastalıkta veya glukokortikoid yan etki riski yüksek hastada: **Rituksimab**
- Azatiyoprin, mikofenolat mofetil

- **Takipte:** klinik bulgu, radyoloji, IgG4, Ig E, eozinofili
- Prognozu: ilaçsız remisyon nadir

Teşekkürler