

CLINICAL MANIFESTATIONS OF IMMUNOGLOBULIN G4-RELATED DISEASE (MULTIFOCAL IDIOPATHIC FIBROSCLEROSIS)



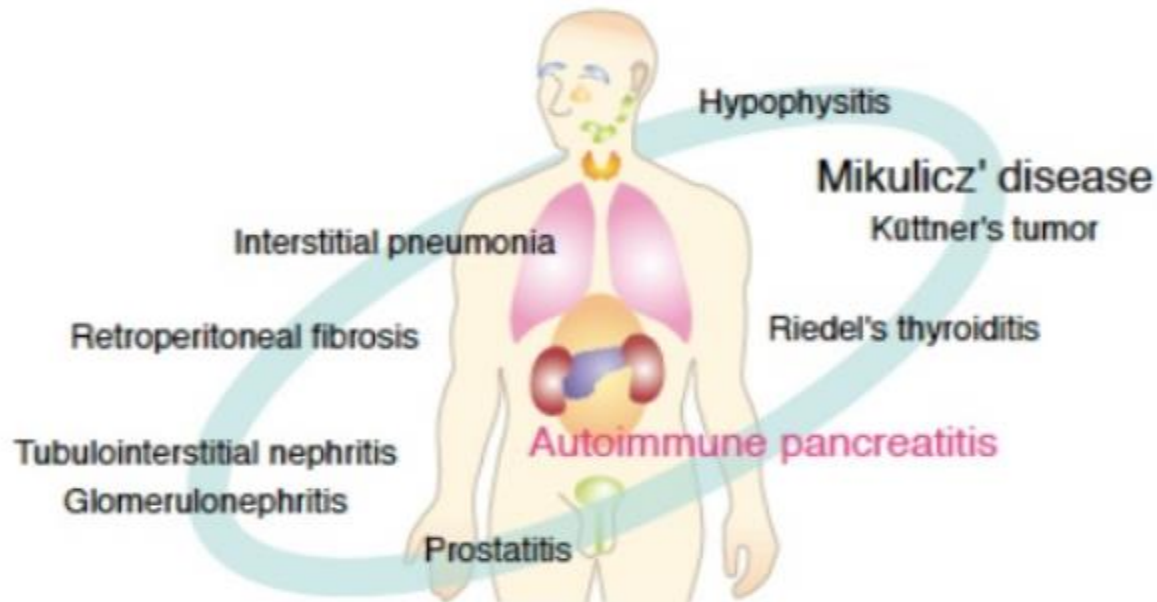
INTRODUCTION

What Is IgG4-RD?

- ▶ IgG4-related disease (IgG4-RD) is an under recognized, multiorgan fibro-inflammatory condition of unknown aetiology that is defined by its unique histopathological features, that are fairly similar regardless of the affected organ.
- ▶ Patients with IgG4-RD also share certain clinical features: a tendency for formation of mass lesion(s), frequent elevations in their serum IgG4 concentration, as well as an excellent response to glucocorticoid treatment.

<http://dx.doi.org/10.1016/j.mpdhp.2013.01.004>

INTRODUCTION



Unifies many diverse conditions, previously thought to be unrelated to each other, as a part of IgG4- RD spectrum

EPIDEMIOLOGY

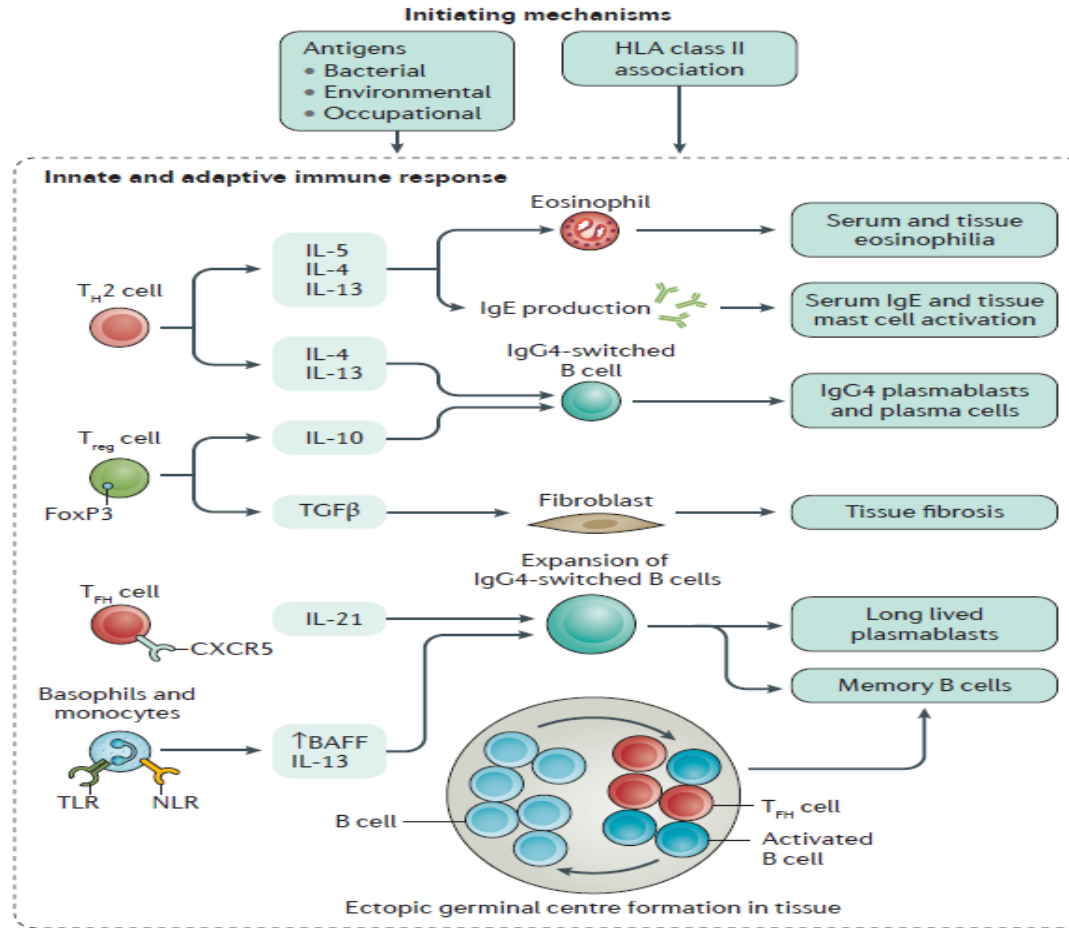
IgG4-related disease (IgG4-RD) generally has a slight predominance for middle-aged and older males.(especially in type 1 (IgG4-related) autoimmune pancreatitis (AIP), retroperitoneal fibrosis, tubulointerstitial nephritis.

in IgG4-related sialadenitis and IgG4-related ophthalmic disease, males and females appear to be affected more equally.

The disease is also increasingly recognized to occur in children.

A clinical overview of IgG4-related systemic disease. Curr Opin Rheumatol 2011; 23:57.

PATHOGENESIS



PATHOGENESIS

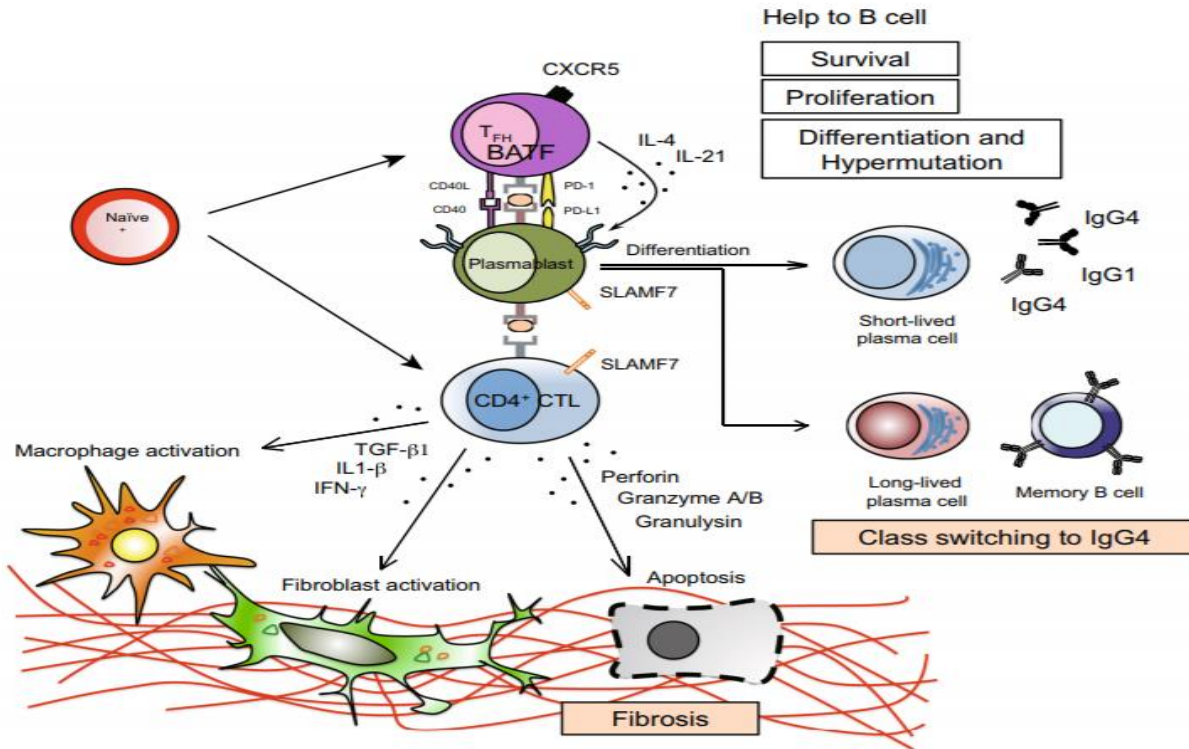
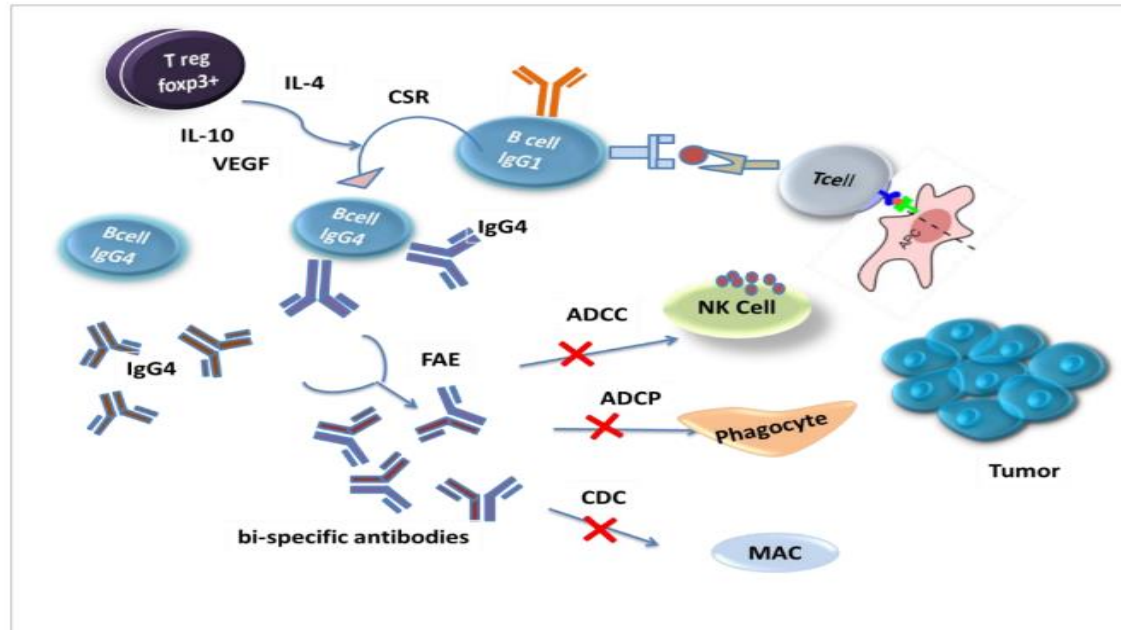


Fig. 2 Schematic model of Th subsets in IgG4-RD. CD4⁺ CTLs and Tfh cells play key roles in IgG4 production by plasmablasts and plasma cells. Moreover, activated CD4⁺ CTLs presumably mediate

fibrosis and inflammation as a result of cytokine secretion or possibly the induction of apoptosis

PATHOGENESIS



شکل ۸. در نمایی کلی از عملکرد آنتی بادی IgG4 در ریز محیط تومور. آنتی ژن های توموری توسط APC ها (سلول های تخصصی ایمنی برای عرضه آنتی ژن) برداشت شده و به سلول های کمکی Th ارائه می شوند و در نهایت B cell محیط با توجه به ساینوکاین ها مترشحه از خود تومور و پیام های سلول T و همچنین ساینوکاین های مترشحه از سلول T(FOXP3⁺) تنظیم کننده، ایزوتایپ آنتی بادی خود را به سمت IgG4 بازآرایی می کند، IgG4 های مترشحه فرایند FAE را انجام داده و دو ظرفیتی می شوند، این آنتی بادی های دو ظرفیتی فاقد عملکرد موثر در ایجاد کشندگی به واسطه ی NK cell (سلول کشنده ی طبیعی) و فاگوسیت ها و MAC (کمپلکس تهاجم غشایی کمپلمان هستند. در واقع به نفع بقای تومور عمل کرده و باعث پیشرفت آن می شود.

CLINICAL MANIFESTATION

The presentation of IgG4-RD is typically **subacute**. Many patients have symptoms and signs for months or even years before the diagnosis is established.

Adv Anat Pathol 2010; 17:303.

IgG4-RD is also often recognized incidentally based upon a radiologic finding or histopathologic examination of a tissue specimen.

True fevers are unusual(exclusion criteria)

CLINICAL MANIFESTATION

constitutional symptoms such as fatigue and weight loss are common.

Many patients have arthralgia and other musculoskeletal symptoms, particularly enthesopathy

but **frank arthritis is atypical and suggests other diseases.**

Rheum Dis Clin N Am 43 (2017)

It can mimic autoimmune rheumatic diseases such as **SLE / SS/ GPA**



CLINICAL MANIFESTATION

Many patients have symptoms of allergy or atopy, for example, allergic rhinitis, nasal polyps, chronic sinusitis, nasal obstruction, and rhinorrhea.

Mild to moderate peripheral eosinophilia and serum IgE concentration elevations that sometimes exceed 10 times the upper limit of normal are common.(eos >3000 exclusion criteria)

Organ involvement



LYMPHADENOPATHY

Asymptomatic (common) /non-tender/rubbery rather than hard
typically no more than 2 centimeters in diameter but may range
up to 5 centimeters

Am J Surg Pathol 2008; 32:671.

Patients with lymphadenopathy may exhibit elevated serum IgG4,
serum IgG and IgE, polyclonal hypergamaglobulinemia, and
ESR.

Lymph nodes are unlikely to show the degree of fibrosis seen in
other organ.

LYMPHADENOPATHY_(CON)

distinguishing from other conditions(lymphoma, multicentric Castleman disease,infection such as TB ,sarcoidosis , or malignancy):

- 1) the modest lymph node enlargement
- 2) histologic distinctions on biopsy
- 3) lack of constitutional features
- 4) the usually striking clinical response to glucocorticoids

SALIVARY AND LACRIMAL GLAND INVOLVEMENT

is a common feature of IgG4-RD

Patients may present with enlargement of lacrimal and salivary glands (parotid and/or submandibular) (**Mikulicz disease**) or with chronic sclerosing sialadenitis and unilateral or bilateral submandibular gland enlargement (**Küttner tumor**).

SALIVARY AND LACRIMAL GLAND INVOLVEMENT_(CON)

Distinguishing from SS ?

- 1) Age distribution and sex (older male)
 - 2) Fewer patients with dry mouth, dry eyes(38, 33 percent versus 87, 94), or arthralgias (16 percent versus 48 percent)
 - 3) Persistent gland swelling (versus recurrent in ss)
 - 4) A higher frequency of allergic rhinitis and bronchial asthma
 - 5) A higher frequency of AIP and interstitial nephritis (17 and 17 percent versus 0 and 7 percent)
- 

SALIVARY AND LACRIMAL GLAND INVOLVEMENT_(CON)

- 6) Low frequencies of autoantibodies, including rheumatoid factor, antinuclear antibodies, anti-SSA, and anti-SSB (27, 23, 2, and 0 percent versus 87, 90, 100, and 100 percent, respectively)
- 7) The pathologic findings are typical of those in other patients with IgG4-RD, including the lymphoplasmacytic infiltrate with IgG4-positive cells, sometimes with obliterative phlebitis and fibrosis .
- 8) Increased IgG4 and IgE serum levels are also present.

Low complement levels may be seen in either condition.

igG4 serum levels morethan 135 mg/dl in 7.5 % of primary ss

SALIVARY AND LACRIMAL GLAND INVOLVEMENT_(CON)

IgG4-related dacryoadenitis

Many exhibited bilateral involvement

Histologic and serologic findings are similar to sialadenitis , although obliterative phlebitis is usually absent.

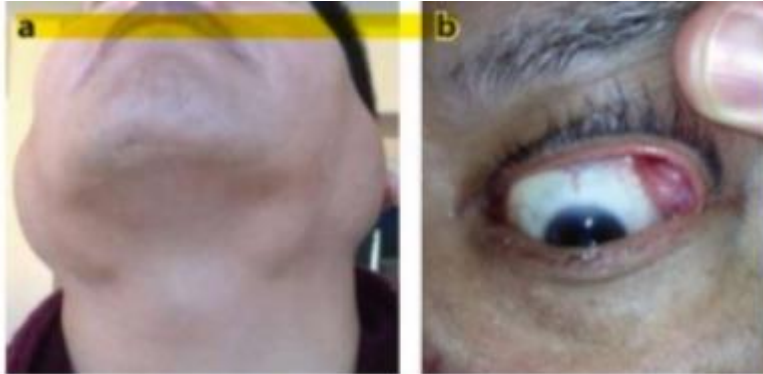
orbital pseudotumors (25 to 50 percent)

IgG4-related orbital myositis that leads most often to proptosis .

Surv .Ophthalmol 2012; 57:26

It is not certain whether IgG4-RD predisposes to the development (MALT) lymphomas or other lymphomas, but several cases have been reported that have raised this concern.

SALIVARY AND LACRIMAL GLAND INVOLVEMENT_(CON)



A – Bilateral enlargement of the parotid and submandibular glands Mikulicz's disease.

B- lacrimal gland disease



C- Proptosis and exotropia orbital pseudotumor associated with IgG4-RD

AUTOIMMUNE PANCREATITIS

AIP has been estimated to account for 2 percent of patients with chronic pancreatitis.

It often presents as a pancreatic mass or as painless obstructive jaundice and can be mistaken for pancreatic cancer.

Most patients have another IgG4-related condition, such as IgG4-related sclerosing cholangitis, lymphadenopathy, or salivary or lacrimal gland involvement.



AUTOIMMUNE PANCREATITIS (CON)

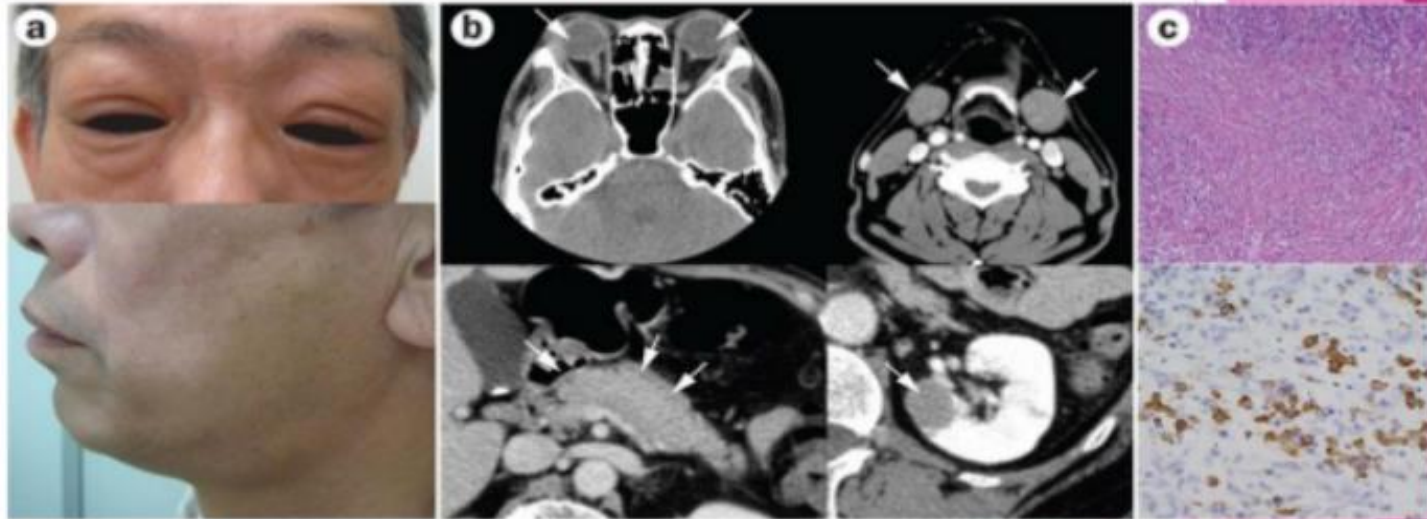
The differentiation of AIP from adenocarcinoma?

Painless jaundice, is common to both

- 1) IgG4-positive plasma cells can also be found in the diseased pancreatic tissue in these conditions, although to a lesser degree than in AIP
- 2) Elevated serum IgG4 levels ($>135\text{mg/dL}$) can also be seen in some patients with pancreatic cancer, although they are usually less than twice the upper limit of normal; thus, increased IgG4 serum levels alone cannot be used to exclude a diagnosis of pancreatic malignancy
- 3) Radiologic features of type I AIP include diffuse enlargement of the pancreas, leading to the descriptor “sausage-shaped” pancreas (diffuse enlargement), delayed enhancement and a halo of edema surrounding the organ.

SALIVARY AND LACRIMAL GLAND INVOLVEMENT_(CON)

A typical case with IgG4-related disease exemplifying key diagnostic features



nature
REVIEWS

RHEUMATOLOGY

Yamamoto, M. et al. (2013) Mechanisms and assessment of IgG4-related disease: lessons for the rheumatologist
Nat. Rev. Rheumatol. doi:10.1038/nrrheum.2013.183

IGG4-RELATED SCLEROSING CHOLANGITIS

IgG4-related cholangitis is the most frequent extrapancreatic manifestation of type 1 AIP (IgG4-related), present in over 70 percent of such patients.

Biopsies performed via ERCP are seldom deep enough to define the histopathologic features of igG4-RD .



IGG4-RELATED SCLEROSING CHOLANGITIS(CON)

Differentiation from PSC :

- 1) Age of onset <40 years in PSC and >50years in IgG4-SC, but not absolute
- 2) presence of other organ manifestations
- 3) increased igG4 serum levels
- 4) IBD (In 75% of PSC and 5% of IgG4-SC or AIP)
- 5) Beaded or pruned-tree appearance and short band-like strictures in PSC
Long continuous strictures with **prestenotic dilatation, involvement of the distal common bile duct** and hilar or intrahepatic cholangiopathy in IgG4-SC
- 6) biopsy (infiltrates of igG4+ plasma cells and severe interstitial fibrosis)
- 7) characteristic response to GC

IGG4-RELATED SCLEROSING CHOLANGITIS(CON)

Differentiation from cholangiocarcinoma:

obstructive jaundice , enlarged pancreas in both of them

1) higher serum bilirubin

2) CA19-9

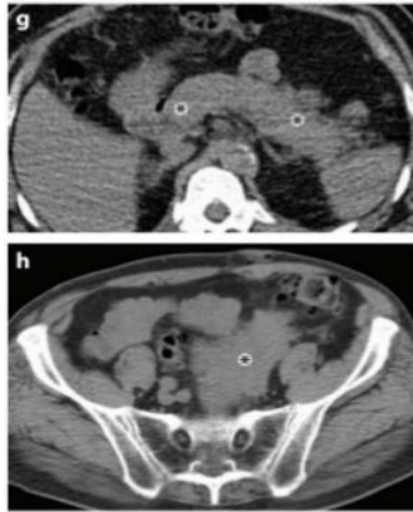
3) lower igG4 concentrations (sIgG4 >5.6 g/l 100% specificity for IgG4-SC versus cholangiocarcinoma)

4) lymphadenopathy

RETROPERITONEAL FIBROSIS

(ORMONDS DIS)

Chronic inflammatory and fibrotic change may be present and can involve regional tissues; it may cause an obstructive uropathy.



(g) Type 1 (IgG4-related) autoimmune pancreatitis. Computed tomography scan of the abdomen revealing diffuse pancreatic enlargement, with loss of normal lobularity.
(h) Retroperitoneal fibrosis

AORTITIS AND PERIAORTITIS

vascular lesions frequently occur in the aorta (abdominal, particularly infrarenal aorta) with or without aneurysmal change.

1%–5% of AAA cases are estimated to be IgG4-RD.

Clinical symptoms might be fever, intestinal obstruction, abdominal pain, hydronephrosis, or few subjective symptoms.

Annals of Vascular Diseases Advance Published Date: March 19, 2018



AORTITIS AND PERIAORTITIS (CON)

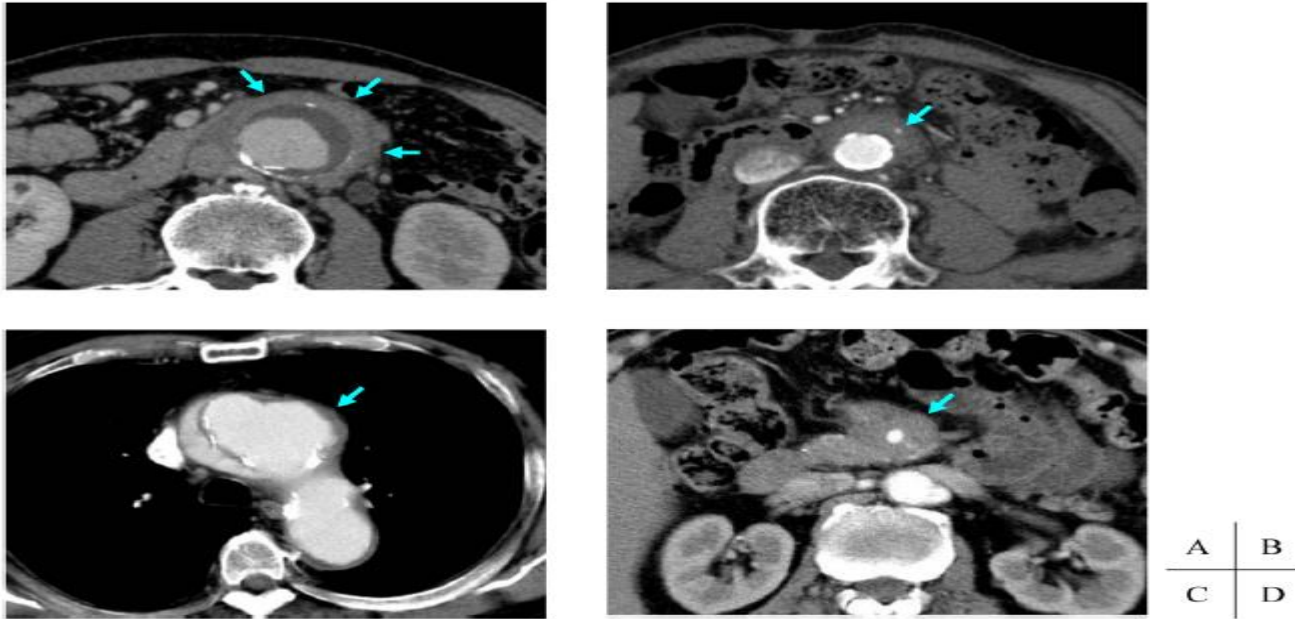


Fig. 1 Contrast-enhanced computed tomography (CT). (A) IgG4-related inflammatory abdominal aortic aneurysm. The aneurysmal wall shows severe thickening, and it looks like a soft tissue mass surrounding the aorta. An enhanced thickening of the adventitia forms 'mantle sign' (arrows). (B) IgG4-related periaortitis. Marked thickening of the aortic wall without aneurysmal change is shown. The inferior mesenteric artery penetrates the lesion without stenosis (arrow). (C) IgG4-related disease of the thoracic aorta. CT shows a saccular aneurysm with a mild wall thickening (arrow). (D) IgG4-related disease of the superior mesenteric artery. CT shows a soft tissue mass surrounding the artery (arrow).

AORTITIS AND PERIAORTITIS (CON)

differentiation from infectious aortic aneurysm :

- 1) image findings such as irregular saccular aneurysms
- 2) rapid enlargement
- 3) blood culturing
- 4) infectious disease markers.

NEUROLOGIC INVOLVEMENT

MENINGEAL DISEASE

IgG4-RD is among the most common causes of nonmalignant meningeal inflammation.

IgG4-RD should be considered in cases with unexplained radiographic evidence of pachymeningeal disease, particularly if hypertrophic or nodular.

A sudden escalation in **headache** severity should raise a suspicion for the occurrence of hydrocephalus.

proptosis, **diplopia**, and **retrobulbar pain** due to IgG4-related pachymeningitis involving the dura around the cavernous sinus

visual acuity problems or visual field loss due to optic nerve and chiasmal compression.

*NEUROLOGIC INVOLVEMENT*_(CON)



Fig. 3. A 60-year-old white woman with a history of SLE and IgG4-related pachymeningitis diagnosed with meningeal biopsy. This T1-postcontrast MRI shows symmetric pachymeningeal thickening and enhancement (*arrows*) intracranially at the orbital apices, left greater than right. There was slight abduction deficit in the left eye without diplopia but no reduction of visual acuity.

NEUROLOGIC INVOLVEMENT (CON)

PITUITARY GLAND AND STALK DISEASE

Panhypophysitis is the most common presentation of IgG4-RD in this area

Hormonal disturbances secondary to hypopituitarism are common in IgG4-related hypophysitis, perhaps more common than in lymphocytic hypophysitis.

Pituitary 2014;17(3):251–6

Hypopituitarism(up to 83%)

diabetes insipidus in up to 72%

NEUROLOGIC INVOLVEMENT (CON)

Spinal involvement

Spinal IgG4-related pachymeningitis can manifest with a syndrome of myelopathy, radiculopathy, or myeloradiculopathy.

ORBITAL DISEASE

the optic nerve (cranial nerve II) and ophthalmic artery

Inflammatory lesions of IgG4-related orbital disease are more frequently isointense or hypointense on T2 MRI sequencing compared with non-IgG4-RD causes of orbital infiltrative disorders.

Eur Radiol 2016;27(4):1335–43



*NEUROLOGIC INVOLVEMENT*_(CON)

PERIPHERAL NERVE DISEASE

Branches of the trigeminal nerve, most characteristically the infraorbital nerve, are perhaps the most frequently involved peripheral or cranial nerves.



Fig. 6. IgG4-RD involving the right eye orbital soft tissue (*white arrows*) and the right infraorbital nerve (*black arrows*) that is thickened and expands the infraorbital canal, seen here on coronal (*right*) and sagittal (*left*) cuts.

NEUROLOGIC INVOLVEMENT (CON)

CENTRAL NERVOUS SYSTEM PARENCHYMAL DISEASE

The substance of the brain and the spinal cord are rarely involved by IgG4-RD.

JAMA Neurol 2014;71(6):767–70.



REIDEL'S THYROIDITIS

This disorder is a fibrotic process associated with a mononuclear cell inflammation that extends beyond the thyroid into the perithyroidal soft tissue.

The perithyroidal fibrosis can involve the parathyroid glands causing hypoparathyroidism, the recurrent laryngeal nerves causing hoarseness, the trachea causing compression, the mediastinum, and the anterior chest wall .

In contrast, other infiltrative and inflammatory conditions of the thyroid do not extend beyond the thyroid capsule.



REIDEL'S THYROIDITIS

Common clinical features are those similar to the presentation of thyroid malignancy.

Patients present with a slowly growing, painless hard goiter; they may have anterior neck pressure, dysphagia, hoarseness, dyspnea, or hypoparathyroidism .

hypothyroidism rates seen between 25 to 32 percent.



LUNG AND PLEURAL DISEASE

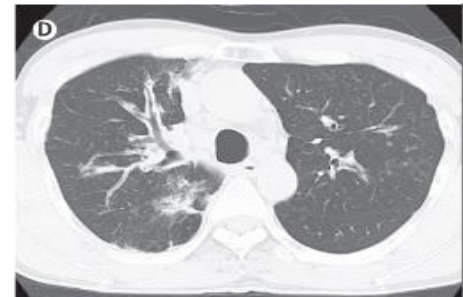
Four patterns of lung involvement have been described:

- 1) Solid nodular
- 2) Bronchovascular(with thickening of Bronchovascular bundles and interlobular septa) characteristic lesion

www.thelancet.com.vol385 april 11,2015

- 3) Alveolar interstitial (with honeycombing, bronchiectasis, and diffuse ground-glass opacities)
- 4) Round-shaped ground-glass opacities

IgG4-RD may mimic sarcoidosis



SKIN LESION

the skin lesions categorized into seven subtypes:

- (1)cutaneous plasmacytosis (multiple papulonodules or indurations on the trunk and proximal part of the limbs)
- (2)pseudolymphoma and angiolymphoid hyperplasia with eosinophilia (plaques and papulonodules mainly on the periauricular, cheek and mandible regions)
- (3)Mikulicz disease (palpebral swelling, sicca syndrome and exophthalmos)
- (4)psoriasis-like eruption (strikingly mimicking psoriasis vulgaris)

SKIN LESION (CON)

- (5) unspecified maculopapular or erythematous eruptions
- (6) Hypergammaglobulinemic purpura (bilateral asymmetrical palpable purpuric lesions on the lower extremities) and urticarial vasculitis (prolonged urticarial lesions occasionally with purpura)
- (7) ischemic digit (Raynaud phenomenon and digital gangrene).

RENAL DISEASE

the most common finding is tubulointerstitial nephritis.

Nodular lesions mimicking renal carcinoma may be seen.

Mild mesangioproliferative glomerulonephritis, and membranous nephropathy .

Patients with igG4-related TIN are likely to be profoundly hypocomplementemic (resemble those seen in SLE and mixed cryoglobulinemia) .

Arthritis Rheumatol 2015,67:246



OTHER MANIFESTATIONS

- Hepatopathy (autoimmune hepatitis ,hepatic pseudotumor)
 - Lymphoplasmacytic gastritis
 - Sclerosing mastitis and pseudotumors of the breast
 - Prostatitis
 - Constrictive pericarditis
 - Nasopharyngeal disease
 - Midline- destructive lesion
 - Amyloidosis
 - Ovary involvement
- 

THANK YOU FOR YOUR ATTENTION



LUNG AND PLEURAL DISEASE

Lung involvement in IgG4-related systemic disease is estimated to occur in 10 percent and pleural involvement in 5 percent .

Am J Surg Pathol 2010; 34:1812.

It may be asymptomatic or present with cough, hemoptysis, dyspnea, pleurisy, or chest pain.

Visceral or parietal pleural thickening may occur.

Obliterative arteritis is more common in the lung than in other organs affected by IgG4-RD.

Sclerotic lesion of mediastinum have been described.

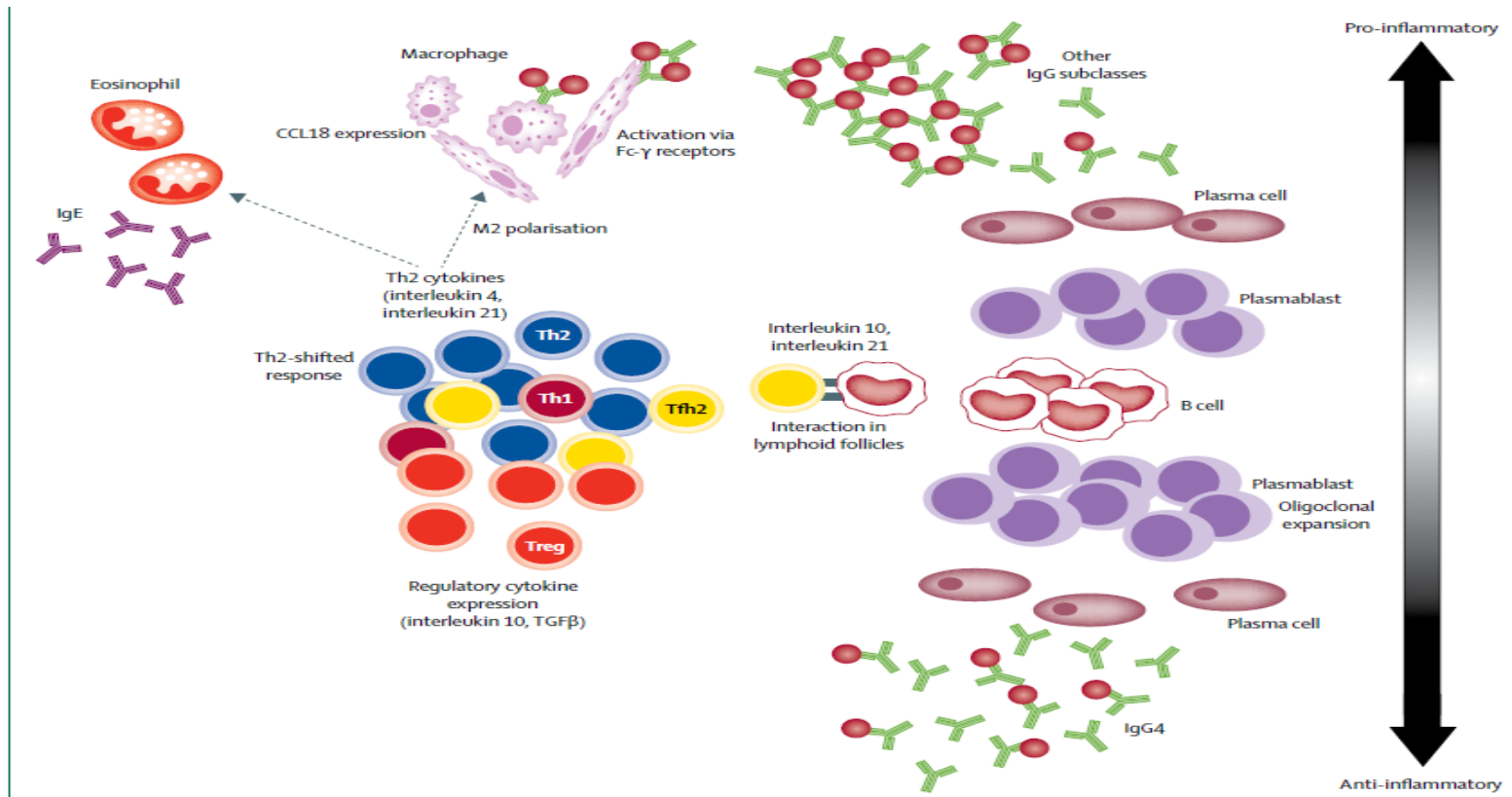


CLINICAL MANIFESTATION

Two major presentations of this condition:

- 1) type 1 autoimmune pancreatitis (IgG4-related pancreatitis)
- 2) salivary gland enlargement (Mikulicz disease) or as sclerosizing sialadenitis (Küttner's tumor)

PATHOGENESIS



PATHOGENESIS

