



IgG4 and Sjogren's: new concepts for Sjogren's

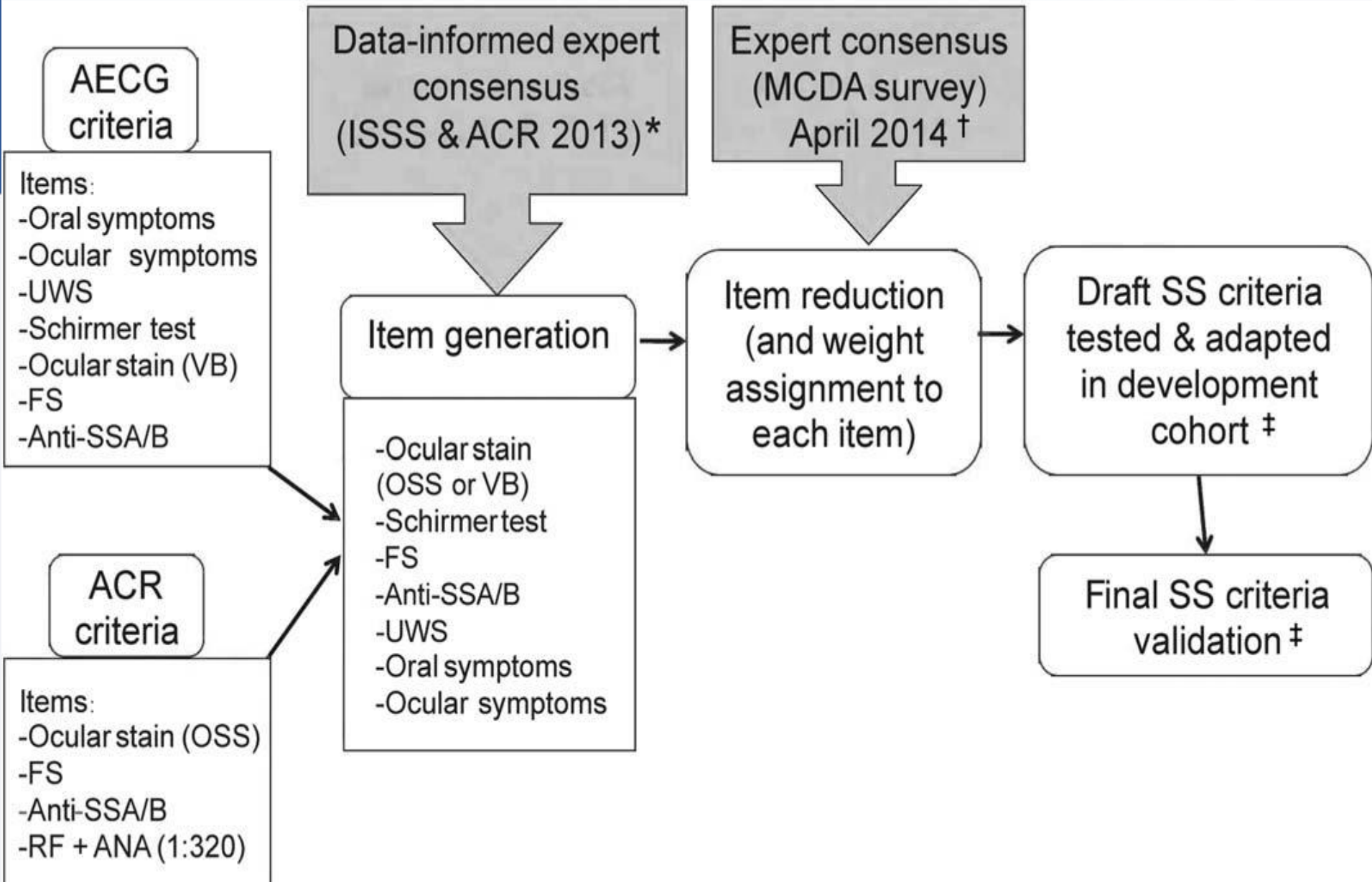
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In memorial of



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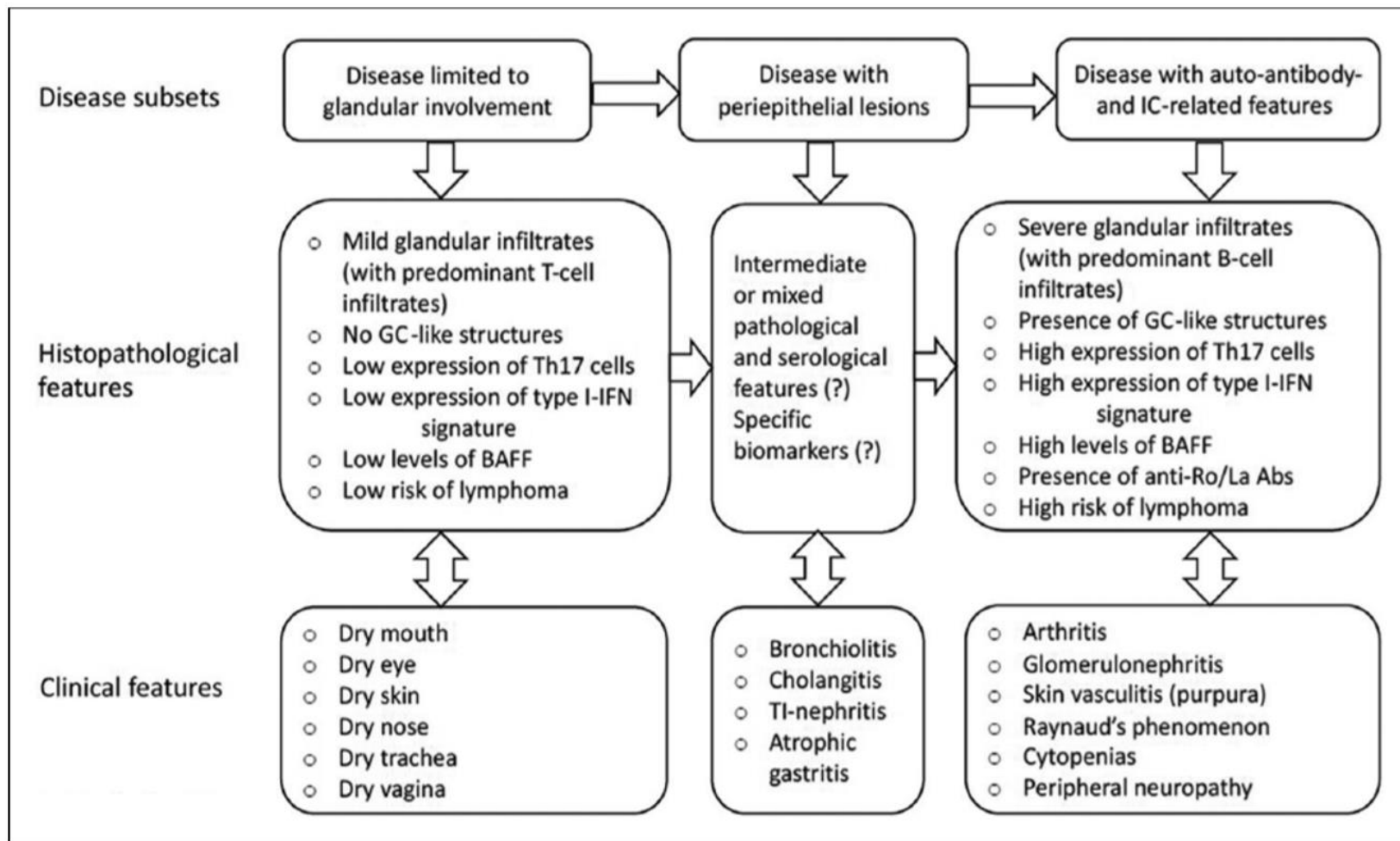


The 2016 ACR/EULAR classification criteria for pSS.

Consensus criteria items for the classification of pSS



- Abnormal unstimulated salivary flow rate* (≤ 0.1 ml/min) (1 point)
- Abnormal Schirmer's test (< 5 mm in 5 min) (1 point)
- Abnormal findings with lissamine green or fluorescein staining ≥ 5 in Ocular Staining Score or ≥ 4 in Van Bijsterveld Score (1 point)
- Presence of anti-Ro/SSA antibodies (3 points)
- Histological evidence of focal lymphocytic sialadenitis, with a focus score ≥ 1 focus/4 mm² (1 focus = 50 lymphocytes/4 mm²) (3 points)
- Diagnosis is considered established if score ≥ 4 points, after application of inclusion and exclusion criteria
Inclusion criteria: Dryness of eyes or mouth for at least 3 months, not explained otherwise (e.g. medications, infection)
- Exclusion criteria: Status post head/neck radiation HIV/AIDS Sarcoidosis Active infection with hepatitis C virus (PCR replication rate) Amyloidosis, graft versus host disease, IgG4-related disease The lack of any other potentially associated disease is the key requirement for classification as pSS





Item	Weight/score
Labial salivary gland with focal lymphocytic sialadenitis and focus score of ≥ 1 foci/4 mm ² ‡	3
Anti-SSA/Ro positive	3
Ocular Staining Score ≥ 5 (or van Bijsterveld score ≥ 4) in at least 1 eye§¶	1
Schirmer's test ≤ 5 mm/5 minutes in at least 1 eye§	1
Unstimulated whole saliva flow rate ≤ 0.1 ml/minute§#	1

American College of Rheumatology/European League Against Rheumatism classification criteria for primary Sjogren's syndrome:

The classification of primary Sjogren's syndrome applies to any individual who meets the inclusion criteria,* does not have any of the conditions listed as exclusion criteria,† and has a score of ≥ 4 when the weights from the 5 criteria items below are summed.

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IgG4 subtype



IgG4, the rarest of IgG subtypes, represents 3% to 6% of total IgG in the serum of normal subjects. IgG4 differs from other IgG isoforms in the composition of the hinge region because of a 25% to 75% loss of covalent interaction between the heavy chains. This intrinsic weakness leads to a dynamic exchange between Fab arms and the formation of bispecific, functionally monovalent antibodies.^{1,28} The exchange of half-molecules decreases the effectiveness of the antibodies that activate complement, and cross-link identical antigens poorly

IgG4-RD definition

- Immunoglobulin (Ig) G4-related disease (IgG4-RD) is a chronic inflammatory disorder characterized by elevated serum levels of IgG4 and histopathological findings of abundant infiltration of IgG4-positive plasma cells, storiform fibrosis, and obliterative phlebitis in the enlarged organs.



IgG4-Dacryocystitis and sialadenitis



IgG4-DS was serologically and histopathologically confirmed using the following diagnostic criteria:

- ❖ **persistent symmetrical swelling involving >2 lacrimal and major salivary glands;**
- ❖ **an elevated serum level of IgG4 (>135 mg/dl);**
- ❖ **and infiltration of IgG4-positive plasma cells (percentage of IgG4-positive cells to IgG-positive cells >40%) on immunostaining.**

IgG4 DS or Mikulicz's disease

- Mikulicz ' s disease (MD) is currently considered to represent lacrimal and salivary lesions of IgG4-RD and is recognized as a quite different disease to Sjögren ' s syndrome (SS). These disorders should be differentiated from each other, but an interesting question is whether SS and MD are able to coexist in the same individual.



Diagnostic criteria for IgG4-RD (modified after Umehara et al. (18))

1	2	3	= Diagnosis of IgG4-RD
Organ involvement: dysfunction, localized or diffuse swelling	Serum IgG4 >135mg/dl	Histopathology: IgG4/IgG Ratio >0.4 and >10 IgG4+ cells per HPF	Definite
Organ specific criteria for IgG4-RD (e.g. AIP, Mikulicz' disease)			Definite
Organ involvement: dysfunction, localized or diffuse swelling	Serum IgG4 <135mg/dl	Histopathology: IgG4/IgG Ratio >0.4 and >10 IgG4+ cells per HPF	Probable
Organ involvement: dysfunction, localized or diffuse swelling	Serum IgG4 >135mg/dl	Histopathology: Not available or not diagnostic	Possible
Organ involvement: dysfunction, localized or diffuse swelling	Serum IgG4 <135mg/dl	Histopathology: Not available or not diagnostic	No

AIP: autoimmune pancreatitis

Mikulicz' disease: IgG4-related dacryoadenitis and sialoadenitis

HPF: high power field

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Criteria for IgG4-RD



- 1) A serum IgG4 concentration ≥ 135 mg/dL
- 2) 40% of IgG-positive plasma cells being IgG4-positive
- 3) 10 cells/high-powered field of biopsy sample

Exclude of: SS and other diseases such as sclerosing cholangitis, multicentric Castleman 's disease and idiopathic retroperitoneal fibrosis

Compares IgG4-associated sialadenitis with Sjogren's syndrome



	IgG4-associated sialadenitis (Mikulicz's disease)	Sjögren's syndrome
Age	Predominantly 40–60	Predominantly 40–60
Sex	Male predominance	Marked female predominance 9 : 1
Gland swelling	Persistent	Recurrent, but not persistent
Keratoconjunctivitis sicca	None to mild	Mild to severe
Dysfunction of salivary secretions	None to mild	Mild to severe
Antinuclear antibody	Typically negative	Typically positive
Anti-SS-A/SS-B antibodies	Negative	Positive (70%/30%)
Serum IgG4	Elevated in virtually all cases	Typically <140mg/dl
Pathology of gland	Lymphocytes with numerous plasma cells Abundant IgG4-positive cells, high IgG4-to-IgG ratio	Predominantly lymphocytes, IgG4 plasma cells virtually absent
Response to steroids/rituximab	Excellent response with decrease in swelling and improvement in salivary gland function	Typically unresponsive

Partial listing of diseases that cause enlarged and inflamed salivary and/or lacrimal gland(s)



	Clinical characteristics	Serology	Pathology
Sialolithiasis	Adults, typically affect Wharton's duct of the submandibular glands, rarely parotid	Normal serum IgG, IgG4 SS-A/SS-B negative	Mild inflammation, acellular fibrosis, absent obliterative phlebitis, IgG4 elevated in some cases (<50/HPF)
IgG4-associated sialadenitis (Mikulicz's disease)	Elderly men Symmetrical involvement of lacrimal glands with or without parotid and submandibular involvement	Serum IgG4↑ Serum IgG4/IgG↑ SS-A/SS-B negative	Lymphoplasmacytic inflammation with IgG4-positive cells ± obliterative phlebitis and fibrosis
IgG4-associated sialadenitis (Chronic sclerosing sialadenitis, Küttner tumor)	Men, average age 61 Unilateral or bilateral submandibular enlargement	Serum IgG4↑ Serum IgG4/IgG↑ SS-A/SS-B negative	Lymphoplasmacytic inflammation with IgG4-positive cells and obliterative phlebitis and fibrosis
Lymphoma	Elderly, female predominance Solitary, rarely multifocal	Normal serum IgG, IgG4 SS-A/SS-B-positive in cases with Sjögren's syndrome	MALT lymphoma diffuse proliferation of atypical-appearing marginal zone B cells, reactive germinal centers and lymphoepithelial lesions



TABLE 1. Summary of Clinicopathologic Features of IgG4-associated Sialadenitis (Küttner Tumor) Versus Chronic Sialadenitis-not Otherwise Specified, Sjögren Syndrome and Lymphoepithelial Sialadenitis

	IgG4-associated Sialadenitis (CSS)	Chronic Sialadenitis, NOS	Sjögren Syndrome (Lip Biopsy)	Lymphoepithelial Sialadenitis
Age in years (mean)	61	55	56	50
Sex M:F	6:7	3:2	1:7	1:1
Focal lesion/diffuse involvement	8 focal 5 diffuse	6 focal 9 diffuse	0 focal 8 diffuse	0 focal 4 diffuse
Interlobular cellular fibrosis	13/13 (100%)	1/15 (6%)	0	0
Bland acellular interlobular fibrosis	0	15/15 (100%)	0	0
Periductal inflammation	7/13 (54%)	7/15 (47%)	0	0
Marked lobular chronic inflammation with sheets of plasma cells	13/13 (100%)	2/15 (13%)	0	0
Phlebitis	9/13 (69%)	0	0	0
Obliterative phlebitis	6/13 (49%)	0	0	0
Follicular hyperplasia	13/13 (100%)	8/15 (53%)	0	4/4 (100%)
Florid follicular hyperplasia	13/13 (100%)	0	0	4/4 (100%)
Lymphoepithelial lesions	2/13 (15%)	0	1/8 (12%)	4/4 (100%)
Mean IgG4 per HPF (range)	229 (75-608)	16 (2-44)	1 (0-3)	6 (0-22)
IgG4/IgG ratio	0.86	0.14	0.02	0.04

CSS indicates chronic sclerosing sialadenitis; NOS, not otherwise specified.

SS Vs IgG4 on USG



On sonography, multiple hypoechoic areas and hyperechoic lines and/or spots in the parotid glands and obscuration of submandibular gland configuration were detected mainly in patients with SS , respectively. Reticular and nodal patterns were observed primarily in patients with IgG4-DS.

Some recommended treatments for sicca symptoms in patients with primary Sjögren's syndrome



- Sicca manifestation Therapeutic measure (grade of recommendation)
- ❖ Keratoconjunctivitis sicca
 - Tear substitutes (A)
 - Secretagogues: pilocarpine, cevimeline (A)
 - Cyclosporine A eye drops 0.1% (B)
 - Short-term topical corticosteroids (C)
 - Punctal plugs (C)
- ❖ Oral dryness Patient education
 - Avoid drugs that promote xerostomia (A)
 - Topical fluorides for caries prevention (A)
 - Secretagogues: pilocarpine, cevimeline (A)
 - Saliva substitutes, sugar-free chewing gum and electrostimulation of salivary glands (C)

Some recommended systemic traditional treatment in patients with primary Sjögren's syndrome



- **Parotid swelling** Short-term oral corticosteroids (C)
Antibiotic treatment, if required (D)
- **Arthritis** Hydroxychloroquine (C) NSAIDs Short-term oral/intraarticular corticosteroids (C) Other DMARDs as with rheumatoid arthritis (C)
- **Interstitial lung disease** Corticosteroids, oral or intravenous (C) Cyclophosphamide for active alveolitis (C)
Pirfenidone, nintedanib (C)
- **Tubulointerstitial nephritis** Potassium and bicarbonate replacement (D) AR-Rajae MD

Some recommended systemic traditional treatment in patients with primary Sjögren's syndrome



- **Glomerulonephritis** Corticosteroids, oral or intravenous (C) Cyclophosphamide Mycophenolate mofetil (according to specific nephrologic guidelines)
- **Peripheral neuropathy** Gabapentinoids (D)
Corticosteroids IVIg (D)
- **Cryoglobulinemic vasculitis**
Corticosteroids, plasmapheresis (C)

B-cell targeted agents

- **Rituximab** therapy
- Other anti-CD20 monoclonal antibodies such as **ocrelizumab** and **obinutuzumab** (humanized B-cell-depleting agent), and **ofatumumab** (fully human B-cell-depleting agent) are now available and have demonstrated an acceptable safety profile in patients with B-cell lymphoma.



Therapies against antigen-presenting cell mechanism and costimulatory molecules

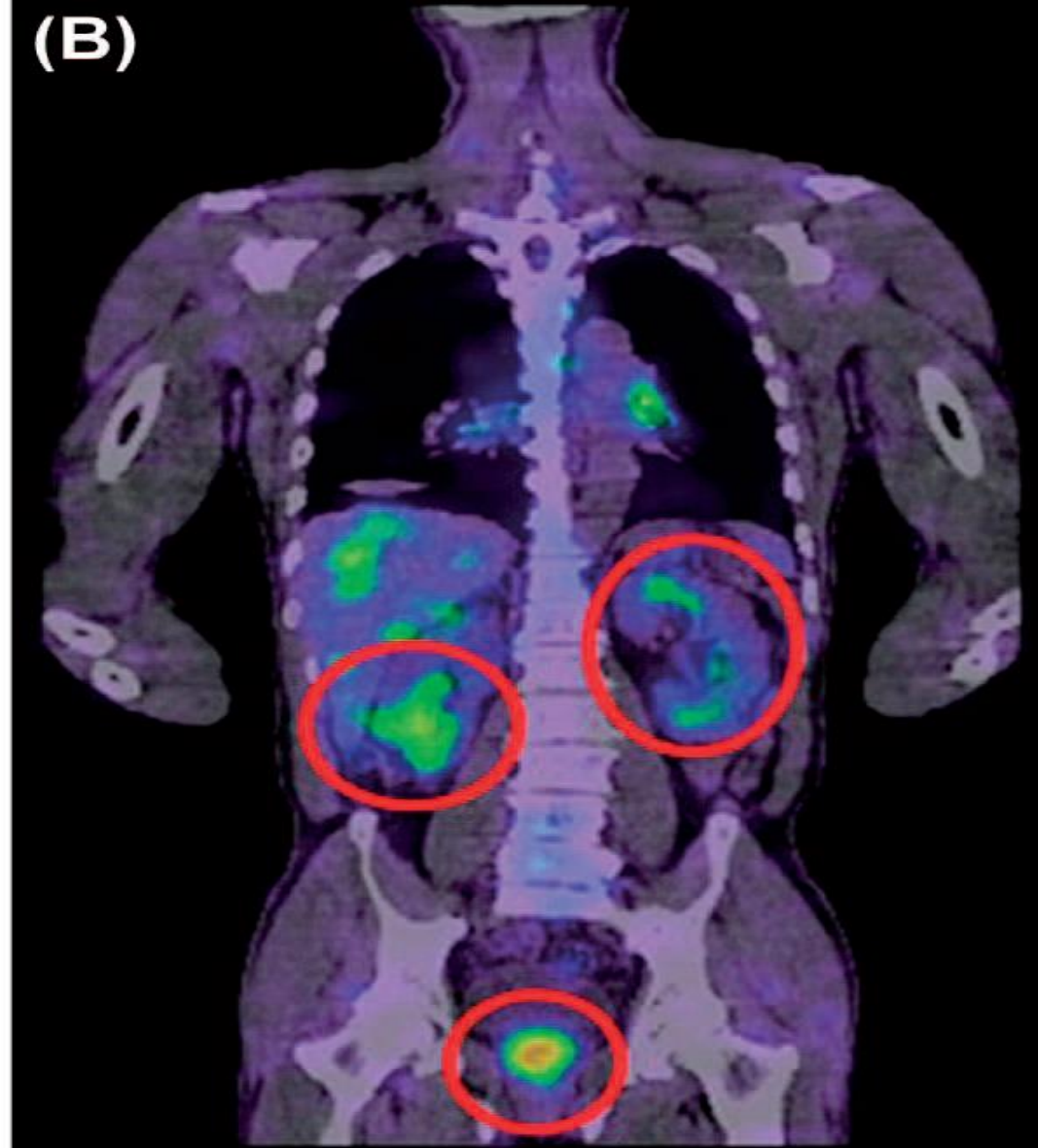
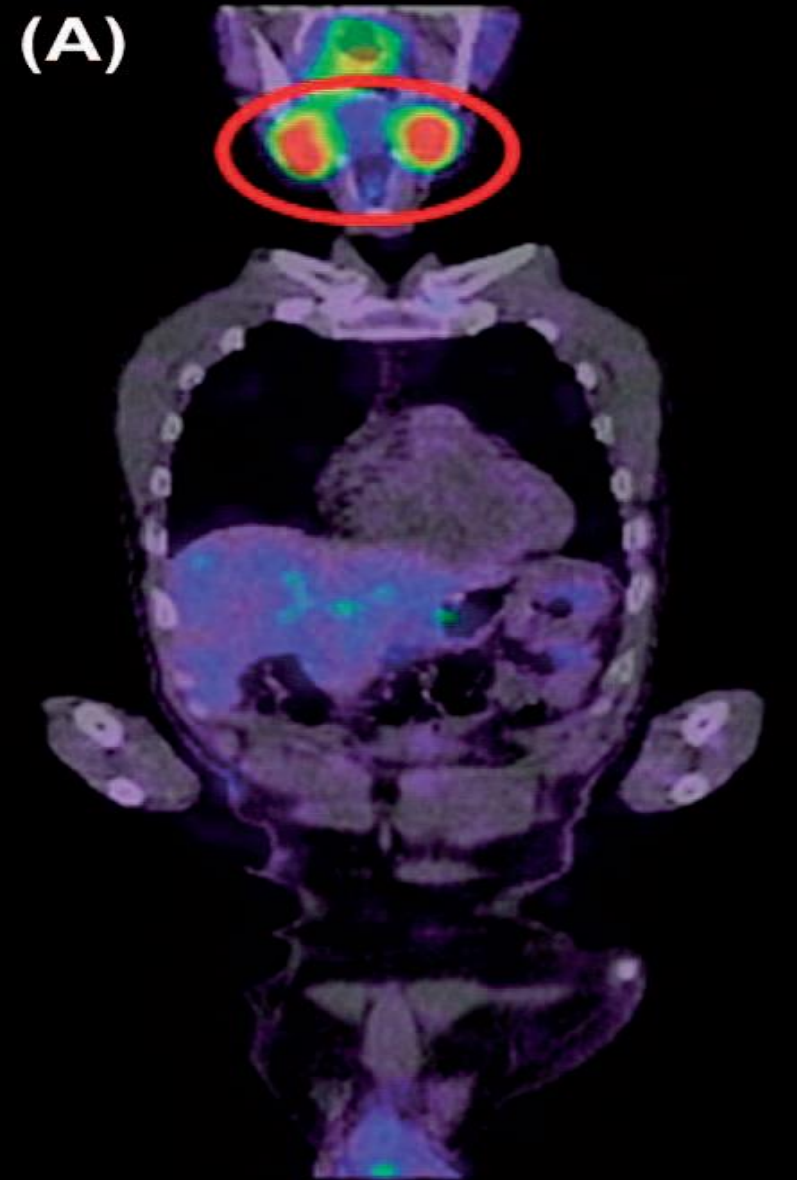


- Abatacept is a fusion protein composed of the Fc region of IgG1 combined with the extracellular domain of CTL4. As previously mentioned CTLA4, competing with CD28, is the natural inhibitor of the B7-CD28 costimulatory system, and so is active in negatively modulating the antigen presentation mechanism.

Anti-cytokine therapies

- Tocilizumab, a monoclonal antibody targeting IL-6, has been considered potentially active in this disorder. RCTs on the effectiveness of tocilizumab in patients presenting with systemic involvement and specific autoantibodies are ongoing and the results are expected relatively soon.





Gallium scintigraphy findings before treatment. Significant accumulation of gallium was observed in the bilateral submandibular glands, the bilateral kidneys and the prostate. Red circled sites demonstrate positive uptake lesions.

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Thank you for attention



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