IgG4 asociované onemocnění- choroba mnoha tváří

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IgG4-RD Diagnostika

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Empowering Rheumatology Professionals

SPECIAL ARTICLE

The 2019 American College of Rheumatology/European League Against Rheumatism Classification Criteria for IgG4-Related Disease

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IgG4-RD - definition

IgG4-related disease is a progressive, immune-mediated fibrotic disease that typically results in **tumor-like masses in many affected organs, such as salivary and lacrimal glands, the pancreas and the kidneys**. Studies have shown that CD4+ cytotoxic T lymphocytes are the predominant immune cell infiltrate in IgG4-related disease, with M2 macrophages, activated B cells and fibroblasts likely also playing a role in the generation of inflammatory masses. **Classic histologic findings seen on biopsies of affected organs include lymphoplasmacytic infiltrate, obliterative phlebitis and storiform fibrosis, with a large proportion of the plasma cells staining positive for IgG4**

Diagnostic Criteria

2019 ACR/European League Against Rheumatism (EULAR)

Step 1: Identify **typical involvement in at least one of the 11 possible organs typically affected by IgG4-related disease** (i.e., pancreas, salivary glands, bile ducts, orbits, lacrimal glands, kidneys, lungs, aorta, retroperitoneum, pachymeninges or thyroid gland [Riedel's thyroiditis]). Such involvement can be based on clinical or radiographic assessment, or pathologic evidence of an inflammatory process accompanied by a **lymphoplasmacytic infiltrate of uncertain etiology in one of these organs**.

Diagnostic criteria

Step 2: Apply exclusion criteria, which includes a total of 32 clinical, serologic, radiographic and pathologic items. This large array of exclusion criteria is meant to ensure patients with a **wide range of autoimmune, hematologic, infectious and malignant conditions are not misdiagnosed as having IgG4-related disease**. Example: Leukopenia and thrombocytopenia are unusual in IgG4-related disease, but often found in myelodysplastic syndromes, hematopoietic cancers and connective tissue diseases, such as systemic lupus erythematosus. Similarly, certain radiographic findings, such as long-bone abnormalities seen in Erdheim-Chester disease, should not be attributed to IgG4-related disease

IgG4-RD – diagnostic criteria

Step 3: Use eight weighted inclusion criteria domains, **which include immunostaining of IgG positive cells, head and neck gland involvement, pancreatic and biliary tree involvement, renal involvement, chest involvement and findings of retroperitoneal fibrosis or periaortitis**. In studying these classification criteria in several validation cohorts, a **threshold of 20 points on the criteria scale has a sensitivity of 97–99% and a specificity of 82–85%**

Two broad disease subtypes

Two broadly overlapping subtypes of disease have been described. One is referred to as a '**proliferative' subtype** and the other as a **'fibrotic' subtype**. These designations are imperfect for a variety of reasons, primarily because the biological differences between these subtypes remain uncertain

Overall principles of therapy

The goals of therapy in IgG4-RD are **to reduce inflammation, induce remission, maintain this remission, and preserve organ function**, all while minimizing the unintended consequences of treatment. Patients whose IgG4-RD is both active and symptomatic all require treatment. In addition, patients who demonstrate signs of disease progression also require treatment even if they have few symptoms. **Watchful waiting is appropriate only for a minority of patients.**

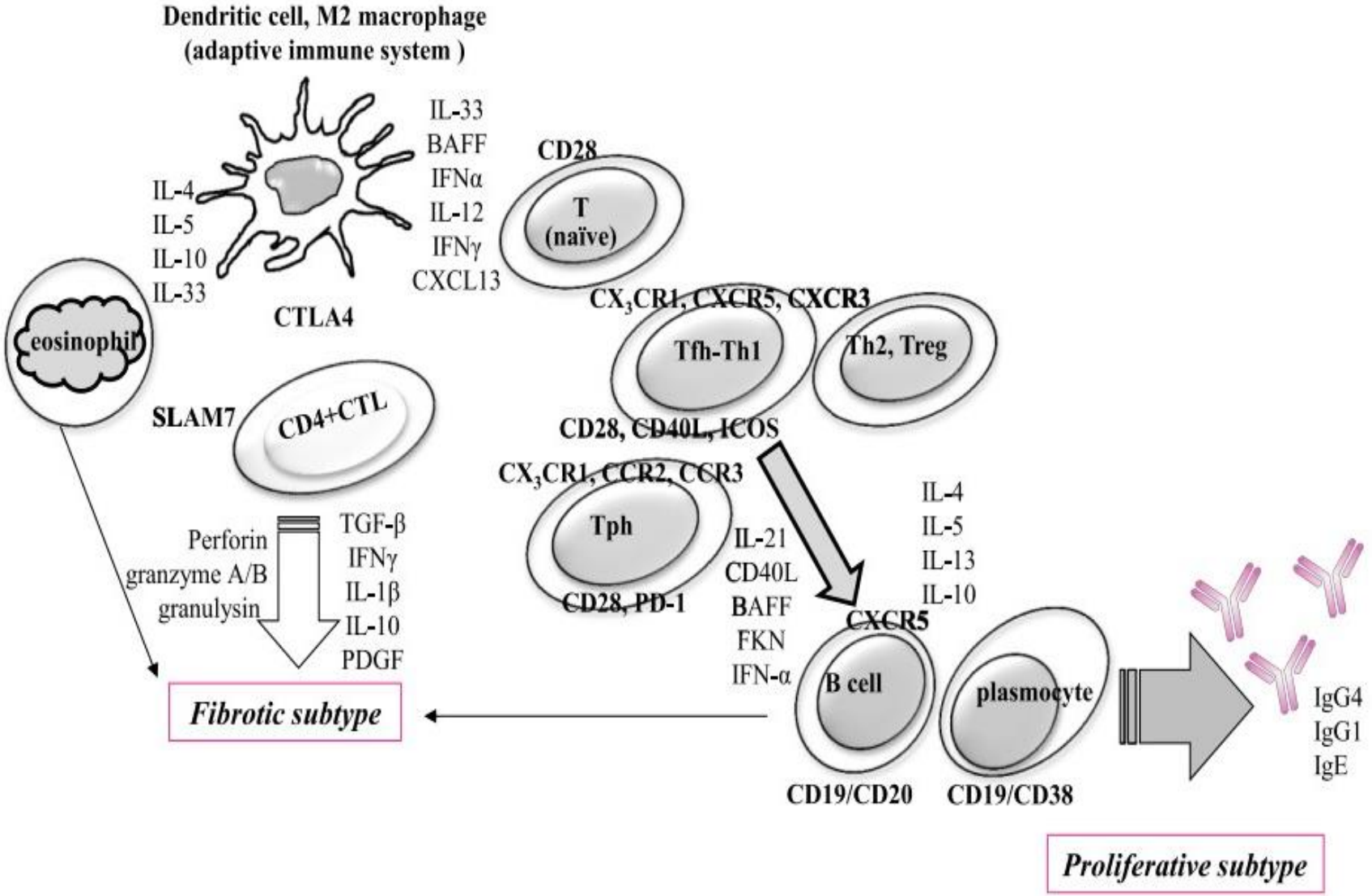
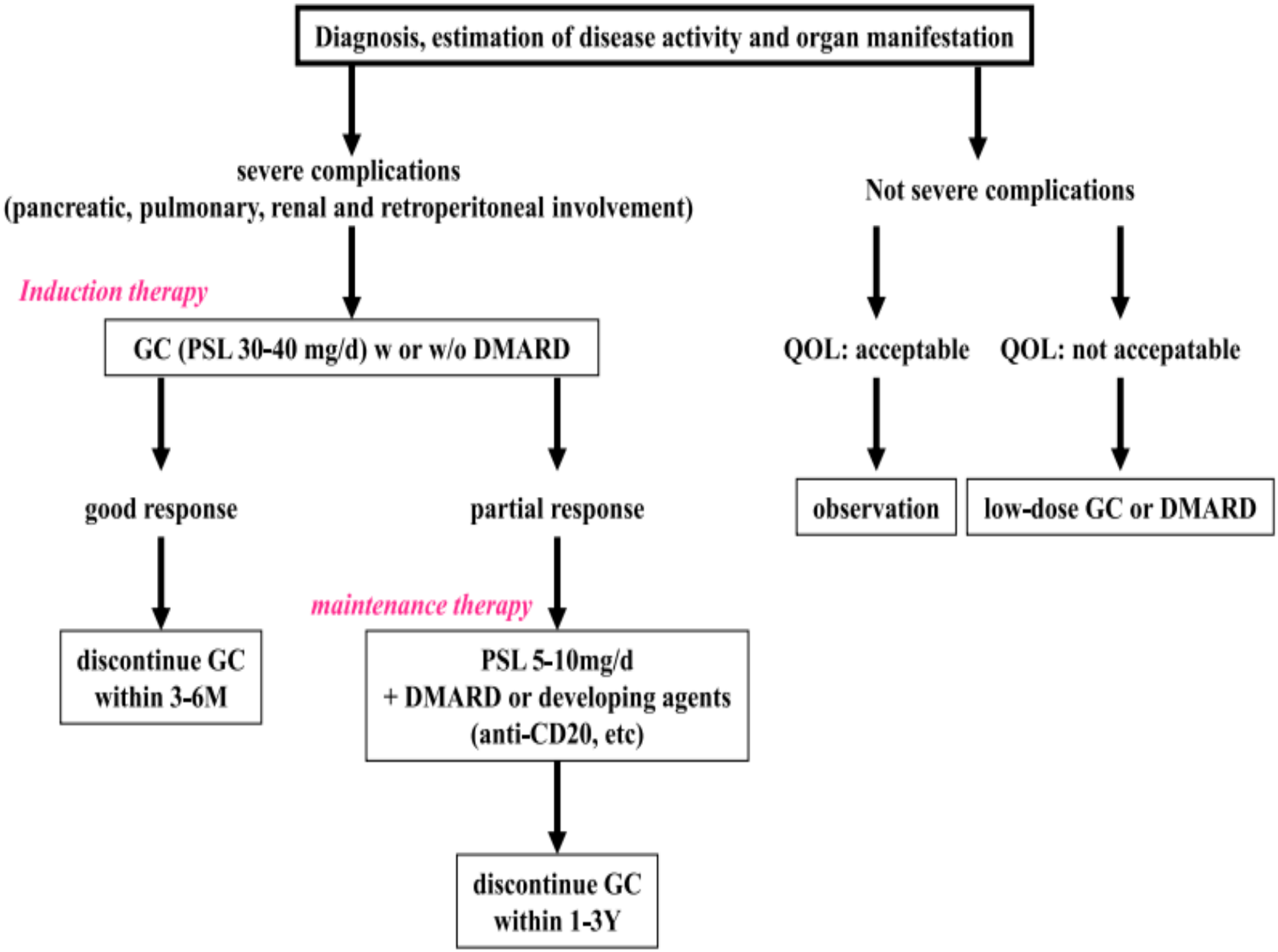


Figure 1. Pathological mechanisms in IgG4-RD.

Adaptive immune system and acquired immune system are differentially involved in fibrotic subtype and proliferative or inflammatory subtype of the IgG4-RD. Systemic cytokines, chemokines, co-stimulatory molecules, and chemokine receptors play roles in induction of the subtypes during the pathological processes.


Diagnosis, estimation of disease activity and organ manifestation
severe complications
(pancreatic, pulmonary, renal and retroperitoneal involvement)
Not severe complications
Induction therapy
GC (PSL 30-40 mg/d) w or w/o DMARD
QOL: acceptable
QOL: not accepatable
good response
partial response
observation
low-dose GC or DMARD
maintenance therapy
discontinue GC
within 3-6M
PSL 5-10mg/d
+ DMARD or developing agents
(anti-CD20, etc)
discontinue GC
within 1-3Y

Statistika – NNH – 27 let

- Ormondova choroba (včetně periaortitidy) 81
- Plíce 5
- Orbita 4
- AAA ve studii ze 120 vzorků bylo 7 pozitivních
- Pankreatitida - 5
- Polysystémové postižení 4

Summary for diagnostic criteria for IgG4-RD in lung involvement

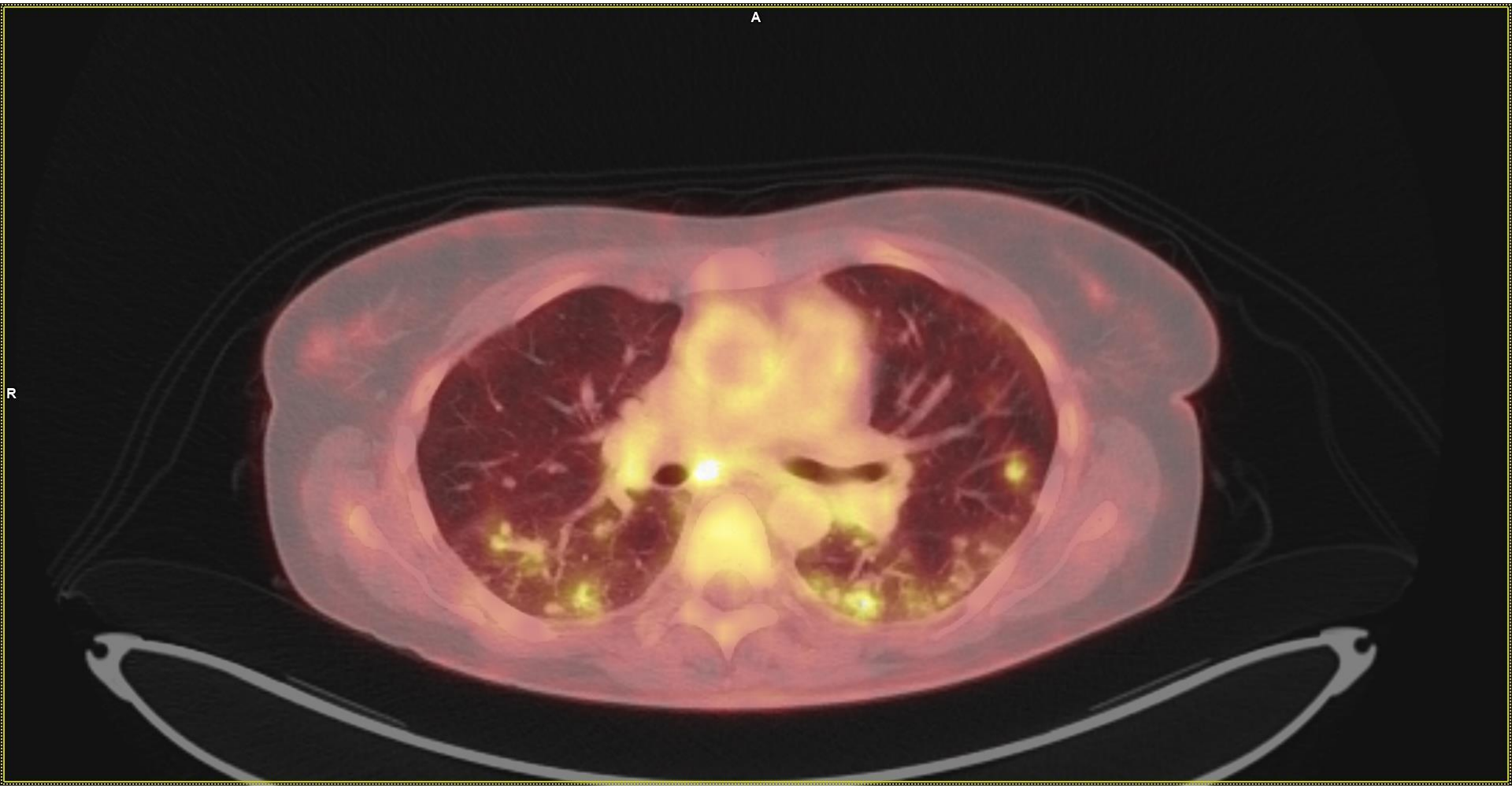
1. Abnormal shadow on chest CT
   * Hilar/mediastinal lymphadenopathy
   * thickening of bronchial wall, bronchovascular bundle, interlobular septal wall
   * nodular shadow, infiltrative shadow, pleutŕal thickening/effusion
2. Elevated serum IgG4
3. Pathological findings satisfaying the following two items or more
   *dense lymphoplasmocytic infiltration into respirátory organ tissues
   * obliterative phlebitis or arteritis
   * Characteristic fibrosis, typically storiform fibrosis

Differential diagnosis for IgG4-RD

- Multicenter Castleman disease (plasma cell type)
- GPA (Wegener granuloma)
- EGPA (Churg Strauss syndrome)
- Sarcoidosis
- Lung cancer, malignant lymphoma
- Nonspecific interstitial pneumonia (idiopathic, collagen vascular disease related)
- RDD (Rosai – Dorfman disease)
- Infection

Kazuistika 1

Pacientka r. 1971 s mnohaletou historií plicního postižení nejasné etiologie, posléze histologicky potvrzeno jako IgG4-RD, s multisystémovým postižením(plíce, retroperitoneum, kosti, lymfatický systém). Léčena již v 90. letech na imunologickém pracovišti s nejasnou diagnózou. Ke mně poslána z plicní kliniky s již histologicky potvrzenou diagnózou IgG4-RD. Léčena systémovými KS s azathioprinem, při detrakci aktivita onemocnění opakovaně. Proto nasazen ke KS mycophenolat mofetil, i při této kombinaci stejný výsledek. Poté nasazena biologická léčba rituximabem, při které je onemocnění v remisi.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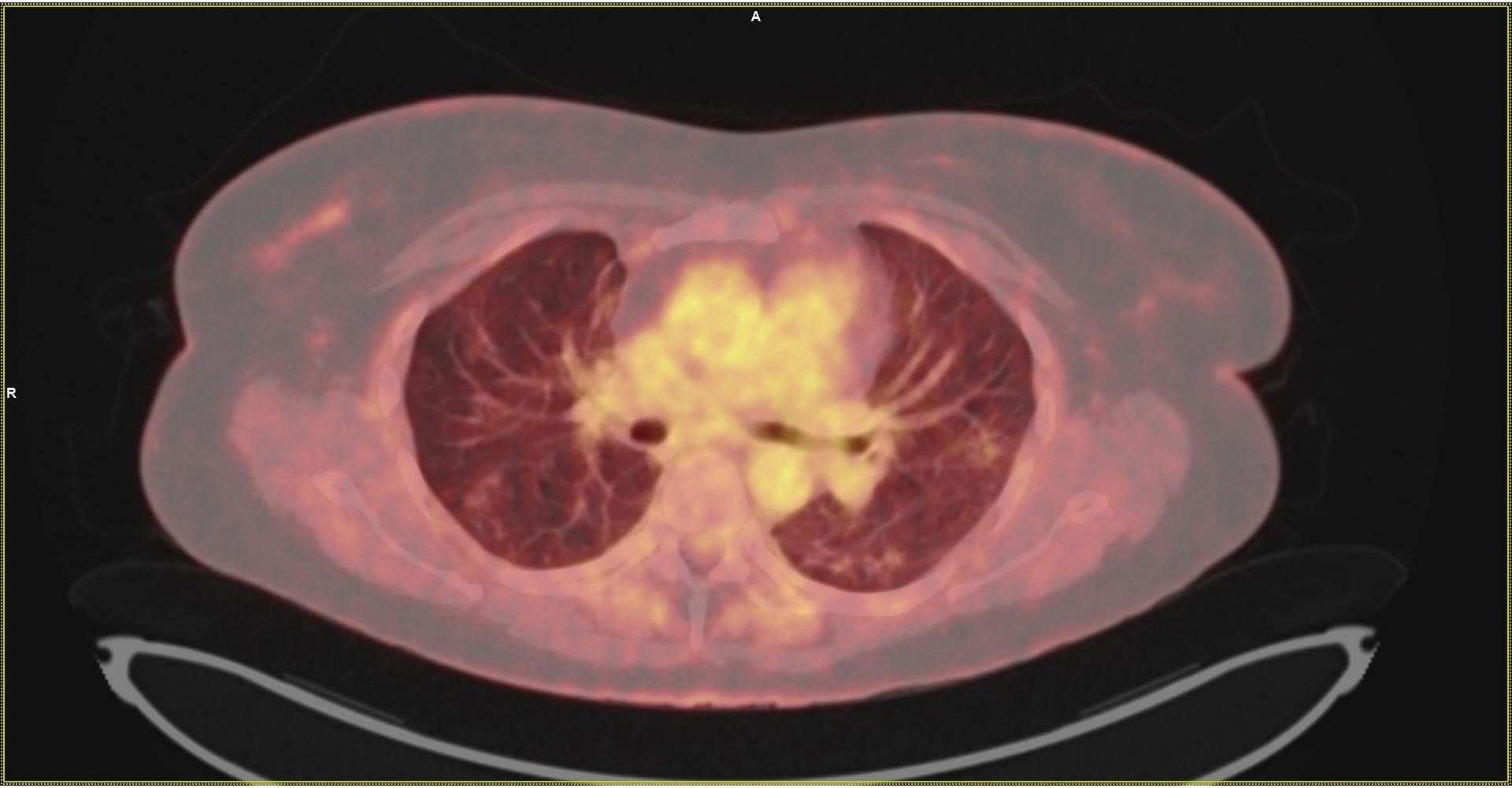
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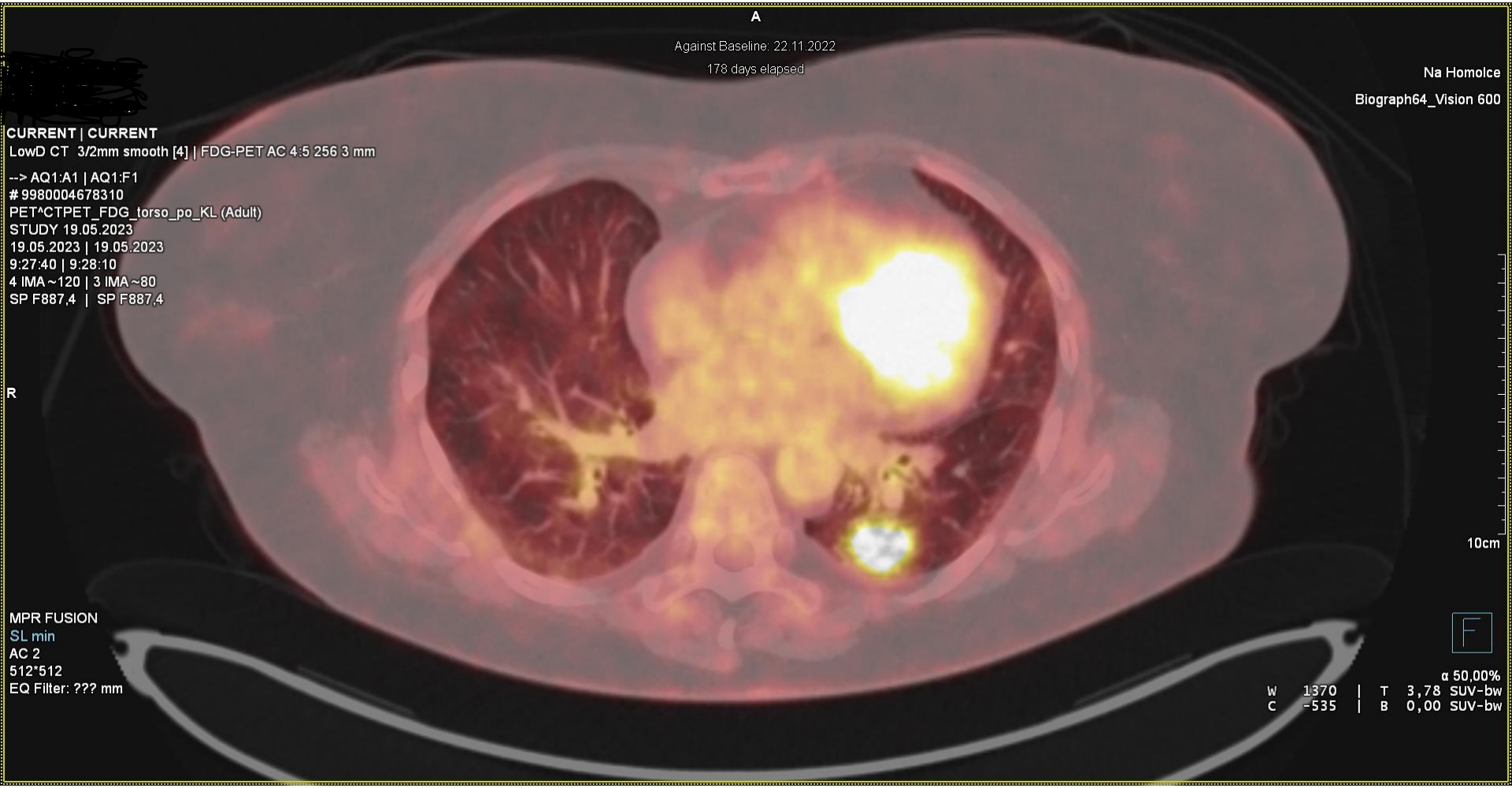
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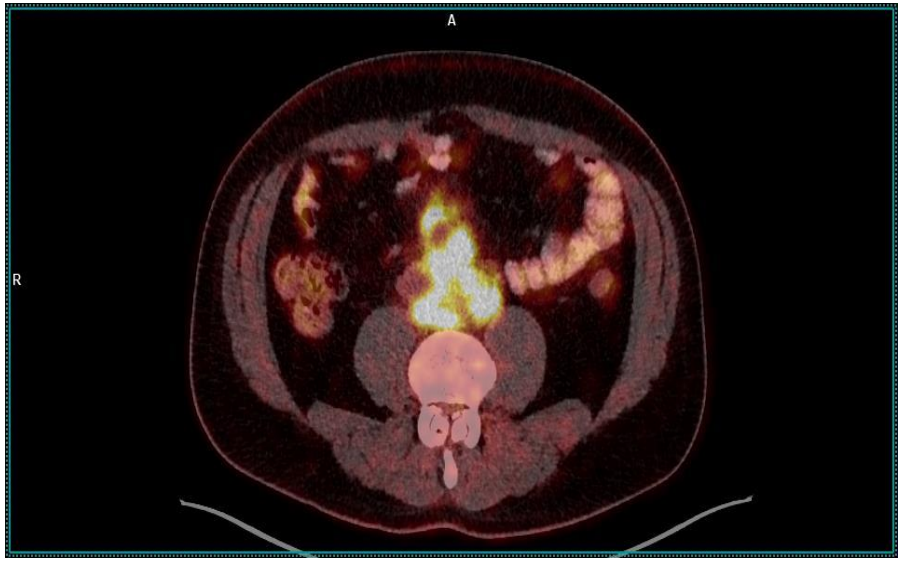
Against Baseline: 22.11.2022
178 days elapsed
Na Homolce
Biograph64_Vision 600
CURRENT | CURRENT
LowD CT 3/2mm smooth [4] | FDG-PET AC 4:5 256 3 mm
--> AQ1:A1 | AQ1:F1
9980004678310
PET^CTPET_FDG_torso_po_KL (Adult)
STUDY 19.05.2023
19.05.2023 | 19.05.2023
9:27:40 | 9:28:10
4 IMA ~120 | 3 IMA ~80
SP F887,4 | SP F887,4
R
10cm
MPR FUSION
SL min
AC 2
512*512
EQ Filter: ??? mm
α 50,00%
W 1370 | T 3,78 SUV-bw
C -535 | B 0,00 SUV-bw

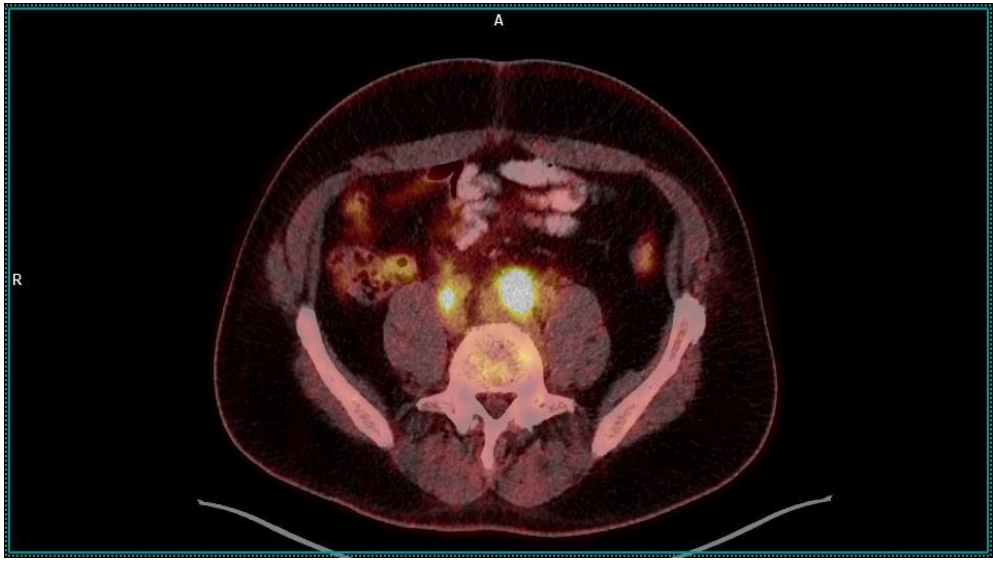
Kazuistika 2

Pacient poslán z urologické kliniky se suspekcí na Ormondovu chorobu, vzhledem k poněkud nespecifickému nálezu indikována biopsie – nemožnost pod CT, proto laparoskopicky .....

Popis CT: subrenálně hypodenzní útvar, který obrůstá odstupující AMi a a.iliace comm. bilat

Histologie: Nález hodnotíme jako germinální tumor nejspíše seminom k jehož primárnímu zdroji se nelze vyjádřit





Souhrn – IgG4-RD

- **Klinická symptomatologie je nespecifická**
- **Neexistují specifické biomarkery onemocnění**
- **Biomarkery zánětu jsou relativně spolehlivým znakem aktivity onemocnění**
- **Výraznou přídatnou hodnotou je použití zobrazovacích metod - PET/CT, CT/AG**

Souhrn - IgG4-RD

- **Diagnóza se stanovuje na základě klinického obrazu, zobrazovacích metod a histologického vyšetření**
- **V diferenciální diagnostice je nutné vyloučit především nádorové onemocnění**
- **Je možná asociace s jinými autoimunitními chorobami (vaskulitidy velkých cév, systémová onemocnění)**
- **Naprosto zásadní je mezioborová spolupráce (imunolog, cévní chirurg, rentgenolog, (intervenční + specialista na zobrazovací metody, patolog, jiný specialista)**