Retroperitoneal fibrosis
from bedside to bench

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THE CONCEPT OF FIBRO-INFLAMMATORY DISEASES

- Tumour-like, fibro-inflammatory lesions (fibrosis develops together with inflammation)
- Inflammation is usually "chronic"
- Organ damage due to inflammation and fibrosis
- Organ damage due to compressive effects of newly formed fibro-inflammatory masses
- Fibrosis in fibro-inflammatory diseases has the potential to regress after appropriate treatment
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**IDIOPATHIC**
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Sclerosing cholangitis
Sclerosing mesenteritis
Retroperitoneal fibrosis/chronic periaortitis
Riedel’s and fibrosing Hashimoto’s thyroiditis
Aortitis
Mikulicz’s disease
Inflammatory pseudotumour
Fibrosing mediastinitis

IgG4-RELATED

Sclerosing pancreatitis
Sclerosing cholangitis
Sclerosing mesenteritis
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Riedel’s and fibrosing Hashimoto’s thyroiditis
Aortitis
Mikulicz’s disease
Inflammatory pseudotumour
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IDIOPATHIC

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<tr>
<th>IDIOPATHIC</th>
<th>IgG4-RELATED</th>
<th>SECONDARY</th>
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</thead>
<tbody>
<tr>
<td>Sclerosing pancreatitis</td>
<td>Drug-related (methysergide, ergot-derivatives, pergolide)</td>
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<tr>
<td>Sclerosing cholangitis</td>
<td>Gadolinium-induced fibrosis</td>
<td></td>
</tr>
<tr>
<td>Sclerosing mesenteritis</td>
<td>Infectious (TB, actinomycosis, histoplasmosis)</td>
<td></td>
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<tr>
<td>Retroperitoneal fibrosis/chronic periaortitis</td>
<td>Malignancies (lymphomas, sarcomas, solid tumours, inflammatory myofibroblastic tumour)</td>
<td></td>
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<tr>
<td>Riedel’s and fibrosing Hashimoto’s thyroiditis</td>
<td>Erdheim-Chester disease</td>
<td></td>
</tr>
<tr>
<td>Aortitis</td>
<td>Other (trauma, Rx-therapy)</td>
<td></td>
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<tr>
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<td></td>
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</table>
FROM RETROPERITONEAL FIBROSIS TO CHRONIC PERIAORTITIS
THE SPECTRUM OF CHRONIC PERIAORTITIS

Clinical presentation
<table>
<thead>
<tr>
<th></th>
<th>Mayo Clinic, Rochester (n=185)</th>
<th>Johns Hopkins University, Baltimore (n=48)</th>
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<td>(pain, varicoce, hydrocele), %</td>
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<td></td>
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<td>Constipation, %</td>
<td>12</td>
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### CLINICAL MANIFESTATIONS

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Disease associations
ASSOCIATION WITH SYSTEMIC AUTOIMMUNE DISEASES

Panel 2: Main associations between retroperitoneal fibrosis and autoimmune or inflammatory diseases

Autoimmune thyroid disease
- Hashimoto’s thyroiditis^{11,12}
- Riedel’s thyroiditis^{52,54-56}
- Graves’ disease^{66}

Small and medium-sized vessel vasculitis
- Wegener’s granulomatosis^{37,50}
- Polyarteritis nodosa^{91}
- Microscopic polyangitis^{60}
- Hepatitis C virus-related cryoglobulinaemia^{69}
- Ankylosing spondylitis^{70,71}

Systemic lupus erythematosus^{14,50,65}

Rheumatoid arthritis^{11,14,72}

Glomerulonephritis
- ANCA-positive rapidly progressive glomerulonephritis^{11,50}
- Membranous nephropathy^{73}

Sclerosing cholangitis^{64,75}

Primary biliary cirrhosis^{26,27}

Sclerosing pancreatitis^{30,28}

Uveitis^{79}

ANCA: anti-neutrophil cytoplasmic antibodies.

## ASSOCIATION WITH ORGAN-SPECIFIC AUTOIMMUNE DISEASES

<table>
<thead>
<tr>
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<th>CP patients (n=73)</th>
<th>Controls (n=71)</th>
<th>P value</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>55.4 (10.6)</td>
<td>55.0 (9.6)</td>
<td>0.85</td>
</tr>
<tr>
<td>Male n (%)</td>
<td>46 (63)</td>
<td>41 (58)</td>
<td>0.52</td>
</tr>
<tr>
<td>TSH mIU/L</td>
<td>1.23 (0.79-1.70)</td>
<td>1.50 (1.07-2.59)</td>
<td>0.86</td>
</tr>
<tr>
<td>FT4 ng/dL</td>
<td>1.22 (0.20)</td>
<td>0.93 (0.18)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>AbTPO positivity n (%)</td>
<td>18 (24.7)</td>
<td>7 (10.6)</td>
<td>0.03</td>
</tr>
<tr>
<td>AbTg positivity n (%)</td>
<td>12 (16.4)</td>
<td>5 (7.0)</td>
<td>0.11</td>
</tr>
<tr>
<td>Ultrasonographic evidence of HT n(%)</td>
<td>50 (69.4)</td>
<td>23 (32.4)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Thyroid volume (mL)</td>
<td>11.42 (5.31)</td>
<td>10.00 (4.43)</td>
<td>0.12</td>
</tr>
<tr>
<td>Thyroid nodules n (%)</td>
<td>18 (25.3)</td>
<td>24 (33.8)</td>
<td>0.27</td>
</tr>
<tr>
<td>Thyroid nodules diameter (mm)</td>
<td>14 (8-15)</td>
<td>10 (8-15)</td>
<td>0.77</td>
</tr>
<tr>
<td>Body Mass Index (kg/m2)</td>
<td>26.90 (3.71)</td>
<td>27.44 (2.70)</td>
<td>0.38</td>
</tr>
<tr>
<td>Smoking (pack-years)</td>
<td>34.20 (26.20)</td>
<td>8.84 (10.32)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>CIRS score</td>
<td>3 (2-5)</td>
<td>0 (0-1)</td>
<td>&lt;.0001</td>
</tr>
</tbody>
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“DIFFUSE” (THORACO-ABDOMINAL) PERIAORTITIS

77 patients with chronic periaortitis (CP)

28 CP patients with thoracic vessel disease

7 (25%) thoracic aortic aneurysm

6 (21%) thoracic aortic aneurysm plus periaortitis

15 (54%) thoracic periaortitis

2 (7%) with epiaortic vessel involvement

4 (14%) without epiaortic vessel involvement

7 (25%) with epiaortic vessel involvement

8 (29%) without epiaortic vessel involvement

"DIFFUSE" (THORACO-ABDOMINAL) PERIAORTITIS
ASSOCIATION WITH OTHER FIBRO-INFLAMMATORY DISORDERS

IDIOPATHIC MEDIASTINAL FIBROSIS: 3 out of 9 cases in our series were associated with CP

ASSOCIATION WITH IgG4-RELATED (SYSTEMIC) DISEASE

Kuttner’s tumour of the parotid gland

Tubulo-interstitial nephritis

RPF

Sclerosing pancreatitis

IgG4-RELATED DISEASE

1. Typical organ involvement (often tumour-like)
2. IgG4 >135 mg/dL
3. Tissue IgG4+ plasma cells >40% of IgG+ plasma cells and >10/hpf

Umehara H, Mod Rheumatol 2012; Corradi D, Cardiovasc Pathol 2016
SERUM IgG4 in CHRONIC PERIAORTITIS

Vaglio A, unpublished
## IgG4-RELATED vs -UNRELATED CP

<table>
<thead>
<tr>
<th></th>
<th>No. pts</th>
<th>IgG4+ cases, n(%)</th>
<th>Criteria to differentiate IgG4+ vs IgG4- CP</th>
<th>Main findings (in the IgG4+ subset)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Castelein T, 2015</td>
<td>17</td>
<td>9 (53)</td>
<td>Serum IgG4 level</td>
<td>Multifocal involvement, male predominance</td>
</tr>
<tr>
<td>Kasashima S, 2008</td>
<td>23</td>
<td>13 (56)</td>
<td>Histology and IHC</td>
<td>Higher incidence of autoimmune diseases</td>
</tr>
<tr>
<td>Khosroshahi A, 2013</td>
<td>23</td>
<td>13 (56)</td>
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<td>Koo B, 2014</td>
<td>19</td>
<td>9 (47)</td>
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<td>Yamashita M, 2008</td>
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**Chronic Periaortitis**

**IgG4-unrelated**

**IgG4-related**

Immunopathogenetic model
IMMUNOPATHOGENESIS OF CHRONIC PERIAORTITIS

Environmental factors (asbestos, smoking)

(Auto-)antigen (?)

Aortic lumen

Aortic wall

Retroperitoneum

APC

CD4+ T cell

TCR
PATHOGENESIS: GENETIC ASSOCIATIONS

- **HLA DRB1*03**
- CCR5 delta 32
- CCL11 haplotype
- FcGR2A

In collaboration with Ana Marquez & Javier Martin

### PATHOGENESIS: ASBESTOS AND SMOKING

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Participants, n</th>
<th>OR (95% CI)</th>
<th>P Value</th>
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<tbody>
<tr>
<td></td>
<td>Control Group</td>
<td>Case</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>153</td>
<td>49</td>
<td>3.15 (1.40–8.11)</td>
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<tr>
<td>Asbestos</td>
<td>8</td>
<td>4</td>
<td>4.91 (0.78–28.02)</td>
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<tr>
<td>Smoking and asbestos</td>
<td>23</td>
<td>27</td>
<td>12.04 (4.32–38.28)</td>
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**Graph:***

[Graph showing OR (95% CI) for smoking, asbestos, and smoking and asbestos]

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IMMUNOPATHOGENESIS OF CHRONIC PERIAORTITIS

- Environmental factors (asbestos, smoking)
- (Auto-)antigen (?)

HLA-DR3

CD4+ T cell

Aortic lumen

Aortic wall

Retroperitoneum
ARCHITECTURAL ORGANISATION OF THE LYMPHOCYTE SUBSETS

IMMUNOPATHOGENESIS OF CHRONIC PERIAORTITIS

Environmental factors (asbestos, smoking)

(Auto-)antigen (?)

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IMMUNOPATHOGENESIS OF CHRONIC PERIAORTITIS

(Auto-)antigen (?)

Environmental factors (asbestos, smoking)

HLA-DR3

CD4+ T cell

CD20+ B cells

IL-6

Aortic lumen

Aortic wall

Retroperitoneum
INTERLEUKIN-6 IN CP

p<0.0001

CP PATHOGENESIS: EOSINOPHILS, MAST CELLS AND EOTAXIN-1

Eosinophils

Tryptase+ degranulating mast cells

Eotaxin/CCL11 expression in retroperitoneal biopsies

Mangieri D, *Nephrol Dial Transplant* 2012
IMMUNOPATHOGENESIS OF CHRONIC PERIAORTITIS

Environmental factors (asbestos, smoking)

(Auto-)antigen (?)

Aortic lumen

Aortic wall

CD4+ T cell

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HLA-DR3

TCR

IL-6

Eotaxin-1

Eosinophils

Mast cells

Fibroblasts

Tryptase, eosinophil granule proteins

IL-6

Trypan blue

IMMUNOPATHOGENESIS OF CHRONIC PERIAORTITIS

Environmental factors (asbestos, smoking)

(Auto-)antigen (?)

Aortic lumen

Aortic wall

CD4+ T cell

CD20+ B cells

HLA-DR3

TCR

IL-6

Eotaxin-1

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fibroblasts

fibrocytes

Aortic lumen

Aortic wall
Fibrocytes are a rare population of (circulating) precursors of tissue fibroblasts, which stain positive for CD45 and type I Col.
IMMUNOPATHOGENESIS OF CHRONIC PERIAORTITIS

Adapted from Vaglio A, J Am Soc Nephrol 2016
Treatment and outcome
GLUCOCORTICOIDS AS FIRST-LINE THERAPY

39 started induction therapy with prednisone (1 mg/kg daily for 1 month)
2 excluded because of severe steroid-related toxic effects
1 declined further participation

36 achieved remission and randomised

18 assigned to prednisone
18 included in primary endpoint analysis (month 8)
1 lost to follow-up
17 completed the additional 18-month follow-up period

18 assigned to tamoxifen
18 included in primary endpoint analysis (month 8)
2 lost to follow-up
16 completed the additional 18-month follow-up period

GLUCOCORTICOIDS AS FIRST-LINE THERAPY

Log-rank test p=0.04

Number at risk

<table>
<thead>
<tr>
<th></th>
<th>Prednisone</th>
<th>Month since randomisation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>18</td>
<td>17</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>18</td>
<td>15</td>
</tr>
</tbody>
</table>
16 consecutive *relapsing* CP patients

MTX (15-20 mg/week) + PDN for 12 months (followed by observation or treatment continuation)

RITUXIMAB FOR RELAPSING-REFRACTORY DISEASE

Before Rituximab

After Rituximab
RITUXIMAB FOR CP

- 16 patients with difficult-to-treat CP
  - 12 relapsing-refractory
  - 4 contraindications to standard-dose GCs
- 14/16 had normal serum IgG4
- No one had evidence of (systemic) IgG4RD

Urban ML, 54th ERA-EDTA congress Madrid 2017 (abstract)
Before and after Tocilizumab

Vaglio A, Arthritis Rheum 2013
18F-FDG PET PREDICTS RESPONSE TO THERAPY IN CP

Accorsi Buttini E, *Eur Urol* 2017
Accorsi Buttini E, et al, unpublished
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