CASE 3

Francesco Fortarezza, Michele Rossini, Maria Grazia Fiore, Domenico Piscitelli, Loreto Gesualdo, Leonardo Resta, Roberta Rossi

Department of Emergency and Organ Transplant
University of Bari, Italy
• 28-year-old man

• Antibiotic-resistant fever

• CT: bilateral thickening of the pulmonary parenchyma. Inter-aorto-caval, para-aortic and left iliac lymph nodes, spleen and liver were increased in volume.

• Dense tissue in the periureteral area of left kidney, extending down into the pelvic excavation

• The patient underwent surgery for removing the obstruction

• The histopathological examination (not available) confirmed the clinical diagnosis of retroperitoneal abscess
• urine protein 680 mg/dl (12 gr/24h), serum albumin 1,6 g/dl, total cholesterol 333 mg/dl, serum creatinine 1.16 mg/dl, normal complement levels
• Blood pressure 145/85 mmHg
• negative anti-HIV and IgM CMV; no evidence of monoclonal protein,
• negative ANCA screening, anti-SSA, SSB and ANA antibodies.
• negative serum anti-PLA2R

CT/PET: hypercaptation in the left kidney. Hypermetabolic adenopathies in the left paraaortic, left perirenal, retro-caval and inter-aorto-caval areas
• Abdominal MRI suspicious for lymphoproliferative process of the left kidney
Immunofluorescence

IgG

κ

λ
Immunohistochemistry

CD20, CD3, MUM1, κ, λ
Immunohistochemistry

MUM1

IgG

IgG4
Immunohistochemistry

IgG4

IgG4
Diagnosis

IgG4-related tubulointerstitial nephritis and membranous glomerulonephritis
IgG4-Related Disease (IgG4-RD)

Chronic Inflammatory Sclerosis of the Pancreas—An Autonomous Pancreatic Disease?

**Fig. 1.** *Top.* Mrs. Pout --- X-ray of pancreas taken after tail of pancreas was cut shows complete stenosis of the duct. *Bottom.* Section cut at level of stenosis shows that pancreatic tissue is completely replaced by sclerosis.

- **Pituitary gland**
  - Headache, visual field deficit, lactation, diabetes insipidus
  - (IgG4-related hypophysitis)
- **Lacral gland**
  - Swollen upper eyelids, dry eyes
  - (IgG4-related dacrcoadenitis)
- **Salivary gland**
  - Swollen submandibular portions, dry mouth
  - (IgG4-related sialadenitis)
- **Thyroid**
  - Neck tightness, malaise, edema
  - (IgG4-related thyroid disease)
- **Respiratory tract**
  - Cough; similar to bronchial asthma
- **Lung**
  - Cough, often asymptomatic
  - (IgG4-related lung disease)
- **Kidney**
  - Often asymptomatic
  - (IgG4-related kidney disease)
- **Biliary tract**
  - Obstructive jaundice
  - (IgG4-related sclerosing cholangitis)
- **Retropertitoneal cavity**
  - Fever, malaise, aneurysm in cases with periarteritis
  - (IgG4-related retropertitoneal fibrosis)
- **Prostate gland**
  - Frequent urination, feelings of residual urine
  - (IgG4-related prostatitis)
- **Pancreas**
  - Upper abdominal discomfort, obstructive jaundice, impaired glucose tolerance
  - (type I autoimmune pancreatitis)
- **Lymph nodes**
  - Swollen lymph nodes
  - (IgG4-related lymphadenopathy)
**Consensus statement on the pathology of IgG4-related disease**

**Histopathological features**

**Major**
- Dens lymphoplasmacytic infiltrate
- Fibrosis, arranged at least focally in a storiform pattern
- Obliterative phlebitis

**Minor**
- Phlebitis without obliteration of the lumen
- Increased numbers of eosinophils
Consensus statement on the pathology of IgG4-related disease

Histopathological features

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Quantitative assessment of the IgG4 stain
• IgG4+ plasma cell counts
• IgG4+/IgG+ ratio > 40%
Diagnosis of IgG4-Related Tubulointerstitial Nephritis

Yassaman Raissian,* Samih H. Nasr,* Christopher P. Larsen,† Robert B. Colvin,‡ Thomas C. Smyrk,* Naoki Takahashi,§ Ami Bhalodia,‖ Aliyah R. Schani,‡ Lizhi Zhang,* Suresh Chari,‡ Sanjeev Sethi,* Mary E. Fidler,* and Lynn D. Cornell*

Table 3. Proposed diagnostic criteria for IgG4-related TIN

<table>
<thead>
<tr>
<th>Histology</th>
<th>Plasma cell-rich tubulointerstitial nephritis with &gt;10 IgG4 + plasma cells/hpf field in the most concentrated field^a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imaging</td>
<td>Tubular basement membrane immune complex deposits by immunofluorescence, immunohistochemistry, and/or electron microscopy^b</td>
</tr>
<tr>
<td>Imaging</td>
<td>Small peripheral low-attenuation cortical nodules, round or wedge-shaped lesions, or diffuse patchy involvement</td>
</tr>
<tr>
<td>Imaging</td>
<td>Diffuse marked enlargement of kidneys</td>
</tr>
<tr>
<td>Serology</td>
<td>Elevated serum IgG4 or total IgG level</td>
</tr>
<tr>
<td>Other organ</td>
<td>Includes autoimmune pancreatitis, sclerosing cholangitis, inflammatory masses in any organ, sialadenitis, inflammatory aortic aneurysm, lung involvement, retroperitoneal fibrosis</td>
</tr>
</tbody>
</table>

Diagnosis of IgG4-TIN requires the histologic feature of plasma cell-rich TIN with increased IgG4 + plasma cells and at least one other feature from the categories of “imaging”, “serology”, or “other organ involvement”.

^aMandatory criterion.
^bSupportive criterion, present in >80% of cases.

Pathogenesis of IgG4 related disease

- Not completely understood
- Trigger not identified
- Role of T lymphocytes subclasses: CD4+ cytotoxic and $T_{fh}$
- ... and IgG4?
IgG4: an ambiguous antibody

Anti-inflammatory and tolerance-induced effects

Fab arm exchange

Weak capabilities bindings with C1q and Fcγ receptors

Attenuated ability to activate the classic complement pathway

Cortazar 2015

Khanal 2017
IgG4: an ambiguous antibody

Implication in the pathogenesis of IgG4-related MNG

- The dominant IgG subclass in primary MGN
- Activates the mannan-binding lectin pathway of the complement
- Other IgG subclasses (IgG1 and IgG3) may be responsible for activating complement via the classical pathway
- Rheumatoid factor activity of IgG4
- Unknown podocytes antigen in IgG4-related MNG?
Primary or secondary MNG?

- Negative anti-PLA2R
- Involvement of other organ (lymphadenopathies)
- High level of serum IgG4
- Coexistence of TIN
- Ultrastructural findings
Conclusion

- The kidney is an important target organ of IgG4-RD with a peculiar, dichotomous manifestation as TIN and MNG
- Pathogenetic mechanisms of MNG occurring in the set of IgG4-RD are unclear
- IgG4-related MNG may occur without TIN and could represent the first manifestation of the disease

Glucocorticoids are currently the first-line treatment for IgG4-RD
- Treatment with rituximab to induce B-cell depletion has yielded promising results
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<th>Date</th>
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<th>02/04/19</th>
<th>24/06/2019</th>
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<tbody>
<tr>
<td>Proteinuria g/24h</td>
<td>12,153</td>
<td>1,293</td>
<td>4,792</td>
<td>3,616</td>
<td>3,96</td>
<td>1,7</td>
<td>0,696</td>
<td>0,636</td>
</tr>
<tr>
<td>Serum Cr (mg/dl)</td>
<td>1,03</td>
<td>0,77</td>
<td>0,91</td>
<td>1</td>
<td>1,19</td>
<td>1,1</td>
<td>1,15</td>
<td>1,06</td>
</tr>
<tr>
<td>Serum Albumin (g/dl)</td>
<td>1,6</td>
<td>2,3</td>
<td>3,2</td>
<td>3,3</td>
<td>4</td>
<td>4,3</td>
<td>4,5</td>
<td>4,6</td>
</tr>
<tr>
<td>IgG4 (mg/dl)</td>
<td>895</td>
<td>161</td>
<td></td>
<td></td>
<td>234</td>
<td></td>
<td></td>
<td>63</td>
</tr>
</tbody>
</table>

- The patient was treated with a combination of prednisone and rituximab. The therapy led to the reduction of proteinuria (0.6 gr/24h) and the serum IgG4 to 60 mg/dl
- Negative PET-CT
- Now the patient is treated with Prednisone 5 mg/die
Thanks for attention

Duomo of Cerignola

Vieste

Basilica of Santa Croce

Seafront of Bari

Polignano a Mare