Session: Retroperitoneum – no man's land or everyone's land?

Case no: Case 5

Speaker: Dr Ayoma Attygalle, Royal Marsden Hospital, London, UK

## CLINICAL HISTORY

Male patient, born in 1942

2018: squamous cell carcinoma of the tongue, stage IVC treated with palliative chemotherapy (carboplatin,5FU, cetuximab, followed by cetuximab maintenance)

Arterial hypertension (treated)

October 2019: follow-up cervico-thoraco-abdominal CT :

- oncological disease: stable
- new right hydronephrosis, to be linked to a circumferential peri-arterial thickening (around right common iliac artery),
- **1st biopsy, 23.01.2020** (peri-iliac transvascular biopsy : non-diagnostic.

Preserved renal function, no hemodynamic consequences, no significant results on immunological work-up that was performed (details not provided), managed by surveillance with radiological follow-up

CT / PET-CT March 2020, September 2020, January 2021: partial regression of peri-iliac thickening, slow progression of peri-aortic thickening, with heterogeneous increase in metabolic activity.

Infrarenal peri-aortic thickening with extension into iliacs – strongly suggestive of IgG4-related disease (IgG4-RD)

**2nd biopsy, 18.02.2021** (needle core biopsies, SLIDE PROVIDED)

**Serum IgG4 levels :** November 2019: 2.22 g/L; March 2021: 3.32 g/L (normal range: 0.01-1.04 g/L)

## HISTOLOGY

The core biopsy displays keloid-type collagenous tissue and focal storiform fibrosis and an inflammatory infiltrate comprising small lymphocytes, plasma cells, histiocytes and a few eosinophils. A single inflamed venule is seen. The lymphocytes form nodular aggregates. There is no necrosis, suppuration, granulomas or features of a histiocytic disorder.

The lymphocytes comprise small CD3+ T-cells (predominantly CD4+), and CD20+ small B-cells. The plasma cells are polytypic for light chains and IgG+, with many IgG4+. The IgG4/IgG ratio is 45% with 20 IgG4 plasma cells per high power field.

Histological features, IgG4/IgG ratio and the number of IgG4 plasma cells/HPF are suggestive of IgG4-RD, but requires correlation with serum IgG4 levels, clinical and radiological findings for confirmation of diagnosis.

DIAGNOSIS: IgG4-RD

TREATMENT AND FOLLOW UP

Treatment: steroids (prednisone, 30mg/d for 2 weeks, 25mg/d for 2 weeks, 20mg/d for 2 weeks, then progressively tapering down to reach 5 mg/d after 3 months)

Follow-up CT: April 2021, July 2021, October 2021, April 2022: partial regression of the peri-arterial thickening and of the right hydronephrosis

Currently: maintenance 5mg/d prednisone

DISCUSSION

IgG4-RD is a fibroinflammatory disorder that may affect almost any organ, forming tumefactive lesions. It may mimic malignancy, infection and other immune mediated conditions. As IgG4-RD is steroid responsive, accurate diagnosis is key.

IgG4-RD mostly affects elderly males and predominantly involves extranodal sites, most commonly, the salivary and lacrimal glands, orbit, pancreas and retroperitoneum. Multiorgan involvement it typical.

Lymph nodes involvement is frequent, with axillary, mediastinal and intra-abdominal sites commonly affected.

Haematologic manifestations include eosinophilia and polyclonal hypergammaglobulinaemia.

Often raised, serum IgG4 levels may be normal in a proportion of cases. Serum IgE levels may be elevated but not IgA or IgM.

Pathogenesis: IgG-RD is associated with chronic antigen stimulation and breach of immune tolerance. The term IgG4-RD reflects increased IgG4 plasma cells in tissues with frequent elevation of serum IgG4 levels and not its pathogenic role. IgG4 antibody is 'non-inflammatory' –dampens inflammation rather than inducing it, and therefore the increase in IgG4+ plasma cells is an epiphenomenon. TFH cells drive the IgG4 class switch. The striking improvement with rituximab therapy is evidence for the role of B-cells in the disease. Circulating IgG4 and non-IgG4 plasmablasts are detected in IgG4-RD, and IgG4 plasmablast levels may be used as a biomarker of disease activity. CD4+ cytotoxic effector T-cells (CTL) play a crucial role, infiltrating tissues and interacting with activated cognate B-cells/plasmablasts that internalise and present antigen to the CTLs that drive fibrosis and inflammation.

Histology plays a key role in diagnosis. IgG4-RD is characterised by a dense lymphoplasmacytic infiltrate containing numerous IgG4 positive plasma cells, storiform fibrosis and obliterative phlebitis (better demonstrated by elastin). Mild to moderate eosinophilia may be observed. Needle core biopsies may not capture all features. Diagnostic IgG4+ plasma cell count varies depending on the site, with superficial sites that present earlier displaying higher counts compared with deep-seated sites of involvement which may be more fibrotic (e.g. skin>retroperitoneum). Regardless of the site,

the ratio of IgG4/IgG is >40%. Both absolute count/HPF and ratio are required for diagnosis. Increase in IgG4+ plasma cells is not specific. In lymph nodes, increased IgG4 plasma cells may be seen in other conditions such as multicentric Castleman disease and Rosai Dorfman disease. Due to low diagnostic specificity of histologic features in lymph nodes, involved extranodal sites may need to be biopsied for definitive diagnosis.

Diagnosis requires integration of clinical, serologic, radiologic and pathologic features. Due to lack of specificity, none of these should be used in isolation. Elevated serum IgG4 is not specific and no longer considered essential for diagnosis.

2020 Revised comprehensive diagnostic criteria (Umehara et al):

item 1] clinical and radiological features

[item 2] serological diagnosis: serum IgG4 levels >135mg/dl (cut off set to improve specificity)

[item 3] pathological diagnosis: Two of three criteria

i. Dense lymphocytic and plasma cell infiltration with fibrosis
ii. Ratio of IgG4/IgG >40% and the number of IgG4+ plasma cells >10/HPF
iii. Typical tissue fibrosis, particularly storiform fibrosis and/or obliterative phlebitis

(i) & (iii) without (ii), used only if immunostaining poor.

Diagnosis: Definite: 1+2+3; Probable: 1+3: Possible: 1+2

Organ specific criteria: Mizushima et al 2019: Diagnostic criteria specific for peri-arterial/retroperitoneal IgG4-RD allows for definite diagnosis without biopsy (if typical radiology, raised serum IgG4 and other involved organs), as access to a representative biopsy may not always possible, and without a raised serum IgG4 (if typical radiology and full-house histology with increase IgG4 plasma cells and IgG4/IgG plasma cell ratio >40%), as serum levels may be normal.

American College of Rheumatology (ACR)/European league against Rheumatism (EULAR) classification criteria (2019): Recognising potential pitfalls and the need for multidisciplinary input, these validated criteria should contribute to clinical trials and epidemiological investigations. They are not intended to be used in clinical practice for the basis of establishing a diagnosis. However, they provide a useful framework for clinicians considering the diagnosis of IgG4-RD in a patient.

It involves a 3-step process commencing with entry criteria (step 1) when the diagnosis is considered on clinical and radiological features or pathologic evidence of a lymphoplasmacytic infiltrate of the same organ, followed by exclusion of mimics of IgG4-RD, by exclusion criteria (clinical, radiological, pathologic & known diagnosis of certain diseases [e.g. multicentric Castleman disease]) tailored to the clinical scenario (step 2), before scoring on the basis of weighted inclusion criteria (step 3).

Biopsy is essential in most settings, for diagnosis and excluding mimickers. However, using these criteria, diagnosis may be made without biopsy, when it is straightforward on the basis of clinical, radiologic and serologic findings. Raised serum IgG4 is also not essential, reflecting normal levels in a proportion of IgG4-RD cases.

The pathologic exclusion criteria are:

- Cellular infiltrates suggesting malignancy that have not been sufficiently evaluated
- Markers consistent with inflammatory myofibroblastic tumour
- Prominent neutrophilic inflammation
- Necrotizing vasculitis
- Prominent necrosis
- Primarily granulomatous inflammation
- Macrophage/histiocytic disorder

TAKE HOME MESSAGES:

- IgG4-RD gives rise to site-specific symptoms that raise suspicion of malignancy.
- Biopsy is important for diagnosis and to exclude mimickers.
- Awareness of histologic features is key to prevent dismissal of biopsy as non-specific inflammation/fibrosis or non-diagnostic perilesional sampling.
- Needle core biopsies may not capture all diagnostic features.
- Diagnosis requires integration of clinical, radiologic, serologic and pathologic features.

REFERENCES


1. Matoo et al. Clonally expanded cytotoxic CD4 $^{+}$ T cells and the pathogenesis of IgG4-related disease. 2017.
2. Wallace at al. Plasmablasts as a biomarker for IgG4-related disease, independent of serum IgG4 concentrations. 2015.
3. Umehara et al. The 2020 revised comprehensive diagnostic (RCD) criteria for IgG4-RD. 2021.
4. Mizushima et al. Clinical and pathological characteristics of IgG4-related periaortitis /periarteritis and retroperitoneal fibrosis diagnosed based on Experts' diagnosis. 2019.
5. Wallace a al. IgG4-Related Disease: Clinical and Laboratory Features in One Hundred Twenty-Five Patients. 2015.

6. Wallace et al. The 2019 American College of Rheumatology/European League Against Rheumatism classification criteria for IgG4-related disease. 2020.