The performance of histological criteria for IgG4-related disease in clinical practice

Sirs,

IgG4-related disease (IgG4-RD) is a rare, slowly progressive, multi-organ disease characterised by mass fibroinflammatory lesions affecting various organs or body regions, with a heterogeneous clinical presentation. A high proportion of patients also have elevated serum IgG4 levels. Histological verification is a crucial part of the diagnostic work-up, with characteristic histopathological changes including dense lymphoplasmacytic infiltrate enriched with IgG4+ plasma cells, storiform fibrosis and obliterative phlebitis. The 2019 ACR/EULAR classification criteria define and score the histological characteristics of the disease (1). In addition to the diagnostic role, histology may also have a prognostic value in IgG4-RD. A recent study showed that a high number of IgG4+ plasma cells/high power field (HPF) (≥100 IgG4+ plasma cells/HPF) was associated with a proliferative disease phenotype, fewer relapses and higher remission rate during follow-up (2). However, considering the diagnosis, histology alone is insufficient for diagnosing IgG4-RD, as various conditions outside the spectrum of IgG4-RD can mimic its histopathological features (3). Similarly, we do not yet have a single highly sensitive and specific laboratory biomarker to distinguish IgG4-RD from mimickers (4). Diagnosis should therefore be based on a synthesis of typical clinical, imaging, laboratory and histological findings.

The aim of our cross-sectional study was to reassess, using the histological scoring system of the 2019 ACR/EULAR IgG4-RD classification criteria, biopsies evaluated at the Institute of Pathology, where pathologists had originally suggested the possibility of IgG4-RD.

Relevant biopsies were ascertained from the period between January 2012 and November 2024 by searching the electronic database of the Institute of Pathology, Medical Faculty Ljubljana, for pathology reports containing the key word 'IgG4'. The biopsy reports retrieved were re-evaluated, and, after excluding unsuspected or unrelated cases, the remaining biopsies were reassessed by an experienced pathologist (VJ). Biopsies were analysed and scored for the presence of dense lympho-plasmocytic infiltrate, storiform fibrosis and obliterative phlebitis, as well as immunohistochemically assessed to determine the number of IgG4+ plasma cells/HPF and the IgG4+ plasma cells/total IgG cell ratio. Finally, the referring specialist was contacted to confirm the final clinical diagnosis.

The key word search retrieved 364 biopsies from 297 patients over a 155-month period. A review of the reports showed that IgG4-RD was mentioned as a diagnostic possibility in 55 biopsies taken from 54 patients, of which 46 were deemed highly suggestive and 9 suspicious for IgG4-RD. Nine of the biopsies that were suspicious were so because of suboptimal sample size (*e.g.* needle biopsy; 5 samples), absence of dense lymphoplasmacytic infiltrate (2 samples), known malignancy (2 cases of peritoneal mesothelioma). All 55 biopsies were reassessed. The remaining 309 biopsies did not contain findings supporting a suspicion of IgG4-RD. Table I, panel A, reports the organs biopsied from the 55 reassessed biopsies. A dense lympho-plasmocytic infiltrate was found in 53/55 biopsies (96.4%), storiform fibrosis in 36/55 (65.4%) and obliterative phlebitis in 27/55 samples (49.1%). All three histological findings were present together in 23/55 biopsies (41.8%). Tissue eosinophils were observed in 26/55 biopsies (47.3%). More than 50 IgG4+ plasma cells/HPF were found in 41/55 (74.5%) biopsies and more than 100 IgG4+ plasma cells/HPF in 11/55 (20%) biopsies.

The IgG4+ plasma cells/IgG cell ratio was <41 in 8 biopsies (14.5%), 41–70 in 24 biopsies (43.6%) and >70 in 23 biopsies (41.8%).

The final clinical diagnoses of the patients are presented in Table IB. The clinical diagnosis was consistent with the histological diagnosis of IgG4-RD in 36 patients (66.7%). However, in 4 patients (7.4%), the final diagnosis was cancer, and in 2 cases, ANCA vasculitis was diagnosed.

IgG4-RD is a relatively new and unique disease entity. Its clinical presentation may mimic a variety of diseases, and elevated serum IgG4 levels (though typical) have a limited sensitivity and specificity as a sole diagnostic biomarker. Therefore, histopathological assessment of the affected organs/tissues is central for making of an appropriate diagnosis and for exclusion of other differential diagnostic possibilities.

Although the literature is dominated by reports of IgG4-RD mimicking another condition, *e.g.* malignancy or other inflammatory disease, the reverse possibility – clinical or even patohistological suspicion of IgG4-RD that turns out to be another disease should not be neglected. Histological or immunohistochemical features suggestive of IgG4-RD have already been described in some other diseases, *e.g.* haematological diseases such as Castleman's disease, Erdheim-Chester disease, ANCA associated vasculitis, Sjögren's disease (5-7). Our study further adds to the existing data and shows the importance of a proper correlation between clinical, laboratory and histopathological data.

In conclusion, in two-thirds of patients with histology supportive of IgG4-RD, clinicians ultimately confirmed the diagnosis. However, a significant proportion of patients received other diagnoses, including cancer. Therefore, careful clinicopathological correlation is needed to avoid overlooking other severe diseases that require distinct and, in some cases, rapid therapeutic interventions (*e.g.* malignancy, systemic vasculitis, infection).

Table I. A. Organ biopsied in histologically suggestive IgG4-RD; **B.** The final clinical diagnosis.

A		B	
Biopsied organ	Number of biopsies (55)	Clinical diagnosis	Number of patients (54)
Orbit	7	IgG4RD	36
Lacrimal gland	6	Descriptive diagnosis*	7
Salivary gland	6	Other/secondary RPF	3
ENT region	5	Malignancy	4
Aorta	3	ANCA vasculitis	2
Retroperitoneal tissue	7	VEXAS syndrome	1
Pleura / Peritoneum / Omentum	5	Cocaine induced ENT lesions	1
Pancreas	5		
Stomach	1		
Kidney	5		
Funiculus spermaticus	2		
Subcutaneous tissue	2		
Lymph node	1		

*2 cases of chronic pancreatitis, 2 cases of sclerosing peritonitis/mesenteritis; 1 case of orbital pseudotumour; 1 case of submandibular gland sialadenitis; 1 case of subglottic fibrosis; RPF retroperitoneal fibrosis; ENT ear nose throat;

A. Hočevar[1,2], *MD, PhD, Assoc. Prof.*
A. Grošelj[2,3], *MD, PhD, Assist. Prof.*
G. Hawlina[2,4], *MD, PhD, Assist. Prof.*
M. Koželj[5], *MD*
A. Škoberne[6], *MD, PhD, Assist. Prof.*
J. Pižem[7], *MD, PhD, Prof.*
V. Jurčić[7], *MD, PhD, Assist. Prof.*

[1]Department of Rheumatology, University Medical Centre Ljubljana, Slovenia;
[2]Faculty of Medicine, University of Ljubljana, Slovenia;
[3]Department of Otorhinolaryngology and Cervicofacial Surgery, University Medical Centre Ljubljana, Slovenia;
[4]Eye Hospital, University Medical Centre Ljubljana, Slovenia;
[5]Department of Gastroenterology, University Medical Centre Ljubljana, Slovenia;
[6]Department of Nephrology, University Medical Centre Ljubljana, Slovenia;
[7]Institute of Pathology, Faculty of Medicine, University of Ljubljana, Slovenia.

Letters to the Editors

Please address correspondence to:
Alojzija Hočevar
Department of Rheumatology,
University Medical Centre Ljubljana,
Vodnikova cesta 62,
1000 Ljubljana,
Slovenia.
E-mail: alojzija.hocevar@gmail.com

ORCID iD
A. Hočevar: 0000-0002-7361-6549
A. Grošelj: 0000-0002-1623-3197
G. Hawlina: 0000-0001-7057-5350
M. Koželj: 0000-0003-3232-7668
J. Pižem: 0000-0003-1207-2514
V. Jurčić: 0000-0003-1231-5600

Competing interests: none declared.

References

1. WALLACE ZS, NADEN RP, CHARI S, CHOI HK, DELLA-TORRE E, DICAIRE JF: The 2019 American College of Rheumatology/European League Against Rheumatism classification criteria for IgG4-related disease. *Ann Rheum Dis* 2020; 79(1): 77-87. https://doi.org/10.1136/annrheumdis-2019-216561
2. MARTÍN-NARES E, GUERRERO-CASTILLO J, ÁNGELES-ÁNGELES A, DELGADO-DE LA MORA J, MONTANTE-MONTES DE OCA D, HERNÁNDEZ-MOLINA G: Beyond diagnosis: exploring the significance of IgG4+ plasma cell count through immunostaining in IgG4-related disease. *Clin Exp Rheumatol* 2024; 42(9): 1842-45. https://doi.org/10.55563/clinexprheumatol/cniut0
3. DESHPANDE V, ZEN Y, CHAN JK *et al*.: Consensus statement on the pathology of IgG4-related disease. *Mod Pathol* 2012; 25(9): 1181-92. https://doi.org/10.1038/modpathol.2012.72
4. IACCARINO L, TALARICO R, BOZZALLA-CASSIONE E *et al*.: Blood biomarkers recommended for diagnosing and monitoring IgG4-related disease. Considerations from the ERN ReCONNET and collaborating partners. *Clin Exp Rheumatol* 2022; 40 Suppl 134(5): S71-80. https://doi.org/10.55563/clinexprheumatol/qq9qup
5. ZOSHIMA T, YAMADA K, HARA S *et al*.: Multicentric Castleman disease with tubulointerstitial nephritis mimicking IgG4-related disease: two case reports. *Am J Surg Pathol* 2016; 40(4): 495-501. https://doi.org/10.1097/pas.0000000000000575
6. KAUSHIK P, STONE JH, ANDERSON JT *et al*.: Medical mirroring: granulomatosis with polyangiitis (formerly Wegener's) mimicking immunoglobulin-G4 related disease. *Int J Rheum Dis* 2018; 21(4): 885-89. https://doi.org/10.1111/1756-185x.12687
7. KAWANO M, SUZUKI Y, YAMADA K *et al*.: Primary Sjögren's syndrome with chronic tubulointerstitial nephritis and lymphadenopathy mimicking IgG4-related disease. *Mod Rheumatol* 2015; 25(4): 637-41. https://doi.org/10.3109/14397595.2013.844303