IgG4-related disease: performance of classification and diagnostic criteria in a single-centre cohort of patients

Sirs,

The diagnosis of IgG4-related disease (IgG4-RD) is challenging because of its pleomorphic manifestations that can mimic a number of neoplastic or inflammatory disorders. Thus, panels of experts have developed diagnostic criteria (1) that have been updated, to take into account the low specificity of serum IgG4 levels and the difficulties inherent in performing and correctly staining biopsy samples (revised comprehensive diagnostic criteria - RCD) (2).

Recently, classification criteria have also been proposed to identify homogeneous patient populations with a high specificity and a reasonable sensitivity (ACR/EULAR criteria) (3).

We compared the performance of the two criteria sets in a single-centre cohort of patients with a suspected diagnosis of IgG4-RD.

Sixty-five subjects with elevated IgG4 level and/or a clinical presentation suggestive of IgG4-RD were recruited. Among these, 35 matched both RCD and classification criteria; 18 fulfilled only the RCD; 4 subjects met the classification criteria without fulfilling the diagnostic criteria, and 8 subjects did not meet either the RCD or classification criteria (Table I). The analysis of discordant cases sheds light on the performance of the two criteria sets in clinical practice.

Among the 18 patients who do not fulfil the classification criteria but still meet the diagnostic ones, the majority, 13, achieve a classification score <20 because of the presence of an extra-abdominal manifestation or the absence of an informative biopsy. Della Torre *et al*. (5) similarly underlined the role of atypical clinical presentations and/or the lack of informative histology in achieving a low score in ACR/EULAR. In our cohort, patients with neurological involvement are less likely to satisfy the classification criteria because only orbits and pachymeninges are part of the inclusion criteria, thus excluding patients with hypophysitis. Moreover, in patients with neurological involvement the affected tissue very often cannot be biopsied, thus limiting the possibility to reach the score for classification. In conclusion, the ACR/EULAR criteria show low sensitivity in detecting patients with extra-abdominal involvement and especially those with neurological manifestations.

The four patients that meet the ACR/EULAR but not the RCD criteria do not fulfill the serologic or histopathological criteria but only the clinical/radiological ones, which out of the 3 items has the lowest specificity, being positive for any tumefactive lesion in any organ involved in IgG4-RD. Elevated serum IgG4 concentration has a specificity of 60%. On the contrary, the histopathological criteria are very specific and are met only if the unique and characteristic features of IgG4-RD are present, such as storiform fibrosis and high IgG4/IgG ratio.

Among *double negative* patients, IgG4-RD was suspected mostly on clinical or radiologic data but pathologic, radiologic and/or serologic evidence did not support the diagnosis. However, in 6 out of 8 patients the diagnosis of IgG4-RD cannot be ruled out.

The comparison of the two sets of criteria shows a concordance of 66% with a Cohen's kappa coefficient of 0.225, similar to what has been previously reported (6).

On the whole, the RCD criteria show good sensitivity and specificity, but are less likely to be fulfilled in retrospective studies, because the specific immunostaining was introduced only a few years ago. On the other hand, patients with neurological manifestations, who cannot be biopsied and may show a low serum IgG4 concentration, are unlikely to satisfy the diagnostic criteria.

In conclusion, both diagnostic and classification criteria should be used in patients under evaluation for a suspected IgG4-RD, as they provide different information and serve different purposes. Particular attention must be paid to those who show non-abdominal manifestations and, when possible and safe, a biopsy should be always performed with appropriate immunostaining.

Table I. Comparison of the two criteria sets in patients with a suspected diagnosis of IgG4-RD.

	RCD+ ACR/EULAR+	RCD+ ACR/EULAR-	RCD- ACR/EULAR+	RCD- ACR/EULAR-
Number	35	18	4	8
Informative biopsy/immunostaining[1]	19	5	4	0
Normal serum IgG4 concentration	1	2	3	2
2–5× upper limit of normal serum IgG4 concentration	16	13	0	5
≥5× upper limit of normal serum IgG4 concentration	18	3	1	1
Pancreas	15	1	1	1
Biliary tree	6	0	0	0
Retroperitoneum[2]	15	3	4	1
Head and neck involvement[3]	9	3	2	0
Neurological Involvement[4]	5	9	3	4
Chest[5]	4	3	3	0
Kidney	4	1	1	0

[1] Presence of any typical pathological evidence (dense lymphocytic infiltrate, obliterative phlebitis and storiform fibrosis) or distinctive immunostaining (IgG4+:IgG+ ratio ≥41% and/or number of IgG4+ cells/hpf ≥10).
[2] Retroperitoneal fibrosis, mesenteritis, thickening of the abdominal aortic wall, soft tissue around the infrarenal aorta/iliac arteries or arteritis in the same tracts.
[3] Salivary glands, lacrimal glands, paranasal sinuses and thyroid.
[4] Orbit involvement, pachymeninges or hypophysitis.
[5] Peribronchovascular and septal thickening.

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