Plasma cell IgG4 positivity in orbital biopsies of non-IgG4-related conditions

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Abstract:
The IgG4-related disease (IgG4-RD) is a systemic condition defined as a fibro-inflammatory disorder, characterized by the occurrence of tumor-like lesions in multiple organs including the eye adnexa. The main diagnostic criterion is based on histopathological findings, especially on the IgG4+/IgG+ plasma cell ratio. In this article, we reviewed the literature of non-IgG4-RD orbital conditions with IgG4 positivity. There were 20 reports of inflammatory non-IgG4-RD orbital lesions and 14 reports of orbital lymphoid proliferations with significant IgG4 positivity. The role of plasma cells IgG4 in the pathogenesis of non-IgG4-RD is not clear. Considering the large spectrum of diseases caused by a variety of different etiopathogenic mechanisms, we think that the common denominator of IgG4+ in these conditions might be related to the peculiar properties of down regulation of immune response of the IgG4 and not to a specific link to IgG4-RD.

Keywords: IgG4, IgG4-related disease, IgG4/IgG ratio, orbit, RosaiDorfman disease

INTRODUCTION

Since 2001 when Hamano reported that several cases of sclerosing pancreatitis were associated with high levels of serum IgG4,[1] the concept of IgG4-related disease (IgG4-RD) emerged as a new systemic condition.[2] IgG4-RD is defined as a fibro-inflammatory disorder characterized by the occurrence of tumor-like lesions in multiple organs including the eye adnexa.[3,4] As elevated serum IgG4 levels can be found in a variety of diseases,[5] the main criterion for the diagnosis of IgG4-RD is the histopathological findings. Dense lymphoplasmacytic infiltrate, IgG4+/IgG+ plasma cell ratio >40%, the number of plasma cells per high-power field, storiform fibrosis, and obliterator phlebitis are the main parameters for IgG4-RD diagnosis.[3] In the eye, adnexa storiform fibrosis and phlebitis are not usually present,[3] and the IgG4+/IgG+ plasma cell ratio >40% is the gold standard for the diagnosis of IgG4-RD.[2] However, even this criterion is not specific for IgG4-RD because biopsies from a variety of non-IgG4-RD entities may display high plasma cell ratios of IgG4+/IgG+.[8,9]

The purpose of the present article is to review the literature of non-IgG4-RD orbital conditions with IgG4 positivity.

METHODS

The authors searched the Medline, Lilac, Scopus, and Embase databases for all articles in English, Spanish, and French that used the terms “IgG4” or “IgG4-RD” AND “orbit” and “IgG4-RD” AND “orbit” AND “lymphoma or lymphoid proliferation.” The only exclusion criterion was the lack of description of the IgG4 positivity and absence of orbital biopsy. The data retrieved included the number of patients biopsied, type of disease, sex, age, imaging of the orbital lesions, and criteria employed to the diagnosis of IgG4 positivity.

RESULTS

The literature review disclosed 20 reports (37 patients) of inflammatory non-IgG4-RD orbital lesions with significant IgG4 positivity.
Table 1: Case reports of biopsy-proven immunoglobulin G4 positivity in non-immunoglobulin 4-related disease orbital inflammatory conditions

| Author/year          | Condition     | Sex  | Age (years) | Orbital imaging/findings                        | IgG4 positivity | Number of IgG4+ cells per hpf | IgG4+/IgG+ plasma cell ratio (%) |
|----------------------|---------------|------|-------------|-------------------------------------------------|-----------------|-------------------------------|----------------------------------|
| Singh et al. 2010    | NXG           | Male | 67          | MRI/inferolateral mass                          |                | 119                           | 55                               |
|                      | NXG           | Female | 62       | NS                                               |                | 152                           | 5                                |
|                      | AXG           | Male  | 36          | NS                                               |                | 55                            | 80                               |
| Mudhar et al. 2011   | AXG           | Male  | 70          | MRI/lateral mass                                |                | NS                            | 80                               |
| Heathcote et al. 2013| Crystal-storing histiocytosis | Male | 69        | CT/diffuse bilateral infiltration                | >100            | NS                            | NS                               |
| Mudhar and Duke 2013 | RDD           | Male  | 9           | None                                            |                | NS                            | >50%                             |
| Chang et al. 2013    | GPA           | NS    | NS          | NS                                              |                | 30                            | 53                               |
|                      | AXG           | Male  | 44          | NS                                              |                | NS                            | 89                               |
|                      | AXG           | Female | 81       | NS                                              |                | 53                            | 81                               |
|                      | AXG           | Male  | 33          | NS                                              |                | 69                            | 83                               |
|                      | AXG           | Female | 44       | NS                                              |                | 139                           | 82                               |
| Verdjik et al. 2014  | NXG           | Male  | 38          | CT/bilateral periocular infiltration+left superior rectus enlargement |                | NS                            | 50                               |
|                      | NXG           | Female | 44       | NS                                              |                | NS                            | 42                               |
|                      | NXG           | Female | 81       | NS                                              |                | NS                            | 89                               |
|                      | NXG           | Male  | 33          | NS                                              |                | NS                            | 82                               |
|                      | AXG           | Female | 44       | NS                                              |                | NS                            | 62                               |
|                      | AXG           | Female | 58       | NS                                              |                | NS                            | 98                               |
|                      | AXG           | Female | 70       | NS                                              |                | NS                            | 68                               |
|                      | AXG           | Female | 63       | NS                                              |                | 139                           | 82                               |
|                      | AXG           | Male  | 41          | NS                                              |                | NS                            | 93                               |
| Kubota et al. 2014   | AXG           | Male  | 38          | CT/bilateral periocular infiltration+left superior rectus enlargement |                | NS                            | 50                               |
|                      | AXG           | Female | 33       | NS                                              |                | >100                          | >50%                             |
| Li et al. 2014       | KD            | Male  | 47          | MRI/enlargement of the left LG                   |                | 30                            | NS                               |
|                      | AXG           | Male  | 65          | MRI/anterior orbital infiltration, LG enlargement |                | 40                            | >50%                             |
|                      | AXG           | Male  | 52          | LG enlargement OU and lateral rectus hypertrophy | >100            | >100                          | >50%                             |
|                      | AXG           | Female | 33       | Enlargement of LGs                              | NS              | >100                          | >50%                             |
| Alexandraki et al. 2016 | GPA       | Female | 38       | MRI/right LG and lateral rectus enlargement     |                | NS                            | >50%                             |
|                      | GPA           | Female | 56       | MRI/left LG enlargement                          |                | NS                            | >40%                             |
|                      | GPA           | Male  | 53          | CT/orbital tumor                                 |                | 90                            | 45                               |
|                      | GPA           | Male  | 73          | MRI/orbital mass                                 |                | 133                           | 70                               |
|                      | GPA           | Female | 50       | CT/bilateral dacryo adenitis                     |                | 78                            | 40                               |
| Honda et al. 2017    | AXG           | Female | 47       | MRI/LGs and eyelids                              |                | 37                            | 67                               |
| Kashani et al. 2017  | GO            | Female | 47       | MRI/levator palpebrae superioris enlargement    | NS              | 96                            | 60                               |
| Jones et al. 2017    | AXG           | Female | 58       | CT/MRI bilateral EOM enlargement and enhancement of the right optic nerve sheath |                | 96                            | 60                               |
| McKelvie et al. 2017 | NXG           | Male  | 36          | CT/infiltration of the upper eyelids and anterior orbits |                | 70                            | 58                               |
| Danlos et al. 2017   | GAPA/EGPA     | NS    | NS          | MRI/lateral, superior, and medial infiltration  | NS              | NS                            | >40%                             |
| Lee et al. 2018      | GAPA/EGPA     | NS    | NS          | NS                                              | NS              | >10                           | NS                               |
| Andron et al. 2020   | AXG           | Male  | 64          | Mass in the right LG                             | NS              | >80                           | >40%                             |
| Iyengar et al. 2020  | RDD           | Male  | 17          | MRI/infiltration of the left orbit               |                 | >50                           | >40%                             |

Total number of cases=37, mean age=51.6 years (SD=16.9), male/female ratio=1.4. IgG: Immunoglobulin G, RD: Related disease, SD: Standard deviation, NXG: Necrobiotic xantogranuloma, AXG: Adult-onset xantogranuloma, RDD: RosaiDorfman disease, GPA: Granulomatosis with polyangiitis or Wegener’s disease, KD: Kimura disease, GO: Grave’s orbitopathy, NS: Not specified, MRI: Magnetic resonance imaging, CT: Computed tomography, LG: Lacrimal Gland, EOM: Extraocular Muscle, OU: "both eyes" (oculus uterque), hpf: High-power field.
and 14 reports (108 patients) of IgG4 positivity in orbital lymphoid proliferations. As shown in Table 1, plasma cells IgG4+ satisfying the criterion established for the diagnosis of IgG4-RD are found in a large spectrum of non-IgG4-RD conditions affecting the orbit including xanthogranulomas (adult-onset or adult-onset xanthogranuloma, \(n = 14\)), C-anti-neutrophil cytoplasmic antibody vasculitis (\(n = 11\)), Kimura disease (\(n = 2\)), and Rosai-Dorfman disease (RDD) (\(n = 2\)). Table 2 shows that out of the 108 patients with lymphoid proliferation, IgG4 positivity was found mainly in the extranodal marginal zone or MALT lymphomas (ENMZL) (89/82% patients).

### Discussion

Since the discovery of the IgG4-RD in 2001, this intriguing condition has been extensively reported in the literature. A quick search in the PubMed database disclosed that the term IgG4-RD appears in the title of 1190 articles.

Table 2: Reports of biopsy-proven immunoglobulin G4 positivity in orbital lymphoid proliferations

| Author/year          | Type of study | Condition | Sex  | Age (years) | Orbital imaging/ findings | IgG4 positivity |
|----------------------|---------------|-----------|------|-------------|---------------------------|----------------|
| Cheuk et al. 2008    | Case reports  | FL        | Female | 69          | NS/right LG mass          | -              | 68             |
|                      |               | ENMZL     | Male  | 69          | CT/diffuse orbital mass   | -              | 94             |
|                      |               | ENMZL     | Male  | 60          | CT/infiltrative orbital   | -              | 91             |
|                      |               | ENMZL     | Male  | 69          | CT/right orbital mass     | 703             | 53             |
|                      |               | ENMZL     | Male  | 72          | NS/right orbital mass     | 691             | 83             |
|                      |               | ENMZL     | Female| 55          | NS/right orbital mass     | 1408            | 209            |
| Kubota et al. 2010   | Case reports  | RLH       | Female| 63          | CT/LG lesion              | -              | 43             |
|                      |               | RLH       | Male  | 62          | CT/LG lesion              | -              | 82             |
| Kubota et al. 2010   | Case series   | ENMZL     |       |             |                           | -              | 43–100         |
| Matsuo et al. 2010   | Case reports  | Benign lymphoid lesion | Male | 60 | LG | - | 82 |
|                     |               |           | Female | 48 |     | -| 90/83 |
|                     |               |           | Female | 32 |     | -| 55 |
|                     |               |           | Female | 60 |     | -| 90/92 |
| Sato et al. 2012     | Case report   | ENMZL     | Male  | 55          | MRI/right LG + superior   | -              | 63             |
| Karamchandani et al. | Case reports  | ENMZL     | Male  | 37          | NS/LG                     | -              | >90            |
|                     |               | ENMZL     | Female| 72          | MIR/Mass in orbital        | -              | 75             |
|                     |               |           | Female | 43 |     |    | Almost 100 |
|                      |               |           | Male  | 60          | CT/bilateral LG enlargement| -              | >90             |
| Mulay and Aggarwal   | Case report   | ENMZL     | Female| 65          | CT: MRI/EOM, and optic nerve sheath | - | >90  |
| Lee et al. 2015      | Case series   | ENMZL     | 5 of 50 patients | >50 | >40 |
| Oleš et al. 2015     | Case series   | ENMZL     | 10 out of 19 patients | - | >40 |
| Ohno et al. 2015     | Case series   | ENMZL     | 5 out of 17 patients | >100 | >40 |
| Peng et al. 2020     | Case report   | Diffuse large B-cell | Male | 44 | MRI/large superior/medial right orbit infiltration | 140 | NS |
| Sohn et al. 2018     | Case series   | ENMZL     | 13 of 30 patients with ENMZL | 19.21 | NS |
| Li et al. 2020       | Case series   | ENMZL     | 37 of 121 patients with ENMZL | - | >40 |
| Liu et al. 2021      | Case series   | ENMZL     | 9 of 39 patients with lacrimal lymphoma | >10 | >30 |

Total number of cases=108, mean age=57.2 (SD=11.7) male/female ratio=1.2. FL: Follicular lymphoma, ENMZL: Extranodal marginal zone lymphoma, RLH: Reactive lymphoid hyperplasia, SD: Standard deviation, NS: Not specified, hpf: High-power field, IgG: Immunoglobulin G, MRI: Magnetic resonance imaging, CT: Computed tomography, LG: Lacrimal Gland, OU: “both eyes” (culus uterque), EOM: Extraocular Muscle
interest in the IgG4-RD spurred the pathologists to stain several types of inflammatory and lymphoid orbital lesions for IgG4 positivity. As a result of this widespread screening, the occurrence of a significant number of plasma cells secreting IgG4 has been documented in different conditions with mechanisms as varied as neutrophils activation (vasculitis), monoclonal proliferation (lymphomas), autoantibodies activation (Grave’s orbitopathy), and polyclonal histiocytosis proliferation (xanthogranulomas etc.). The role of these plasma cells IgG4+ in the pathogenesis of non-IgG4-diseases is not clear. The speculations are divided between a concomitance of IgG4-RD with different diseases, an epiphenomenon of other immunologic diseases or a causal relationship. Most authors that reported lymphoproliferative cases discussed the possibility that IgG4 presence is the basis for a further malignant lesion development, whereas the authors that commented on the inflammatory conditions attributed those concurrent findings to a possible common immune disorder. Although we are not in a position to clarify this controversy, we believe that the immunobiology of the IgG4 suggests that the epiphenomenon might be a plausible explanation for the IgG4 positivity of some non-IgG4-RD diseases.

IgG4 is the least abundant class of IgG antibodies making up only 5% of the total IgG. This antibody does not activate the classical complement pathway and might also inhibit the binding of C1q to IgG1 avoiding the complement cascade, it is thus considered to be anti-inflammatory. On a molecular basis, inter-heavy chains of IgG4 are structurally more unstable and may change to intra-heavy chains. This shift can cause the dissociation into two half molecules, each one with a heavy and a light chain. Different half molecules unify to form an IgG4 with two different antigen-binding sites, a process that is known as “Fab-arm exchange” and explains its inability to form large immune complexes, which are fundamental to antigen removal by the humoral immune defense.

IgG4 production is increased after long standing or strong antigen stimulation when it can have a protective function as an anti-inflammatory antibody. A typical protective property of IgG4 is its effect against IgE in a variety of allergic conditions. In these cases, the increase in the IgG4 levels is an indication of tolerance development. Even when IgG4 is implicated in some autoimmune diseases such as glomerulonephritis, pempigus Vulgaris, thrombotic thrombocytopenic purpura, and muscle-specific kinase in myasthenia gravis, the pathogenic mechanism of IgG4 is to block protein interaction instead of provoking inflammatory injury.

The association of IgG4 with the poor prognosis in different types of cancers is also attributed to its anti-inflammatory action promoting a detrimental increase in tolerance to the malignant cells. Instead of destroying tumor cells, IgG4 inhibits the response of the immune system against the malignant cells and favor the tumor cells to evade immune surveillance. As shown in Table 1, polyclonal plasma cells IgG4+ are also present in RDD. This peculiar form of histiocytosis, characterized by histiocytic cells S100+, CD68+, and CD1a+ often displaying emperiploisis, has been classified in the latest version of Histiocyte Society as part of the R Group. Although RDD is not considered a neoplastic disorder, some papers have shown point mutations in the mitogen-activated protein kinase/extracellular signal-regulated kinase pathway suggesting that at least a subset of the RDD diseases have a clonal origin. In any case, the clinical significance of IgG4+ in RDD is not clear.

Considering the large spectrum of diseases caused by a variety of different etiopathogenic mechanisms, we think that the common denominator of IgG4+ in these conditions might be related to the peculiar properties of down regulation of immune response of the IgG4 and not to a specific link to IgG4-RD.

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**Conflicts of interest**

There are no conflicts of interest.

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