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,[5,6] 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 obliterative 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.[7] 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

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Table 1: Case reports of biopsy-proven immunoglobulin G4 positivity in nonimmunoglobulin 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[10]	NXG	Male	67	MRI/inferolateral mass	119	55
	NXG	Female	62	NS	152	5
	AXG	Male	36	NS	55	80
Mudhar *et al*./2011[11]	AXG	Male	70	MRI/lateral mass	NS	80
Heathcote *et al*./2013[12]	Crystal-storing histiocytosis	Male	69	CT/diffuse bilateral infiltration	>100	NS
Mudhar and Duke/2013[13]	RDD	Male	9	None	NS	>50%
Chang *et al*./2013[15]	GPA	NS	NS	NS	24	53
	GPA	NS	NS	NS	53	81
	GPA	NS	NS	NS	69	83
	GPA	NS	NS	NS	139	82
Verdjik *et al*./2014[14]	NXG	Male	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	NS	77
	AXG	Male	41	NS	NS	93
Kubota *et al*./2014[16]	AXG	Male	38	CT/bilateral periocular infiltration+left superior rectus enlargement	NS	50
Li *et al*./2014[17]	KD	Male	47	MRI/enlargement of the left LG	30	NS
London *et al*./2015[18]	AXG	Male	65	MRI/anterior orbital infiltration, LG enlargement	40	>50
	AXG	Male	52	LG enlargement OU and lateral rectus hypertrophy	>100	>50
	AXG	Female	33	Enlargement of LGs	>100	>50
Alexandraki *et al*./2016[19]	GPA	Female	38	MRI/right LG and lateral rectus enlargement	NS	>50
Della-Torre *et al*./2016[20]	GPA	Female	56	MRI/left LG enlargement	NS	>40
Karim *et al*./2017[21]	GPA	Male	53	CT/orbital tumor	90	45
	GPA	Male	73	MRI/orbital mass	133	70
	GPA	Female	50	CT/bilateral dacryoadenitis	78	40
Honda *et al*./2017[22]	AXG	Female	47	MRI/LGs and eyelids	NS	80
Kashani *et al*./2017[23]	GO	Female	78	MRI/levator palpebrae superioris enlargement	37	67
Jones *et al*./2017[24]	AXG	Female	58	CT/MRI bilateral EOM enlargement and enhancement of the right optic nerve sheath	96	60
McKelvie *et al*./2017[25]	NXG	Male	36	CT/infiltration of the upper eyelids and anterior orbits	70	58
Danlos *et al*./2017[26]	GPA/EGPA	NS	NS	MRI/lateral, superior, and medial infiltration	NS	>40
	GPA/EGPA	NS	NS	NS	>10	NS
Lee *et al*./2018[27]	Kimura	Male	30	CT/Inferolateral mass	>80	>40
Andron *et al*./2020[28]	AXG	Male	64	Mass in the right LG	NS	80
Iyengar *et al*./2020[29]	RDD	Male	17	MRI/infiltration of the left orbit	>50	>40
				Left maxillary sinus, pterygopalatine fossa, infratemporal fossa, and surrounding soft tissues		

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 polyangeiitis 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

positivity[10-29] and 14 reports (108 patients) of IgG4 positivity in orbital lymphoid proliferations.[30-43] 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 xantogranuloma, *n* = 14 and necrobiotic or necrobiotic xantogranuloma, *n* = 6), C-anti-neutrophil cytoplasmic antibody vasculitis (*n* = 11), Kimura disease (*n* = 2), and RosaiDorfman 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,[1] 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. The

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	
						Number of IgG4+cells per hpf	IgG4 +/IgG+plasma cell ratio (%)
Cheuk *et al*./2008[30]	Case reports	FL	Female	69	NS/right LG mass	-	68
		ENMZL	Male	69	CT/diffuse orbital infiltration OU	-	94
		ENMZL with large cell transformation	Male	60	CT/infiltrative orbital masses OU	-	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*./2010b[31]	Case reports	RLH	Female	63	CT/LG lesion	-	43
		RLH	Female	49	CT/LG lesion	-	93
		RLH	Male	62	CT/LG lesion	-	82
Kubota *et al*./2010[32]	Case series	ENMZL	of 114 patients with ENML 9 had IgG4 positivity			-	43–100
Matsuo *et al*./2010[33]	Case reports	Benign lymphoid lesion	Male	60	LG	-	82
			Male	48		-	90/83
			Female	32		-	55
			Female	60		-	90/92
Sato *et al*./2012[35]	Case report	ENMZL	Male	55	MRI/right LG + superior complex	-	63
Karamchandani *et al*./2012[34]	Case reports	ENMZL	Male	37	NS/LG	-	>90
		ENMZL	Female	72	MRI/Mass in orbital periphery OU	-	75
		RLH	Female	43	NS/infiltration EOM, LG, preseptal tissues OU	-	Almost 100
		RLH	Male	60	CT, MRI/EOM, and optic nerve sheath		>90
Mulay and Aggarwal/2014[36]	Case report	ENMZL	Female	65	CT/bilateral LG enlargement	-	60/75
Lee *et al*./2015[37]	Case series	ENMZL	5 of 50 patients			>50	>40
Oleś *et al*./2015[44]	Case series	ENMZL	10 out of 19 patients			-	>40
Ohno *et al*./2015[43]	Case series	ENMZL	5 out of 17 patients			>100	>40
Peng *et al*./2020[41]	Case report	Diffuse large B-cell	Male	44	MRI/large superior/medial right orbit infiltration	140	NS
Sohn *et al*./2018[39]	Case series	ENMZL	13 of 30 patients with ENMZL			19.21	NS
Li *et al*./2020[40]	Case series	ENMZL	37 of 121 patients with ENMZL			-	>40
Liu *et al*./2021[42]	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"(oculus 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 histiocytes 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,[11] an epiphenomenon of other immunologic diseases[17] 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[45,46] 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.[47,48] 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.[45] Even when IgG4 is implicated in some autoimmune diseases such as glomerulonephritis, pemphigus 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.[49]

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.[50] 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.[51]

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 emperipolesis, has been classified in the latest version of Histiocyte Society as part of the R Group.[52] 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.[53] 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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