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A Subset Of Rosai-Dorfman Disease Cases Exhibit Increased IgG4 Positive Plasma Cells: Another Red Herring or a True Association With IgG4 Related Disease?

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Sir

Sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease) is a disease of unknown etiology caused by a proliferation of non-clonal S100 positive histiocytes. It occurs predominantly in the young (median age, 20) presenting either in lymph nodes or extranodal sites. Several observations about increased IgG4 positive cells in Rosai-Dorfman (RD) disease have been made previously, either through case reports or smaller case series restricted to certain anatomic sites ^{1–10}. Shrestha et al. demonstrated increased IgG4 positive cells in six out of eight RD disease cases involving both nodal and extranodal sites ⁹. The IgG4/IgG ratio ranged from 10% to 70% ⁹. Kuo et al observed varying degrees of increased IgG4 positive cells in 12 cases of cutaneous RD disease ⁸. 10/12 cases had >50/hpf IgG4 positive cells with a range of 55–204. However, the IgG4/IgG ratio was >40% in only 3/12 cases ⁸. Elevated levels of serum IgG4 were detected in one of two cases tested ⁸. In a study of 26 specimens from 15 patients Zhang et al. found more than 10 IgG4 positive plasma cells/hpf in 73.1% of specimens analyzed ¹⁰. 30.8% of lesions demonstrated more than 40% of IgG4 positive cells as a subset of IgG positive cells ¹⁰.

We undertook a study of IgG4 positivity in 70 patients with RD disease in order to more fully assess clinical correlates. The analysis of a larger cohort of cases gave us the ability to investigate potential differences in age, sex or anatomical location (nodal versus extranodal) in IgG4 positive versus IgG4 negative cases. We followed the recently published consensus guidelines for quantitative assessment of IgG4 immunostains for IgG4 related disease ¹¹. The numbers of IgG4 and IgG positive cells were obtained after averaging three high power fields (40×/0.65) with the highest density. Statistical analysis was performed using GraphPad Prism version 6 for Windows (La Jolla, California) and included Student's T test for significance of difference in means and Mann-Whitney U test for significance of difference in medians.

We studied 40 cases from consultation files of the authors' institution between 2005 and 2013. An additional 30 cases (15 nodal, 15 extranodal) were obtained from the RD registry ¹². Previously, an association between RD disease and autoimmune lymphoproliferative syndrome was reported by our group ¹³. However, those cases were not included for analysis in this study. The median age of the cohort was 39 yrs. with an age

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range from 0.5 to 82 yrs. Overall, 40% of cases (28/70) demonstrated elevated IgG4 positive cells to varying extents (Table 1). However, 17.4 % (12/70) had more than 40% IgG4/IgG positive cells (an absolute requirement according to the consensus guidelines for a histologic diagnosis of IgG4 related disease). All but one of these cases (11/12) satisfied the consensus guidelines organ dependent threshold for absolute IgG4 positive cells/hpf in order to fit either of the two recommended diagnostic terminologies i.e. 1) histologically highly suggestive of IgG4 related disease or 2) probable histologic features of IgG4-related disease. Case 12 (Subcutis mass) had 166 IgG4 positive cells/hpf which is below the threshold of 200 IgG4 positive cells/hpf, the recommended numerical cutoff for skin ¹¹.

Our observations provide some novel insights. In the 12 cases with >40% IgG4/IgG positive cells, there was a male predominance (9 males and 3 females, M: F of 3:1) (Table 1). The median age for the 12 cases with >40% IgG4/IgG positive cells (55 yrs) as well as for all IgG4 positive cases (54 yrs) was significantly higher than the IgG4 negative cases (27 yrs) (Table 2). In addition, the mean age was also significantly different (Table 2). However, there were no major differences in the anatomical distribution (extranodal vs. nodal) or sex (male or female) between the IgG4 negative (21 males, 21 females, 19 nodal, 23 extranodal) and all IgG4 positive cases (15 males, 13 females, 16 nodal, 13 extranodal).

Even using the strict criteria based on the consensus guidelines ¹¹, the levels of IgG4 positive cells in RD disease are comparable to the levels seen in IgG4 related disease. However, the significance of these findings is unclear. It is certainly possible that these cases lie within the spectrum of IgG4 related disease and merely demonstrate morphologic RD disease- like features. However, we lack data related to serum IgG4 levels or clinical follow up to confirm this theory. Nevertheless, this subset does exhibit some unique features and while typically only a small percentage of RD cases demonstrate complete response to steroids ¹⁴, it is tempting to speculate that the IgG4 positive subset represents a more steroid responsive group akin to IgG4 related disease. On the other hand, increased IgG4 positive plasma cells have been reported in a myriad of disorders, apart from IgG4 related disease, including both inflammatory conditions and lymphomas, in particular marginal zone lymphomas ^{3, 11, 15}. Hence, one cannot completely discount the possibility that the presence of increased IgG4 positive cells in these cases is coincidental and does not necessarily typify IgG4 related disease.

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Figure 1.

Case 2 (A & B), lymph node with RD disease showing SHML (sinus histiocytosis with massive lymphadenopathy) cells with emperipolesis and surrounding marked plasmacytosis; IgG4 positive cells (C) are increased in absolute count as well as percentage of IgG positive plasma cells (D). Case 3, Inferior nasal mass with RD disease showing respiratory epithelium (E) with underlying SHML cell proliferation and high power (F) demonstrates SHML cells with surrounding plasmacytosis; IgG4 positive cells (G) are increased in absolute count as well as percentage of IgG positive plasma cells (H). IgG4 stains were performed on formalin-fixed paraffin-embedded tissue sections with a mouse monoclonal antibody directed against IgG4 (Invitrogen, CA, clone HP6025). Dako Envision+ System-HRP labelled anti-mouse and 3,3'-diaminobenzidine (DAB)+chromogen (K4011) were used for detection.

TABLE 1

Cases of Rosai Dorfman disease positive for IgG4

#	Site	Age	Sex	IgG/hpf	IgG4/hpf	IgG4/IgG%
1	Perihilar/renal mass	52	m	228	223	97%
2	Lymph node, nos ***	66	m	380	320	84%
3	Lymph node, axilla ***	66	m	160	130	81%
4	Lymph node, axilla	81	m	437	350	80%
	Salivary gland			227	100	44%
5	Mesenteric mass	52	m	106	84	79%
6	Lymph node, axilla	78	f	220	160	72%
7	Nostril/inferior nasal mass	unknown	f	257	157	61%
8	LN, cervical	27	m	370	180	48%
9	Dural lesion	55	f	180	86	47%
10	Lymph node, axilla	71	m	220	97	44%
11	Lymph node, axilla	53	m	434	185	42%
12	Subcutis, flank	46	m	396	166	41%
13	Soft tissue, gluteus	58	m	266	88	33%
14	Lymph node, nos	35	m	343	107	31%
15	Lymph node, axilla	54	f	456	133	29%
16	Dural lesion	65	f	193	47	24%
17	Breast mass	39	f	152	36	24%
18	Nasal mass	59	f	273	64	23%
19	LN, mesenteric	82	f	237	52	22%
20	Breast mass	38	f	178	38	21%
21	Lymph node, cervical	5	f	287	55	19%
22	Lymph node, axilla	49	f	83	15	18%
23	Lymph node, cervical	3	m	267	38	14%
24	Lymph node, axilla	20	m	303	41	13%
25	Lymph node, cervical	71	f	143	16	11%

*	Site	Age	Sex	IgG/hpf	IgG4/hpf	IgG4/IgG%
26	Lymph node, nos	65	m	133	13	10%
27	Arm mass	56	m	283	15	5%
28	CNS frontal lobe mass	11	f	204	10	5%

* Shaded region of the table represents cases with >40% IgG4/IgG positive cells

** Case 4 had lymph node as well as salivary gland biopsies

Abbreviations: LN, lymph node; nos, not otherwise specified; CNS, central nervous system

TABLE 2

Median and Mean age of IgG4 negative, IgG4 positive (>40% IgG4/IgG positive) and IgG4 positive (all cases) groups.

	IgG4 negative group	IgG4 positive group (>40% IgG4/IgG)	IgG4 positive group
Median age (yrs)	27	55 (p=0.0003)	54 (p=0.0009)
Mean ($\pm$SEM) (yrs)	30.8 $\pm$ 3.4	58.5 $\pm$ 4.7 (p=0.0003)	50.2 $\pm$ 4.2 (p=0.0007)

P values represent significance of difference in medians and means as compared to the IgG4 negative group