

IgG4-positive plasma cells in cutaneous Rosai-Dorfman disease: an additional immunohistochemical feature and possible relationship to IgG4-related sclerosing disease

Background: Cutaneous Rosai-Dorfman disease (CRDD) shares the histopathological features of abundant plasma cells and stromal fibrosis with IgG4-related sclerosing disease. The possible role of IgG4+ plasma cells in CRDD was investigated.

Methods: Twelve cases of CRDD were reviewed, and their lesions were immunostained with anti-IgG4 and anti-IgG antibodies. The number of IgG4+ and IgG+ plasma cells and their ratios were estimated. Serum IgG4 and IgG concentrations were measured in two recent cases.

Results: Many IgG4+ and IgG+ plasma cells were found in all 12 cases. IgG4+ plasma cells ranged from 21 to 204 per high-power field (HPF) (mean 117/HPF), and IgG+ plasma cells ranged from 114 to 759/HPF (mean 349/HPF). All cases had more than 30 IgG4+ cells/HPF, except one case. The IgG4/IgG ratio ranged from 16% to 51% (mean 34%). Serum IgG4 concentration and serum IgG4/IgG ratio were increased in one recent case. Various degrees of stromal fibrosis were present in all cases.

Conclusions: The presence of many IgG4+ plasma cells and stromal fibrosis suggests that CRDD may be related to IgG4-related sclerosing disease. Many IgG4+ plasma cells is another feature of CRDD, and serum IgG4 may be elevated.

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IgG4+ plasma cells have been found in autoimmune pancreatitis and a variety of extrapancreatic lesions.^{1–5} This group of diseases is now known as IgG4-related sclerosing disease,^{1,4} which is characterized by the presence of abundant IgG4+ plasma cells in the lesion, with tissue sclerosis and elevated serum IgG4 concentration.^{3–6} One of the histopathological features of cutaneous Rosai-Dorfman disease (CRDD) is

an abundance of plasma cells,^{7–11} which led us to investigate whether IgG4+ plasma cells might be present in CRDD.

Materials and methods

Two recent and 10 retrospective cases of proven CRDD with adequate tissues were reviewed for their

histopathological features, and formalin-fixed and paraffin-embedded tissues were immunostained with antibodies to IgG4 (1 : 300, clone HP6025; Zymed), IgG (1 : 200, clone A57H; Dako), and S-100 protein (1 : 1000, polyclonal; Dako) in a Ventana Auto-immunostainer. Selected cases were also immunostained with antibodies to IgM (1 : 500, clone R1/69; Dako), IgA (1 : 500, clone GE2C1; Dako), CD3 (1 : 100, polyclonal; Dako), and CD20 (1 : 800, clone L26; Dako). A case of autoimmune IgG4-related sclerosing pancreatitis was used as a control. Three high-power fields (HPFs) ($\times 10$ eyepiece and $\times 40$ objective lens) of areas with the highest density of IgG4+ plasma cells and corresponding areas of IgG+ plasma cells were counted using a digital microscopic system (Olympus BX61 with DP71 camera) and Image-Pro Plus 6.2 computer software. Serum IgG4 and IgG concentrations of both recent cases were measured. A blood sample was obtained 1 week after the lesion was excised in one case and 2 weeks after intralesional injection of corticosteroids in another.

Results

All the cases showed histopathological features of CRDD,⁷⁻¹¹ with a cutaneous nodular mass of mixed infiltrates of lymphocytes, plasma cells, neutrophils, and histiocytes, including pathognomonic large, pale histiocytes that exhibited emperipolesis (Fig. 1). The lesions were mainly in the dermis, with a variable degree of involvement of the subcutis. The essential

histopathological features were semiquantitated and are summarized in Table 1. The majority of cases had many plasma cells and few to many S-100-protein-positive large histiocytes (Fig. 2). Histiocytes other than those positive for S-100 protein were fewer in cases 8-12, while more lymphocytes were present in those cases. Various degrees of stromal fibrosis were present in all cases ranging from mild to marked (Fig. 1B,E). The presence of neutrophils was a constant feature, except in case 5. Six cases also had germinal centers. No phlebitis was seen. IgG4+ and IgG+ plasma cells were detected in all lesions (Fig. 3A,B). The number of IgG4+ and IgG+ cells and their ratios are listed in Table 2. The average number of IgG4+ cells ranged from 21 to 204/HPF, with a mean of 117/HPF, and the average number of IgG+ cells ranged from 114 to 759/HPF, with a mean of 349/HPF. All cases had an average of > 30 IgG4+ cells/HPF, with the exception of case 10. Even in case 10, one highest count reached 33 IgG4+ cells/HPF. The ratio of IgG4+ to IgG+ cells ranged from 16% to 51% with a mean of 34%. This ratio exceeded 30% in cases 1-7.

The possibility of a correlation between the amount of IgG4+ plasma cells and the histological changes was analyzed. In general, more histiocytes were present in those cases with an IgG4/IgG ratio $> 30\%$ (cases 1-7), while more lymphocytes were present in those cases with $< 30\%$ IgG4/IgG (cases 8-12). The degree of stromal sclerosis, the number of plasma cells, neutrophils, and S-100-protein-positive

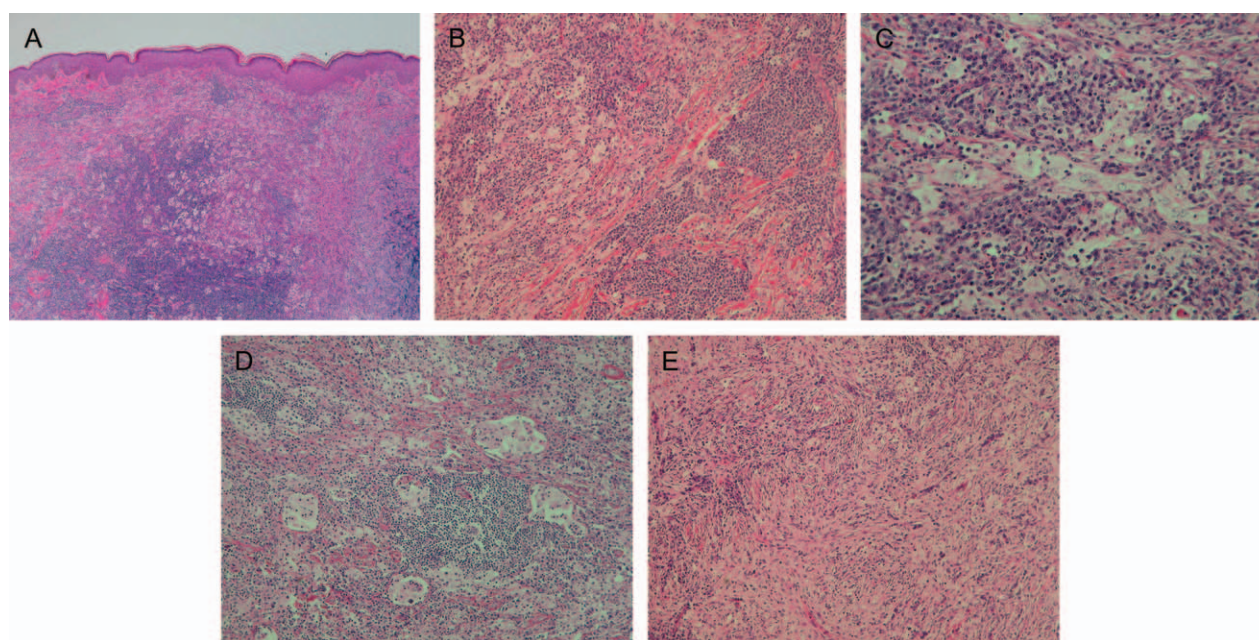


Fig. 1. A) Scanning view of the cutaneous Rosai-Dorfman disease showing dermal mixed inflammatory infiltrates with scattered large pale histiocytes. B) Sheets of plasma cells with large pale histiocytes and neutrophils in a moderately sclerotic stroma. C) Higher magnification to show large pale histiocytes with emperipolesis surrounded by many plasma cells. D) Dilated lymphatics containing large histiocytes with emperipolesis. Note stromal sclerosis. E) Marked stromal sclerosis in a storiform pattern with scattered plasma cells.

Table 1. Histopathological features of cutaneous Rosai-Dorfman disease

Case no.	Plasma cells	S-100 protein+ large histiocytes	Histiocytes*	Lymphocytes	Neutrophils	GC	Stromal fibrosis	Others
1	+++	++	+	+	+	+	Mild	
2	+++	+	+++	+	+	—	Marked	
3	++	+++	++	+	+++	+	Moderate	Microabscesses
4	+++	++	++	++	+	—	Moderate	
5	+++	++	+	+	—	—	Mild	
6	+++	+++	+++	++	+++	+	Mild	Nodules of xanthomatous histiocytes with Touton giant cells
7	+++	++	+++	+	++	+	Moderate	
8	++	++	+	+++	+	+	Mild	Dilated lymphatics containing histiocytes
9	++	+++	—	+++	++	++	Mild	
10	+	+	+	+++	+	—	Mild	
11	+++	++	+	++	+	—	Marked	Dilated lymphatics containing histiocytes
12	++	+	++	++	+	—	Moderate	

+, few; ++, moderate; +++, many; GC, germinal center.

*Histiocytes other than the S-100-protein-positive large histiocytes.

large histiocytes and the presence or absence of germinal centers did not affect the number of IgG4+ cells and the IgG4/IgG ratio. In selected cases, only a few IgM+ cells were detected. No IgA+ cells were found in the lesions. There were CD3+ T cells that surrounded aggregates of CD20+ B cells. The serum IgG4 and IgG concentrations measured were 385 and 1200 mg/dl, respectively, for case 7 and 38.5 and 801 mg/dl, respectively, for case 12. The serum IgG4/IgG ratio was 32% and 4.8% for case 7 and 12, respectively. None of our cases had pancreatic and/or extrapancreatic IgG-related sclerosing disease.

Discussion

Autoimmune pancreatitis was shown to have a high serum IgG4 concentration by Hamano et al.⁶ in 2001, and IgG4+ plasma cells were first detected in the pancreatic and ureteral lesions by Hamano et al.¹² in 2002. Subsequent immunohistochemical demonstra-

tion of abundant IgG4+ plasma cells in sclerosing pancreatitis, with or without extrapancreatic lesions, led Kamisawa et al.^{1,4} to propose a new clinicopathological entity of IgG4-related sclerosing disease. The reported extrapancreatic sites included the biliary tract, gallbladder, liver, salivary gland, lacrimal gland, kidney, lung, thyroid, prostate, breast, retroperitoneum, mediastinum, inflammatory aortic aneurysm, and lymph nodes.^{2–5,13–18} The extrapancreatic lesions may be accompanied by a pancreatic lesion.

Histopathologically, IgG4-related sclerosing disease is characterized by an abundance of IgG4+ plasma cells and stromal sclerosis, with or without phlebitis.^{3–5,13} The microscopic findings of CRDD in this study confirmed that it shares the histological features of abundant plasma cells and various degrees of stromal fibrosis seen in IgG4-related sclerosing disease. However, CRDD also has S-100-protein-positive large histiocytes and an absence of phlebitis.^{7–9,11} Various degrees of stromal fibrosis have been mentioned in previous reports of CRDD.^{7–9,11} Our study also showed the presence of IgG4+ plasma cells in all cases and a substantially increased IgG4/IgG ratio. Therefore, it is plausible that CRDD might be related to the spectrum of IgG4-related sclerosing disease. However, there is still no consensus about the number of IgG4+ plasma cells required in the lesions for the diagnosis of IgG4-related sclerosing disease.^{1–4,16,18–23} In general, > 30/HPF is considered to be diagnostic.^{1,4,21} In the present series, the number of IgG4+ plasma cells all exceeded 30/HPF, except in case 10 (21/HPF). However, one of the three fields counted in case 10 had 33 IgG4+ cells/HPF. Therefore, we believe that all our cases had the required number of IgG4+ cells for a diagnosis of IgG4-related sclerosing disease. The IgG4/IgG ratio might be more significant than the absolute number of IgG4+ cells for defining

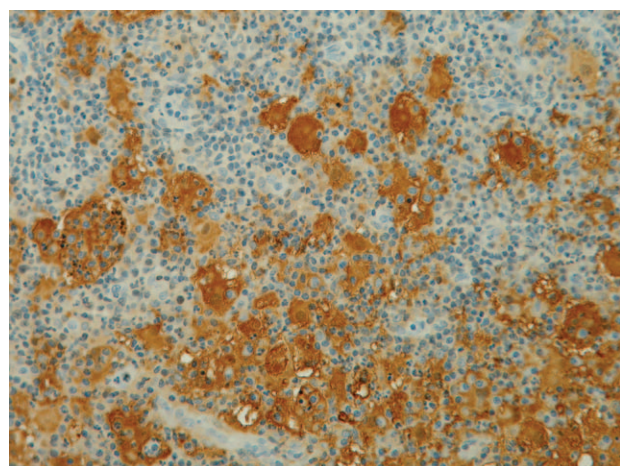


Fig. 2. Many S-100-protein-positive large histiocytes with emperipolesis.

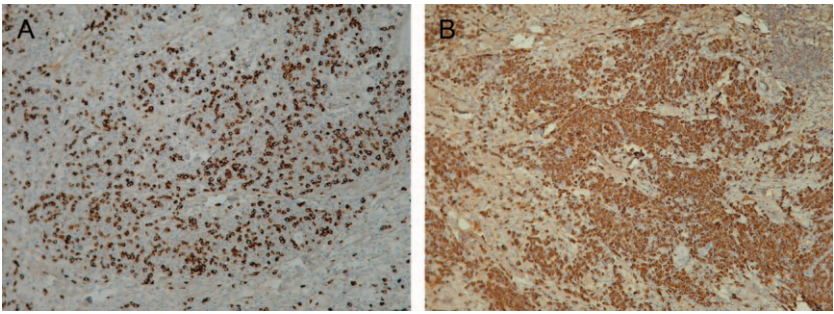


Fig. 3. A) IgG4+ plasma cells (case 7). B) IgG+ plasma cells (case 7).

IgG4-related sclerosing disease. Unfortunately, no agreement has been reached in the literature regarding the diagnostic value of IgG4/IgG ratio. In the present study, the mean IgG4/IgG ratio was 34%, and in 7 of 12 cases, it exceeded 30%.

Elevated serum IgG4 concentration is an ancillary feature of IgG4-related sclerosing disease.^{3,4,6,24} Normally, IgG4 accounts for 2–6% of total IgG in the serum, and IgG4 concentration > 135 mg/dl is considered to be elevated.^{3,4,6,24} In cases 7 and 12, we had the opportunity to check their serum IgG4 and IgG levels. The IgG4 level of 385 mg/dl and the ratio of IgG4/IgG of 32% in case 7 were above the normal levels 1 week after the lesion was excised, which further suggests that CRDD is related to IgG4-related sclerosing disease. However, the serum concentration of IgG4 and serum IgG4/IgG ratio were not elevated in case 12, even though the average number of IgG4+ cells in the lesion was 82/HPF, which exceeded the diagnostic criterion of 30/HPF. In this case, the serum sample was obtained 1 week after intralesional injection of corticosteroid, which might have affected the results. This case indicates that serum IgG4 level may not be elevated in some cases.

In Taiwan, most cases of RDD occur in the skin.^{9,10} Nodal RDD has rarely been seen. We did not have a significant number of nodal cases for the IgG4 study.

Two cases of nodal RDD were included in the study of nodal IgG4-related sclerosing disease by Cheuk et al.¹⁷ The IgG4+/IgG+ plasma cells in those two cases were estimated to be 73/423 (17.3%) and 83/282 (29.4%), respectively. They were not considered to be significant for IgG4-related sclerosing disease because they adopted a cut-off value of > 40%, although both cases had > 30 IgG4+ cells/HPF. The number of cases included in their study was small. In view of the results for CRDD in the present study, more cases of nodal RDD should be investigated for their possible relationship with IgG4-related sclerosing disease.

The etiology of CRDD remains elusive. RDD has been regarded as a histiocytic disorder since its initial description of nodal RDD,²⁵ and S-100-protein-positive large histiocytes are considered to play a major role in its pathogenesis. Our data suggest that CRDD could belong to the spectrum of IgG4-related sclerosing disease and hence it may be an autoimmune disease. The relationship between IgG4+ plasma cells and S-100-protein-positive large histiocytes in CRDD remains to be elucidated in future studies.

Although some cases of CRDD have been observed to regress spontaneously, there is no widely accepted effective treatment for CRDD. Our study reveals that CRDD may be related to IgG4-related sclerosing disease, and because the latter generally responds favorably to corticosteroid treatment,^{4,5} this may be a promising treatment for CRDD. There have been sporadic case reports of successful topical or intralesional corticosteroid treatment of CRDD.^{26,27}

Table 2. IgG4+ and IgG+ plasma cells in cutaneous Rosai-Dorfman disease

Case no.	IgG4+ Cells/HPF*				IgG+ cells/HPF*				IgG4/IgG ratio (%)
	1	2	3	Mean	1	2	3	Mean	
1	131	146	135	137	370	259	173	267	51
2	92	149	143	128	261	429	355	348	37
3	89	136	95	107	245	313	312	290	37
4	231	71	62	121	202	405	461	356	34
5	251	155	171	192	535	448	224	402	48
6	82	110	146	113	324	266	299	296	38
7	235	215	164	204	442	409	417	422	48
8	39	65	61	55	133	280	304	239	23
9	49	57	42	49	170	325	399	298	16
10	33	17	14	21	125	108	108	114	19
11	79	239	251	190	502	696	1080	759	25
12	51	79	117	82	251	459	496	402	20
Average				117				349	34

*HPF, high-power field (the numbers listed are in three corresponding fields counted).

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