

## Evaluation of IgG4<sup>+</sup> Plasma Cell Infiltration in Patients with Systemic Plasmacytosis and Other Plasma Cell-infiltrating Skin Diseases

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**Systemic plasmacytosis is a rare skin disorder characterized by marked infiltration of plasma cells in the dermis. IgG4-related disease is pathologically characterized by lymphoplasmacytic infiltration rich in IgG4<sup>+</sup> plasma cells, storiform fibrosis, and obliterative phlebitis, accompanied by elevated levels of serum IgG4. Reports of cases of systemic plasmacytosis with abundant infiltration of IgG4<sup>+</sup> plasma cells has led to discussion about the relationship between systemic plasmacytosis and IgG4-related disease. This study examined IgG4<sup>+</sup>/IgG<sup>+</sup> plasma cell ratios in 4 patients with systemic plasmacytosis and 12 patients with other skin diseases that show marked infiltration of plasma cells. Furthermore, we examined whether these cases met one of the pathological diagnostic criteria for IgG4-related disease (i.e. IgG4<sup>+</sup>/IgG plasma cells ratio of over 40%). Only one out of 4 patients with systemic plasmacytosis met the criterion. These results suggest that systemic plasmacytosis and IgG4-related disease are distinct diseases.**

**Key words:** systemic plasmacytosis; IgG4-related disease; plasma cell; IgG4.

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Plasma cells produce various immunoglobulins, which are classified into 5 isotypes: IgG, IgA, IgM, IgD and IgE. There are 4 IgG subclasses (IgG1, 2, 3 and 4), named in order of serum concentration. Thus, IgG4 is the least, and IgG1 the most abundant (1). The mean serum concentration of IgG4 is only 0.35–0.51 mg/ml (2). IgG4 possesses a unique structure and function (1). Although IgG4 was traditionally considered to play a role only in immune activation, it has been shown that IgG4 does not effectively activate the classical complement pathway. Since the disulphide bonds between heavy chains of IgG4 are unstable, some IgG4 antibodies form intrachain disulphide bonds in the hinge region. These interactions may prevent inflammatory responses by shielding the Fc region from other immune-related molecules. Another unique feature of IgG4 is the half-antibody exchange reaction (3). Through this exchange, IgG4 can bind the Fc region of other IgG

antibodies, which may result in the anti-inflammatory function of IgG4 (4). IgG4 production is induced by the type 2 helper T (Th2) cytokines, interleukin (IL)-4 and IL-13. Although the production of IgE, as well as IgG4, is induced by those cytokines, IgG4 production is favoured in the presence of IL-10, IL-12 or IL-21 (1).

IgG4-related disease (IgG4-RD) is an immune-mediated disease involving multiple organs, such as the pancreas, salivary glands, and lacrimal glands, characterized by a distinctive fibro-inflammatory change. IgG4-RD is pathologically characterized by lymphoplasmacytic infiltration rich in IgG4<sup>+</sup> plasma cells, storiform fibrosis, and obliterative phlebitis. Patients with IgG4-RD have elevated serum IgG4 levels (5). Skin lesions have been reported in IgG4-RD, but this is still controversial (6).

Systemic plasmacytosis (SP) is a rare disorder that affects various organs and is mainly observed in Japan. Its characteristic skin manifestations are red-brown eruptions distributed predominantly on the trunk (7). Pathologically SP is characterized by marked, superficial and deep perivascular and periadnexal infiltration of mature plasma cells without atypia. Patients with SP often show generalized lymphadenopathy and polyclonal hypergammaglobulinaemia. Its aetiology and pathogenesis remain to be elucidated, although environmental factors, genetic disposition and infectious aetiology have been presumed based on its geographical distribution (8). Recently, since patients with SP show marked plasma cells infiltration of the skin and some cases of SP demonstrate prominent IgG4<sup>+</sup> cell infiltration, it has been debated whether SP is a manifestation of IgG4-RD or a disease distinct from IgG4-RD (6, 9–11).

Apart from SP, previous studies have shown that prominent IgG4<sup>+</sup> plasma cell infiltration and high IgG4<sup>+</sup>/IgG<sup>+</sup> plasma cell ratio also occur under certain inflammatory conditions, such as chronic inflammation of the oral cavity and rheumatoid arthritis (12, 13). These studies indicate that prominent IgG4<sup>+</sup> plasma cell infiltration into tissues, resulting in high IgG4<sup>+</sup>/IgG<sup>+</sup> plasma cell ratio alone cannot be used to decisively diagnose IgG4-RD. To date, it is not known how frequently IgG4<sup>+</sup> plasma cells are seen among patients with plasma cell-infiltrating skin diseases other than IgG4-RD. Therefore, in this study, we examined the number of infiltrating IgG4<sup>+</sup> and IgG<sup>+</sup> plasma cells per

high-power field (HPF) in 4 patients with SP and 12 patients with abundant plasma cell infiltration of the skin, including one patient with IgG4-RD as a control.

## METHODS

### *Measurement of the numbers of IgG4<sup>+</sup> and IgG<sup>+</sup> cells*

Skin and serum samples were obtained from 4 patients with SP. All 4 patients were diagnosed with SP and treated at the Department of Dermatology, Teikyo University Hospital, Tokyo, Japan. We have previously reported cases 2–4 as having SP and being positive for human herpesvirus 8 by having detected its messenger RNA using PCR (14). We also obtained skin samples by biopsy from 12 patients with abundant plasma cell infiltration of the skin; epidermal cyst, soft fibroma, systemic lupus erythematosus (SLE), cheilitis granulomatosa, squamous cell carcinoma (SCC), lichen planus (LP), post-inflammatory scar, granuloma reactive to foreign body, chronic bacterial infection, superficial bacterial skin infection, plasmacytosis circumorificialis, and IgG4-RD. SCC is not an inflammatory disease but a cancer; however, this case demonstrated inflammation with an abundant infiltration of plasma cells as part of an immune response to tumour.

All biopsy specimens were fixed in 10% formalin, embedded in paraffin, and sliced into 3- $\mu$ m thick sections. Morphological characteristics were assessed on standard haematoxylin and eosin (H&E) sections. Immunohistochemical staining was performed using the BOND-III automated immunostainer (Leica Biosystems, Wetzlar, Germany). The following antibodies were applied: anti-IgG (1:60,000, DAKO, Santa Clara, CA, USA); anti-IgG4 (1:8,000, DAKO); and immunoglobulin  $\kappa$ - (1:40,000, DAKO) and  $\lambda$ -light chains (1:50,000, DAKO).

The number of IgG<sup>+</sup> and IgG4<sup>+</sup> plasma cells was counted at 3 different HPFs in each section, and the mean number  $\pm$  standard deviation (SD) of positive cells per HPF was calculated. Then, the mean ratio  $\pm$  SD of IgG4<sup>+</sup>/IgG<sup>+</sup> plasma cells was calculated (15). The serum IL-6 level was measured at the central clinical laboratory of Teikyo University Hospital.

## RESULTS

### *Clinical features of the 4 patients with systemic plasmacytosis*

The clinical characteristics of the 2 male and 2 female patients with SP are shown in **Table I**. All patients presented with multiple reddish-brown papules over the trunk and face that had persisted for 5 (case 1), 2 (case 2), 5 (case 3) or 1 (case 4) year, respectively. Laboratory test results were as follows. The haemoglobin level was decreased in cases 2 and 3 (10.0 g/dl (case 2), 7.8 g/dl (case 3); normal, 13.0–16.6 g/dl). The erythrocyte sedimentation rate was elevated in cases 2, 3 and 4 ((137 mm/h (case

2), 121 mm/h (case 3), 27 mm/h (case 4); normal, 2–10 mm/h). The serum C-reactive protein level was increased in cases 2 and 3 (4.2 mg/dl (case 2), 15.7 mg/dl (case 3); normal, <0.2 mg/dl). In all 4 cases, the total serum protein level was elevated, and serum protein electrophoresis revealed polyclonal hypergammaglobulinaemia. Case 1 showed a slightly elevated serum IgG4 level (120 mg/dl; normal 4.8–105 mg/dl), while the serum IgG4 level was not available in the other 3 patients as shown in Table I. All cases with SP did not involve any other organs including salivary glands or pancreas.

### *Pathological findings in the skin of patients with systemic plasmacytosis*

Biopsy specimens were taken from a papule on the trunk of the 4 patients with SP. Histopathology showed moderately dense perivascular and periadnexal cell infiltration throughout the dermis, composed largely of plasma cells without atypia (**Fig. 1**). None of the cases showed obliterative phlebitis or any other vascular changes, or dermal fibrosis. Immunohistochemical studies revealed that the infiltrating plasma cells were positive for IgG  $\kappa$ , and that none of the plasma cells were positive for IgG  $\lambda$ . A diagnosis of plasmacytosis was made from both the clinical features and histopathology of biopsy specimens. Among the 4 patients diagnosed with SP, only case 1 met one of the pathological diagnostic criteria of IgG4-RD, namely that the ratio of IgG4<sup>+</sup>/IgG<sup>+</sup> plasma cells is over 40% and the number of IgG4<sup>+</sup> plasma cells per HPF is more than 10 (11) (IgG4<sup>+</sup>/IgG<sup>+</sup> plasma cell ratio  $\pm$  SD, number of IgG4<sup>+</sup> plasma cells per HPF  $\pm$  SD; 61  $\pm$  17%, 80.7  $\pm$  11 (case 1)). Although the case met one of the pathological criteria, it did not meet the other pathological criterion of fibrosis. In addition, the only slightly elevated serum IgG4 level did not meet haematological criterion (more than 135 mg/dl). Therefore, the case was not diagnosed with IgG4-RD. The remaining 3 patients with SP did not meet any criteria (23  $\pm$  18%, 15  $\pm$  3.3 (case 2), 9  $\pm$  9%, 7.7  $\pm$  3.9 (case 3), 29  $\pm$  11%, 34  $\pm$  4.9 (case 4); Table I). There were no other clinical and histopathological differences between case 1 and the other 3 cases.

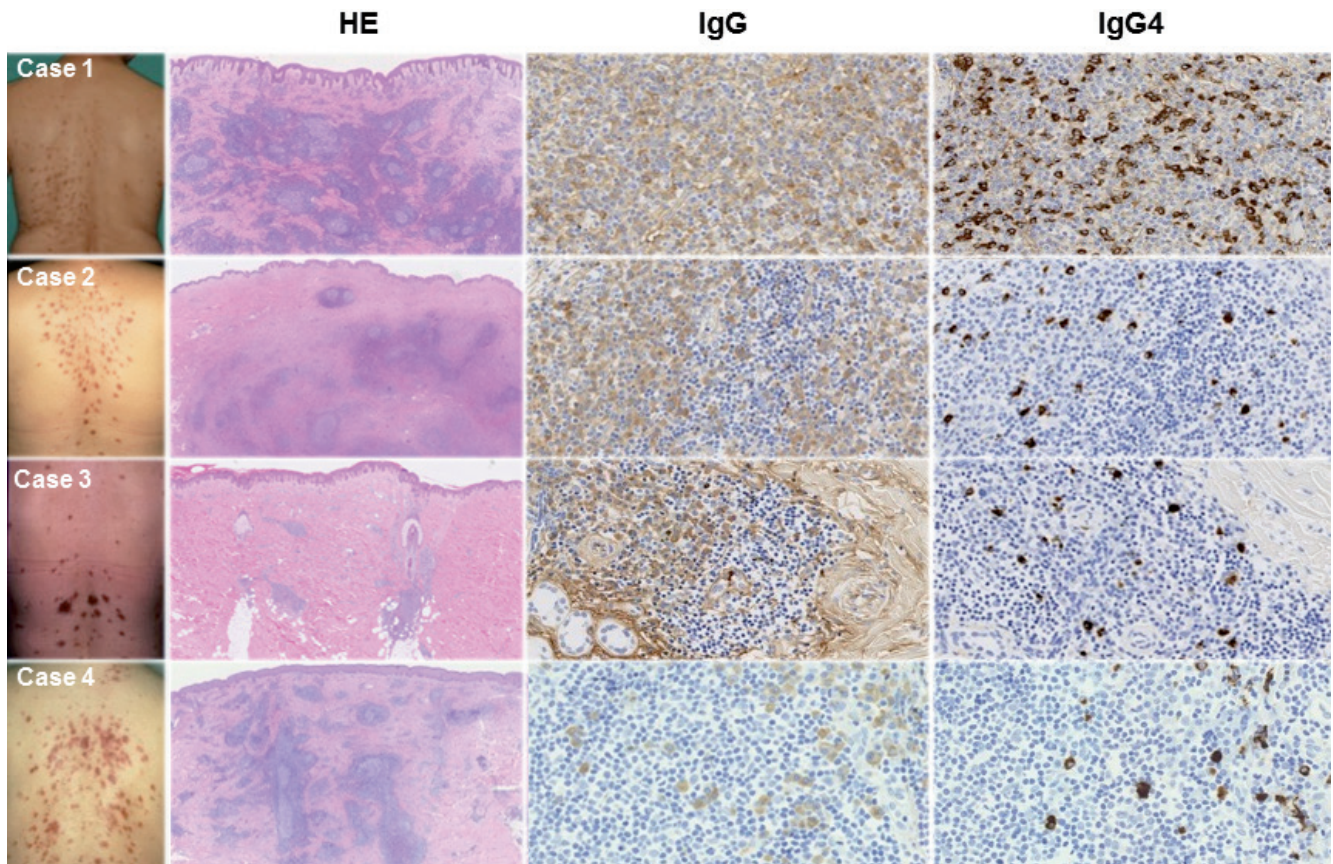
### *IgG4<sup>+</sup> plasma cell infiltration in skin diseases other than systemic plasmacytosis*

We next studied the number of IgG4<sup>+</sup> plasma cells in 12 patients with abundant plasma cell infiltration of the

**Table I. Clinical characteristics and IgG4<sup>+</sup>/IgG<sup>+</sup> plasma cell count and ratio in 4 patients with systemic plasmacytosis**

Patient	Age, years/ Sex	Lymph node swelling	Serum IgG (mg/dl)	Serum IgG4 (mg/dl)	Serum IL-6 (pg/ml)	Associated disease	IgG4 <sup>+</sup> /IgG <sup>+</sup> plasma cells/high- power field in skin specimens <i>n</i> (%)
Case 1	58/M	+	1,420	120	0.8	Hypertension Hyperlipidaemia	81/132 (61)
Case 2	51/F	+	4,910	Not available	10.3	Anaemia	15/65 (23)
Case 3	41/F	+	3,850	Not available	5.2	Anaemia	8/85 (9)
Case 4	69/M	+	2,254	Not available	<4.0	Hypertension	34/117 (29)

IgG: normal range, 870–1,700 mg/dl; IgG4: normal 4.8–105 mg/dl; IL-6: normal <4 pg/ml.



**Fig. 1.** Skin manifestations, haematoxylin and eosin staining (H&E;  $\times 40$  magnification), immunostaining of IgG and IgG4 ( $\times 400$  magnification) of 4 patients with systemic plasmacytosis.

skin (Fig. 2). The specimen from one IgG4-RD patient served as a positive control. Histopathology of biopsy specimens taken from these patients showed prominent plasma cell infiltration. The specimens from the cheilitis granulomatosa patient ( $73 \pm 27\%$ ,  $37 \pm 5.1$ ), SCC patient ( $44 \pm 21\%$ ,  $42.3 \pm 6.6$ ), post-inflammatory scar ( $48 \pm 11\%$ ,  $24 \pm 3.5$ ), granuloma reactive to foreign body ( $78 \pm 8.6\%$ ,  $63 \pm 2.1$ ), superficial bacterial skin infection ( $68 \pm 15\%$ ,  $103 \pm 8.0$ ), plasmacytosis circumorificialis ( $82 \pm 13\%$ ,  $75 \pm 25$ ), and the IgG4-RD patient ( $91.9 \pm 4\%$ ,  $129 \pm 29$ ) met one of the pathological diagnostic criteria of IgG4-

RD (Table II). Thus, 5 out of 11 patients (epidermal cyst, soft fibroma, SLE, LP, and chronic bacterial infection) did not meet the pathological diagnostic criteria of IgG4-RD.

The cell counts of IgG<sup>+</sup> plasma cells and IgG4<sup>+</sup> plasma cells per HPF and the IgG4<sup>+</sup>/IgG<sup>+</sup> plasma cell ratios of all cases examined in this study are summarized in Figs 3 and 4, respectively.

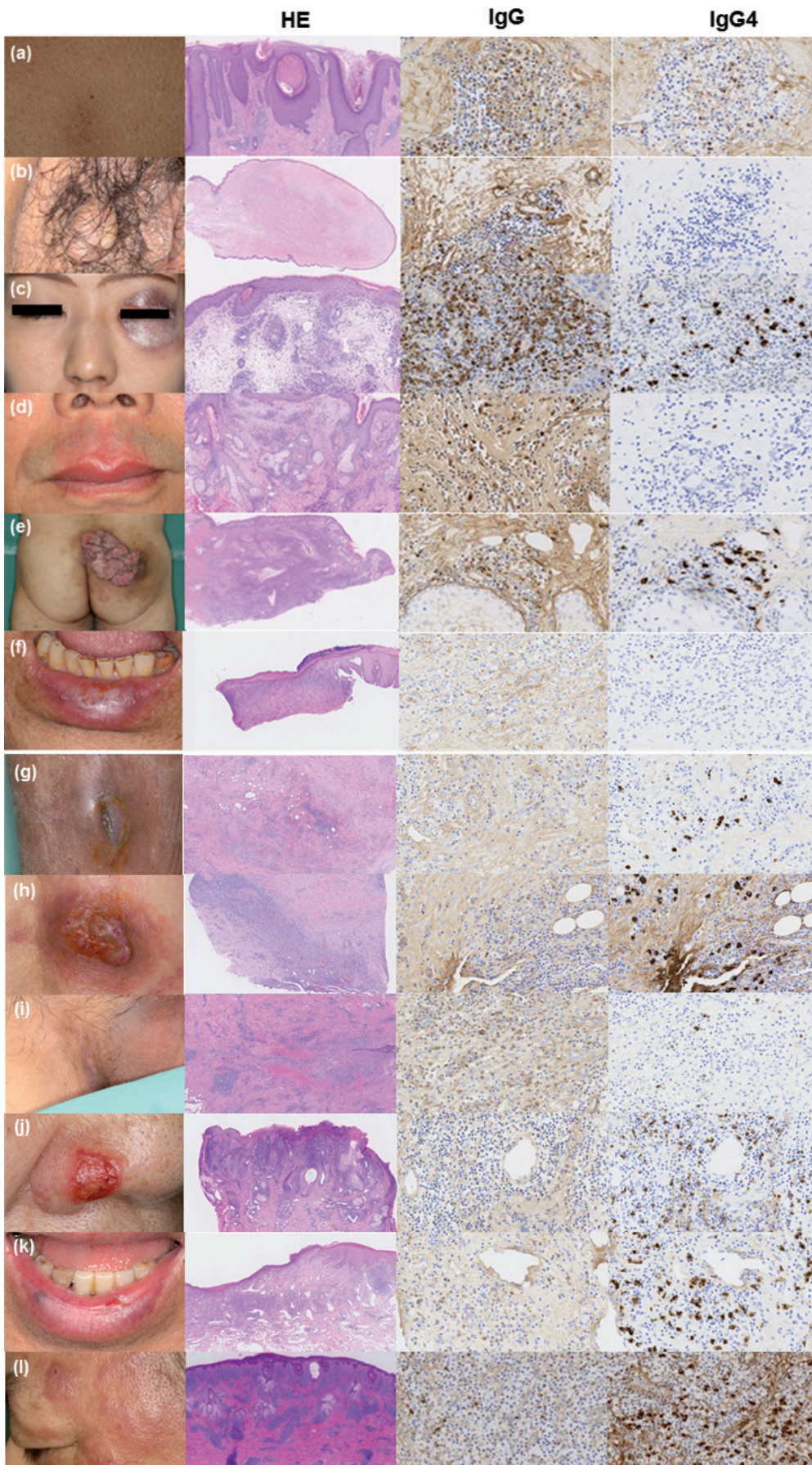
## DISCUSSION

In our study, only one of the 4 patients with SP met one of the pathological diagnostic criteria of IgG4-RD, suggesting that SP and IgG4-RD are distinct diseases. To date, 4 previous papers discussed the possibility of an association between IgG4-RD and SP (Table III) (9–11, 16). Three out of the 4 reports claimed that SP was the cutaneous manifestations of IgG4-RD (9–11). Among the 10 patients with SP described in the previous papers (9–11, 16), 5 (50%) out of the 10 had a ratio of IgG4<sup>+</sup>/IgG<sup>+</sup> plasma cells of over 40%, which is one of the pathological diagnostic criteria of IgG4-RD. Adding the 4 cases in our study together with the previous cases, 6 (43%) out of 14 patients met one of the pathological diagnostic criteria of IgG4-RD (Table III). None of our SP cases showed storiform fibrosis or obliterative phlebitis, even in the patient with a ratio of IgG4<sup>+</sup>/IgG<sup>+</sup> plasma

**Table II.** IgG4<sup>+</sup>/IgG<sup>+</sup> plasma cell count and ratio in patients with 12 plasma cell-infiltrating skin diseases

Pat. No.	Skin disease	IgG4 <sup>+</sup> /IgG <sup>+</sup> plasma cells/HPF in skin specimens (%)
1	Epidermal cyst	20/54 (38)
2	Soft fibroma	4/36 (11)
3	SLE	1/27 (3)
4	Cheilitis granulomatosa	37/51 (73)
5	SCC	42/97 (44)
6	Lichen planus	3/36 (7)
7	Post-inflammatory scar	24/51 (48)
8	Granuloma reactive to foreign body	63/81 (78)
9	Chronic bacterial infection	16/134 (12)
10	Superficial bacterial skin infection	103/155 (66)
11	Plasmacytosis circumorificialis	75/94 (80)
12	IgG4-RD	129/140 (92)

HPF: high-power field; SLE: systemic lupus erythematosus; SCC: squamous cell carcinoma.



**Fig. 2. Skin manifestations, haematoxylin and eosin staining (HE;  $\times 40$  magnification), immunostaining of IgG and IgG4 ( $\times 400$  magnification) of patients with various skin diseases with prominent plasma cell infiltration. (a) Epidermal cyst, (b) soft fibroma, (c) systemic lupus erythematosus, (d) cheilitis granulomatosa, (e) squamous cell carcinoma, (f) lichen planus (LP), (g) post-inflammatory scar, (h) granuloma reactive to foreign body, (i) chronic bacterial infection, (j) superficial bacterial skin infection, (k) plasmacytosis circumorificialis, (l) IgG4-RD.**

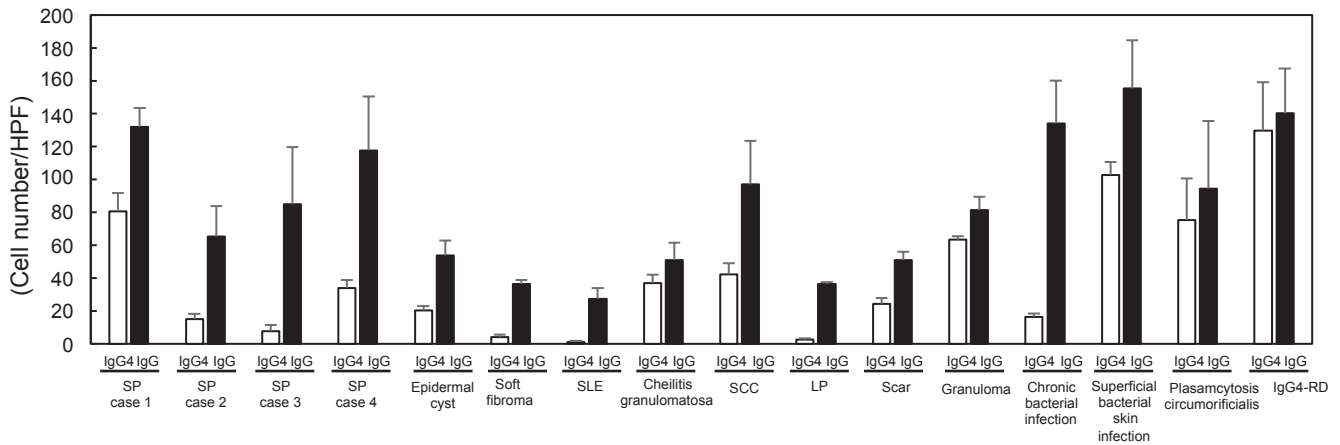


Fig. 3. Cell counts of IgG<sup>+</sup> plasma cells and IgG4<sup>+</sup> plasma cells per high-power field (HPF). Data are presented as mean ± standard deviation (SD).

cells of over 40%. Moreover, our study demonstrated that 5 out of 11 plasma cell-infiltrating diseases other than SP showed a ratio of IgG4<sup>+</sup>/IgG<sup>+</sup> plasma cells of over 40%. Strehl et al. reported that IgG4<sup>+</sup> plasma cells are ubiquitous in patients with non-specific chronic inflammatory conditions (17). Although the characteristic histopathological feature of abundant infiltration of IgG4<sup>+</sup> plasma cells is essential for the diagnosis of IgG4-RD, abundant infiltration of IgG4<sup>+</sup> plasma cells *per se* does not necessarily mean that the patient has IgG4-RD. To diagnose IgG4-RD, clinical and other pathological manifestations should also be considered.

IgG4 itself is not believed to be a driver of the pathogenesis of IgG4-RD. As stated in the “Introduction” section, IgG4 antibodies do not directly fix complement. They bind poorly to activated Fc receptors. Therefore, they are thought to be non-inflammatory. It is also known that the IgG4 level increases after IgE decline in patients with allergic disorders (5). Our study revealed infiltration of IgG4<sup>+</sup> plasma cells into the skin in inflammatory conditions. These facts suggest that infiltration of IgG4<sup>+</sup> plasma cells is a certain consequence of some inflam-

matory immune conditions. Kamisawa et al. advocated a plausible model of the pathogenesis of IgG4-RD (5). In genetically susceptible individuals, some triggers drive a self-antigen-driven, polarized CD4<sup>+</sup> Th response, which induces a fibrotic pathological process (18–20). Some event induced by fibrosis triggers a T-follicular helper response, which induces development of germinal centres and the IgG4-secreting plasmablasts (21). IgG4-RD is a multi-organ disease. It is postulated that through the same or similar pathogenesis as mentioned above, IgG4<sup>+</sup> plasma cells infiltrate affected organs.

On the other hand, other immune conditions, such as chronic inflammation, can also induce IgG4 production as our study and previous reports demonstrated. However, those conditions lack the pathological features of fibrosis and obliterative phlebitis, which are usually seen in IgG4-RD. In addition, some patients with SP also show high infiltration of IgG4<sup>+</sup> plasma cells, but lack fibrotic change and any vascular change pathologically, suggesting that the pathogenesis of SP is different from that of IgG4-RD.

IgG4-RD is not easily diagnosed, since certain immune conditions, such as chronic inflammation, can

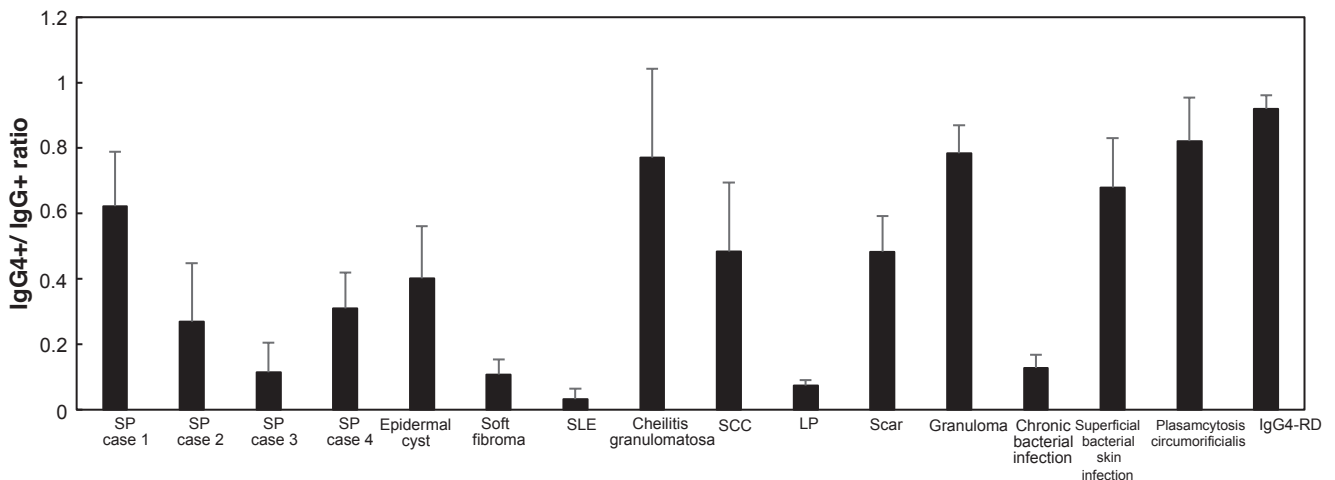


Fig. 4. IgG4<sup>+</sup>/IgG<sup>+</sup> plasma cell ratio. Data are presented as mean ± standard deviation (SD).

**Table III. IgG4+/IgG+ plasma cell ratios of 14 patients with systemic plasmacytosis**

Reference	Pat. No.	Age, years/Sex	Serum IgG4 (mg/dl)	IgG4+/IgG+ plasma cells in skin specimens (%)
Miyagawa-Hayashino et al. (9)	Case 1	54/M	610	42.2
	Case 2	55/M	Not available	43.7
	Case 3	61/M	Not available	58.1
	Case 4	46/M	3,040	50.1
Kato et al. (10)	Case 5	63/M	Not available	33.0
	Case 6	38/M	0	0
	Case 7	58/M	Not available	12.0
	Case 8	58/F	56.9	22.4
Yamaguchi et al. (11)	Case 9	63/M	1,250	54.0
Mizuno et al. (16)	Case 10	60/M	287	10.0
Our hospital	Case 11	51/F	Not available	23.0
	Case 12	41/F	Not available	9.0
	Case 13	69/M	Not available	28.9
	Case 14	58/M	120	61.1

IgG4: normal 408–105 mg/dl.

induce IgG4<sup>+</sup> plasma cell infiltration, as reported in the current study and previous papers. Abundant infiltration of IgG4<sup>+</sup> plasma cells does not necessarily indicate IgG4-RD. There is evidence to suggest that SP is a distinct disease from IgG4-RD. However, the entity of IgG4-RD was proposed relatively recently, and its causes and mechanism remain to be elucidated. Furthermore, both SP and IgG4-RD appear to be heterogeneous. Further investigation is needed to clarify this controversial issue.

*The authors have no conflicts of interest to declare.*

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