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High ratio of IgG4-positive plasma cell infiltration in cutaneous plasmacytosis-is this a cutaneous manifestation of IgG4-related disease?

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TITLE PAGE

High ratio of IgG4-positive plasma cell infiltration in cutaneous plasmacytosis

- Is this a cutaneous manifestation of IgG4-related disease?

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Abbreviations: Ig, immunoglobulin; Th2, T helper 2; Dsg, desmoglein; HPF, high power fields; IL, interleukin

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Abstract

Cutaneous plasmacytosis is a rare condition affecting middle-aged individuals, characterized by multiple red-brown papules and plaques over the trunk. It has been reported mainly in Japan. The condition is accompanied by polyclonal hypergammaglobulinemia and superficial lymphadenopathy. Lung or retroperitoneal involvement occurs rarely. In the present study, three consecutive cases of cutaneous plasmacytosis were observed histologically to have abundant infiltration of IgG4-bearing plasma cells. All three were associated with superficial lymphadenopathy, one with interstitial lung involvement showing ground-glass opacity on CT and the others with bone marrow plasmacytosis, showing histological evidence of an increased number of IgG4-positive plasma cells. All three had polyclonal hypergammaglobulinemia, one had high serum concentration of IgG4, and all had elevated serum IL-6. The ratios of IgG4+ to IgG+ plasma cells were assessed using skin biopsy specimens with pemphigus (n=7), discoid lupus erythematosus (n=5) and morphea (n=2) (mean ratios; 19%, 0%, and 0%, respectively); we noted the proportion of IgG4-positive plasma cells in cutaneous plasmacytosis (mean: 48%).

IgG4-related sclerosing disease is a newly recognized systemic disorder characterized by lymphoplasmacytic infiltration and fibrosis, and by a high serum IgG4 level and increased IgG4-positive plasma cells in the tissues. Skin manifestations of this disorder have not been described. Although cutaneous plasmacytosis could be a chronic allergic hypersensitivity reaction, our findings raise the possibility of a relationship in pathogenesis between cutaneous plasmacytosis and IgG4-related sclerosing disease.

Introduction

Cutaneous plasmacytosis is a rare skin disorder of unknown etiology. It manifests as brown to red papules containing polyclonal plasma cells, predominantly on the trunk.¹⁻³ This condition has been recognized principally in Asian patients, with a few cases in Caucasians.⁴⁻⁷ The condition is accompanied by polyclonal hypergammaglobulinemia and superficial lymphadenopathy. Histology shows a dense perivascular and periadnexal infiltrate composed almost entirely of polyclonal plasma cells.

Patients with cutaneous plasmacytosis often have systemic manifestations, including anemia, fever, hepatosplenomegaly and superficial lymphadenopathy. Lymphadenopathy occurs in more than 50% of patients.⁸⁻¹⁰ The lung,¹⁰⁻¹² breast⁴ and retroperitoneum¹³ are involved less frequently. In the lung, cutaneous plasmacytosis may present as lymphoid interstitial pneumonia¹⁰ or as multiple tiny nodules.¹¹ In such cases, some investigators have called the disorder systemic plasmacytosis.¹⁴ Most cases have followed a chronic and benign clinical course over a decade without spontaneous remission, suggesting that the condition is a benign reactive proliferation of plasma cells^{1,9}. A few cases have followed an aggressive clinical course as lymphoma¹⁵, lymphoid interstitial pneumonia¹⁰, or renal failure^{8,9}. Treatment has included topical and systemic corticosteroids¹⁶, cyclophosphamide⁴, topical tacrolimus,¹⁷ PUVA and other chemotherapy.^{6,9,18,19,20}

Recent studies have shown that sclerosing pancreatitis is a unique immunoglobulin (Ig) G4-related disease.²¹ Many IgG4-positive plasma cells are present in extrapancreatic organs in patients with sclerosing pancreatitis, and IgG4-related systemic disorder has been proposed as a distinct disease entity.²² Four subclasses of IgG have been defined from the antigenic uniqueness of their heavy chains. The subclasses are designated

IgG1, IgG2, IgG3 and IgG4, in order of their serum concentrations, which are respectively ~60, 25, 10 and 5%. Each IgG subclass expresses a unique profile of effector activities. The IgG4 subclass, which is known to have poor complement- and leucocyte-activating properties, may be characteristic of chronic antigen stimulation.²³ Sclerosing pancreatitis is manifest as multifocal fibrosclerosis,²⁴ which in turn shows as various combinations of the following conditions: orbital pseudotumor,²⁵ sclerosing sialoadenitis,²⁶ hepatic inflammatory pseudotumor, sclerosing cholangitis,²⁷ mediastinal and retroperitoneal fibrosis,^{28,29} inflammatory aortic aneurysm³⁰, lymphoid interstitial pneumonia³¹ or inflammatory pseudotumor of the lung,³² lymphadenopathy,^{29,33} tubulointerstitial nephritis,³⁴ and hypophysitis.³⁵ Histological findings are similar in these diseases, and there is marked lymphoplasmacytic infiltration with sclerosis, obliterative phlebitis and occasional eosinophils. Serum assay for IgG4 is useful for diagnosis, and abundant IgG4-bearing plasma cells found histologically are a hallmark of these diseases.²⁴

No cutaneous manifestations of multifocal fibrosclerosis and/or autoimmune pancreatitis have been reported. IgG4-bearing plasma cells were assessed on skin biopsy specimens in these patients in order to investigate the association with IgG4-related systemic disorder, since cutaneous plasmacytosis is likely to be a skin manifestation of systemic disorder. Since autoantibodies belong mainly to the IgG4 and IgG1 subclasses in pemphigus,²³ the controls were pemphigus (n=7), discoid lupus erythematosus (n=5) and morphea (n=2).

Material and Methods

Skin and serum samples were obtained from three patients having cutaneous plasmacytosis; two were treated at Kyoto University Hospital and the third at the Dermatology Department of Osaka University Hospital. We examined various tissues, including lymph node, lung, and bone marrow.

We also obtained skin biopsies from 7 patients with pemphigus (pemphigus vulgaris, n=4; pemphigus foliaceus, n=3), 5 with discoid lupus erythematosus, and two with morphea, taken from the database of the Department of Diagnostic Pathology, Kyoto University Hospital; they were used as controls in IgG4 immunohistochemistry. Control subjects were included in this study according to the following criteria for pemphigus: (i) the clinical presence of intraepidermal blisters; (ii) the presence of squamous epithelial intercellular deposition of IgG and/or C3 according to direct immunofluorescence studies; (iii) the presence of antibodies against desmosomal cadherins desmoglein (Dsg) 1 for pemphigus foliaceus and/or Dsg 3 for pemphigus vulgaris on Enzyme-Linked ImmunoSorbent Assay; and (iv) histological findings consistent with pemphigus foliaceus: subcorneal blister with acantholytic keratinocytes and pemphigus vulgaris; suprabasal acantholysis with blister formation.³⁶ For discoid lupus erythematosus we required: (i) the presence of a well-demarcated red-purple macule or papule with a superficial scale; (ii) histological evidence of vacuolar interface dermatitis with dense perivascular, interstitial, and periadnexal inflammation, with occasional basement membrane thickening and dermal mucin deposition; or (iii) positive lupus band test.³⁷ For morphea (localized scleroderma), we required: (i) the thickening and fibrosis to be limited clinically to the skin; and (ii) histological findings of thickening and sclerosis of the reticular dermis, with increased width of collagen bundles, and a superficial and

deep perivascular lymphocytic infiltrate containing plasma cells.³⁸

All biopsy specimens were fixed in neutral buffered formalin, embedded in paraffin, and sliced into sections 4 μ m thick. Morphological characteristics were assessed on standard HE sections. Immunohistochemistry was performed using an autoimmunostainer (Ventana XT System Benchmark; Ventana Medical System, Inc., Tucson, AZ, USA). The following antibodies were applied: anti-IgG (polyclonal; Ventana), IgG4 (1:500, clone HP6025; Serotec, Oxford, UK), IgA (polyclonal; Ventana), IgM (polyclonal; Ventana), CD3 (2GV6; Ventana), CD20 (1:1000, L26; DakoCytomation, Denmark), CD79a (1:400, JCB117; DakoCytomation), and immunoglobulin κ and λ -light chains (polyclonal; Ventana). The number of IgG+ and IgG4+ plasma cells at three different high power fields (HPF) was counted in each section, and an average number of positive cells per HPF was calculated. The percentage of IgG4+/IgG+ plasma cells was determined.³³

To compare continuous variables we used the unpaired Student t test or Mann-Whitney's U test. Statistical analysis was performed using StataSE 9.0 (Stata corporation, TX). A p-value smaller than .05 was taken to be statistically significant.

Results

Clinical features

Table 1 lists the clinical characteristics of patients with cutaneous plasmacytosis. All three were men, aged 54, 55 and 61 years. One case has been reported previously in detail.¹⁷ All three patients came to our attention because of multiple reddish-brown papules over the trunk and face, which persisted for 5 (Pt 1), 3 (Pt 2) and 1.5 (Pt 3) years, respectively; see Fig. 1A. Their general conditions were relatively good, except that one had fatigue and one other had night sweat. All exhibited superficial lymphadenopathy. CT revealed diffuse lymphadenopathy, involving cervical, parotid, axillary, para-extriliac, and inguinal locations. Chest CT revealed ground glass attenuation, with a slight reticular shadow in the middle and lower lobe bilaterally in one patient (Fig.1B). No honeycombing was noted. No fever or hepatosplenomegaly was found in any patient. All patients denied sicca syndrome and weight loss.

Laboratory test results were as follows. Blood cell count with differential was normal. The erythrocyte sedimentation rate was raised in two of the patients tested (116 mm/h (Pt 1), 44 mm/h (Pt 3), normal 2-10 mm/h). C-reactive protein was raised in all three patients (2.1 mg/dL (Pt 1), 12.9 mg/dL (Pt 2), and 0.6 mg/dL (Pt 3); normal is <0.2 mg/dL). Total serum protein was elevated, and serum protein electrophoresis revealed polyclonal hypergammaglobulinemia with IgG (4637 mg/dL (Pt 1), 6480 mg/dL (Pt 2), and 2624 mg/dL (Pt 3); normal is 826-1840 mg/dL), IgA (475 mg/dL (Pt 1), 480 mg/dL (Pt 2), and 332 mg/dL (Pt 3); normal is 93-426 mg/dL) and IgM (112 mg/dL (Pt1), 325 mg/dL (Pt 2), and 80 mg/dL (Pt 3); normal is 27-205 mg/dL). One of the patients had an elevated serum IgG4 of 610 mg/dL (13.2% of total IgG, normal 4.8-105 mg/dL) and a

high serum IgE of 2600 IU/mL (normal 27.5-138.3 IU/mL). Serum interleukin (IL)-6 level was raised (6.9 pg/mL (Pt 1), 74.5 pg/mL (Pt 2), and 4.6 pg/mL (Pt 3); normal is <4.0 pg/mL). Antinuclear antibody was positive in one patient (1:40). There was no measurable Bence-Jones protein in the urine. Flow cytometric evaluation on a lymph node in one patient revealed a polytypic lymphoplasmacytic infiltrate based on cell marker analysis.

Prednisolone at low dosage (15 mg/day, 0.25 mg/kg) was started for cutaneous lesions in two patients, and tacrolimus ointment for the third. The third patient had severe plaques particularly on the face. Therefore, the tacrolimus ointment was applied to facial lesions. All patients were well at follow-up from 3 months to 3 years (Table 1). The treatment reduced the erythema and induration of the facial lesions for the third patient after 3 months. Therapeutic intervention via oral steroid had little effect in other two patients, and –although not complete– a reduction in size of the skin lesions was observed. There was clinical response to prednisolone, with diminution in size of lymph nodes and symptomatic improvement.

Pathological findings

Biopsy specimens of a papule on the trunk showed a moderately dense superficial and deep perivascular and periadnexal infiltrate, composed largely of plasma cells without atypia (Fig. 1C, 2A). None of the cases showed obliterative phlebitis or other vascular changes, or dermal sclerosis. An immunohistochemical study found that the infiltrating plasma cells were positive for IgG, IgA, IgM, κ , and λ -chains. There was no light chain restriction. A diagnosis of plasmacytosis was made. The number of IgG4+ plasma cells

was elevated (53 per HPF (Pt 1), 62 per HPF (Pt 2), and 72 per HPF (Pt 3)); see Figs. 2B, C. The proportion of IgG4+/IgG+ plasma cells was 42.2 % (Pt 1), 43.7% (Pt 2), and 58.1 % (Pt 3); see Table 2.

Histology, obtained by transbronchial lung biopsy from segment 4 of the right lobe, showed thickening of the alveolar septum with marked infiltration of lymphoplasmacytic cells, consistent with lymphocytic interstitial pneumonia (Fig. 1D). IgG4+ plasma cells were slightly increased in the interstitium (IgG4+/IgG+ plasma cells 15.4%).

Lymph nodes from all three patients demonstrated interfollicular expansion, with variable sized follicles. The lymph node architecture was well preserved. The reactive follicle comprised a germinal center surrounded by a discrete mantle zone. The interfollicular region showed a mild increase in high endothelial venules, and large numbers of mature plasma cells (Fig. 3A, B). CD20+ B cells were confined to the follicles, and the CD3+ T cells resided mainly in the interfollicular regions. There was no immunoglobulin light chain restriction. The number of IgG4+ plasma cells was elevated (136 per HPF (Pt 1), 43 per HPF (Pt 2), and 94 per HPF (Pt 3)). The proportion of IgG4+/IgG+ plasma cells was 72.0% (Pt 1), 49.4% (Pt 2), and 53.4% (Pt 3); see Table 2, Fig. 3C, D.

A bone marrow aspiration from one patient showed a normocellular marrow, with a normal myeloid to erythroid ratio, a normal number of megakaryocytes, and moderate plasmacytosis (12%). Discrete polyclonal plasmacytosis was found in the bone marrow aspiration. The mean number of IgG4+ plasma cells per HPF was 15, and the proportion of IgG4+/IgG+ plasma cells was 60.8 %.

Immunostaining of control skins

Table 3 lists clinical features and the results of IgG4 and IgG immunostaining in controls. An increased proportion of IgG4+/IgG+ plasma cells was observed in pemphigus vulgaris and pemphigus foliaceus, ranging from 0 to 36.7% (mean 19.4%); in contrast there were none in discoid lupus erythematosus and morphea (vs pemphigus, $P<.05$). The inflammatory cells, including IgG4+ plasma cells, were more sparse in pemphigus than in cutaneous plasmacytosis. The lower number of IgG+ or IgG4+ plasma cells (pemphigus vs skin lesions of cutaneous plasmacytosis, $P<.05$), and the histology, are capable of distinguishing the pemphigus group with cutaneous plasmacytosis.

Discussion

Since patients with sclerosing pancreatitis are recognized to have extrapancreatic lesions, and patients with extrapancreatic disease but with otherwise similar serological and histological features can have no pancreatic lesion, such lesions have been proposed as a manifestation of IgG4-related systemic disease.^{29,39} This disorder commonly presents with a high serum IgG4 level and/or abundant IgG4+ plasma cells in the tissues involved. Skin lesions have not been described in patients with typical IgG4-related systemic disease, such as sclerosing pancreatitis or sclerosing cholangitis. Our cases showed marked IgG4-positive plasma cell infiltration in the skin; this is not known as a feature of cutaneous plasmacytosis. All of our patients with cutaneous plasmacytosis had associated extracutaneous lesions (lymph node, lung, and bone marrow), in which numerous IgG4-positive cells were found by immunohistochemistry. Systemic involvement has also included a peri-ureteric retroperitoneal mass causing hydronephrosis,¹³ breast masses⁴, hepatomegaly¹⁰, and lymphoid interstitial pneumonia¹⁰ in association with cutaneous plasmacytosis. Histology shows diffuse lymphoplasmacytic infiltration within fibrous tissue.

Concomitant lymphadenopathy is common in IgG4-related systemic disease. Lymph node histology in IgG4-related systemic disease that is associated with autoimmune pancreatitis, sclerosing cholangitis, sclerosing dacryoadenitis or sclerosing sialadenitis can be categorized into three patterns: Castleman disease-like, follicular hyperplasia, and interfollicular expansion by immunoblasts and plasma cells.³³ The lymph nodes in our cases showed reactive lymphoid follicles and marked distension of the interfollicular area by numerous plasma cells, and also a mild increase in thickened venules with a preserved nodal architecture. Histology of the lymph node in cutaneous plasmacytosis

was indistinguishable from lymph node lesions described in IgG4-related sclerosing disease; two of our cases fit best into the pattern of follicular hyperplasia, and one into the interfollicular expansion pattern specified in IgG4-related sclerosing disease.³³ Moreover, most patients are middle-aged to elderly ethnic Asians, with male predominance in both diseases.⁴⁰ The clinicopathological similarities between cutaneous plasmacytosis and IgG4-related sclerosing disease indicate a relation with cutaneous plasmacytosis as a manifestation of IgG4-related disease.

Allergic symptoms and atopic dermatitis are associated with high serum levels of specific IgG subclass antibodies to allergens, particularly IgG4. In pemphigus, autoantibodies belong mainly to the IgG4 and IgG1 subclasses. IgG1 antibodies against desmoglein are present with equal frequency in individuals with and without pemphigus, but IgG4 antibodies are present almost exclusively in patients with active disease.^{23,36} The present study finds increased IgG4+ plasma cells in patients with pemphigus group, although the significant increase in IgG4+ plasma cells (>40% IgG4+/IgG+ plasma cells) is likely to represent IgG4-related sclerosing disease, since all reactive lymph nodes not associated with IgG4-related systemic disease have a proportion below 30%.³³ Abundant IgG4-bearing plasma cell infiltration, exceeding 40% of IgG+ cells, is a characteristic histological finding for cutaneous plasmacytosis, and is not found in skin biopsies of control patients. The IgG4+/IgG+ plasma cell ratio in the lung biopsy specimen was lower than in skin or lymph node. This is probably because the specimen was small and unrepresentative of the whole lesion, although it might have been due to a different disease process. Involvement of the lung as a form of lymphoid interstitial pneumonia in cutaneous plasmacytosis has been recognized.¹⁰

There is also some evidence that interstitial pneumonia occurs during the course of autoimmune pancreatitis.^{31,41} Chest CT revealed diffuse ground-glass attenuation with honeycomb changes at the base of the lower lobe, or mild interstitial shadows. The histology in one case showed thickening of the lower lobe septum, with marked IgG4-positive plasma cells.³¹ We suspect that there is a close relation between these pulmonary changes and cutaneous plasmacytosis, because of elevated serum IgG4 and the infiltration of IgG4-positive plasma cells in the lung tissue.

Cutaneous plasmacytosis could be a type of chronic allergic/hypersensitivity reaction, since allergic and atopic dermatitis are both associated with elevated IgE and IgG4. Our data were limited because of a lack of serum level of IgE and IgG4 in two of the three patients. None of our cases showed obliterative phlebitis or tissue fibrosis characteristic of IgG4-related sclerosing disease. Although our cases exhibited lymphadenopathy, bone marrow involvement, and possible evidence of lung infiltrates in one case, the evidence for cutaneous plasmacytosis as a skin lesion of an IgG4-related sclerosing disease was not convincing, because of the lack of pancreatic involvement. Activation of T helper 2 (Th2) cells is believed to play a major role in allergic sensitization. The Th2 cytokines produce IL-4, IL-5 and IL-13, leading to the secretion of IgG4 and IgE by B cells. Allergic diseases are characterized by activation of the immune system and formation of IgE antibodies against specific allergens; IgG4 represents blocking antibody to IgE-coated mast cells.⁴² A parallel increase in the serum IgE concentration was found in 20% of patients with sclerosing pancreatitis.²¹ IgG4-related sclerosing disease is an immune reaction mediated by Th2 cells and T regulatory cells.⁴³, suggesting that cutaneous plasmacytosis and IgG4-related sclerosing disease have a common disease

process. Unknown environmental agents might trigger the production of IgG antibodies against unknown antigens, and trigger the subclass switching to IgG4 in B-cells. The geographical distribution of both cutaneous plasmacytosis and IgG4-related sclerosing disease has led to speculation that a HLA susceptibility gene is necessary for pathogenic activity of the disease. Another possibility is a primary infectious cause. Hyperproduction of IL-6 is also considered to be an important factor in the pathogenesis of cutaneous plasmacytosis. IL-6 induces B-cell proliferation and terminal differentiation, immunoglobulin secretion, and induces the acute inflammatory-phase response. An increase in IL-6 concentration has also been reported in cutaneous plasmacytosis.^{13,16,44} Our cases were all associated with elevated serum IL-6. Further studies are needed to determine the role of IgG4 in the pathogenesis of this disease. Since cutaneous plasmacytosis and IgG4-related sclerosing disease are both extremely rare, to learn more it is necessary to investigate a large series of patients and to provide more evidence of systemic lesions for cutaneous plasmacytosis.

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Figure legends

Fig. 1 Skin and lung findings in patient 1

A: Diffuse red-brown papules on the chest and abdomen

B: Chest CT showing ground-glass opacities and slight reticular shadows.

C: Low-magnification photograph of cutaneous plasmacytosis showing dense perivascular and periadnexal infiltration of plasma cells in the deep dermis (HE, original magnification x20)

D: Histological findings of lung biopsy specimen from the right middle lobe. Thickened alveolar septa due to lymphoplasmacytic infiltration (HE, x200)

Fig. 2 Skin biopsy from patient 3

A: Numerous infiltration of plasma cells in the dermis (x100).

B, C: Immunostaining for IgG (B) and IgG4 (C) in the corresponding field. Increased IgG4+ cells are seen (x100).

Fig. 3 Lymph node from patient 1

A: Lymph node showing intact nodal architecture with reactive follicular hyperplasia (x200).

B: The interfollicular zone is expanded and is densely populated by mature plasma cells accompanied by high endothelial venules (x200).

C: Immunostaining for IgG. Numerous IgG+ cells are present between the follicles (x200).

D: Immunostaining for IgG4. The number of IgG4+ cells is slightly higher than that of IgG4+ cells in the corresponding field. The IgG4+/IgG+ cell ratio exceeds 50% (x200).

Table 1: Clinical features of patients with cutaneous plasmacytosis

Patient	Age (yr)	Gender	Serum IgG (mg/dL)	Serum IgG4 (mg/dl)	γ-globulin (%)	IL-6 (pg/mL)	Associated disease	Treatment	Follow-up (yr)
1	54	M	4637	610 (13.2%)	46	6.9	lymphadenopathy, interstitial lung disease	PSL 15mg	1.5
2	55	M	6480	NA	elevated	74.5	lymphadnopathy	tacrolimus ointment	0.3
3	61	M	2624	NA	26.8	4.6	lymphadenopathy, bone marrow plasmacytosis	PSL 15mg	3

IgG, normal value 870-1700mg/dL; IgG4, normal 4.8-105 mg/dL; γ-globulin, normal 10.6-20.5%; IL-6, normal <4 pg/mL; NA, not available; PSL, prednisolone

Table 2: IgG4+/IgG+ plasma cell count and ratio in the various involved tissues of patients with cutaneous plasmacytosis

Patient	Location	IgG4+/IgG+ plasma cells per HPF (%)
1	Skin	53/153 (42.2)
	Lymph node	136/189 (72.0)
	Lung	14/91 (15.4)
2	Skin	62/142 (43.7)
	Lymph node	43/87 (49.4)
3	Skin	72/124 (58.1)
	Lymph node	94/176 (53.4)
	Bone marrow	15/25 (60.8)

Table 3: IgG4+/IgG+ plasma cell count and ratio of control

A. Patients with pemphigus vulgaris

Patient	Age	Gender	Dsg1 IgG (normal <14)	Dsg3 IgG (normal <7)	IgG4+/IgG+ Plasma Cells per HPF (%)
1	53	F	119	>150	6.6/18 (36.7%)
2	73	F	105	2420	0/6 (0)
3	47	F	33	29	1.6/11 (14.5%)
4	63	M	43	2500	8.6/42 (20.5%)

B. Patients with pemphigus foliaceus

Patient	Age	Gender	Dsg1 IgG (normal <14)	Dsg3 IgG (normal <7)	IgG4+/IgG+ Plasma Cells per HPF (%)
5	77	F	+	-	11/53.7 (20.5%)
6	64	F	+	-	10/65.7 (15.2%)
7	21	F	240	-	5.6/19.6 (28.6%)

Dsg1, anti-desmoglein 1 antibody; Dsg3, anti-desmoglein 3 antibody

Table 3 (cond't)

C. Patients with discoid lupus erythematosus

Patient	Age	Gender	IgG4+/IgG+ Plasma Cells per HPF (%)
8	46	F	0/327 (0)
9	32	F	0/13 (0)
10	16	F	0/5 (0)
11	11	F	0/5.3 (0)
12	23	F	0/49 (0)

D. Patients with morphea

Patient	Age	Gender	IgG4+/IgG+ Plasma Cells per HPF (%)
13	51	M	0/3 (0)
14	56	M	0/4 (0)

A

B

C

D