

Isolated cutaneous manifestation of IgG₄-related disease

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ABSTRACT

Aims The cutaneous manifestation of IgG₄-related disease has rarely been reported. The aim of this study is to identify and describe the cutaneous manifestations associated with IgG₄-positive plasma cell infiltration in the skin.

Methods The authors investigated two cases of IgG₄-related disease with solitary skin lesions and compared the immunohistochemical characteristics of infiltrating cells among IgG₄-related disease, Kimura's disease and cutaneous pseudolymphoma.

Results IgG₄-related disease manifested as an indurated plaque on the anterior chest in one case and a nodule on the toe in the other case. Histopathologically, skin lesions of IgG₄-related disease showed a dense, mixed-cell infiltrate containing lymphocytes, plasma cells and eosinophils along with fibrosis. Plasma cells stained positively with anti-IgG and anti-IgG₄ antibodies, and the ratio of IgG₄⁺/IgG⁺ cells was more than 50%. Serum levels of IgG and IgG₄ were not elevated and no lesions were found in other organs. Skin samples taken from Kimura's disease showed histopathological features similar to those of IgG₄-related disease. The proportion of IgG₄⁺/IgG⁺ was high in Kimura's disease, but not in cutaneous pseudolymphoma.

Conclusions The solitary skin lesions of IgG₄-related disease were similar histologically and immunohistochemically to the skin lesions of Kimura's disease. The concept of IgG₄-related disease may help clarify the pathomechanism of diseases of unknown aetiology that possess features of IgG₄-related disease.

IgG₄-related disease is a recently proposed entity characterised by the presence of abundant IgG₄-positive plasma cells in lesions accompanied by tissue fibrosis and elevated serum IgG₄.^{1–4} One or more organs may be involved, but there are no reports of isolated IgG₄-related skin lesions. We report herein the clinicopathological features of two cases of IgG₄-related disease with solitary skin lesions characterised by abundant IgG₄-positive plasma cells.

The two patients, one woman and one man, with IgG₄-related disease were 58 and 40-years-old, respectively (table 1). The female patient had a 1-year history of an ill-defined, indurated plaque on the anterior chest (figure 1A,B) and the male patient had a 3-month history of a nodule on the toe (figure 1C). In case 1, the initial diagnosis was cancer en cuirasse secondary to metastatic carcinoma of the skin or lymphoma; it was noted that she had no history of breast cancer. In case 2, sporotrichosis was suspected; however, fungal culture was negative and oral potassium iodide

treatment was ineffective. Laboratory investigations showed that serum IgG and IgG₄ levels were not elevated (table 1). CT and MRI did not show additional lesions of IgG₄-related disease in the pancreas, bile duct, liver, kidneys, lungs, lymph nodes, lacrimal gland, thyroid gland, pituitary gland, mammary gland or retroperitoneal area. Sjögren's syndrome and Mikulicz's disease were unlikely in both cases. The plaque seen in case 1 showed some flattening after 16 months of treatment with a topical steroid. The nodule was resected in case 2, and no recurrence was noted at 9-months follow-up.

Histopathological examination of a skin specimen from case 1 showed fibrosis and a dense, mixed-cell infiltrate containing numerous lymphocytes, plasma cells and eosinophils with formation of lymphoid follicles, involving both the dermis and subcutaneous tissue (figure 2A,C). Most lymphoid follicles had irregularly shaped germinal centres. The lymphoid infiltrate comprised of a mixed population of CD20 B cells in the lymphoid follicles interspersed with CD3 T cells. IgG⁺ and IgG₄⁺ plasma cells were observed mainly in the inter-follicular areas (figure 2E,G). The number of IgG₄⁺ plasma cells was 49.2±18.5 (mean ± SD) per high power field (HPF) with an area of 40 000 μm², constituting 57.1% of the number of IgG⁺ cells (table 1). The specimen taken from the nodule of case 2 showed diffuse infiltrates of numerous mature plasma cells in the dermis accompanied by fibrosis around the infiltrate (figure 2B,D). The infiltrating cells were composed of numerous CD79α cells interspersed with CD3 T cells and a few eosinophils (figure 2D). The number of IgG₄⁺ plasma cells was 136.2±23.3 per HPF, and the proportion of IgG₄⁺/IgG⁺ cells was 59.7% (table 1). Neither light chain restriction nor clonal gene rearrangement of heavy chain was detected in either case.

The aetiology of cutaneous lymphoplasmacytic disorders, such as Kimura's disease and cutaneous pseudolymphoma, remains unknown. As these diseases demonstrate histological features similar to IgG₄-related disease, we hypothesised that IgG₄⁺ plasma cells might be involved in the pathogenesis. Thus, we reviewed cases of Kimura's disease and cutaneous pseudolymphoma and performed an immunohistochemical study assessing IgG₄ expression in these disorders. Table 1 lists the clinical and histological features and results of IgG₄ and IgG immunostaining in two cases of Kimura's disease (cases K1 and K2) and two cases of cutaneous pseudolymphoma (cases P1 and P2). Histopathological examination of specimens from these

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Table 1 Clinicopathological features of patients with cutaneous IgG₄-related disease, Kimura's disease and cutaneous pseudolymphoma

Case	Age	Sex	Area	Diagnosis	Duration	Blood tests		Histological findings			Immunohistochemistry			
						IgG	IgG ₄	Distribution	Eosinophils	Fibrosis	IgG+ cells/HPF	IgG ₄ + cells/HPF	IgG ₄ + /IgG+	
1	58	F	Chest	IgG ₄	1 y	1612 mg/dl	52 mg/dl	D-S	Abundant	(+)	86.2±39.7	49.2±18.5	57.1%	
2	40	M	Lt l toe	IgG ₄	3 m	802 mg/dl	25 mg/dl	D	Rare	(+)	228.2±42.6	136.2±23.3	59.7%	
K1	62	M	Rt cheek	KD	2 y	3013 mg/dl	ND	D-S	Abundant	(+)	136.0±35.8	135.8±20.7	99.9%	
K2	57	F	Rt lw eyelid	KD	2 y	ND	ND	D-S	Abundant	(+)	20.8±11.4	19.0±6.3	91.3%	
P1	56	F	Back	PL	1 y	1064 mg/dl	ND	D-S	None	(-)	58.6±27.8	8.0±4.5	13.7%	
P2	79	F	Forehead	PL	2 y	ND	ND	D-S	Rare	(-)	151.0±64.6	15.4±11.3	10.2%	

D, dermis; F, female; HPF, high power field; IgG₄, IgG₄-related disease; KD, Kimura's disease; Lt, left; lw, lower; M, Male; m, months; ND, not done; PL, cutaneous pseudolymphoma; rt, right; S, subcutis; y, year(s).

cases revealed dense infiltrates of mononuclear cells with the formation of lymphoid follicles in the dermis and subcutaneous tissue. Certain features, such as abundant eosinophils and distinct fibrosis, were peculiar to Kimura's disease in contrast to pseudolymphoma (table 1). Of note, the proportion of IgG₄⁺/IgG⁺ plasma cells was extremely high in Kimura's disease (99.9% and 91.3%), but this was not seen in pseudolymphoma (13.7% and 10.2%) (table 1). Serum IgG was elevated in one patient with Kimura's disease (case K1), but additional information was unavailable (table 1).

Although no globally accepted diagnostic criteria of systemic IgG₄-related disease exists, in Japan, it has been proposed that the diagnosis of IgG₄-related disease requires the presence of an elevated serum IgG₄ (>135 mg/dl) and histopathological evidence of lymphocyte and IgG₄-positive plasma cell infiltration (IgG₄⁺ plasma cells/IgG⁺ plasma cells >50% in five different HPF).⁵ According to the proposed Japanese diagnostic criteria, our two cases do not fulfil the criteria for the diagnosis of IgG₄-related disease since serum IgG₄ was not elevated. Thus,

our cases may be considered as possible IgG₄-related disease or cutaneous IgG₄-related disease.

There have been only a few reports of skin involvement in IgG₄-related disease.^{6–8} In these reports, all patients had extracutaneous involvement and serum IgG and IgG₄ levels were elevated in all but one patient. Although skin involvement is rare, these observations suggest that the skin is a target organ of IgG₄-related disease.

In this study, the solitary skin lesions of IgG₄-related disease were similar histologically and immunohistochemically to the skin lesions of Kimura's disease. We propose that these cutaneous lymphoplasmacytic disorders may overlap with IgG₄-positive plasma cells playing a central role in the development of these diseases (figure 3). IgG₄-related disease is a new disease concept focusing on abundant infiltration of IgG₄-positive plasma cells and fibrosis in lesions associated with elevated levels of serum IgG₄. This new concept may help clarify the pathomechanism of diseases of unknown aetiology that possess features of IgG₄-related disease.

Figure 1 (A) Erythematous, ill-defined, unevenly elevated and indurated plaque on the anterior chest in case 1. Close up photo of the plaque (B) Erythematous and ill-defined nodule on the dorsum of the left big toe in case 2 (C) The dried scab on the nodule at the site of the punch biopsy is visible.

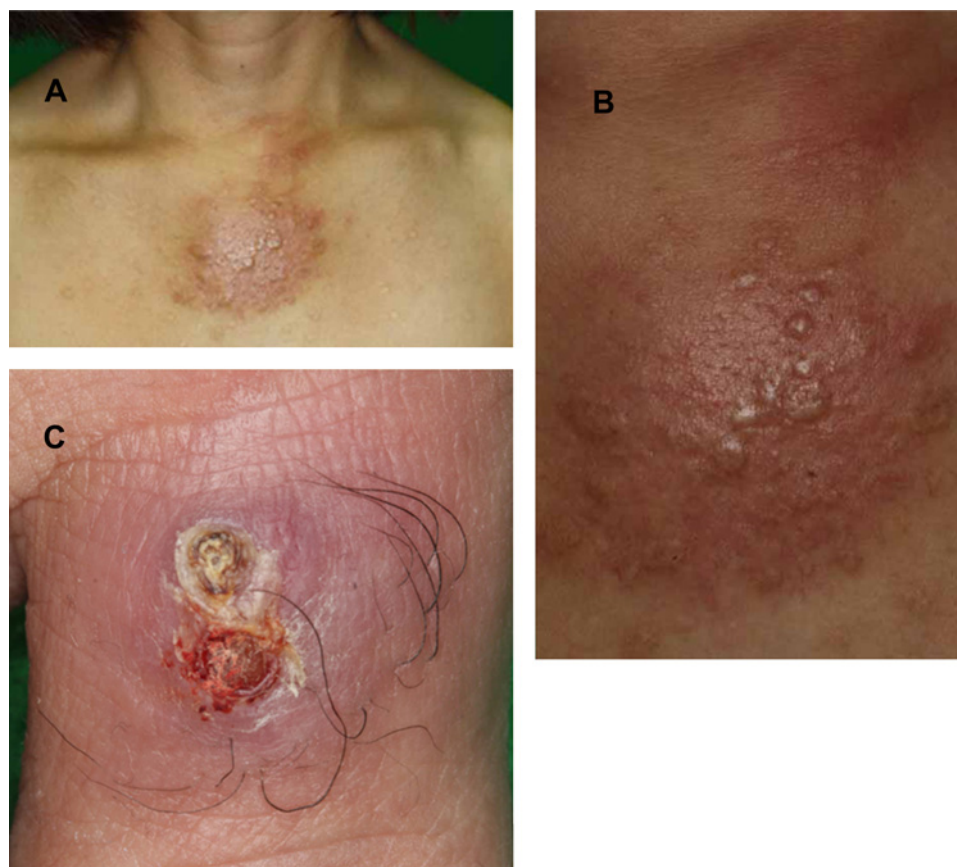


Figure 2 Histopathological examination of a skin biopsy taken from the plaque of case 1 showed fibrosis, a dense mixed-cell infiltrate and formation of lymphoid follicles (A). The infiltrate contained numerous lymphocytes, plasma cells and eosinophils (C). IgG and IgG₄ immunostaining show prominent IgG⁺ and IgG₄⁺ plasma cells within the interfollicular areas (E and G, respectively). Histopathological examination of a specimen taken from the nodule of case 2 showed a diffuse infiltrate in the dermis surrounded by fibrosis (B). Numerous mature plasma cells were present in the infiltrate (D). The plasma cells were positive for IgG (F) and IgG₄ (H) as assessed by immunohistochemistry. (A–D) H&E. Original magnification: (A, B) $\times 40$; (C, D) $\times 400$; (E–H) $\times 200$.

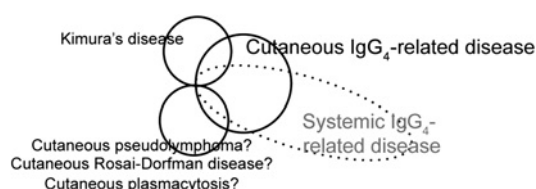
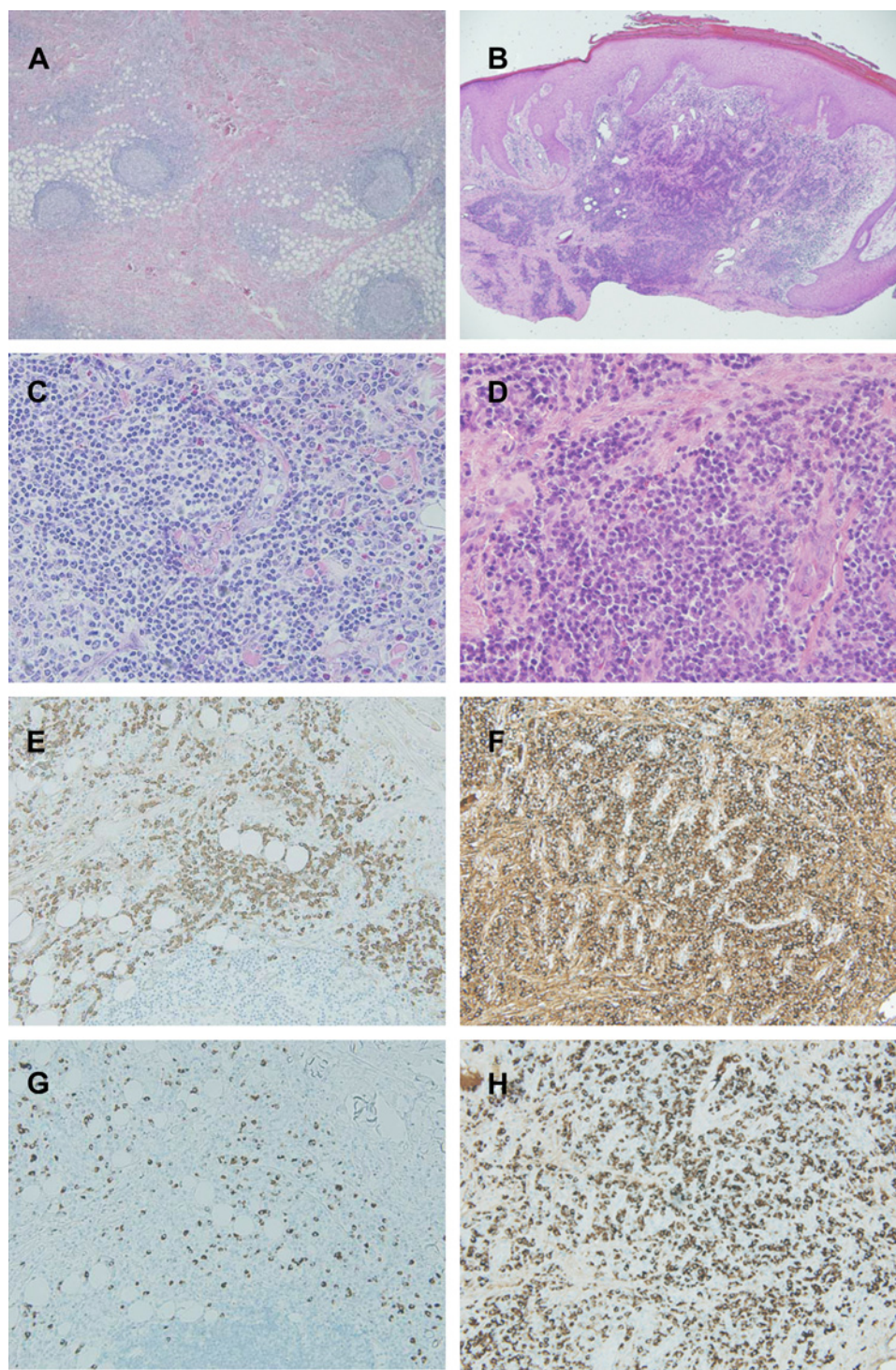


Figure 3 Schematic illustration of cutaneous lymphoplasmacytic disorders.

Take-home messages

- ▶ IgG₄-related disease is a new disease concept focusing on abundant infiltration of IgG₄-positive plasma cells and fibrosis in lesions associated with elevated serum IgG₄.
- ▶ Solitary skin lesions may appear in IgG₄-related disease.
- ▶ The solitary skin lesions of IgG₄-related disease were similar histologically and immunohistochemically to those of Kimura's disease.

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Competing interests None.

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