formation of the severe phenotype in our patient. Further functional studies are required to elucidate the pathomechanisms of the severe DD underlying this mutation. Moreover, no neuropsychiatric symptoms were presented in our patient. It is possible that compensatory mechanisms might include increased expression of the normal *ATP2A2* allele and/or compensation by other SERCA pumps expressed in the brain [4].

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Letter to the Editor

YKL-40 (chitinase 3-like-1) as a biomarker for psoriasis vulgaris and pustular psoriasis

To the Editor

Psoriasis is a chronic inflammatory skin disease characterized by inflammatory cell infiltrates and hyperproliferation of epidermal cells. There are several types of psoriasis, including psoriasis vulgaris (PV), psoriasis guttata, psoriatic arthritis, psoriatic erythroderma, and generalized pustular psoriasis (GPP). The severity of psoriasis is commonly evaluated by clinical findings of skin and blood tests including inflammatory markers such as white blood cell count (WBC), C-reactive protein (CRP), and cytokines such as IFN-γ, IL-8, IL-12, IL-18, and VEGF [1]. However, a more sensitive and specific marker is required to evaluate and standardize the severity of psoriatic disorders.

Table 1
Baseline characteristics of patients.

	Controls	PV	GPP	*P*-value		
				Controls vs. PV	Controls vs. GPP	PV vs. GPP
Patients, no.	21	41	21			
Male sex, no. (%)	14 (66.6)	35 (85.4)	13 (61.9)	$P > 0.05$	$P > 0.05$	$P > 0.05$
Age (years)						
Mean	45.5	52.6	51.2	$P > 0.05$	$P > 0.05$	$P > 0.05$
Range	28–78	21–82	2–86			
YKL-40 (ng/mL)						
Mean	29.4	99.1	493.5	$P < 0.001$	$P < 0.001$	$P < 0.001$
Range	7.6–66.2	17.3–310	38.8–2486			

YKL-40 (chitinase 3-like protein 1, CHI3L1) and its mouse homologue BRP-39 are chitinase-like proteins that lack chitinase activity [2]. The physiological functions of YKL-40 have not been fully delineated, but BRP-39 and YKL-40 must at least play a pivotal role in antigen sensitization [3] because BRP-39$^{-/-}$ mice have markedly diminished antigen-induced T cell responses. Clinically, increased serum levels of YKL-40 have been reported in conditions with inflammation and/or tissue remodeling, such as rheumatoid arthritis, Crohn's disease and cancers [2]. This prompted us to assess serum levels of YKL-40 as a potential biomarker for psoriasis.

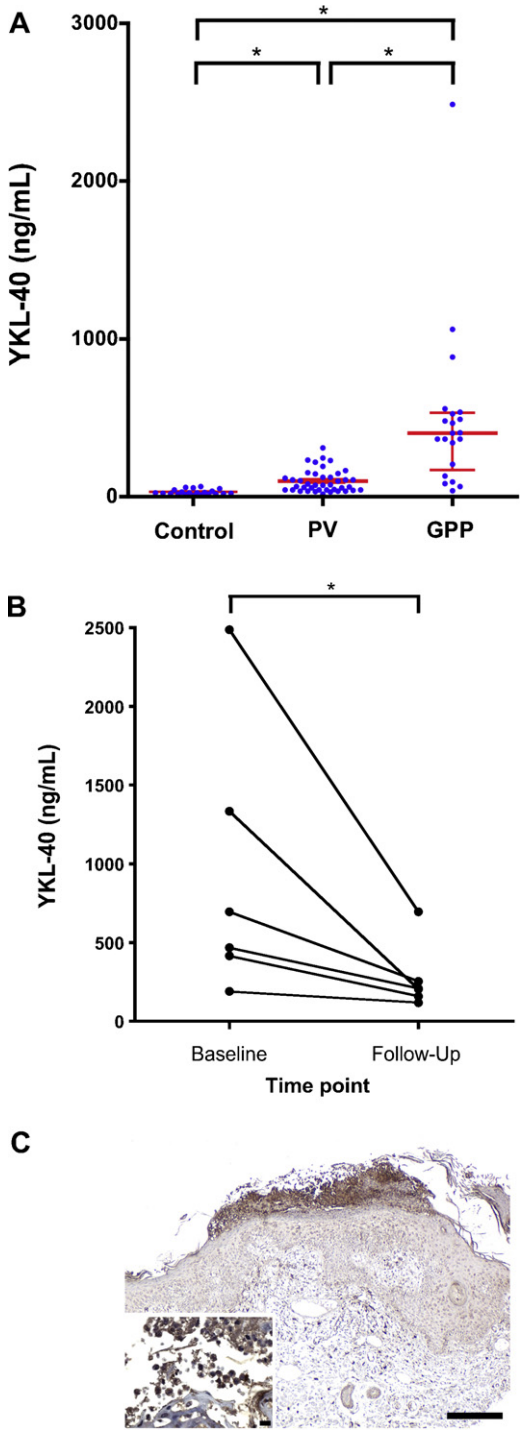

Fig. 1. (A) Serum YKL-40 levels in patients with PV or GPP and in healthy controls. Values are expressed as means (horizontal lines) and SEMs (top and bottom of each bar). $^*P < 0.001$. (B) Serum YKL-40 levels before and after the treatment of 6 patients with GPP. $^*P < 0.05$. (C) Immunolocalization of YKL-40 in skin biopsy specimens from patients with GPP. Neutrophils are positive for YKL-40 (inset). Bars, 500 μm for (C); 10 μm for (inset).

Participants of the study included 21 healthy volunteers and 62 patients with psoriasis who presented to the Department of Dermatology, Hyogo College of Medicine College Hospital and of the Okayama University Hospital. Patient characteristics are summarized in Table 1. They had no anamnesis of atopic and/or allergic disorders. This study was approved by the Institutional Ethics Committees, and informed consent for the research was obtained from each participant.

Serum concentrations of YKL-40 were measured using an ELISA kit (Quidel, San Diego, CA). The mean serum values of YKL-40 in patients with PV or GPP were 99.1 (range: 17.3–310.0) or 493.5 (range: 38.8–2486.0) ng/mL, respectively, whereas the mean serum value of YKL-40 in the healthy controls was 29.4 (range: 7.6–66.2) (Fig. 1A). The serum values of YKL-40 in patients with PV or GPP were significantly higher than in the healthy controls (Dunn's test, $P < 0.001$). Moreover, the serum values of YKL-40 in patients with GPP were significantly higher than in the PV patients ($P < 0.001$). The high serum YKL-40 levels for 6 patients with GPP (Baseline) were significantly improved after (Follow-Up) the treatment (Wilcoxon signed rank test, $P < 0.05$) (Fig. 1B). In comparison with the common inflammatory markers and serum cytokines in patients with GPP, the YKL-40 levels were significantly correlated with WBC, neutrophil count and CRP (Spearman's test, $r = 0.31$, $P < 0.05$; $r = 0.298$, $P < 0.05$; and $r = 0.35$, $P < 0.05$, respectively). The expression of YKL-40 in skin biopsy specimens was examined by immunohistochemistry using an anti-YKL-40 antibody (R&D Systems, Minneapolis, MN) [4]. A goat-IgG (Jackson ImmunoResearch Laboratories, West Grove, PA) was used for the control. YKL-40 was evident in the cytoplasm of neutrophils that had infiltrated the Kogoj's spongiform pustules in the epidermis of patients with GPP (Fig. 1C).

This is the first report describing YKL-40 as a novel serum biomarker for psoriasis. Serum levels of YKL-40 on average in PV were about 3 times higher than in healthy subjects. Elevated serum levels of YKL-40 have been reported in other inflammatory disorders, such as asthma [4,5] and rheumatoid arthritis [6], but YKL-40 levels in those diseases were limited to around 2-fold higher than the controls. In patients with GPP, the serum levels of YKL-40 were much higher than in patients with PV. Possibly, the elevated levels of YKL-40 in psoriasis may suggest the involvement of joint inflammation or of more systemic or severe inflammatory conditions. The YKL-40 levels in GPP also correlated with other common inflammatory markers, and decreased along with the improvement of skin symptoms. A major source of serum YKL-40 in GPP may be activated neutrophils, because neutrophils strongly express YKL-40 in the epidermis to form spongiform pustules of Kogoj. Therefore, YKL-40 may be a useful biomarker which reflects the clinical course and severity of GPP, although the advantage of YKL-40 over other serum cytokines remains to be investigated.

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Letter to the Editor

Merkel cell carcinoma with cytokeratin 20-negative and thyroid transcription factor-1-positive immunostaining admixed with squamous cell carcinoma

Merkel cell carcinoma (MCC) is an aggressive cutaneous tumor with a rapidly increasing incidence. Merkel cell polyomavirus (MCPyV) is a recently identified virus that may be involved in the oncogenesis of MCC [1].

The diagnosis of MCC requires immunohistochemical markers. Distinguishing primary MCC from small cell carcinoma of the lung (SCCL) is a critical issue. Most MCC stain positive for cytokeratin 20 (CK20) and negative for thyroid transcription factor-1 (TTF-1). MCPyV, identified using polymerase chain reaction (PCR), is a specific marker for MCC that can be helpful for differentiating MCC from SCCL and other neuroendocrine tumors [2]. Here we report a collision tumor comprising a rare variant type of MCC with CK20-negative and CD56/TTF-1-positive immunostaining and invasive SCC.

An 89-year-old woman presented with an erythematous protruding nodule measuring approximately 2.5 cm in the left temporal area (Fig. 1A). The nodule had grown rapidly over the previous 4 months. Physical examination revealed no other abnormal findings, including lymph node enlargement. Imaging studies revealed no regional or distant metastatic spread of the disease. The lesion was completely excised with a clear margin. Histopathologic examination revealed two distinct lesions: a dermal nodule comprising round basophilic cells and an epidermal lesion adjacent to the dermal nodule with showing proliferation of atypical squamoid cells with an infiltrative pattern (Fig. 1B–D). The immunohistochemical profile of the dermal neoplastic cells was distinctively positive for CD56 and TTF-1 with diffuse cytoplasmic staining (Fig. 1E and F), and negative for CK20 (Fig. 1G), leukocyte common antigen (LCA), and S-100. Squamoid proliferations admixed with dermal MCC were strongly stained with AE1/AE3, but not CK20, CD56, TTF-1, LCA, or S-100. There was no clear transition in the staining patterns between the dermal and epidermal components. Ultrastructural examination of tumor cells within the dermis from formalin-fixed tissue showed round, membrane-bound granules, approximately 100 nm in diameter, with a dense core and a submembranous lucent halo, indicating neurosecretory granules, but not the characteristic paranuclear whorls of intermediate filaments (Fig. 1H). Tumor cells were

Table 1
Immunohistochemical expression of CK20, CD56, TTF-1, AE1/AE3, and CM2B4 in Merkel cell carcinoma, squamous cell carcinoma, and small cell lung cancer.

	CK20	CD56	TTF-1	AE1/AE3	CM2B4
MCC	86.7%	90.6%	0%	94.2%	75%
SCC	Neg.	Neg.	Neg.	Posi.	Neg.
SCLC	4.6%	100%	85.2%	33%	0%

Abbreviations: CK20, cytokeratin 20; TTF-1, thyroid transcription factor-1; MCC, Merkel cell carcinoma; SCC, squamous cell carcinoma; SCLC, small cell lung carcinoma; Neg., negative; Posi., positive.