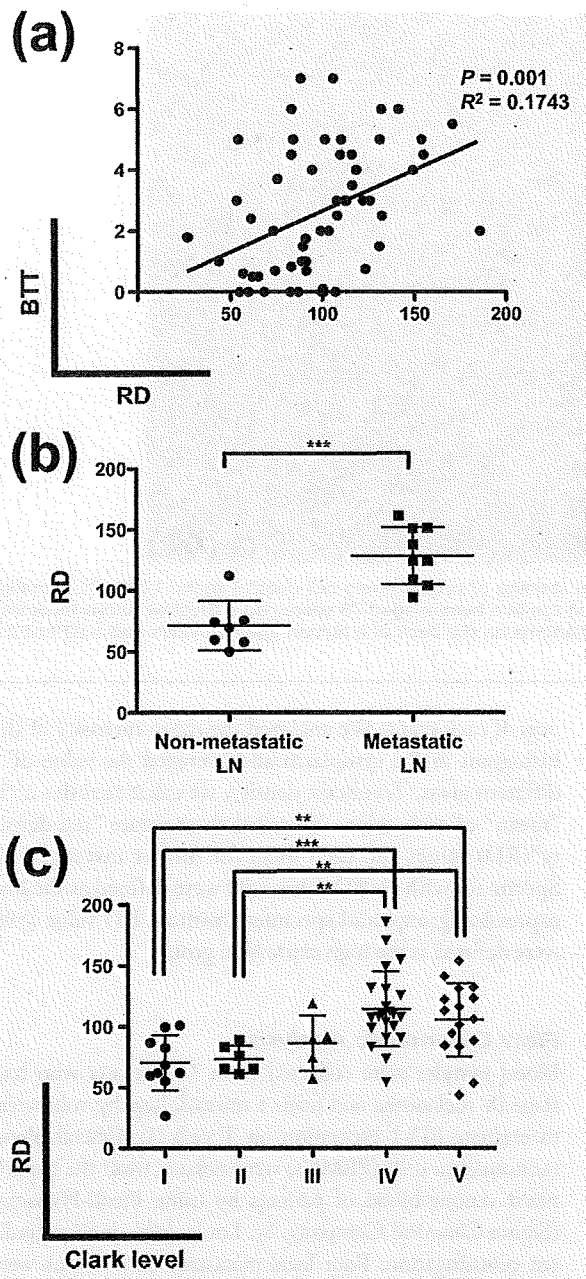

Figure 2. Correlations of programmed cell death-1 (PD-1) expression levels with Breslow tumor thickness (BTT), lymph node (LN) metastasis, and Clark level are illustrated. (a) A linear correlation was observed between red density (RD) and BTT. (b) In this comparison, RD in resected LNs was analyzed using an analysis of variance (ANOVA) between 2 groups: 1 with and 1 without LN metastasis. Error bar represents the mean ± standard deviation. (c) In this comparison, RD was analyzed by ANOVA among 5 groups with different Clark levels. Error bars represents the mean ± standard deviation; double asterisks, $P < .01$ (between the means); triple asterisks, $P<.001$ (between the means).

NaN_3 and 1% fetal calf serum. After incubation for 30 minutes at 4°C with MoAbs or isotype-matched controls, cells were washed twice and analyzed on a FACSCanto (Becton Dickinson, Mountain View, Calif). The mean fluorescence intensity (MFI) was calculated on a log scale.

Statistical Analyses

Fisher exact tests, chi-square tests, and Student *t* tests for unpaired data were used to analyze the association between PD-L expression and various clinicopathologic factors. The Pearson coefficient test was used to evaluate the correlation between RD and BTT. Univariate analyses of overall survival and progression-free survival were conducted with the log-rank test, and Kaplan-Meier curves were generated. Overall and progression-free survival was calculated from the date of operation to the date of first recurrence, death, or last follow-up. Multivariate comparisons were made using the Cox proportional hazards model. Except for the Cox multivariate analysis, every analysis was performed by using GraphPad Prism 5.0 software (GraphPad Software, Inc., San Diego, Calif). The Cox multivariate analysis was performed by using the JMP 5.0.1J software package (SAS Institute, Cary, NC). All *P* values $<.05$ were considered statistically significant.

RESULTS

Clinical Patient Profiles

The clinical characteristics of 59 patients (ratio of men to women, 38:21) are summarized in Table 1 in relation to expression levels of PD-L1 in tumor cells (low and high). The average patient age was 69.47 years (range, 25-87 years; standard deviation, 13 years). The most common site of melanoma was the extremity (78%), followed by the trunk (15.3%), and head and neck (6.8%). Thirty-nine patients were diagnosed with acral lentiginous melanoma, 10 patients were diagnosed with nodular melanoma, 8 patients were diagnosed with superficial spreading melanoma, and 2 patients were diagnosed with lentigo maligna melanoma. According to the AJCC staging system,[29] 8 patients (13.6%) had stage 0 melanoma, 6 patients (10.2%) had stage IA melanoma, 9 patients (15.3%) had stage IB melanoma, 8 patients (13.6%) had stage IIA melanoma, 7 patients (11.9%) had stage IIB melanoma, 5 patients (8.5%) had stage IIC melanoma, 3 patients (5.1%) had stage IIIA melanoma, 5 patients (8.5%) had stage IIIB melanoma, 7 patients (11.9%) had stage IIIC melanoma, and 1 patient (1.7%) had stage IV

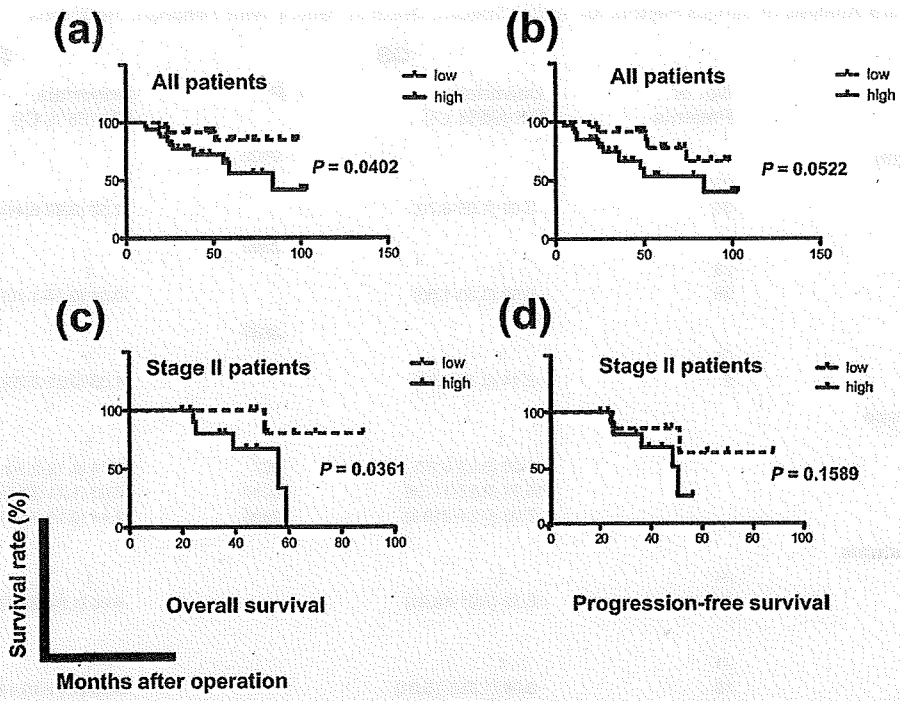

Figure 3. These Kaplan-Meier curves illustrate (a) an analysis of overall survival for patients who had high or low expression of programmed cell death-1 ligand 1 (PD-L1), (b) an analysis of progression-free survival for patients who had high or low expression of PD-L1, (c) an analysis of overall survival for patients with stage II disease who had high or low expression of PD-L1, and (d) an analysis of progression-free survival for patients with stage II disease who had high or low expression of PD-L1.

melanoma. Ulceration was present in 18 patients (30.6%). LN metastases were observed in 16 patients.

PD-L1 Expression and Tumor Cell Expression

The primary tumors from each patient was stained immunohistochemically for PD-L1, and the intensity of its expression level was analyzed as described above (see Materials and Methods). There were 25 patients in the "low-expression" group (RD value, <90) and 34 patients in the "high-expression" group (RD value, ≥90). Representative histopathologic photomicrographs for the high-expression and low-expression groups are provided in Figure 1a and Figure 1b, respectively. The correlations between the PD-L1 expression level and clinical patient profiles are summarized in Table 1. There was no significant correlation between sex and RD or between age and RD. The BTT in the high-expression group was significantly higher than that in the low-expression group ($P = .0298$). The correlation coefficient between the BTT and the RD value was statistically significant (Fig. 2a), indicating that there was a correlation between PD-L1 expression and the vertical growth of malignant melanoma. Tumors that were classified as T3-T4 exhibited a significantly higher PD-L1 expression than tumors that were classified as T0-T2 ($P = .0072$). PD-L1 expression was not associated with ulceration ($P = .4031$). PD-L1 expression in primary tumors from patients with LN metastasis was significantly higher than that in patients without LN metastasis ($P = .0375$). Furthermore, PD-L1 expression in metastatic LNs was significantly higher than that in nonmetastatic LNs (Fig. 2b) (mean RD value, 128.7 vs 71.4; $P < .0001$). Patients with Clark level IV and V tumors expressed significantly higher RD values than patients with Clark level I and II tumors (Fig. 2c).

Survival and Multivariate Analyses

The overall survival rate was significantly lower in the PD-L1 high-expression group compared with the low-expression group (Fig. 3a, Table 2) according to Kaplan-Meier survival analyses and log-rank tests. The progression-free survival rate tended to differ between the low-expression and high-expression groups (Fig. 3b, Table 2). Among the other clinicopathologic factors, including the clinical melanoma type (superficial spreading melanoma), primary tumor status,

Table 2. Univariate Analysis of Various Factors for Tumor-Specific Death in Patient With Malignant Melanoma

Variable	No. of Patients	OS Univariate RR (95% CI)	OS P	PFS Univariate RR (95% CI)	PFS P
PD-L1 expression			.0402		.0522
Low	25	1		1	
High	34	3.02 (1.05-8.70)		2.52 (0.99-6.44)	
Age, y			.3399		.3685
≤69	23	1		1	
≥70	36	0.62 (0.23-1.66)		0.64 (0.24-1.70)	
Sex			.3685		.5292
Men	14	1		1	
Women	9	2.44 (0.78-7.65)		1.38 (0.51-3.76)	
Clinical tumor type					
ALM		1		1	
NM		1.20 (0.23-6.37)	.827	0.74 (0.19-2.90)	.6616
SSM		15.94 (2.27-111.8)	.0054	6.03 (1.11-32.71)	.0375
LMM		7.06 (0.24-210.8)	.2596	2.44 (0.16-37.91)	.523
Primary tumor status					
pTis-pT2	24	1		1	
pT3-pT4	35	6.32 (2.01-19.91)		6.66 (1.94-22.89)	
Ulceration					
Absent	41	1		1	
Present	18	3.98 (1.058-15.01)		3.35 (1.11-10.14)	
LN metastases					
pN0	44	1		1	
pN1-pN3	15	22.66 (5.776-88.89)		29.32 (7.18-119.8)	

OS indicates overall survival; PFS, progression-free survival; RR, risk ratio; CI, confidence interval; PD-1, programmed cell death-1 ligand 1; ALM, acral lentiginous melanoma; NM, nodular melanoma; SSM, superficial spreading melanoma; LMM, lentigo maligna melanoma; pT, pathologic tumor classification; pTis, pathologic tumor in situ; pN, pathologic lymph node status.

ulceration, and LN metastasis differed significantly between the 2 expression groups in both overall survival and progression-free survival (Table 2). In patients with stage II melanoma, the high PD-L1 expression group had a significantly lower survival rate than the low-expression group according to log-rank tests (Fig. 3c), and the progression-free survival rate was marginally low without significance in the high-expression group (Fig. 3d). In patients with stage II melanoma, both the low-expression group and the high-expression group exhibited the same BTT levels, but the high-expression group had a significantly lower survival rate. Therefore, we determined that PD-L1 expression is a BTT-independent factor for prognosis.

Multivariate analyses using a Cox proportional hazards model indicated that overall and progression-free survival rates for the high PD-L1 expression group were significantly lower than those for the low-expression group (Table 3). The other factors that contributed to the overall poor survival were primary tumor status, ulceration, and LN metastasis (Table 3), whereas age, sex, and clinical type had no correlation. These data clearly demonstrate that PD-L1 expression in tumor cells is correlated inversely with the prognosis of patients with malignant melanoma and that PD-L1 expression is an independent prognostic factor for both overall and progression-free survival in these patients.

Elevated PD-1 Expression on T Cells in Stage IV Patients

We evaluated PD-1 expression on CD8-positive and CD4-positive T cells in the peripheral blood from patients with stage IV malignant melanoma. Representative flow cytometric data are shown in Figure 4a, which indicates that there was high expression of PD-1 on CD8-positive T cells and on some populations of CD8-negative cells from a patient with melanoma compared with a normal individual. In all patients that we examined who had stage IV melanoma, both CD8-positive and CD4-positive T-cell populations had significantly higher PD-1 levels

Table 3. Cox Multivariate Analysis of Independent Risk Factors for Tumor-Specific Death in Patients With Malignant Melanoma

Variable	No. of Patients	OS		PFS	
		Multivariate RR (95% CI)	*P*	Multivariate RR (95% CI)	*P*
PD-L1 expression			.0125		.0364
Low	25	1.00		1.00	
High	34	2.04 (1.15-4.26)		1.67 (1.04-2.95)	
Age, y			.904		
≤70	24	1			
≥70	35	0.81 (0.49-1.36)	.403	0.80 (0.51-1.30)	.358
Sex					
Men	38	1.00			
Women	21	1.11 (0.65-1.83)	.685	0.96 (0.57-1.53)	.867
Clinical tumor type					
ALM	39	1.00		1	
SSM	8	1.58 (0.73-2.97)	.2162	1.79 (0.92-3.27)	.0841
NM	10	1.34 (0.63-2.50)	.4133	1.22 (0.57-2.23)	.5696
LMM	2	1.01 (0.00-2.34)	.9868	0.96 (0.23-2.20)	.9404
Primary tumor status					
pTis-pT2	24	1		1	
pT3-pT4	35	4.40 (1.96-18.78)		2.67 (1.52-5.57)	
Ulceration					
Absent	41	1.00		1.00	
Present	18	1.73 (1.04-3.00)		1.84 (1.16-3.05)	
LN metastasis					
pN0	44	1.00		1.00	
pN1-pN3	15	1.69 (1.02-2.80)		1.66 (1.04-2.63)	

OS indicates overall survival; PFS, progression-free survival; RR, risk ratio; CI, confidence interval; PD-1, programmed cell death-1 ligand 1; ALM, acral lentiginous melanoma; SSM, superficial spreading melanoma; NM, nodular melanoma; LMM, lentigo maligna melanoma; pT, pathologic tumor classification; pTis, pathologic tumor in situ; LN, lymph node; pN, pathologic lymph node status.

compared with the levels in normal, healthy controls (Fig. 4b,c). We also examined PD-1 expression levels in tumor-infiltrating, CD8-positive cells in metastatic skin lesions from 2 patients. The tumor-infiltrating, CD8-positive T cells, as represented by the data from 1 patient obtained at the initial occurrence of melanoma and 3 months later (Fig. 5a), revealed increased expression of PD-1 as the disease progressed. The changes in the degree of PD-1 expression on the CD8-positive T cells from these 2 patients are illustrated in Figure 5b.

DISCUSSION

We investigated the expression of PD-L1 in resected specimens from patients with malignant melanoma and observed that there is a correlation between the degree of PD-L1 expression and the vertical growth of primary malignant melanoma. Moreover, our multivariate analysis demonstrated that PD-L1 expression is an independent, poor prognostic factor for malignant melanoma. A representative finding is that the survival rate of the PD-L1 high-expression group was significantly lower than that of the low-expression group with stage II melanoma. Although there has been a report regarding PD-L1 expression on melanoma cells,[19] the clinical significance of PD-L1 in melanoma has not been fully elucidated. Our current study clearly demonstrated the relevance of PD-L1 expression to the growth and prognosis of melanoma cells. The direct involvement of PD-L1 has been demonstrated through the mechanism by which cancer cells escape from the lysis by activated T cells.[28] The expression of PD-Ls on the cell surface of tumor cells, per se, or on antigen-presenting cells in the tumor environment may induce the apoptosis of tumor-reactive T cells through the engagement of PD-1 and, consequently, may promote tumor growth.[19]

Alternative mechanisms underlying the immunosuppression by melanoma cells have been postulated. Patients with melanoma have high serum levels of IL-10,[7] and the number of IL-10–producing monocytes are increased in these patients.[13] It is possible that the elevated

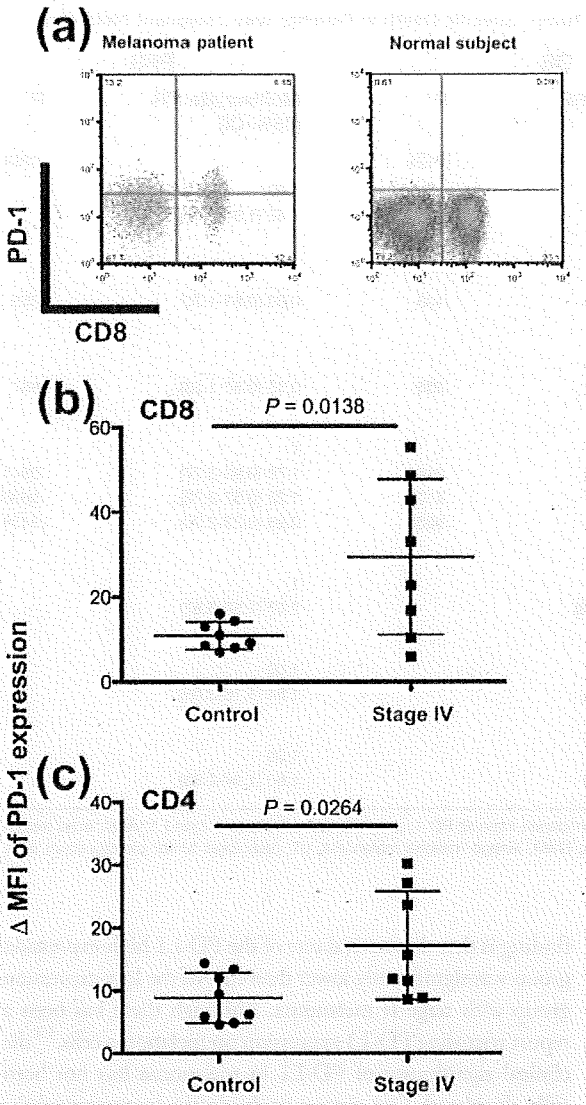

Figure 4. Programmed cell death-1 (PD-1) expression is illustrated in CD8-positive (CD8+) and CD4+ cell populations in peripheral blood. Peripheral blood mononuclear cells were isolated from the peripheral blood of patients with stage IV melanoma and subjected to flow cytometric analysis. Representative flow cytometric analyses of PD-1 expression on CD8+ cells are illustrated in (a) a patient with stage IV melanoma and (b) a normal, healthy control. PD-1 expression is illustrated (a) on CD8+ cells, (b) on CD4+ cells, and in normal, healthy controls. Error bars represent the mean ± standard deviation. MFI indicates mean fluorescence intensity.

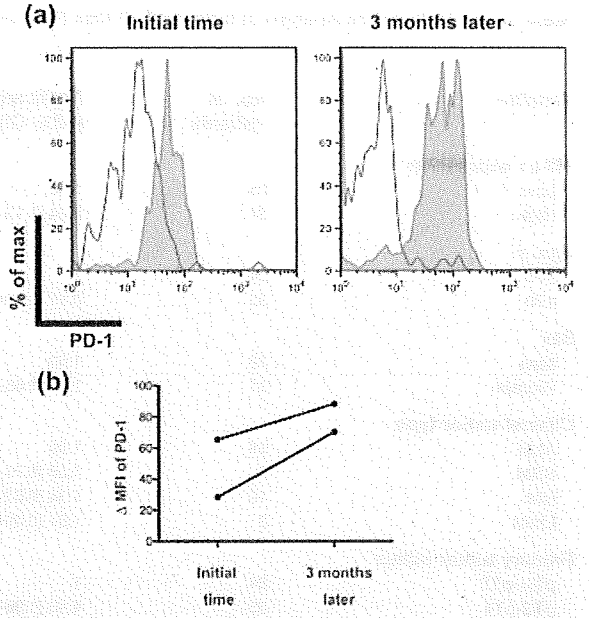

Figure 5. Elevated programmed cell death-1 (PD-1) expression in tumor-infiltrating CD8-positive T cells during tumor progression is shown. (a) PD-1 expression on CD8-positive cells from tumor-infiltrating lymphocytes is illustrated (left) at the initial occurrence of a metastatic skin tumor and (right) 3 months later. The tinted area indicates PD-1 expression; solid line, isotype control. Max indicates maximum. (b) In 2 patients, the alteration of PD-1 expression on CD8-positive cells was monitored. The mean fluorescence intensity (MFI) was calculated as (MFI of PD-1 expression) – (MFI of isotype control).

production of IL-10 by those cells leads to the immunosuppression of tumor immunity by inhibiting cytotoxic T cells or tumor antigen-presenting cells. In addition, IL-10[30] and transforming growth factor-b[31] can be produced by melanoma cells. In another scenario, the melanoma cell also can induce CD25-positive/Foxp3-positive Treg cells.[8] The presence of a high percentage of Treg cells in metastatic LNs also has been reported.[31] Tumor cells spreading into the LN may induce Treg cells, which allow tumor cells to grow locally, and Treg cells may be activated further by unique or shared tumor antigens.[31] A recent finding demonstrated that PD-L1 signaling regulates the conversion of naive, CD4-positive/CD25-negative/Foxp3-negative T cells into FoxP3-positive Treg cells.[32] These findings suggest that PD-L1 on melanoma cells causes immunosuppression by PD-L1–induced Treg cells as well as PD-1/PD-L1 interaction.

PD-1 is expressed on "exhausted" T cells and suppresses immune activation.[33] PD-1 is expressed on post-vaccination, melanoma antigen-specific, cytotoxic T lymphocytes (CTLs).[34] PD-1 blockade during peptide stimulation augmented the absolute numbers of vaccine peptide tetramer-positive CTLs.[34] Our study also demonstrated that PD-1–bearing, CD8-positive cells were increased in PBMCs and in the tumor microenvironment. The number of circulating PD-1–positive/CD8-positive

T cells increased further as the disease progressed. Therefore, it is likely that the exhausted tumor-killing T cells are elevated in number in parallel with the elevation of its ligand on the tumor cell. This dual alternation strongly suggests the clinical importance of PD-L1 expression on melanoma cells. Our findings provide evidence of the clinical relevance of PD-L1 expression. When PD-L1 is highly expressed on tumor cells in biopsy or excised specimens from patients with melanoma, more careful follow-up and management may be required because of the predicted poor prognosis. Although treatments for melanoma are performed on the basis of the stage of this neoplasm,[29] the PD-L1 expression level may be an additional informative item for the consideration of treatments. Furthermore, it is possible that patients who have high PD-L1 expression are refractory to immunotherapies because of their "exhausted" tumoricidal T cells. For example, immunotherapy using tumor-antigenic peptides induces CTLs against tumor cells; however, when CTLs express PD-1, they may be less functional. Likewise, therapy with tumor antigen-specific MoAbs by antibody-dependent cellular cytotoxicity[2] may be ineffective in patients who have high PD-L1 expression.

Malignant melanoma is an immunogenic[1] but immunosuppressive[7] tumor. Our current finding that PD-L1 expression is correlated with tumor proliferation and patient survival indicates the immunosuppressive aspect of melanoma. Many groups of investigators have reported that blockade of the PD-1/PD-L1 interaction promotes tumor immunity.[35-37] Conversely, there remains a problem regarding PD-1/PD-L1 blockade because of the possible expansion of poorly immunogenic cells.[38] Further studies may be required to clarify the therapeutic effect of PD-1/PD-L1 blockade in malignant melanoma models and clinical trials.

CONFLICT OF INTEREST DISCLOSURES

Supported in part by the program for Promotion of Fundamental Studies in Health Sciences of the National Institute of Biomedical Innovation.

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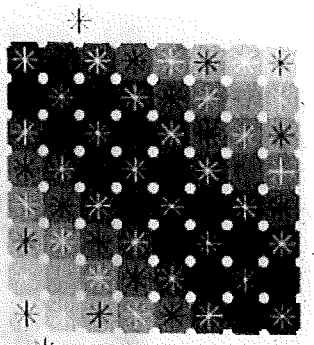
皮膚外科による治療



門野岳史
東京大学大学院医学系研究科皮膚科学教室講師

皮膚外科では皮膚におけるさまざまな問題を，主として外科的に解決します。

皮膚がんや皮膚の良性の腫瘍をおもに扱いますが，そのほかにも，あざ，熱傷，感染症，瘢痕，皮膚潰瘍，陥入爪（巻き爪）といった，さまざまな皮膚疾患も対象となります。本稿ではいくつかの具体例とともに，皮膚外科による治療がどのようなものであるかについて述べます。

皮膚がんの治療

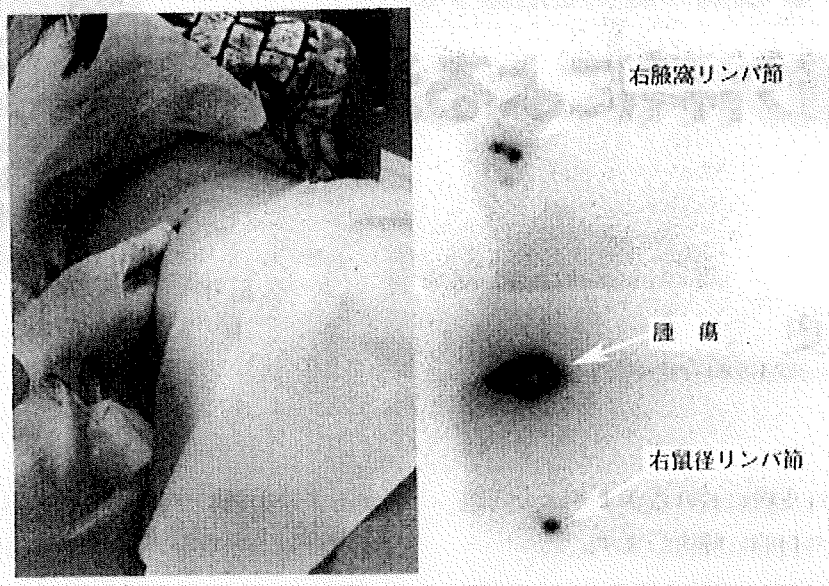
●悪性黒色腫に対するセンチネルリンパ節生検

皮膚がんにはさまざまな種類がありますが，そのなかでもホクロ（黒子）のがんである悪性黒色腫（メラノーマ）は有名です。病気の詳細については別稿に譲りますが，この悪性黒色腫の予後を決める重要な因子はほかのがんと同様，リンパ節に腫瘍細胞が転移するかどうかです。悪性黒色腫がその近傍にある所属リンパ節に転移していれば，その複数個ある所属リンパ節すべてを取るリンパ節郭清術が必要になるのですが，問題はリンパ節に実際に転移しているかどうかを術前に見分けることが困難であることです。肉眼上明らかに腫れている場合や，超音波やCTなどの画像検査で明らかに異常がみられた場合は別ですが，多くの例では悪性黒色腫が所属リンパ節に転移しているかどうか，明らかではありません。

リンパ節郭清をするかどうかによって，術後の生活の質には大きな差が生じます。たとえば日本人の悪性黒色腫は下肢にできることが多く，その場合は所属リンパ節が股の付け根にある鼠径リンパ節になります。この鼠径リンパ節は通常10個以上のリンパ節からなり，これらをすべて郭清すると高率に下肢がむくみ，下肢がすぐにだるくなるという症状が出ます。同様に上肢に悪性黒色腫が生じた場合は，腋窩のリンパ節が所属リンパ節となりますが，郭清することによって上肢の浮腫が生じ，生活に支障をきたします。したがって，悪性黒色腫が所属リンパ節に転移しているかどうかはっきりしない場合に，そのリンパ節すべてを郭清するかどうかということは重要な問題です。

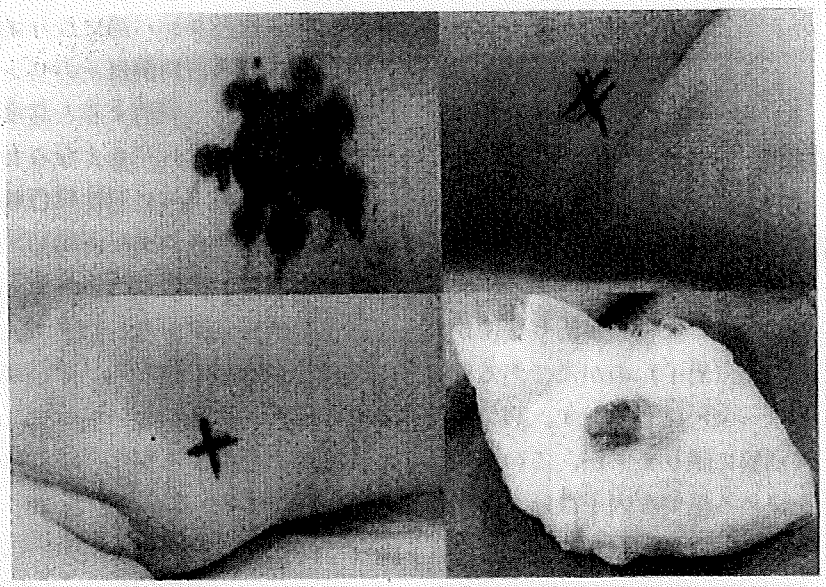
この問題を解決するために，近年ではセンチネルリンパ節生検という先進医療が用いられるようになってきました。センチネルとは「番人，歩哨」という意味で，この場合は悪性黒色腫がいちばん転移しやすい特定のリンパ節のことを指します。具体的には，手術の前日に放射性物質である^{99m}Tc（テクネシウム）で標識されたフィチン酸を腫瘍の周囲の皮内に注射します（図1左）。

図1　センチネルリンパ節生検の実際（手術前日）



左：悪性黒色腫の周囲に放射性物質である^{99m}Tc（テクネシウム）-フィチン酸を注射している
右：腫瘍周囲に注射した放射性物質がリンパの流れを伝って右腋窩と右鼠径の計３個のセンチネルリンパ節に集積している

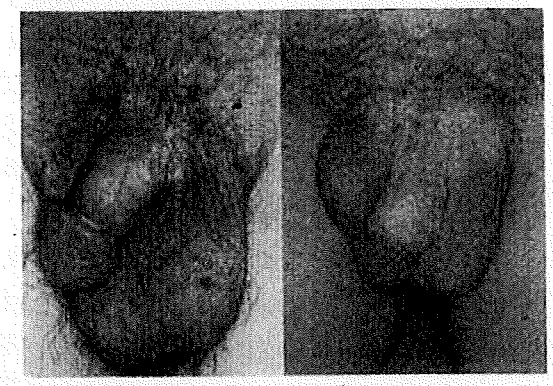
図2　センチネルリンパ節生検の実際（手術当日）



左上：悪性黒色腫の周囲にパテントブルーという青い色素を注射する
左下，右上：前日につけた目印を用いてセンチネルリンパ節を右腋窩と右鼠径から摘出する
右下：摘出したリンパ節は青く染まり，ガンマプローブにて放射性物質の集積が確認された

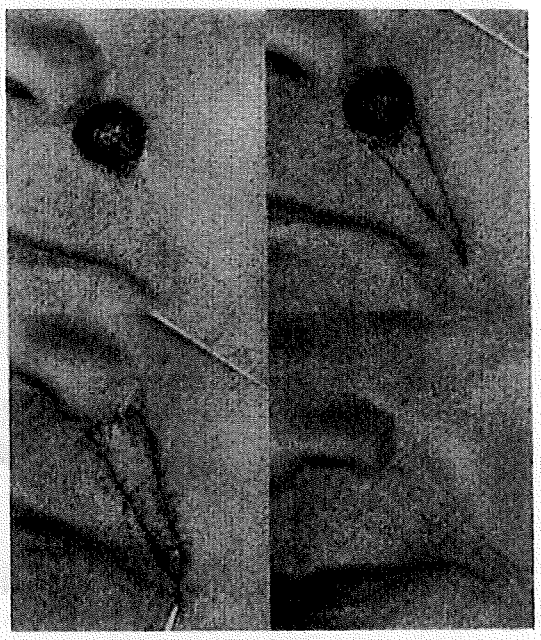
このフィチン酸は，腫瘍細胞が転移するのと同じように腫瘍周辺からのリンパの流れにそって動くため，もし悪性黒色腫が転移する場合，もっとも転移しやすいリンパ節へと向かい，集積します。この症例では悪性黒色腫は右腰にあったため，所属リンパ節としては右の腋窩リンパ節，もしくは右の鼠径リンパ節が考えられました。実際，フィチン酸を注

図3　外陰部パジェット病に対する植皮術



左：外陰部の病変。一見湿疹にみえる
右：腫瘍を切除し，植皮術を行なった。術後10年の状態

図4　基底細胞癌に対する局所皮弁術



左上：左上口唇の基底細胞癌
右上：術前の局所皮弁のデザイン
左下：術直後の状態。三角の局所皮弁を鼻翼方向に挙上し，欠損部を被覆した
右下：術後1年の状態

射して10分後には，右の腋窩リンパ節のうち二つのリンパ節と（図1右上），右の鼠径リンパ節のうち一つのリンパ節に（図1右下）放射性物質の集積がみられました。これらのリンパ節をセンチネルリンパ節と考え，印をつけました。

手術の当日には，パテントブルーという青い色素を腫瘍の周囲に注射します（図2左上）。この色素も，腫瘍周辺からリンパの流れに沿い，腫瘍がもっとも転移しやすいと思われるリンパ節へと向かいます。前日に付けた印を参考に（図2左下，右上），リンパ節を摘出すると，たしかにそのリンパ節は色素で染まっており（図2右下），またガンマプローブを用いることにより放射性物質の集積を確認でき，これがセンチネルリンパ節にまちがいないことがわかりました。

このセンチネルリンパ節を病理組織学的に検討し，悪性黒色腫の転移がなければ，これ以上の手術は行なわず，転移があれば所属リンパ節すべての郭清を行なうことになります。この症例では転移はなかったため，所属リンパ節の郭清は行ないませんでした。

●外陰部パジェット病に対する植皮術

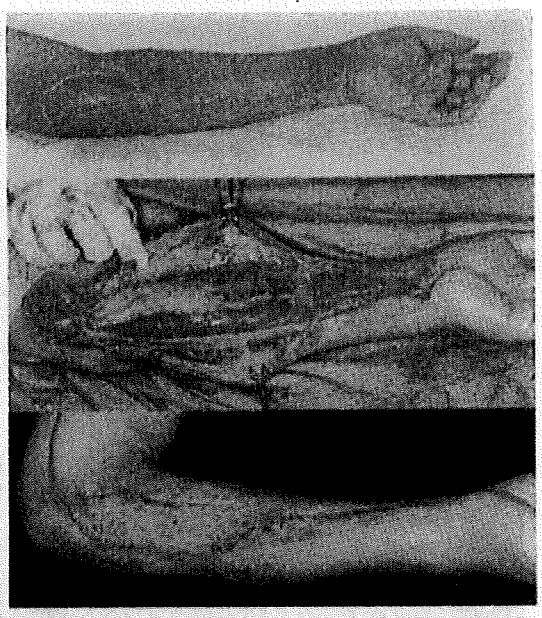
あまり一般的に馴染みはありませんが，気をつけないといけない皮膚がんとして，外陰部パジェット病というものがあります。多くは男性の外陰部にできるのですが，しばしば湿疹と見誤られます（図3左）。

この皮膚がんの手術の問題点としては，腫瘍細胞が見た目よりも広い範囲に広がっていることです。そのため見かけの病変の境界から数cm離して切除を行ないます。すると当然皮膚が足りなくなりますので，通常はどちらかの大腿より皮膚を採取して植皮を行ないます。植皮は当初は見た目があまりよくないのですが，長い年月が経つとそれなりに周囲に馴染んできます（図3右）。

●基底細胞癌に対する局所皮弁術

基底細胞癌（癌は「がん」のうち上皮性のものを指す病理学用語）も皮膚がんの一つですが，この癌の問題点として，ほとんどが顔面に生じることがあげられます（図4左上）。したがって，単に癌を摘出するだけでなく，

図5　壊死性筋膜炎に対する手術



上：初診時の状態。左上肢は肘部まで著明な発赤腫脹がみられ、びらんや水疱をともなっている
中：デブリードマンを行なったところ，脂肪組織が広範囲に渡って壊死に陥っており，膿の排出がみられた
下：デブリードマンの後，抗生物質による治療で感染は沈静化し，徐々に肉芽も新生してきたため，縫縮および植皮により皮膚欠損部を閉じることができた

整容的な面も配慮して手術を行なう必要があります。前述した植皮による腫瘍摘出後の創の被覆は，整容面ではいまひとつのことが多いため，局所皮弁という手法が繁用されます。図4右上のように，三角形の皮弁をデザインします。

基底細胞癌を摘出した後，三角形の皮弁を鼻翼方向に挙上し，欠損部を被覆します（図4左下）。術後1年の状態では癌の再発はなく，整容上も満足のいく結果となりました（図4右下）。

皮膚がん以外の治療

●壊死性筋膜炎に対する緊急デブリードマンとその後の再建

壊死性筋膜炎は，細菌による感染が皮下を超えて筋膜に沿って急速に拡大し，短時間で広範囲に組織が壊死する致死率の高い疾患です。糖尿病患者に多く，数時間単位で症状が急激に悪化します。この疾患に対しては，できるだけ早期に壊死した組織を取り除くこと，すなわちデブリードマン（débridement）が必要であり，緊急手術が必要になります。

図5上に，左上肢に生じた壊死性筋膜炎の一例を示します。初診時，左上肢は肘部まで著明な発赤腫脹がみられ，びらんや水疱をともなっていました。緊急手術を行ない，皮膚を切開し筋膜まで達したところ，脂肪組織が広範囲に渡って壊死に陥っており，膿の排出がみられたため，十分にこれを取り除き，デブリードマンを行ないました（図5中）。その後，抗生物質による治療で感染はしだいに改善し，徐々に肉芽も新生してきたため，最終的に縫縮および植皮により皮膚欠損部を閉じることができました（図5下）。

＊

皮膚外科では，臨床所見，診断，検査，手術から病理までのすべてを首尾一貫して扱い，治療にあたります。個々の症例の全体を把握したうえで，適切な治療を選択しますので，何でもかんでも手術にもっていくというわけではなく，レーザー，外用薬，保存的療法などを駆使して問題の解決にあたります。また，皮膚がんにおいては手術だけではなく，抗がん剤による加療や放射線療法も扱い，総合的に最善と考えられる治療が提供できるようにしています。

［かどの・たかふみ／皮膚科］

MB Derma, 160：33-38，2009.

◆特集／知っておきたい皮膚病の常識・非常識

手術が適応となる皮膚疾患・ならない皮膚疾患

門野岳史*

Key words：有棘細胞癌(squamous cell carcinoma)，脂腺母斑(sebaceous nevus)，炎症性線状疣状表皮母斑(inflammatory linear verrucous epidermal nevus)，血管腫(hemangioma)，ケロイド(keloid)，pseudocyst of the scalp

Abstract　手術が適応となる皮膚疾患・ならない皮膚疾患を厳密に区別することは難しく，ある皮膚疾患に対して手術が適応になるかどうかを決めるに当たっては病変の大きさ，自覚症状，患者背景などさまざまな要素を含めて考える必要がある．皮膚悪性腫瘍に関しては腫瘍の進展範囲が重要な要素であり，また患者の年齢も考慮する必要がある．母斑に関しては整容面を考慮する必要があるとともに，先天性色素性母斑や脂腺母斑については悪性化のリスクをどう評価するか，また炎症性線状疣状表皮母斑では再発のリスクをどう考えるかで手術の適応が決まる．血管腫やリンパ嚢腫については病変の範囲やシャントの有無の把握が重要で，その他ケロイドやpseudocyst of the scalpについても言及した．いずれにせよ，手術の適応の決定に当たっては正確な診断および病状の評価が必要であると考えた．

はじめに

種々の皮膚疾患において手術が適応となるかどうかは非常に難しい問題である．絶対的に適応となるもの，相対的に適応となるもの，また相対的に適応とならないもの，絶対的に適応とならないものとに分かれるが，相対的に適応となるかどうかは医師各々の考え方に応じてさまざまであり一概にいえない．また，一昔前であったら絶対的もしくは相対的手術適応であったものも，医学の進歩や疾患に対する考え方の変化のため，現在では変わってきているものもある．本稿では，いくつか具体例を挙げながら筆者が考える手術が適応となる皮膚疾患・ならない皮膚疾患について記す．

皮膚悪性腫瘍

手術が適応となる皮膚疾患・ならない皮膚疾患については疾患名ごとに明瞭に区分されることは少なく，むしろある皮膚疾患に関して手術が適応になる場合とならない場合とに分かれることのほうが多い．これの代表的な例として悪性黒色腫，有棘細胞癌，外陰部パジェット病といった皮膚悪性腫瘍が挙げられる．

皮膚悪性腫瘍で手術が適応になるかどうかに関して一番重要であるのは腫瘍の進展範囲である．遠隔転移や広範なリンパ節転移があれば通常は手術の適応にならない．また，局所病変も状況によっては最初から手術を行うのでなく，術前に放射線療法や化学療法を行って腫瘍を縮小させてから手術を行うほうがよい場合もある．図1-aは慢性膿皮症から発生した臀部の有棘細胞癌の症例である．病変は広範囲に及び，また，画像上坐骨に達していた．結核の既往があり化学療法が行いにくかったため，60 Gyの放射線療法を単独で術前に行ったところ図1-bのように腫瘍は縮小した．遠隔転移および所属リンパ節転移はなく，結果的にcurativeな切除を行うことができた．一般的

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図 1.
a：慢性膿皮症から発生した大型の腎部の有棘細胞癌の症例．病変は広範囲で，画像上坐骨に達していた．
b：60 Gy の放射線照射後の状態

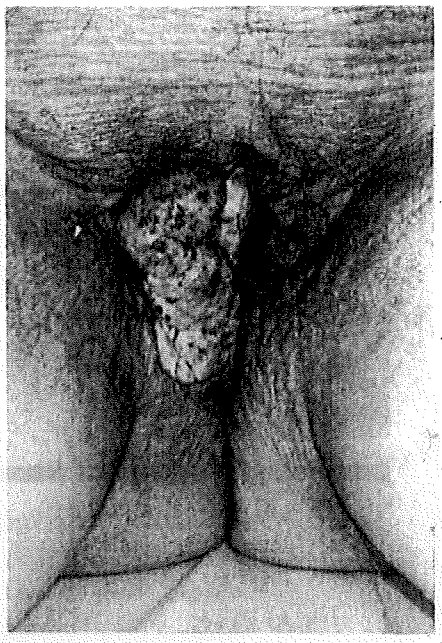


図 2. 85 歳，女性に発症した外陰部パジェット病の症例

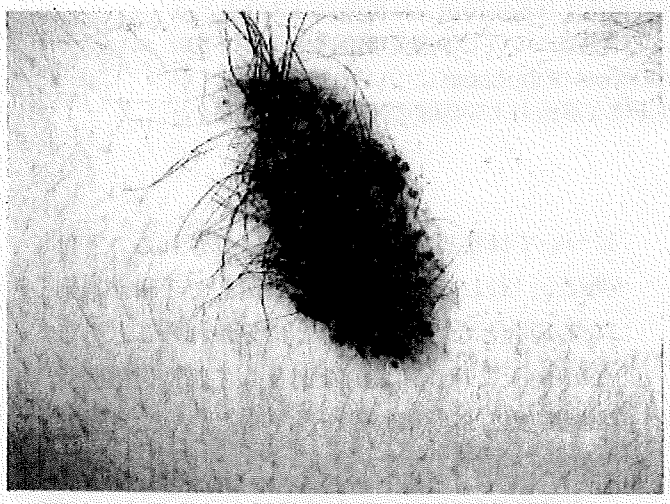


図 3. 右前腕に生じた有毛性の先天性色素性母斑の症例

に有棘細胞癌は放射線療法や化学療法に反応することが多く，最初からなんでも手術ということにはせず，症例に応じて使い分けるのがよいのではないかと考えられる．

手術が適応になるかどうかに関して年齢も重要な要因である．図 2 は 85 歳，女性の外陰部パジェット病の例である．この症例では腫瘍は尿道口に達しており，また肺に転移を疑わせる病変があった．肺の病変は孤立性であったため，胸腔鏡下肺切除術といった選択肢もないわけではなかったが，年齢などを考慮し，本人・家族と相談のうえ経過観察することにした．また，仮に転移がなかったとしても本症例は原発巣が尿道口に達していたため手術が適応となるかどうかは微妙なところである．姑息的に腫瘤部だけ切除するという方法も考えられるであろう．

母斑

先天性の疾患も手術が適応になるかどうか微妙なものが多い．代表的な例として先天性色素性母斑が挙げられる．20 cm 以上の巨大型のものに関しては悪性黒色腫を発症するリスクを考え，手術が可能なら予防的切除を選択すべきであろうが[2]，症例によっては手術が難しくレーザー治療などが行われる場合もあるであろう．難しいのはそれより小型のものである（図 3）．先天性母斑のない人と比較し，10 倍弱悪性黒色腫の発症が高くなるという報告もある[3]が一定の見解はなく，悪性黒色腫の予防目的で手術が適応となるかどうかは難しいところである．いずれにせよ思春期前に悪性黒色腫を発症することは稀とされているので[4]，局所麻酔が可能になったころに切除を考えるのがよいのではないかと思う．

同様に悪性腫瘍のリスクをどう判断するかによって手術適応が決まると考えられるのが脂腺母斑である（図 4-a）．従来は基底細胞癌などが発症

a | b

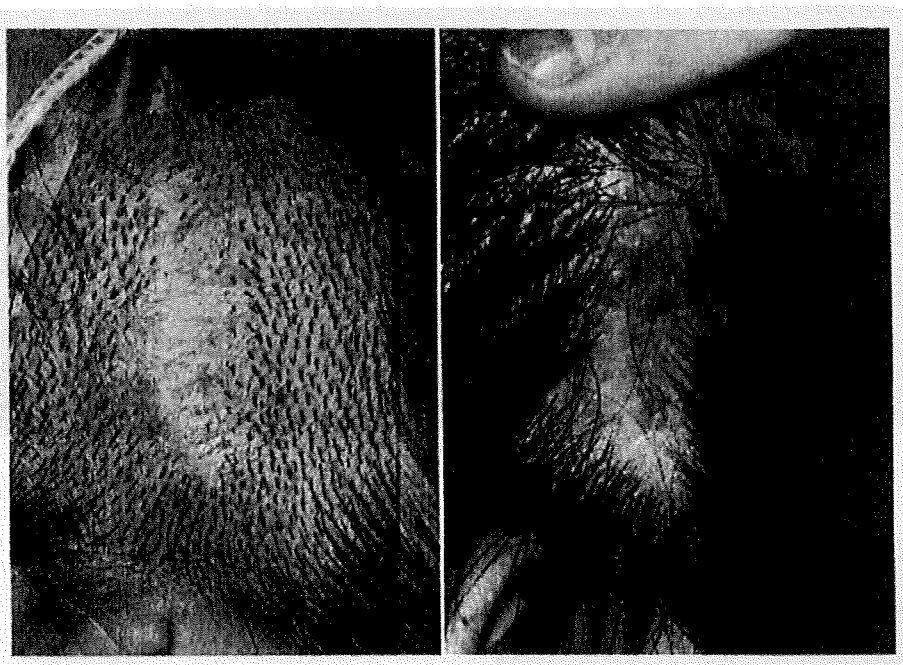


図 4.
a：側頭部に生じた脂腺母斑の症例
b：術後1年の状態．縫合線がやや広がっている．

するリスクを考えて早期に切除することが一般的であった．しかしながら，頭部に生じた例ではその形状より毛流に垂直に切除線をおくのが難しい場合が多く，またしばしば縫合線が広がることも多い(図4-b)．近年公表された皮膚悪性腫瘍ガイドラインにもあるとおり，基底細胞癌の発生予防のために脂腺母斑を切除したほうがよいという十分なエビデンスは存在しないという報告[9]が出てきた．従って，脂腺母斑が手術の適応になるかどうかは二次的腫瘍発症のことだけでなく，整容面も考慮したうえで判断する必要がある．

炎症性線状疣状表皮母斑(inflammatory linear verrucous epidermal nevus：ILVEN)も手術が適応になるかどうか意見の分かれる疾患である．多くは出生時～幼小時にかけて下肢中心に発生し，瘙痒を伴う黄褐色の疣状丘疹が列序性に配列する(図5)[9]．組織学的に乾癬に類似し，母斑の性格と湿疹，皮膚炎の両者の性格を有する[7]．治療としては削皮術，二酸化炭素レーザー，また近年ではビタミンD製剤やエトレチナートなどの外用も試みられている[9][10]が再発することも多い．手術でも再発や瘢痕の問題があるが，完全に病変を取り除くことができるので相対的適応と考えられる[10]．図5に提示した症例は凍結療法や二酸化炭素レーザーによる治療に抵抗性であったため，最終的に切除，全層植皮を行った．

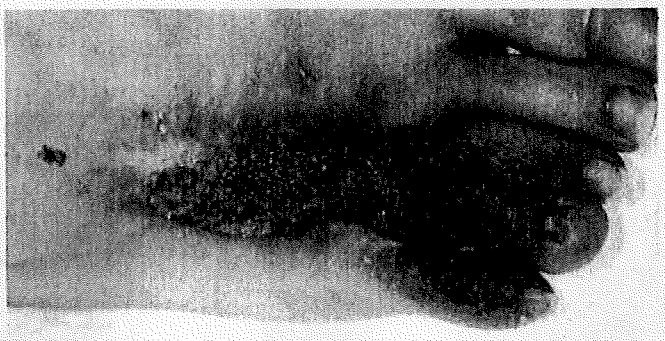
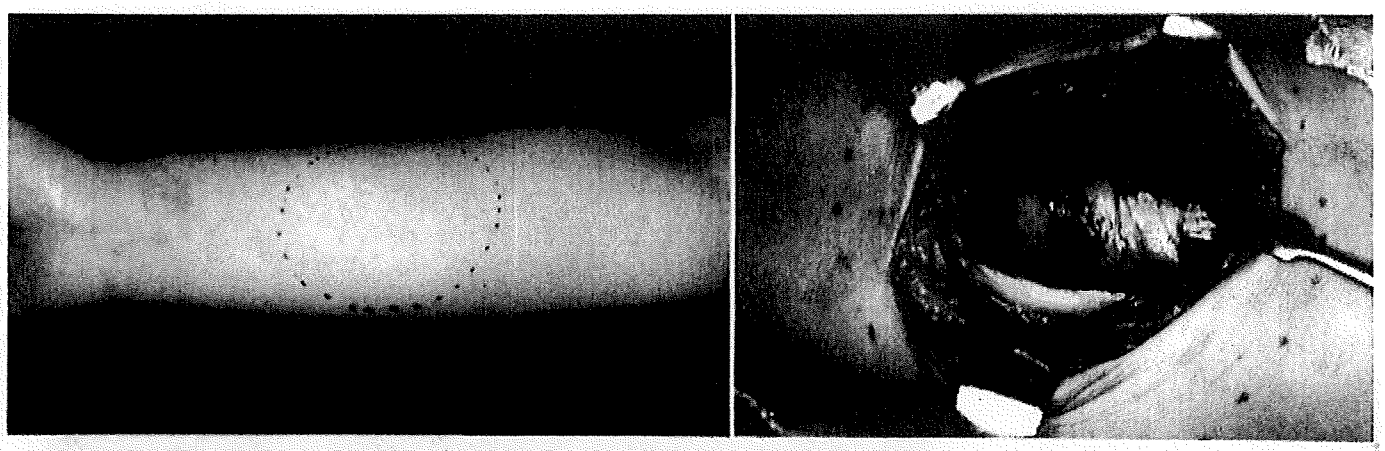


図 5. 右足背に生じた炎症性線状疣状表皮母斑の症例

血管腫・リンパ管腫

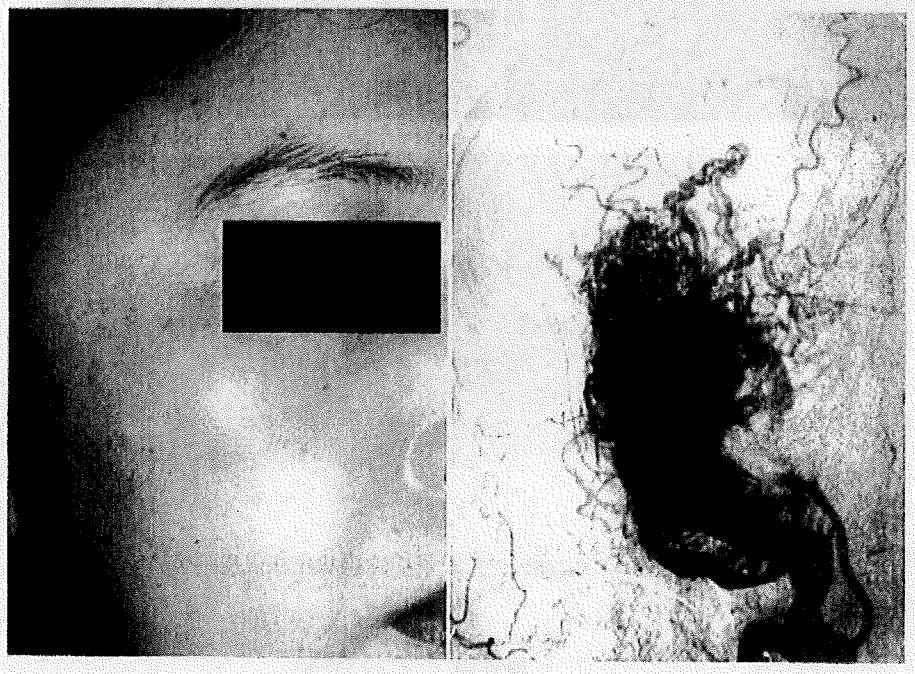
これらの疾患も多くは先天性である．血管腫のなかで，時代とともに手術の適応が変化したのが単純性血管腫であろう．アルゴンレーザー，またその後登場し，現在広く用いられる色素レーザーが登場する以前は，単純性血管腫に対する治療としては切除，植皮や放射線照射が一般的であった．植皮には整容面での限界があり，現在では単純性血管腫の治療はほとんどがレーザーによってなされ，手術が適応とならない疾患となった．同様のことが太田母斑にもいえるであろう．

しかしながら，単純性血管腫以外の血管腫，例えば海綿状血管腫などでは手術の適応になるものが多い．例えば図6-aは長趾指屈筋内の血管腫であるが手術の適応であると考えた(図6-b)．逆にAV malformationがあるような例では手術は危



a．右前腕に生じた血管腫　　b　術中所見．血管腫は長橈指伸筋内に存在した．

図 6.



a　b

図 7.
a：右頬部に生じた血管腫
b：血管造影を行ったところ AV malformation であることが確認された．

険である．図 7-a に右頬部に生じた血管腫の症例を示す．血管造影を行ったところ，AV malformation であることが確認され(図 7-b)，手術の適応ではないと判断した．

リンパ管腫も手術の適応になる場合とならない場合がある．範囲が限局していれば手術の適応であるが，皮膚に出ているのは氷山の一角であることがしばしばあり，皮下に広範囲に病変があることが多い．このような場合は手術をしても病変を取り切れずに再発するだけでなく，深追いすると出血のコントロールがつかなくなるおそれがある．また，リンパ管腫自体は良性の疾患であるので整容面も加味して手術の適応を決める必要がある[11]．図 8 に示したように病変が広範囲にわたる場合は手術の適応となりにくい．手術以外の方法としては OK-432 などによる硬化療法があり，高い効果を挙げている[12]．同様のことがいえるのが NF-1 における plexiform neurofibroma であろう．安易に手を出すと大量出血を招き，かといって手をこまねいていると拡大傾向を示す．術前の評価を十分に行ったうえで手術の適応を決め，また手術に当たっては自己血を準備するなどの必要があるであろう．

その他の良性疾患

手術が適応となりにくい皮膚疾患の代表といえばケロイドである．ケロイドは肥厚性瘢痕との鑑別が困難な場合もあるが，最初の外傷部位を超え

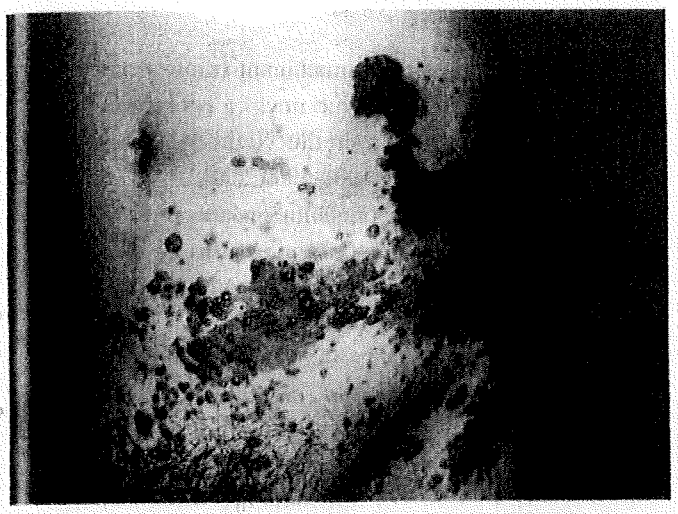


図 8. 左腰部の広範囲にわたるリンパ管腫

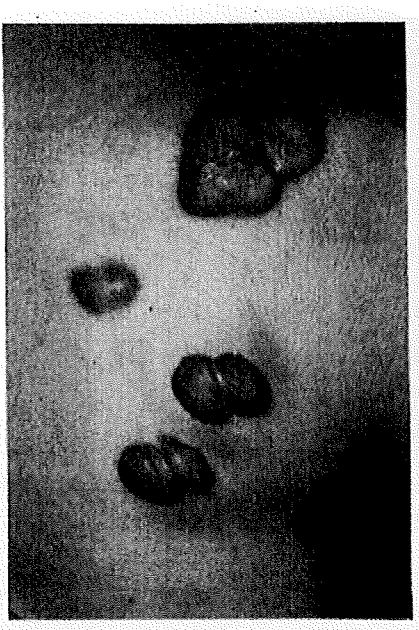


図 9. 肩～背部にかけて生じたケロイド

a|b

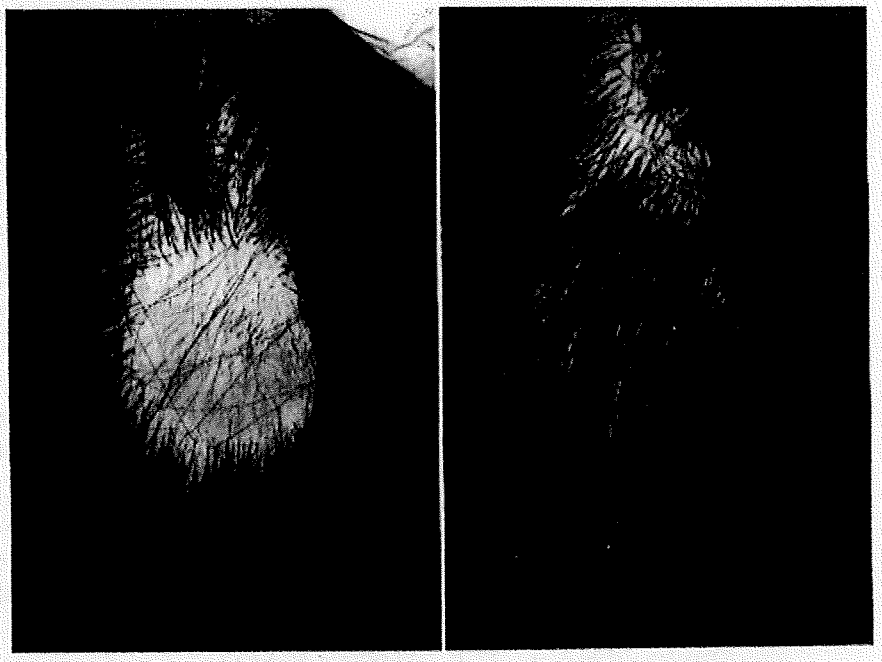


図 10.
a：後頭部に生じた pseudocyst of the scalp の症例．脱毛を生じている．
b：穿刺吸引，ステロイド局注後の状態，発毛がみられている．

る大きさになること，隆起や紅色調が強いことなどから区別する(図 9)[12]．肥厚性瘢痕は手術が適応となる疾患であり，一定の年月を経た後は退縮傾向がみられることが多く，この時期を狙って瘢痕修正を行う．一方，ケロイドの場合は単独で手術を行ってもほとんどの場合再発し，またさらにケロイドが拡大する．従って，あえて手術を行う場合は電子線照射，トラニラスト内服，ステロイド局注，圧迫，シリコンゲルシートによる保護，585 nm パルスダイレーザー照射などと組み合わせて行う必要がある[13]．

あまり頻度は高くないが覚えておいたほうがよいと思われる疾患として，pseudocyst of the scalp が挙げられる(図 10-a)．Trichlemmal cyst との鑑別は臨床上困難であるが，漿液性の液体が引けることが特徴で，臓皮症に近い性格を持つものと考えられる[15]．この疾患に対しては一般的には手術が行われるが，取り残しによって再発することや，またかえって脱毛が手術によって目立つようになることもあり，穿刺吸引とステロイド局注をまず試す[16]のがよいのではないかと考える(図 10-b)．

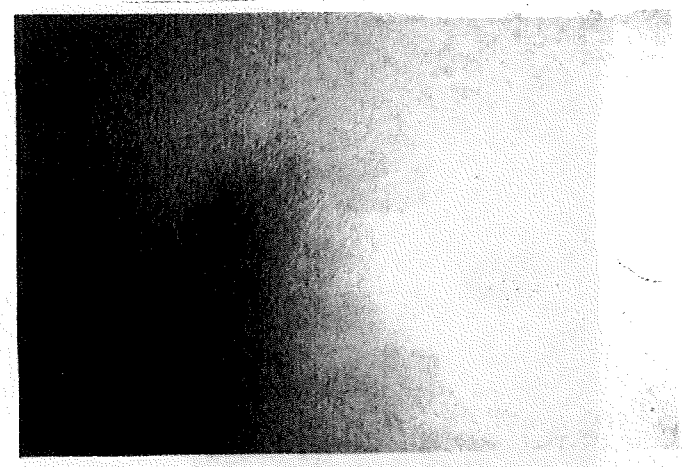


図 11. 胸部に生じた隆起性皮膚線維肉腫の症例
腫瘍は比較的軟らかく，粉瘤と間違えやすかった．

おわりに

手術が適応となる皮膚疾患・ならない皮膚疾患の区別は明確でないことが多く，また人によって意見は異なり，個々の症例の背景によって適応は変化する．従ってあまり常識・非常識といえないことが多く，またその常識も時代とともに変遷する．ただ一つ最後に言いたいのは手術をする場合は術前の診断や準備をしっかりしたほうがよいということである．術前診断が誤っていれば手術が適応になるかどうか以前の問題となるし，手術の準備や方法も全く異なってくる．よくある例として，「粉瘤と思って摘出したら悪性腫瘍だった」(図11)というのがある．あまり思い込みにとらわれず，冷静に個々の症例において考えうる疾患を整理し，必要な検査・準備を行い，手術の適応を決めるのがよいであろう．以上，自戒の念を込めて本稿を終わりにしたいと思う．

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Table 1 (*Continued*)

No.	Age	Sex	Diagnosis	Severity (no. of patches)	Intensity		Disease duration (m)
					Epidermis	Inflamed follicles	
9	50	M	AA	4	+	+	4
10	46	F	AA	6	++	+	12
11	23	M	AA	6	+	+	10
12	2	M	AA	7	++	+	1
13	50	F	AA	7	+	+	5
14	7	F	AA	9	+	+	2
15	53	M	AA	4	++	+	4
16	22	M	AST	AST	++	+	8
17	20	M	AST	AST	+	+	36
18	35	M	AST	AST	0	0	0.7
19	31	F	AT	AT	+	0	2
20	43	M	AU	AU	++	+	36
21	43	F	AU	AU	0	0	24
22	43	F	AU	AU	+	0	120
23	25	M	AU	AU	+	+	12

Abbreviation; AA: alopecia areata, AST: alopecia subtotalis, AT: alopecia totalis, AU: alopecia universalis.

were found to be higher than in normal controls [10]. Therefore, alteration of the oxidant-antioxidant enzymatic system might play a crucial role in AA pathogenesis.

In conclusion, decreased HO-1 expression may play a role in AA pathogenesis, due to the impairment of the protective mechanism from oxidative stress in the scalp.

Acknowledgements

This study was supported by grants of Korean Healthcare technology R&D Project, Ministry of Health, Welfare and Family Affairs, Korea (A080870) and the Chonnam National University Hospital Research Institute of Clinical Medicine (CRI 07070-1, A050174).

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5 August 2008

doi:10.1016/j.jdermsci.2008.11.009

Letter to the Editor

Increased CCL1 levels in the sera and blister fluid of patients with bullous pemphigoid

ARTICLE INFO

Keywords:
CCL1; Bullous pemphigoid; Atopic dermatitis; Cutaneous T cell lymphoma; Mast cells; Th2

Bullous pemphigoid (BP) is an autoimmune blistering skin disease characterized by large, tense blisters. Production of autoantibodies against the 180-kDa hemidesmosomal protein of the basement membrane zone is regarded as the first event of the pathomechanism [1]. Once the autoantibodies bind to the basement membrane, a cascade of inflammatory events occurs, resulting in subsequent blister formation at the dermoepidermal junction. During this process, cytokines and chemokines are considered to play crucial roles in inflammatory cell recruitment, deposition and perpetuation [2]. Therefore, clarifying the serum and local levels of cytokines and chemokines may help in understanding the immune dysregulation in the pathomechanism of BP.

CCL1 belongs to the CC chemokine family and is secreted by Langerhans cells, endothelial cells, mast cells, monocytes, lymphocytes, and epithelial cells. CC chemokine receptor (CCR)-8, a sole receptor for CCL1 [3], is preferentially expressed on T helper type 2 (Th2) cells [4], and regulatory T cells [5]. CCL1 is a potent

attractant for Th2 cells [4], suggesting that it plays a key role in the progression of Th2 type diseases such as asthma [6]. It was reported that serum levels of CCL1 in atopic dermatitis (AD) patients were higher than levels in healthy individuals [7]. The objective of this study was to investigate CCL1 levels in sera of patients with AD, BP and other skin diseases. We also performed immunohistochemical study to investigate the source of CCL1 in the skin.

Thirty-nine patients with BP (mean ± standard deviation (S.D.) age: 72.9 ± 16.8 years), 38 patients with AD (28.8 ± 6.6 years), 26 patients with psoriasis vulgaris (51.5 ± 14.8 years), 33 patients with cutaneous T cell lymphoma (CTCL; 59.8 ± 14.1 years), and 34 healthy controls (50.4 ± 18.5 years) were enrolled in this study. The blister fluid of 11 patients with BP (78.4 ± 11.0 years) and that of 9 patients with burn (30.3 ± 21.6 years) were obtained. All serum and blister fluid samples were obtained before the treatment. Immunoreactive CCL1 in sera and blister fluids was quantified by a human CCL1 ELISA kit (R&D Systems, Minneapolis, MN).

Serum CCL1 levels of patients with AD were 11.3 ± 4.0 pg/ml (Fig. 1a). They were a little higher than those from healthy controls (10.1 ± 2.6 pg/ml), but they were not statistically different. Serum CCL1 levels of patients with psoriasis were 8.2 ± 2.0 pg/ml, which were significantly lower than those of controls. Serum CCL1 levels of patients with CTCL (13.6 ± 4.0 pg/ml) and BP (23.0 ± 15.5 pg/ml) were significantly higher than those of controls.

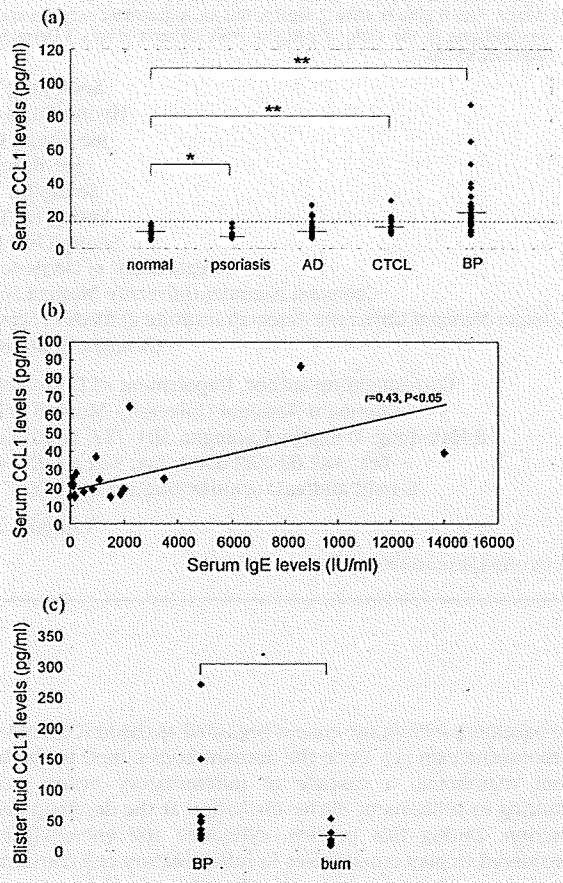

Fig. 1. (a) Serum levels of CCL1 in patients with psoriasis vulgaris, atopic dermatitis (AD), cutaneous T cell lymphoma (CTCL), bullous pemphigoid (BP) and in healthy controls (control). The measured values from individual patients were plotted by dots. (b) Correlations between serum CCL1 levels in patients with BP and serum IgE levels. (c) Blister fluid levels of CCL1 in patients with BP and burn. The measured values from individual patients were plotted by dots. Each bar indicates the mean of each group. Statistical analysis between two groups was performed using the Mann–Whitney's *U*-test. Correlation coefficients were determined by using the Spearman's rank correlation test. A dotted horizontal line indicates the cut-off value (mean + 2S.D. of the control samples). $^{*}P < 0.05$, $^{**}P < 0.01$.

We next compared serum CCL1 levels with other clinical and laboratory data: age, sex, serum levels of LDH, IgE, anti-BP180 antibody, titers of indirect immunofluorescence, numbers of eosinophils in peripheral blood. Serum CCL1 levels were significantly correlated with serum IgE levels (Fig. 1b). Other factors were not correlated with serum CCL1 levels (data not shown).

CCL1 levels in blister fluid from patients with BP were 64.9 ± 75.8 pg/ml (Fig. 1c), which were significantly higher than those from patients with burn (18.3 ± 14.4 pg/ml). This suggests that concentrations of CCL1 are increased not only in the serum but also in the lesional skin in patients with BP.

We next performed immunohistochemical staining for CCL1 with the lesional skin of patients with BP ($n = 5$), CTCL ($n = 5$), AD ($n = 5$), psoriasis ($n = 5$) and with normal skin ($n = 2$). Briefly, 5-μm tissue sections from formaldehyde-fixed and paraffin-embedded blocks were dewaxed and rehydrated. These sections were then stained with goat anti-human CCL1 polyclonal antibodies (R&D Systems Inc., Minneapolis, MN, USA) and goat IgG followed by ABC staining (Vector Lab. Inc., Burlingame, CA, USA). In some experiments, toluidine blue staining was performed to identify mast cells. In both normal skin and lesional skin of BP, dermal endothelial cells were slightly positive for CCL1, which was consistent with previous papers (Fig. 2a and b) [8]. In addition, some dermal infiltrating cells expressed CCL1. Because most CCL1-positive dermal infiltrating cell looked like mast cells, we performed toluidine blue staining. Consistent with previous studies [9], a larger number of mast cells were seen in lesional skin of BP than in normal skin (Fig. 2c and d). The distribution of mast cells and CCL1-positive cells were similar, suggesting that mast cells were one of the sources of CCL1 in lesional skin of BP. In the lesional skin of CTCL and AD, dermal endothelial cells and some dermal infiltrating cells expressed CCL1, whereas in the lesional skin of psoriasis, only very few, if any, dermal infiltrating cells expressed CCL1 (data not shown).

Recently, most immunologists try to explain pathogenesis of inflammatory skin diseases in the view of Th1/Th2 balance. AD and BP are considered to be dominantly mediated by Th2 responses. Moreover, CTCL is considered as malignancy of Th2 clones. On the contrary, psoriasis vulgaris is considered to be dominantly mediated by Th1 responses. From our study and the previous report [7], although further study is needed to investigate roles of CCL1 in pathogenesis of BP, it can be suggested that serum CCL1 levels are elevated in patients with Th2 type skin diseases, whereas they are decreased in patients with Th1 type skin diseases. The idea is consistent with recent findings associating the CCL1–CCR8 interactions with other Th2 type diseases [4,6].

Most patients with BP show increased serum IgE levels. In the pathogenesis of BP, IgE is important as one of the major immunoglobulins targeting the NC16A domain of the 180-kDa hemidesmosomal protein of the basement membrane zone [10]. In our study, we showed that serum CCL1 levels were slightly, but statistically significantly, correlated with serum IgE levels in patients with BP. Sequential histological examination of lesions of BP has shown that mast cell degranulation is an early event followed by migration of eosinophils into the lesion [9]. It is possible that mast cells release CCL1 by binding and cross-linking of IgE, playing an important role in this blister formation phase by inducing migration of Th2 cells.

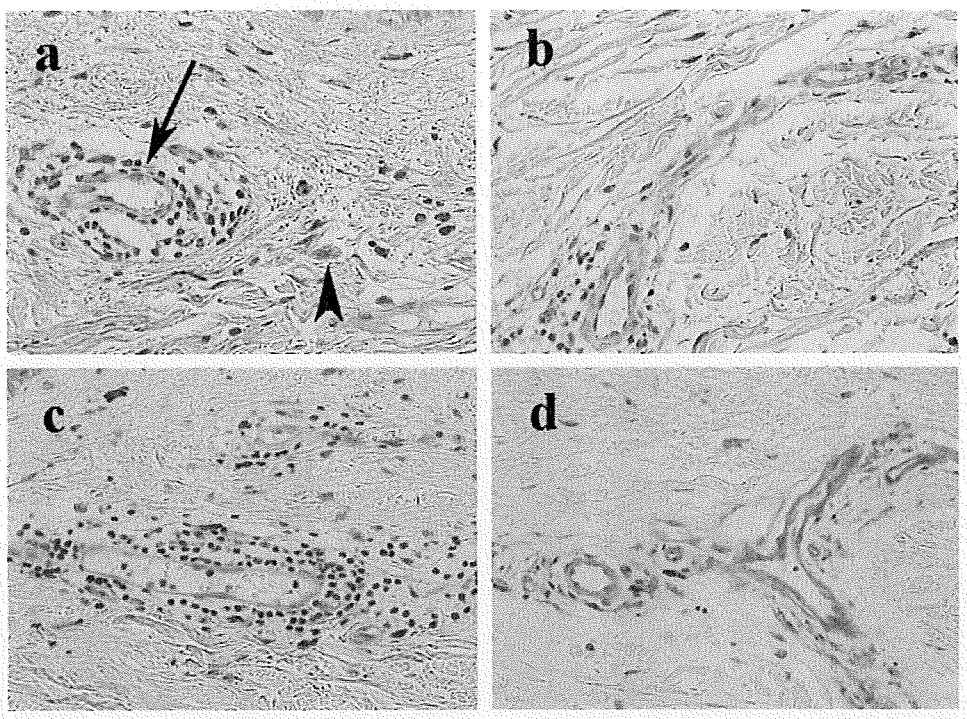

Fig. 2. (a) CCL1 expression in dermal endothelial cells (arrows) and infiltrating cells (arrow heads) in the lesional skin of BP (×400). (b) CCL1 expression in normal skin (×400). (c) Mast cells in the lesional skin of BP detected with toluidine blue staining (×400). (d) Mast cells in normal skin detected with toluidine blue staining (×400).

Conflicts of interest

The authors state no conflict of interest.

Acknowledgments

We thank Kiyoko Nashiro for technical assistance. These studies were supported by grants from the Ministry of Education, culture, sports and technology.

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18 March 2008

doi:10.1016/j.jdermsci.2008.10.012