CADM1 is a diagnostic marker in early-stage mycosis fungoides: Multicenter study of 58 cases

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Background: Mycosis fungoides (MF) is the most common cutaneous T-cell lymphoma. Early-stage MF patches or plaques often resemble inflammatory skin disorders (ISDs), including psoriasis and atopic dermatitis. Cell adhesion molecule 1 gene (*CADM1*), which was initially identified as a tumor suppressor gene in human non–small cell lung cancer, has been reported as a diagnostic marker for adult T-cell leukemia/lymphoma.

Objective: We investigated *CADM1* expression in MF neoplastic cells, especially during early stages, and evaluated its usefulness as a diagnostic marker for MF.

Methods: We conducted a retrospective study by using immunohistochemical staining and confirmed the expression of *CADM1* in MF. In addition, we compared *CADM1* messenger RNA expression in microdissected MF samples and ISD samples.

Results: In the overall study period, 55 of 58 MF samples (94.8 %) stained positive for CADM1. None of the 50 ISD samples showed positive reactivity ($P < .0001$). We found *CADM1* messenger RNA expression in the intradermal lymphocytes of patients with MF but not in those of patients with an ISD.

Limitations: We did not conduct a validation study for MF cases in other institutions.

Conclusions: CADM1-positive cells can be identified in early stages with fewer infiltrating cells and may be useful as a diagnostic marker for early-stage MF. (J Am Acad Dermatol 2018;79:1039-46.)

Key words: adult T-cell leukemia/lymphoma; cell adhesion molecule 1; cutaneous T-cell lymphoma; mycosis fungoides.

Mycosis fungoides (MF) is the most common cutaneous T-cell lymphoma (CTCL).[1] Early-stage MF (stages IA, IB, and IIA) patches or plaques often resemble inflammatory skin disorders (ISDs), including psoriasis and atopic dermatitis.[2] Although most patients in the early

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stages survive for decades after diagnosis, progressive disease usually has high mortality.[3] Therefore, it is fundamental to differentiate between early-stage MF and ISDs. Immunophenotypic analyses and/or T-cell receptor gene (*TCR*) clonal rearrangements in neoplastic cells are often used to support histologic diagnoses. MF originates from $CD3^+$, $CD4^+$, and $CD45RO^+$ memory T cells[1,4,5]; the loss of CD7 and/or CD26 and decreased expression of CD2, CD3, CD4, and CD5 are common supportive diagnostic markers.[6-9] Although these aberrantly expressed CD markers are commonly used, combinations of several markers are required. In addition, diagnosis using CD markers is difficult when lymphocyte infiltration is low.

Adult T-cell leukemia/lymphoma (ATLL), which also presents a $CD4^+$ T-cell neoplasm etiology, can be distinguished from MF by its association with human T-cell leukemia virus 1.[1] Cell adhesion molecule 1 (CADM1), which was initially identified as a tumor suppressor gene in human non–small cell lung cancer,[10] has been reported as a diagnostic marker for ATLL; immunohistochemical analyses have identified 33 of 36 ATLL cases (91.7%) as positive for CADM1.[11] Neoplastic cells in ATLL, which originate from $CD3^+$, $CD4^+$, and $CD25^+$ regulatory T cells, are similar to those in MF.[1,12,13] We investigated *CADM1* expression in MF neoplastic cells, especially during early stages, and evaluated its usefulness as a diagnostic marker for MF.

CAPSULE SUMMARY

- Cell adhesion molecule 1 (CADM1) has been reported as a diagnostic marker for adult T-cell leukemia/lymphoma.
- Our study suggests that CADM1 is expressed not only in adult T-cell leukemia/lymphoma but also in mycosis fungoides.
- CADM1 can be useful for differentiating mycosis fungoides from inflammatory skin disorders.

METHODS

Patients

In total, 58 skin samples of lesions from 58 patients with MF (12 with stage IA MF, 20 with stage IB, 2 with stage IIA, 15 with stage IIB, 7 with stage IIIA; 1 with stage IVA1, and 1 with stage IVA2) were immunohistochemically stained for CADM1 (Table I). We conducted a retrospective study of 58 patients with MF. Data from 58 cases in which a diagnosis of MF was made at Niigata University Medical and Dental Hospital and Hokkaido University Hospital in Japan between January 2010 and October 2017 were analyzed in a retrospective study. A total of 50 samples from patients with an ISD (11 with pityriasis lichenoides chronica, 14 with lichen planus, 13 with drug eruption, 4 with nummular eczema, and 8 with basal cell carcinoma with inflammatory infiltrates) were used for the control. MF was diagnosed on the basis of a progressive clinical course; histology; immunophenotypic analyses for CD3, CD4, CD5, CD7, CD8, and CD30; and *TCR* rearrangement analyses. Clinical staging was based on the TNM classification of the International Society for Cutaneous Lymphoma/European Organization for Research and Treatment of Cancer.[14] This study was approved by the institutional review boards at Hokkaido University and Niigata University, in accordance with the Declaration of Helsinki.

Immunohistochemical analysis

CADM1 expression was assessed by immunohistochemical staining as previously described with slight modifications.[11] Briefly, 5-μm frozen sections were incubated first with 1% bovine serum albumin and then with 0.3% H_2O_2 in methanol. Then, the sections were incubated with antihuman CADM1 antibody (clone 3E1, 1:400 dilution, MBL, Nagoya, Japan) followed by incubation with antichicken IgY conjugated with biotin (1:400 dilution, R&D Systems, Minneapolis, MN). After washing, the sections were incubated with horseradish peroxidase–conjugated streptavidin (Histofine SAB Kit, Nichirei Bioscience, Tokyo, Japan) and visualized with diaminobenzidine. Sections were counter-stained with hematoxylin. The percentage of the total number of infiltrating lymphocytes in the ×200 microscopic field that were CADM1-positive lymphocytes was measured by using ImageJ image analysis software.[15] Positivity for CADM1 was evaluated quantitatively via 4 scores: 0, less than 5%; 1+, 5% to 25%; 2+, 25% to 50%; and 3+, more than 50%. Antihuman CADM1 antibody (clone 3E1, MBL) and CD4 antibody (clone 4B12, Leica, Newcastle upon Tyne, UK) were used for double staining.

Analysis by reverse-transcription PCR

We used laser microdissection to select infiltrating lymphocytes in the dermis from fresh frozen samples and exclude the influence of *CADM1* expression in the epidermis. A serial section of 10-μm-thick fresh frozen tissue was stained with hematoxylin and then microdissected by using the LMD 7000 laser microdissection system (Leica Microsystems, Tokyo, Japan). Only infiltrating

Abbreviations used:

ATLL:	adult T-cell leukemia/lymphoma
CADM1:	cell adhesion molecule 1
CTCL:	cutaneous T cell lymphoma
ISDs:	inflammatory skin disorders
MF:	mycosis fungoides
mRNA:	messenger RNA
PCR:	polymerase chain reaction
ROC:	receiver operating characteristic

lymphocytes in the dermis were microdissected from fresh frozen tissue.

Total cellular RNA was extracted from the microdissected sections by using the RNeasy Micro Kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions. Expression of CADM1 in the microdissected sections was detected by reverse-transcription polymerase chain reaction (PCR). An aliquot of total cellular RNA was reverse-transcribed by using the SuperScript IV First-Strand Synthesis System (Invitrogen, Carlsbad, CA). PCR was carried out with a Veriti Thermal Cycler (Applied Biosystems, Foster City, CA). The primers used were as follows: *CADM1* forward primer, 5′-ATACCGATCCCCCACAGGAA-3′; *CADM1* reverse primer, 5′-CTTCCACCTCCGATTTGCCT-3′; *CD4* forward primer, 5′-CCTGGTAGTAGCCCCTCAGT-3′; and *CD4* reverse primer, 5′-GGCCTTCTGGAA AGCTAGCA-3′. Agarose gel electrophoresis of the amplicons was used to confirm or discard *CADM1* messenger RNA (mRNA) expression. The expression of glyceraldehyde-3-phosphate dehydrogenase was examined as an internal control to confirm RNA integrity.

Statistical analysis

Statistical analysis was carried out with JMP 14 software (SAS Institute Inc, Cary, NC). The Tukey-Kramer test was performed to evaluate statistically significant differences between early- and advanced-stage cases of MF and between each ISD. To determine whether CADM1 was efficient as a diagnostic marker for MF and to obtain a cutoff point, we performed receiver operating characteristic (ROC) analysis. A value of $P < .05$ was considered statistically significant.

RESULTS

The clinical information for each case and overall results are summarized in Table I. The subjects included 58 patients with MF (38 men and 20 women) with ages ranging from 26 to 91 years (median age at diagnosis, 65.0 years). All patients were negative for the anti–human T-cell leukemia virus 1 antibody.

In the retrospective study, 55 of 58 MF samples (94.8%) and 33 of 34 (97.0%) particularly early-stage samples stained positive for CADM1, respectively (Table I and Fig 1, *A-D*). In quantitative analyses of the 55 positive samples, CADM1 expression was scored at 1 + in 38 cases, at 2 + in 16 cases, and at 3 + in 1 case (Table I and Fig 1, *B-D*). Human cancer cells losing CADM1 expression include those in gastric, cervical, and pancreatic cancers.[16-19] Furthermore, advanced cases have been associated with a loss of CADM1.[16] However, we found no statistically significant difference in the rate of CADM1 positivity (≥1+) between early- and advanced-stage MF. In the ISD cases, CADM1 expression was observed in less than 5.0% of infiltrates, but none of the 50 ISD samples showed a positive reactivity score of 1 + or more (Figs 1, *E* and 2, *A*); and the difference in CADM1 expression between MF and ISD patients was significant ($P < .0001$) (Fig 2, *A*). There was no statistically significant difference in rate of CADM1 positivity rate between each ISD. To evaluate the usefulness of CADM 1 as a diagnostic marker in the discrimination between MF and ISDs, ROC analysis was performed (Fig 2, *B*). As a result, the area under the curve sensitivity, and specificity were 0.97, 94.8% and 98.0%, respectively. Furthermore, a cutoff value of 5.0% was obtained (Fig 2, *A*). After double staining for CADM1 and CD4, the $CD4^+$ T cells of MF sample expressed CADM1 on the cell surfaces (Fig 3). Our results suggest that CADM1 is highly expressed in patients with MF and that it can be useful for differentiating between MF and ISDs (Fig 4).

We compared *CADM1* mRNA expression in MF samples (1 stage IB case and 1 stage IV case) and ISD samples (1 case of pityriasis lichenoides chronica and 1 case of lichen planus). *CADM1* is expressed in most epithelial tissues, including the epidermis, and is important for cell adhesion.[16] In addition, normal $CD4^+$ T cells (except regulatory T cells) lack *CADM1* expression.[20] We used laser microdissection to select infiltrating lymphocytes in the dermis from fresh frozen samples and exclude the influence of *CADM1* expression in the epidermis. We found *CADM1* mRNA expression in the intradermal lymphocytes of the patients with MF, but not in those of the patients with an ISD (Fig 5).

Table I. Clinical characterization and results of *CADM1* expression tests at initial diagnosis

Case	Age, y	Sex	Stage	CD3	CD4	CD7	*TCR* rearrangement	*CADM1*
1*	67	M	IA	+	+	−	−	1+
2	37	F	IA	+	+	−	+	1+
3	76	M	IA	+	+	−	+	2+
4*	26	M	IA	+	+	−	− → +†	1+
5	56	M	IA	+	+	−	+	2+
6	66	F	IA	+	+	−	ND	1+
7	76	M	IA	+	+	−	+	1+
8	82	M	IA	+	+	−	ND	1+
9	54	F	IA	+	+	−	+	1+
10	78	F	IA	+	+	−	ND	1+
11	41	F	IA	+	+	−	+	1+
12	68	M	IA	+	+	−	ND	1+
13*	69	F	IB	+	+	−	− → +†	2+
14*	58	M	IB	+	+	−	− → +†	2+
15	65	M	IB	+	+	−	+	3+
16	70	F	IB	+	+	−	ND	1+
17	37	M	IB	+	+	+	+	1+
18	74	M	IB	+	+	−	+	1+
19	69	M	IB	+	+	−	+	2+
20	54	M	IB	+	+	−	+	1+
21	63	F	IB	+	+	−	ND	1+
22	34	M	IB	+	+	−	ND	1+
23	63	M	IB	+	+	−	ND	1+
24	58	F	IB	+	+	−	ND	1+
25	57	F	IB	+	+	−	ND	1+
26	81	M	IB	+	+	−	ND	2+
27	70	F	IB	+	+	−	ND	1+
28	27	M	IB	+	+	−	+	2+
29	66	F	IB	+	+	−	+	1+
30	48	F	IB	+	+	−	−	1+
31	74	F	IB	+	+	−	ND	2+
32	39	M	IB	+	+	−	ND	1+
33	68	F	IIA	+	+	−	+	2+
34	65	F	IIA	+	+	−	ND	0
35	65	M	IIB	+	+	−	+	2+
36	49	M	IIB	+	+	−	+	0
37	63	M	IIB	+	+	−	+	1+
38	33	F	IIB	+	+	−	+	1+
39	41	M	IIB	+	+	−	+	2+
40	78	M	IIB	+	+	−	+	2+
41	51	M	IIB	+	+	−	+	1+
42	74	M	IIB	+	+	−	+	1+
43	66	M	IIB	+	+	−	+	1+
44	87	F	IIB	+	+	+	+	1+
45	68	M	IIB	+	+	−	+	0
46	58	M	IIB	+	+	−	+	1+
47	44	F	IIB	+	+	−	+	1+
48	54	M	IIB	+	+	−	+	1+
49	65	F	IIB	+	+	+	+	2+
50	91	M	IIIA	+	+	−	+	1+
51	60	M	IIIA	+	+	−	ND	1+
52	58	M	IIIA	+	+	−	ND	2+
53	75	M	IIIA	+	+	−	+	2+
54	70	M	IIIA	+	+	−	−	1+
55	74	M	IIIA	+	+	+	−	2+

Continued

Table I. Cont'd

Case	Age, y	Sex	Stage	CD3	CD4	CD7	*TCR* rearrangement	*CADM1*
56	81	M	IIIA	+	+	–	+	1+
57	71	M	IVA1	+	+	–	ND	1+
58	63	M	IVA2	+	+	–	+	1+

Positivity for CADM1 was quantitatively evaluated via 4 scores according to the percentage of positive cells: 0, less than 5%; 1+, 5% to 25%; 2+, 25% to 50%; and 3+, more than 50%.
CADM1, Cell adhesion molecule 1 gene; *F*, female; *M*, male; *ND*, not determined; *TCR*, T-cell receptor gene.
*The initial diagnosis of cases 1, 4, 11, and 12 was parapsoriasis en plaque; *CADM1* expression was evaluated by using initial skin biopsy samples.
†Initially negative; mycosis fungoides was diagnosed during follow-up.

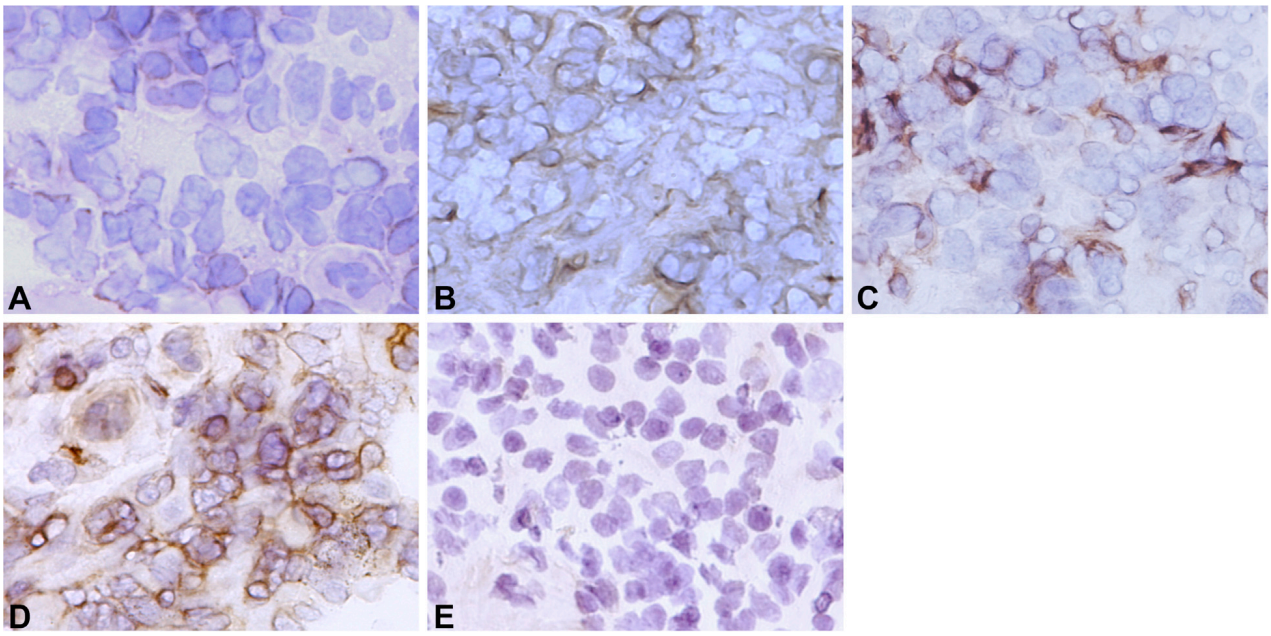

Fig 1. Expression of cell adhesion molecule 1 (CADM1) in representative immunohistochemistry samples. **A,** Score of 0, CADM1 expression in case 31. **B,** Score of 1+, CADM1 expression in case 32. **C,** Score of 2+, CADM1 expression in case 34, **D,** Score of 3+, CADM1 expression in case 13. **E,** Pityriasis lichenoides chronica lesions were negative for CADM1.

DISCUSSION

Because early-stage MF patches or plaques often resemble ISDs, we often experience misdiagnosed cases. To date, there are no specific single molecular markers for diagnosing MF. In the present study, we examined whether CADM 1 is a novel diagnostic marker for MF in 58 patients with MF and 50 MF mimickers. Our results suggest that CADM1 is expressed in patients with MF and that it can be useful for differentiating between MF and ISDs. Incidentally, CADM1 expression was observed in a few infiltrates in ISD cases (Fig 2, *A*). CADM1 is not expressed in normal T lymphocytes, but it is expressed in some B lymphocytes, monocytes, and neutrophils.[20] It is presumed that these cells mimic tumor cells of MF expressing CADM1, but the cutoff value of 5.0% obtained by ROC analysis indicated that CADM1 is useful to discriminate between MF and inflammatory mimickers.

In previous reports, 3 of 15 samples of natural killer/T-cell lymphoma (20%), 4 of 13 samples of ALK-negative anaplastic large cell lymphoma (30.7%), and 14 of 88 samples of peripheral T-cell lymphoma not otherwise specified (15.9%) expressed CADM1.[11,21] Whether expression of CADM1 is restricted to MF and ATLL or is a general feature of CTCLs is still unclear. Further studies to analyze the importance of CADM1 expression in various types of CTCL are required.

The disease of 4 patients was initially diagnosed as parapsoriasis en plaque (Table I, cases 1, 4, 13, and

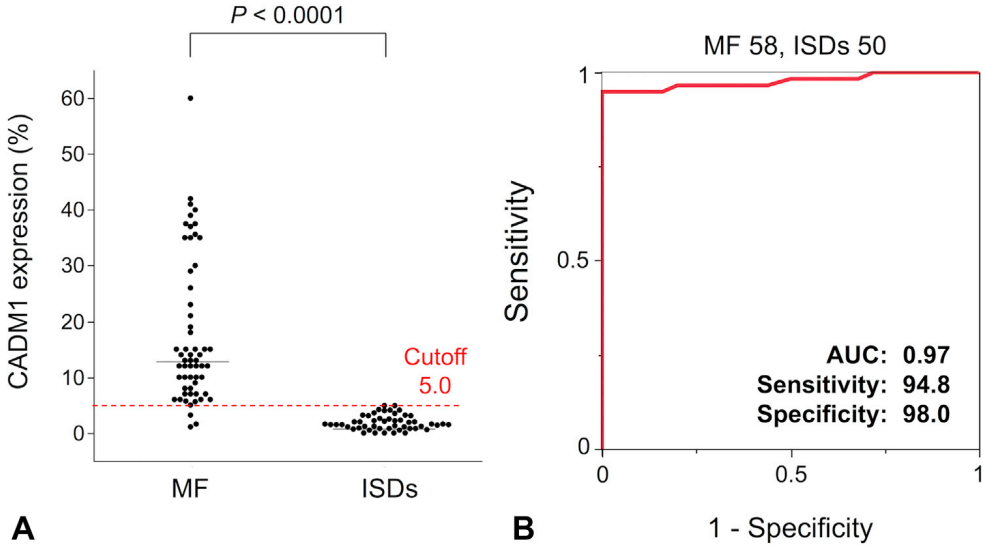

Fig 2. Statistical analysis of expression of cell adhesion molecule 1 (CADM1). **A,** Relative quantitation of CADM1 expression between cases of mycosis fungoides (MF) and inflammatory skin disorder (ISD). Dot plot graph shows the CADM1-positive lymphocytes as a percentage of the total number of infiltrating lymphocytes in the ×200 microscopic field (as measured by using the freely available image analysis software ImageJ). The cutoff point obtained by receiver operating characteristic curve analysis is shown on the graph (*red line*). **B,** Receiver operating characteristic curve analysis for discriminating between MF and ISDs (*red line*). The area under the curve (AUC), sensitivity, and specificity for discriminating between MF and ISDs, are shown on the graph.

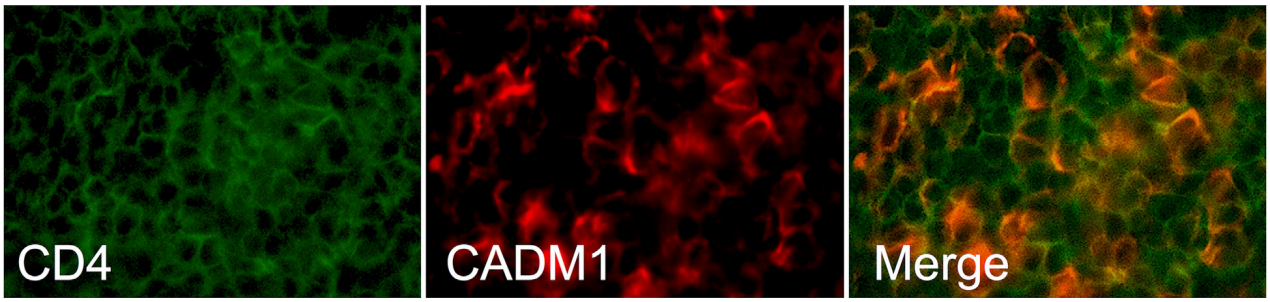

Fig 3. Results of double staining. A mycosis fungoides sample (case 40) shows expression of cell adhesion molecule 1 (CADM1) in some $CD4^+$ T cells. The right panel is a merged image of the left (CD4 [*green*]) and middle (CADM1 [*red*]) images.

14) because infiltrating lymphocytes had poor cellular atypia and the results of *TCR* rearrangement analyses were negative. However, they had progressing skin lesions and the final diagnosis was MF on the basis of histopathologic findings showing cell atypia and *TCR* rearrangement analyses performed again during the follow-up periods. Interestingly, CADM1 was expressed in the initial skin biopsy samples from these 4 patients (Fig 6). *TCR* rearrangement is a reliable test for clonal expansion of T cells; however, the sensitivity varies from 50% to 90%[22-24] and the rearrangement is found in some benign reactive disorders.[25] We found *TCR* rearrangements of clonal T-cell expansion in 33 of 58 cases (56.8%) at initial diagnosis, but in only 14 of 34 early-stage MF cases (41.1%). Histologic diagnosis of MF, especially early-stage MF, on the basis of CADM1 expression might be more useful than *TCR* rearrangement analyses.

In epithelial cells, CADM1 acts as a tumor suppressor protein through downstream erythrocyte membrane protein band 4.1 like 3 and membrane-associated guanylate kinase homologs. In ATLL, the binding of T-lymphoma invasion and metastasis 1 to CADM1 promotes tumor cell invasion by activating Rac.[26] However, the mechanisms regulating the expression of CADM1 and its downstream pathways in MF remain unclear. Because MF and ATLL tumor

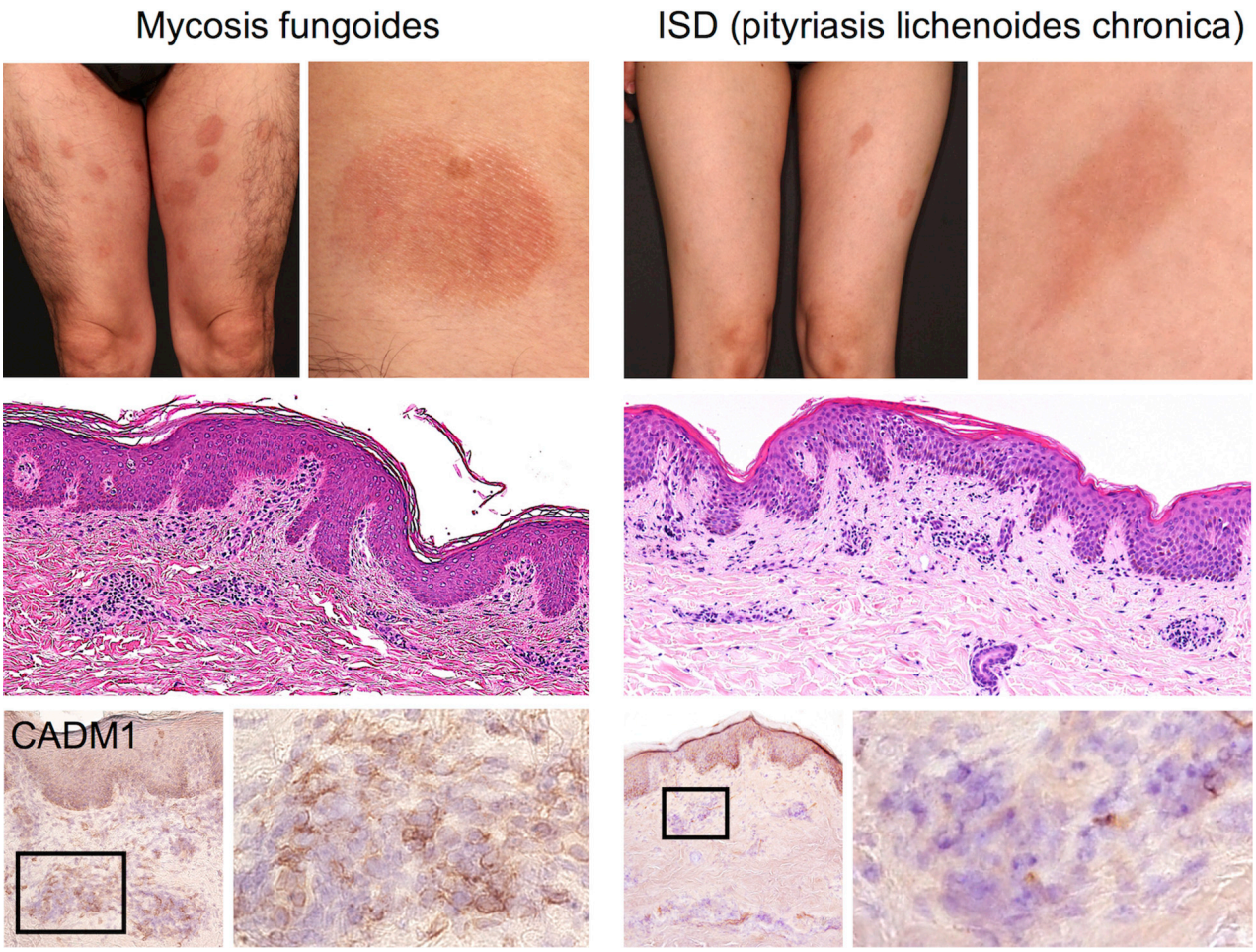

Fig 4. Comparison of expression of cell adhesion molecule 1 (CADM1) between a sample of mycosis fungoides (MF) and a sample of inflammatory skin disorder. Skin manifestations and histologic findings are similar between early-stage MF and inflammatory skin disorder. However, there is a significant difference in the rate of expression of CADM1 in dermal lymphoid cells in each disease. The left panels show a patient with MF (case 20), and the right panels show a patient with pityriasis lichenoides chronica (a representative case).

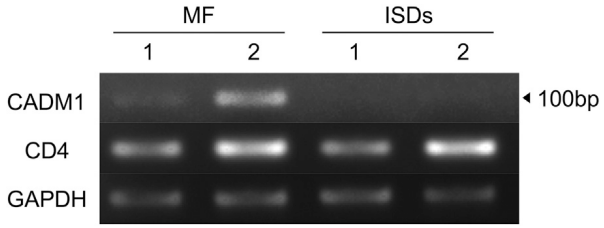

Fig 5. Result of reverse-transcription polymerase chain reaction analysis of cell adhesion molecule 1 gene (*CADM1*) messenger RNA in mycosis fungoides (MF) and inflammatory skin disorders (ISDs) in samples of microdissected tissue. Expression of *CADM1* messenger RNA was identified in the intradermal lymphocytes of the patients with MF (1, case 29; 2, case 58), but not in those of patients with ISD case (1, pityriasis lichenoides chronica; 2, lichen planus) by analysis using agarose gel electrophoresis. *bp*, Base pair; *GAPDH*, glyceraldehyde-3-phosphate dehydrogenase.

cells have similar surface molecule patterns, our study of CADM1 expression provides important information on the pathogenesis of MF. The primary limitation of this study is that we did not conduct a validation study for MF cases in other institutions. Further validation studies should be required.

CONCLUSION

Although the skin manifestations and histologic findings between early-stage MF and ISDs are similar, there is a significant difference in the expression of CADM1 in each disease. The results of testing for CADM1 expression were positive in all MF stages. CADM1-positive cells can be identified in early cases with fewer infiltrating cells and may be useful as a diagnostic marker for MF.

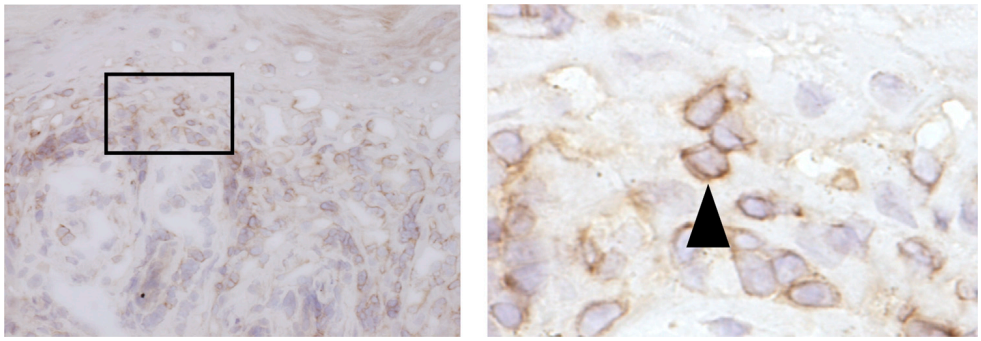

Fig 6. Expression of cell adhesion molecule 1 (CADM1) in a sample from a patient in whom the initial diagnosis was parapsoriasis (case 4). The right panel shows the section of the left panel (*rectangle*) in which neoplastic epidermis cells can be seen expressing CADM1 (*black triangle*).

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