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Specificity of *IRF4* translocations for primary cutaneous anaplastic large cell lymphoma: a multicenter study of 204 skin biopsies

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Current pathologic criteria cannot reliably distinguish cutaneous anaplastic large cell lymphoma from other CD30-positive T-cell lymphoproliferative disorders (lymphomatoid papulosis, systemic anaplastic large cell lymphoma with skin involvement, and transformed mycosis fungoides). We previously reported *IRF4* (interferon regulatory factor-4) translocations in cutaneous anaplastic large cell lymphomas. Here, we investigated the clinical utility of detecting *IRF4* translocations in skin biopsies. We performed fluorescence *in situ* hybridization (FISH) for *IRF4* in 204 biopsies involved by T-cell lymphoproliferative disorders from 182 patients at three institutions. In all, 9 of 45 (20%) cutaneous anaplastic large cell lymphomas and 1 of 32 (3%) cases of lymphomatoid papulosis with informative results demonstrated an *IRF4* translocation. Remaining informative cases were negative for a translocation (7 systemic anaplastic large cell lymphomas; 44 cases of mycosis fungoides/Sézary syndrome (13 transformed); 24 peripheral T-cell lymphomas, not otherwise specified; 12 CD4-positive small/medium-sized pleomorphic T-cell lymphomas; 5 extranodal NK/T-cell lymphomas, nasal type; 4 gamma-delta T-cell lymphomas; and 5 other uncommon T-cell lymphoproliferative disorders). Among all cutaneous T-cell lymphoproliferative disorders, FISH for *IRF4* had a specificity and positive predictive value for cutaneous anaplastic large cell lymphoma of 99 and 90%, respectively ($P = 0.00002$, Fisher's exact test). Among anaplastic large cell lymphomas, lymphomatoid papulosis, and transformed mycosis fungoides, specificity and positive predictive value were 98 and 90%, respectively ($P = 0.005$). FISH abnormalities other than translocations and IRF4 protein expression were seen in 13 and 65% of cases, respectively, but were nonspecific with regard to T-cell lymphoproliferative disorder subtype. Our findings support the clinical utility of FISH for *IRF4* in the differential diagnosis of T-cell lymphoproliferative disorders in skin biopsies, with detection of a translocation favoring cutaneous anaplastic large cell lymphoma. Like all FISH studies, *IRF4* testing must be interpreted in the context of morphology, phenotype, and clinical features.
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Cutaneous CD30-positive T-cell lymphoproliferative disorders include primary cutaneous anaplastic large cell lymphoma (designated heretofore as cutaneous anaplastic large cell lymphoma), lymphomatoid papulosis, transformed mycosis fungoides/Sézary syndrome with CD30 expression, and

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secondary skin involvement by systemic anaplastic large cell lymphoma. Distinguishing cutaneous anaplastic large cell lymphoma from lymphomatoid papulosis and systemic anaplastic lymphoma kinase- (ALK)-negative anaplastic large cell lymphoma is particularly challenging.[1–3] Histologic and immunophenotypic features of these diseases may be identical, and clinical correlation always is required; in addition, the differential diagnosis with lymphomatoid papulosis sometimes requires lengthy follow-up before a diagnosis can be established.[1] Even with follow-up, borderline clinical and pathologic presentations make certain cases difficult to classify. Accurate classification is important, however, because prognosis and therapy differ considerably depending on the diagnosis.[4]

We recently reported novel translocations involving the *IRF4* gene locus in cutaneous anaplastic large cell lymphomas.[5] *IRF4* encodes interferon regulatory factor-4 (IRF4), also known as multiple myeloma oncogene-1 (MUM1). IRF4 is a transcription factor expressed in activated T cells as well as plasma cells, some B cells, and their corresponding malignant counterparts.[6] Using fluorescence *in situ* hybridization (FISH), we reported the translocation status at the *IRF4* locus in 155 peripheral T-cell lymphomas. A majority of translocated cases were cutaneous anaplastic large cell lymphomas (8/14 tested), with occasional translocations detected in peripheral T-cell lymphomas, not otherwise specified (3/64) and systemic ALK-negative anaplastic large cell lymphoma (1/23). Other systemic peripheral T-cell lymphomas, including systemic ALK-positive anaplastic large cell lymphoma, lacked *IRF4* translocations. Recently, a French series reported by Pham-Ledard *et al*[7] confirmed the predilection of *IRF4* translocations to occur in cutaneous anaplastic large cell lymphomas, and also found translocations in a minority of cases of transformed mycosis fungoides. Taken together, these data suggest the possibility that clinical testing for *IRF4* translocations in skin specimens may aid in the classification of T-cell lymphoproliferative disorders. However, neither our previous study[5] nor that of Pham-Ledard *et al*[7] was sufficient to determine the clinical role of *IRF4* FISH testing because of the limited number of cases, particularly with regard to cutaneous involvement by systemic anaplastic large cell lymphoma and other cutaneous T-cell lymphoproliferative disorders besides cutaneous anaplastic large cell lymphoma, lymphomatoid papulosis, and mycosis fungoides/Sézary syndrome. Therefore, we undertook this multi-institutional study of 204 skin biopsies involved by T-cell lymphoproliferative disorders to determine the specificity of *IRF4* translocations for cutaneous anaplastic large cell lymphoma and define the clinical utility of *IRF4* FISH in evaluation of cutaneous T-cell lymphoproliferative disorders.

Patients and methods

Patients

We examined 204 skin biopsy specimens from 182 patients diagnosed with cutaneous T-cell lymphoproliferative disorders based on 2008 World Health Organization (WHO) criteria.[8] None of the specimens or patients was reported in our previous series.[5] All patients were seen and staged by a clinical dermatologist with experience in cutaneous lymphoid disorders. There were 106 men and 76 women (M:F ratio, 1.4:1), with a mean age of 59 years (range, 5–96 years). Diagnoses included: 47 cutaneous anaplastic large cell lymphomas; 44 cases of mycosis fungoides/Sézary syndrome (31 without and 13 with large cell transformation); 32 cases of lymphomatoid papulosis (24 type A, 1 type B, and 7 type C); 25 peripheral T-cell lymphomas, not otherwise specified; 13 CD4-positive small/medium T-cell lymphomas; 5 extranodal NK/T-cell lymphomas, nasal type; 4 gamma-delta T-cell lymphomas; 4 systemic ALK-negative anaplastic large cell lymphomas; 3 systemic ALK-positive anaplastic large cell lymphomas; 3 subcutaneous panniculitis-like T-cell lymphomas; 1 CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma; and 1 T-cell prolymphocytic leukemia. Of the patients in whom multiple biopsies were examined, the same process was seen in all biopsies (one patient had mycosis fungoides in the initial biopsy and transformed mycosis fungoides in the subsequent biopsy). Clinical information included site(s) of disease, status at last follow-up, time to extracutaneous spread (in primary cutaneous diseases) and time to death (if reached). The study was approved by the respective Institutional Review Board of each institution providing cases for the study (Mayo Clinic, Cleveland Clinic, and University of Michigan).

Fluorescence *In Situ* Hybridization

Breakapart FISH for *IRF4*, localized to 6p25.3, was performed as described previously.[5] Briefly, DNA from bacterial artificial chromosome clones (ResGen, Invitrogen, Carlsbad, CA, USA) was isolated using the Plasmid Maxi Kit (Qiagen, Valencia, CA, USA). DNA was labeled either with Texas Red-dUTP (CTD-2308G5, telomeric; Molecular Probes, Invitrogen) or SpectrumGreen-dUTP (RP11-164H16, centromeric; Abbott Molecular, Des Plaines, IL, USA) using the Nick Translation Kit (Abbott). Probe validation and determination of upper limits of normal were described previously.[5] Paraffin-embedded whole-tissue sections were digested in 0.4% pepsin solution, hybridized with probe, washed, and counterstained with 4′,6-diamidino-2-phenylindole dihydrochloride. Between 50 and 200 cells per case were analyzed by a microscopist (MEL), with a minimum of 20 abnormal cells

required for a sample to be considered abnormal. In some cases, a centromere 6 probe (CEP6 α-satellite SpectrumAqua; Abbott) was applied. In some cases, FISH was combined with CD30 immunofluorescence. Slides were treated with EDTA antigen retrieval, stained with CD30 antibody (Ber-H2, 1:20; Dako, Carpinteria, CA, USA), and detected using biotinylated anti-mouse linker (Dako) and Alexa Fluor 532-labeled streptavidin (Invitrogen). Slides were jet air-dried and hybridized with *IRF4* probe as described above.

Immunohistochemistry

IRF4 (MUM1) immunohistochemistry was performed on paraffin-embedded whole-tissue sections as previously reported.[5] Briefly, after pretreatment in 1 mM EDTA buffer (pH 8.0) for 30 min at 98 °C (PT Module, LabVision, Fremont, CA, USA), sections were stained using a monoclonal mouse anti-human IRF4 antibody (MUM1p, 1:50; Dako) and signal was detected using Dual-Link Envision+/DAB+ (Dako). Additional immunostains were performed as appropriate to assist in disease classification and IRF4 scoring using antibodies and methods previously published.[9,10] IRF4 was scored as positive (nuclear staining in >30% of tumor cells), partial (10–30%), or negative (<10%). Per 2008 WHO criteria, a diagnosis of cutaneous anaplastic large cell lymphoma required positive CD30 staining in >75% of tumor cells.[3]

Statistics

Fisher's exact test was used to evaluate differences observed in the frequency of *IRF4* translocations between groups. *P*-values <0.05 were considered statistically significant.

Results

Frequency of *IRF4* Translocations in Cutaneous T-cell Lymphoproliferative Disorders

IRF4 FISH was successful in 178 of the 182 patients tested (98%). *IRF4* translocations were seen in 10 of the 182 patients (5%), including 9 of 45 (20%) cutaneous anaplastic large cell lymphomas and 1 of 32 (3%) cases of lymphomatoid papulosis (Figure 1a; Table 1). No *IRF4* translocation was seen in the other entities tested, including transformed mycosis fungoides (of 13 cases tested: 10 CD30-positive and 3 CD30-negative). One of the nine patients with *IRF4*-translocated cutaneous anaplastic large cell lymphoma had two biopsies tested, taken 14 months apart: the translocation was present in both biopsies. The percentage of cells with abnormal split FISH signals in translocated cases ranged from 33 to 97% (mean, 62%). These data indicate an overall specificity and positive predictive value of an *IRF4* translocation for cutaneous anaplastic large cell lymphoma of 99 and 90%, respectively ($P=0.00002$; sensitivity, 20%; negative predictive value, 79%). The diseases with morphologic and phenotypic overlap with cutaneous anaplastic large cell lymphoma for which a genetic test would be most helpful include systemic anaplastic large cell lymphoma, lymphomatoid papulosis, and transformed mycosis fungoides.[2,3] Among these entities, the specificity and positive predictive value of an *IRF4* translocation for cutaneous anaplastic large cell lymphoma in the current data set are 98 and 90%, respectively ($P=0.005$; sensitivity, 20%; negative predictive value, 59%). Combining the current data set with data from our previous study[5] and from the study of Pham-Ledard *et al*[7] (Table 1), the specificity and positive predictive value for cutaneous anaplastic large cell lymphoma relative to systemic anaplastic large cell lymphoma, lymphomatoid papulosis, and transformed mycosis fungoides are 95 and 88%, respectively ($P=0.00007$; sensitivity, 28%; negative predictive value, 54%).

Morphologically, differences were not observed between cutaneous anaplastic large cell lymphomas with and without *IRF4* translocations. Lesions showed confluent sheets of large tumor cells, often with cytologic features of so-called 'hallmark' cells (Figure 2), similar to those seen in systemic anaplastic large cell lymphoma.[11] By defining criteria,[3] CD30 was expressed in the majority (>75%) of tumor cells in all cases; combined FISH/immunofluorescence in selected cases allowed confirmation that the FISH findings were present in the CD30-positive tumor cells (Figures 3a–c). Similar morphologic and phenotypic characteristics also were seen in the single case of lymphomatoid papulosis with an *IRF4* translocation, but the clinical features favored lymphomatoid papulosis (type C) over cutaneous anaplastic large cell lymphoma (see below).

Clinical characteristics of the 45 patients with cutaneous anaplastic large cell lymphomas successfully tested for *IRF4* translocations are shown in Table 2. Gender and age were similar in patients with and without *IRF4* translocations. Translocated cases occurred somewhat more frequently on the head and neck, although this difference was not significant. There was no difference in the incidence of extracutaneous spread (11% of patients) in the two groups; median follow-up was somewhat longer in the untranslocated group (49 months *vs* 10 months in the translocated group.) Deaths, unrelated to the cutaneous disease in all cases, were similar in both groups. The single lymphomatoid papulosis patient with an *IRF4* translocation was a 70-year-old male who presented with a 2-year history of small, spontaneously resolving cutaneous papules. The lesion biopsied was the largest of his skin lesions (1–2 cm in size). Staging studies were otherwise negative, and he remained healthy at last follow-up 4 years after biopsy.

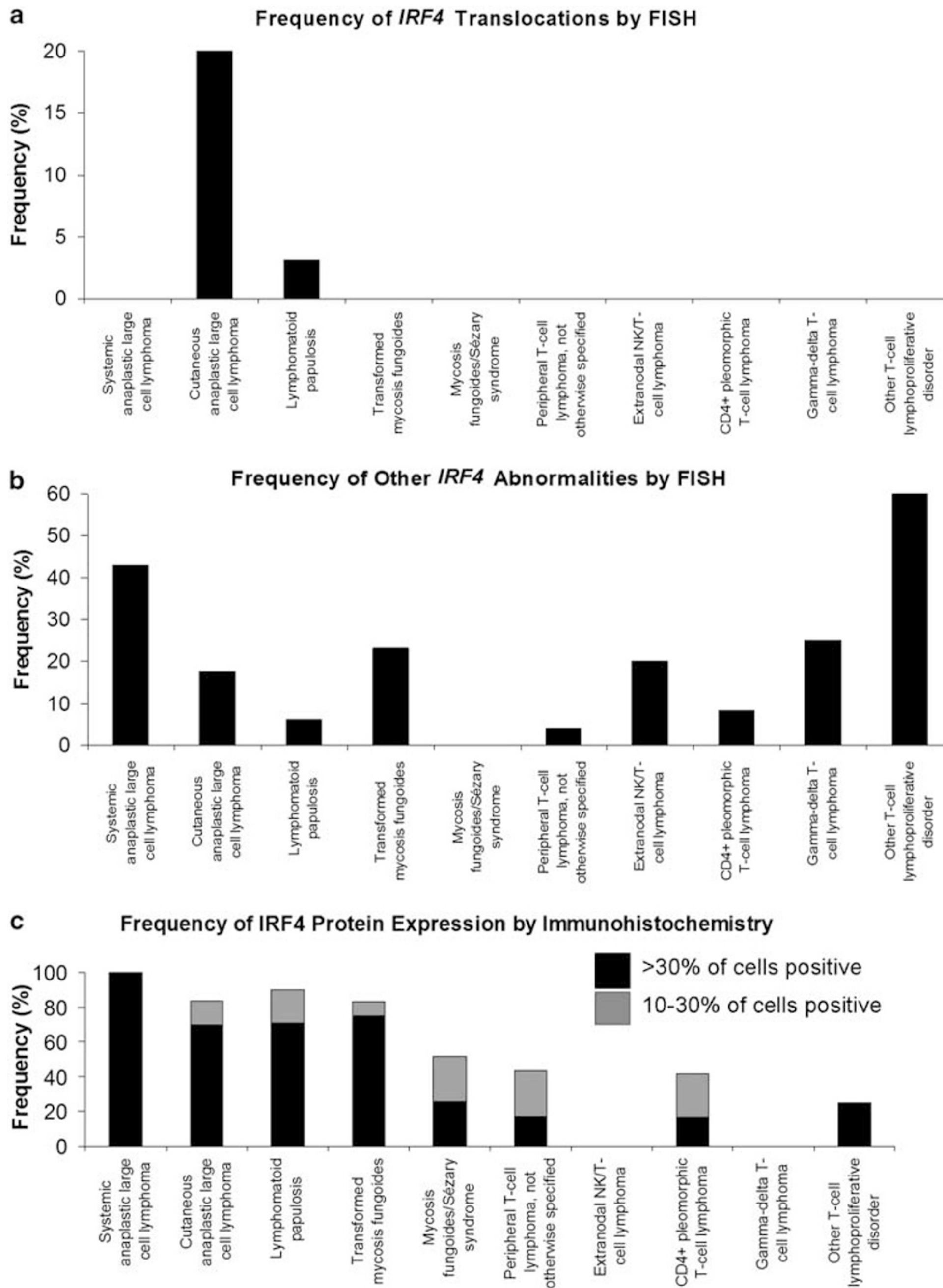

Figure 1 Frequencies of *IRF4* FISH abnormalities and IRF4 protein expression, stratified by T-cell lymphoproliferative disorder subtype. (**a**) *IRF4* translocations were limited to cutaneous anaplastic large cell lymphomas (20%) and a single case of lymphomatoid papulosis (3%). (**b**, **c**) Other *IRF4* FISH abnormalities and IRF4 protein expression were widely distributed over T-cell lymphoproliferative disorder subtypes.

Frequency of Other *IRF4* Locus Abnormalities in Cutaneous T-cell Lymphoproliferative Disorders

Other FISH abnormalities were seen in 23 of the 178 cases (13%; Figure 1b). Most of these involved extra copies of the *IRF4* locus (21 cases; Figures 3c and e). These cases were mutually exclusive with the translocated cases; that is, cases with translocations did not also demonstrate additional copies of *IRF4* (Figure 3d). The number of extra copies ranged from 1 to 5; while some of these extra copies could be attributable to extra copies of chromosome 6, FISH with a centromere 6 probe demonstrated that in some cases the number of intact *IRF4* signals exceeded the number of centromeres (Figure 3e). Unlike the presence of *IRF4* translocations, the presence of other *IRF4* FISH abnormalities was distributed widely over the T-cell lymphoproliferative disorder subtypes tested (Figure 1b). The only patient with multiple biopsies whose FISH results differed between biopsies was a patient with transformed mycosis fungoides in two biopsies taken 19 months apart, with normal FISH in the earlier biopsy and 1–2 extra copies of *IRF4* in the

Table 1 Incidence of *IRF4* translocations in skin biopsies involved by cutaneous T-cell lymphoproliferative disorders: summary of three reported series

	Translocations identified/cases tested (%)					
	Systemic anaplastic large cell lymphoma	*Cutaneous anaplastic large cell lymphoma*	*Lymphomatoid papulosis*	*Transformed mycosis fungoides*	*Other T-cell lymphoproliferative disorders*	*Total cases*
Feldman *et al*[5a]	0/1 (0)[b]	8/14 (57)	Not tested	Not tested	0/5 (0)	8/20 (40)
Pham-Ledard *et al*[7]	Not tested	6/23 (26)	0/7 (0)	2/11 (18)	0/13 (0)	8/54 (15)
Current study	0/7 (0)	9/45 (20)[c]	1/32 (3)	0/13 (0)	0/81 (0)	10/178 (6)
Total	0/8 (0)	23/82 (28)[d]	1/39 (3)	2/24 (8)	0/99 (0)	26/252 (10)

[a]Patients with skin biopsies only.

[b]Of 41 systemic anaplastic large cell lymphomas at any anatomic site, 1 (2%) had an *IRF4* translocation.

[c]Cutaneous anaplastic large cell lymphoma *vs* lymphomatoid papulosis: $P = 0.04$; cutaneous anaplastic large cell lymphoma *vs* lymphomatoid papulosis, transformed mycosis fungoides, and systemic anaplastic large cell lymphoma: $P = 0.005$; cutaneous anaplastic large cell lymphoma *vs* all other diagnoses: $P = 0.00002$.

[d]Cutaneous anaplastic large cell lymphoma *vs* lymphomatoid papulosis: $P = 0.0005$; cutaneous anaplastic large cell lymphoma *vs* lymphomatoid papulosis, transformed mycosis fungoides, and systemic anaplastic large cell lymphoma: $P = 0.00007$; cutaneous anaplastic large cell lymphoma *vs* all other diagnoses: $P < 0.000001$.

later biopsy. In all, *IRF4* abnormalities were seen in 3 of 13 cases of transformed mycosis fungoides (23%; all CD30-positive and all involving extra copies of *IRF4*), but in no case of non-transformed mycosis fungoides/Sézary syndrome (of 31 cases tested). Extra proximal (green) signals were seen in three cases. In two cases (one cutaneous anaplastic large cell lymphoma and one systemic ALK-negative anaplastic large cell lymphoma), there was one extra proximal signal, whereas one case (cutaneous anaplastic large cell lymphoma) had four extra proximal signals (Figures 3f and g). Heterozygous deletion of the *IRF4* locus was seen in one case (T-cell prolymphocytic leukemia).

Frequency of IRF4 (MUM1) Protein Expression in Cutaneous T-cell Lymphoproliferative Disorders

A majority of anaplastic large cell lymphomas (85%) were at least partially positive for IRF4 by immunohistochemistry regardless of whether they were cutaneous or systemic and whether or not they expressed ALK (Figure 1c). Among cutaneous anaplastic large cell lymphomas, 70% were positive for IRF4 (including all cases with *IRF4* translocations; Figure 2d), and another 14% were partially positive. IRF4 expression also was seen in most cases of lymphomatoid papulosis (71% positive, 25% partial) and transformed mycosis fungoides (75% positive, 8% partial). Varying degrees of IRF4 expression were seen in non-transformed mycosis fungoides/Sézary syndrome; peripheral T-cell lymphoma, not otherwise specified; and other T-cell lymphoproliferative disorders. Among all T-cell lymphoproliferative disorders, IRF4 was positive in 47% of cases and partially positive in another 18%. All patients with multiple biopsies showed concordance of IRF4 expression among their biopsies.

Discussion

In this large, multicenter study, we demonstrate that FISH positivity for an *IRF4* translocation is highly specific for cutaneous anaplastic large cell lymphoma in skin biopsies involved by T-cell lymphoproliferative disorders. This finding is important, because current pathologic criteria are insufficient to distinguish cutaneous anaplastic large cell lymphoma from cutaneous involvement by ALK-negative systemic anaplastic large cell lymphoma, lymphomatoid papulosis, and, in some cases, transformed mycosis fungoides.[2,3] The specificity of *IRF4* translocations for cutaneous anaplastic large cell lymphoma was 98% among these entities (99% overall). In contrast, IRF4 protein expression was distributed widely across numerous T-cell lymphoproliferative disorder subtypes. These data indicate a clinical role for *IRF4* FISH, but not IRF4 immunohistochemistry, in the differential diagnosis of cutaneous T-cell lymphoproliferative disorders.

As discussed above, cutaneous anaplastic large cell lymphoma must be differentiated from cutaneous involvement by systemic ALK-negative anaplastic large cell lymphoma, lymphomatoid papulosis, and transformed mycosis fungoides. Distinguishing between cutaneous anaplastic large cell lymphoma and systemic ALK-negative anaplastic large cell lymphoma currently rests on clinical staging.[2,3] However, even clinical staging is imperfect. For example, the originating tumor site cannot always be determined in patients presenting with both skin lesions and lymphadenopathy. In other cases, only lymph node involvement is apparent to the pathologist and/or clinician; subsequently (or perhaps never), the history of a previous skin biopsy is discovered (which turns out to have been cutaneous anaplastic large cell lymphoma). Correct diagnosis in such cases is important, because the presence of isolated regional lymph

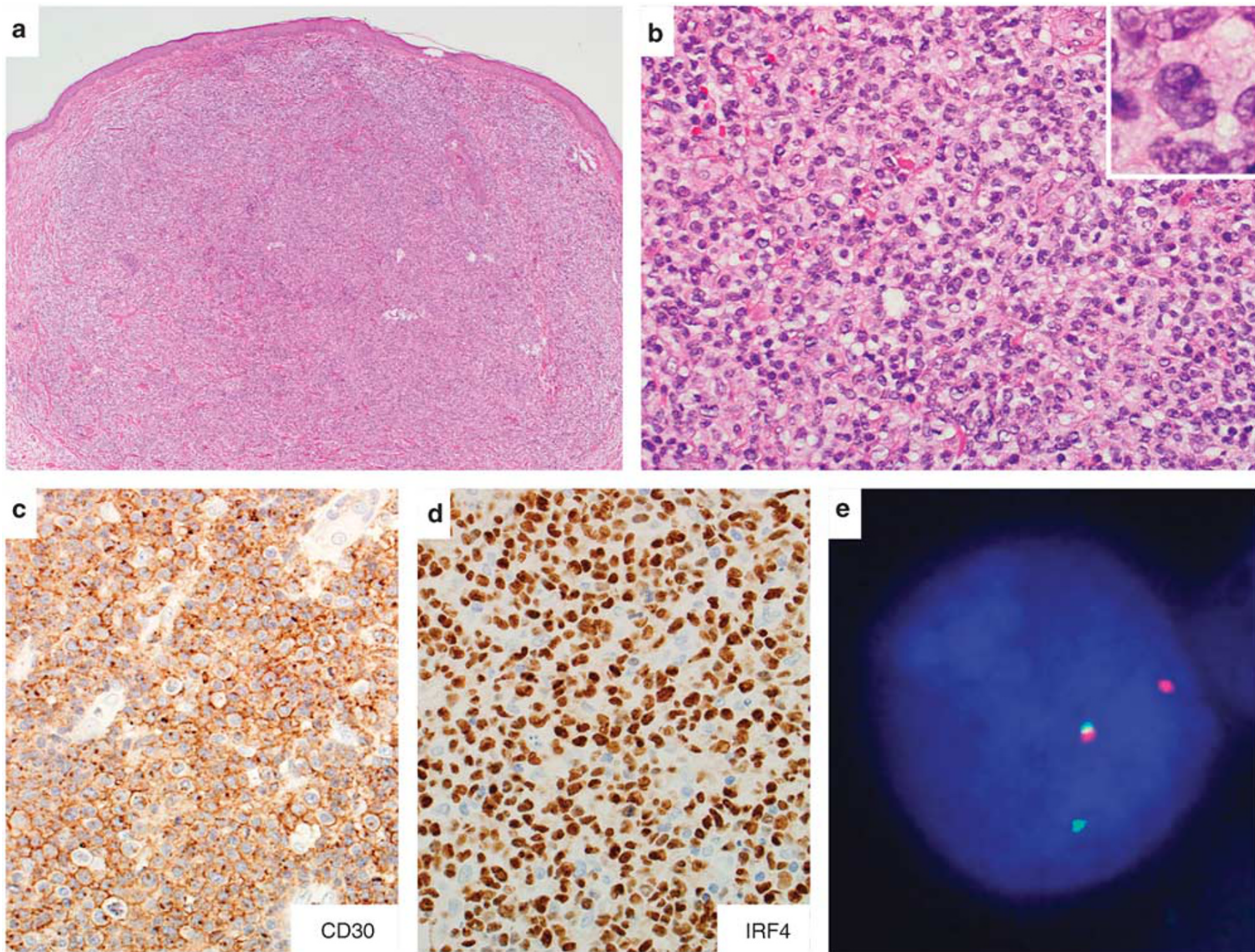

Figure 2 Representative case of primary cutaneous anaplastic large cell lymphoma with *IRF4* translocation. (**a**) A nodular infiltrate expands the dermis (hematoxylin and eosin (H&E), original magnification ×40). (**b**) At higher power (H&E, ×400), sheets of large tumor cells with abundant cytoplasm are seen. Many have cytologic features of so-called 'hallmark' cells (inset; H&E, ×1000). (**c**, **d**) By immunohistochemistry (×400), the tumor cells are positive for CD30 and IRF4 (MUM1). (**e**) FISH using an *IRF4* breakapart probe shows one normal fusion signal and an abnormal split signal (separated red and green signals), indicating a translocation.

node involvement has no significant effect on the prognosis of cutaneous anaplastic large cell lymphoma,[4] and the 5-year overall survival of cutaneous anaplastic large cell lymphoma is 90%, compared with 49% in systemic ALK-negative anaplastic large cell lymphoma.[12] Several immunohistochemical markers previously have been investigated to distinguish these entities, including clusterin, TRAF1, and IRF4 itself, but none has demonstrated clinical utility in this differential diagnosis.[5,13–16] Our data suggest that detecting an *IRF4* translocation favors a diagnosis of cutaneous anaplastic large cell lymphoma over systemic ALK-negative anaplastic large cell lymphoma in skin biopsies. FISH testing should not, however, replace proper staging. We previously described a single nodal case of systemic ALK-negative anaplastic large cell lymphoma with an *IRF4* translocation (of 41 systemic ALK-negative anaplastic large cell lymphomas tested, 2%) (Feldman *et al*[5]): although not identified in the current series, such cases theoretically could involve the skin. In addition, we emphasize the importance of ALK testing in cutaneous CD30-positive T-cell lymphoproliferative disorders. Although rare ALK-positive anaplastic large cell lymphomas with clinical features suggesting primary cutaneous disease have been reported,[17] the majority of ALK-positive anaplastic large cell lymphomas are systemic.[18] In our studies to date, we have not encountered any ALK-positive anaplastic large cell lymphoma with an *IRF4* translocation.[5]

The distinction between cutaneous anaplastic large cell lymphoma and morphologically identical lymphomatoid papulosis is particularly challenging to the pathologist, because it requires an accurate clinical history and/or observation of the patient over time. Lymphomatoid papulosis is characterized by skin lesions that typically wax and wane; however, this history is not always available, depending on the practice setting. Immunohistochemical tests do not aid in this distinction: a single study suggested that IRF4 protein itself could be

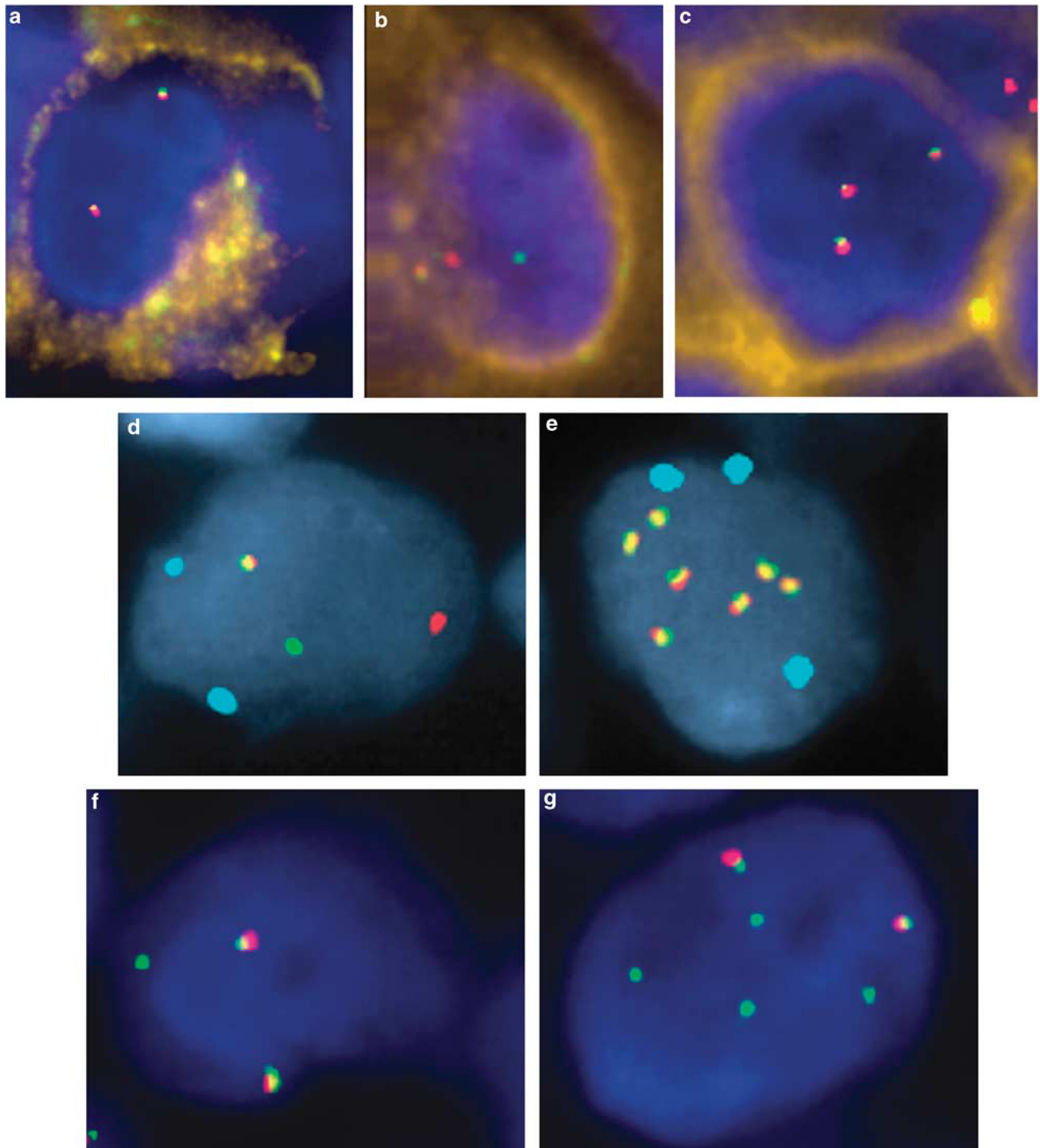

Figure 3 Spectrum of *IRF4* FISH abnormalities in cutaneous CD30-positive T-cell lymphoproliferative disorders. Combined FISH/immunofluorescence allows evaluation of the FISH signal pattern in the tumor cells expressing CD30 (gold color): (**a**) cutaneous anaplastic large cell lymphoma with a normal signal pattern (two fusion signals); (**b**) cutaneous anaplastic large cell lymphoma with *IRF4* translocation (one fusion signal and one split signal); (**c**) systemic ALK-negative anaplastic large cell lymphoma with extra copy of *IRF4* locus (three fusion signals). Addition of CEP6 probe (aqua) allows comparison of copies of *IRF4* locus with copies of centromere 6: (**d**) cutaneous anaplastic large cell lymphoma with *IRF4* translocation and two copies of centromere 6; (**e**) subcutaneous panniculitis-like T-cell lymphoma with seven copies of the *IRF4* locus and three copies of centromere 6. Extra proximal (green) signals were seen in three cases and ranged from (**f**) one extra signal (cutaneous anaplastic large cell lymphoma) to (**g**) four extra signals (cutaneous anaplastic large cell lymphoma).

used to differentiate lymphomatoid papulosis from cutaneous anaplastic large cell lymphoma,[19] but there is no evidence for this in this study or in several previous studies.[7,13,15,20] Clusterin staining similarly has not been helpful.[16,21] In this study, we detected an *IRF4* translocation in a single case of lymphomatoid papulosis, type C (of 31 cases of lymphomatoid papulosis; 3%). This was the only

Table 2 Clinical characteristics of patients with primary cutaneous anaplastic large cell lymphoma, based on results of *IRF4* FISH

	IRF4 FISH result			
	IRF4 translocation	*Normal*	*Abnormal without translocation*[a]	*All cases without translocation*
n	9	28	8	36
M:F	5:4	14:14	5:3	19:17
Age in years: mean (range)	60 (45–70)	60 (21–96)	45 (16–74)	57 (16–96)
Anatomic site				
Head and neck (%)	38	19	0	13
Upper extremity (%)	13	25	14	22
Trunk (%)	25	31	42	35
Lower extremity (%)	25	25	42	30
Follow-up in months: median (range)	10 (0–74)	51 (0–292)	47 (2–147)	49 (0–292)
Extracutaneous spread: cases (%)	1 (11)	2 (7)	2 (25)	4 (11)
Deaths: cases (%)	2 (22)	8 (29)	1 (13)	9 (25)

[a]Includes six cases with extra copies of intact *IRF4* locus and two cases with extra proximal signals (see text).

T-cell lymphoproliferative disorder other than cutaneous anaplastic large cell lymphoma to show an *IRF4* translocation. This finding may represent genetic evidence for the hypothesis that cutaneous anaplastic large cell lymphoma and lymphomatoid papulosis constitute a clinical and histologic spectrum;[1,22] in fact, classification of 'borderline' cases may be difficult, as cutaneous anaplastic large cell lymphoma may regress spontaneously, while type C lymphomatoid papulosis may be histologically indistinguishable from anaplastic large cell lymphoma.[3] Our data suggest that, in most cases, the presence of an *IRF4* translocation predicts clinical behavior resembling cutaneous anaplastic large cell lymphoma.

By WHO criteria, the diagnosis of cutaneous anaplastic large cell lymphoma requires exclusion of a history of mycosis fungoides.[3] Lesions resembling cutaneous anaplastic large cell lymphoma in the context of a history of mycosis fungoides are considered transformed mycosis fungoides. In this study, we did not identify *IRF4* translocations in either mycosis fungoides/Sézary syndrome or transformed mycosis fungoides. Pham-Ledard *et al* reported two cases diagnosed as transformed mycosis fungoides with *IRF4* translocations (of 11 tested), both histologically resembling cutaneous anaplastic large cell lymphoma.[7] The *IRF4* translocation status and clonal relatedness of the original mycosis fungoides lesions were not described. Thus, the possibility that *IRF4* translocations represent a transforming event in mycosis fungoides requires further study.

The prognostic significance of *IRF4* translocations in cutaneous anaplastic large cell lymphoma remains uncertain. Although we did not find clear differences in outcome between translocated and non-translocated cases, the difference in median follow-up (10 *vs* 49 months, respectively) and generally short overall follow-up times limit the ability to draw conclusions regarding prognostic significance of the translocation. The possible clinical significance of non-translocation abnormalities by *IRF4* FISH (principally extra copies of the intact *IRF4* locus) merits study of additional cases with longer follow-up.

Our study confirms earlier findings[5,7] that most cutaneous anaplastic large cell lymphomas express IRF4 protein regardless of the presence of *IRF4* translocations. An analogy may be drawn to multiple myeloma, in which *IRF4* translocations are present in the minority of cases[23] but IRF4 protein is expressed universally.[6] Thus, the relationship between *IRF4* translocations and IRF4 protein expression is uncertain in both myeloma and cutaneous anaplastic large cell lymphoma. IRF4 has been shown to be critical for myeloma cell growth and represents a potential therapeutic target for that disease.[24] Therefore, the role of IRF4 in cutaneous anaplastic large cell lymphoma and related T-cell lymphoproliferative disorders merits further study.

It is possible that the biologic effects of *IRF4* translocations are related to neighboring genes on 6p25.3. The *IRF4* FISH probe used also flanks the phosphatase gene, *DUSP22*, located immediately telomeric to *IRF4*; bacterial artificial chromosomes mapping to the region between *IRF4* and *DUSP22* cross-hybridize when used for FISH.[5,7] In addition, the gene *EXOC2*, which encodes a component of the exocyst complex, partially overlaps the centromeric portion of the *IRF4* FISH probe. Pham-Ledard *et al*[7] suggested a minor breakpoint region may exist in the *IRF4* region involving *EXOC2*. *IRF4* FISH does not distinguish between this possibility and an extra copy of *EXOC2* in cases with one extra proximal signal; however, existence of extra copies of *EXOC2* is suggested by our case with four extra proximal signals. Finally, biologic significance of *IRF4* translocations may derive from the role of the partner gene(s), which remain to be identified.

In summary, we propose that *IRF4* FISH is a useful adjunct in the differential diagnosis of cutaneous CD30-positive T-cell lymphoproliferative disorders. In patients without mycosis fungoides/Sézary syndrome, presence of a translocation favors a diagnosis of cutaneous anaplastic large cell lymphoma rather than systemic ALK-negative anaplastic large cell lymphoma or lymphomatoid papulosis. *IRF4* FISH represents the most specific test for cutaneous anaplastic large cell lymphoma to date. Like all FISH testing, however, *IRF4* FISH should be used in the context of clinical, morphologic, and phenotypic data. The biologic significance of *IRF4* translocations and their implication in patients with mycosis fungoides/Sézary syndrome merit further study.

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Disclosure/conflict of interest

Mayo Clinic and authors MEL, AD, and ALF have a potential financial interest in technology associated with this research. Mayo Clinic has filed a non-provisional patent application for that technology.

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