Recurrent translocations involving the IRF4 oncogene locus in peripheral T-cell lymphomas

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Abstract

Oncogenes involved in recurrent chromosomal translocations serve as diagnostic markers and therapeutic targets in hematopoietic tumors. In contrast to myeloid and B-cell neoplasms, translocations in peripheral T-cell lymphomas (PTCLs) are poorly understood. Here, we identified recurrent translocations involving the multiple myeloma oncogene-1/interferon regulatory factor-4 (IRF4) locus in PTCLs. IRF4 translocations exist in myeloma and some B-cell lymphomas, but have not been reported previously in PTCLs. We studied 169 PTCLs using fluorescence in situ hybridization and identified 12 cases with IRF4 translocations. Two cases with t(6;14)(p25;q11.2) had translocations between IRF4 and the T-cell receptor-alpha (TCRA) locus. Both were cytotoxic PTCLs, unspecified (PTCL-Us) involving bone marrow and skin. Eight of the remaining ten cases were cutaneous ALCLs without TCRA rearrangements (57% of cutaneous ALCLs tested). These findings identified IRF4 translocations as a novel recurrent genetic abnormality in PTCLs. Cytotoxic PTCL-Us involving bone marrow and skin containing IRF4/TCRA translocations might represent a distinct clinicopathologic entity. Translocations involving IRF4 but not TCRA appear to occur predominantly in cutaneous ALCLs. Detecting these translocations may be useful in lymphoma diagnosis. Further, due to its involvement in translocations, MUM1/IRF4 protein may play an important biologic role in some PTCLs, and might represent a possible therapeutic target.

Keywords
MUM1; IRF4; T-cell receptor-alpha; PTCL; ALCL; translocation; CD30; cutaneous lymphoma

Peripheral T-cell lymphomas (PTCLs) are malignant neoplasms of mature (peripheral) T lymphocytes, and represent approximately 10% of non-Hodgkin lymphomas.1 Despite treatment with conventional chemotherapy, the majority of patients with PTCLs die of their disease.2 New, targeted therapies might be aimed at genes involved in recurrent chromosomal translocations.3-5 but, in contrast to myeloid neoplasms and B-cell lymphomas,1 translocations in most PTCLs remain poorly understood. Identifying novel...
recurrent translocations in PTCLs also may help define specific disease entities and serve as the basis for clinical diagnostic testing, as they have in the case of chromosomal translocations involving ALK in ALK-positive anaplastic large-cell lymphomas (ALCLs). However, ALK-positive ALCLs represent only about 6% of PTCLs.

In this report, we demonstrate for the first time the presence of translocations involving the multiple myeloma oncogene-1/interferon regulatory factor-4 (IRF4) locus on 6p25 in PTCLs. Based on the observation of a PTCL, unspecified (PTCL-U), with a karyotype including t(6;14)(p25;q11.2), we studied 169 PTCLs and found 12 with IRF4 translocations (including the index case). Two had t(6;14)(p25;q11.2) translocations that fused the IRF4 and T-cell receptor-alpha (TCRA) gene loci. Both were cytotoxic PTCLUs that presented in the bone marrow and rapidly developed skin lesions. Such tumors might represent a distinct clinicopathologic entity.

Eight cutaneous ALCLs (C-ALCLs) had translocations involving IRF4 but not TCRA (57% of C-ALCLs tested). One systemic ALK-negative ALCL and an additional PTCL-U showed translocations involving IRF4 but not TCRA. IRF4 translocations were not detected in ALK-positive ALCLs. C-ALCL is an indolent disease that currently lacks specific pathologic features to distinguish it from skin involvement by systemic ALK-negative ALCL, which is aggressive and often fatal. Testing for IRF4 translocations may have clinical diagnostic utility in C-ALCL. While molecular pathways associated with ALK translocations in ALK-positive ALCLs have been studied extensively, corresponding pathways in ALCLs lacking ALK translocations are poorly understood. MUM1/IRF4 protein could play a biologic role in PTCLs with IRF4 translocations, since IRF4 is oncogenic in vitro. Utilization of MUM1/IRF4 as a therapeutic target in patients with PTCL merits exploration.

**Materials and methods**

**Cases**

We studied specimens from 169 patients with PTCL diagnosed by WHO criteria. There were 104 males and 65 females (M:F ratio, 1.6:1), with a median age of 58 years (range, 5−92 years). Cases included 23 angioimmunoblastic T-cell lymphomas (AITLs, 13%), 72 PTCL-U (43%), 18 ALK-positive ALCLs (11%), 24 ALK-negative ALCLs (14%), 14 C-ALCLs (8%), and 18 other PTCLs (Table 1). The study was approved by the Institutional Review Board and the Biospecimens Committee of Mayo Clinic.

**Fluorescence In Situ Hybridization (FISH)**

IRF4 and TCRA FISH probes were developed as previously described. BAC clones (Table S1) were identified using the University of California Santa Cruz Genome Browser (http://www.genome.ucsc.edu) and ordered from ResGen Invitrogen (Carlsbad, CA). Since telomeric IRF4 clones showed minimal cross-hybridization to 16p11, positive cases were confirmed using a second breakapart IRF4 probe (probe #2, Table S1). BAC DNA was isolated using the Qiagen (Valencia, CA) Plasmid Maxi Kit and fluorescently labeled using SpectrumOrange-dUTP or SpectrumGreen-dUTP and the Abbott Molecular (Des Plaines, IL) Nick Translation Kit. Centromeric and telomeric BAC DNA was labeled with different
fluorophores for breakapart probes, and with the same fluorophore for dual-fusion (D-FISH) probes. Probe validation was conducted based on previously described ‘familiarization’ procedures. Specificity of hybridization was confirmed on metaphases from a splenic marginal zone lymphoma with IRF4-IGH fusion, a PTCL with a TCRA translocation, and normal samples. TCRB and TCRG probes were purchased from Dako (Carpinteria, CA). The upper limit of the normal range for each probe was determined using a 95% confidence interval as previously described. Upper limits of normal for IRF4, TCRA, TCRB, and TCRG were 6%, 9%, 5%, and 6%, respectively.

Paraffin tissue microarrays (TMAs) were constructed as described. In cases with insufficient tissue, whole-tissue sections were analyzed. B5- and formalin-fixed cases were included, since we have shown similar FISH results with both fixatives. FISH was performed as previously described. Sections were sequentially immersed in Citrisolve, Lugol solution, and sodium thiocyanate. Slides were microwaved for 5 minutes in citrate buffer, then digested in 0.4% pepsin solution at 37°C. Ten microliters of FISH reagent (7 μL LSI buffer and 3 μL probe) were placed on each slide and slides were cover-slipped, denatured, and incubated in a humidified chamber at 37°C for 12 hours. Slides were washed, counterstained with 4,6-diamidino-2-phenylindole dihydrochloride, and analyzed by a microscopist (ML) using a fluorescent microscope with appropriate filter sets. A minimum of 50 cells and a maximum of 200 cells were scored per case. A minimum of 20 abnormal cells were required for a sample to be considered abnormal. Some cases were non-informative due to hybridization failures. Positive cases detected on TMAs were confirmed on whole tissue sections. Scoring for IRF4 in 4 translocated cases with areas showing confluent sheets of tumor cells areas revealed a mean of 71% positive cells (range, 55% –93%).

**Immunohistochemistry (IHC)**

Five-micron paraffin whole-tissue sections were immunostained using previously described techniques and antibodies to assist in disease classification. For MUM1/IRF4 immunostaining, whole-tissue or TMA sections were pretreated in 1 mM EDTA buffer at pH 8.0 for 30 min at 98°C (PT Module, Lab Vision, Fremont, CA), then stained for MUM1/IRF4 using a monoclonal mouse anti-human antibody (MUM1p, 1:50; Dako). Detection was with Dual Link Envision+/DAB+ (Dako). Scoring was performed in correlation with H&E and appropriate immunostains (e.g. CD20 and CD3). MUM1/IRF4 was considered positive when >30% of tumor cells demonstrated nuclear staining. Technical factors precluded scoring in rare cases. Diagnosis of C-ALCL required CD30 positivity in >75% of tumor cells, per WHO criteria. This cutoff also was used to define CD30 positivity in cases of PTCL-U.

**Conventional Cytogenetics**

Results of karyotype analysis prepared at the time of biopsy using previously described methods were reviewed retrospectively when available.
Results and discussion

We identified 12 PTCLs with IRF4 translocations among 155 PTCLs with informative FISH results (8%; Tables 1,2). These included 3/64 PTCL-Us (5%), 1/23 ALK-negative ALCLs (4%), and 8/14 C-ALCLs (57%). IRF4 translocations were not seen in ALK-positive ALCLs, AITLs, or other PTCL subtypes. MUM1/IRF4 protein was detected in the majority of ALCLs, regardless of type (Table 1). MUM1/IRF4 was positive in 72% of CD30-positive PTCL-Us and 13% of CD30-negative PTCL-Us, and was negative in other PTCL subtypes. All cases with IRF4 translocations were positive for MUM1/IRF4 by IHC.

Two PTCL-Us with IRF4 translocations by FISH had karyotypes with t(6;14)(p25;q11.2) (Cases 1 and 2, Table 2). Karyotypes were not performed in the other 10 PTCLs with IRF4 translocations. Karyotypes of 35 PTCLs without IRF4 translocations by FISH and 2 PTCLs in which IRF4 FISH failed showed no anomalies of 6p25 (Table S2). The PTCL-Us with t(6;14)(p25;q11.2) had similar clinicopathologic features. Both presented in older adult males with mild cytopenias and without significant lymphadenopathy or hepatosplenomegaly. In both patients, imaging showed diffuse skeletal uptake and renal mass lesions (not biopsied). No tumor cells were seen in the peripheral blood. Both patients had extensive bone marrow infiltration by tumor with admixed plasma cells and reticulin fibrosis (Fig. 1 a,g). The cells were larger and more pleomorphic in Case 1 (Fig. 1 b,h). Both tumors were positive for CD3, beta-F1, TIA1, and MUM1/IRF4 (Fig. 1 c,d,e,i). They were negative for CD5, CD30, CD25, FoxP3 and EBV. Case 1 was positive for granzyme B and CD4, and partially positive for CD8. In both cases, the t(6;14)(p25;q11.2) corresponded to IRF4/TCRA fusion by D-FISH (Fig. 1 j,k). The patient in Case 1 received chemotherapy (Table 2) but developed progressive skin lesions and probable cerebrospinal fluid involvement. Despite additional therapy his skin lesions progressed (Fig. 1 f); he is alive with disease 4 months after presentation. The patient in Case 2 developed skin and soft tissue lesions during the course of evaluation (not biopsied). Chemotherapy was recommended but follow-up data are not available. We classified these cases as PTCL-Us.

IRF4 translocations were detected in 8/14 C-ALCLs tested (57%). All initial diagnostic biopsies were reviewed. Clinical or pathologic features of lymphomatoid papulosis were not observed. None of the patients had a history of mycosis fungoides (MF) or dermatitis suggestive of clinical MF. Four patients developed nodal disease 1 to 126 months after diagnosis (Table 2). The patient with a 1-month interval between cutaneous and nodal disease (Case 7) had multiple skin nodules and local adenopathy. Staging was otherwise negative, suggesting C-ALCL with locoregional spread; however, it is possible the disease originated in the lymph node. Cases 3 and 8 showed different histology in cutaneous and nodal specimens. The skin showed mostly medium-sized tumor cells with admixed histiocytes in the background (Fig. 2 a), and occasional perivascular “hallmark” cells, reminiscent of the small-cell variant of systemic ALCL.21 The subsequent lymph node
biopsies showed sheets of large “hallmark” cells (Fig. 2 b). Histologic progression associated with nodal involvement also was seen in a C-ALCL without IRF4 translocation (not shown). The remaining C-ALCLs with IRF4 translocations had typical histologic features (Fig. 2 c-e). CD30 and MUM1/IRF4 were positive (Fig. 2 f,g). FISH showed IRF4 translocations (Fig. 2 h); TCRA, TCRA, and TCRG were negative (not shown). C-ALCLs with and without IRF4 translocations showed similar clinicopathologic features (Table 3). TIA1 positivity was somewhat less common in IRF4-translocated cases than in untranslocated cases and in C-ALCLs in the literature.22-24 Only one untranslocated case developed nodal disease.

We identified two additional PTCLs with translocations of IRF4 but not TCRA. Case 11 was a PTCL-U in the pleura of a 73 year-old female who also had multiple lung nodules. The tumor cells were medium to large and pleomorphic. “Hallmark” cells were not seen. Staging was negative. Case 12 was an ALK-negative ALCL in a 79 year-old male with generalized lymphadenopathy but without cutaneous disease. Lymph node biopsy showed sheets of “hallmark” cells (fig. 2 i). Both cases were positive for CD30 and MUM1/IRF4 and were non-cytotoxic. FISH for TCRB and TCRG was negative in Case 12; hybridization failed in Case 11. Follow-up is not available.

C-ALCL is an indolent, cutaneous disease with an excellent prognosis,2,25,26 while systemic ALK-negative ALCLs have a poor prognosis and ALK-positive ALCLs have an intermediate prognosis.25,27 Comparative genomic hybridization and gene expression profiling show molecular differences among these three ALCL subtypes,28-30 but have not established the biologic basis for the disparate clinical behaviors. Unlike ALK-positive ALCLs,1,6,9 recurrent translocations have not been reported previously in C-ALCLs or systemic ALK-negative ALCLs. The finding of IRF4 translocations in a subset of these cases (but not in ALK-positive ALCLs) may provide new clues to understanding the biology of these diseases.

MUM1/IRF4 is a transcription factor expressed in normal plasma cells, some B cells, and activated T cells.31 IRF4 is translocated in some multiple myelomas and B-cell lymphomas and causes MUM1/IRF4 overexpression.10,13,32-34 Rearrangements involving 6p have been reported in T-cell neoplasms,35-37 but the involved gene(s) were not identified and IRF4 translocations have not been previously reported. Translocations involving TCR loci in T-cell neoplasms upregulate oncogene expression on the partner chromosome, but are uncommon in PTCLs other than T-cell prolymphocytic leukemia.11,38-40 As in previous series,31,41-43 we found that MUM1/IRF4 expression in PTCLs tended to parallel CD30 expression. The PTCL-U with IRF4/TCRA were the only CD30-negative PTCLs with IRF4 translocations; thus, the MUM1/IRF4 expression in these PTCL-U likely resulted from the translocations (rather than CD30-associated activation pathways). This study does not address whether IRF4/TCRA is lymphomagenic, but the marked similarity between the two cases with IRF4/TCRA suggest the translocation may have biologic significance and that such cases might represent a distinct clinicopathologic entity.

Since most CD30-positive PTCLs express MUM1/IRF4 protein regardless of IRF4 translocation status, the biologic significance of IRF4 translocations not involving TCRA in
CD30-positive PTCLs is unclear, and merits further study. IRF4-translocated cases might have higher MUM1/IRF4 expression than non-translocated cases, but limitations of IHC precluded quantitative comparison. Alternatively, the IRF4 breakpoint might lead to altered MUM1/IRF4 protein function, or might affect expression of another gene near IRF4. Finally, the biologic consequences of IRF4 translocations might result from altered expression of the non-TCRA partner gene(s). Among B-cell lymphomas, for example, high expression levels of known BCL6 partner genes have been reported in cases with BCL6 translocations involving non-IgH partners.44

Testing for IRF4 translocations may be useful in the diagnosis of C-ALCL, which can be morphologically and immunophenotypically indistinguishable from systemic ALK-negative ALCL with secondary skin involvement.1,7,8 Since rare PTCL-Us and systemic ALK-negative ALCLs showed IRF4 translocations, the specificity of IRF4 translocations for C-ALCL in skin biopsies requires further study; identifying the IRF4 partner gene(s) may be helpful in this regard. Lymphomatoid papulosis and transformed MF also should be evaluated for IRF4 translocations, since these disorders express CD30 and MUM1/IRF443,45 but were not included in the present study. Finally, IRF4 translocations might be prognostic in C-ALCL, since lymph node involvement was more common in translocated C-ALCLs than in untranslocated C-ALCLs or in previous series.26

Because IRF4 overexpression is oncogenic in vitro,10 and because most PTCLs lack good treatment options, MUM1/IRF4 might represent a therapeutic target in patients with PTCL. MUM1/IRF4 expression in PTCLs recently was linked to expression of PRDM1, another regulatory protein expressed in some PTCLs.46 PTCL cell lines treated in vitro with the proteasome inhibitor bortezomib down-regulated MUM1/IRF4, an effect dependent on NF-κB inhibition and associated with PRDM1 down-regulation. Bortezomib is effective in the treatment of myelomas,47 which express MUM1/IRF4, and occasional clinical responses have been reported in PTCL patients.48,49 Further studies should examine whether MUM1/IRF4 positivity, and particularly the presence of IRF4 translocations, might select PTCLs likely to respond to proteasome inhibition.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Peripheral T-cell lymphomas, unspecified (PTCL-Us) with *IRF4/TCRA* translocations involving bone marrow and skin. (a) Diffuse infiltration of bone marrow (75% involvement) in a 67 year-old male (Case 1; H&E, x 4); reticulin fibrosis is present (inset, x 40). (b) Medium to large tumor cells with plasma cells in the background (H&E, x 40; inset, x 100). Tumor cells are positive for (c) CD3, (d) TIA1, (e) and MUM1/IRF4 (x 40; inset, x 100). (f) Skin biopsy from the same patient 4 mos later. Compared to the bone marrow, the tumor cells are more uniformly large and pleomorphic, and are accompanied by apoptotic debris without admixed plasma cells (H&E, x 40; inset, x 100). (g) Diffuse infiltration of bone marrow (40% involvement) in a 71 year-old male (Case 2; H&E, x 4; reticulin, inset, x 40). (h) Mostly medium-sized tumor cells with plasma cells in the background (H&E, x 40;
inset, x 100). (i) Tumor cells are positive for MUM1/IRF4 (x 40; inset, x 100). (j) Karyotype shows t(6;14)(p25;q11.2). (k) Dual-fusion fluorescence in situ hybridization (D-FISH) shows IRF4/TCRA fusion signals (arrows).
Figure 2.
Anaplastic large-cell lymphomas (ALCLs) with IRF4 translocations. (a) Primary cutaneous ALCL (C-ALCL), 48 year-old female (case 3). Medium to large tumor cells with admixed histiocytes (H&E, x 40; inset, x 100). (b) Lymph node involvement, same patient, 10 years later. Confluent sheets of large “hallmark” cells (H&E, x 40; inset, x 100). (c) C-ALCL, 67 year-old male (case 4; H&E, x 20; inset, x 100). (d) Lymph node involvement, same patient, 7 mos later (H&E, x 40; inset, x 100). Both biopsies show sheets of “hallmark” cells. (e) C-ALCL, 89 year-old female (case 5), showing positivity for (f) CD30 and (g) MUM1/IRF4 (x 10; insets, x 100). (h) Breakapart fluorescence in situ hybridization (BAP-FISH) shows separation of red and green signals flanking the IRF4 gene locus (arrows). (i) Systemic ALK-negative ALCL, cervical lymph node, 79 year-old male (case 12). Large “hallmark” cells surround a residual reactive follicle (lower left; H&E, x 40; inset, x 100).
## Table 1

**IRF4** Translocations and MUM1/IRF4 Protein Expression in Peripheral T-cell Lymphomas

| Diagnosis                                      | FISH | Immunohistochemistry |
|------------------------------------------------|------|----------------------|
|                                                | # pos. | % | # pos. | % |
| Angioimmunoblastic T-cell lymphoma             | 0/19   | 0 | 0/23 | 0 |
| PTCL, unspecified                             | 3/64   | 5 | 20/72 | 28 |
| *(CD30-positive)*                             | (1/17) | (6) | (13/18) | (72) |
| *(CD30-negative)*                             | (2/47) | (4) | (7/54) | (13) |
| Anaplastic large cell lymphoma, ALK-positive   | 0/18   | 0 | 16/17 | 94 |
| Anaplastic large cell lymphoma, ALK-negative   | 1/23   | 4 | 20/22 | 91 |
| Cutaneous anaplastic large cell lymphoma       | 8/14   | 57 | 13/14 | 93 |
| T-cell large granular lymphocyte leukemia      | 0/4    | 0 | 0/4 | 0 |
| Hepatosplenic T-cell lymphoma                  | 0/3    | 0 | 0/3 | 0 |
| Subcutaneous panniculitis-like T-cell lymphoma | -      | - | 0/1 | 0 |
| Enteropathy-associated T-cell lymphoma         | 0/2    | 0 | 0/2 | 0 |
| Extramedullary NK/T-cell lymphoma, nasal type  | 0/8    | 0 | 0/8 | 0 |
| **Total**                                      | **12/155** | **8** | **69/166** | **42** |

*Includes informative cases only, of 169 total cases tested.
| Case | Age/Sex | Diagnosis          | Site   | Time from diagnosis (mos) | Cytotoxic phenotype<sup>a</sup> | IRF4 FISH | IRF4/TCRA Fusion | Karyotype                                                                                           | Treatment        | Follow-up                                      |
|------|---------|-------------------|--------|---------------------------|-------------------------------|-----------|-----------------|----------------------------------------------------------------------------------------------------|------------------|-----------------------------------------------|
| 1    | 67/M    | PTCL-U            | BM     | -                         | YES                           | -         | -               | 46−49,XY,+5[5],+8,der(6)(p14.1q25)p(11.2),add(7)(p11.2)−,+8,+16[5],−20,+22[4],+1−2mar(p6)P95−98,idem(x2)+3−6mar[2] | CHOP, ICE, ITMTX | alive, progressive cutaneous disease, 4 mos                                                     |
|      |         |                   | skin   | 2                         | YES                           | -         | -               | -                                                                                                  | -                |                                               |
| 2    | 71/M    | PTCL-U            | BM     | -                         | YES                           | POS      | POS              | 49−50,XY,+add(3)(q27),t(6;14)(p25;q11.2),+8,+19,+21<sup>b</sup>                                  | -                |                                               |
|      |         |                   | skin   | 4                         | NO                            | POS      | -               | -                                                                                                  | -                |                                               |
|      |         |                   | skin   | 1                         | YES                           | -         | -               | -                                                                                                  | -                |                                               |
|      |         |                   | LN     | 126                       | NO                            | POS      | -               | -                                                                                                  | -                |                                               |
|      |         |                   | LN     | 134                       | NO                            | POS      | NEG              | -                                                                                                  | -                |                                               |
| 3    | 48/F    | Cutaneous ALCL    | skin   | -                         | -                             | -         | -               | -                                                                                                  | PUVA, IFNα-2A, CHOP | alive, in remission, 154 mos                  |
|      |         |                   | skin   | 83                        | YES                           | POS      | NEG              | -                                                                                                  | -                |                                               |
|      |         |                   | LN     | 126                       | NO                            | POS      | -               | -                                                                                                  | -                |                                               |
|      |         |                   | LN     | 134                       | NO                            | POS      | NEG              | -                                                                                                  | -                |                                               |
| 4    | 67/M    | Cutaneous ALCL    | skin   | -                         | -                             | -         | -               | -                                                                                                  | -                | alive, LN involvement, 7 mos                 |
|      |         |                   | LN     | 7                         | NO                            | POS      | NEG              | -                                                                                                  | -                |                                               |
| 5    | 89/F    | Cutaneous ALCL    | skin   | -                         | -                             | -         | -               | -                                                                                                  | XRT, CHOP        | died, progressive cutaneous disease, no autopsy, 4 mos |
| 6    | 65/M    | Cutaneous ALCL    | skin   | -                         | YES                           | POS      | NEG              | -                                                                                                  | -                |                                                                                             |
| 7    | 52/M    | Cutaneous ALCL    | skin   | -                         | YES                           | POS      | NEG              | -                                                                                                  | CHOP             | alive, skin recurrence, 27 mos               |
|      |         |                   | LN     | 1                         | NO                            | -         | -               | -                                                                                                  | -                |                                               |
| 8    | 74/M    | Cutaneous ALCL    | skin   | -                         | NO                            | -         | -               | -                                                                                                  | -                | alive, LN involvement, 34 mos               |
|      |         |                   | LN     | 34                        | NO                            | POS      | NEG              | -                                                                                                  | -                |                                               |
| 9    | 35/M    | Cutaneous ALCL    | skin   | -                         | -                             | NO       | -               | -                                                                                                  | -                |                                               |
| 10   | 50/M    | Cutaneous ALCL    | skin   | -                         | -                             | NO       | -               | -                                                                                                  | -                |                                               |
| 11   | 73/F    | PTCL-U            | pleura | -                         | NO                            | POS      | NEG              | -                                                                                                  | -                |                                               |
| 12   | 79/M    | ALK-negative ALCL | LN     | -                         | -                             | NO       | -               | -                                                                                                  | -                |                                               |

<sup>a</sup> Positive for TIA-1 by immunohistochemistry.

FISH, fluorescence in situ hybridization; BM, bone marrow; LN, lymph node; PTCL-U, peripheral T-cell lymphoma, unspecified; ALCL, anaplastic large-cell lymphoma; PUVA, psoralen UVA phototherapy; IFNα-2A, interferon alpha-2A; CHOP, cyclophosphamide + hydroxydoxorubicin + vincristine + prednisone; ICE, ifosfamide + carboplatin + etoposide; ITMTX, intrathecal methotrexate; XRT, radiotherapy.
FISH for BCL6 at 3q27 was normal (data not shown).
### Table 3

Clinicopathologic Features of Primary Cutaneous Anaplastic Large Cell Lymphomas With and Without IRF4 Translocations

|                         | IRF4 Translocation |          |          |
|-------------------------|--------------------|----------|----------|
|                         | Present            | Absent   |          |
| n (%)                   | 8 (57)             | 6 (43)   |          |
| M:F                     | 6:2                | 3:3      |          |
| Age, mean (range), y    | 60 (35–89)         | 64 (12–92)|          |
| Immunophenotype (%)     |                    |          |          |
| CD30                    | 8/8 (100)          | 6/6 (100)|          |
| CD3                     | 6/8 (75)           | 2/6 (33) |          |
| CD4                     | 5/8 (63)           | 4/6 (67) |          |
| CD8                     | 0/8 (0)            | 1/6 (17) |          |
| ALK                     | 0/8 (0)            | 0/6 (0)  |          |
| TIA1                    | 2/8 (25)           | 3/6 (50) |          |
| MUM1/IRF4               | 8/8 (100)          | 5/6 (83) |          |
| Subsequent extracutaneous disease | 4 | 1 |          |
| Follow-up, mean (range), mos | 29 (0–154) | 30 (0–76) |          |