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The significance of MUM1/IRF4 protein expression and IRF4 translocation of CD30(+) cutaneous T-cell lymphoproliferative disorders: A study of 53 cases

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ABSTRACT

Current laboratory technics, clinicopathologic findings cannot always reliably distinguish primary cutaneous CD30(+) lymphoproliferative disorders (LPD), such as lymphomatoid papulosis (LyP), primary cutaneous CD30(+) anaplastic large cell lymphoma (PCALCL), transformed mycosis fungoides (T-MF) and systemic ALK(−) anaplastic large cell lymphoma (ALCL) with skin involvement. We investigated the presence of IRF4 translocation with break apart DNA-FISH method of these entities according to the recent studies of Feldman et al.

In our study group with 53 cases, the detection of IRF4 translocation had a specificity and positive predictive value for PCALCL of 100%. In contrast MUM1/IRF4 protein expression was distributed widely without any predictive value.

1. Introduction

Current laboratory technics, clinical and morphologic findings cannot always reliably distinguish primary cutaneous CD30(+) lymphoproliferative disorders (LPD), such as lymphomatoid papulosis (LyP), primary cutaneous CD30(+) anaplastic large cell lymphoma (PCALCL), transformed mycosis fungoides (T-MF) and systemic ALK(−) anaplastic large cell lymphoma (ALCL) with skin involvement. Differentiation of LyP and PCALCL can pose diagnostic challenges in certain cases. Besides histologic and immunophenotypic features, accurate clinical history is essential. However, the history is not always available in a routine setting. As a result, sometimes long periods of follow up are needed for an exact diagnosis. Moreover, the morphology in the lesions of PCALCL and T-MF may be identical. Distinguishing PCALCL from its systemic counterpart rests on clinical staging. However, even after the clinical staging, it may still be unclear. An isolated regional lymph node involvement may be a finding without any prognostic significance in PCALCL. On the other hand, it may point out a systemic lymhoma, as well. Feldman et al. identified the presence of translocation involving the multiple myeloma oncogene-1 (MUM1)/interferone regulatory factor-4 (IRF4) locus on 6p25 in peripheral T-cell lymphomas [1]. IRF4 is a transcription factor expressed in activated T cells, as well as plasma cells, some B cells, and their corresponding malignant counterparts [2]. In recent studies, the presence of IRF4 translocation with break apart DNA FISH method was discovered to be a valuable tool in distinguishing these cutaneous T cell lymphomas, expressing CD30 antigen [3–5]. The aim of our study was to investigate the value of IRF4 translocation and MUM1/IRF4 expression in skin biopsies.

2. Materials and methods

2.1. Case selection

Our study group was composed of 54 skin biopsies from 53 patients with cutaneous lymphomas, diagnosed according to the 2008 World Health Organization (WHO) classification [6]. The cases analyzed for this study were 26 LyP, 13 PCALCL, 9 T-MF, displaying CD30(+) large cells. In total, there were 11 cases of T-MF in our achieves, containing more than 25% of large cells, however only 9 of them demonstrated CD30 immunreactivity. CD30(−) T-MF cases were excluded. There were 2 biopsies from one case of PCALCL. Three cases of systemic ALK(−) ALCL, 1 systemic ALK(+) ALCL and 1 classic Hodgkin Lymphoma (CHL) were included as a control group. H&E and immune stained slides of all cases were histologically and clinically reviewed. The follow-up data were obtained from a combination of chart reviews and telephone interviews. Clinical information included age, gender, the site(s) of disease, the number and type of lesions, duration of follow-up, status at last follow-up, extracutaneous spread and death, if any. None of the patients of PCALCL had any systemic disease at the time of diagnosis during routine evaluation, which included complete blood cell count, physical and radiologic examination, as well as bone marrow biopsy performed in some cases.

We developed a dual color break apart FISH probe from related BAC clones for the detection of IRF4 rearrangements from tissue samples. We performed IRF4 FISH with tissue break apart dual color probe and at the same time immunohistochemistry for the expression of MUM1/IRF4.

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2.2. Florescence in situ hybridization

We used the National Center for Biotechnology Information (NCBI)'s database for the determination and selection of IRF4 related BAC clones. We checked the cytogenetics location of each BAC clone related to the IRF4 gene from the NCBI Map viewer. CTD-2308G5 (5′ IRF4-flanking BAC clone) and RP11-164H16 (3′ IRF4-flanking BAC clone) BAC clones were selected and ordered from Invitrogen (Life Technologies, USA). The break point is lying between the 3′ end of CTD-2308G5 and the 5′ end of RP11-164H16 BAC probes, suggesting the existence of a major breakpoint region and spanning almost 130 kb [4].

BAC clones were plated and propagated and glycerol stocks were prepared. A standard alkaline lysis procedure was used to isolate BAC DNA. The DNA was purified using the High Pure PCR Clean-up Micro Kit (Roche Applied Science, USA). FISH probes were created using purified CTD-2308G5 and RP11-164H16 BAC DNA's and labeled with Spectrum Green dUTP (Abbott Molecular Inc., USA) and Cyanine-3 dUTP (Enzo Life Sciences, Inc., USA) respectively, using Nick Translation Reagent Kit (Abbott Molecular Inc., USA). The labeled DNA probes were tested on interphase and metaphase cells and tissue samples for the control of chromosomal location and signal quality.

Tissue sections were placed on positively charged slides with 4–6 μm and deparafinized using the Depamiks Tissue Fish Deparafinization and Pretreatment Kit (Medimiks Biotechnology, Turkey). They were digested in enzyme working solution for 15 min at 37 °C. After enzymatic pretreatment, slides were immersed in 2× SSC solution (Abbott Molecular, USA) for 2 × 3 min, followed by dehydration in graded ethanol for 3 min (ethanol 70%, 85%, 99.9%) respectively and dried at RT.

The hybridization mix was prepared (2 μl dual color break apart IRF4 FISH probe and 8 μl miksish™ FISH Hybridization Buffer (Medimiks Biotechnology, Turkey) for each slide). Hybridization was performed in a humidified and airtight chamber at 37 °C for 16 h.

After hybridization, the coverslips were removed and slides washed in Wash Solution I (containing 2% 20× SSC, NP-40 (conc. 0.3%)) in a 73 °C water bath for 2 min and then in Wash Solution II (10% 20× SSC, NP-40 (conc. 0.1%)) for 10 s.

Totally dried slides were then counterstained with 10 μl DAPImiks™ (4′,6-diamidino-2-phenylindole dihydrochloride) (Medimiks Biotechnology, Turkey). The slides were kept at −20 °C for at least 15 min to optimize the antifading effect before microscopy and analyzed using the Duet, Automated Combined Mass Scanning and Analysis System (Bioview, Israel).

Cells with two fusion signals were considered normal cells without translocation. Cells with one fusion, one green, and one red signal (split signal pattern) were considered positive for translocation, when the distance between green and red signals was more than or equal to 1.5 μm. When the distance between the split signals was between 1 and 1.5 μm, it was classified as suspect for positive and when the distance was less than 1 μm or equal to 1 μm, it was classified as normal.

2.3. Immunohistochemistry

Formalin-fixed paraffin-embedded tissue sections were a incubated in 1 mM EDTA buffer (pH 8.0) for 60 min for pretreatment and then reacted with MUM1/IRF4 (MUM1 S clone EAU32, Novacastra) at a dilution of 1:100 for 80 min at 37 °C. Ventana Benchmark XT immunostainer was used and signals were detected using the Ultraview Universal DAB Kit. MUM1/IRF4 staining was evaluated together with the CD30 antibody stained sections. A positive MUM1/IRF4 staining was defined as a nuclear labeling in more than 10% of the large cells and semiquantitatively scored as follows: −, zero or less than 10% of large tumor cells; +, 10–50% of the stained large tumor cells; ++, 50–85% of the stained large tumor cells; +++, >85% of the stained large tumor cells [4].

2.4. Statistics

Fischer's exact test was used to evaluate the differences observed in the frequency of IRF4 translocation and MUM1/IRF4 expression.

3. Results

The clinical information of all the patients, except the control group, is given in Table 1.

All cases of LyP were characterized by skin lesions that typically wax and wane, leaving atrophic scars. The most common type of lesion was papules (54%). The distribution of the lesions was mostly generalized (64%). The median age was 41 years (range, 1–78 years), with male:female (M:F) ratio 1:1. Out of 26 cases of LyP, 21 were type A (81%), while 5 were type C (19%). Within a follow-up period of 1–96 months (median 25 months), 8 (31%) cases still had LyP lesions, while 5 (19%) cases were without lesions at the last follow-up. None of the cases had extracutaneous involvement.

Table 1
The clinical data of all patients.

	LyP (n = 26)	PCALCL (n = 13)	T-MF (n = 9)
Gender			
Female	13 (50%)	7 (54%)	5 (55%)
Male	13 (50%)	6 (46%)	4 (45%)
Age			
Range	1–78	27–85	21–56
Median	41	62	38
Type of lesions			
Papule	14 (54%)	3 (24%)	–
Papulonodule	4 (15%)	1 (7%)	–
Nodule	8 (31%)	8 (62%)	–
Tumor	–	–	5 (56%)
Plaque	–	–	4 (44%)
Not known	–	1 (7%)	–
Number of lesions			
5>	5 (19%)	6 (46%)	–
5–10	3 (12%)	2 (15%)	1 (11%)
10<	17 (65%)	5 (39%)	8 (89%)
Not known	1 (4%)	–	–
Site of lesions			
Generalized	15 (58%)	1 (7%)	7 (78%)
Localized	11 (42%)	8 (62%)	2 (22%)
Solitary	–	4 (31%)	–
Extracutaneous spread			
Present	–	1 (7%)	3 (33%)
Not present	25 (97%)	11 (86%)	6 (67%)
Not known	1 (3%)	1 (7%)	–
Therapy			
Total exicion	–	1 (7%)[a]	–
PUVA/UV-B	4 (15%)	–	–
Topical corticosteroid	3 (12%)	1 (8%)	–
Chemotherapy (CT)	–	4 (31%)	3 (33%)
Radiotherapy (RT)	–	4 (31%)	–
CT + RT	–	2 (15%)	2 (22%)
Without therapy	2 (8%)	–	–
Not known	17 (65%)	2 (15%)	4 (45%)
Duration of follow up (month)			
Range	1–96	12–288	2–60
Median	25	97	20
Status at last follow up			
Stable disease	8 (31%)	4 (31%)	4 (45%)
Complete remission	5 (19%)	5 (38%)	–
Died of disease	–	–	2 (22%)
Died of other reasons	–	–	–
Not known	13 (50%)	4 (31%)	3 (33%)

[a] After total exicion, RT was performed in one case.

In cases of PCALCL, the patients primarily experienced nodules (62%), either localized (62%) or solitary (31%). The median age was 62 years (range, 27–85 years), with M:F ratio 1:1. In a follow-up period between 12 and 288 months (median 97 months), only one patient had regional lymph node involvement without any further dissemination. In the last follow-up, 4 cases (31%) were living with lesions, while 5 cases (38%) were without.

Out of 9 MF cases with CD30(+) large cell transformation, 3 cases (33%) were in the plaque stage and 5 cases (56%) were in the tumor stage. The remaining case of T-MF, was a folliculotropic MF (11%). The median age was 38 years (range, 21–56 years), with M:F ratio 1:1. CD30(+) large cells varied from 20 to 50% among the dermal infiltration in cases of T-MF.

3.1. MUM1/IRF4 expression

Among 26 cases of LyP, the expression of MUM1/IRF4 was present in 16 cases (61.5%). Out of 21 cases of LyP type A, 9 cases

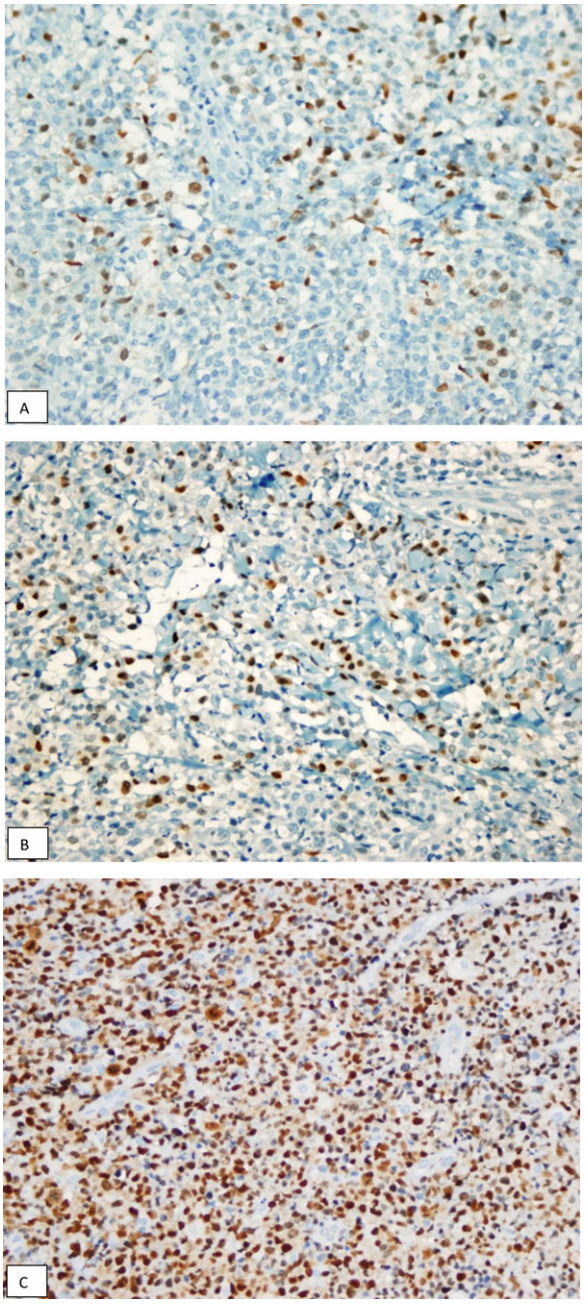

Fig. 1. (A) Immunostaining shows IRF4/MUM1 expression by 10–50% of large tumor cells in a case of T-MF; (+). (B) Immunostaining shows IRF4/MUM1 expression by 50–85% of large tumor cells in a case of LyP Type A; (++) and (C) immunostaining shows IRF4/MUM1 expression by more than 85% of tumor cells in a case of PCALCL; (+++) (400×).

were negative. On the other hand, 2 cases were (+), 5 cases were (++), and 5 cases were (+++). Out of 5 cases of LyP type C, only one case was negative, while one case was (+), and 3 cases were (+++). The majority of PCALCL and T-MF were at least partially positive for MUM1/IRF4 (92.3% and 88.9%) (Fig. 1). Among PCALCL, 3 cases were (+), 1 case was (++) and 8 cases were (+++). Out of 9 cases of T-MF, 3 cases were (+), 2 cases were (++) and 3 cases were (+++). All the cases in the control group, except one, displayed immunreactivity with MUM1/IRF4 (80%). MUM1/IRF4 protein expression was distributed widely in all these entities, without any predictive value.

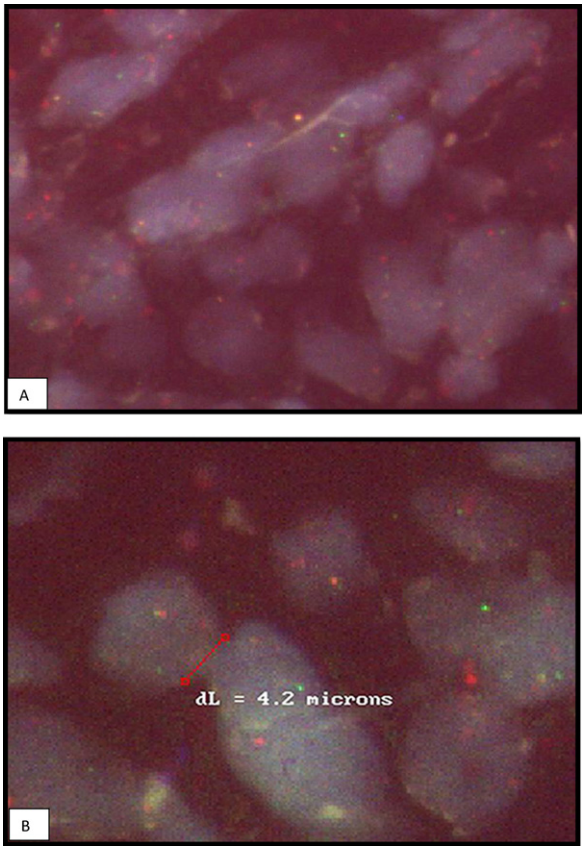

Fig. 2. (A and B) Split FISH signal pattern, 1 fusion (F), 1 red (R) and 1 green (G) signal with dual color break apart FISH method. Skin section of PCALCL case with IRF4 translocation. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

3.2. IRF4 translocation

Forty of 53 (75.5%) cases were successfully evaluated with the IRF4 FISH method. Six of 8 (75%) PCALCL cases had IRF4 translocation while the remaining cases of 1PCALCL, 19 LyP, 8 T-MF, 3 systemic ALK(−) ALCL, 1 systemic ALK(+) ALCL and 1 CHL had no IRF4 translocation (Figs. 2 and 3). Another case of PCALCL was suspected to be positive. This case was not included in the statistical analysis as a positive case. In all the cases, the detection of IRF4 translocation by FISH had a specificity and positive predictive value of 100% for PCALCL by Fisher's exact test. The sensitivity of IRF4 translocation by the FISH method was 85.7%. All 6 cases of PCALCL with translocation, displayed immunreactivity with the MUM1/IRF4 antibody (1 case (+), 5 cases (+++)) (Table 2). In one case with suspicous positivity for translocation, MUM1/IRF4 expression was (+). None of the patients who had PCALCL with translocation had an extracutaneous spread or died of lymphoma in a follow-up period, varying from 12 to 240 months (median, 60 months) (Table 3).

4. Discussion

Differentiation of CD30(+) lymphoproliferative diseases located in the skin was the subject of many studies in recent years. Both immunohistochemical and molecular techniques were investigated and used, since morphology had limitations. In 2009, Feldman et al. identified a translocation involving IRF4 locus on 6p25 predominantly in PCALCL, among 169 peripheral T-cell lymphomas [1]. In this study, IRF4 translocation was detected in 57% of PCALCL (8/14) by FISH, while expression of the MUM1/IRF4 by

Table 2
Correlation of IRF4 translocation and IRF4 expression results.

	LyP		PCALCL			T-MF	
	With IRF4 translocation $n=0$	Without IRF4 translocation $n=19$	With IRF4 translocation $n=6$	With suspected IRF4 translocation $n=1$	Without IRF4 translocation $n=1$	With IRF4 translocation $n=0$	Without IRF4 translocation $n=8$
MUM1/IRF4 (−)	–	7	–	–	–	–	1
MUM1/IRF4 (+)	–	3	1	1	–	–	3
MUM1/IRF4 (++)	–	5	–	–	–	–	2
MUM1/IRF4 (+++)	–	4	5	–	1	–	2
MUM1/IRF4 positivity ratio of cases with or without translocation *n* (%)	–	12 (63%)	6 (100%)	1 (100%)	1 (100%)	–	7 (87.5%)

Table 3
Clinical features compared with IRF4 translocation status in PCALCL.

	Cases with IRF4 translocation $n=6$	Cases with suspected IRF4 translocation $n=1$	Cases without translocation $n=1$
M:F	2:4	1:0	0:1
Age (range/median)	27–77/43	65	78
Anatomical site			
Head	2 (33%)	–	–
Extremity	2 (33%)	1 (100%)	1 (100%)
Trunk	1 (17%)	–	–
All sites	1 (17%)	–	–
Follow up in months (range/median)	12–240/60	12	276
Extracutaneous spread	–	–	1 (100%)
Died of disease or other reasons	–	–	–

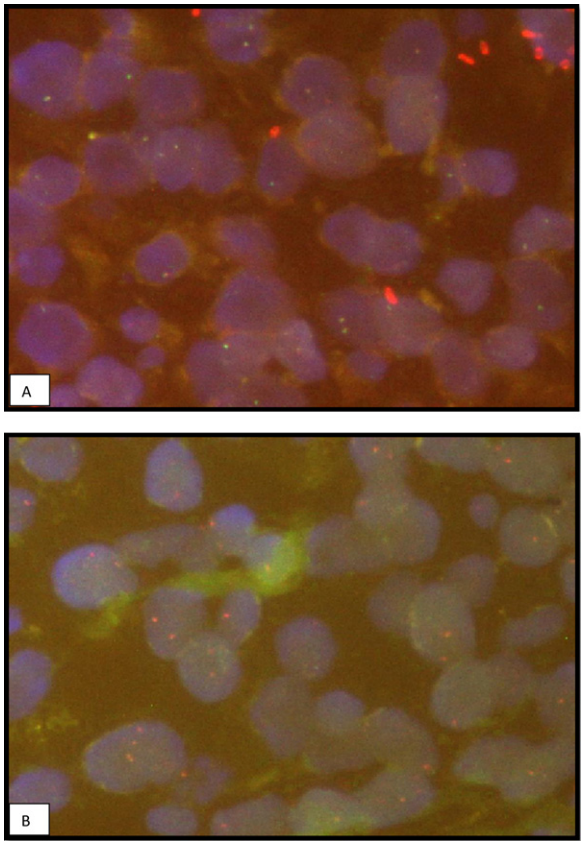

Fig. 3. (A and B) Normal FISH signal pattern 2F with dual color break apart FISH method. (A) Skin section of LyP Type A without IRF4 translocation and (B) skin section of T-MF case without IRF4 translocation.

immunohistochemistry was seen in 93% (13/14). IRF4 translocation was not specific to PCALCL. Among the other peripheral T-cell lymphomas, ALK(−) systemic ALCL and peripheral T-cell lymphoma, unspecified were the other lymphomas with IRF4 translocation (4% and 5% respectively). According to their data, PCALCL with or without translocation showed similar clinicopathologic features. However, extracutaneous spread was seen to be more common in the translocated cases. Therefore, Feldman et al. suggested that the MUM1/IRF4 protein might also have prognostic significance, indicating clinical aggressiveness [1].

Pham-Ledard et al. studied the presence of IRF4 rearrangement in LyP, T-MF, Sezary syndrome (SS), besides PCALCL [4]. They observed a split FISH signal pattern indicating a translocation at IRF4 locus in 26% of PCALCL (6/23) and in 18.2% of T-MF (2/11). Neither cases of LyP nor SS showed any IRF4 rearrangement. CD30(+) T-MF with IRF4 translocation exhibited histological lesions, resembling PCALCL, but since these lesions occurred in the course of MF, they were T-MF. In practice, according to the histological findings, the signs which help to differentiate T-MF from PCALCL are the presence of small to medium sized and convoluted atypical lymphocytes among anaplastic large cells and epidermotropism. However, the authors pointed out that these cases may correspond to the development of PCALCL in MF patients rather than large cell transformation due to the translocation detected. In their series, IRF4 locus rearrangement was not found to be predictive of lymph node involvement, cutaneous relapse or shorter survival. Although Kempf et al. suggested previously that MUM1/IRF4 expression may be a valuable tool for the distinction of LyP and PCALCL, Pham-Ledard et al. demonstrated strong expression in LyP and T-MF, as well as in PCALCL in their series, as in other studies [4,7–10].

In a large multicenter study by Wada et al., 20% of PCALCL (9/45) and 3% of LyP (1/32) demonstrated IRF4 translocation [3]. The single case of LyP with translocation was LyP, type C. The authors interpreted this finding as genetic evidence for the hypothesis that PCALCL and LyP constitute a clinical and histologic spectrum. Remaining cases of systemic ALCLs, MF/SS, peripheral T-cell lymphomas, unspecified, CD4(+) small/medium-sized pleomorphic

T-cell lymphomas, extranasal NK/T-cell lymphomas, nasal type, gamma-delta T-cell lymphomas and some other uncommon T-cell lymphoproliferative disorders were negative for a translocation. In their series, IRF4 translocation had a specificity and positive predictive value for PCALCL of 99% and 90%, compared with other T-cell lymphoproliferative disorders [3]. MUM1/IRF4 expression was found to be nonspecific. In regard to prognostic significance of IRF4 translocation, they did not find clear-cut differences in outcome between translocated and non-translocated cases in this large series.

In a recent study, Feldman et al. [5] suggested that down-regulation of DUSP22 gene may be more relevant than IRF4 translocation, which is associated with t(6;7) (p25.3;q32.3) in both systemic and primary cutaneous ALCLs. They indicated that the translocation was associated with changes in expression of DUSP22, but not IRF4 [5]. This can be a subject for further studies.

In our study, we included mainly skin lesions containing CD30(+) large cells: 26 cases of LyP (21 type A, 5 type C), 13 cases of PCALCL and 9 cases of CD30(+) T-MF. Among them, 19 cases of LyP, 8 cases of PCALCL and 8 cases of T-MF were successfully evaluated by using the FISH method with tissue break apart dual color probe. Out of 8 cases of PCALCL, 6 cases (75%) had IRF4 translocation. One more case of PCALCL was suspect for being positive. The rest of the cases, including the control group, composed of 3 cases of systemic ALK(−) ALCL, 1 systemic ALK(+) ALCL and 1 CHL had no signals. Compared with the other studies, the ratio of IRF4 rearrangement in PCALCL was much higher. The reason for this may be due to the small number of cases, as well as the geographic differences. Neither the cases of LyP, even type C, nor the cases of T-MF demonstrated any translocation. Although we had only 3 cases of systemic ALK(−) ALCL, they were also negative for translocation. In light of these findings, IRF4 translocation by FISH had a specificity and positive predictive value of 100% for PCALCL ($p = 0.0001$, Fisher's exact test), close to the findings of Wada et al. [3].

It should be noted that in regard to the recent findings of Feldman et al. [5], considering that both DUSP22 and IRF4 are located in our FISH probe, DUSP22 down-regulation may also play role in the gene rearrangements, detected in our series.

Most cases of PCALCL (92.3%) displayed MUM1/IRF4 expression regardless of the presence of IRF4 translocation. All 6 cases of PCALCL,, with translocation, except one, displayed strong immunreactivity (+++) with MUM1/IRF4 antibody. The remaining case was (+). In one case with suspicious positivity for translocation, MUM1/IRF4 expression was (+). MUM1/IRF4 expression was distributed widely among LyP (80.8%) and T-MF (88.9%). In addition, most of the cases in the control group showed immunreactivity with MUM1/IRF4 (80%). This data indicated that IRF4 FISH plays a role in the differentiation of cutaneous T-cell lymphoproliferative disorders, but not MUM1/IRF4 immunohistochemistry, as confirmed by the previous studies [1,3,4].

We tried to determine whether the cases of PCALCL with translocation displayed any specific clinical or evaluative features. None of the cases of PCALCL with translocation had an extracutaneous spread or died of lymphoma in a follow-up period, varying from 12 to 240 months (median 60 months), which was a longer period than the one mentioned by Wada et al. But still, short or uncertain follow-up limits the ability to draw the prognostic significance of translocation. Therefore, in order to define the clinical and prognostic utility of IRF translocation more reliably, studies with additional cases with a longer period of follow-up are needed.

As NF-κB pathway activation upregulates IRF4 expression in a subset of B and T cell lymphomas, it could be possible that both CD30 and IRF4 act synergistically in cutaneous T-cell lymphomas, expressing both proteins [11]. Therefore, the hypothesis that IRF4, CD30 and NF-κB might individually or in combination represent therapeutic targets in IRF4(+) cutaneous T-cell lymphomas, merits further studies, as suggested by Pham-Ledard et al. [4].

In conclusion, IRF4 FISH seems to be a promising adjunct in the differential diagnosis of skin lesions, with T-cell lymphoproliferative disorders, containing CD30(+) large cells. The presence of IRF4 translocation favors PCALCL, with high specificity and positive predictive value. On the other hand, MUM1/IRF4 expression by immunohistochemistry, was distributed widely without any predictive value. However, it should be kept in mind that IRF4 translocation must be interpreted together with the clinical, histopathological and immunophenotypical findings.

Conflict of interest

All authors have no conflict of interest to declare.

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Contributions. TK, CD and NT contribute all the steps of the study except designation of IRF4 DNA FISH probe. HK and CE contribute designation of the IRF4 DNA FISH probe, analysis of FISH results and writing of FISH method of the article.

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