Primary Cutaneous CD30-Positive T-Cell Lymphoproliferative Disorders with Biallelic Rearrangements of DUSP22

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TO THE EDITOR

The presence of recurrent chromosomal translocations in multiple leukemias and lymphomas suggests that altered chromosomes have an integral role in tumor development (Drexler et al., 1995). Identifying chromosomal translocations has led to diagnostic, prognostic, and therapeutic advances for a variety of hematologic malignancies (Rowley, 2008). The anaplastic lymphoma kinase (ALK) gene is translocated in approximately half of systemic T-cell anaplastic large-cell lymphomas (ALCLs), resulting in overexpression of ALK fusion proteins (Savage et al., 2008; Feldman et al., 2009). The search for recurrent translocations in the remaining half of ALCLs, which are ALK negative, has led to the discovery of recurrent translocations involving the DUSP22–IRF4 locus on 6p25.3 (Feldman et al., 2011). These recurrent translocations have been found in both systemic and primary cutaneous (pc) ALK-negative ALCLs, as well as rarely in lymphomatoid papulosis and transformed mycosis fungoides (Pham-Ledard et al., 2010; Wada et al., 2011).

Translocations involving 6p25.3 can have breakpoints in or near either IRF4 or DUSP22, which lie only ~40 kb apart at the extreme telomeric tip of 6p (Feldman et al., 2009). IRF4 encodes IFN regulatory factor-4, also known as multiple myeloma oncogene-1 (MUM1), a transcription factor expressed in activated T lymphocytes, plasma cells, and some B cells (Falini et al., 2000). DUSP22 encodes a dual-specificity phosphatase protein that inhibits TCR signaling and has been proposed as a possible tumor-suppressor gene (Alonso et al., 2002). Gene expression studies have shown that, regardless of whether the translocation breakpoint involved DUSP22 or IRF4, DUSP22 expression was up to 50 times lower in ALCLs with 6p25.3 translocations than in cases without the translocation, whereas IRF4 expression was unchanged (Feldman et al., 2009). The mechanisms for the downregulation of DUSP22 expression remain incompletely understood, as previous reported cases had translocations involving only one copy of chromosome 6. In this paper, we present three cases of cutaneous ALCL, classified according to the WHO/EORTC (World Health Organization/European Organization for Research and Treatment of Cancer) classification system (Willemze et al., 2005), with at least two copies of chromosome 6 bearing a 6p25.3 translocation and no intact copies of the normal 6p25.3 allele. These cases indicate at least one mechanism for abolishing DUSP22 expression in T-cell lymphomas, and provide additional evidence that DUSP22 may represent a tumor-suppressor gene, the loss of which may contribute to the pathogenesis of cutaneous ALCL.

Case 1

A 54-year-old woman with a history of pcALCL on her left arm presented with a 50-pound weight loss explained by dieting and a single 2.5 cm ipsilateral axillary lymph node. She had a positron emission tomography (PET) scan and bone marrow biopsy that were negative. There has been no evidence of extra-cutaneous disease after 2 years without treatment, effectively excluding systemic ALCL. Histology of the lymph node showed CD30+, ALK− anaplastic cells infiltrating the paracortical T zone, sparing of germinal centers, and sinus infiltration. Immunohistochemistry revealed atypical cells to be positive for CD30, CD3, partially for CD15, and weakly for B-cell lymphoma 2 (Bcl-2). They were negative for ALK-1, CD4, CD5, CD8, pankeratin, MelanA, HBME-1, S100, Cyclin D1, CD20, CD79A, BCL-6, CD56, and CD57. This was diagnostic of ALK-negative ALCL, consistent with spreading from pcALCL.

Case 2

A 71-year-old man presented with a nodular forehead lesion. The dermis was expanded by a proliferation of medium-sized to large atypical lymphoid cells, including “hallmark” cells. Atypical cells were positive for CD2, CD3 (weak), CD30, CD45, and TCR-β (β-F1), and negative for CD5, CD7, CD8, TIA-1, granzyme B, and ALK. A single regional lymph node showed some PET activity that was interpreted as not suspicious for lymphoma. He had no evidence of disease 3 months after presentation.

Case 3

A 79-year-old woman presented with an isolated skin lesion on the left thigh. The lesion contained large atypical lymphoid cells within the dermis, including “hallmark” cells. Atypical cells were positive for CD2, CD3 (weak), CD30, CD45, and TCR-β (β-F1), and negative for CD5, CD7, CD8, TIA-1, granzyme B, and ALK. Another lesion appeared on the abdomen 1 month later and was excised with similar histology. Clinical
evaluation, including PET scan, showed no evidence of systemic disease. She was without further lesions 5 months after presentation.

Fluorescence in situ hybridization (FISH) was performed as described previously, with minor modifications (Feldman et al., 2009). For break-apart FISH, bacterial artificial chromosome (BAC) DNA corresponding to the DUSP22–IRF4 locus on 6p25.3 was labeled as follows: telomeric (red) CTD-3234E6 and CTD-2308G5; centromeric (green) CTD-3104D10, RP11-963H23, and RP11-1104N17. For dual-fusion (D-) FISH to detect t(6;7)(p25.3;q32.3), all five BACs corresponding to 6p25.3 were labeled red, whereas the previously reported BACs corresponding to 7q32.3 were labeled green (Feldman et al., 2011). In one case, the centromeric 6p25.3 BACs were labeled red and cohybridized with CEP 6 (D6Z1) labeled in green (Vysis/Abbott Molecular, Abbott Park, IL).

All cases demonstrated at least two copies of chromosome 6 bearing a 6p25.3 translocation and no copies of an intact DUSP22–IRF4 locus, as shown in Figure 1. In case 1 (Figure 1a), there were four copies of chromosome 6, two of which were involved in a balanced translocation with chromosome 7 [t(6;7)(p25.3;q32.3)], which is the most common partner locus for 6p25.3 translocations and is seen in 45% of cases (Feldman et al., 2011). The remaining two copies of chromosome 6 had separations of the DUSP22–IRF4 locus with deletions of the telomeric fragments of 6p. Although we cannot exclude the possibility that the translocation detected in the lymph node occurred as a “second hit,” we have never seen this abnormality acquired over sequential biopsies from the same patient (Wada et al., 2011 and AL Feldman, unpublished data). In case 2 (Figure 1b), there were two copies of chromosome 6 involving unbalanced translocations, der(6)t(6;7)(p25.3;q32.3). In case 3 (Figure 1c), there were two copies of chromosome 6 involved by 6p25.3 translocations with an unknown (non-7q32.3) partner [t(6;?)(p25.3;?)].

The complete absence of an intact DUSP22–IRF4 locus on 6p25.3 seen in these three cases represents at least one mechanism to explain the profound downregulation of DUSP22 expression in T-cell lymphomas with 6p25.3 translocations. DUSP22 is a dual-specificity phosphatase that regulates the c-Jun N-terminal kinase (JNK) and extracellular signal–regulated kinase (ERK) mitogen-activated protein kinase signaling pathways, and inhibits TCR signaling in T cells (Falini et al., 2000). DUSP22 overexpression has been shown to reduce estrogen receptor activity and to inhibit estrogen receptor signaling in breast cancer cells (Sekine et al., 2007).

In chronic lymphocytic leukemia, DUSP22 expression is associated with mutated IGVH gene status, which is associated with improved survival (Jantus Lewintre et al., 2009). Our findings suggest that loss of the DUSP22 allele, if acting as a tumor-suppressor gene, could contribute to the pathogenesis of these cases of pcALCL.

Each case demonstrated multiple copies of the abnormal chromosome 6 involved in 6p25.3 translocations. It is
not clear whether these multiple alleles represent separate translocation events or aneumyos of a previously translocated chromosome. The latter possibility is favored, given that: (1) the partner status (7q32.3 or other) was identical in the allele pairs from each case; (2) two of the three cases demonstrated aneuploidy; and (3) 6p25.3 translocations appear to be an early event during lymphomagenesis, based on our constant finding of this translocation in initial biopsies from patients with multiple tumor specimens over time (AL Feldman, unpublished observation).

In addition to the lack of a normal copy of the 6p25.3 allele, multiple copies of the translocations could have implications on the partner locus. For example, we previously reported overexpression of microRNAs (especially MIR29B1) that reside near the 7q32.3 breakpoint in ALK-negative ALCLs with t(6;7)(p25.3;q32.3) (Feldman et al., 2009).

In summary, we present three cases of pcALCL with biallelic rearrangements of 6p25.3 and no intact copies of the DUSP22–IRF4 locus. These cases indicate one mechanism by which both copies of the DUSP22 gene can be disrupted or deleted in T-cell lymphomas, and provide further evidence that DUSP22 may represent a tumor-suppressor gene.

CONFLICT OF INTEREST
The authors state no conflict of interest.

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Lysophosphatidic Acid Mediates the Release of Cytokines and Chemokines by Human Fibroblasts Treated with Loxosceles Spider Venom

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TO THE EDITOR
Loxosceles spiders are a genus of arachnids, whose bites cause necrotizing skin lesions. They are distributed worldwide in temperate and tropical regions. In Brazil, approximately 10,000 cases of Loxosceles spider bites are reported annually. L. intermedia, L. gaucho, and L. laeta are prevalent in most of the southern states of Brazil, whereas L. similis has been described mainly in the state of Minas Gerais. L. reclusa and L. deserti cause the majority of accidents in North America. The venoms of these species all have similar biochemical and pharmacological profiles (Barbaro et al., 2005; Silvestre et al., 2005; Chatzaki et al., 2012). The envenomation, described as loxoscelism, is characterized by pain, local edema, and erythema, followed by dermonecrosis that require weeks to heal. The genesis of loxoscelism is attributed to a family of sphingomyelinase D enzymes, also known as

Abbreviations: LPA, lysophosphatidic acid; LPC, lysophosphatidylcholine; LsV, L. similis venom; PLD, phospholipase D; recLiD1, recombinant L. intermedia dermonecrotic protein 1
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