Correspondence

To the editor:

Cutaneous tumor lysis syndrome in a patient with HTLV-1 adult T-cell lymphoma/leukemia

Marneros and colleagues have described multiple skin erosions in a patient receiving pralatrexate, a novel inhibitor of dihydrofolate reductase, for the treatment of adult T-cell lymphoma/leukemia (ATLL). These skin erosions were not due to the toxicity of the drug on keratinocytes but rather to the apoptosis of intra-epidermal atypical T cells as evidenced by the selective erosions on pre-existing tumoral skin lesions and by the positive labeling of the atypical T cells for activated caspase 3. The skin erosions healed a few days later and did not recur with subsequent cycles of pralatrexate therapy.

We report the case of a patient with ATLL who had multiple skin erosions limited to areas previously affected by the tumoral infiltration and that recurred after 2 chemotherapies that did not include pralatrexate. The patient was a 50-year-old male from Guadeloupe in the French West Indies who was diagnosed 1 year earlier with smoldering human T-lymphotropic virus type 1 (HTLV-1)–induced T-cell lymphoma (erythematous patches with epidermotropic virus type 1 (HTLV-1)–induced T-cell lymphoma (erythematous patches with epidermotropic infiltrate atypical T cells, HTLV-1 antibody titer positive and clonal integration of HTLV-1 genes in the skin) according to international criteria. Interferon-α2b treatment was given but in addition to the cutaneous lesions (Figure 1A), the patient developed generalized fatigue, leukocytosis (217,000 white blood cell count with 95% atypical lymphocytes positive for CD4 and CD25 by immunophenotyping), and hypercalcemia consistent with leukemic conversion of his ATLL. The patient received 2 cycles of cyclophosphamide associated with VP16, allowing partial decrease of the leukocytosis (81,000 white blood cell count). An additional chemotherapy with hyper-CA VD (cyclophosphamide, adriamycin, vincristine, dexamethasone) was administered, and 4 days later the patient developed multiple skin erosions on the previously infiltrated areas. The skin lesions spontaneously healed and 19 days later, the patient received high-dose methotrexate. Five days later, he developed multiple skin erosions on the same areas (Figure 1B). Skin erosions were negative for herpes simplex virus. Histologic examination of the skin erosions showed extensive epidermal ulceration with large atypical CD3+CD4+CD25+ T lymphocytes in the dermis. In nonulcerated areas, many epidermotropic atypical lymphocytes were present. The epidermis was atrophic without pathologic evidence for toxic epidermal necrolysis or pemphigus. The skin lesions spontaneously healed with topical application of antiseptic solutions and Vaseline, but the patient died 2 weeks later because of a septic shock.

Our case report is consistent with the fact that intra-epidermal atypical T lymphocytes in patients with ATLL may undergo apoptosis after numerous chemotherapies and not only after pralatrexate. The mechanism of these lesions may be linked to what happens during tumor lysis syndrome in patients having chemotherapy for cancer. Therefore, we propose the denomination “cutaneous tumor lysis syndrome” should be used to describe skin erosions not otherwise explained in patients receiving chemotherapy for ATLL.

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Figure 1. Photographs show patient at leukemic conversion phase of ATLL (A) and 5 days after methotrexate injection (B).
To the editor:

**Integrity of the CBL gene in mature B-cell malignancies**

Identification of biomarkers for response to novel therapeutic agents is an essential step for the success of tailored treatments in cancer. Preliminary data from clinical trials indicate that inhibitors of the spleen tyrosine kinase (SYK) may be efficacious in subsets of diffuse large B-cell lymphomas (DLBCL) and chronic lymphocytic leukemias (CLL).1

SYK is a component of the signaling cascade initiated by engagement of the B-cell receptor (BCR) and a key element in the transduction and amplification of these responses. SYK activity is induced by its binding to the immunoreceptor tyrosine-based activation motifs (ITAM) of the BCR, by SRC family kinases, and by autophosphorylation.2 In turn, SYK expression and activity is abrogated by the E3 ubiquitin ligase activity of the Casitas B-lineage lymphoma (CBL) protein, a central negative regulator of multiple tyrosine kinases in hematopoietic lineages.3

Recent in vitro observations suggested that elevated SYK activity could predict response to SYK inhibitors in DLBCL and CLL.4,5 However, it is unclear whether the high SYK activity found in these tumors relates to an innate program of the cancer cell’s normal counterpart, or to a well-defined pathogenetic event. Concerning the latter, loss of CBL activity is a prime candidate because mouse models with B cell–specific ablation of both Cbl and Cblb (Cbl−/−Cblb−/−) display enhanced Syk phosphorylation.6 Furthermore, several recent reports showed that somatic CBL mutations in the critical linker and ring finger domains (exons 8 and 9) are frequent in myeloid malignancies, particularly (but not exclusively) in myelodysplasia/myeloproliferative neoplasms (MDS/MPN) with acquired uniparental disomy (aUPD) at chromosome 11q.7,8 These recent findings, together with the prominent negative regulatory role of CBL toward SYK and the elevated SYK activity in subsets of mature B-cell malignancies, prompted us to investigate the integrity of the CBL gene in a large collection of mature lymphoid tumors.

We directly sequenced the polymerase chain reaction (PCR) products of exons 8 and 9 of the CBL gene in 203 tumors, including 92 DLBCLs (72 primary lymphomas and 20 cell lines), 79 CLLs, 15 mantle cell lymphomas, 9 multiple myelomas and 8 T-cell lymphomas, obtained according to the guidelines of the institutional review board of the University of Texas Health Science Center at San Antonio. The clinical and molecular characterization of this tumor collection has been reported previously.9,10 Our strategy involved using PCR primers localized to intronic regions of exons 8 and 9 of the CBL gene (described in Grand et al11), thus also allowing for the detection of disrupted splice sites, which were previously associated with aberrant exon 8 splicing in acute myeloid leukemias.7,9 Automated sequencing of the PCR products was performed at Agencourt Bioscience Corporation, and the sequence traces analyzed with Mutation Surveyor, Version 2.6 (SoftGenetics).

No pathogenetic nucleotide changes were identified in the CBL gene in any of the mature lymphoid malignancies analyzed. Considering the number of cases investigated, and the reported frequency of CBL mutations in unselected or selected myeloid malignancies (~1% to ~33%),9,11 we conclude that CBL mutations are not a prominent feature of mature B-cell malignancies. These data agree with recent evidence showing that aUPD at 11q is rare in B-cell lymphomas,17 and indicate that the molecular mechanism for the elevated SYK activity found in subsets of DLBCL and CLL remains to be defined.

**References**


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