Global Quantitative Techniques for Positron Emission Tomographic Assessment of Disease Activity in Cutaneous T-Cell Lymphoma and Response to Treatment

Fluorodeoxyglucose positron emission tomography (FDG-PET) imaging has been suggested as a useful modality in staging, assessing response to treatment, and detecting disease recurrence in primary cutaneous T-cell lymphoma (CTCL). Indices of FDG uptake include conventional measurements such as maximum standardized uptake value (SUV\text{max}) mean SUV (SUV\text{mean}) and global measurements such as global metabolic volume (GMV) and global lesion glycolysis (GLG). Some investigators support conventional metrics, while others have demonstrated greater value in global tumor measurements.

Herein we present the cases of 2 patients with CTCL who had PET scans performed at baseline and follow-up in addition to the usual clinical and laboratory assessments. The FDG-PET images were analyzed by ROVER software (ABX Advanced Biochemical Compounds GmbH), which is capable of measuring whole body disease burden by GMV and GLG. This software also measures SUV\text{max} and SUV\text{mean}.

**Report of Cases**

**Case 1.** The first patient was a woman in her 40s with gamma/delta T-cell lymphoma. Histopathologic analysis demonstrated infiltration of subcutaneous fat by neoplastic cytotoxic T cells with apoptosis, necrosis, and angioinvasion. There was a moderately dense, predominantly lymphocytic, inflammatory infiltrate in relation to the superficial and deep vascular plexus, with interstitial and periadnexal involvement as well. There was also an increase in interstitial mucin.

She had received 6 cycles of R-CHOP therapy (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone) before this study. Her lactate dehydrogenase level (LDH) was 962 U/L (normal, 140-280 U/L) at initial evaluation. After 3 months of treatment with bexarotene and hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone), her LDH increased to 5856 U/L. The FDG-PET scan showed more extensive lesions after 3 months than at baseline despite treatment (Figure 1). Measuring FDG uptake activity in the tumors demonstrated that GMV (131.3 cm$^3$ at baseline to 342.7 cm$^3$ at follow-up) and GLG (161.2 to 429.8 g) increased significantly, which was expected considering tumor extension and LDH level elevation at the follow-up visit. In contrast, SUV\text{mean} (1.2 to 1.3 g/mL) had a minimal increase and SUV\text{max} showed significant reduction (5.7 to 3.7 g/mL).

**Case 2.** The second patient was a man in his 60s with mycosis fungoides, which is the most common type of CTCL. Histopathologic analysis demonstrated epidermotropic atypical lymphocytes. The patient underwent treatment with narrowband UV-B phototherapy but did not respond well. The PET scan showed significant tumor reduction after 3 months of treatment with ro-
midepsin and irradiation (Figure 2). Serum LDH level correspondingly decreased (261 U/L to 144 U/L). Based on the FDG uptake measurement, GLG showed significant decrease (from 834.7 g at baseline to 265.7 g at follow-up) as did GMV (from 111.1 to 14.7 cm³), which were in line with decreased LDH levels and tumor extension, but SUV mean (7.5 to 18 g/mL) and SUV max (19.3 to 35.3 g/mL) indicated elevated tumor activity.

Discussion | The utility of global assessment for evaluation of primary tumors and response to treatment has not been well studied. Herein we demonstrate greater accuracy of global quantitative FDG-PET indices such as GLG and GMV in reflecting extension of malignant tumors and changes in blood LDH. Conventional metrics including SUV max and SUV mean are useful regional indices that may be effective in showing tumor behavior and aggressiveness in a single location, but they may not be informative in describing degree of tumor extension and global tumor activity. Moreover, these indices may be affected by tumor heterogeneity, which is a common phenomenon in malignant solid tumors.5 Since cutaneous lymphomas can be unpredictable in their progression, the analysis approach provided by the methodology described herein allows assessment of global activity regardless of focal clinical involvement. Therefore, we believe that by adopting this methodology, we will be able to determine the extent of disease and response to treatment soon after treatment and be able to detect recurrence in a timely and effective manner.

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Eruptive Keratoacanthomas Associated With Leflunomide

The keratoacanthoma (KA) is a rapidly growing, well-differentiated epidermal neoplasm that may be locally invasive or may spontaneously resolve. Most often, KA presents as a solitary lesion; however, multiple KAs can be seen in various syndromes, including Muir-Torres syndrome, the autosomal dominant Ferguson-Smith syndrome, and Grzybowski-type eruptive KAs.1

Several medications have been temporally associated with eruptive KAs. Recently in the literature there has been a report of eruptive KAs following treatment with leflunomide.2 The KAs resolved after stopping treatment with the medication. Herein, we report another case of multiple KAs in a patient undergoing treatment with leflunomide.

**Report of Case** | A woman in her 50s presented for evaluation of skin lesions located on the arms, trunk, and legs. She had similar lesions for the past 2 years, but they had recently increased in number.

Her medical history included the following diagnoses: systemic lupus erythematosus, rheumatoid arthritis, and sarcoidosis. She had undergone recent abdominal surgery to remove a carcinoid tumor. Her medications at the time of presentation included intermittent infusions of rituximab, oral leflunomide, insulin, benazepril hydrochloride, cyclobenzaprine hydrochloride, hydromorphone hydrochloride, morphine sulfate, esomeprazole magnesium, potassium chloride, rosuvastatin calcium, and duloxetine hydrochloride.

The patient reported developing keratotic papules a few months after initiation of leflunomide therapy, approximately 2 years prior to her presentation. Several other dermatologists treated the patient with clobetasol propionate ointment and hydroxyzine hydrochloride for a presumed diagnosis of prurigo nodularis. She was sent to general surgery for removal of several larger lesions on her legs, which were interpreted as multiple, well-differentiated proliferative squamous lesions with hyperkeratosis and underlying mixed inflammation.

Physical examination at presentation revealed numerous 2- to 4-mm keratotic papules on her arms and legs (Figure 1A) in addition to multiple ulcerations on the legs secondary to prior excisions. Two biopsies performed on arm papules found verrucous and crateriform squamoproliferative lesions associated with squamous epithelial protrusions containing keratotic material, inflammatory debris, and elastic fibers associated with focal pustule formation (Figure 2). A diagnosis of eruptive keratoacanthomas was made.

The patient was started on a regimen of oral isotretinoin, 40 mg/d, and her leflunomide treatment was discontinued.

**Figure 1. Leflunomide-Associated Eruptive Keratoacanthomas**

A, Multiple keratotic papules consistent with eruptive keratoacanthomas seen at presentation. B, Resolving eruptive keratoacanthomas 2 months after beginning oral isotretinoin treatment and stopping leflunomide treatment.

**Figure 2. Punch Biopsy Specimen From Eruptive Keratoacanthoma Papule on the Arm**

An endophytic cystic squamoproliferative lesion shows accumulation of keratin and basophilic inflammatory debris within the cyst cavities, consistent with keratoacanthoma (hematoxylin-eosin, original magnification ×40).