Folliculotropic Mycosis Fungoides

An Aggressive Variant of Cutaneous T-Cell Lymphoma

Pedram Gerami, MD; Steve Rosen, MD; Timothy Kuzel, MD; Susan L. Boone, MD; Joan Guitart, MD

Objectives: To study the clinical features, therapeutic responses, and outcomes in patients with folliculotropic mycosis fungoides (FMF) and to compare our single-center experience of 43 patients with the findings from the Dutch Cutaneous Lymphoma Group.

Setting: A single-center experience from the Northwestern University Multidisciplinary Cutaneous Lymphoma Group.

Patients: Forty-three patients with FMF were included in the study and compared with 43 age- and stage-matched patients with classic epidermotropic mycosis fungoides (MF) with similar follow-up time.

Results: Folliculotropic mycosis fungoides showed distinct clinical features, with 37 patients having facial involvement (86%) and only 6 having lesions limited to the torso (14%). The morphologic spectrum of lesions is broad and includes erythematous papules and plaques with follicular prominence with or without alopecia; comedonal, acneiform, and cystic lesions; alopecic patches with or without scarring; and nodular and prurigo-like lesions. Sixty-five percent of patients had alopecia, which in 71% of cases involved the face. Severe pruritus was seen in 68% of patients. In general, patients responded poorly to skin-directed therapy and in almost all cases required systemic agents to induce even a partial remission, including patients with early-stage disease. Overall survival was poor. Patients with early-stage disease (≤IIA) had a 10-year survival of 82%, which took a steep drop off to 41% by 15 years. Patients with late-stage disease (≥IIB) had an outcome similar to those patients in the control group with conventional epidermotropic MF of a similar stage.

Conclusions: The morphologic spectrum of clinical presentation for FMF is broad and distinct from those in conventional MF. This is at least partially attributed to the ability of FMF to simulate a variety of inflammatory conditions afflicting the follicular unit. The disease course is aggressive, and many patients, including those with early disease, show a poor outcome particularly between 10 and 15 years after the initial onset of disease. Response to skin-directed therapy is poor even in early-stage disease, and our best results were seen with psoralen plus UV-A (PUVA) therapy with oral bexarotene or PUVA with interferon alfa. These findings corroborate those of the Dutch Cutaneous Lymphoma Group and further validate the classification of FMF as a distinct entity.

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FOLLICULOTROPIC MYCOsis fungoides (FMF) is a variant of cutaneous T-cell lymphoma (CTCL) with pathogenetic similarities to conventional mycosis fungoides (MF). Both most often consist of CD4+ lymphocytes with a cerebriform morphologic characteristic, a shift toward helper T cells, type 2 (Th2) cytokines, epitheliotropism, and a tendency to form Pautrier microabscesses. However, the mechanism of folliculotropism is still poorly understood. In our group's previous studies, we have seen high densities of CD1a+ Langerhans cells in the follicular epithelium.1 It is unclear whether folliculotropism is a function of specific cell-surface antigens of the T cells or an abnormality within the follicular epithelium.

Distinct clinical and histologic features, survival outcome, and therapeutic responses have been identified in patients with FMF.3 In light of its unique clinical and histopathologic features, FMF has been designated as a distinct variant of CTCL in the new World Health Organization–European Organization for Research and Treatment of Cancer classification system for cutaneous lymphomas.3 There is scant information in the literature regarding its clinical manifestations.4-10 Data regarding optimal therapies in FMF are similarly limited. In addition, only 2 other studies have provided any survival data for patients with FMF.11,12 Over the last 20 years, our cutaneous lymphoma group has observed 43 patients with FMF, with a median follow-
was to corroborate their findings and to characterize the roughly similar to conventional tumor-stage MF. Our aim included that the prognosis in FMF is worse than in conventional generalized patch- or plaque-stage MF and is

data in FMF.

comprehensive analysis of the clinical features of FMF and of-

clinical and histologic features specific to this cohort. We have

up time of 8 years, ranging from 1 to 23 years. During this period we have recognized a variety of characteristic clinical and histologic features specific to this cohort. We have previously published an in-depth analysis of the histologic patterns seen with this disease.1,3 The present study is a comprehensive analysis of the clinical features of FMF and offers, to our knowledge, the first major US study of survival data in FMF.

The Dutch Cutaneous Lymphoma Group2 concluded that the prognosis in FMF is worse than in conventional generalized patch- or plaque-stage MF and is roughly similar to conventional tumor-stage MF. Our aim was to corroborate their findings and to characterize the myriad clinical presentations seen in FMF. Finally, while the early stages of conventional MF often respond to skin-directed therapy, in our experience, skin-directed therapy is inadequate in most cases of FMF.

### METHODS

After obtaining approval from the institutional review board and The Robert H. Lurie Comprehensive Cancer Center study review board from Northwestern University, we searched the Northwestern Cutaneous Lymphoma Group database for patients with FMF, defined by both clinical and histologic parameters. The initial and predominant clinical presentations consisted of papules or plaques with follicular prominence, comedonal or cystic lesions, or alopecia. Histologic criteria re-

### Table 1. Clinical and Histologic Features of Patients With Folliculotropic Mycosis Fungoides

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<th>Patient No./Sex/Age, y</th>
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<th>Stage at Presentation</th>
<th>LDH, mg/dL</th>
<th>Pruritus</th>
<th>Alopecia</th>
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Abbreviations: BF, basaloid follicular hyperplasia; CL, classic; CY, cystic; EF, eosi

9nophilic folliculitislike; Epi, epidermotropic; GR, granulomatous; I, indeterminate; LCT, large-cell transformation; LDH, lactate dehydrogenase; NA, not applicable; ND, not determined; SY, syringotropic; TCR, T-cell receptor clonality; +, positive clonality; −, negative clonality.

SI conversion factor: To convert LDH to microkatal per liter, multiply by 0.0167.

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quired a predominance of 1 of the 5 patterns previously established as characteristic of FMF. In each case, at least focal areas of the prototypical pattern with atypical folliculotropic lymphocytes was required. All cases were reviewed by our lymphoma group who have focused expertise in dermatology, dermatopathology, and oncology of cutaneous lymphomas.

Time of onset was defined as the time from initial characteristic clinical features. Progression was defined as onset of histologically documented tumor lesions or generalized erythroderma in patients previously having patch- or plaque-stage disease, biopsy-proven nodal involvement in patients with previous skin-limited disease, visceral involvement in patients with previous skin- or nodal-limited disease, and death with disease in any patient.

For each patient meeting our criteria, the medical records, photographs, and histopathology slides were reviewed, and data pertinent to the study were recorded. For all facial photographs, written consent was obtained from the patient.

All patients with FMF as well as a cohort of 43 age- and stage-matched patients with conventional MF with similar time of presentation and follow-up were randomly selected from our clinic. Patients were divided into 4 cohorts: those with early disease, defined as stage IIA or lower, and those with advanced disease, defined as stage IIB or higher for FMF and conventional MF. Overall survival curves and progression-free survival curves were calculated from the time of disease onset to the date of last contact using the Kaplan-Meier technique. P values were determined to compare outcomes between groups.

RESULTS

CLINICAL CHARACTERISTICS

Among the 43 patients in the study (Table 1), 31 were men and 13 were women. The average age was 49 years, and the ages ranged from 19 to 92 years. At the time of staging, 32 of 43 patients had disease limited to patches or plaques, stage IA or IB. In 30 patients, pruritus was a significant feature and required distinct medical attention (68%). Unlike conventional MF, which favors a bathing suit distribution, 37 of the patients with FMF had lesions involving the scalp or face (86%). Thirty-five patients had lesions on the torso along with scalp and face involvement (81%). Only six patients had lesions limited to the torso (14%), and 2 patients had lesions limited to the scalp or facial area (5%). Among the 6 patients with lesions limited to the torso, 2 had prominent syringotropism and folliculotropism. Only 1 other patient in our group had prominent syringotropism. In 28 patients (65%), alopecia was a direct consequence of FMF. In 20 of these 28 patients (71%), the alopecia involved the face, particularly the eyebrows.

Prominent eyebrow plaques with accompanying alopecia was a conspicuous finding in 14 cases (33%) (Figure 1). These plaques frequently showed follicular accentuation, and in 3 cases, coalescence of eyebrow and forehead plaques resulted in a leonine facies (Figure 2). Erythematous plaques with alopecia and follicular prominence on other sites of the head and neck were also frequently seen. Acneiform lesions were common, such as nodulocystic lesions, pustules, milia, and clustered comedones (Figure 3). Other patterns included follicular-based papules, nodules, or tumors, which in a few cases had a mucinous discharge. Rarer forms of facial involvement included an alopecia areata–like pattern and 1 case that closely resembled granulomatous rosacea.

Involvement of the scalp with alopecia was seen in 6 patients. In all 6 patients, the pattern was that of a scarring alopecia. The findings ranged from a minimally inflammatory scarring alopecia without prominent papules to follicular keratosis pilaris–like papules and large papulonodular or boggy lesions (Figure 4). Interestingly, in 2 cases,
the histologic changes were primarily those of an inter-
face dermatitis with a lichen planopilaris–like pattern. In
fact, in both cases, the patients were presumed to have li-
chen planopilaris until they later developed tumor le-
sions. Retrospectively, in review of the previous biopsy speci-
mens, folliculotropism could be appreciated. In 1 patient,
the prominent scalp involvement and alopecia resulted in
changes of cutis verticis gyrata (Figure 5).

Trunk involvement also showed a variety of pat-
terns. Very few patients showed any signs of conven-
tional patches or plaques. Most trunk involvement con-
sisted of poorly defined patches and plaques with follicular
accentuation and confluent follicular papules and nod-
ules (Figure 6 and Figure 7). Other patterns in-
cluded large patches of alopecia without accompanying
erythema. Nodulocystic and comedonal lesions could also
occasionally be seen in a widespread distribution on the
trunk. Several patients presented with erythematos
patches with keratosis pilaris–like papules on the arms
or legs. Clinically, these changes could be distinguished
from routine keratosis pilaris because of the extent of dis-
ease, notable asymmetry, prominent erythema, and ac-
companying alopecia. Histologically, these lesions showed
unequivocal FMF. In the 3 patients with prominent syring-
gotropism, there was impressive involvement of gla-
brous skin with atrophic plaques, purpura, and punctuate erythema (Figure 8).

Another significant and unique observation in 6 patients was the presence of pseudotumors. In 22 of the 26 patients with true tumor lesions, the tumors involved the head and neck region. Of the 26 cases of true tumors, 22 involved the face or scalp. Generalized erythrodema was the initial presentation in 3 cases, 2 of which met the International Society for Cutaneous Lymphomas criteria for Sézary syndrome.

Other lymphoproliferative conditions were present in 3 cases, including 2 cases of chronic lymphocytic leukemia and 1 case of lymphomatoid papulosis.

**HISTOLOGIC FEATURES**

In our group’s previous study on the histologic features of FMF, we determined 5 characteristic patterns, which included the classic pattern of folliculotropism with or without follicular mucinosis, an eosinophilic folliculitis-like pattern, a cystic pattern, basaloid folliculolymphoid hyperplasia, and a granulomatous pattern (Figure 9). More detailed information regarding these five specific patterns can be found in the study by Gerami and Guitart. In the present study, we also included 3 patients who showed prominent syringotropism in addition to the prototypical folliculotropic changes. The histologic changes in our patients are summarized in Table 1. All cases showed folliculotropism with atypical lymphocytes.

Other features examined included frequency of follicular mucinosis, accompanying epidermotropism, and large-cell transformation (LCT). Prominent follicular mucinosis was seen in 22 of 43 patients. Accompanying epidermotropism was seen in 11 of 43 patients. Fifteen patients had LCT (35%), defined as having 25% of T cells with a large-cell morphologic character or nodular aggregates.

Immunohistochemical analysis was performed in 38 cases, and in each case the phenotype consisted of CD3+, CD4+, CD8− lymphocytes. Results of molecular studies using polymerase chain reaction to evaluate clonality of the T-cell receptor gamma gene were available in 34 cases. A positive clone was identified in the lesional tissue in 28 cases (82%). In 5 cases, a negative result was found, and in 1 case, the result was indeterminate or equivocal.

**THERAPY**

In 13 patients with primarily stage IA and IB disease, the initial therapy consisted of skin-directed therapy such as psoralen plus UV-A (PUVA), narrowband UV-B (NBUVB), nitrogen mustard, bexarotene gel with or without topical steroids, and in 1 case localized irradiation alone (Table 2). Among these 13 cases, 3 patients had a partial response (PR) or a complete response (CR). Two of these 3 patients also required localized irradiation to achieve this response. In all 3 patients, the disease was localized to less than 3% of the body surface area. Included among these 3 patients was the patient treated with localized irradiation alone.

Twenty-six patients were treated with a combination of PUVA and oral retinoids. This was initial therapy in 20 patients, while the remaining 6 were patients for whom skin-directed therapy had failed. In 24 cases, the retinoid used was bexarotene, while in the remaining 2 cases it was acitretin. These 26 patients included 8 patients with stage IA disease, 8 with stage IB, 2 with IIA, 5 with stage IIB, 1 with stage III, and 2 with stage IVA. Among these 26 patients, 16 achieved a satisfactory response (PR or CR), while the remaining 10 showed no response. One patient with stage IA disease was treated with bexarotene and NBUVB with no response. This patient later showed PR to local irradiation but continues to have progressive disease.

Eighteen patients from the PUVA-retinoid group, including 9 for whom treatment failed, were treated with PUVA with interferon alfa. These patients included 1 with...
stage IA disease, 2 with stage IB, 10 with IIB, 2 with stage III, and 2 with stage IVA. Nine of these patients achieved PR or CR. The other 9 patients showed no response to PUVA with interferon alfa. Six of these 9 patients had an aggressive course with disease refractory to multiple subsequent chemotherapeutic agents, and they eventually died of disease.

In general, among those patients with advanced disease (≥ IIB), there was a very poor response to chemotherapeutic agents. A total of 14 patients received either

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**Table 2. Therapy Provided for Study Patients**

<table>
<thead>
<tr>
<th>Therapeutic Intervention</th>
<th>Patients</th>
<th>Patients Achieving Either Complete or Partial Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin directed&lt;sup&gt;b&lt;/sup&gt;</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>Irradiation alone</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>PUVA with or without oral retinoids</td>
<td>26</td>
<td>16</td>
</tr>
<tr>
<td>PUVA with or without interferon alfa</td>
<td>18</td>
<td>9</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Alemtuzumab</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Allogeneic stem cell transplantation</td>
<td>4</td>
<td>2</td>
</tr>
</tbody>
</table>

<sup>a</sup>All data are reported as number of patients.

<sup>b</sup>Skin-directed therapies included psoralen plus UV-A (PUVA), narrowband UV-B, nitrogen mustard, or bexarotene gel in combination with topical steroids.

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**Figure 9.** Five characteristic patterns of folliculotropic mycosis fungoides (FMF) (hematoxylin-eosin). A. Prototypical pattern of FMF with follicular mucinosis (original magnification ×20). B. Basaloid folliculolymphoid hyperplasia (original magnification ×40). C. Eosinophilic folliculitis (original magnification ×100). D. Granulomatous pattern with atypical lymphocyte and multinucleate cells surrounding area of a ruptured follicle (original magnification ×200). E. Cystic pattern with atypical lymphocytes within the epithelium of the cyst as well as an area of more prototypical FMF in left upper corner (original magnification ×40).

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**Figure 10.** Kaplan-Meier curve comparing overall survival among patients with early- and late-stage folliculotropic (FMF) and conventional (control) mycosis fungoides.
CHOP (cyclophosphamide, Adriamycin, vincristine, and prednisone), liposomal doxorubicin, gemcitabine, or a combination of these drugs, none of which brought about a satisfactory response. Only 4 of these 14 patients were able to later achieve a PR or CR. In 2 cases, patients received alemtuzumab, and 1 of these also received localized irradiation. The other 2 patients achieved a complete remission with an allogeneic stem cell transplantation.

OUTCOMES

Overall survival among patients with FMF, stage IIA or lower, was 87% at 5 years and 82% at 10 years. However, as shown in Figure 10, a number of patients died shortly after 10 years, steeply dropping the 15-year survival closer to 41%. Patients with conventional MF, stage IIA or lower, showed a 5-year survival of 91% and 10-year survival of 91% and maintained this same survival at 15 years. Comparing the 10-year survival of patients with FMF, stage IIA or lower, with that of patients with conventional MF, stage IIA or lower, we found a clearly worse prognosis for FMF ($P=0.03$) (Table 3), and this despite the patients with FMF receiving more aggressive therapies such as PUVA with bexarotene or interferon alfa. Patients with early-stage conventional MF were predominantly treated with skin-directed therapies alone.

Among patients with FMF of stage IIB or higher, the 5- and 10-year overall survival rates were 83% and 67%, respectively. Similar to the stage IIA and lower FMF group, this cohort had a steep drop in survival after 10 years. At 15 years, the overall survival was close to 25% (Figure 11). In the conventional MF group, the 5- and 10-year overall survival rates were 73% and 41%, respectively. By 15 years, survival between the FMF and conventional MF patients with stage IIB or worse both approximated 25%. This suggests that in advanced disease (stage IIB or worse), there is less difference in outcome between the conventional MF and FMF groups. Treatment methods in the patients with advanced FMF and conventional MF were similar.

Progression-free survival, similarly, differed between FMF and conventional MF groups with stage IIA or lower disease. In the FMF group, progression-free survival at 10 years was only 45%, while for the conventional MF group this number was 91% ($P<.01$) (Figure 12) (Table 3). While among patients with more advanced disease (stage IIB or higher), patients with FMF had a progression-free survival rate of 25%, and patients with conventional MF had a progression-free survival of 8%, again showing a lesser degree of difference in advanced disease (Figure 13).

As in the study by van Doorn et al., our findings support the current classification of FMF as a distinct disease entity in the WHO-EORTC system. Appreciating the distinct differences between FMF and conventional
MF is paramount to optimizing therapy and management of this variant of CTCL.

The most salient difference in the clinical presentation of FMF is the distribution of the lesions, often involving the head and neck region, as well as the distinct follicular-based distribution, which often results in alopecia. This presentation is in contrast to the common bathing suit distribution of conventional MF, which rarely involves the face.

Although FMF occasionally presents with sharply demarcated lesions with follicular prominence, more commonly the lesions are ill defined with localized or confluent papules with an acnelike appearance. The clinical spectrum of FMF includes presentations mimicking scarring and nonscarring alopecias, keratosis pilaris, comedonal and cystic acne, and rosacea. In our experience, eyebrow plaques with follicular prominence with or without alopecia may be highly indicative of FMF, which was seen in a third of our cases. Recognition of pseudotumors is another significant factor in management of patients with FMF. Biopsy specimens should be taken of tumorous lesions to exclude this possibility. These lesions clinically resemble tumors but historically consist of epithelial or follicular hyperplasia and granulomatous changes with only minimal lymphoma cells.

Pruritus is especially common in patients with FMF. Among our cases, 68% had severe pruritus requiring separate treatment aside from the lymphoma (n=30). Clinically this often results in xerosis, frequent excoriations, and prurigo-like lesions. This can be further aggravated by superinfection by *Staphylococcus aureus* and subsequent pyoderma. In our experience, successful treatment of the lymphoma often coincides with improvement of the pruritus. Our treatments include high doses of antihistamines, pregabalin or gabapentin, emollients, antibiotics, and chlorine bleach baths for the superinfection.

As with the clinical presentation, the histologic features in early FMF are distinctive from conventional MF.1,8,13,14,21-25 Our group’s previous study1 on histologic findings in FMF showed 5 distinct patterns. In each pattern, folliculotropic lymphocytes with or without follicular mucinosis may be seen. Follicular mucinosis was observed in 22 cases (51%). Importantly, coexisting epidermotropism of the nonfollicular epithelium was seen in only 11 cases (25%). Syringotropism was seen in a total of 3 patients. In our experience, all patients with syringotropism have coexisting folliculotropism, while only a small minority of patients with folliculotropism have coexisting syringotropism.1

The difficulty in histologic recognition of FMF is further exacerbated by frequent nondiagnostic biopsies that include neutrophilic pustular lesions or lichenoid lesions with interface dermatitis toward the follicle. In these cases, multiple biopsy specimens are required until a definitive diagnosis can be reached. Hence, familiarity with the clinical presentation and a high degree of suspicion accompanied by frequent biopsies and familiarity with the range of histologic features may help reach the proper diagnosis.

The importance of distinction between MF and FMF is not merely an academic exercise but is emphasized by the differences in therapeutic response and clinical outcomes in these 2 groups. Skin-directed therapy alone is inadequate in most cases of FMF and rarely results in complete remission.3 While in the Dutch study,4 many patients responded to radiation therapy, many of our patients also showed a good response to PUVA with retinoids or interferon alfa. In our opinion, appropriate starting therapy for patients with early-stage FMF should include phototherapy, preferably PUVA in combination with a retinoid such as bexarotene or acitretin or PUVA with interferon alfa. Narrowband UV-B treatment is probably inadequate therapy for patients with FMF because the rays do not reach the deep adnexal component, leaving deep residual disease even when the epidermal component may seem to improve.

For patients with advanced disease (≥IIb), prognosis is poor and requires aggressive therapy. In the present study, these patients responded poorly to conventional chemotherapies such as CHOP, liposomal doxorubicin, and gemcitabine. Partial or complete remissions were20 seen with alemtuzumab, irradiation, and allogeneic stem cell transplantation.

To our knowledge, this is largest series of patients with FMF from the United States, and our findings regarding the outcomes in patients with FMF support those from the European study by van Doorn et al.2 Interestingly, the differences in outcomes between patients with FMF and conventional MF are most marked in patients with early disease (stage IIA or lower). The differences are statistically significant at 10 years, with an overall survival of 82% in FMF and 91% in conventional MF. This is further highlighted at the 15-year mark, with overall survival in the FMF group steeply dropping to 41%, while in conventional MF the overall survival is maintained at 91%. One possible explanation for this divergence in overall survival from conventional MF is the difficulty and rarity of achieving CR. Even those patients receiving aggressive treatments often continue to have foci of residual disease that, over time, increase the probability of a transforming event. Conversely, an alternative explanation for the aggressive behavior of FMF may be related to the intrinsic gene expression of the tumor cells. Shin et al20 recently identified 4 of 7 cases of FMF with a
In our study, the Kaplan-Meier curve in early FMF falls between the curves for conventional early and late MF, more closely simulating that for patients with late-stage conventional MF.

Patients with conventional MF and FMF in the cohort with advanced disease (stage IIB or higher), appear to have a more homogeneous outcome, with the prognosis being universally poor. Similarly, there is a significant difference in progression-free survival between FMF and conventional MF in patients with early-stage disease (< 1IA) at 10 years (45% vs 91%) (P < .01). In this cohort of patients with early FMF, if progression occurred, it was frequently seen between 5 and 10 years and frequently resulted in death between 10 and 15 years.

In summary, there are significant differences in clinical presentation, histologic features, therapeutic responses, and outcomes in FMF compared with conventional MF. The overall data strongly support the classification of FMF as a distinct entity. Familiarity with these features can greatly assist in the recognition of these patients, who require a separate therapeutic algorithm and have a distinct prognosis.

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Author Contributions: Dr Guitart had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Gerami, Rosen, Kuzel, and Guitart. Acquisition of data: Gerami and Boone. Analysis and interpretation of data: Gerami, Rosen, Kuzel, and Guitart. Drafting of the manuscript: Gerami and Guitart.

Critical revision of the manuscript for important intellectual content: Gerami, Rosen, Kuzel, Boone, and Guitart.

Administrative, technical, and material support: Gerami, Rosen, Kuzel, and Boone. Study supervision: Gerami, Rosen, and Kuzel.

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