Magnetic Resonance Imaging in Sclerotic-Type Chronic Graft-vs-Host Disease

Jason Clark, MD; Lawrence Yao, MD; Steven Z. Pavletic, MD, MS; Michael Krumlauf, RN; Sandra Mitchell, CRNP, PhD; Maria L. Turner, MD; Edward W. Cowen, MD, MHSc

Background: Sclerotic-type chronic graft-vs-host disease (cGVHD) of the skin is an uncommon but potentially debilitating sequela of allogeneic hematopoietic stem cell transplantation. There is no standardized assessment measure for this form of cGVHD. Because a full-thickness incisional biopsy specimen to the level of the fascia may be needed to make a definitive histologic diagnosis of cGVHD-related fasciitis, a noninvasive technique for the assessment and monitoring of sclerotic-type cGVHD, particularly cGVHD-related fasciitis, would be of potential value.

Observations: Sixty-two consecutive patients with cGVHD following allogeneic hematopoietic stem cell transplantation were evaluated for sclerotic skin disease. Forty-four patients (71%) had cutaneous cGVHD, and 28 patients (45%) had evidence of sclerotic involvement based on physical examination findings. Fifteen patients agreed to undergo research magnetic resonance imaging to evaluate quantifiable changes in the dermis, subcutaneous tissue, and muscle. Among 15 patients, magnetic resonance imaging identified abnormalities in the skin in 7 (47%), subcutaneous fibrous septa in 13 (87%), deep fascia in 12 (80%), epimysium in 9 (60%), and muscle in 3 (20%).

Conclusions: Magnetic resonance imaging should be considered in the evaluation of patients with cGVHD suspected of having subcutaneous or fascial involvement. Additional studies are needed to validate this noninvasive modality for serial monitoring of disease activity and response to therapy.

Trial Registration: clinicaltrials.gov Identifier: NCT00331968

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SCLEROTIC-TYPE CHRONIC GRAFT-VS-HOST DISEASE (cGVHD) is associated with fibrosis of the dermis, subcutaneous tissue, or fascia. Superficial dermal fibrosis results in small atrophic plaques resembling lichen sclerosus, localized thickening of the dermis leads to firm circumscribed plaques resembling morphea, widespread hide-bound thickening resembles scleroderma, and subcutaneous involvement of the fat septae and deeper fascial tissues resembles eosinophilic fasciitis.1-4

Patients with sclerodermalike fibrosis and those with fibrosis of the subcutaneous and fascial tissues develop range-of-motion limitations and joint contractures that may significantly affect daily activities. In patients with fasciitis, functional limitation may occur in the absence of overt superficial skin thickening or pigmented changes characteristic of the morphea-like and scleroderma-like forms of cGVHD. Visible signs in these patients may consist of prominent “grooves” in the skin caused by thickening of fascia enshrouding muscle groups or large superficial veins. Thickening of the fibrous fat septae imparts a subtle rippled or cellulitelike appearance of the skin, as well as a “nodular” texture appreciated by deep palpation.2

There are no standardized assessment measures for sclerotic-type cGVHD involving the skin and subcutaneous tissues. Because a full-thickness incisional biopsy specimen to the level of the fascia may be needed to make a definitive histologic diagnosis of cGVHD-related fasciitis, a noninvasive technique for the assessment and monitoring of this form of cGVHD would be of value. Magnetic resonance (MR) imaging is of diagnostic and prognostic usefulness in the evaluation of several diseases associated with soft-tissue abnormalities. Short tau inversion recovery (STIR) MR imaging has been
Sclerotic-type cGVHD. In this study, we examined a presentation of new-onset GVHD-related fasciitis. How-in acute evaluation of limb swelling, a common pre-mine the depth and extent of soft-tissue involvement netic resonance imaging has also been used to deter-

E.W.C.) at the National Institutes of Health (NIH) Clinical Cen-
ter, Bethesda, Maryland, as a part of an observational cross-sectional protocol studying the natural history of cGVHD (clinicaltrials.gov identifier: NCT00331968). Clinical evi-dence of sclerotic-type cGVHD was determined by the pres-ence of overt skin thickening, rippling or nodularity of subcu-taneous tissues with deep palpation, groove sign on physical examination, or range-of-motion limitations. Every adult pa-tient determined as having sclerotic involvement was invited to undergo an MR imaging procedure.

After intravenous administration of a gadolinium chelate (Magnevist; Bayer HealthCare Pharmaceuticals Inc, Wayne, New Jersey), magnetic resonance imaging was performed at 1.5 T and included T1-weighted spin echo, STIR, 3-dimen-sional gradient recalled echo at out-of-phase echo time, and fat-suppressed 3-dimensional gradient recalled echo at inphase echo time. Structures analyzed on MR imaging included skin, subcutaneous septae and superficial fascia, deep fascia, epimy-sium, and muscle. The presence of edema was based on hy-perintensity depicted by STIR imaging. Thickening of fascia and septae was assessed on T1-weighted spin echo and 3-dimen-sional gradient recalled echo out-of-phase imaging.

A 3-point scoring system (0 for negative, 1 for equivocal, or 2 for abnormal) was used to grade the degree of MR imaging abnormalities at the following 5 anatomical levels: skin, subcutaneous septae, deep fascia, epimysium, and muscle. Skin, subcutaneous septae, and deep fascia were each assessed for thickening, edema (STIR), and enhancement (gadolinium); epi-mysium was assessed for edema and enhancement; and muscle was assessed for edema. The highest score for thickening, edema, or enhancement at each anatomical level was used in the com-posite score for that site and in calculation of the overall MR imaging score. A maximum score of 10 indicated definite ab-normalities at all 5 tissue levels.

The Institutional Review Board of the National Cancer In-stitute approved the research protocol. All subjects gave in-formed consent in accord with the Declaration of Helsinki.

Sixty-two consecutive adult and pediatric patients with a history of cGVHD involving 1 or more organ systems following allogeneic hematopoietic stem cell transplantation were evaluated by an interdisciplinary team (S.Z.P., S.M., M.L.T., and E.W.C.) at the National Institutes of Health (NIH) Clinical Cen-
ter, Bethesda, Maryland, as a part of an observational cross-sectional protocol studying the natural history of cGVHD (clinicaltrials.gov identifier: NCT00331968). Clinical evi-dence of sclerotic-type cGVHD was determined by the pres-ence of overt skin thickening, rippling or nodularity of subcu-taneous tissues with deep palpation, groove sign on physical examination, or range-of-motion limitations. Every adult pa-tient determined as having sclerotic involvement was invited to undergo an MR imaging procedure.

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Sixty-two consecutive patients with cGVHD were evaluated. Forty-four patients (71%) had clinical evidence of cutaneous cGVHD, and 28 patients (45%) had diagnostic evidence of sclerotic involvement based on physical examination findings according to National Institutes of Health consensus criteria. Fifteen patients agreed to undergo research MR imaging. In this study, we examined a presentation of new-onset GVHD-related fasciitis. How-ever, there is limited experience using MR imaging in sclerotic-type cGVHD using MR imaging to determine the value of this imaging modality for the identification of cutaneous and soft-tissue abnormalities.
development of sclerosis. Abnormality of the fat septae was the most frequently identified finding (13 of 15 patients [87%]). Twelve of fifteen patients (80%) had similar abnormalities of the deep fascia. Epimysial edema or enhancement was detected in 9 of 15 patients (60%), and muscle inflammation was observed in 3 of 15 patients (20%). Skin sclerosis was identifiable by MR imaging in 7 of 15 patients (47%). Figure 1 and Figure 2 show clinical and magnetic resonance images of abnormalities in 2 patients with cGVHD-related skin sclerosis and fasciitis. A mean total MR imaging score of 5.27 was calculated, suggesting that in most patients with sclerotic disease soft-tissue abnormalities are present in multiple tissue planes. In general, STIR imaging was more sensitive than contrast medium–enhanced MR imaging for detection of soft-tissue abnormalities. Three patients underwent second MR assessments several months later. In each patient, the MR images remained stable over time in concordance with physical examination findings.

Table 2. Magnetic Resonance (MR) Imaging Findings

| Patient No. | Erythema Type | Sclerosis Type | Duration of Sclerosis, mo/Subtype | MR Imaging Location | MR Imaging Score
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>40.0</td>
<td>26/Subcutaneous fibrosis/fasciitis</td>
<td>Bilateral thigh</td>
<td>8</td>
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<tr>
<td>2</td>
<td>9.9</td>
<td>62.1</td>
<td>4/Subcutaneous fibrosis/fasciitis, dermal</td>
<td>Bilateral thigh</td>
<td>8</td>
</tr>
<tr>
<td>3</td>
<td>7.7</td>
<td>48.6</td>
<td>21/Subcutaneous fibrosis/fasciitis, dermal</td>
<td>Bilateral thigh</td>
<td>0</td>
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<tr>
<td>4</td>
<td>0</td>
<td>1.4</td>
<td>17/Dermal, lichen sclerosis–like</td>
<td>Right arm</td>
<td>0</td>
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<tr>
<td>5</td>
<td>3.4</td>
<td>25.6</td>
<td>20/Subcutaneous fibrosis/fasciitis, dermal, lichen sclerosis–like</td>
<td>Bilateral thigh</td>
<td>2</td>
</tr>
<tr>
<td>6</td>
<td>1.8</td>
<td>39.6</td>
<td>90/Subcutaneous fibrosis/fasciitis, dermal</td>
<td>Bilateral thigh</td>
<td>5</td>
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<tr>
<td>7</td>
<td>0</td>
<td>25.6</td>
<td>18/Subcutaneous fibrosis/fasciitis</td>
<td>Bilateral thigh</td>
<td>7</td>
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<tr>
<td>8</td>
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<td>50.2</td>
<td>8/Subcutaneous fibrosis/fasciitis, dermal</td>
<td>Bilateral thigh</td>
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<tr>
<td>9</td>
<td>0</td>
<td>62.3</td>
<td>6/Subcutaneous fibrosis/fasciitis, dermal</td>
<td>Bilateral thigh</td>
<td>6</td>
</tr>
<tr>
<td>10</td>
<td>1.7</td>
<td>64.0</td>
<td>7/Subcutaneous fibrosis/fasciitis, lichen sclerosis–like</td>
<td>Bilateral thigh</td>
<td>0</td>
</tr>
<tr>
<td>11</td>
<td>0</td>
<td>7.4</td>
<td>25/Subcutaneous fibrosis/fasciitis, dermal</td>
<td>Right ankle</td>
<td>3</td>
</tr>
<tr>
<td>12</td>
<td>0</td>
<td>40.0</td>
<td>3/Subcutaneous fibrosis/fasciitis</td>
<td>Right forearm</td>
<td>4</td>
</tr>
<tr>
<td>13</td>
<td>0</td>
<td>78.0</td>
<td>39/Subcutaneous fibrosis/fasciitis, dermal</td>
<td>Bilateral thigh</td>
<td>6</td>
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<tr>
<td>14</td>
<td>0</td>
<td>15.6</td>
<td>16/Dermal, subcutaneous fibrosis/fasciitis</td>
<td>Abdomen</td>
<td>1</td>
</tr>
<tr>
<td>15</td>
<td>0</td>
<td>20.0</td>
<td>1/Dermal, subcutaneous fibrosis/fasciitis, lichen sclerosis–like</td>
<td>Abdomen</td>
<td>4</td>
</tr>
</tbody>
</table>

Abbreviation: cGVHD, chronic graft-vs-host disease.

a Score of 0 indicates no change; 1, equivocal; and 2, abnormal.
b Using 3 T with gadolinium contrast medium.
c Using 3 T without gadolinium contrast medium.

development of sclerosis. Abnormality of the fat septae was the most frequently identified finding (13 of 15 patients [87%]). Twelve of fifteen patients (80%) had similar abnormalities of the deep fascia. Epimysial edema or enhancement was detected in 9 of 15 patients (60%), and muscle inflammation was observed in 3 of 15 patients (20%). Skin sclerosis was identifiable by MR imaging in 7 of 15 patients (47%). Figure 1 and Figure 2 show clinical and magnetic resonance images of abnormalities in 2 patients with cGVHD-related skin sclerosis and fasciitis. A mean total MR imaging score of 5.27 was calculated, suggesting that in most patients with sclerotic disease soft-tissue abnormalities are present in multiple tissue planes. In general, STIR imaging was more sensitive than contrast medium–enhanced MR imaging for detection of soft-tissue abnormalities. Three patients underwent second MR assessments several months later. In each patient, the MR images remained stable over time in concordance with physical examination findings.

Imaging in 14 of 15 patients was consistent with the clinical impression, suggesting that careful clinical examination by a trained clinician may detect subcutaneous involvement and fasciitis. One patient (patient 4 in Table 1 and Table 2) with negative findings on MR images described a history of gradual improvement of tightness in the upper extremities. The patient had minimal superficial sclerosis of the upper extremities; therefore, the negative findings were not unexpected. In several other patients, MR imaging detected deeper and more extensive involvement than could be appreciated by physical examination alone. In 3 patients, muscle involvement was detected in the absence of an elevation in the serum creatine kinase level, suggesting that MR imaging may be particularly helpful for the detection of fascial and muscle inflammation.

Although most patients in this study agreed to provide punch skin biopsy specimens, fascial biopsy specimens were not obtained, and MR imaging abnormalities require clinical correlation. In addition, because MR imaging was performed only in patients with clinical evidence of sclerotic disease, the sensitivity of MR imaging for subclinical subcutaneous or fascial disease in patients with cGVHD is unknown. The high prevalence of sclerotic-type cGVHD among our cohort (28 of 45 patients [45%]) is not representative of cutaneous cGVHD in general, as the referral population for this study consisted primarily of severely affected patients with multiorgan involvement.

We believe that MR imaging is a useful adjunct to careful clinical assessment to evaluate soft-tissue fibrosis and may be considered in the clinical setting to confirm the presence of suspected muscle and fascial abnormalities before the development of extensive range-of-motion limitations. However, consideration must also be given to the cost of MR imaging and to the potential risk of nephrogenic systemic fibrosis associated with exposure to gadolinium contrast medium. Although we did not observe the development of nephrogenic systemic fibrosis in our cohort, patients with cGVHD may be at higher risk for...
nephrogenic systemic fibrosis owing to renal dysfunction from previous chemotherapy exposure or ongoing immunosuppressive therapy, particularly treatment with calcineurin inhibitors.

Better assessment tools are needed to differentiate disease activity vs damage and to evaluate treatment efficacy in patients with sclerotic-type cGVHD. Skin scoring systems based on body surface area estimates and degree of ability to pinchability or ability to move the skin are inadequate for precise monitoring of subcutaneous and fascial disease. Surrogate markers of skin fibrosis such as joint range of motion are helpful if sclerosis overlies a joint, but evaluation requires a trained professional to perform the assessment in a standardized and reproducible manner, and findings may be affected by other factors, including pain, deconditioning, and unrelated joint disease. Therefore, MR imaging may be useful in the research setting for serial long-term monitoring of patients with sclerotic soft-tissue disease. Optimization of MR imaging as a response assessment tool will require correlation of imaging, histologic findings, and meaningful clinical change over time.

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Author Contributions: Dr Cowen had full access to the data in the study and takes responsibility for the integrity of the data in the study and the accuracy of the data analysis. Study concept and design: Clark, Turner, and Cowen. Acquisition of data: Yao, Pavletic, Mitchell, and Cowen. Analysis and interpretation of data: Clark, Yao, and Cowen. Drafting of the manuscript: Clark and Cowen. Critical revision of the manuscript for important intellectual content: Pavletic, Turner, and Cowen. Statistical analysis: Clark and Cowen. Administrative, technical, or material support: Yao, Pavletic, Mitchell, and Cowen.
support: Krumlauf. Study supervision: Pavletic and Cowen.

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REFERENCES


