The lymphoid follicle variant of dermatomyositis

ABSTRACT

Objective: To investigate the clinical and morphologic spectrum of early adult-onset dermatomyositis (DM), an inflammatory disease that affects small vessels of the muscle and the skin.

Methods: Histologic evaluation of frozen muscle samples was employed to visualize the cellular organization of ectopic lymphoid structures in muscle biopsies obtained from 2 patients diagnosed with DM. Clinical presentation and morphologic features, as well as treatment and follow-up, were assessed and documented. Electron microscopy was used to confirm the light microscopic diagnosis of DM. Clonality analysis of B-cell populations using PCR was performed.

Results: Muscle biopsy of both patients fulfilled the morphologic European Neuromuscular Centre criteria of DM. Analyses of muscle biopsy samples revealed ectopic lymphoid follicle-like structures that showed a remarkable similarity to secondary lymphoid organs (SLOs) with distinct T- and B-cell compartmentalization. Our 2 patients exhibited an atypical and mild clinical presentation and responded favorably to therapy.

Conclusions: The clinical and histopathologic features of DM can be atypical, and the presence of SLOs is not inevitably linked to an unfavorable prognosis.

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GLOSSARY

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tr>
<td>CK</td>
<td>creatine kinase</td>
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<td>COX</td>
<td>cytochrome c oxidase</td>
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<td>DM</td>
<td>dermatomyositis</td>
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<td>GC</td>
<td>germinal center</td>
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<td>IIM</td>
<td>idiopathic inflammatory myopathy</td>
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<td>IVIg</td>
<td>IV immunoglobulin</td>
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<td>jDM</td>
<td>juvenile dermatomyositis</td>
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<td>LFLS</td>
<td>lymphoid follicle-like structures</td>
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<tr>
<td>MAC</td>
<td>membrane attack complex</td>
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<td>MHC</td>
<td>major histocompatibility complex</td>
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<td>SLO</td>
<td>secondary lymphoid organ</td>
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Dermatomyositis (DM) is considered a complement-mediated vasculopathy. Diagnostic criteria have been defined and include characteristic skin findings, subacute onset of proximal symmetrical muscle weakness, and histologically membrane attack complex (MAC) deposition on capillary walls, or reduced capillary density, or major histocompatibility complex (MHC) class I expression of perifascicular fibers associated with perivascular, perimysial inflammatory cell infiltrate consisting of macrophages and CD4+ lymphocytes as well as ultrastructurally undulating tubules in endothelial cells. Although regularly mentioned as being involved in pathogenicity of DM, the precise role of B lymphocytes is not fully understood and not used as an individual diagnostic criterion. Recently it has been suggested that the presence of ectopic lymphoid structures in juvenile DM (jDM) was associated with adverse disease outcome.

METHODS

Histologic, enzyme histochemical, and immunohistochemical studies. Histologic, immunohistochemical, and enzyme histochemical stains were performed on 9-μm cryostat sections. Hematoxylin & eosin and Gomori trichrome stains were prepared according to standard procedures. Immunohistochemistry and enzyme histochemical stains were performed as previously described. Primary antibodies used in this study are listed in table e-1 at Neurology.org/nn. Omission of the primary antibody resulted in no staining.
Electron microscopy. Muscle specimens were also examined by electron microscopy, which was performed as described previously.4

B-cell clonality analysis. B-cell clonality was assessed in both patients' specimens by PCR amplification using a set of BIOMED-2 assays (InVivoScribe Technologies, San Diego, CA). Loci for IGH [IGHA: FR1 (variable region framework 1)-J; IGHB: FR2-J; IGHc: FR3-J] and for IGL (V-J) were targeted.5

RESULTS Patient 1, a 27-year-old woman, had a 7-year history of unilateral swelling of her left biceps muscle and hand as well as wrist pain and morning stiffness of her finger joints. A contrast-enhanced MRI of her left biceps showed diffuse gadolinium uptake, thickening of the muscle fascia, and muscle edema (figure 1). On neurologic examination she showed normal symmetrical muscle strength and normal fine motor skills. Thorough examination of the skin did not reveal any abnormalities. Laboratory examination of her blood serum showed elevated immunoglobulin E, C-reactive protein, and antinuclear and anti-cyclic citrullinated peptide antibodies. Serum creatine kinase (CK) was normal. There was no evidence of rheumatoid arthritis. Based on the international consensus criteria,1 biopsy of the left biceps gave a diagnosis of DM with accompanying B-cell-rich follicle-like structures. An initial high-dose (1 mg/kg/d) prednisolone treatment over 4 weeks followed by a low-dose treatment (5 mg/d) led to rapid improvement and persistent resolution of her symptoms over a 1-year period.

Patient 2, a 17-year-old girl, was referred because of a 5-month history of painful reddish swellings of the left upper arm followed by similar symptoms in her right upper arm. There were no alterations of the skin or muscle weakness. Three weeks prior to referral she had arthralgia of the hands, knees, and feet, and morning stiffness. On neurologic examination no additional abnormalities were found. She had a normal serum CK and erythrocyte sedimentation rate and a positive anti-nuclear antibody titer. MRI of the upper arms revealed hyperintensity in the right deltoid and left triceps muscles (figure 1, A and B). A biopsy of the left triceps showed a picture consistent with DM1 with accompanying B-cell-rich follicle-like structures. She was treated with methylprednisolone pulse therapy (1,000 mg for 3 consecutive days) and monthly IV immunoglobulin (IVIg) and subsequently received 60 mg prednisone daily and methotrexate (17.5 mg) weekly. Shortly after initiation of treatment she developed Gottron papules. Otherwise she responded favorably to therapy. Both IVIg and prednisone were successfully tapered, and currently she receives subcutaneous methotrexate and hydroxychloroquine, which has led to sustained improvement of her symptoms. Except for some minor alterations of the skin there remained no signs of active disease.

Muscle morphology. Muscle biopsies of both patients revealed extensive infiltration by inflammatory cells mainly in the perimysium and endomysium (figure 2, A–D). In addition, the infiltrates were located at perivascular sites. CD68+ macrophages (figure 2F) were diffusely distributed throughout the perimysium. MAC (C5b-9) deposition was mainly found on small capillaries and on the sarcolemma of single muscle fibers (figure 2G, arrowhead). MHC class II expression was detected on the lymphoid cells and was found on numerous muscle fibers, predominantly in the perifascicular area (figure 2L). Sarcolemmal MHC class I expression was detected on all muscle fibers with perifascicular enhancement (figure 2J). Combined cytochrome c oxidase (COX)/succinate dehydrogenase histochemistry revealed scattered COX-negative fibers as a sign of accompanying mitochondrial dysfunction (figure 2K). CD123+ dendritic cells (figure 2L) and CD138+ plasma cells (figure 2M) were found in close proximity to T- and B-cell areas. The lymphoid follicle-like structures (LFLS) were mainly composed of CD45+ leukocytes (figure 2E) with CD8+ (figure 2N) and CD4+ (figure 2O) T cells distributed around CD79+ B cells (figure 2P). Expression patterns of peripheral Bcl-2 (figure 2Q), central Bcl-6 (figure 2R), and BOB.1 (figure 2S) paralleled the specific lymphoid follicle-like B-cell pattern. The Ki67/Mib-1 proliferation index was increased within the center of the follicle-like structures (figure 2T).

Electron microscopy revealed undulating tubules in endothelial cells of both patients, which supported the light microscopic diagnosis of DM (figure 2H, arrowheads).

To exclude the presence of a neoplastic B-cell population as described for B-cell lymphomas within skeletal muscles (A, B).
Serial sections of muscle biopsy stained with hematoxylin & eosin revealed ectopic lymphoid follicle-like structures (patient 1: A and B; patient 2: C and D). Sections were stained with an antibody against CD45^+ leukocytes (E) to highlight the follicle-like inflammatory infiltrate. CD68^+ macrophages (F) were diffusely distributed throughout the perimysium. C5b-9 was mainly found in walls of small capillaries and on the sarcolemma of single muscle fibers (G, arrowhead). Electron microscopy revealed ultrastructural evidence of undulating tubules (patient 1: H, arrowheads, 50,000 ×; patient 2: not shown). Major histocompatibility complex (MHC) class II was expressed by the lymphoid cells and was found on numerous muscle fibers, predominantly in the perifascicular area (I). Sarcolemmal MHC class I expression was detected on all muscle fibers (J). Combined cytochrome c oxidase (COX)/succinate dehydrogenase staining revealed blue-stained fibers indicating reduced COX activity (K). The lymphoid follicle-like structures consisted
of CD123+ dendritic cells (L), CD138+ plasma cells (M), and CD8+ (N) and CD4+ (O) T cells that were distributed around CD79a+ (P) B cells. Expression patterns of Bcl-2 (Q), Bcl-6 (R), and BOB.1 (S) illustrate lymphoid follicle-like structures with increased proliferative activity in the B-cell areas as indicated by Ki67/Mib-1 immunostaining (T). Scale bars: A, D, E, F, K: 200 μm; B, C, G, S: 50 μm; I, J, L–R, T: 100 μm.

Our observations illustrate the presence of LFLS in early adult–onset DM, which to our knowledge has not been reported yet. We show that the presence of LFLS is not necessarily evidence of an unfavorable prognosis in adult DM as opposed to reports in jDM. In conclusion, this report enlarges the nosologic spectrum of DM.

**DISCUSSION**

We present 2 patients diagnosed with DM with unusual clinical features. Since both patients initially presented with unilateral muscle swellings, no detectable muscle weakness, and lack of CK elevation, the diagnostic criteria of DM, according to the European Neuromuscular Centre,1 and jDM, according to the international consensus criteria,7 were not present. However, the morphologic criteria to diagnose DM1 were perfectly fulfilled, including the presence of undulating tubules known to be detectable in early-stage DM,6 emphasizing the need for muscle biopsy in these patients. Muscle biopsy of both patients also showed characteristic LFLS with defined T- and B-cell compartmentalization, which is a very rare finding in a very small subset of patients with jDM2 and "overlap syndrome."78 Ectopic lymphoid follicles are a well-known histopathologic feature in other autoimmune diseases, including multiple sclerosis with meningeval inflammation, Sjögren syndrome affecting salivary glands,9 and focal myositis. Nevertheless, it remains unclear which factors lead to formation of LFLS in these diseases.

The lymphoid aggregates present in our muscle biopsies show a remarkable similarity to secondary lymphoid organs (SLOs) with distinct T- and B-cell compartmentalization. Expression of specific germinal center (GC) B-cell markers (BOB.1/Bcl-6) in the central B-cell-rich areas suggests a GC-like reaction in DM, similarly seen in true SLOs. It was previously reported that jDM patients with lymphoid follicle-like organization of the inflammatory infiltrate in muscle have a more severe and difficult-to-treat disease.2 However, our patients, who slightly exceeded the age at onset of jDM, exhibited a rather mild clinical presentation and responded favorably to therapy. Brachio-cervical inflammatory myopathy, focal myositis, and "overlap syndrome"8 were discussed as potential differential diagnoses and ruled out based on histologic, clinical, and ultrastructural (presence of undulating tubules) features. The outcome in patients with idiopathic inflammatory myopathy (IIM) has been studied recently.10 Most patients (68%) with IIM (including DM) developed a polyphasic or chronic disease course. There were no significant differences between the different myositis subtypes with regard to disease course, mortality, and quality of life.10

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**REFERENCES**


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