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EXPERT PERSPECTIVES ON CLINICAL CHALLENGES

Expert Perspective: Diagnostic Approach to Differentiating Juvenile Dermatomyositis From Muscular Dystrophy

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Introduction

A 4-year-old boy had 2 months of persistent fatigue, leg pain, inability to keep up with peers, and difficulty going up stairs. He exhibited an uncoordinated gait and inability to squat or rise from the ground but no joint swelling, tenderness, or rashes. His creatine kinase (CK) level was 1,681 units/L (upper limit of normal 257 units/L). He was referred to the Pediatric Neurology department to consider a muscular dystrophy (MD) diagnosis. Genetic testing for neuromuscular disorders revealed two variants of unknown significance. A magnetic resonance imaging (MRI) scan of the left pelvis and thigh demonstrated patchy T2 hyperintensity and enhancement with mild diffusion restriction and no atrophy or fatty replacement. His weakness progressed, and 6 months after symptom onset he was referred to the Pediatric Rheumatology department. Examination revealed a faint bilateral heliotrope rash and marked drop out, dilation, and hemorrhage of nailfold capillaries. His CK level remained elevated at 618 units/L, as did the aspartate aminotransferase, aldolase, lactate dehydrogenase, von Willebrand factor antigen, and neopterin levels. Muscle biopsy showed perifascicular atrophy, increased major histocompatibility complex class I (MHC-I) and myxovirus resistance A (MxA) expression, complement deposition in capillaries, and acute myopathic changes, including degeneration/regeneration, consistent with juvenile dermatomyositis (JDM). Myositis-specific antibody testing was positive for anti–nuclear matrix protein 2 (NXP2). The patient was initiated on intravenous and oral corticosteroids, subcutaneous methotrexate, intravenous Ig, and physical therapy, leading to a recovery of muscle strength nearly 1 year after symptom onset.

Background

Despite different disease pathogenesis, pediatric patients with MD and JDM can present very similarly, especially if there is no prominent rash typical of JDM. Reaching a confirmed diagnosis can be difficult. The time to diagnosis is often prolonged, with an average delay to diagnosis of 6 months in JDM[1,2] and 2 years in Duchenne MD (DMD).[3,4] In this article, we focus on a diagnostic approach to differentiate JDM from MD. We recommend a more standardized use of nailfold capillaroscopy (NFC), myositis-specific autoantibody (MSA) testing, and muscle biopsy to aid in more quickly achieving diagnostic certainty.

The term juvenile myositis (JM) or juvenile idiopathic inflammatory myopathy (IIM) describes a group of rare, multisystem autoimmune diseases in children that predominantly affect the muscles and variably affect other organ systems, including the skin, lungs, gastrointestinal tract, and heart. JDM is the most common form of JM, affecting approximately 85% of children with myositis.[5] Although JDM traditionally presents with characteristic rashes, including Gottron papules and heliotrope rash,[6–8] the pathognomonic rash can be subtle or even absent at presentation.[9] Children with JDM can also display heterogeneous disease phenotypes and even, at times, present first with other organ manifestations, such as interstitial lung disease (ILD). Although the discovery of MSAs has aided greatly in increased recognition of specific JDM phenotypes,[10] other rarer forms of JM are less studied, often lack characteristic skin manifestations, and hence can still be difficult to classify and diagnose.[8]

The current classification criteria used for JM are the 2017 European League Against Rheumatism/American College of Rheumatology classification criteria for adult and juvenile IIM.[6] These criteria are composed of a weighted point system for

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clinical variables, including age at onset, patterns of muscle weakness, skin manifestations, laboratory test findings, and muscle biopsy features[6]; the resultant score leads to a predictive probability of whether or not the patient has IIM. With characteristic rash and muscle findings, one can fairly confidently reach a diagnosis of juvenile IIM; indeed, 97% of patients with JDM were correctly classified without a muscle biopsy. Without a rash, however, biopsy is usually required to fulfill the points for definite IIM. The criteria were developed to include juvenile IIM and so may be used in pediatric patients. For juvenile IIM, though, the criteria only distinguish between (1) JDM and (2) JM other than JDM, because there were too few pediatric patients in the latter category to further delineate their JM classification subgroup. This classification system is an update from the 1975 Bohan and Peter diagnostic criteria[11] and allows more flexibility in JDM classification for patients with variable phenotypes and who have not had muscle biopsy or electromyography performed.

The myositis community is currently working to update the IIM classification criteria to include further differentiation of IIM subtypes in children, such as antisynthetase syndrome and immune-mediated necrotizing myopathy (IMNM), and to include additional clinical variables with diagnostic utility. An international survey of JDM specialists in 2006 identified additional findings that could be helpful in diagnosis and included muscle MRI and ultrasound scans, NFC abnormalities, calcinosis, and dysphonia.[12] The 2012 Single Hub and Access point for Rheumatology in Europe (SHARE) initiative, an evidence-based guideline out of Europe, also developed 33 diagnostic recommendations for JDM and provided strength-of-evidence support for each, including a recommendation that muscle biopsy be performed in patients with JDM who are atypical or lacking classic rash, which was a recommendation based on expert opinion, as were the majority of recommendations.[13]

The most well-known forms of MD are dystrophinopathies, including DMD and Becker MD (BMD). However, there is increasing recognition with more widescale genetic testing that there are more than 40 different genes associated with an MD phenotype.[14] These diseases are all genetic and progressive and have some typical findings on muscle biopsy.[14]

Similar to MD, the diagnostic categories of other noninflammatory myopathies in children are also diverse groups of diseases with variable phenotypes. Noninflammatory myopathies important to consider include congenital and metabolic myopathies.[15] Other causes of weakness that are not of primary muscle origin must also be considered, such as infection, malignancy, thyroid disease, and other toxic/metabolic causes, including medication side effects. To better evaluate children with a presenting symptom of proximal muscle weakness, we worked with a multidisciplinary team, including experts in rheumatology, neurology, genetics, dermatology, pathology, radiology, and physical therapy, to develop guidance on diagnostic tools to aid in the work-up of pediatric patients with myopathy, with a specific focus on differentiating between JDM and MD and the ultimate goal of shortening the time to diagnosis to improve patient outcomes.

Approach

Clinical history. The history is the first step in discerning between JDM and MD, and subtle differences in disease presentation can be important first clues to heighten suspicion for JDM compared with MD. Figure 1 provides an algorithm for diagnostic work-up based on our expert opinion while also drawing from recommendations of previously published guidelines and classification schemes.[6,11–13] Table 1 highlights key differences between JDM and MD and provides additional context to accompany the Figure 1 algorithm. The expected time course for the development of weakness can provide the first branch point in making a diagnosis. In MD, the presentation is usually chronic with gradual disease progression; whereas, in JDM, the time course can be variable from chronic to more rapid in onset. JDM presentation can also be severe and fulminant, more often involving hospitalization when compared with MD.[4] In JDM, there may also be a trigger noted before disease onset, especially infection or an environmental factor such as exposure to increased UV light.[16,17] Although we do not expect definite disease triggers in MD, occasionally a worsening of disease can occur with illnesses, weight gain, linear growth, and some medications, particularly with anesthesia.[18] In MD, the developmental delay of gross motor skills is expected. In some forms of MD, motor delay can start very early, even with decreased movement in utero. Dysphonia and dysphagia are rarer in MD and, if present, may occur later, whereas in JDM, they can be seen at presentation.

The associated extramuscular symptoms can be different in JDM compared with MD. Patients with JDM are more likely to report associated skin changes, although subtle rashes may go unnoticed. Some patients with JDM also have constitutional symptoms like fatigue, weight loss, or fever,[9] which are uncommonly reported in MD or other noninflammatory myopathies.[4] JDM, as a vasculopathy, may involve multiple other organ systems, which may manifest as symptoms of dyspnea, abdominal pain, and hematochezia. Additional symptoms of Raynaud phenomenon, sclerodactyly, arthritis, and mucositis can raise suspicion for overlap myositis. Some features of clinical history may also suggest other types of noninflammatory myopathy in children. Global developmental delay and abnormal facies, for example, would immediately raise suspicion for an underlying genetic syndrome and should lead to earlier genetic testing. Exercise intolerance and intermittent symptoms, including episodes of rhabdomyolysis, might point to a metabolic myopathy, which would necessitate a prompt, focused laboratory work-up.

In JDM, family history of autoimmune disease is variable, but it can be supportive of a diagnosis if present.[4] Family history of

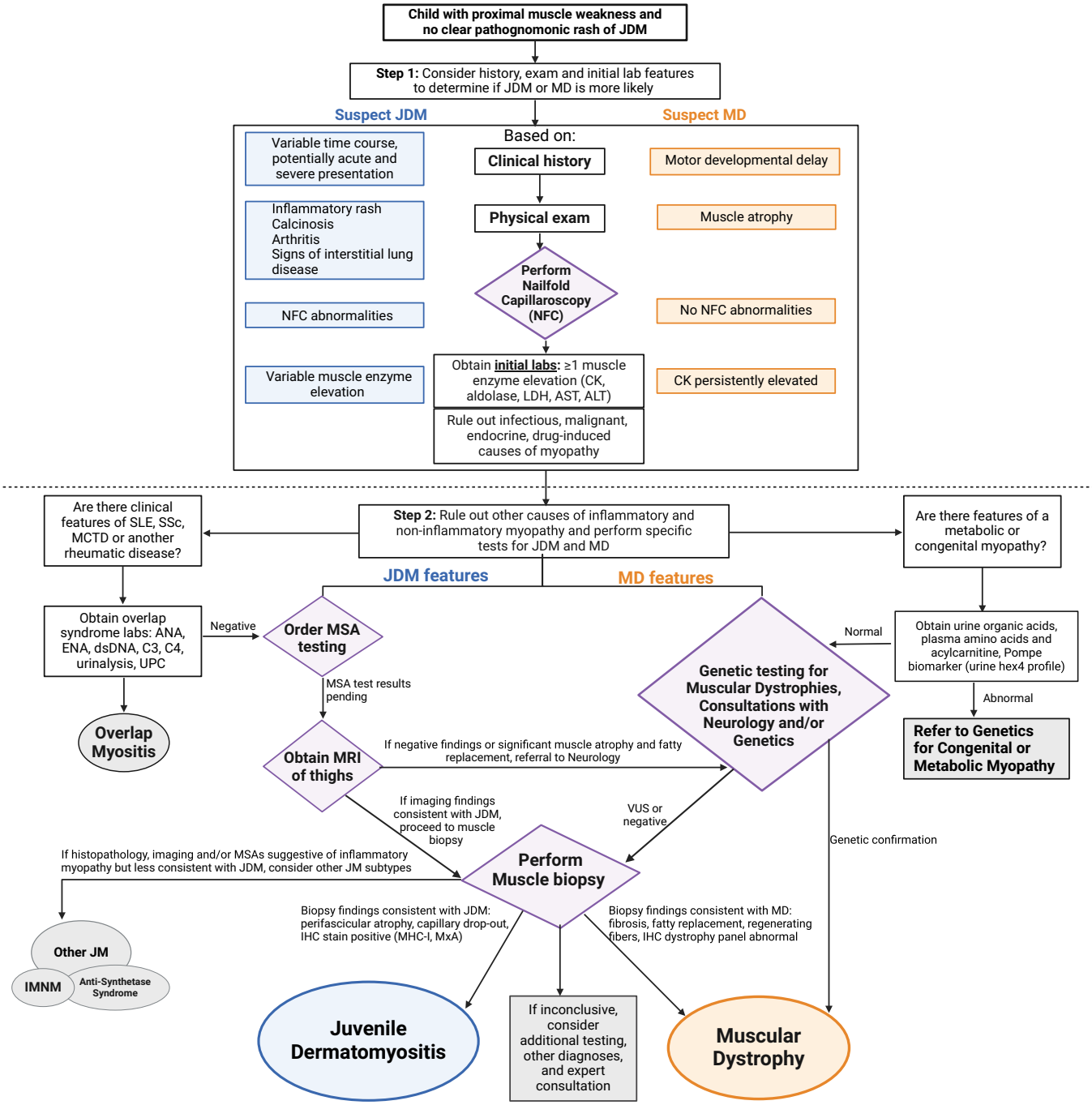

Figure 1. A proposed diagnostic algorithm of the approach to the medical examination of a child presenting with proximal muscle weakness and no clear pathognomonic rash of JDM with the goal of differentiating between JDM and MD and ruling out other diagnoses. Throughout the algorithm, purple diamonds indicate highlighted diagnostic tools which, in our expert opinion, may be especially helpful in differentiating diagnostic possibilities. In the first step, clinical history, physical examination, and initial laboratory features more consistent with JDM or MD are in the laterally placed colored boxes. ALT, alanine transaminase; ANA, antinuclear antibody; AST, aspartate transaminase; CK, creatine kinase; dsDNA, double-stranded DNA; ENA, extractable nuclear antigen; IHC, immunohistochemistry; IMNM, immune-mediated necrotizing myopathy; JDM, juvenile dermatomyositis; JM, juvenile myositis; LDH, lactate dehydrogenase; MCTD, mixed connective tissue disease; MD, muscular dystrophy; MHC-I, major histocompatibility complex class I; MRI, magnetic resonance imaging; MSA, myositis-specific autoantibody; MxA, myxovirus resistance A; NFC, nailfold capillaroscopy; SLE, systemic lupus erythematosus; SSc, systemic scleroderma; UPC, urine protein creatinine; VUS, variant of unknown significance.

MD is supportive, but de novo mutations do occur (for example, one-third of DMD is from de novo variants), so a lack of family history does not rule out MD.[19]

Physical and musculoskeletal examination. The physical examination is a critical part of clinical assessment in a child with reported muscle weakness to establish the

Table 1. Comparison of diagnostic features between JDM and MD*

Feature	JDM	MD
History	• Variable time course in disease presentation • May have trigger to disease onset, including association with infection or environmental exposure, such as UV light • **Symptom presentation may be more acute and severe, resulting in hospitalization** • **Rash, even if subtle, and redness at nailbeds** • Constitutional symptoms (fatigue, weight loss, and fever) • Other system involvement: dyspnea and GI (abdominal pain and hematochezia) • Strong family history of rheumatic disease	• **Motor developmental delay** • Chronic, gradual progression of disease course • Family history of MD • Possibly acute worsening with anesthesia • Rarely decreased movement in utero
Examination	• Weakness of proximal muscles, trunk/core, and neck • Dysphonia and dysphagia • **Rash: heliotrope, Gottron papules or sign, calcinosis, subcutaneous edema, ulcerations, and other; may be subtle** • **Abnormal nailfold capillaroscopy (dropout, hemorrhage, dilation, and abnormal morphology)** • Other: lung crackles as a sign of ILD and abdominal tenderness as a sign of GI involvement • Sometimes range of motion deficit and concurrent arthritis	• Weakness of proximal muscles and particular distinguishing muscle groups: **pectorals, periscapular, biceps, and facial muscles** • **Muscle atrophy** • Dysphonia and dysphagia rare and later
Laboratory tests	• **MSAs** • MAAs • Muscle enzymes elevated to variable degree (CK, aldolase, LDH, AST, and ALT) • vWF Ag and neopterin elevated	• CK persistently elevated in most cases • **Genetic testing for MDs** via neuromuscular panel or WES
Imaging	• **MRI with patchy or diffuse symmetric muscle edema in proximal musculature** and subcutaneous edema	• **MRI with muscle atrophy and fatty replacement** of muscle
Histopathology	• **Perifascicular atrophy** and/or perifascicular basophilic fibers • **Lymphocytic inflammation** (perivascular/perimysial and/or endomysial) • **Immunohistochemical staining: MHC-I positivity, MxA positivity, C5b9 (perifascicular capillary positivity and dilation)**, CD31 (capillary drop out), CD3, and CD20	• **Fibrosis** • **Fatty replacement** • **Regenerating muscle fibers (individual or group)** • Diffuse variation of myofiber size and fiber hypertrophy • **Abnormalities seen on dystrophy immunohistochemical panel** for DMD, BMD, dystrophins, and others
Other testing	• EMG notable for complex repetitive discharge • Work-up for ILD: PFTs and chest CT scan • Cardiac work-up: EKG and echocardiogram	• Work-up for cardiomyopathy: EKG and echocardiogram

* The distinguishing features are in bold. ALT, alanine transaminase; AST, aspartate transaminase; BMD, Becker muscular dystrophy; CK, creatine kinase; CT, computed tomography; DMD, Duchenne muscular dystrophy; EKG, electrocardiogram; EMG, electromyography; GI, gastrointestinal; ILD, interstitial lung disease; JDM, juvenile dermatomyositis; LDH, lactate dehydrogenase; MAA, myositis-associated autoantibody; MD, muscular dystrophy; MHC-I, major histocompatibility complex class I; MRI, magnetic resonance imaging; MSA, myositis-specific autoantibody; MxA, myxovirus resistance A; PFT, pulmonary function test; vWF Ag, von Willebrand factor antigen; WES, whole-exome sequencing.

(1) presence, severity, and pattern of weakness and (2) presence of other organ involvement and/or inflammation, such as in the skin or lungs, which might aid in the differential diagnosis. The initial musculoskeletal evaluation should include an assessment of strength, range of motion, joint mobility, gait, flexibility, balance, and functional mobility (ie, skipping, jumping, and squatting). In JDM, initial muscle weakness appears in the quadriceps, biceps, neck flexor, and abdominal muscles.[20] Joint range of motion can be limited secondary to both muscle and joint inflammation; this is more frequently observed in the elbows, wrists, fingers, knees, and ankles.[21] Patients with JDM typically present with functional mobility deficits, including difficulty with tasks such as supine to sit, sit to stand, reaching overhead, lifting head from supine, and stair negotiation.[22]

Standardized muscle assessments have been tested and validated in the evaluation of muscle disease for JDM and should be performed whenever possible.[23–25] We standardly perform Manual Muscle Testing (MMT-8) and the Childhood Myositis Assessment Scale (CMAS) at initial evaluation and then follow the scores over time to assess response to therapy and guide changes in treatment plan. The MMT-8 evaluates a set of eight muscles tested unilaterally or bilaterally in addition to axial (neck flexor) testing (the highest score is 80 [unilateral] or 150 [bilateral]). Our case report patient's MMT-8 score at diagnosis was 95 of 150. The CMAS is a 14-item observational, performance-based instrument with a maximum total score of 52 that was developed to evaluate muscle strength, physical function, and endurance and has been validated for those aged 4–18 years.[23]

It is difficult to differentiate between JDM and MD with the musculoskeletal examination alone, because both diseases can present with a similar pattern of proximal muscle weakness (Table 1). In our experience, JDM can present with more

weakness in the upper body, primarily the neck and shoulder flexors, compared with DMD. Patients with DMD can present with interscapular weakness, leading to scapular winging, a unique finding.[26] Joint mobility is not typically impacted in the early stages of DMD, but muscle length restrictions of the gastrocnemius-soleus complex and tensor fasciae latae are often observed.[26] A typical gait pattern in DMD consists of increased lateral sway, toe walking, and increased lumbar lordosis.[26] Muscle atrophy is another feature seen on examination more commonly, but not exclusively, in patients with MD compared with JDM.[4]

Skin examination. In JDM, there are well-described dermatologic manifestations, but in practice, skin findings can be variable, ranging from pathognomonic to nonspecific, sometimes subtle findings.[6–8] Skin findings may precede, accompany, or postdate muscle involvement.[27] Pathognomonic cutaneous findings include Gottron papules, also known as atrophic dermal papules of dermatomyositis, which appear as erythematous, scaly papules on the extensor surfaces of the metacarpophalangeal joints classically, although they can also appear on other joints and are specific to JDM. Rash can also present as Gottron sign, less discrete, erythematous, scaly plaques on the extensor surfaces of joints. Heliotrope rash is manifested by a violaceous periorbital erythema accompanied by edema and sometimes scale. Patients with JDM can have severe skin manifestations, including calcinosis and cutaneous vasculopathy.[28] Without characteristic skin findings, more diagnostic tests may be required to firmly establish a diagnosis.[6] It is also important to note that some forms of JM, in particular IMNM, may lack skin manifestations and are at particular risk of being misdiagnosed as MD. There are no commonly reported skin findings in MD.

NFC. NFC is a noninvasive technique that allows for detailed examination of microcirculation changes that may occur with myositis or other autoimmune diseases. The gold standard for NFC assessment is video capillaroscopy[29,30]; however, the use of more traditional instruments, such as the dermatoscope and ophthalmoscope, are still useful in capturing NFC abnormalities seen in JDM.

In NFC assessment, the EULAR study group on microcirculation in rheumatic diseases has developed recommendations for standardized NFC parameters to collect, and "normal" NFCs appear like "teeth-on-a-comb" and are characterized by regular density (more than eight end-row capillary loops per millimeter), a capillary diameter of <20 mm measured from the apex, and normal morphology or lack of abnormal morphology, such as branched or ramified capillaries[30,31] (Figure 2A). The most common abnormal nailfold findings in JDM include decreased density ("dropout," less than eight end-row loops per millimeter), dilated capillaries (>20 mm diameter), hemorrhage, and branched or "bushy" capillaries[31,32] (Figure 2D–G). In a recent AI-based study, a deep neural network model achieved a high accuracy of differentiating NFC images in JDM versus controls with a sensitivity of 0.85 and a specificity of 0.90, providing further evidence that NFC has the potential to aid in diagnosis.[33] In 2023, Melsens et al evaluated NFC findings across different pediatric rheumatic diseases and identified abnormal capillary morphology to be distinctive to JDM and mixed connective tissue disease, even compared with lupus and systemic scleroderma in children.[31] Even within IIM, disorganization of capillaries, avascularity, and giant capillaries (>50 mm diameter) have been demonstrated as characteristic of DM and overlap myositis but are typically absent in antisynthetase syndrome and IMNM.[32,34]

The severity of NFC changes in JDM can also be a potential indicator of disease stage and activity. Fewer end-row loops have been shown to associate with a longer duration of untreated disease and higher disease activity scores for skin at diagnosis.[35–37] 37 NFC density has also been associated with muscle disease activity, with higher modified disease activity scores and lower CMAS scores associating with decreased NFC density.[38] A study analyzing NFC changes in 140 treatment-naive patients with JDM also identified decreased NFC density in anti–transcription intermediary factor 1 γ (TIF1γ)–positive JDM and increased NFC hemorrhage in patients with dysphagia.[36]

In our patient's case, classic JDM NFC findings were seen at diagnosis and aided in diagnostic certainty, including NFC dropout, dilation, nonconvex tips, and overall disorganization (Figure 2B). After 4 months receiving immunosuppressive therapy, our patient demonstrated remarkable capillary regeneration, an absence of dilated or giant capillaries, and a "straightening out" of previously abnormal loops (Figure 2C). These findings are consistent with recent literature that immunosuppressive treatment seems to reduce NFC abnormalities.[32]

In patients with clinical myopathy for whom there is diagnostic uncertainty or lack of pathognomonic JDM rash, the presence of NFC abnormalities can be one of the first more rapid indicators of an inflammatory myopathy. We recommend that NFC be performed at initial assessment in a child with proximal muscle weakness (Figure 1) to guide additional diagnostic work-up. There have not been studies to evaluate the utility of NFC in MD; although there is no suspicion of abnormal findings, this should be confirmed by rigorous testing.

Initial laboratory evaluation

Serum muscle enzymes are frequently elevated in JDM to a variable degree[2,39,40] (Table 1 and Figure 1); however, different muscle enzymes may be elevated in individual patients, and normal muscle enzymes do not rule out a diagnosis of JDM or another JM subtype. Although patients with MD usually have a more persistent elevation in muscle enzymes, specifically CK, throughout the early disease course, the level of muscle enzyme elevation is generally not helpful in differentiating JDM from MD.[4]

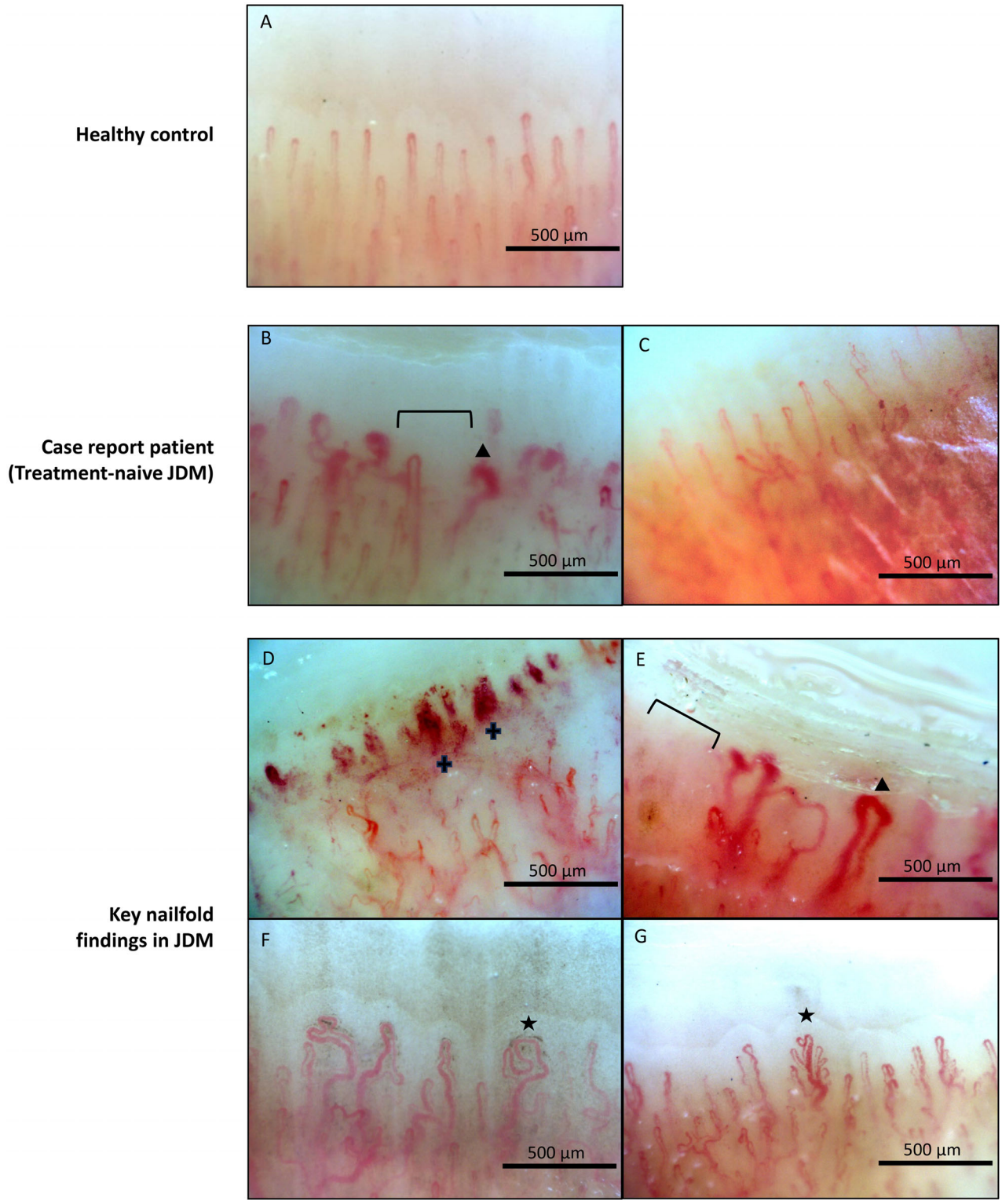

Figure 2. Nailfold video capillaroscopy findings from a (A) healthy control, (B) the case study patient with JDM at treatment-naive visit, and (C) 4 months after treatment initiation and (D–G) examples of key nailfold findings in JDM. (A) A healthy control patient; note the teeth-on-a-comb appearance, regular spacing and organization, no hemorrhage, no dropout (>8 end-row loops/mm), and lack of dilation (<20mm diameter measured from the apex). (B) Case study patient with JDM at treatment-naive visit. Note the nailfold capillary drop out (bracket), dilation (triangle), and overall disorganization. (C) Case study patient with JDM 4 months after treatment initiation. The image shows the recovery of normal density, no dilation, and regular spacing. (D) Example of microhemorrhage (plus sign) and decreased density in treatment-naive patient with JDM. (E) Example of dilation (triangle) and dropout (bracket) in treatment-naive JDM. (F) Example of abnormal morphology (star) in JDM, defined by a nonconvex tip. (G) Example of abnormal morphology (star) with branched, "bushy" capillary in JDM. JDM, juvenile dermatomyositis.

We suggest a broad initial laboratory work-up to rule out other causes of myopathy and then a narrowing in on focused testing based on the most likely diagnosis, as highlighted in our proposed algorithm in Figure 1. Levels of neopterin and von Willebrand factor antigen are additional biomarkers that have been found to correlate with JDM disease activity; their levels in MD have not been established.[41–43] For a patient with suspected metabolic myopathy, additional laboratory evaluation is critical to aid in the identification of metabolic causes, such as fatty acid oxidation disorders, mitochondrial disorders, and glycogen storage diseases, such as Pompe disease. Initial laboratory testing should also include an acylcarnitine profile to identify specific patterns indicative of impaired fatty acid oxidation. Urine organic acid analysis is invaluable for diagnosing mitochondrial disorders because it can detect characteristic organic aciduria resulting from impaired mitochondrial metabolism. Additionally, screening for Pompe disease biomarkers, specifically the enzyme acid alpha-glucosidase activity in blood and measurement of urine hexose tetrasaccharide levels are crucial.[44] These tests, when used collectively, can provide a comprehensive overview of the metabolic pathways involved and guide the differential diagnosis toward specific metabolic myopathies.[45]

MSAs. Approximately 40% to 70% of patients with JDM will test positive for an MSA.[46–50] Testing for MSAs, autoantibodies against several intracellular proteins, is indicated in the initial work-up of JDM (Figure 1 and Table 1), because MSA subtyping can aid in clinical phenotyping and prognostication[51] (Table 2). The gold standard for MSA detection is immunoprecipitation, although in recent years, several commercially available immunoassays have been developed and are performed by line blot or enzyme-linked immunosorbent assay.[52] These tests may have low sensitivity for identifying key MSAs commonly seen in JDM, including TIF1γ, and high rates of false positives.[53] The timing of sampling may impact MSA results, because certain MSA titers have been shown to decrease in response to treatment.[54] There are some additional potential issues associated with MSA testing, including a lack of uniformity of results from different laboratories

Table 2. MSAs and MAAs in children*

	Diagnosis	Features[48–51]	Frequency in pediatrics,[48,49] %
MSA			40–70
TIF1γ (anti-p155/140)	JDM	Severe skin manifestations, photosensitivity, skin ulcerations, lipodystrophy, and chronic disease course. No increased risk of malignancy as seen in adults	18–36
NXP2 (anti-MJ)	JDM	Severe muscle involvement with dysphagia and dysphonia and increased risk of calcinosis	15–23
MDA5	JDM	ILD including rapidly progressive in Asia; mild muscle disease; arthritis and ulcerations	7–8 in US, 38–54 in Japan
Mi-2	JDM	High CK and severe histologic features on muscle biopsy yet benign clinical course; classic JDM rash; responds well to standard therapies	3–5
SAE	JDM	Amyopathic disease initially with later muscle involvement	1
Jo-1 PL-12 OJ EJ PL-7 KS Zo Ha	Antisynthetase syndrome	Myositis, arthritis, Raynaud phenomenon, mechanic's hands, and ILD	<5
SRP	IMNM	Severe muscle disease with high CK and significant weakness; refractory to therapy; no skin manifestations; possible cardiac involvement	1
HMGCR	IMNM	Severe muscle disease with high CK and significant weakness; often lacks skin manifestations; refractory to therapy	1
MAA			16–20
PM/Scl	Overlap myositis	PM/Scl overlap; increased risk of ILD, arthritis, Raynaud phenomenon, and mechanic's hands	3–5
Ro52	Overlap myositis	Frequently associated with MSAs, especially antisynthetase antibodies; increased risk of ILD	6
U1RNP	Overlap myositis	Overlap myositis with SLE and scleroderma	5–15

* The associated disease, clinical features, and frequency of MSAs and MAAs in pediatric patients with myositis. CK, creatinine kinase; EJ, glycyl-tRNA synthetase; Ha, tyrosyl-tRNA synthetase; HMGCR, 3-hydroxy-3-methylglutaryl CoA reductase; ILD, interstitial lung disease; IMNM, immune-mediated necrotizing myopathy; JDM, juvenile dermatomyositis; Jo-1, histidyl-tRNA synthetase; KS, asparaginyl-tRNA synthetase; MAA, myositis-associated autoantibody; MDA5, melanoma differentiation associated protein 5; MSA, myositis-specific autoantibody; NXP2, nuclear matrix protein 2; OJ, isoleucyl-tRNA synthetase; PL-12, alanyl-tRNA synthetase; PL-7, threonyl-tRNA synthetase; PM, polymyositis; SAE, small ubiquitin-like modifier activating enzyme; Scl, scleroderma; SLE, systemic lupus erythematosus; SRP, signal recognition particle; TIF1γ, transcription intermediary factor 1 γ; U1RNP, U1 ribonucleoprotein; Zo, phenylalanyl-tRNA synthetase.

and delays of weeks in receiving results during a critical time in which other testing and even treatment may need to be pursued. The absence of an MSA does not rule out JDM—approximately one-third of children with JDM will not test positive for an MSA,[47] but the presence of an MSA was one of the most important features in distinguishing JM from MD in a series of 48 cases.[4]

The most prevalent MSAs in children with JDM are TIF1γ and NXP2, which differs from the MSA distribution reported in adults with dermatomyositis.[55] Table 2 describes the clinical phenotypes observed in JDM and other patients with JM with specific MSAs.[46–49,54–56] A subset of patients with JM (16%–20%) can have myositis-associated autoantibodies (MAAs), including anti-Ro52, anti-U1RNP, and anti-PM/Scl. These patients may have clinical phenotypes of overlap symptoms with scleroderma and systemic lupus erythematosus or they may have predominant myositis.[46,47] The presence of MAAs in patients with JM has been associated with an increased risk of refractory disease and death.[57]

Genetic testing. The role of genetic testing for patients with suspected MD or metabolic myopathies has become increasingly common because of decreasing costs, improved availability, and simultaneous evaluation of numerous genetic conditions.[58–60] Generally, when a child presents with neuromuscular symptoms and no other health concerns, starting with a panel focused on neuromuscular conditions is reasonable. Choosing from evaluable panels should be based on the number of genes and the inclusion of medically actionable disorders, such as Pompe disease and DMD. When a child has multiple health problems or features of MD accompanied by intellectual disability, however, then whole-exome sequencing becomes the preferred method of testing.[61,62] The presence of intellectual disability or developmental regression in addition to myopathy concerns should prompt a referral to medical genetics for comprehensive evaluation.

Although genetic testing can confirm a genetic diagnosis, it may also identify variants of uncertain significance (VUS).[63] These VUSs can pose challenges, but it is important to consider the mode of inheritance. If a VUS is identified in a gene associated with an autosomal recessive condition, it likely indicates carrier status and is not diagnostic. When in doubt, it is advisable to discuss these results with a geneticist or genetic counselor. Because genetic testing is more widely available and comprehensive, it is typically the next step after clinical history and examination for suspected MD; but, if additional testing is needed, muscle biopsy and MRI scans can also assist with diagnosis.[64–66]

Imaging

MRI scans are highly sensitive at identifying edema and fatty degeneration in myopathies. The pattern of muscle involvement on MRI may suggest a particular type of myopathy when the diagnosis remains uncertain and may narrow the differential diagnosis[67–69] (Figure 1 and Table 1). MRI can be helpful even in clinically apparent cases of JDM, such as those with characteristic rash, to define the extent of muscular inflammation and determine the presence of muscle damage. Patients with JDM with either skin-predominant disease or longer disease duration may have evidence of muscle inflammation on MRI scans despite normal muscle enzyme levels.[70,71] Finally, MRI scans can guide the clinician in selecting a muscle with active inflammation for biopsy.[72,73]

A standard MR protocol is to scan the pelvis and both thighs using axial T1-weighted images, axial T2-weighted images with fat saturation or mDixon technique and coronal STIR images. Postgadolinium-based intravenous contrast T1-weighted images and diffusion-weighted images will show abnormality in the same distribution as the T2-weighted and STIR images and thus are not usually additive and can be omitted. This allows for a relatively short imaging time and alleviates the need for sedation or general anesthesia in most patients.

Differential diagnosis in a case of suspected myopathy is narrowed based on the degree of muscle edema and pattern of muscle involvement: symmetry, portions of proximal muscle involvement, and involvement of distal and axial muscles (Figure 3). High signal intensity on T2-weighted imaging (Figure 3A) and STIR (Figure 3C) is indicative of edema consistent with active inflammation in JDM, as seen in our case report patient. Although muscle edema is seen in other clinical settings, including the early stages of MD, a high degree of muscle edema is suggestive of an inflammatory myopathy.[67] T1-weighted images (Figure 3E) demonstrate muscle atrophy and fatty infiltration, which predominates in MD but is also seen secondary to chronic inflammation and steroid use. In a patient with JDM, MRI scans show high-intensity edema in skeletal muscle especially along the fascia, which is diffuse, symmetric, and inclusive of proximal musculature. Subcutaneous inflammation and calcinosis may also be apparent.[67,74]

Muscle biopsy and histopathology

In a child without a clear diagnosis of JDM or MD after thorough history, examination, laboratory tests, imaging, and possibly genetic testing, it is important to obtain a muscle biopsy (Figure 1). There has been a trend toward a reduced frequency of obtaining muscle biopsies, especially when pathognomonic rash is present; however, it can be a critical step to differentiate JDM from other types of childhood myopathies and may provide prognostic information.[50,75,76] Considering continued advances in genetic testing for MD and other congenital myopathies, many practitioners will order genetic testing before or in lieu of muscle biopsy. However, one recent retrospective study highlighted that the diagnostic yield of genetic testing was higher when performed after muscle biopsy.[77] Also of note, the development of the recently approved genetic therapy for DMD was dependent on demonstrating the

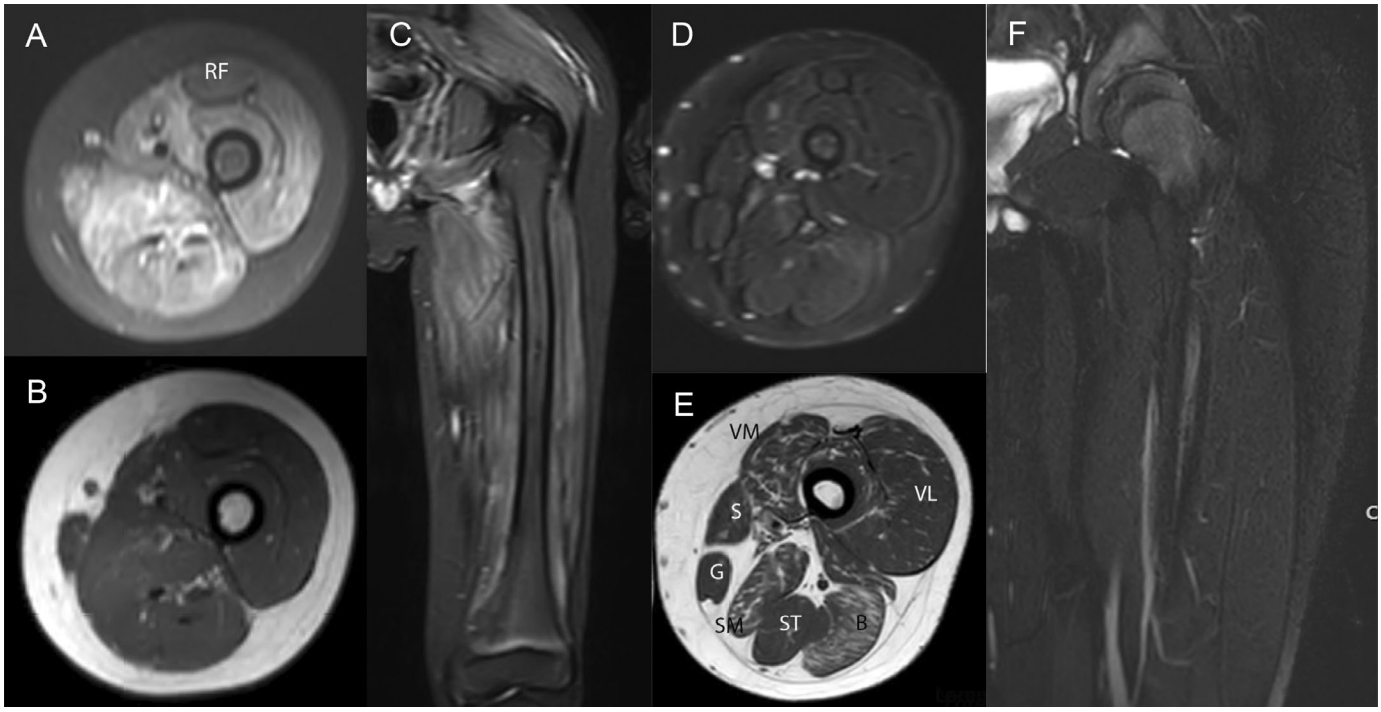

Figure 3. (A–C) Magnetic resonance imaging scan of the case report patient: a boy aged 4 years with juvenile dermatomyositis. (A) Axial T2-weighted spectral attenuated inversion recovery image of the midthigh shows diffuse increased signal within muscles of the thigh consistent with edema/inflammation. There is relative sparing of the distal RF muscle. (B) Axial T1 image of the midthigh shows normal muscle signal without fatty infiltration. (C) Coronal STIR image also shows diffuse increased signal within muscles of the thigh consistent with edema/inflammation. (D–F) Magnetic resonance imaging scan of a boy aged 12 years with noninflammatory myopathy. (D) Axial T2-weighted modified Dixon image of the midthigh with fat signal nulled shows normal signal with no areas of high signal to suggest edema/inflammation. (E) Axial T1-weighted image of the midthigh shows feathery high signal in muscle consistent with fatty infiltration; the VM, SM, and long-head of the B muscles are most affected with relative sparing of the VL, ST, G, and S muscles. (F) Coronal STIR image also shows normal muscle signal. B, biceps; G, gracilis; RF, rectus femoris; S, sartorius; SM, semimembranosus; ST, semitendinosus; VL, vastus lateralis; VM, vastus medialis.

presence of the microdystrophin protein in muscle biopsy samples from treated patients.[78]

Histopathologic differentiation of JDM vs MD

JDM hematoxylin and eosin. JDM histopathologic features on muscle biopsy include perivascular inflammation, perifascicular atrophy, muscle fiber degeneration/regeneration, endothelial cell swelling, narrowing and obliteration of the vessel lumens, inflammatory cells within vessel walls (microvasculitis), and capillary dropout[75] (Table 1). In patients with perifascicular atrophy, basophilia of the atrophic fibers is most common. Other less common findings include muscle infarction (well-demarcated regional muscle fiber necrosis), endomysial or perimysial fibrosis, sarcoplasmic vacuolation, and internal myonuclei.[75] In our case report patient, we noted perifascicular atrophy and perifascicular basophilic fibers (Figure 4A). Although routine histologic analysis has been reported to appear normal in up to 20% of patients,[9] additional immunohistochemical and/or electron microscopic analysis may reveal abnormalities.[75] More recently, distinct pathologic patterns have been described in patients with JDM with different MSAs.[79] Specifically, muscle biopsies from patients with high-titer anti–Mi-2 antibodies showed prominent perifascicular myofiber necrosis, whereas myofiber necrosis was limited in patients with anti-NXP2 antibodies. Patients with anti-MDA5 antibodies showed near-normal muscle histology.[79]

JDM immunohistochemistry. It is important to complement standard hematoxylin and eosin staining with immunostaining for proteins commonly dysregulated in JDM. JDM muscle biopsies often demonstrate increased sarcolemmal expression of MHC-I in muscle fibers, capillary deposition of complement (C5b9 by immunohistochemistry or multiple complement components by direct immunofluorescence[76]), sarcoplasmic MxA expression[80] (Figure 4C, E, and G), or sarcoplasmic CD56 expression.[75] Complement deposition can occur in capillaries or small intramuscular arteries,[76] and variation in pattern based on MSA has been described, such as prominent capillary C5b9 deposition with anti-NXP2 and anti-TIF1γ autoantibodies and limited capillary C5b9 deposition with anti–Mi-2 and anti-MDA5 autoantibodies.[79,81] Increased C5b9 muscle fiber sarcolemmal staining was reported in patients with anti–Mi-2 antibodies.[81]

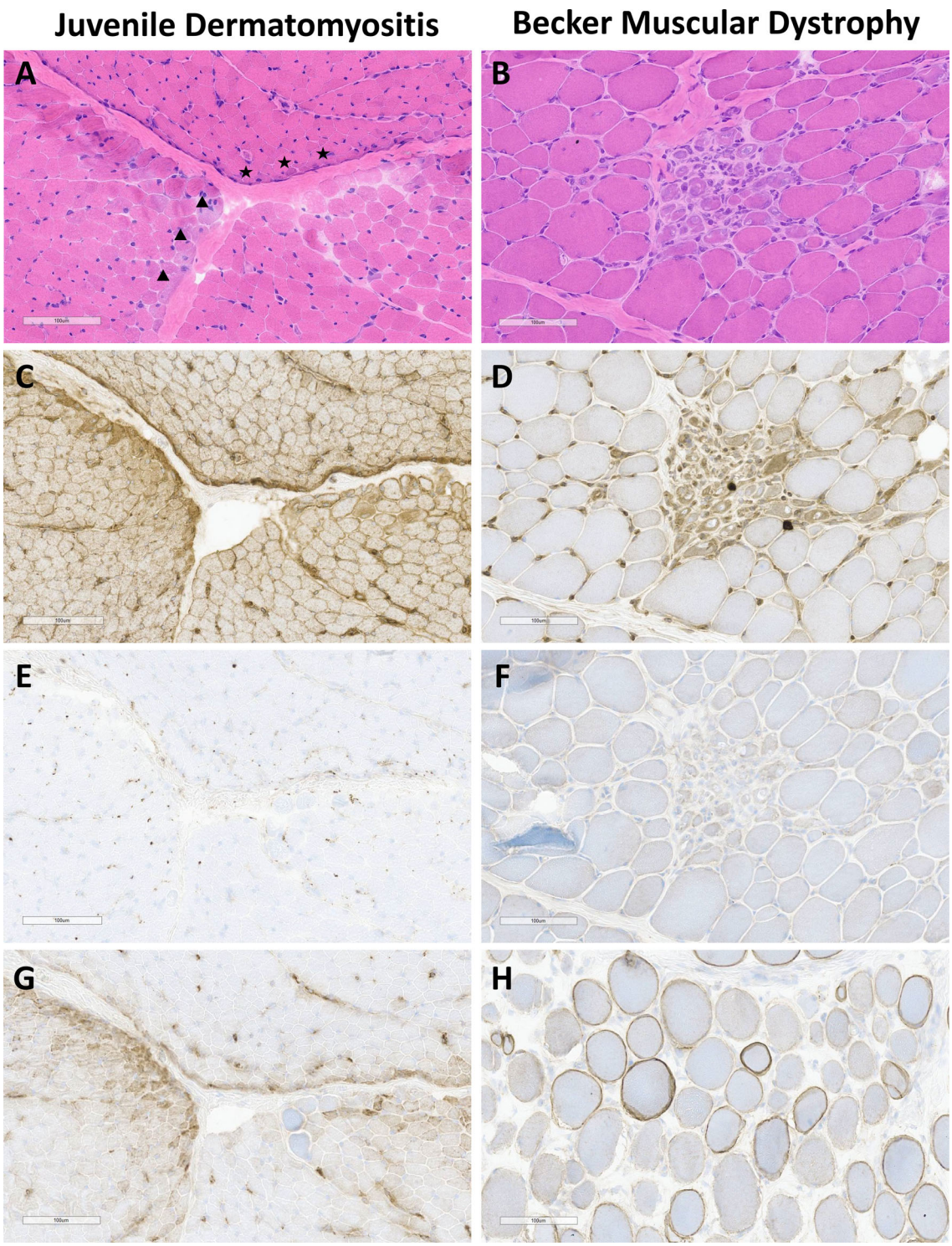

Figure 4. Muscle biopsy histopathology findings from the case of JDM described in the clinical scenario (A, C, E, and G) and a case of Becker MD in a 7-year-old boy confirmed with genetic testing (B, D, F, and H). (A) JDM hematoxylin and eosin: notable characteristics include perifascicular atrophy (subtle in this case), and perifascicular basophilic fibers. (B) MD hematoxylin and eosin: grouped atrophic, rounded, and basophilic fibers in the center of the image surrounded by abnormally large fibers. Patchy endomysial fibrosis is also present. (C) JDM Major Histocompatibility Complex class I: diffuse sarcolemmal staining with perifascicular accentuation. (D) MD Major Histocompatibility Complex class I: essentially negative for sarcolemmal staining and shows sarcoplasmic staining only in grouped atrophic fibers. (E) JDM C5b9: positive for capillary staining in areas of perifascicular atrophy and perifascicular basophilic fibers. (F) MD C5b9: negative for capillary staining. (G) JDM: positive for perifascicular sarcoplasmic myxovirus resistance A staining. (H) Dystrophin (C-terminal) staining in MD showing an abnormal mosaic pattern, which is the most common pattern seen in patients with Becker MD. Myxovirus resistance A staining not performed for the patient with MD; expected to be negative and similar in appearance to slide F. JDM, juvenile dermatomyositis; MD, muscular dystrophy.

Neonatal myosin can also be increased. Vascular markers (CD31 or CD34) can be used to evaluate for capillary dropout, which can also be seen in JDM muscle biopsies. Lymphocyte markers (CD3, CD4, CD8, and CD20) can be used to evaluate for and characterize perivascular lymphocytic inflammation. CD68 or CD163 stains can be used to evaluate for macrophage infiltration.[75] In histologically ambiguous cases, electron microscopic analysis can be performed to evaluate for tubuloreticular inclusions in endothelial cells, a highly specific finding for JDM in muscle biopsies.[82]

MD histopathology. Muscle biopsy can distinguish MD from JDM by identifying "dystrophic changes," which include marked fiber size variation, internal nuclei, necrotic fibers, associated inflammation, and endomysial fibrosis[83] (Figure 4B). Compared with JDM, the range of histologic findings that can be seen in MD and related disorders is extremely broad and varied,[77] and classical "dystrophic" findings may only be seen in a minor subset of muscle biopsies[77,84] (Figure 4B). Other abnormal findings can include fiber type predominance, atrophy of specific fiber types, neurogenic changes, chronic myopathic changes, inflammatory changes, or evidence of mitochondrial or metabolic disease.[77] There may also be no pathologic abnormalities seen, or the findings may be mild and challenging to differentiate from within the range of normal. To evaluate for MD, a panel of immunohistochemistry stains specific to proteins encoded by genes disrupted in various MDs (limb-girdle MDs, DMD, BMD, sarcoglycanopathies, dystrophinopathies, dysferlinopathies, calpainopathies, collagen 6A–related myopathies, and merosin-negative congenital muscular atrophy) can be performed as a screening tool.[84] As an example of an abnormal and diagnostic staining pattern in a muscle biopsy, we demonstrate the presence of abnormal mosaic dystrophin staining in a case of BMD (Figure 4H). Certain MD subtypes can demonstrate significant inflammation, complicating the differentiation from JM. One study suggested that the pattern of inflammation may be different in inflammatory versus noninflammatory myopathy, with inflammatory myopathy most often demonstrating "inflammatory clusters" (groups of ≥20 inflammatory cells), rather than smaller groups and scattered inflammatory cells in dysferlinopathy, calpainopathy, or BMD.[85]

Histopathologic features of other JM subtypes. As opposed to the classical finding of perifascicular atrophy in JDM muscle biopsies, perifascicular necrosis is the most common histopathologic feature in antisynthetase syndrome–associated myositis.[86–88] Lymphocytic and histiocytic inflammation is common, often most prominently in perimysial areas.[88] A pattern of edematous, fragmented, and cellular perimysial tissue is commonly seen, often with increased perimysial alkaline phosphatase staining.[87] MHC-I staining is often diffusely positive (similarly to many other IIMs), with MHC-II staining more specifically highlighting a perifascicular pattern in antisynthetase syndrome.[87]

The key features of muscle biopsies from patients with IMNM are variable amounts of scattered necrotic and/or regenerating muscle fibers and a concurrent limited amount of lymphocytic inflammation ("pauci-immune").[89–91] In fact, approximately 80% of muscle biopsies from patients with IMNM do not show significant lymphocytic infiltrates.[86] Other features of muscle biopsies from patients with IMNM may include (1) variable sarcolemmal MHC-I expression,[89,92,93] (2) sarcolemmal complement deposition, and (3) endomysial fibrosis.[92] Of note, this combination of features can overlap with muscle biopsy findings from patients with MD.[90] Most patients with IMNM will show a characteristic fine punctate sarcoplasmic p62 staining pattern in scattered fibers not reported in MD,[94,95] although it is sometimes positive in other IIMs.[96]

Other testing

Screening for other organ involvement is not only important for informing prognosis and treatment decisions, but it may also help differentiate JDM from noninflammatory myopathy (Table 1). One of the most serious extramuscular complications in several types of JM is ILD, which in JDM can develop chronically or be rapidly progressive. At JDM diagnosis, pulmonary function tests (PFTs) are recommended to screen for lung disease.[13] PFTs may reveal a restrictive pattern with decreased total lung capacity or decreased diffusing capacity for carbon monoxide. A restrictive pattern on PFTs should be followed up with a high-resolution chest computed tomography scan to assess for imaging evidence of ILD. Subgroups most at risk for ILD include anti-MDA5 patients; those with overlap syndromes with particular MAAs, specifically anti-Ro52; and those in antisynthetase syndrome.[55] Baseline echocardiogram and electrocardiogram are also recommended for all patients with JDM at diagnosis. Acute symptomatic cardiac complications, such as congestive heart failure, arrhythmias, and pericardial disease, are rare, although patients have been shown to have increased rates of asymptomatic diastolic and systolic function of unclear significance with long-term follow-up.[13] For any symptoms of dysphagia or dysphonia, swallow evaluation with speech and language pathology and video fluoroscopic swallow study should be performed.[13] If any of these complications are present early, they might raise suspicion for JDM or another JM subtype.

Cardiac or pulmonary complications may occur in MD as the disease progresses and are usually the cause of death.[97,98] Cardiac complications include potentially life-threatening arrhythmias and the development of hypertrophic or dilated cardiomyopathy.[98] Respiratory failure is secondary to progressive weakness of respiratory muscles, leading to hypoventilation as well as difficulties managing secretions. Patients with MD require regular monitoring of heart and lung function with echocardiogram, electrocardiogram, 24-hour Holter monitor, PFTs, and sleep study.

In our practice, electromyography or nerve conduction studies are generally performed primarily to rule out other diagnoses, for instance if there is a specific question of nerve or neuromuscular junction versus muscular origin of weakness. The needle studies are not very well tolerated, and the results can be very similar between JM and MD, although there may be an increase in complex repetitive discharge in JM as a distinguishing feature.[4]

Conclusions

A child presenting with proximal muscle weakness has a broad differential diagnosis, which requires a thoughtful, detailed work-up to arrive at a specific diagnosis. In our case report patient, diagnosis was delayed by 6 months because of an initial presumed diagnosis of MD. When genetic testing did not reveal a clear cause of myopathy, the diagnosis was reconsidered. To more quickly differentiate between JDM and MD, which can present very similarly, and improve time to diagnosis and treatment, we have presented a proposed diagnostic work-up algorithm to aid in clinical assessment and decision-making when a child presents with weakness and no definite rash of JDM (Figure 1). We highlight a few key decision points that can aid in more quickly arriving at a definitive diagnosis of JDM: (1) NFC, (2) MSA testing, and (3) muscle biopsy.

NFC is a fast, noninvasive imaging tool that can be paired with initial diagnostic examination to reveal clues as to whether a patient has an underlying systemic inflammatory process or vasculopathy. Next, if there is a high index of suspicion for JDM based on clinical features, MSA testing can be ordered with the initial laboratory tests. If positive, MSAs facilitate diagnostic clarity and assist in clinical phenotyping to further direct urgency of screening for other major organ involvement. Finally, obtaining a pretreatment muscle biopsy can provide invaluable insight into tissue-specific changes to differentiate an inflammatory from noninflammatory myopathy and can also provide prognostic information. Moreover, muscle biopsies can be stored, with anticipated later application of novel technologies to guide personalized medical care, such as single-cell RNA-sequencing. In looking to the future in JDM diagnosis, we anticipate not only advances in the utility of NFC, MSA testing, and biopsy but also the development of novel biomarker signatures to guide care based on precision medicine.

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AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Turnier confirms that all authors have provided the final approval of the version to be published and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

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